EVOKED POTENTIAL MANUAL

EVOKED POTENTIAL MANUAL

A Practical Guide to Clinical Applications

SECOND REVISED EDITION

edited by

E. J. COLON

Delft Municipal Hospital Rotterdam, Postgrad. Dr. Netherlands and Erasmus University Rotterdam, Rotterdam, The Netherlands

and

S. L. VISSER

Department of Clinical Neurophysiology, Free University of Amsterdam, Amsterdam, The Netherlands Present address: Alkmaar, The Netherlands

Kluwer Academic Publishers

Dordrecht / Boston / London

Library of Congress Cataloging-in-Publication Data

Evoked potential manual : a practical guide to clinical applications / edited by E.J. Colon, S.L. Visser. -- 2nd rev. ed.
p. cm.
Includes bibliographical references.
Includes index.

1. Evoked potentials (Electrophysiology) 2. Nervous system--Diseases--Diagnosis. I. Colon, E. II. Visser, S. L.
[DNLM: 1. Evoked Potentials. 2. Nervous System Diseases--diagnosis.]
[illegible]
616.8'047547--dc20
DNLM/DLC

[illegible]

ISBN-13: 978-94-010-7424-7 e-ISBN-13: 978-94-009-2059-0
DOI: 10.1007/978-94-009-2059-0

Published by Kluwer Academic Publishers,
P.O. Box 17, 3300 AA Dordrecht, The Netherlands.

Kluwer Academic Publishers incorporates
the publishing programmes of
D. Reidel, Martinus Nijhoff, Dr W. Junk and MTP Press.

Sold and distributed in the U.S.A. and Canada by
Kluwer Academic Publishers,
101 Philip Drive, Norwell, MA 02061, U.S.A.

In all other countries, sold and distributed by
Kluwer Academic Publishers Group,
P.O. Box 322, 3300 AH Dordrecht, The Netherlands.

Printed on acid free paper

Contents

Preface

Evoked potentials are potentials that are derived from the peripheral or central nervous system. They are time locked with an external stimulus and can be influenced by subjective interference.

Evoked potentials have become increasingly popular for clinical diagnosis over the last few years.

Evoked potentials from the visual system are used by ophthalmologists in order to localize the abnormalities in the visual pathway. The otologists are mainly involved in brainstem auditory evoked potentials, while the pediatricians, neonatologists, neurologists and clinical neurophysiologists make use of multimodal stimulation. The psychiatrists and psychologists, generally, examine the slow potentials such as P300 and CNV. Anesthesiologists use short latency somatosensory and visual evoked potentials in order to monitor the effectiveness of the anesthesia.

Pharmaco evoked potentials are very promising measures for the quantification of the effectiveness of drug action on the cerebral cortex. Urologists are more and more involved in pudendal somatosensory evoked potentials and in the intensive care unit evoked potentials are used in order to monitor the functional state of the central nervous system of the patient. This overwhelming number of examinations and examinators clearly demonstrates the need for guidelines and standardization of the methods used.

The evoked potential methodology is restricted by the relative poor signal to noise ratio. In many diseases this signal to noise ratio decrease rapidly during the progression of the illness. Optimal technical equipment and methodology are therefore essential.

Adequately trained technicians can help to optimize the obtained signals by influencing the state of mind of the patient, and thus to diminish the number of artifacts. Testing the reproducibility of the evoked potentials by repetition of the examination is necessary to avoid misinterpretations.

Source identification of evoked potentials would be the most desirable method for clinical interpretation of evoked potentials findings. So far a minority of evoked potential generators have been identified unambiguously.

We can divide evoked potential generators in near field and far field generators. Near field generators can only be derived close to generator, and far field generators can be derived over a large area.

From the theoretical point of view it would be better to define stationary potentials instead of far field potentials.

Sometimes the generators show a monopolar surface distribution and in other cases a multipolar distribution. By means of topography (mapping or chronotopography) insight in the location and distribution of evoked potential distribution can be obtained. In clinical use these topographical evoked potential representations are a real challenge. The relative simple evoked potential configuration can be followed in time and space by topography and abnormalities in processing of sensory information in the central nervous system can be analysed in a nontraumatic way.

The purpose of this book is to review for those who are, or intend learn working with evoked potentials, the methodology and clinical applications of various evoked responses, both on the cortical and the subcortical level. Furthermore recommendations for the standardization of these examinations are proposed.

In the first chapter a comprehensive analysis of the technical problems that are dealt with in EP studies is given. Then the methodology of elicitation, the clinical uses and problems with clinical interpretation of the various evoked potentials is covered. The anatomy and physiology of the visual, auditory, somato-sensory and motoric modalities are also discussed.

E.J. Colon and S.L. Visser

List of contributors

G. Cursi
Division of Neurology, S. Raffaele Hospital, University of Milan, Milan, Italy

E.J. Cohen
Chief Psychiatric Education, Delta Municipal Hospital Rotterdam, Poortugaal, The Netherlands and Erasmus University, Rotterdam, Rotterdam, The Netherlands

J.J. Eggermont
Department of Psychology, University of Calgary, Calgary, Alberta, Canada

L. Garcia Larrea
EEG Department, Neurological Hospital, University of Lyon, Lyon, France

V. Himberg
Neurological Therapy Center, University of Düsseldorf, Düsseldorf, F.R.G.

E. Lichtl
Pedological Institute, Free University of Amsterdam, Amsterdam, The Netherlands

F. Mauguière
EEG Department, Neurological Hospital, University of Lyon, Lyon, France

J.J. Rotteveel
Department of Neuropaediatrics, University Hospital Nijmegen, Nijmegen, The Netherlands

P.H. Schimidt
Department of Otorhinolaryngology, Leiden University Hospital, Leiden, The Netherlands

H. Spekreijse
Interuniversity Institute of Ophthalmology, Academic Medical Centre, Amsterdam, The Netherlands

D.F. Swaab
Department of Clinical Neurophysiology, University of Nijmegen, Nijmegen, The Netherlands

S.L. Visser
Department of Clinical Neurophysiology, Free University of Amsterdam, Amsterdam, The Netherlands
Present address: Koningsweren 17, Alkmaar, The Netherlands

A. de Weerd
Department of Clinical Neurophysiology, Westeinde Hospital, The Hague, The Netherlands

J.P.C. de Weerd
Nicolet Biomedical Institute, Madison, Wisconsin, U.S.A.

PART ONE

Technical aspects

Technical and methodological considerations on the measurement of evoked potentials

J.P.C. DE WEERD and D.F. STEGEMAN

1. Introduction

The quality of an evoked potential study depends first and foremost on the reliability of the acquired waveforms. Although the recording of evoked potentials has largely become a matter of routine clinical practice, there is a number of technical and methodological aspects which need attention. These aspects are:

1. choice of stimulus parameters;
2. proper recording and amplification of the signals evoked by the stimuli;
3. application of signal enhancement techniques in view of the generally small waveform amplitudes;
4. recognition and possible elimination of technical and biological artifacts;
5. assessment of waveform reliability;
6. identification and labeling of waveform components;
7. comparison to normative data for the purpose of reporting possible abnormalities;
8. choice of a suitable way to present the results numerically or graphically.

In modern, commercially available equipment, most or all of the above aspects have been integrated. This fact, however does not eliminate the need to have a basic understanding of the technical requirements and operating principles of evoked potential systems. It is the intent of this chapter to discuss these issues in some detail, providing practical examples along with any pertinent theoretical background.

2. Stimulation

Since the actual form of stimulation is different for the different modalities and the choice of a particular stimulus largely depends on the clinical problem at hand, a discussion concerning modality specific stimulation aspects is incorporated in the corresponding subsequent chapters. The present section will deal with a common aspect in all modalities, i.e. stimulus timing.

K. J. Colon and K. E. Visser (eds), Evoked potential manual, pp. 3–17.

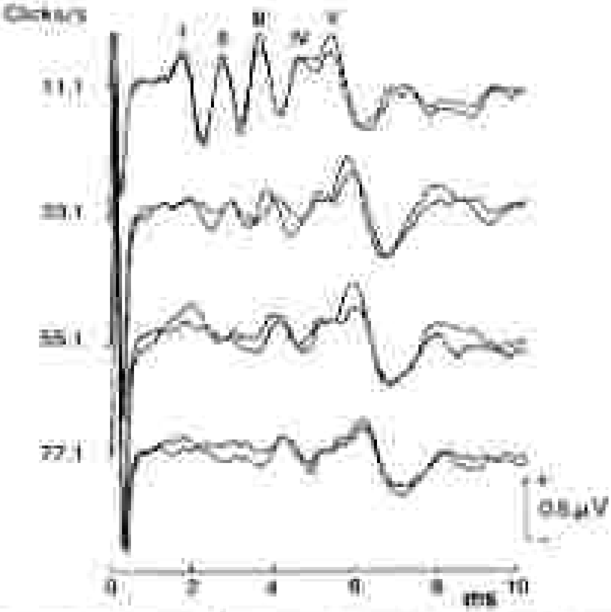


Figure 1. Brainstem auditory evoked potentials (C_z to ipsilateral mastoid) from a normal subject in response to monaurally applied 80 dB, 100 μs condensation clicks. Bandpass used: 150 Hz – 3 kHz. With increasing stimulus repetition rate the various waveform components show increased latencies and reduced amplitudes.

We confine ourselves to the so-called transient evoked potentials. Steady-state periodic stimuli, as for instance a constant tone in the auditory domain, are not considered because of their limited clinical application.

2.1. Stimulus repetition rate

The selection of a proper stimulus repetition rate depends on which part of the sensory system will be investigated. *Short latency* peripheral, spinal and brainstem evoked potentials have relatively short recovery cycles. Thus, for these potentials relatively high stimulus rates can be used. However, some authors [Pratt *et al.*, 1980; Stockard and Westmoreland, 1981; Suzuki *et al.*, 1986] suggest that rates no higher than approximately 10 Hz should be used, since with increasing frequencies the latency of the various components gradually increases while their amplitude decreases [Salamy *et al.*, 1978; Van Olphen *et al.*, 1979; Colon and De Weerd, 1986] (see Fig. 1).

Moreover, it has been demonstrated that the rate of change shows variability among individuals [Stockard *et al.*, 1978]. Because of this variability it is important to use always a standard repetition rate. Even better is to use two distinctly different (i.e. low and high) rates, since some abnormalities may only be revealed at high repetition rates [Pratt *et al.*, 1981; Yagi and Kaga, 1981]. Simple fractions or multiples of the mains frequency (50 or 60 Hz)

should be avoided to eliminate the possibility of stimulus locked mains interference. Methods have been described to use mains locked triggering on alternate phases in the cycle to improve mains interference reduction (e.g. [Sgro and Emerson, 1985]).

To adequately measure *middle latency* components one can use repetition rates similar to or slightly lower than the rates used in measuring subcortical components, i.e. 5–10 Hz. At higher stimulation rates similar changes in latency, but more pronounced changes in amplitude take place as compared to short latency components (Fig. 2).

The measurement of *long latency* components requires significantly lower stimulus repetition rates, 1 Hz being approximately the upper limit (Fig. 3). In fact, for these evoked potentials the recovery cycle is much longer (about 5 to 10 seconds) than the total duration of the long latency potential components

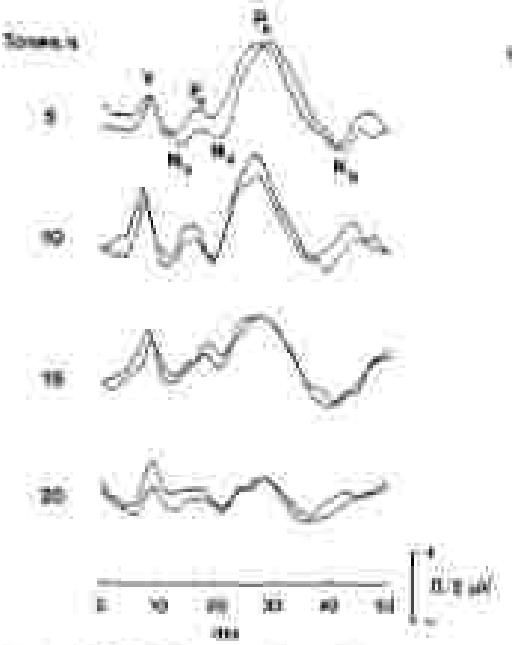


Figure 2. Middle latency auditory evoked potentials (P_a) in ipsilateral montage from a normal subject in response to acoustically applied 55 dB, 10 ms, 5 ms rise-fall click stimuli. The bandpass used was 30–250 Hz. These examples illustrate how the amplitude of middle latency components rapidly decreases as the stimulus repetition rate exceeds approximately 10 Hz.

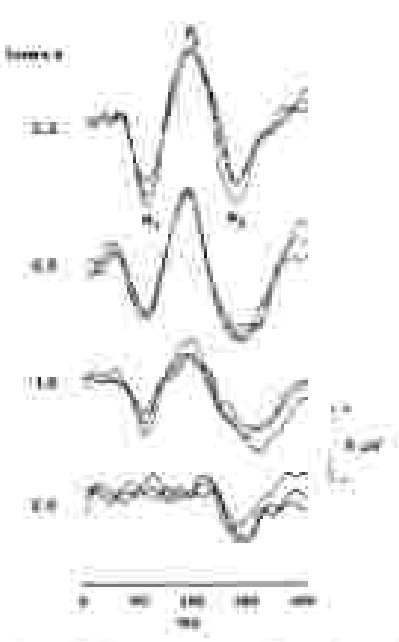


Figure 3. Long latency auditory evoked potentials (P_3) in ipsilateral montage from a normal subject in response to acoustically applied 55 dB, 10 ms, 3 ms rise-fall click stimuli. The bandpass used was 1–100 Hz. At each stimulus repetition rate three replicate recordings were obtained. Note that at a rate of 1 Hz or higher, the amplitude of the various waveform components become significantly attenuated.

themselves (about 0.5 s) [Allison, 1962; Rothman *et al.*, 1970; Woods *et al.*, 1980].

Theoretically, the stimulus repetition rate should thus be lower than approximately 0.1 to 0.2 Hz. Higher rates cause an amplitude diminution as well as a possible latency increase [Stockard *et al.*, 1978]. In practice, a rate of 0.1 Hz would lead to unacceptably long recording sessions, so that often higher rates, in combination with a certain random variation in the stimulus interval time, are used.

2.2. *Regular and pseudo-random stimulation*

There are several misconceptions with respect to the merits of periodic versus pseudo-random stimulation. In pseudo-random stimulation the stimuli occur, within certain limits, at random time intervals (Fig. 4). Typically, the interval follows a rectangular distribution with a range of 30% of the mean stimulus interval (e.g. 4 ± 2 s). This type of stimulation has certain advantages when recording long latency evoked potentials. Due to the random fluctuation in stimulus interval, the temporal uncertainty of the stimulus increases [Jackson and Barber, 1980]. It has been suggested that this factor is responsible for a diminution in habituation, which means, in turn, a shortening of the recovery cycle [Wastell, 1980].

Consequently, pseudo-random stimulation allows higher repetition rates than periodic stimulation. Moreover, pseudo-random stimulation has favourable properties related to the suppression of background EEG if the background has a steady state rhythmic character, such as the alpha rhythm [Ruchkin, 1965].

As stated previously, the latency and amplitude of the various components depend to some extent on the stimulus repetition rate. At high repetition rates the random variation might therefore introduce a certain 'jitter' (i.e. variability in latency) causing a smearing-out effect of the various components. Although these effects are expected to be small, it appears that for short

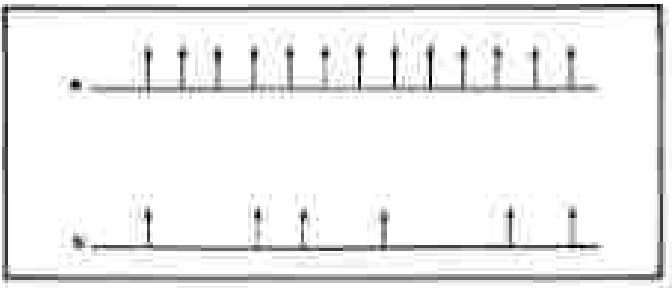


Figure 4. a. Short latency evoked potentials can be adequately measured by using regular, or periodic, stimulation (depicted as arrows) at relatively high repetition rates. b. For long latency evoked potentials pseudo-random stimulation is the most suitable method of choice.

latency responses, pseudo-random stimulation is an unnecessary expense in view of the fact that early components do not show habituation.

3. Recording

3.1. Electrodes

The majority of evoked potential recordings is performed non-invasively by means of standard surface EEG electrodes. These usually consist of small round caps of silver, silver-silverchloride, tin or stainless steel. In auditory and visual evoked potential recordings, a similar electrode is used as ground electrode. For somatosensory evoked potentials the ground electrode is usually placed on the limb at which the stimulus is applied. Different ground electrodes are used. One possibility is the use of a relatively large metal plate, but we have found a wrap-around ground electrode, soaked in saline solution prior to use, to be most effective.

It is important to degrease and lightly abrade the skin (e.g. with alcohol) and to apply electrode paste before or after attaching the electrodes. Such a procedure will reduce the electrode impedance considerably. Values less than about 5 kΩ are usually recommended.

Electrodes form a very critical link in evoked potential recordings and they should therefore be carefully applied. A thorough cleaning after each recording, periodic inspection and chlorination, in each case of silver-chloride electrodes, are essential prerequisites to keep the electrode impedance low and to obtain recordings free of artifacts and interference.

3.2. Amplifiers

The amplifiers used in evoked potential systems are always of the differential type. This means that ideally only the difference of the signals at both inputs is amplified and that the common component is cancelled. In practice, total cancellation is impossible because of the ever present imbalance of the electrode/amplifier circuit at both inputs which results in different amplification characteristics. The quality of this aspect of amplifiers is expressed in the so-called common mode rejection ratio (CMRR). It is defined as the ratio between the output amplitude of a differential input (one input minus the other one) and the output amplitude of a the same signal at both inputs simultaneously.

With a high common mode rejection ratio effective suppression of interference signals can be achieved. This is a consequence of the fact that most sources of interference (such as the power distribution system) are relatively distant from the recording electrodes, and therefore cause fairly equal voltage variations at two closely spaced electrodes. Nearby sources of interference as a stimulus artifact or muscle activity can sometimes be suppressed by a

proper positioning of the ground electrode [McGill *et al.*, 1982].

Apart from a high common mode rejection ratio, other important requirements of the amplifier include a sufficiently high input impedance in order to avoid distortion and loss of amplitude [Geddes, 1975] and a low noise level. Input impedances of 50 MΩ or more, which are usual in modern physiological amplifiers, easily fulfill practical needs. The noise level should be in the order of a few microvolts peak-to-peak for a bandwidth between 10 Hz and 3 kHz. When modern amplifier techniques are employed, this requirement does not pose a significant problem as well.

3.3. Filters

The bandpass of the recording system is a major issue in evoked potential recordings since it has important implications for the waveforms and, consequently, for the interpretation of the results [Campbell and Leander, 1984; Maccabee *et al.*, 1985; Romani *et al.*, 1981].

Defining the evoked potential to be measured as the *signal* and the disturbing background as the *noise*, the main problem in evoked potential recordings is that of a low 'signal- to-noise ratio' (SNR). Essentially, there are two complementary ways for improving the SNR, namely averaging (see Section 4.2.) and filtering.

Simply stated, the objective of filtering is to remove as much of the noise as possible, without any significant distortion of the signal. In principle, this can be done by suppressing those frequency regions with noise only and passing the other frequency regions where both signal and noise components are present.

In reality, the frequency content of the evoked potential waveform is not confined to a sharply defined frequency region. Selecting a proper filter cut-off frequency is therefore largely a matter of judgement. In addition, no filter is ideal in the sense that its amplitude response has a sharp transition between the frequency region where it passes versus where it rejects all frequencies. In practice there is always a region where the signals become gradually more attenuated outside the passband.

According to their function, filters can be classified in two basic types, namely *lowpass* filters, which pass low frequencies and reject high ones vs. highpass filters which have the opposite characteristic.

In evoked potential recordings one always deals with bandpass filters, which are in essence a series connection of a lowpass and a highpass filter.

Note that the cut-off frequency of the lowpass filter is in the *high* frequency range, while the cut-off frequency of the highpass filter is in the *low* frequencies, a point that often causes confusion. Therefore, a different terminology is sometimes used, e.g. 'high bandpass' and 'low bandpass', or 'high filter' and 'low filter'.

The cut-off frequencies are usually specified in terms of the -3 dB points. This custom stems from engineering practice where filter attenuation, as well

as amplifier gain, are oftentimes expressed in the logarithmic decibel scale (dB).

At the -3 dB points the attenuation is 0.707 (= $1/\sqrt{2}$) with respect to the nominal passband.

The actual choice of filter cut-off frequencies in routine clinical evoked potential readings always remains a compromise between effective background suppression and possible waveform distortion for which no dogmatic rules can be given. Recently, the American Electroencephalographic Society (1984) [Chatrian *et al.*, 1984], has published its recommendations for short-latency SEPs.

Filters can also be applied for other means, such as exaggerating one spectral part (e.g. the higher frequency components) of the signal [Kraus *et al.*, 1987; Elton *et al.*, 1984] or to separate the low and the high frequency parts of the signal for some physiological reasons [Maccabee *et al.*, 1986; Suzuki *et al.*, 1986].

1.4. Phase shift

Often more critical than the choice of filter cut-off frequency is the actual phase response of the filter. The phase response curve describes the phase difference between the filter's input and output as a function of frequency. For conventional analog filters, the amplitude and phase response are interdependent. As a practical consequence it is impossible to obtain a bandwidth reduction without causing phase shifts as well. This interdependency is absent for computer aided digital filtering (see Section 5.1). In fact, the phase response can introduce considerable phase shifts at frequencies where the amplitude response is still relatively unattenuated. This results in shifts in the time of occurrence (latency) of peaks and troughs in the waveform [Boston and Ainsle, 1980].

Since latency measures play a key role in the interpretation of evoked potentials these effects are of more than marginal importance. As a rule, an increase in either the low or high cut-off frequency results in a decrease in latencies, while a decrease in either cut-off frequency causes an increase in latencies.

The phase shifts depend on the type of frequency response of the filter being employed [Doyle and Hyde, 1981]. This point cannot be overemphasized, especially because it is ignored in the majority of evoked potential publications. The filters currently employed in evoked potential equipment typically have frequency response curves of either the simple RC, Bessel or Butterworth type (Fig. 5). Each filter is further specified by its 'order', which determines both the roll-off slope of the amplitude response curve outside the passband and the phase shifts between input and output (see e.g. [Stapells and Picton, 1981]). For simplicity, we assume here that phase shifts simply imply an overall time shift of the entire waveform, affecting all components in a similar manner. For some filters, however, such a simplification does not hold true, particularly

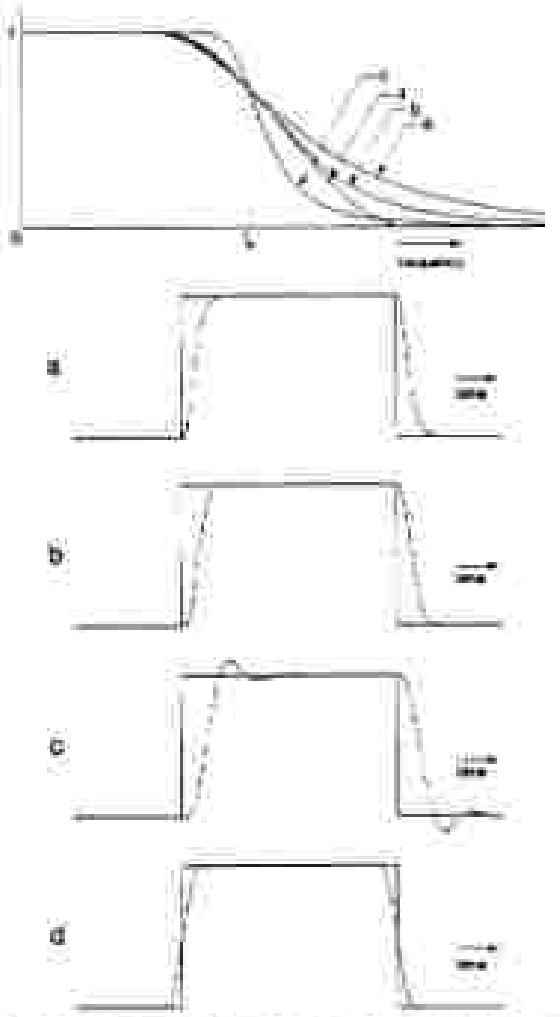


Figure 7. Amplitude response curves (top 3 panels) and filter responses to a calibration pulse (lower figure a–d) for four different filter types: a/ RC filter; b. Bessel filter; c. Butterworth filter; d. Cosine half-signal filter (see Section 5.1). As can be seen in the top figure, all filters have the same cut-off frequency f_c, but the shape of their amplitude response curves near the edge of the band pass differs considerably and so do the filter responses to the calibration pulse shown in each of the lower figures.

Comment: a. The simple RC filter does not show any overshoot in response to an input step, but it has a bad flat response in the pass band and suppression of the frequencies just beyond the cut-off frequency is less effective due to the moderate slope of the amplitude response curve. b. The Bessel filter does rather well regarded as the lower upper and shows virtually no overshoot in the example. c. The amplitude response curve of the Butterworth filter offers a good compromise between flatness of the response in the pass band and suppression beyond the cut-off frequency, but this is at the expense of considerable overshoot in the time domain. d. In a later section (Section 5.1) cosine-based filters will be described. This special filter shown here provides a fair compromise between time and frequency domain characteristics. When appropriately sized the filter does not show any time lag, or latency shift, as opposed to the other filters. Note, however, that the digital filter is responding before the actual calibration pulse is applied.

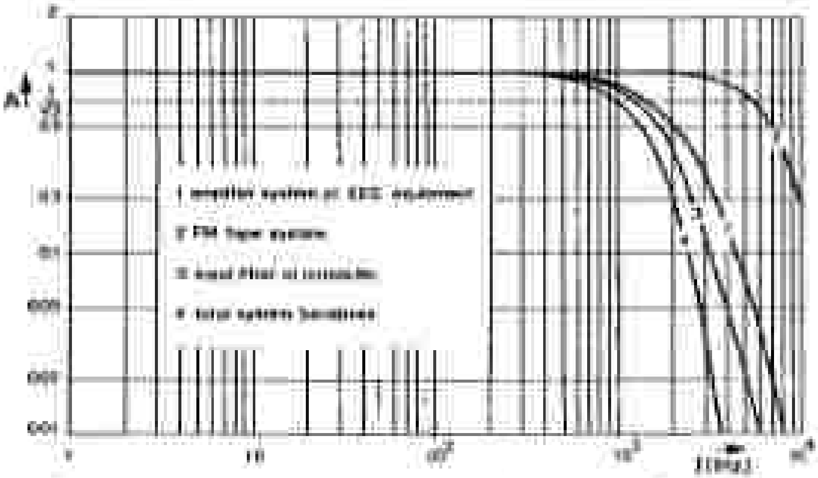


Figure 6. In complex evoked potential systems where several, sometimes unknown, filters may be linked in series, the effective (total) bandwidth of the system may be reduced well beyond the bandwidth of the each component individually due to the cumulative nature of the filtering process. In the above example the bandwidth of the EEG amplifiers (1) exceeds that of the input filters for the sampler (3), but convolution reduces the overall bandwidth of the system (4). The bandwidth of the FM recorder (2) plays a minor role, it is much larger than that of the other components.

not when the order of the filter is increased. In such cases the waveform will be distorted.

From the foregoing it can be concluded that specification of the cut-off frequencies of a bandpass filter alone (e.g. in terms of -3 dB points) does neither fully specify its amplitude nor its phase response and thus the waveform distortion introduced by that filter. This fact may well be one of the major reasons for the variability in normative data as found by different laboratories. Therefore, one should be well aware of this point when comparing one's own normative values to those found in the literature (see also Section 10). In more complex instrumentation set-ups one may suspect the possible presence of several filters in series, which may cause unexpected cumulative filter effects (Desmedt *et al.*, 1974) (Fig. 6).

4. Acquisition and processing

As mentioned in the foregoing, the main problem in evoked potential measurements lies in the fact that these potentials are usually very small compared to the background activity (Table 1). Since filtering does not suffice for extracting the desired waveform from the background activity, additional signal processing techniques are necessary, with averaging being the most commonly applied method.

Present day averagers operate, without exception, on a *digital* basis and

Table 1. Global indications of normal amplitude range, duration and bandwidth of various evoked potentials

Evoked potential type	Amplitude (μV p-p)	Duration (ms)	Bandwidth (Hz)
Auditory			
brainstem	0.5–1	8	30–3000
middle latency	1–5	50	30–500
long latency	10–20	100	0.1–70
Visual			
early (multisensory component)	1–2	30	30–250
middle and long latency	10–20	100	0.1–70
Somatosensory			
short and middle latency median nerve	1–5	30	30–1500
short and middle latency tibial nerve	1–2	60	5–250
long latency	10–30	100	0.1–70
Spontaneous EEG	50	-	0.1–70

for that reason the incoming signals have to be sampled and digitized, a process known as analog-to-digital (A/D) conversion. Furthermore, modern evoked potential equipment includes facilities for the functions summarized in the introduction to this chapter. The present section is intended to make the reader familiar with some basic principles of digital signal processing.

4.1. A/D conversion

The first step in making an analog signal suitable for digital processing is that of sampling the signal at equidistant time intervals. The amplitude at subsequent sample moments is then converted into a digital code and stored in an ordered sequence of numbers. The rank of a particular number in the sequence reflects the time at which the corresponding sample was taken, while the content of that number gives the actual amplitude of the original signal at that point (Fig. 7).

From a theoretical point of view, the sampling interval Δt, or inversely, the sampling rate $f_s = 1/\Delta t$ should be such that f_s equals at least twice the highest frequency which is present in the signal in order not to loose any information and to avoid the problem of so-called aliasing (Fig. 8).

However, in practice, where one is interested in a reasonable wave shape reproduction by simply displaying consecutive sample points, a sample rate of at least five times the highest signal frequency is more appropriate (Fig. 9).

As an example one may consider brainstem auditory evoked potentials whose the highest relevant frequency is usually taken to be 3 kHz. The sampling

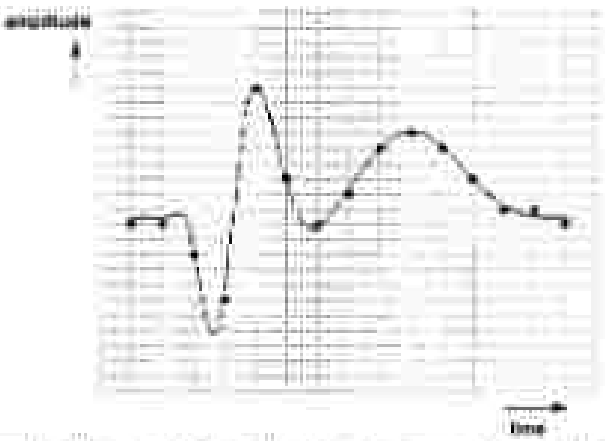


Figure 7. Schematic illustration of the analog-to-digital conversion process. At equidistant points in time a signal sample is taken and the actual amplitude converted to the closest nearby digital value (binary code). The precision by which the numerical values reflect the original waveform amplitudes depends on the resolution (number of bits) of the analog-to-digital converter.

frequency should thus be at least 15 kHz. A related issue is the desired time resolution for measuring the latency of individual waveform components, a factor which is also determined by the sampling interval Δt. In general, when the above rule of taking five times the highest signal frequency is followed, the associated time resolution will be appropriate. In the above example this resolution is $1/15 \cdot 10^3 = 0.07$ ms.

Although the sampling interval thus appears to be a relevant parameter, in most equipments its actual value cannot be explicitly chosen. Rather it is determined by the choice of the sweep speed or time base T and the number of available sample points N, i.e. the sampling interval $\Delta t = T / N$. For instance, when measuring long latency components of a somatosensory evoked

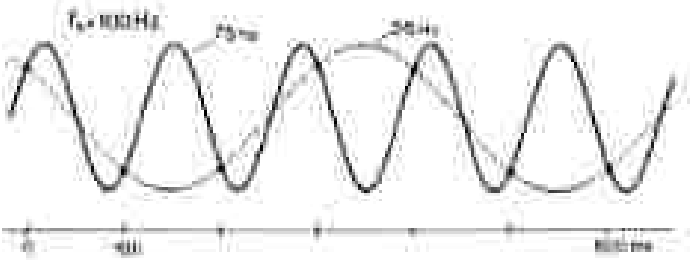


Figure 8. If a signal is sampled at too low a rate, a correct reconstruction from the sampled values is no longer possible. In the above example a 75 Hz sine wave is sampled at a rate of 100 Hz (heavy dots). Upon reconstruction, a sine wave of much lower frequency (25 Hz, dotted curve) results, an effect called aliasing. Theoretically, the minimum sampling rate should be twice that of the highest frequency component in the signal (50 Hz in the example).

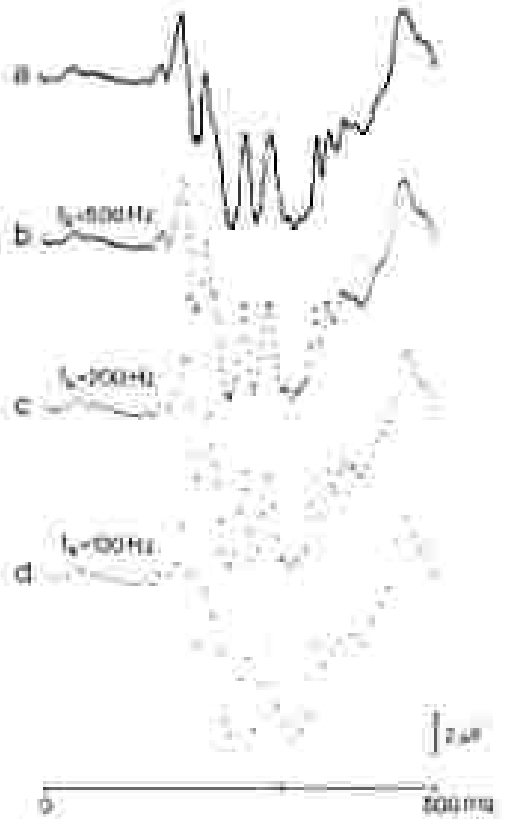


Figure 9. For an adequate visual reconstruction of sampled data on a raster type display it is necessary to sample the data much faster than would be necessary from the theoretical viewpoint. In the above example the frequency content of the evoked potential (a) extends to approximately 100 Hz which means that a sampling frequency of at least 200 Hz is required to allow a reasonable waveform display (b). Theoretically, a 200 Hz sampling frequency would have been sufficient in order not to lose any information (c). A sampling frequency of 100 Hz some of the higher frequency components already get lost (d).

potential, where T may be as long as 500 ms. We have, assuming a memory size of 500 words, a sample interval $\Delta t = 1$ ms. Evidently, this sampling interval is inadequate for measuring spinal or short latency components at the same time. One should be especially aware of this problem when either short and middle latency or middle and long latency evoked potentials are to be measured simultaneously.

Of much less importance than the sampling interval is the actual number of quantization levels or "bits", by which the magnitude of the signals is represented. Usually, A/D conversion takes place with 8, 10 or 12 bits, which corresponds to a data resolution of 1 : 256 ($= 2^8$); 1 : 1024 ($= 2^{10}$) or 1 : 4096 ($= 2^{12}$).

Since an evoked potential is always an average of several sweeps, possible errors in quantization of the individual sweeps tend to average out more than

this assumes that the average has a higher resolution than the A/D converter used).

Also note the importance of properly amplifying the incoming signals such that the full range of the A/D converter is effectively utilized.

4.2. *Signal averaging*

The basic premise underlying the method of averaging is that the repeated presentation of an identical stimulus will each time lead to essentially the same evoked potential (the signal), which can be thought of to be additive to the distorting background activity (the noise) which is totally unrelated to that stimulus. The desired result is obtained by averaging a collection of individual responses, whereby the underlying evoked potential will remain unchanged and the background activity, occurring with random amplitudes and polarity will tend to average out (Fig. 10).

It can be proved that, under conditions analysed below, the signal-to-noise ratio (S/N) improves by the square root of the number of responses that are averaged. For example, when 100 responses have been averaged, the amplitude of the remaining noise has been reduced by a factor of 10 as compared to the noise in individual responses.

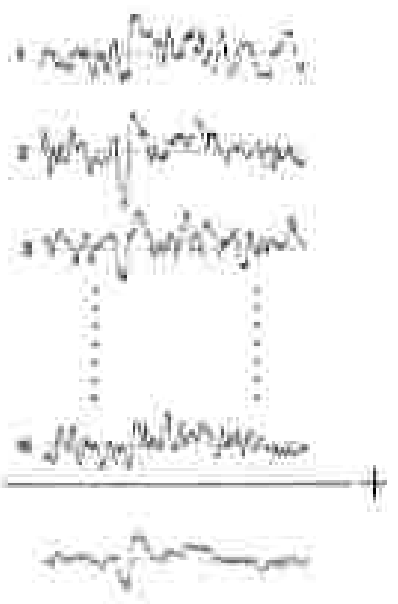


Figure 10. Schematic illustration of the averaging process. N represents the total number of sweeps averaged.

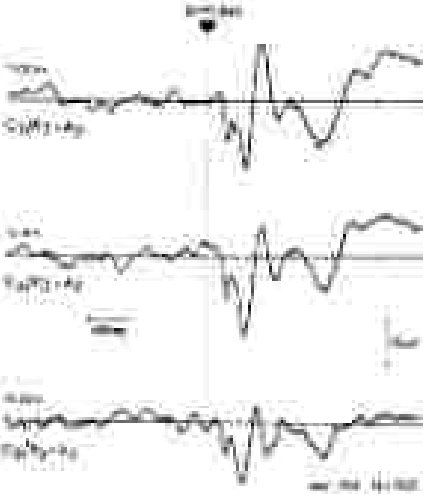


Figure 11. Example of the waveform variability that may occur in subsequently recorded (and averaged) evoked potentials (auditory brainstem evoked potentials). The most prominent effect is usually a reduction in the amplitude of the various waveform components in recordings from progressive

In practice, the improvements in signal-to-noise ratio through averaging is limited by several factors. Firstly, as pointed out above, it is essential that upon repeated stimulation the evoked potential waveform remains the same. Particularly when recording cortical evoked potentials this requirement is difficult to maintain due to various physiological factors, such as attention and habituation, which influence the response. Such influences may cause a variability in the time of occurrence of the evoked potential relative to the stimulus (so-called 'latency-jitter'), in the amplitude of the various components and even in the waveform morphology (Fig. 11).

Secondly, the square root law for SNR improvement mentioned above only applies when the background activity consists of 'pure' (uncorrelated) and stationary noise. Ongoing EEG activity, in particular alpha rhythm, and electromyographic activity, however, may show a distinct frequency or time structure such that averaging is much less effective in these cases. As a consequence of the above factors, it is an uncommon experience that averaging over long periods of time degrades, rather than further enhances the averaged evoked potential waveform. Particularly under these circumstances it is advisable to superimpose a number of duplicate recordings, each comprised of a lower number of sweeps, instead of making only one average of a very large number of sweeps (see also Subsection 11.1). In addition more advanced processing methods may prove valuable in these cases (see Section 5.3).

4.3. Artifact rejection

Artifact detection and rejection capabilities are indispensable in evoked potential work. Artifact rejection is especially important when relatively few responses are averaged, such as e.g. in visual evoked potential recordings. In these cases a single large artifact may easily remain visible in the averaged waveform. In its simplest form, an artifact detection circuit flags the condition that the absolute magnitude of an incoming response exceeds a certain threshold, which is normally set close to the upper and lower range of the analog-to-digital converter. If this condition occurs, that response is rejected, i.e. not included in the averaging procedure.

In more sophisticated methods of artifact detection one can specify a minimal time interval for which the threshold must be exceeded (in order to avoid that a single sharp spike in the response causes that response to be rejected), or one can define a certain time window around the moment of stimulation to be excluded from artifact detection. The latter option is particularly important in electric and earphone stimulation, since in these cases the stimulus artifact may easily be an order of magnitude larger than the response recorded.

5. Processing of averaged evoked potentials

After averaging, the evoked potential waveforms are available in digital form.

This opens up possibilities for further improvement of the 'signal-to-noise ratio' through digital filtering or the essentially equivalent method of 'smoothing'. These operations can either be preprogrammed or data adaptive.

3.1. *Digital filtering*

The main characteristic of digital filters is that they operate on sampled data. In principle, any type of analog filter can also be mimicked in a digital equivalent. Unlike analog filters, however, digital filters have the interesting property that the amplitude and phase response curves can be designed independent from each other.

It is thus possible and widely practiced, to design digital filters according to a predetermined amplitude response curve, while maintaining zero phase response over the entire frequency range. This has the great advantage that the filtering operation can be performed without introducing any latency shifts in the filtered waveform (cf. Fig. 5).

As an aside it may be noted that the above property has not to do with the sampled or digitized character of the data but rather with the fact that the data is filtered in retrospect, instead of in real time. Application of a zero phase filter requires the processing, not only of past input data but also of input data that occur conceptually later than the actual output of that filter and hence such a filter is not realizable in real time.

In view of the clear advantages of digital filtering vs. analog filtering, one could ask why its use is not more widespread. One reason for this is that there always remains a necessity for analog low-pass filtering, so as to limit the frequency range prior to the sampling process in order to avoid the problem of aliasing (see Subsection 4.1). Another, practical, reason lies in the more complicated instrumentation needed for the realization of digital filters. However, digital filters can be easily realized in the form of a computer program and as evoked potential equipment becomes more and more based on micro and minicomputer systems, the use of digital filters will certainly become much more widespread in the near future (e.g. [Moller, 1983; Elmes *et al.*, 1984]). Finally, it should be noted that there is no difference in applying a filter to each of the individual responses prior to averaging or only once to the final average. Averaging and filtering are so-called commutative operations, which implies that their order of application to the data can be interchanged. This property enables the final evoked potential to be studied with different filters without the need to acquire new data.

3.2. *Waveform smoothing*

Smoothing is a special case of digital low-pass filtering, available on several modern evoked potential systems. The smoothing is performed by weighing each data point with its nearest neighbours which causes fluctuations in neighbouring sample points ('high frequency noise') to flatten out. One of the most frequently

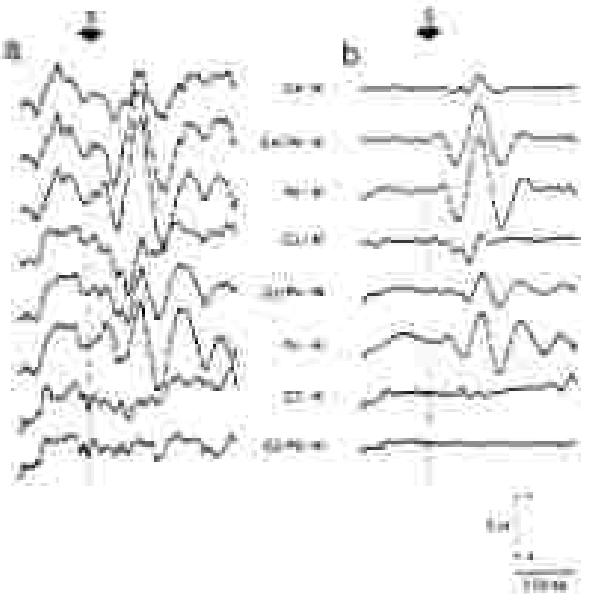


Figure 12. Smoothing is essentially a low-pass filtering process whereby local fluctuations in the evoked potential waveform are flattened out by applying a moving average window. In the above example a nine point "Hanning" window (right side weights 1/4, 1/2, 1/4) is applied to the raw waveform (a), resulting in the smoothed waveform, (b). Mathematically, each individual data point (c) is formed by the weighted sum $\frac{1}{4}x(t-1) + \frac{1}{2}x(t) + \frac{1}{4}x(t+1)$.

used smoothing windows is the 'Hanning' window (Fig. 12). The equivalent filter in the frequency domain has a cut-off frequency of 1/4 of the sampling frequency.

Smoothing corresponds to zero phase filtering and does therefore not affect the latency of the evoked potential components. The smoothing operation may be repeated a number of times to obtain more pronounced low-pass filtering (see e.g. [Wastell, 1979]) but the net effect diminishes on repeated application since the effective cut-off frequency does not reduce proportionally with the number of repetitions.

5.3. *Adaptive digital filtering*

In the foregoing, the use of digital filters with an a priori chosen amplitude response curve (and a zero phase curve) was discussed. The use of such filters is based on (implicit) knowledge about the global frequency contents of the acquired evoked potentials as well as that of the background noise. Clearly such filters cannot be really optimal for each individual case. A better method would be to establish the frequency content of the signal and noise for each individual evoked potential and devise a filter accordingly which is optimal for that particular case. This is precisely what is done in so-called "a posteriori"

types of filtering, such as "Wiener" and "time-varying filtering" [Walter, 1969; De Weerd, 1981a; De Weerd, 1981b]. These methods employ special averaging techniques to simultaneously estimate the frequency spectrum of the evoked potential and the background noise from which an optimal filter can be computed.

Adaptive filtering methods can be used to improve the signal-to-noise ratio of the averaged evoked potential. They may also be helpful in situations where changing physiological conditions are studied such as during operating room monitoring. In such cases a reduction in the number of stimulus presentations necessary to obtain a reliable result is the most beneficial aspect of advanced filtering methods. Because of the non-intuitive aspects of the behaviour of adaptive filtering one should be careful in their application. It is recommended to use such methods only as a supplement to the usual averaging procedure, not as its substitute [Mocks *et al.*, 1986].

Another class of problems where conventional averaging is suboptimal, is in situations where a large sweep-to-sweep variability of the response is expected. This variability itself may be important in which case averaging large numbers of sweeps is clearly not the method of choice. Under these circumstances, adaptive filtering may be helpful in evaluating small numbers of sweeps. [Mocks *et al.*, 1984]. Additionally, some forms of response variability seriously degrade the performance of conventional averaging (see Section 4.2), which also makes investigators search for alternative methods (e.g. [Sgro *et al.*, 1995]).

At the present time, the above techniques require extensive computing facilities both in terms of computer memory as well as of processing capacity. However, with the current trend of improvements in micro-processor technology coupled with a steadily decreasing price, a more widespread application of these and similar techniques clearly comes into view.

6. Waveform analysis

6.1. Identification and labeling of components

Once an averaged evoked potential has been obtained the next step is to analyse its waveform. This is done by identifying various components, i.e. peaks and troughs in the waveform, from which both the latency and amplitude are determined. Generally only a selected number of peaks and troughs are measured, the actual choice being dependent on the type of evoked potential.

Obviously, it is important to have exact knowledge of the electrode montage and the polarity of the evoked potential. The latter aspect is often a source of confusion. For auditory brainstem potentials it is common practice to display active electrode positivity upwards. For all other evoked potentials active electrode negativity is displayed upwards.

The latency of a particular component is determined as the time difference

between the onset of the stimulus and the occurrence of a peak or a trough. In commercial equipment the latency can be determined by using a marker or cursor which generates an unmodified dot or a vertical line across the waveform displayed. The latency is then indicated on either a mechanical or an electronic time display.

The amplitude of a component can be measured either with respect to the baseline or 'peak-to-peak' with respect to the nearest neighbouring component of opposite polarity. The baseline can be defined in a variety of ways. A frequently employed method is the use of a 'technical zero' i.e. for instance the midvalue of the A/D converter range. In doing so, one should be aware of a possible long term drift in the actual zero level due to a variety of technical factors. Another approach is to use the mean voltage of the pre-stimulus interval (see Section 11.4.). Peak-to-peak amplitude measurements are less susceptible to definition problems and tend to provide more reproducible and reliable results.

Generally, amplitude measures show a significantly larger variability than latency measures. This reflects mostly a physiological fact rather than a technical problem. Thus, increased measurement precision or standardization will have little effect on this variability. It is generally agreed that evoked potential components be designated according to their polarity and nominal peak latency [Donchin *et al.*, 1977; Chatrian *et al.*, 1984]. Negative and positive polarities should be designated *N* and *P* respectively. It is further recommended [Chatrian *et al.*, 1984] that latencies of idealized components believed to characterize a normal subject should be identified by a line over the latency value. Several other nomenclatures are still in use and are even preferable when the polarity of components changes with the location of the recording electrode or when the interpretation of evoked potentials is studied with a associated morphology and latency changes within the waveform (e.g. [Rothwell *et al.*, 1987]). Historically auditory brainstem potentials have been labelled with roman numerals [Jewett and Williston, 1971].

8.2. *Waveform documentation*

Besides describing the recorded evoked potentials in terms of latencies and amplitudes of various components it is good practice to document the acquired waveforms themselves also. Not only does this provide the additional information of waveform morphology and possible time-relationships between various recorded channels but it allows visual appreciation of the quality of the recorded potentials in terms of remaining background activity and possible (stimulus) artifacts.

Since an averaged evoked potential waveform is of little value without complete knowledge of the stimulus and recording parameters as well as times and amplitude calibrations, such information should be presented along with the waveforms. Essential parameters such as type, intensity, frequency and duration of the stimulus and high and lowpass filter settings should be included.

The same applies to administrative data such as a patient identification, the recording date and a short descriptive statement on the course of the investigation and the patient's state. Some of the more sophisticated evoked potential systems have facilities for producing listings of such data, which is an advantageous feature in terms of efficiency and reliability. When recording evoked potential waveforms on paper re-evaluation and quantification at a later stage can only be performed using a ruler. The storage of waveforms in digital form allows for additional, retrospective processing. Evoked potential can be stored on flexible disks, Winchester disks or optical disks, interfaced with the equipment. For digital waveform storage too, it is important that relevant parameters and administrative data are stored and can easily be retrieved along with the waveforms.

A final remark to be made is that, as with paper documentation, unlimited digital storage of data without a well-designed archival and retrieval system will sooner or later lead to an unmanageable monster.

7. Topography of averaged evoked potentials

So far we discussed waveforms recorded from a single electrode location. Like in EEG recordings, knowledge of the topographical distribution of the evoked electric activity of the nervous system is often desired (e.g. [Colon *et al.*, 1984]). This calls for a simultaneous recording from a number of electrodes.

An increasing number of studies deals with the calculated topography of EEG and evoked potential fields over the whole scalp (ref. [Duffy, 1986]). In this section we will discuss how such a presentation can be based on data from a manageable set of electrodes on the scalp.

7.1. Spatial sampling and interpolation

The (sub)cortical neural generators cause, at any point in time, a spatial potential profile over the scalp, which is 'sampled' by the electrodes. In order not to loose or to misinterpret any information by this 'sampling', a minimum electrode spacing is required. This requirement is analogous to the waveform sampling requirement in the time domain (see Section 4.1.). Essentially, the spatial sampling frequency (which is the inverse of the inter-electrode distance) should be at least twice the highest spatial frequency present in the potential distribution over the scalp. Since, unfortunately, no spatial frequency maps for all possible experimental data exist, no general recommendation for the interelectrode distance can be given on the basis of the above theoretical considerations. In practice it appears that the familiar number of 19–21 electrodes evenly distributed over the scalp (e.g. according to the 10–20 system) represents a borderline situation [Gevins, 1984]. A number of 28 to 30 electrodes

is generally considered sufficient [Duffy, 1986; Desmedt *et al.*, 1987]. In some situations, as in the localization of sharp epileptic spikes in EEG topography a higher spatial resolution is required [Munro *et al.*, 1986].

In Section 4.1 (Fig. 9) sampling with at least five times the highest (temporal) frequency was recommended for sufficient visual accuracy of an evoked potential waveform without additional processing. Twenty scalp electrodes will by far not meet the equivalent spatial requirement. As a consequence, some form of interpolation is necessary to fill in potential values at sites where no electrode was actually present. In an illustrative paper Desmedt *et al.* [Desmedt *et al.*, 1987] show that for an acceptable two dimensional presentation the potential value should be calculated for about 4000 sites on the scalp. The algorithm providing the necessary interpolation between electrode locations has been subject of discussion. It should be stressed once more that the interpolation technique can never compensate for an inadequate spatial sampling by too few electrodes. Most widespread are the so-called nearest neighbour interpolation schemes. In these schemes usually four electrodes nearest to the site considered contribute to the calculated value taking the distance to each electrode into consideration. The distance may enter in an inverse linear, square or cubic way [Desmedt *et al.*, 1987] (Fig. 13). The conceptual simplicity makes these schemes attractive, although a number of disadvantages are readily apparent. More advanced interpolation techniques such as the so-called spline interpolation certainly have a better theoretical basis [Perrin *et al.*, 1987], but are often discarded because of limited computer resources and the somewhat unpredictable results in case of contaminated data.

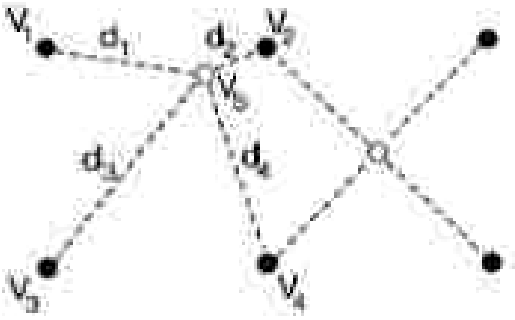


Figure 13. Principle of spatial interpolation by the second nearest neighbour scheme, based on four electrodes. The closed circles represent sites on the scalp where electrodes are attached. The potentials at the sites indicated by the open circles can be estimated taking the distances d_i to the four nearest neighbours into account. For instance in an inverse linear way. In the left case in the figure the potential V_5 is calculated as:

$$V_5 = \frac{V_1/d_1 + V_2/d_2 + V_3/d_3 + V_4/d_4}{1/d_1 + 1/d_2 + 1/d_3 + 1/d_4} \qquad (1)$$

The denominator ensures the result is the mean (more) distance.

7.2. Source localization

The final aim of many topographic evoked potential studies is not the determination of the scalp distribution as such, but the identification and characterization of the generators underlying the measured activity. The character of neural generators is the subject of lively discussions in recent literature. Even passive discontinuities in the brain such as an anatomical change-over or a change in electric conductivity can also be the cause of a dipole potential field [Kimura *et al.*, 1983; Cunningham *et al.*, 1988; Stegeman *et al.*, 1987].

With increasing a priori knowledge of the source (can it be considered as a single dipole?, is its location and/or orientation known?, what is known on the structure of the region of origin? etc.), the precision of a characterization with mathematical techniques increases. The number of electrodes necessary for source identification also depends on such a priori knowledge and can be considerably less than the 26–30 mentioned in the previous subsection. [Jewett *et al.*, 1987]. Scherg and Von Cramon [Scherg and Von Cramon, 1986], for instance, describe situations in which valuable source information from the auditory cortex can be obtained using only four electrodes. A single dipole with unknown properties can reasonably well be identified by using 19 electrodes in the 10–20 montage [Elriksen and Wright, 1987].

The deeper the sources lie in the head, the more the structures within the head will influence the resulting potential waveform at the scalp. Recording of the magnetic field distribution (instead of, or in addition to the potential field distribution) will the eventually decrease this dependence [Kaufman and Williamson, 1982; Ilari, 1986; Meijs *et al.*, 1987]. The magnetic technique has, up to now, not found widespread clinical application.

8. Evoked potential instrumentation

Thus far we have considered the various technical aspects of evoked potential measurements from a rather theoretical point of view. We will now discuss more practical aspects, starting with the equipment that is required.

8.1. The evoked potential system

The basic configuration of an evoked potential system consists of the following elements (Fig. 14):

- Stimulators and associated transducers. Depending on the specific modality to be tested and the type of stimulus to be delivered this may include: auditory stimulator and earphones; current stimulator and stimulus electrodes; stroboscope, light-emitting-diode (LED) goggles, slide projector or a TV monitor;
- Recording electrodes and amplifiers. For most evoked potential studies at least two, and preferably four or more amplifiers are required.

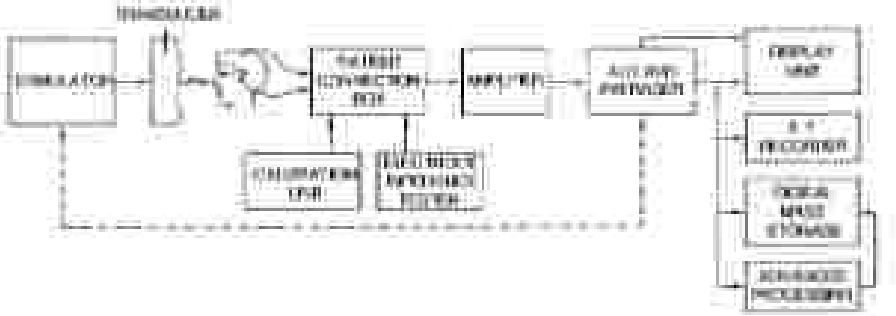


Figure 14. Block diagram of an evoked potential system.

- Averager, either a special purpose device or a micro- or minicomputer system. Artifact detection and rejection are the minimally required processing facilities;
- Display unit and system for documenting the waveforms, e.g. digital plotter, photocamera, or hardcopy device;
- Electrode impedance tester;
- Calibration unit. It is preferable to have a unit that can be plugged directly into the patient connection box so that the entire system can be checked and proper calibration is guaranteed.

From the above summary it is obvious that evoked potential systems have a lot in common with electromyographic equipment. Indeed, more and more systems with both EP and EMG capabilities are now available. However, not all EMG systems have electrode-impedance testing facilities, which must be considered as absolutely essential for evoked potential studies. Also, the available filter settings on some EMG systems may deviate from what is needed in part of the evoked potential studies.

In addition to the above mentioned elements, evoked potential systems often include:

- Cursor controls for on-line determining latency and amplitude of evoked potential waveform component;
- Programmable stimulator, capable of delivering specific stimulus sequences and/or random (irregular) stimulus intervals;
- Eight or more input channels, which allow the study of the topographic distribution of evoked potential over the scalp;
- Waveform manipulation facilities (such as smoothing, addition, subtraction);
- Waveform annotation facilities (stimulus and recording parameters, administrative data etc.);
- Digital storage media, such as floppy, hard disks, or optical disks;
- Temperature unit and sensor, particularly important when measuring somatosensory evoked potentials;
- Advanced digital signal processing and display facilities as discussed in Section 5, such as digital filtering and smoothing, and the calculation and

display of topographic evoked potential data (Section 7).

Most nowadays commercially available evoked potential systems include many of the above features and many have general purpose computer capabilities, so that the user can define his own data manipulations. In the latter type of equipment all stimulus and recording parameters can be set under computer control, thus simplifying testing procedures and eliminating possible sources of error.

8.2. Periodic inspection and calibration

To ensure proper operation of the equipment over extended periods of time, periodic inspection and calibration is necessary. Although this statement may seem rather trivial, the experience in practice is, that this type of maintenance is usually deferred until such time that a defect occurs. As stated previously, it is essential that proper attention is paid to the electrodes. The state of the electrode surface and the integrity of the cable connection should be inspected and the entire electrode tested on a regular basis, which can be done by using a simple ohmmeter.

Inspection of the equipment typically will start by acquiring a dummy average (see Subsection 11.2.1) with the electrodes short-circuited. This enables a check on proper operation of the instrument, the base-line noise and possible DC drift. It is advisable to keep a log-book with each evoked potential system where test results, including recorded waveforms, are documented for periodic comparison. Adjustments, repairs etc. should be noted in the book as well.

In modern equipment, the necessity for calibration is reduced to a minimum and usually does not extend beyond adjustments of amplifier gain and DC base-line and, sometimes, X and Y gain and offset of the XY recorder. As a rule, the manufacturer provides detailed guidelines for the procedures to be followed. The calibration unit should deliver a stable waveform of precisely known shape, duration and amplitude, triggered by the stimulus. Calibration units need regular inspection too, even though they are an order of magnitude more accurate and stable than the equipment to which they are applied.

9. Electrical safety

9.1. Safety standards for equipment

Electromedical equipment should comply with a number of strict regulations for safety and reliability. Even in case of a possible defect (such as an interrupted ground lead in the power cord), the apparatus must still provide sufficient protection against electrical shock hazard. Although mandatory safety standards do not exist at present, the recommendations of the Underwriters Laboratories 1980, in the U.S.A. ([Underwriters Laboratory, 1969], Standard UL544) or the International Electrical Committee 1977 [International Electrical

Committee, 1977], in Europe (Standard IEC 601-1) are generally accepted. An important aspect of these standards is the criterion for maximally permissible *leakage currents* in medical apparatus during normal operating conditions and in the case of an equipment defect (a so-called 'single fault condition'). Two different types of leakage current are of major concern.

The first type is the *ground leakage current*, which is normally shunted to ground by the ground lead. This current is mainly a consequence of the capacitive and inductive coupling of the power line transformer to other parts of the equipment. Normally this current presents no danger, unless for example the ground connection becomes interrupted, in which case the current might pass the patient via the connected electrodes. The IEC standard requires that the ground leakage current is less than 0.5 mA under normal operation and less than 5 mA in case of a single fault condition. The UL544 standard does not deal with ground leakage current as a separate item.

The second type of leakage current normally does not flow through the ground lead, but through the patient or person operating the equipment. One can distinguish between the so-called patient and the enclosure leakage currents, which can present a danger even under normal operating conditions. Unlike UL544, the IEC standard distinguishes between general patient care equipment (categorized as class B or BF) and equipment which may come in direct conductive connection to the patient's heart (class CF equipment). According to the IEC standard, the maximally allowable patient and enclosure leakage currents for class B or BF equipment are 0.1 and 0.5 mA for normal operating and for a single fault condition respectively. The UL544 standard poses stricter requirements. Under a single fault condition the patient and enclosure leakage currents should not exceed 10 μA and 100 μA respectively. Many of the commercially available evoked potential systems are designed to comply with these regulations. The equipment should be inspected when put into use for the first time and periodically thereafter, especially on ground connections and leakage currents. A detailed description on the inspection procedures can be found in the IEC 601-1 report.

9.2. Power line safety measures

Although medical equipment generally carries adequate electrical protection, the risk of electrocution is not entirely imaginary in case of a gross defect. As an additional protection both for the patient and the operator, the installation of a 'Ground Fault Circuit Interrupter' is therefore desirable. Such an interruptor detects any leakage current flowing in the ground circuit (see Section 9.1) and automatically interrupts the power if this leakage current exceeds a preset limit (e.g. 5 mA). However, this type of protection is not ideal should the leakage current unexpectedly flow through the patient or operator: only the duration of the current flow will be limited, but the peak intensity may be far above the safety norms.

A better but more *costly* protection method is to supply the entire laboratory

from a power line isolation transformer provided with a 'line isolation monitor' (see e.g. 'Electricity in patient care facilities' by the National Fire Protection Association [Nat. Fire Prot. Ass., 1975]). An isolation transformer has a very small capacitance between the primary and the secondary windings and offers a complete galvanic separation from the 'normal' power distribution system. The great advantage of this is that the leakage current remains under the safety norm even if the patient, e.g. as a result of a serious defect in the apparatus, should come into contact with one of the current-carrying wires of the (isolated) power circuit. The low leakage results from the fact that the secondary supply lines are completely 'floating' with respect to ground.

The line isolation monitor essentially is a very sensitive leakage current detector. These monitoring devices are designed such that already at very small leakage currents in the order of a few tens of μA an alarm signal is set off. Isolation transformers should be installed in the immediate neighbourhood of the laboratory, since it is important to have the secondary leads kept as short as possible.

Finally, it is important to have a uniform 'ground potential' throughout the laboratory. This means that between the various grounding points there should essentially be no difference in potential and all the ground leads should be connected to a common point with very low ohmic resistance.

9.3 Safety in practice

The main risk associated with leakage currents, as discussed in the previous sections, is that of a possible current flow through the heart, causing e.g. ventricular fibrillation. This risk may be considerably reduced by observing some basic rules for proper grounding and, when measuring somatosensory evoked potentials, for proper electrical stimulation.

Firstly, care must be taken that the patient is not grounded twice, which may also occur accidentally e.g. when a grounded metal frame of a bed is touched or when the system is used in the operating room where other equipment has already been connected to the patient. Although under normal conditions this does not necessarily lead to hazardous situations, usually a troublesome interference voltage will result which is due to flow of so called potential equalizing currents in different ground leads.

Secondly, when recording somatosensory evoked potentials, using electrical stimulation, additional risks are introduced, due to the fact that electrical stimulators may induce lethal currents if improperly applied. The two stimulating electrodes should never be attached to different limbs. Unlike for auditory and visual evoked potentials where the ground electrode is placed near the recording electrodes on the head, the ground electrode must preferably be positioned in the neighbourhood of the stimulating electrodes and always on the same limb. This helps keeping possible current fields local so that no significant current flow through the heart can occur. As an additional safety feature and to reduce stimulus artifact (see Section 10.2.) modern

stimulators are equiped with an isolated output which is galvanically separated from the ground.

Finally, one should be careful when connecting auxiliary equipment, in particular non-medical equipment, to an evoked potential system, as this may violate the electrical safety of that system. Even if auxiliary equipment meets the safety standards connected, it is important that all apparatus is grounded at the same point and supplied from the same phase of the power distribution system.

10. Interference and artifacts

If one realizes that problems with interference and artifacts can be quite troublesome when recording the spontaneous EEG, then it is not difficult to understand that these problems can be a veritable plague when recording evoked potentials, whose amplitudes usually are an order or even two orders of magnitude smaller than the EEG.

The three most common types of artifacts are (i) mains interference, (ii) stimulus artifacts and (iii) bioelectric artifacts. Stimulus artifacts are, by definition, time-related to the stimulus and, this type of artifact is particularly annoying because it does not average out. Similarly, some bioelectric artifacts, such as scalp muscle reflexes, may be stimulus-related. Finally, mains interference may become stimulus related if the stimulus repetition rate is improperly chosen (see Section 2.1.). As a general rule technical and bioelectric artifacts should not be 'eliminated' by averaging, but should be removed as properly as possible prior to any evoked potential measurement.

10.1. Electrical interference

A primary requirement for avoiding mains and other electrical interference is a careful planning of the location of an evoked potential laboratory inside a larger complex such as a hospital. Notorious sources of interference include diathermy and radiological apparatus, elevators and paging systems. In order to avoid the interfering fields introduced by such equipment, the laboratory must be located sufficiently remote from these sources and should preferably connected to a different phase of the power distribution system. Also, the wiring within the laboratory requires special attention in relation to the prevention of mains interference. In principle, mains interference can be introduced in two ways, namely *capacitively* and *inductively*.

Capacitive transfer of mains interference occurs because the body is a conductor, which has a certain capacitance both with respect to the power circuit and to ground. As a consequence a (very small) 'leakage current' flows through the body, which results in a voltage difference (or "hum") with respect to ground. This effect can be reduced considerably by grounding the patient. This is usually done with a ground electrode, which has, however, still a

certain impedance (1 kΩ or more) so that this hum voltage will never disappear completely.

Inductive transfer of mains interference can occur in the cables forming part of the electrode and amplifier input circuit (e.g. the electrode cables). If these cables form a loop (in the electrical sense) and are subjected to a varying magnetic field, for example of a power-line transformer, an interfering voltage is induced. An effective method for eliminating both types of interference is to enclose the power wiring in seamless, grounded metal tubes. In addition, it is important to equip all electrical appliances within the laboratory (including desk lamps etc.) with shielded and grounded power cables (this applies, of course, also to possible extension cords). It is further desirable to ground all appliances, lamps, armatures etc. For the lighting of the laboratory incandescent rather than fluorescent lights should be used. Dimmer switches should be avoided. Equipment not directly needed for the investigation should preferably be removed or disconnected by unplugging the power cord. If all these precautions are taken, it will only rarely be necessary to provide complete shielding of the laboratory by means of a so-called Faraday cage.

10.2 Stimulus artifacts

Stimulus artifacts can occur in a variety of ways. Irrespective of the type of stimulation used, it is always advisable to keep the leads from the recording electrodes as remote as possible from the stimulating source and stimulator cables. Also, recording electrode leads should not be longer than strictly necessary.

In *auditory* brainstem recordings the main source of electrical artifact is the pick-up of the currents used to drive the headphones. This type of artifact can significantly be reduced by shielding the earphones and their connecting cables. When alternating click polarities (rarefaction vs. condensation) are used, the artifact cancels out during the averaging process. However, from a physiological point of view stimulating with alternate polarities is sometimes described as being less desirable.

Visual evoked potential recordings usually show the least problems with stimulus artifacts due to the stimulator generally being quite remote. When using high intensity diffuse light flashes it may sometimes be necessary to place a grounded copper screen directly in front of the lamp to reduce electromagnetic radiation.

In *somatosensory* evoked potential recordings the situation is more complex. Here, stimulus artifact results from the currents induced into the body, which set up a potential field and hereby current in the ground lead due to capacitive coupling between the floating stimulator outputs and ground.

Carefully applied electrodes with a low skin-to-electrode impedance remain a basic requirement for low stimulus artifacts. McGill et al. (McGill *et al.*, 1982), in a theoretical discussion on this subject, discuss the importance of the following factors: (i) a close spacing between the stimulating electrodes,

which keeps the current field local and reduces the extent of the potential field; (ii) the ground electrode placed relatively close to the recording electrodes such that the common mode components due to the above currents remain small; and (iii) a search for the optimal position of the anode (keeping the stimulating cathode in place), so as to minimize the potential gradient across the recording electrodes. Suggestion (iii) may not always be practical for safety reasons (see Section 9.7.).

10.3. *Bioelectrical and other artifacts*

In evoked potential studies one has to cope with artifacts due to EEG and EKG, eye blinks, eye movements and muscle activity. The particular solution for avoiding each of these artifacts will largely depends on the type of evoked potential measured. As a general rule it is advised that the patient is comfortably seated or lying down on a bed in a quiet, well-heated, room. Adequate attention should be given to making the patient feel at ease and explaining the entire investigation procedure. These measures greatly contribute to lowering the "baseline" of bioelectric artifacts. Particular attention should be paid to proper positioning of the head, so that neck, scalp and jaw muscles are completely relaxed. In difficult situations it sometimes helps to present auditory feedback of one or more recording channels to the patient prior to or in between acquisition sessions.

When recording brainstem and short latency evoked potentials both spontaneous EEG and EKG activity can be largely eliminated by proper highpass filtering, e.g. at 30 Hz. Of course this is not possible when measuring longer latency (cortical) evoked potentials, for which case it is advisable to record under the eyes open condition.

When recording spinal evoked potentials the EKG artifact can be eliminated by delivering the stimuli triggered on the QRS-complex, in an electrically silent interval of the heart action (McKay and Calloway, 1979, Dimitrijevic *et al.*, 1978). However, it is usually more efficient to use higher stimulus rates and discard EKG contaminated sweeps, using standard artifact detection and rejection techniques.

Eye blinks and eye movement artifacts are particularly troublesome when recording long latency cortical evoked potentials. Usually, however, the potentials associated with eye movements and eye blinks are relatively large and can be dealt with through standard artifact rejection (cf. Section 4.3.).

There are several other types of artifacts, both of bioelectric and of technical origin, the most important of which are related to the electrodes and electrode connectors. Skin potentials are slowly varying potential changes which are due to a poor electrode-to-skin interface. They can be avoided by assuring a sufficiently low electrode-to-skin impedance (< 5kΩ). Also, electrodes not carefully attached to the skin may produce large transients, commonly denoted as movement artifacts. A similar effect may be caused by intermittent breaks in electrode wires or their connections. In all these cases one must not rely

on a proper artifact rejection but, instead, search for and remove the cause of the artifact.

11. Assessing reliability and reproducibility

To assess the quality and the reliability of a measured waveform in a quantitative manner, several techniques can be employed, preferably in combination with one another.

11.1. Acquisition of duplicate waveforms

It is good practice to acquire duplicate waveforms under identical stimulation and recording conditions, in order to obtain an impression of waveform reproducibility. Duplicate waveforms can be obtained in a sequential manner or, alternately, by averaging even and odd responses in different buffers. Although the latter method is instrumentally more complex it has the advantage that a possible trend in the evoked potential waveform will influence both averages in a similar way. A practical advantage of the former method is that on several evoked potential instruments the result of the first average can be analysed and evaluated while the second average is being acquired, thus saving time.

In appreciating the similarity of duplicate waveforms one should be aware of the various factors that can influence waveform reproducibility. Habituation, vigilance effects and response variability are almost negligible for spinal and subcortical components. They may, to some extent, influence short latency cortical components, but they generally have a large impact on long latency cortical responses (Fig. 11).

11.2. Acquisition of a 'dummy' average

A 'dummy' average is obtained by switching off the stimulus, using an otherwise standard protocol. After a nominal number of sweeps has been averaged, a virtually flat baseline should emerge when the nominal amplifier gain is used. This procedure is particularly valuable for periodic inspection of the system. Technical, stimulus-locked artifacts of unexpected origin can be effectively traced in this manner. It is important that the stimulus be switched off close to the patient, preferably by disconnecting the stimulation electrodes, so that as many sources of artifact as possible are included and can thus be localized.

11.3. Acquisition of a plus minus average

When subsequent responses are alternately added and subtracted the underlying evoked potential cancels out, so that an impression of the remaining back-

ground activity can be obtained [Schimmel, 1967]. In principle, this procedure can be carried out in parallel to normal averaging. This allows a direct comparison of the 'noise floor' thus obtained with that remaining in the normal average. A drawback of the method is that stimulus locked artifacts that appear in the normal average are not reflected in the plus/minus average since these cancel as well.

11.4 Averaging a prestimulus interval

One of the most elegant and simple methods to obtain an impression of the background noise is to average the activity over some time interval prior to stimulus presentation. This method enables a fair judgement as to which part of the response is actually induced by the stimulus. In particular, one may obtain a qualitative impression of the reliability of various waveform components by comparing their amplitudes to the variations in amplitude occurring prior to stimulus presentation (Fig. 15).

In many evoked potential systems it is possible to include a prestimulus analysis interval, but if this provision is not available it can be simply realized by digitally delaying the stimulus. Typical prestimulus intervals range from 10% to 25% of the full time range.

12. Normative data and criteria for abnormality

When can an evoked potential be considered abnormal? In the first place one will observe waveform morphology and look for the presence or absence

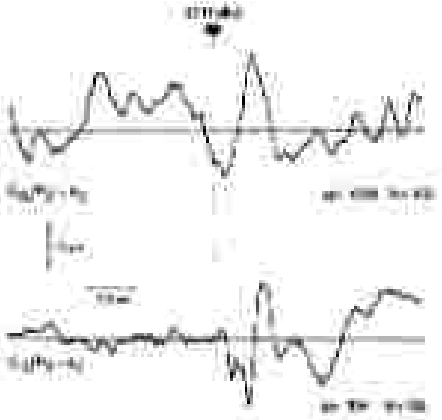


Figure 15. Normal averages, including a 100% prestimulus interval. From the large fluctuations in the prestimulus interval of the upper average it may be concluded that the evoked potential is seriously contaminated by background activity.

of various waveform components. This will provide a first indication of the degree of possible abnormality, although it should be noted that the absence of certain waveform components per se does not necessarily indicate pathology. Next, latencies and amplitudes (either absolute or relative) of preselected components are determined and compared to a data base of normative values. This sounds fine in theory but the actual practice certainly requires additional explanation and comment.

Comparison of actually obtained values to a set of matched normative data requires, first of all, the availability of a core base. From many scientific publications on evoked potentials one obtains the impression that it is a mistake to adopt normative data from other laboratories instead of acquiring one's own values. There can be little doubt that this is, in essence, a wise attitude, but on the other hand the acquisition of reliable normative data of a sufficient sample size for the various evoked potential types, under different stimulation and recording conditions and as a function of age, sex and possible other factors, is a life task in its own. For the average clinical laboratory this clearly is an impractical approach.

A reasonable alternative procedure is to acquire a limited normative data base for a selected set of evoked potentials, following standard protocols as described in the literature. This data base should then be compared to normative data from the same literature. It is thereby important to include both females and males spanning the entire age range and to account for all other variables that affect latencies and/or amplitudes. Specific factors, besides age, that influence somatosensory evoked potentials are temperature of the stimulated limb and body size. Temperature and body size mainly influence latencies, while age is known to affect both latencies and amplitudes (Desmedt *et al.*, 1976; Rappaport, 1986[3]). If these factors are taken into account and the sparse normative data thus obtained agree well with the normative data from the literature, it is not unreasonable to adopt the latter data in toto. If, on the other hand, the data do not agree well, one must carefully consider all the various technical and physiological factors which may have an impact. If the cause for deviation cannot be eliminated, the acquisition of one's own normative data is mandated.

Once the normative data are available, the question arises what criteria should be used for characterizing and evoked potential as either normal or abnormal. The typical approach is to define some upper (or lower) limit of normality which is derived from the underlying distribution of normative values, more specifically, from the mean and standard deviation. This approach assumes that the parameter under consideration has a Gaussian distribution, an assumption which generally holds well for latency, but less so for amplitude measures. Another implicit assumption is that the mean and standard deviation derived from the normative data represent exact, error free values. However, normative data are generally based on results of a limited number of subjects (20–50) so that the derived means and standard deviation are in themselves subject to variability.

It is therefore more appropriate to use so-called *tolerance limits* rather than confidence limits. Essentially, the use of tolerance limits leads to a wider range of normality since the standard deviation is scaled up by a factor which depends on the sample size of the normative group. For example, the commonly used 95% confidence limits correspond to mean ± 1.96 SD, whereas the 95% tolerance limits correspond to mean ± 2.38 SD (N=50), mean ± 2.75 SD (N=20) or mean ± 3.38 SD (N=10), where N represents the sample size of the normative data group. (For a comprehensive account on the subject, see Bowker and Lieberman, Chapter 8 [Bowker and Lieberman, 1972]). It can be argued that it is more acceptable to incur an increased number of false negatives (i.e. classification as normal while the evoked potential is actually abnormal) in favor of a reduced number of false positives (i.e. classification as abnormal, while the evoked potential is actually normal). This implies that one should use a more conservative approach than the mean ± 2 SD rule which is often used for the range of normality.

Finally, as mentioned before, latency measures tend to have significantly lower intraindividual variability than amplitude measures. In fact, absolute amplitudes as such prove to be less useful in assessing evoked potential abnormality. On the other hand, intraindividual differences in amplitude (and latency) generally provide significant clinical information. It should be noted that whenever ratios (e.g. amplitude ratios) are used, it is advisable to take the logarithm of the ratio in order to transform the distribution to Gaussian so that the above mentioned statistics become applicable.

References

Allison T. Recovery function of somatosensory evoked responses in man. Electroencephalogr clin Neurophysiol 1967; 14: 331–343.

Barnes JB, Austin PJ. Effects of analog and digital filtering on brainstem auditory evoked potentials. Electroencephalogr clin Neurophysiol 1986; 65: 363–368.

Bowker AH, Lieberman GJ. Engineering Statistics. Prentice Hall, Englewood Cliffs, 1972.

Campbell IA, Lindahl M. The effects of high pass filters on computer-measured evoked potentials. Electroencephalogr clin Neurophysiol 1988; 37: 369–370. Clarke GE, Pfeiffer WF, Calhoun GG. Statistical Electrographic guidelines for clinical evoked potential studies. J Clin Neurophysiol 1984; 1: 3–53.

Cohn EJ, Van Manen E, Hommes OR, Bonnet J, Eecken R, Dirven C. SSEP abnormalities in patients with multiple sclerosis. Acta Neurol Scand 1984; 69: 35–41.

Coles EJ, De Weerd AW. Long-latency somatosensory evoked potentials. J Clin Neurophysiol 1986; 3: 279–295.

Cunningham K, Hilleby AM, Jones SJ. Simulation of "abnormal" SAP and SEP phenomena by 2-dimensional potential field modelling. Electroencephalogr clin Neurophysiol 1986; 65: 419426.

Desmedt JE, Brunko E, Debecker J and Carlyniet C. The noise threshold required to avoid distortion of early components when averaging to obtain reproducible evoked potentials. Electroencephalogr clin Neurophysiol 1976; 37: 407–411.

Desmedt JE, Brunko E, Debecker J. Maturation of somatosensory evoked potentials in normal infants and children, with special reference to the early N1 component. Electroencephalogr clin Neurophysiol 1978; 46: 43–58.

Desmedt JE, Nguyen TH, Bourguet M. Bit-mapped color imaging of human evoked potentials with reference to the N20, P22, P27 and N30 somatosensory responses. Electroencephalogr clin Neurophysiol 1987; 68: 1–19.

De Weerd JPC. Facts and fancies about a posteriori "Wiener" filtering. IEEE Trans Biomed Engng 1981a; BME-28: 252–257.

De Weerd JPC. A posteriori time-varying filtering of averaged evoked potentials. I. Introduction and conceptual basis. Biol Cybern 1981b; 41: 211–222.

Dimitrijevic MR, Larsson LE, Lehmkuhl D and Sherwood A. Evoked spinal cord and nerve root potentials in humans using a noninvasive recording technique. Electroencephalogr clin Neurophysiol 1978; 45: 331–340.

Donchin E, Callaway E, Cooper R. Publication criteria for studies of evoked potentials in man. Report of a committee. In: Desmedt JE (ed). Attention, voluntary contraction and event-related cerebral potentials in man. Prog Clin Neurophysiol 1977; 1: 1–11.

Doyle DJ, Hyde ML. Bessel filtering of brain stem auditory evoked potentials. Electroencephalogr clin Neurophysiol 1981; 51: 446–448.

Duffy FH (ed.). Topographic Mapping of Brain Electrical Activity. Butterworth, 1986.

Eisen A, Roberts K, Low M, Hoirch M, Lawrence P. Questions regarding the sequential neural generator theory of the somatosensory evoked potential raised by digital filtering. Electroencephalogr clin Neurophysiol 1984; 59: 388–395.

Elton M, Scherg M, Von Cramon D. Effects of high pass filter frequency and slope on BAEP amplitude, latency and waveform. Electroencephalogr clin Neurophysiol 1984; 57: 490–494.

Erwin RJ, Wright EW. Influence of electrode montage on dipole localization. J Clin Neurophysiol 1987; 4: 206–210.

Geddes LA. Bioelectrodes. Am J EEG Technol 1975; 15: 99–106.

Gevins AS. Analysis of the electromagnetic signals of the human brain: Milestones, obstacles, and goals. IEEE Trans Biomed Engng 1984; BME-31: 833–850.

Hari R, Ilmoniemi RJ. Cerebral magnetic fields. CRC Crit Rev Biomed Engng 1986; 14: 93–126.

International Electrical Committee. IEC 601-1: Safety of medical electrical equipment. Part 1: General requirements. IEC, Geneva, 1977.

Jackson JA, Barber C. The effect of [illegible] stimulus parameters upon the VEP. In: Evoked potentials. Proceedings of Int. Evoked Potential Symposium, Nottingham. MTP Press, Lancaster, 1980.

Jewett DL, Martin WH, Sininger YS, Gould JV. The 3-channel Lissajous' trajectory of the auditory brain-stem response. I. Introduction and overview. Electroencephalogr clin Neurophysiol 1987; 68: 323–326.

Jewett DL, Williston JS. Auditory-evoked far fields averaged from the scalp of humans. Brain 1971; 94: 681–696.

Kraus N, Reed N, Smith DI, Stein L, Cartee C. High-pass filter settings affect the detectability of MLRs in humans. Electroencephalogr clin Neurophysiol 1987; 68: 234–236.

Kimura J, Mitsudome A, Beck DO, Yamada T, Dickins QS. Field distributions of antidromically activated digital nerve potentials: model for far-field recording. Neurology (NY) 1983; 33: 1164–1169.

Maccabee PJ, Pinkhasov EI, Cracco RQ. Short latency somatosensory evoked potentials to median nerve stimulation: Effect of low frequency filter. Electroencephalogr clin Neurophysiol 1983; 55: 34–44.

Maccabee PJ, Hassan NF, Cracco RQ, Schiff JA. Short latency somatosensory and spinal evoked potentials: Power spectra and comparison between high pass analog and digital filter. Electroencephalogr clin Neurophysiol 1986; 65: 177–187.

McGill KC, Cummins KL, Dorfman LJ. On the nature and elimination of stimulus artifact in nerve signals evoked and recorded by surface electrodes. IEEE Trans Biomed Engng 1982; BME-29: 129–137.

Möcks J, Gasser T, Tuan PD. Variability of single evoked potentials evaluated by two new statistical tests. Electroencephalogr clin Neurophysiol 1984; 57: 571–580.

Mirkin S, Gasser T, [illegible] W, De Weerd JPC. Does filtering and smoothing of average evoked potentials really pay? A statistical comparison. Electroencephalogr clin Neurophysiol 1986; 64: 469–486.

Miller AE, Jaskiw PE. Evoked potentials from the inferior colliculus of man. Electroencephalogr clin Neurophysiol 1983; 55: 6–2–630.

Moore HM, Lidov H, Lewis RF, Hymes DB, Klein GM. Localizing sleep spindles: Skull vs. scalp recordings. Electroencephalogr clin Neurophysiol 1986; 63: 107–111.

Meijs JWH, Bosch FGC, Peters MJ, Lopes da Silva FH. On the magnetic field distribution generated by a dipolar current source situated in a conductively shielded compartment: model of the head. Electroencephalogr clin Neurophysiol 1987; 67: 200–209.

McKay WB, Gallaway BC. Technological aspects of recording evoked potentials from the cranial nerves and brainstem of infant and man. Ann J EEG Technol 1978; 18: 83–96.

National Fire Protection Association. Installation of patient care facilities. NFPA 1975; 70-B-T, Boston.

Pratt H, Polinsky D, Sagi A. Multimodality and electrode evoked somatosensory potentials in humans. Effects of standing prolonged use. Electroencephalogr clin Neurophysiol 1980; 48: 340–348.

Pratt H, Ben-David Y, Peled R, Podoshin L, Scharf Y. Auditory brainstem evoked potentials. Clinical promise of assessing stimulus rate. Electroencephalogr clin Neurophysiol 1981; 51: 40–49.

Perrin F, Pernier J, Bertrand O, Giard MH, Echallier JF. Mapping of scalp potentials by surface spline interpolation. Electroencephalogr clin Neurophysiol 1987; 66: 75–81.

Rothman HH, Davis H, Hay IS. Slow evoked cortical potentials and temporal features of stimulation. Electroencephalogr clin Neurophysiol 1970; 29: 225–232.

Ruchkin DS. An analysis of average responses to compression based upon symbolic stimuli. IEEE Trans Biomed Engng 1965; BME-12: 95–106.

Ruhm PM, Cranor BQ, Cranor JB, Howe WJ. Short latency somatosensory evoked potentials in cervical nerve root avulsion. Scalp topography and the effect of different frequency filters. Electroencephalogr clin Neurophysiol 1981; 52: 546–552.

Rumsey JF. The relationship of auditory evoked response to preterm and term infants. Ph D Thesis, Univ of Nijmegen, ISBN 90-9000-, 1985.

Rumsey JF, Cohen RJ, Hegstrom DF, Vitiello VM. The maturation of the central auditory conduction in preterm infants and term newborns. IV. Composite group averages of the central auditory evoked response (ACER). Hearing Res 1987; 27: 83–91.

Salami A, Mikkelsen CM, Perrott G, Mendelson T. Auditory brainstem recovery processes from birth to adulthood. Psychophysiology 1978; 15: 214–219.

Scherg M, Von Cramon D. Evoked dipole source potentials of the human auditory cortex. Electroencephalogr clin Neurophysiol 1986; 65: 344–360.

Schimmel H. The (+/-) reference: accuracy of estimated mass components in average evoked potential studies. Science, 1967; 157: 92–94.

Spitz EA, Emerson RG. Phase synchronized triggering: a method for coherent noise elimination in evoked potential recording. Electroencephalogr clin Neurophysiol 1985; 60: 464–468.

Spitz EA, Sapienza RG, Duffey TA. Real-time reconstruction of evoked potentials using a new two dimensional filter method. Electroencephalogr Neurophysiol 1981; 52: 373–388.

Stapells DR, Picton TW. Technical aspects of brainstem evoked potential audiometry using tones. Ear and Hearing, 1981; 2: 30–36.

Stegeman DF, Van Oosterom A, Colon EJ, Pacifici evoked potential components caused by a propagating generator: Computational evidence. Electroencephalogr clin Neurophysiol 1987; 67: 176–187.

Stockard JJ, Stockard JE, Sharbrough FW. Nonpathologic factors influencing brainstem auditory evoked potentials. Am J EEG Technol 1978; 18: 177–209.

Stockard JJ, Stockard JE, Sharbrough FW. Visually evoked potentials in clinical pattern reversal: Latency variation with gender, age and evaluation factors. Am J EEG Technol 1979; 19: 171–204.

Hosford JE, Wennerstrand BP. Tutorial considerations in the recording and interpretation of the brainstem auditory evoked potential for neurosurgical diagnosis. Am J EEG Technol 1983; 23: 31–54.

Suzuki T, Kobayashi K, Taniguchi K. Effects of click intensity on the first and fifth components of auditory brainstem responses. Electromyogr Clin Neurophysiol 1986; 26: 159–168.

Guthrie/Mayfield Laboratories. DL266 Standard 2ch evoked and digital equipment. 1989. New York.

Van Dijkhuizen AF, Rodenburg M, Verweij C. Influence of the stimulus repetition rate on brainstem evoked responses in man. Audiology 1979; 18: 379–389.

Weber DO. A personal "Wiener filtering" of auditory evoked responses. Electromyogr clin Neurophysiol 1989; Suppl. 27: 61–76.

Worrell DG. The application of low-pass linear filters to evoked potential data. Filtering without phase distortion. Electromyogr clin Neurophysiol 1978; 46: 253–256.

Worrell DG. Temporal uncertainty and the recovery function of the auditory BP. In: Evoked Potentials, Proceedings of the Evoked Potentials Symposium, Birmingham, 1977. Penn. 1980. Lancaster.

Woods DL, Clayworth L, Hillyard SA, Galambos R. Recovery cycles of event-related potentials in multiple-interval tasks. Electromyogr clin Neurophysiol 1986; 26: 335–347.

Kaufman L, Williamson SJ. Magnetic location of cortical sources. Ann New York Acad Sc 1982; 388: 197–213.

Yagi T, Kaga K. The effect of the click repetition rate on the latency of the auditory evoked brainstem response and its clinical use for a neurological diagnosis. Acta Otorhinolaryngol 1976; 33: 81–91.

PART TWO

Auditory evoked potentials

The auditory brainstem response

J.J. EGGERMONT and P.H. SCHMIDT

1. Introduction

In evoked potential work the action of the inner ear is too often ignored and seen only as the necessary mechanism for obtaining responses to auditory stimuli. In discussions this cochlear action is furthermore reduced to only the action of the basal part of the cochlea, since popular belief is that click evoked potentials (EP) are only measured by the high frequency fibers emanating from this part of the cochlea. Subsequently the opinion is heard that no matter what stimulus is used, one can only test the integrity of this basal part of the cochlea. This of course is not the case and introductions dedicated to these aspects of cochlear and auditory nervous system physiology appears necessary for the interpretation of auditory brainstem responses (ABR). We will observe that the application in neurology is straightforward when one is only concerned with the distinction normal or abnormal brainstem. The difficulties arise when false positives (i.e. diagnosing an abnormality of the brainstem when in fact it is normal) resulting from cochlear abnormalities, have to be eliminated. For this important purpose alone an understanding of cochlear action and its influence on the generation and the interpretation of the ABR is indicated.

2. Anatomy and physiology

The auditory system basically consists of four distinct parts. Part one comprises the *transformation* of the acoustic stimulus through the external and middle ear into the vibrations of the stapes footplate. Part two comprises the transformation from stapes vibrations into the movement of the hair cell cilia in the inner ear. This stage incorporates a *distribution* of energy along the basilar membrane. Part three is the *transduction* of the mechanical movement of the cilia into electrical potential changes in the hair cells resulting in turn in the release of chemical substances into the synaptic cleft. Part four, and by far the largest one, comprises the *coding* and *representation* of stimulus

E. J. Colon and S. L. Visser (eds), Electrical potential manual, pp. 41–77.

parameters in the auditory nerve and central nervous system. Although this distinction in four parts is not completely proportional to the amount of knowledge that exists, it describes the basic aspects of the functioning of the auditory system and understanding thereof is crucial for correct use of auditory evoked potentials in clinical diagnoses.

2.1. The outer and middle ear: Protection and impedance matching

Although the main function of the external ear, at least in evolutionary sense, is a protective one, it also collects acoustic energy and changes the spectral content of the auditory stimulus. The spectral-filtering action mainly takes place for frequencies above 1 kHz and enhances considerably our directional sensitivity. Since most of the evoked potential studies are carried out using headphones, we will not deal with directional properties. The transformations produced by the enclosed ear as in the case of an insert earphone are completely determined by the acoustic impedance of the eardrum. The average resonance frequency of the external ear in such a case is around 4 kHz. Well designed earphone and headphone calibration-couplers mimic as much as possible the properties of the average external ear, and the pressure measured in such calibrators provides a measurement well correlated with the pressure at the eardrum of the average ear.

These considerations imply that it is not very informative when we specify that 'a click of 100 microseconds in duration was used'. First of all there are the transformations produced by the headphone, and in addition those by the external ear. One should in fact in reports always show the acoustic waveform and its spectrum.

The middle ear provides the necessary transformations to provide for the passing of sound from air to the inner ear fluid. Normally sound transmission from air to a water-like fluid is not very effective: only 0.1% of the energy is transmitted, the other 99.9% is reflected from the surface. In terms of dB this means a loss of about 30 dB. The transformer action of the middle ear results in an amplification of the pressure at the stapes footplate in comparison to that at the eardrum. This is accomplished by two mechanisms: the tympanic membrane to stapes footplate surface area ratio transformation, and the lever action provided by the middle ear ossicles. Together this results in a transformer ratio of about 30 for the middle ear. This corresponds to 26 dB, nearly compensating the otherwise expected loss in the transmission of sound from air to water.

The pressure gain produced by the middle ear is not the same for all frequencies since the middle ear is a resonant structure, consisting of inertial and elastic components. For normal human ears the elastic component dominates at frequencies up to about 1.5 kHz, the resonance frequency of the middle ear. We can view the frequency dependent action of the middle ear as a filter action. The ratio of stapes displacement to tympanic membrane displacement, which is proportional to the sound pressure at the eardrum,

can be expressed as a frequency dependent gain. The frequency response curve is basically low pass with a weak resonance at 1.5 kHz, then falls off with a slope of 12 dB/octave.

2.2. The inner ear: Frequency analysis and transduction

The basilar membrane analyses the incoming sound according to its spectral properties and distributes the frequency components of the sound along the sensory transducers, the haircells. This distribution is in such a way that high-frequency components only produce movements in the basilar membrane at the most basal end, i.e., at the stapes, and lower frequency components also at progressively more apical regions. This means that when a low frequency tone is used as a stimulus every part of the basilar membrane basally from the point that is tuned to that particular frequency is vibrating. At very low stimulus levels the displacement of the membrane is too small to cause any excitation of the auditory nerve fibers innervating these more basal parts of the cochlea. At higher levels there is a disproportionate growth in the vibration

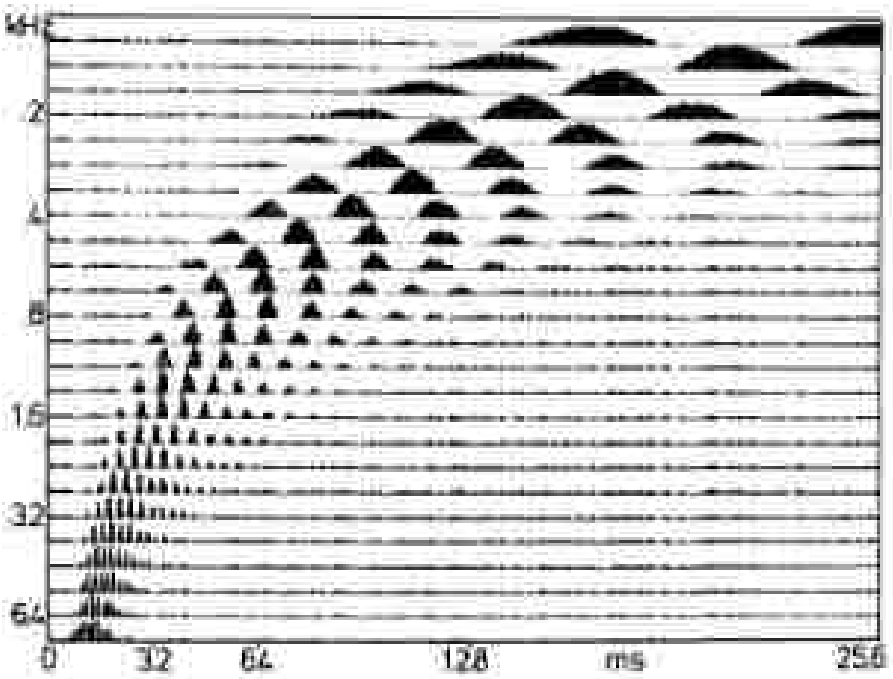


Figure 3. Schematic plots of neural patterns in auditory nerve with different characteristic frequencies (CF) to click stimulation. The horizontal axis represents the cochlear traveling wave delay plus a fixed synaptic delay, and thus gives the CF dependent latency of the nerve fibers. Vertically CF runs from 500 Hz to 8000 Hz in quarter octave steps. The normally present adaptation and refractoriness is not included.

amplitude of the more basal parts of the basilar membrane: the membrane moves non-linearly.

The coupling of the movement of one part of the membrane to neighboring points via the cochlear fluid, together with the time it takes for a particular point to reach its maximum vibration amplitude results in a so called travelling wave delay. While the base of the cochlea is excited nearly instantaneously, it takes about 2 ms to reach the point tuned to 1 kHz, and nearly 4 ms to set the 500 Hz point in motion. We can also say that a time equivalent to about 2 periods of the sine wave are needed to excite the point on the membrane tuned to that frequency. Thus the basilar membrane distributes the multifrequency acoustic click across the array of haircells sitting on it, but does so with a frequency dependent delay (Fig. 1). This has profound implications for the interpretation of evoked potentials to click stimuli, as we will see shortly.

Hair cells have developed an exquisite sensitivity to mechanical deformations. This mechanical sensitivity is localized mainly at the cuticular plate and the cilia that are embedded therein. Deformation of the cilia results in a change in the membrane potential of the hair cell. The hair cells in the mammalian cochlea start to show detectable changes in the membrane potential for cilia displacements of 0.1–0.5 nm, in the direction of maximal sensitivity. Movement of the stereocilia influences the opening and closing of transduction channels in the hair cell membrane. When the channels open, potassium-ions enter the cell which then becomes polarized and in turn leads to opening of calcium channels and the release of transmitter at the base of the hair cell.

Hair cells come in two kinds: outer hair cells and inner hair cells. These two kinds of hair cells are morphologically quite distinct; they differ in number and above all in the way they are innervated by nerve fibers. There are about 3.5 times as many outer hair cells as inner hair cells, however, around 90–95% of the afferent nerve fibers innervate the inner hair cells. On basis of numbers alone we can deduce that the role of the outer hair cells obviously is not in the afferent processing of information from the cochlea to the Central Nervous System, that is clearly the role of the inner hair cells.

In the vicinity of the hair cells one can record potentials that reflect the electrical processes in the hair cells: the reflection of the intracellular AC (alternating current) response is known as the Cochlear Microphonics (CM), that of the DC (direct current) response as the Summating Potential (SP). These extracellular potentials are compound responses, they reflect the activity of many hair cells. The contribution of a particular hair cell to the potentials recorded depends strongly on the distance to the recording electrode, and in case of the CM adding contributions of the individual hair cell has to take into account that those generally have different phases, loss of hair cells might therefore even result in an increased CM! The difference in phase is simply the result of the travelling wave delay: the hair cells that innervate different parts of the cochlea are not activated simultaneously, except in case of stimulation with a long very low frequency tone. When the outer hair

cells are damaged one observes a loss in sensitivity for the CM of around 30 dB.

The SP is slightly less susceptible to phase cancellation than the CM, however, the sign of the extracellularly recorded SP depends on the integrity of the hair cells along the travelling wave pattern. The hair cells activated by the basal part of the travelling wave pattern give rise to a positive SP, those activated by the more apical part of the travelling wave to a negative SP contribution to the round window or promontory.

2.3. *The auditory nerve: Coiling*

2.3.1. Single fiber responses to sound. About 95% of the auditory nerve fibers in mammals innervate the inner haircells. Tuning curves of auditory nerve fibers are composed of a sharp tip region around the characteristic frequency (CF) and for low and high CF-fibers of a tail region as well. Neural tuning curves are as sharp as basilar membrane tuning curves although it is not settled whether they follow the displacement response or the velocity response of the basilar membrane. Tuning quality depends on the CF of the fiber, and so does response latency, however, both are independent of the spontaneous rate. From population studies of cochlear nerve fibers it is evident that a pure tone at low intensity levels (~ 20 dB SPL) only activates a small part of the cochlea and leaves the nerve fibers responding at rates below the saturation firing rate. At intermediate levels (40 dB SPL) excitation with saturation occurs over a 3-4 octave wide region, and at a level of around 70 dB SPL nearly all fibers appear to be saturated in case of stimulation with a 1 kHz tone.

Due to the rectifying nature of the transmitter release one only observes nerve fiber discharges for one direction of the stimulus: that one for which the basilar membrane moves towards the scala media, and the stereocilia in the rarefaction line. A convenient overview of the action of the entire auditory nerve to a click stimulus is provided by the so called Neurogram (Anniil-Candela and King, 1978), it can be viewed as a compound peri stimulus time histogram (PSTH) of a large number of contributing nerve fibers (Fig. 1).

2.3.2. The compound action potential. When studying evoked potentials one always deals with compound responses. The compound action potential (AP) is the gross activity of the auditory nerve, usually measured extracochlearly. In the last decade it has become well established that the AP in response to short tonebursts presented within 10–20 dB from threshold gives frequency specific information of the cochlea in the normal hearing. This has been demonstrated in N (audiograms (or electrocochleograms). The advantage of using AP's is the possibility to quickly and reliably monitoring the status of the cochlea, furthermore AP's have opened the possibility of objectively measuring the electrical activity from human ears.

The size and shape of the compound action potential is determined by 1) the size and shape of the single fiber contribution at the recording site, 2) the number of active nerve fibers, and 3) the time of activation of each nerve fiber. The Neurogram is, in fact, combines the effect of the number of active nerve fibers and the activation times of each nerve fiber. Since the single fiber contribution is a biphasic waveform the result of the weighted average is the characteristic biphasic AP that has a latency corresponding to that of the short-latency high-frequency fibers in the PSTH.

A technique to derive AP's from only a limited part of the cochlea is to mask auditory nerve fibers outside the region of interest. This can be done by using notched noise, however, has the disadvantage that at higher stimulus levels there is some residual masking in the unmasked 'notch'. A better technique is to apply high-pass noise (obtained by passing *wide-band* noise through a high-pass filter) as a masker, determine the AP under the partially masked condition, use another masker cut-off frequency to determine again the AP, and subtract one AP from the other to arrive at a so called narrow-band AP (NAP). This NAP is thought to represent the click synchronous of nerve fibers that are active under one masking condition but masked under the other. The technique plays an important role in the interpretation of click evoked AP's in audiological (e.g. Don *et al.*, 1979) and neurological applications (e.g., Eggermont and Don, 1986).

2.6. *The brainstem nuclei and nerve fiber tracts*

2.6.1. The human auditory brainstem. The human brainstem differs in some respects from that in experimental animals. Certain neuronal groups are well developed in the human, notably the large relay neurons in the cochlear nucleus, the medial superior olive (MSO), the dorsal nucleus of the lateral lemniscus, and also the inferior colliculus. Much poorer developed cells are the small cells in the cochlear nuclei, the entire lateral superior olive (LSO), the nucleus of the trapezoid body and the ventral nucleus of the lateral lemniscus. Moore (1987a) sees this as a reduction in complexity and diversity in sub collicular structures in humans compared to e.g. cats.

2.6.2. Field potentials in the brainstem and pons. Field potentials are dependent on the number of contributing neuronal elements, on the potential contributed by each element, on the spatial alignment and on the temporal synchronization of the neural activity. Field potentials from aligned neural units, such as nerve tracts (as in the case of the compound action potential) and cells organized in laminar structures, are proportional to the number of contributing elements. Field potentials of randomly oriented neurons increase only with the square root of the number of contributing elements. Scalp surveys of filtered field potential activity are weighted sum of the contribution of all the active neural elements. The weighting consists of the latency distribution and the size and shape of the unit contribution. In other words, whenever the contributing

units are independent, the ABR is equal to the convolution of the unit response and the compound latency distribution, in the same way as for the compound AP.

This simple model can be used to test the feasibility that the ABR components are generated by dendritic potentials. Assume, as Buchwald (1983) suggests, that wave II is generated by dendritic potentials in the cochlear nucleus (CN) and wave III in the superior olivary complex, and specifically in the MSO since this is the dominant structure in humans. The histological data provided by Moore (1987a,b) indicate that the 10⁴ or so neurons in the cochlear nucleus are randomly oriented, while the 24-30² cells in the MSO are parallel oriented. The field potential in the MSO will be proportional to the number of cells and that in the CN will be proportional to the square root of the number. The ratio of the field potentials, assuming that the unit contributions are identical, is then 24,000 to 1500 which is about 8. This means that the model of Buchwald would predict a wave III that is approximately 8 times as large as wave II, which is obviously not the case. With the new interpretation of the ABR, where wave III is actually cochlear nucleus and wave IV/V is probably generated in part by the MSO, the actual ratio is even more closer to unity. This all points to ABR generation by nerve tracts instead of somatic potentials (see also Section 5).

3. Method of stimulation

3.1. *The acoustic impulse: The click*

The most frequently used stimulus in evoking the ABR is the acoustic click, it is the acoustic counterpart of the light flash and the electric shock which are used in visual and somatosensory evoked potential studies. The click is usually produced by exciting an earphone with a rectangular impulse. The duration of the electric impulse together with the frequency response of the earphone determine the acoustic spectrum of the click. For a given earphone increasing the duration of the electric impulse will result in a reduction in the level of the higher frequency components relative to the low frequency components. When the click is too short the total power that can be delivered is generally insufficient to reach high levels of stimulation. A useful compromise is to use a 0.1 ms impulse. The acoustic click in this case will contain frequencies that are of approximately the same level up to 6–7 kHz, depending on the type of earphone used. The middle and external ear will change the spectrum of the click because of resonances in the 1.5–3.0 kHz range, therefore click-ABR threshold estimations in a normal ear and mildly pathological ears will usually reflect the threshold in this frequency range.

Besides duration also the polarity of the electric impulse is important. When the initial movement of the earphone's diaphragm is outward we call the resulting click a condensation click, when it is in the other direction we have

a rarefaction click. The click polarity interacts in a very complex way with the morphology, latency and amplitude values of the ABR. Quite often one reads the advice to use only rarefaction clicks, because it gives a sharper definition of the various waves, however this is not always the case and it is wise to establish normative data for rarefaction clicks, condensation clicks as well as for ABRs evoked by clicks of alternating polarity. The latter form of stimulations is sometimes useful in case of large stimulus artefacts, it also constitutes a useful test to find out if Wave I is contaminated by CM: the CM contribution will disappear for alternating polarity click stimulation.

Stimulation rates differ with the application: for neurological applications where the identification of wave I is crucial it is advised not to use faster repetition rates than about 11 per second, in case of threshold determination based on wave V one can without any problem use rates up to 40 per second.

3.2. Continuous tones

The use of continuous tones is restricted to frequencies below 600–700 Hz; for these low frequencies it is possible to register a so called frequency following response. The threshold of this response can be obtained without too much difficulty and can be used to predict the threshold of hearing. Care should be taken not to confuse this neural potential, which is probably a negative wave III–V complex, with the cochlear microphonic potential.

3.3. Tone bursts

A stimulus intermediate between the click and the continuous tone is the tonepip or short tone burst. This stimulus combines a relatively fast onset with some frequency specificity. An advisable stimulus configuration is to use a two-period rise-time and decay-time optionally combined with some periods plateau. This stimulus type has proven to be quite adequate to estimate auditory thresholds for the frequencies of 1000 Hz and higher. Some authors also obtained acceptable results for 500 Hz (for a representative overview see Eggermont, 1976). This stimulus is frequency specific but at high stimulus levels a large part of the cochlea is stimulated. Due to the non-linear character of the ear frequency specific thresholds are only obtained in small to moderate hearing losses. For cochlear losses of more than 60 dB the dominant contribution to any toneburst-evoked ABR will originate from the most basal part of the cochlea, i.e., the high frequency end. Thus special care must be given to limit the activity pattern of these tone bursts, however, for audiological applications they are far superior to clicks.

3.4. AM and FM stimuli

Occasionally amplitude modulated and frequency modulated stimuli are used, they are so far not of clinical importance.

3.3. High-pass and notched-noise masking

Both high-pass noise masking and notched-noise masking are used to limit the excitation region of either clicks or short tonebursts. The masking noise limits especially the extension of the excitation toward the basal parts of the cochlea. In case of the notched noise the threshold to the click or tone burst depends on the frequency of the notch, by varying the click or tone burst level together with that of the noise one can obtain so called place-specific stimulation over an extended intensity range (e.g. Stapells *et al.*, 1985). When using high-pass noise masking we can obtain place-specific contributions by a successive subtraction technique. Audiological applications, including audiogram estimations, have been described (e.g. Don *et al.*, 1979) and hold great promise. The original objections that it is too time consuming are nowadays less important with the increase in computer memory allowing off-line evaluation of the recorded data. Applications in acoustic neuroma diagnosis allowing a topodiagnosis of the tumor have been described by Eggermont and Don (1986).

4. Method of analysis

4.1. Recording: Electrodes, amplification, filtering

For recording ordinary silver-silver chloride or gold-plated EEG electrodes are used, which are attached to the scalp by collodion or by using a sticky electrode paste. The latter method is faster, the electrodes are more easily removed and skin irritation is avoided. The paste or electrode jelly ensures that the resistance between electrode and scalp is reduced. The interelectrode impedance (resistance measured at 1 kHz) should be less than 5 kOhms. A disadvantage of the use of paste to attach the electrodes is that they can come off during recording especially in restless patients. Registration is preferably performed simultaneously between the vertex (C_z) and the ipsilateral (A_i) and contralateral (A_c) mastoid or ear. There are two conventions in use for displaying the ABR: either the vertex electrode positive signal is plotted as an upward deflection (most commonly used), or the vertex negativity is plotted upward (used e.g. in the Scandinavian countries).

Sometimes a larger wave I can be obtained by placing the ear electrode on the tragus, most often an improvement is only obtained by using an electrode close to the tympanic membrane in the external ear canal.

The ABR signal is very small compared to the ongoing EEG. In order to register a recognizable signal one first of all has to eliminate as much of the EEG as possible, this is done by high-pass filtering: only signals with frequencies above 100 Hz are allowed to pass. In addition one improves the signal-to-noise ratio by averaging. Ideally the ABR to background noise (both neural and myogenic) ratio improves with the square root of the number

of sweeps. Thus 2000 sweeps yield a factor 2 better signal-to-noise ratio than do 500 sweeps, and in order to improve another factor 2 requires 8000 sweeps. This illustrates the importance of filtering: one can in addition reduce to noise by low-pass filtering, usually the low-pass cut-off frequency is set at 3000 Hz.

An important fact to be aware off is that most types of filtering introduce latency changes in the ABR, both in peak latencies and interpeak intervals. Lowering the low-pass cut-off frequency will increase the latency of the peaks and also the interpeak latencies. Increasing the high-pass cut-off frequency reduces the latencies. Thus normative values and actual recordings should always be taken with the same filter settings. In addition to the cut-off frequencies filters are characterized by filter slopes, the steeper the slopes the larger the changes in latency. Thus one cannot simply compare filters that have identical cut-off frequencies but different slopes. More information is given in Part One.

4.2. Averaging: Artifact rejection, weighted averaging

As we have seen averaging recovers the ABR from the background noise. A necessary condition for averaging to work is that both the signal and the background noise are stationary. An important event that disrupts stationarity is the so called artifact, usually a large voltage resulting from muscle activity through the movement of the patient, e.g. by eye blinks or jaw movement. It is important to avoid artifacts in the recording since they are usually persistent against averaging and show up in the final signal. Modern equipment always has an artifact rejection option, where possible adjust it in such a way that about 10% of the sweeps is rejected under normal quiet conditions.

Another way to deal with unwanted large signals is to perform a weighted averaging: signals are added together after multiplication with a factor that is, e.g., inversely proportional to the size of the single sweep signal. This method of averaging reduces the effect of artifacts greatly.

4.3. Response detection and threshold estimation

Response detection is the most important part in the application of the ABR: one first has to be sure that there is a response then one can indicate the various waves and estimate peak latencies and interpeak intervals. One of the ways to establish the presence of a response or response component is to repeat the recording and assure that the response is reproducible. In addition one wants also an estimate of the signal-to-noise ratio in the averaged signal, this serves as an indicator for the likelihood of the presence of a signal. A simple way to obtain such an estimate is to include a pre-trigger interval in which there is obviously no response. One then compares the amplitude in the pre-trigger interval with that after the stimulus. Another useful estimator of the residual noise is the +/− reference obtained by subtracting the response

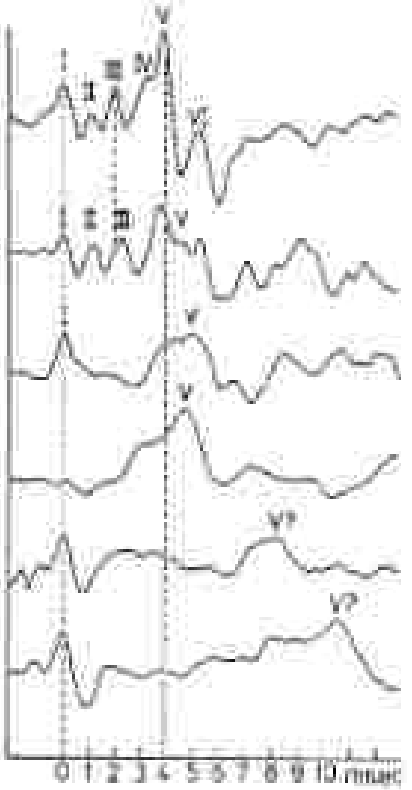


Figure 2. Peak identification in ABR. The normal ABR to a 60 dB SL click in the normal ear shows a well defined set of peaks followed by flatter materials, usually wave V is the most pronounced peak. In pathological cases identification can be more difficult: the normal trace shown as example is taken when wave IV is the largest wave, and wave V is only a small inflexion between waves IV and VI. In the third trace wave I presents no problem, but waves III, IV and V seem to merged into a diffused broad complex. A comparable case is shown in the next trace. The last two traces show broadly well defined waves I very late components but may represent wave V. All abnormal cases shown are from acoustic neuromata.

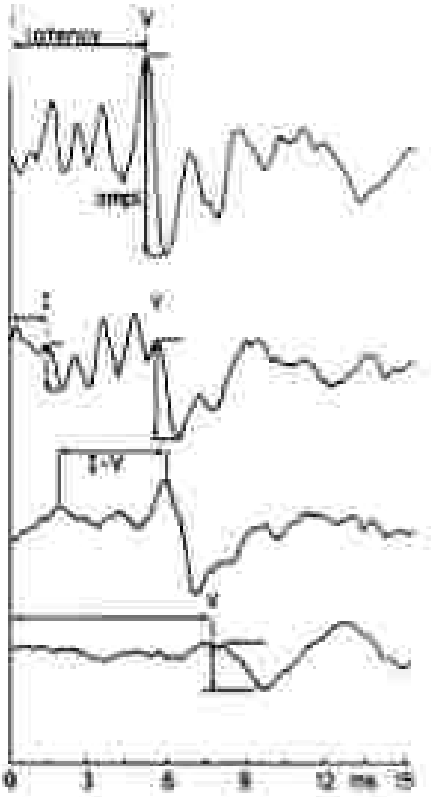


Figure 3. Peak latency and amplitude measurement. In a normal ABR the arithmetic mean checks the definitions of latency and amplitude for the various peaks is straight forward. In the upper trace we have indicated the latency (from the start of the stimulus artifact up to the peak of the wave) and the amplitude (peak to immediate trough) of wave V. The second trace shows the same for both wave I and wave V. In the third trace the I-V interpeak interval is indicated, and in the last trace the latency and amplitude of Wave V for a low intensity click ABR.

to the even numbered stimuli from those of the odd numbered stimuli. Clearly there will be no response left in the average, a comparison with the normally added series of responses usually suffices to ensure one of the presence of an ABR. Note: this only works when either rarefaction or condensation clicks are used, in case of alternating polarity stimulation one ends up with the CM and stimulus artifact in the '+/-' average.

All these methods are subjective in that the investigator has to decide whether there is a response present or not. Objective means have recently be devised by Elberling and Don (1984), they estimate the variance of a single point in the sweep for repeated stimulus presentations, both for a part where there is no response (e.g. prior to the stimulus) and where one expects a response. The F-ratio, based on these two variances, then serves as an objective criterion for the presence of a response (component). Threshold estimation then is the repeated establishment of the presence of a response component (usually wave V).

4.4. Peak identification

Given that a response is present one usually starts off with the identification of wave V, thereafter the other components are labelled. By starting with a response at a relatively high stimulus level (e.g. 70 dB SL) one is assured of all of the components (in the absence of profound hearing loss or neurological disease). Comparing the ipsi and contralateral derivation usually is helpful in identifying wave I (only present in the ipsilateral recording) and the IV/V complex (usually split up in the contralateral recording). At lower stimulus levels wave V is the most prominent. Peak identification is a matter of inspired guesswork when not all the components are present as is often the case in patients with tumors of the eighth nerve (Fig. 2).

4.5. Latency and amplitude measurement

Latencies are measured with respect to the arrival of the sound at the eardrum. In practice one measures them with reference to the stimulus artifact, the difference is usually negligible (with an earcanal length of 3 cm and a velocity of sound of 34 cm/ms, the delay is about 0.14 ms) and anyway incorporated in the particular normative data set. Latencies can be measured using a ruler and a hardcopy of the ABR, by using a movable cursor on the screen of the EP apparatus, or by an automatic peak picking program. The latter case always requires a close visual inspection of the raw data to ensure that no spurious high points are used (Fig. 3).

Amplitude measurements are usually done from peak to succeeding through, some visual averaging might be needed to arrive at the correct reading. Most of the time only amplitude ratio's are used, such as between wave V and wave I, because the variability in absolute amplitude is too large (Fig. 3).

5. Localization of components

5.1 *Intra-cranial recording*

It was long taken for granted that the successive waves of the ABR were generated through the serial activation of auditory nerve and nuclei in the brainstem and midbrain. In addition the idea has been promoted that dendritic potentials or somatic potentials are the only possible candidate for generating the ABR (Buchwald, 1983). Both conceptions are partially if not completely wrong. Intra cranial recordings from the surface of the auditory nerve by Møller and Jannetta (1981) and by Hashimoto *et al.* (1981) have changed our ideas as to what structures are responsible for the various ABR waves. The commonly accepted idea nowadays is that both waves I and II are generated by the auditory nerve, the first wave by the peripheral end and wave II by the intra cranial part. Wave III is generated by the cochlear nucleus, wave IV and V by superior olive and lateral lemniscus. Some believe that waves VI and VII are generated in part by the inferior colliculus. It is probably safe to assume that in addition to this, still serial, model of generation multiple sources are responsible for all waves beyond wave II (e.g. Eggermont, 1987).

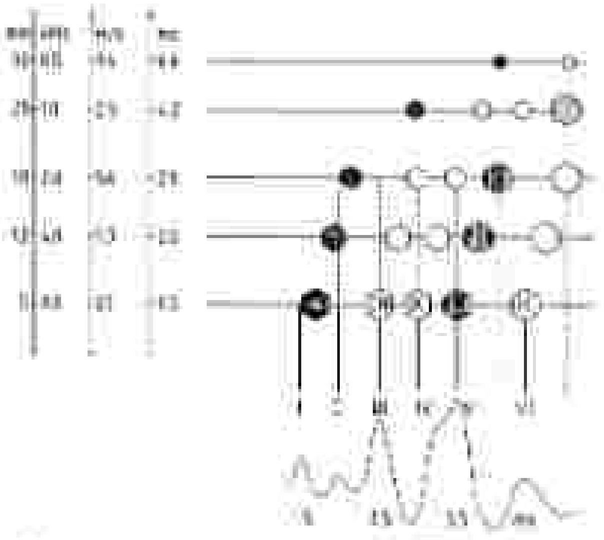


Figure 4. Contribution of multiple generators to the ABR. The major generators for the normal ABR are those parts of nerve, tract and nuclei that are activated by the basal part of the cochlea. More apical parts of the cochlea are activated with a CF-dependent delay, and those from the lower CF parts of the nuclei and nerve tracts are also activated with some delay. The result is that the later waves, III to VI, have multiple generators. The inset shows the tonotopic organization of the cochlea (the relation between distance from the stapes and CF), the travelling wave velocity which depends on the distance from the stapes as well, and the total delay (travelling wave, synaptic, and conduction delay) for the compound AP generated by that part of the cochlea (From Eggermont, 1987).

For instance the delayed activation of more apical parts of the cochlea will give rise to later activity in the brainstem structures, such that activation of the Lateral Lemniscus by the basal part of the cochlea coincides in time with activation of the cochlear nucleus from more apical parts (Fig. 4)

5.2. Nerve tracts or synaptic potentials

A thorough analysis of the cat and human auditory brainstem responses by Fullerton *et al.* (1987) has made it very likely that the fast ABR complex (obtained by high-pass filtering at 270 Hz) is generated by the synchronized activity in nerve tracts, while the low frequency potential (obtained by low-pass filtering at 270 Hz) is of somatic or dendritic origin. Analysis of the distribution of the ABR across the scalp and computing the location, orientation and strength of the equivalent dipoles (Scherg and von Cramon, 1985) revealed that the waveforms recorded from the scalp can be separated into the far fields of six quasi-stationary equivalent dipoles. Each of the equivalent dipoles had the same temporal structure resembling the familiar triphasic shape of the compound AP. The locations of the equivalent dipoles corresponded with the peripheral end of the auditory nerve, with the internal auditory meatus, with the ipsilateral cochlear nucleus complex, with the activation of the trapezoid body, with the ipsilateral MSO, the contralateral MSO and the lateral lemniscus. This confirms both the action potential nature of the fast waves in the ABR as well as its multiple origin and generation restricted to the brainstem.

6. Description of the normal ABR

6.1. Variable morphology

Waveform morphology generally ranks low on the list of attributes and criteria used in the clinical evaluation of the ABR. The obvious reason is that it is too difficult to quantify morphology and to express it as a number such as latency and amplitude. Thus judgement on the basis of morphology is usually regarded as subjective and intuitive while that based on latency and amplitude as more objective.

An obvious reason for the lack of quantification in morphology is the variability among normal hearing age-matched subjects, and even between ears in the same subject. As we have already indicated filter settings have a profound effect on ABR morphology, and so does the type of earphone that is used. In this chapter we will also evaluate other effects such as stimulus induced changes, changes due to recording site and physiological changes.

Figure 5a shows a set of 8 ABRs recorded for rarefaction clicks presented at a rate of 11.9 /s to normal hearing subjects. Recording was between vertex and ipsilateral mastoid with a filter setting between 100 and 3000 Hz. One

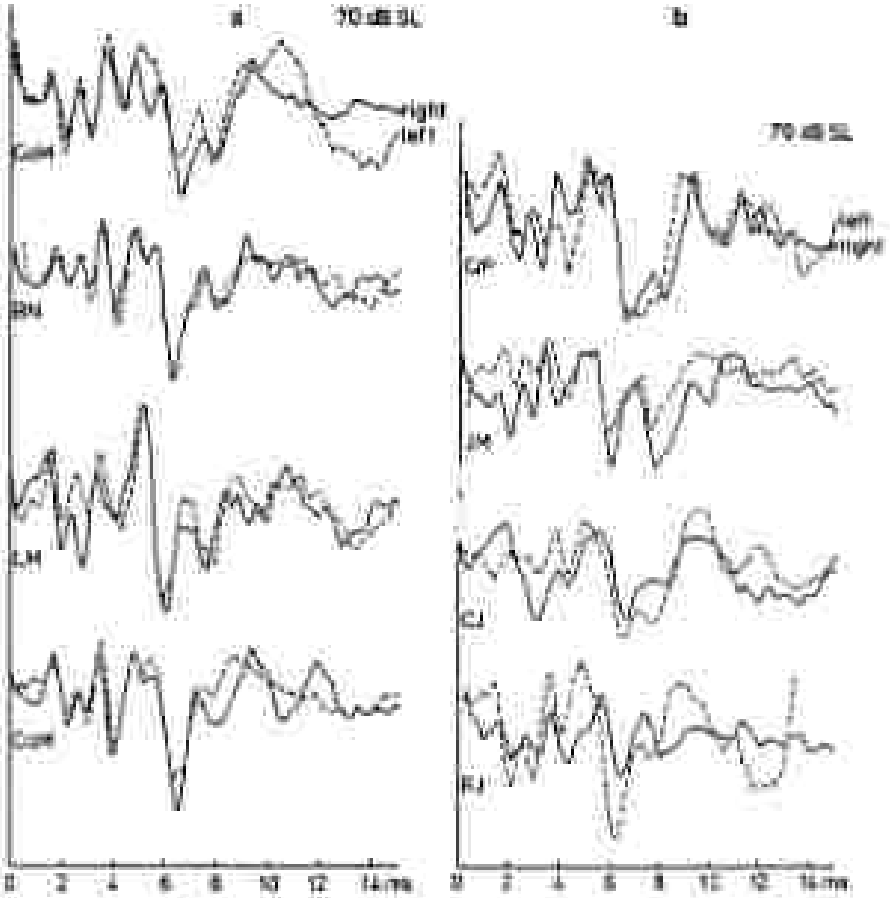


Figure 5. In part a we show four examples of normal ABRs where the left and right ear produce virtual identical responses. In part b four cases are shown where there is a distinct difference between the ABRs to stimulation of the left and right ear.

observes that the between-subject variability is larger than the between-ears variability in the same subject. Despite the differences one can easily identify the first 5 waves and also waves VI and VII. Figure 5b shows 4 other ABRs, again recorded in four normal hearing subjects but now with also a large inter-ear variability.

Few studies have dealt with morphology in a clinical setting, some use in the diagnosis of acoustic neuromas is presented in a paper by Rosenhamer (1977). Some investigations have indicated a way to quantify overall morphology of the ABR: Elberling (1979) has used cross-correlation of the ABR waveform with a normal template, usually formed by the grand average of the normative set available. The correlation coefficient at the appropriate delay then gives a measure of "sameness" between the template and the ABR. Another

approach is called dynamic time-warping (Pitzalis *et al.*, 1988). While the cross-correlation procedure shifts the ABR with respect to the template until an optimal match is obtained, time-warping stretches and shrinks (parts of) the ABR until it optimally matches the template. The integrated amount of stretch and shrink can then be used as a degree of normality of the morphology of the ABR.

6.2. *Stable latencies and variable amplitudes*

Latencies of the various peaks at specified stimulus levels are reasonably stable across normal subjects and allow the establishment of normative latency-intensity curves. Interpeak interval values are even more stable and are comparable between clinics. A sufficiently large sample of e.g. I-V delay values is normally distributed with a mean close to 4.0 ms and a standard deviation of 0.16 ms (Eggermont *et al.*, 1980; Stockard *et al.*, 1978). Values differ slightly between laboratories: Schwarz and Berry (1985) list 7 mean values of which four are 4.0 ms and the extremes are 3.83 and 4.27 ms. Thus it is wise to establish one's own normative values to be used in the diagnosis since relying on published values requires that the conditions under which the values were obtained are also present in the readers clinical setting.

Amplitudes appear much more variable from one subject to another, a range of a factor 10 is not uncommon. It has therefore become clinical practice to use the amplitude ratio of wave V with respect to wave I, the premise is that normally wave I and wave V amplitude will covary linearly (which definitely is not the case). The mean ratio in adults is around 3, depending on filter settings and stimulus repetition rate (among others). Ratios smaller than 1 are suspect for neurological abnormality. A careful analysis of the amplitude ratio shows that it is a skewed distribution and can be approximated by a log-normal distribution. Hence a strict criterion for abnormality can be established just as for the I-V delay.

6.3. *The effect of stimulus type*

Stimulus-type, click or tone-pip, has a profound effect on the morphology, the amplitude, and the latency of the various ABR components. The main difference between the two stimulus types is that properly shaped tone-pips are frequency specific stimuli that can be used to measure ABR threshold as a function of frequency. In contrast clicks are multifrequency stimuli that can only be used for very crude audiometric screening. In order to have these stimulus-specific properties the tone-pips need a relatively long rise- and fall-time. A longer rise-time means a longer latency and a reduced amplitude, even for fixed rise-time tone-pips the latency depends on the frequency. Wood *et al.* (1979) report latencies at 70 dB above threshold of 7.5 ms for 500 Hz decreasing to 6.56 for 4000 Hz tone-pips. The best compromise between an acceptable frequency specificity and an as small as possible rise time is

to take it equal to two periods of the frequency. This makes the rise and fall times frequency dependent, e.g., at 2 kHz a two period rise time is equal to 1 ms but at 500 Hz the rise time will be equal to 4 ms. Longer rise times have a more profound effect on the detectability of wave I than on that of wave V. This is not much of a problem in audiological applications since wave V is used for the estimation of threshold, however, it is detrimental in neurological applications where it is crucial to determine the I–V delay. Therefore the stimulus of choice in neurological applications is the click.

Clicks can be presented in rarefaction-first or condensation-first polarity (the properties of the headphone will ensure that a rarefaction phase is always followed by a condensation phase and *vice versa*), or with alternate polarity. Polarity of the click has a complex effect on the morphology, amplitude and latency of the ABR. This effect is dependent on intensity as well as on the type of headphone, and is exaggerated for clicks of longer duration (i.e. above 0.2 ms) and in patients with a high frequency hearing loss. The effect is more pronounced for wave I than for the later waves (Stockard and Stockard, 1977). Therefore it is advised to collect normative data for both click polarities as well as for the alternate polarity clicks, and use whatever type of clicks is most sensitive to detect abnormalities. Although most clinicians, at least those who publish their findings, prefer rarefaction clicks this is not necessarily always the best stimulus to use. Experience has to be the ultimate guideline.

8.4. The effect of stimulus intensity

Stimulus intensity has a well documented effect on the ABR: increase in intensity results in an increase of amplitudes, a decrease in latencies, and a better defined morphology. At 60–70 dB HL all the waves are clearly present when hearing loss is small, at 40 dB HL the detectability of wave I has already deteriorated, at 20 dB HL usually only wave V can be clearly distinguished (Fig. 6).

The effect of intensity on the latencies of the various waves is somewhat larger for wave I than for wave V. Thus the interpeak intervals are slightly dependent on stimulus level, and become longer for higher stimulation levels. From the diminished detectability of wave I at lower intensities one can infer that intensity has a differential effect on amplitude. In general wave I amplitude decreases more abrupt than that of wave V, on the other hand wave V amplitude tends to saturate at stimulus levels above 70 dB while that of wave I keeps increasing. This makes the wave V- wave I amplitude ratio also intensity dependent.

8.5. The effect of repetition rate

Repetition rate of clicks changes the various components of the ABR in a differential way: the effect on amplitude is most pronounced on the earlier waves, notably on wave I. In contrast the effect on latency tends to be identical for all waves as long as the rate stays below 30/s, thereafter the wave V

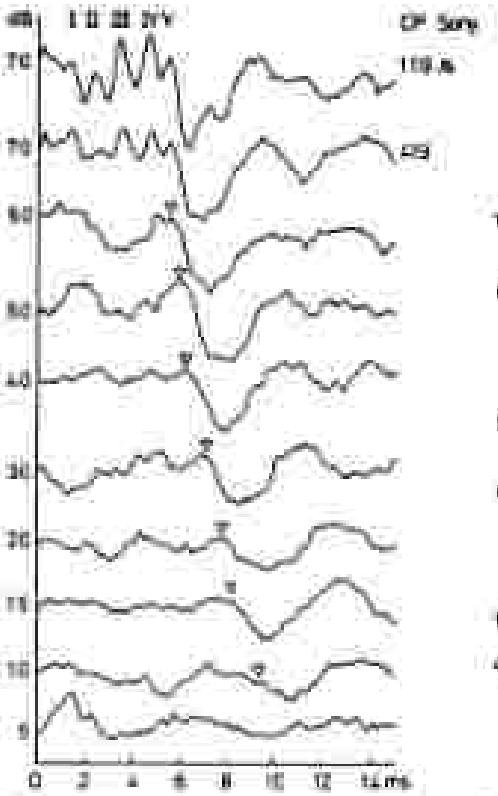


Figure 6. Threshold estimation for the ABR as a normal ear. For a noise with decreasing intensity the ear effectively the gradual increase in latency for wave V together with a reduction in its amplitude. The cases where wave V can be identified as sufficient, threshold is between 10 and 5 dB SL.

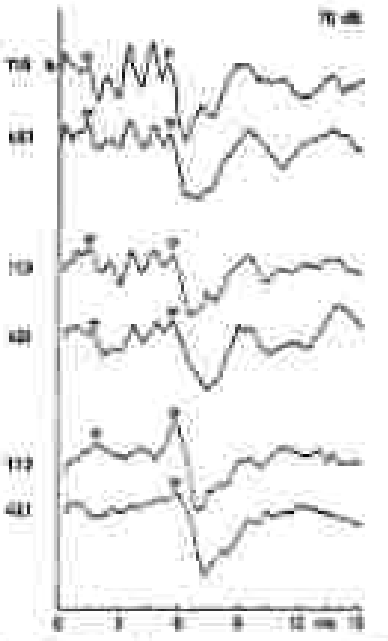


Figure 7. Effect of repetition rate on the ABR. For three normal ears the ABRs evoked with clicks presented at 10.9 and 49.1 per second are shown. Small but distinct differences can be seen, mostly these is a reduction in amplitude, an increase in latency and a reduced threshold for wave I for the higher rate.

latency increases somewhat more than that for the earlier waves. Thus the I–V interval is slightly increased with repetition rate, and the wave V to I amplitude ratio is also increased (Fig. 7).

A notable lack of effect of repetition rate on the ABR threshold is well worth mentioning. It appears that for rates up to say 50/s no difference in ABR threshold is found. This is understandable from the adaptation properties of the synapses which are responsible for the repetition rate effects (e.g. Eggermont, 1985b). Thus the amplitude-intensity curve is steeper when a rate of 10/s is used than for a rate of 40 1/s, but the curves pass through the same point: the threshold. This allows one to use a relatively high repetition rate for audiometric threshold estimations.

6.6. *The effect of background (office) noise*

Noise is any unwanted sound, but noise can also be a particular, random, wide-band signal used for masking purposes. An example of the first category is office noise which interferes with the recording of the ABR. Ideally all ABR recordings should be carried out in sound treated rooms that attenuate environmental sounds with noise 40 dB (at least). In practice ABRs are recorded in the office where the background noise level usually is – for a quiet office – in the range of 50–60 dB SPL. This noise is partially shielded when circumaural head phones are used but it is still important to understand how background masking noise affects the ABR parameters.

Background noise increases the ABR threshold but does not affect the high intensity ABR morphology or parameters. For intermediate stimulus intensities the latencies are prolonged the most for wave V, but the I–V delay is usually prolonged by an amount depending on the click-to-noise level ratio. Since office noise has the tendency to vary from one day to another as well as during the day, and normative values will reflect noise average effect (if they are collected in the same setting) this can corrupt the diagnostic process in an unpredictable way.

Masking the contralateral ear with noise in order to prevent cross hearing is common practice in audiometry. Especially when there is a large difference in the hearing thresholds for both ears one needs contralateral masking of the good ear when testing the hearing loss ear. It has been demonstrated that a contralateral masking level of 20 dB below the click level does not in any way affect the ABR parameters (Reid and Thornton, 1983). Therefore we recommend masking of the contralateral ear whenever the hearing thresholds in both ears differ by more than 30 dB.

6.7. *The effect of recording site*

The generators of the ABR are in the auditory nerve and brainstem, with the exception of those for waves I and II they are relatively far removed from electrodes placed on the scalp. Therefore electrode position does not have a dramatic effect on the ABR late waves. Then the recording is between vertex and ipsilateral mastoid or earlobe all waves are in principle clearly resolved. Recording between vertex and contralateral mastoid or earlobe usually results in a loss of wave I or it a very small one. In addition the wave III latency is usually shorter, and the IV/V complex is somewhat separated (e.g. Starr and Squires, 1992).

Although a recording montage between forehead (hairline) and mastoid can be justified by the ease of application, the vertex-earlobe recording usually gives larger response and is therefore preferred.

6.8. The effect of core temperature

Temperature affects the conduction velocity of action potentials along fiber tracts as well as the synaptic delay. It has been demonstrated that all latencies increase with decreasing temperature, however the later waves latencies increase more. As a result the I–V delay shows an increase of about 0.15–0.2 ms/°C decrease. Changes in latency for 1–2 degrees drop in temperature are comparable to the effect of a small tumor of the eighth nerve. One should therefore be careful with ABR diagnosis in patients who are prone of having a low core temperature such as drug and alcohol abusers and comatose patients. It appears that temperature in the esophagus and nasopharynx correlates best with the changes in ABR and should be used as a control.

6.9. The effect of gender

Sex has a differential effect upon ABR latencies and interpeak intervals. Females have shorter I–V delays than their age-matched male controls. Elberling and Parbo (1987) report mean values of respectively 4.01 and 4.19 ms, both with standard deviations of 0.30 ms. Thus separate normative data must be obtained for males and females.

6.10. The effect of age

In the neonate ABR latencies and interpeak intervals are considerably longer than in adults, however the ABR is well differentiated from about 30 weeks conceptional age on (Fig. 8). Wave I latency reaches adult level values for click evoked ABR at about 1 month after full term birth, and regardless of prematurity at a conceptional age of about 45 weeks. The later waves, i.e., III and V need much more time to reach adult latency values, a conservative estimate is that their latencies are indistinguishable from adults. The same is of course true for the I–III and the III–V intervals.

Healthy premature have the same I–V delays as their full term peers at the same conceptional age, thus retardation in development may be diagnosed on the basis of the latency-age profiles for full term infants and children. The wave V-wave I amplitude ratio does not change very much with age, its mean value is between 1 and 2 with a slight tendency to increase. ABR threshold at birth is around 30 dB HL and is indistinguishable from that in adults at the age of 3–5 years.

At the other end of the age spectrum the changes are much less clear. There is of course the interfering effect of presbycusis and the effect of noise induced hearing loss. These influences usually result in a high-frequency hearing loss for which the ABR shows an increase in peak latencies related to the profoundness of the hearing loss, and a decrease in the I–V delay. So if there is a tendency for the interpeak latencies to increase with old age this can easily be offset by the hearing loss effect. A study in 684 neurologically normal

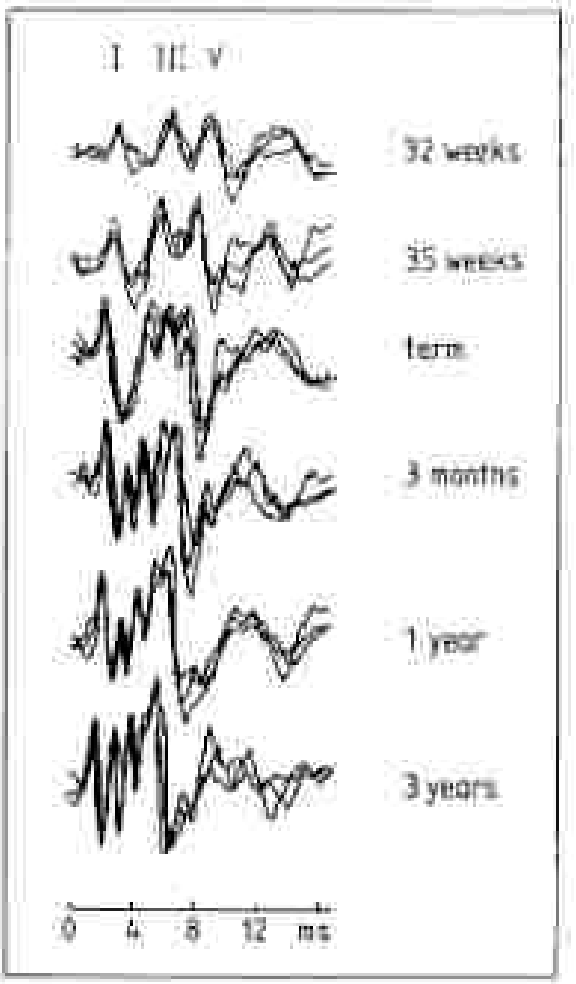


Figure 8 Waveforms in infancy. The ABR changes dramatically in the first 3 years of life, while values and morphology are usually obtained at or by age of 3–5 years. Infants with waves I, III, and V are present, at about 3 months all waves are clearly visible but interpeak latencies are still prolonged. Wave I usually obtains adult values at about 6 weeks of adjusted age (After Salamy *et al.*, 1985).

patients revealed a positive correlation between age and the amount of hearing loss (Uberling and Parbo, 1987). Rosenhall *et al.* (1985) did not find a I–V interval difference across age groups (from 3–over 55 years), however, when excluding subjects with hearing loss they found an increase in the I–V interval in older subjects (Rosenhall *et al.*, 1986).

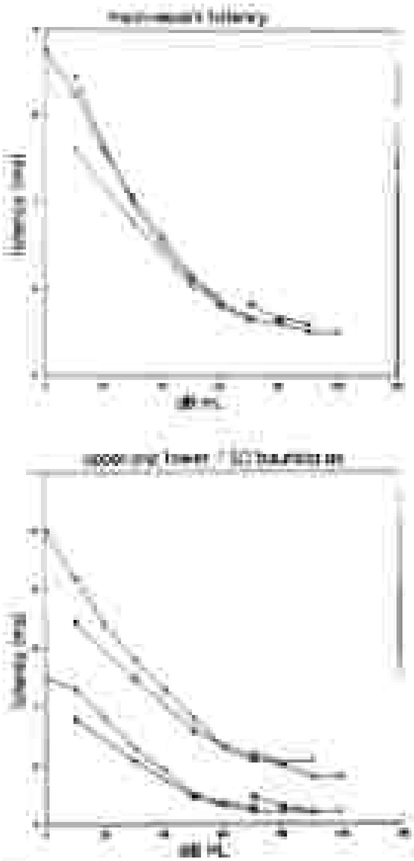


Figure 9. Adult latency intensity curves (upper part) and 2.5 [illegible] boundaries for 60 dB HL clicks, as reported in the literature. There is a quite large latency shift over the 100 dB intensity range; results compare very well between institutions.

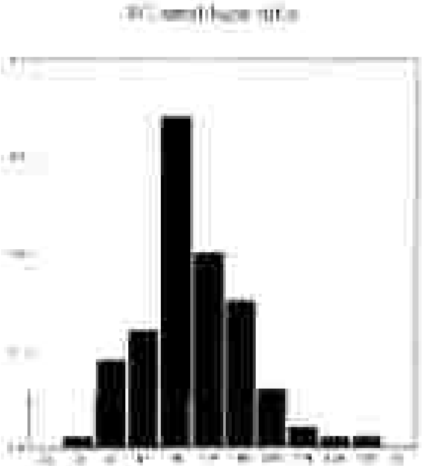


Figure 10. Distribution of wave V latency for [illegible] neonates within a day after birth. One observes a nearly symmetrical distribution with a mode [illegible] around 7.5 ms.

7. Normative values

7.1. The adult normative values

7.1.1. The latency-intensity function. In the audiometric application of the click-ABR, diagnostics for the site of the lesion, middle ear or inner ear, are usually based on the so-called latency intensity curve. This is a plot of the latency of wave V as a function of click level. In Fig. 10 we have assembled the mean values of latency intensity functions or parts thereof as reported in the literature. One observes the general trend that with increasing intensity the latency

decreases. At high click levels the latencies are about 5.5 ms, at lower levels especially below 20 dB there are considerable differences between the reported values. This again necessitates the establishment of normative values for each particular setting. Fig. 9 also shows the lower and upper 2.5 standard deviation boundaries for three studies, again there is fair agreement at the higher intensities, above 50 dB, but considerable differences at the lower levels.

7.1.2. Latency distributions at 60–70 dB nHL. As one can infer from the latency intensity function and the 2.5 standard deviation boundaries the latency distribution is relatively narrow at 60–70 dB HL. Salamy *et al.* (1982) found a mean value of 5.66 ms with a standard deviation of 0.23 ms. This is fully in line with other values extracted from the literature: 5.80 (0.20), 5.54 (0.22), 5.67 (0.16), 5.83 (0.15), 5.90 (0.20). The latency distribution for wave V at 60–70 dB nHL can be approximated with a normal distribution with a mean of about 5.7 and a standard deviation of 0.2 ms. This means that latencies of longer than 6.2 ms (mean plus 2.5 standard deviations) are suspect for abnormalities.

7.1.3. The central conduction time. An analysis of 12 reports in the literature revealed that the I–V delay on average is very close to 4.00, with a minimum of 3.83 and a maximum of 4.27. The 95% confidence levels for the mean are 3.94 – 4.07. A careful analysis of the distribution curve that again a normal distribution is a good approximation, the standard deviations for the individual reports ranged from 0.15 to 0.27. A conservative estimate of the standard deviation for a normative data set will turn out to be close to 0.2 ms. Again this means that a I–V interval that exceeds 4.5 ms is suspect for a neurological disorder. In Eggermont *et al.* (1980) the data used were 4.01 with a standard deviation of 0.16 ms. Again there will be differences from institute to institute but they are generally small and probably the result of different make up of the population in terms of number of males and number of females. As Elberling and Parbo (1987) have shown for a very large population the mean value for the male subpopulation is about 0.18 ms longer than that for the female group. Thus false positives can result for males and false negatives for females when a mixed reference set is used.

7.1.4. The wave V – wave I amplitude ratio. There are not too many data with respect of the wave V – wave amplitude ratio. Stockard (1982) reports a mean value of 3.14 with a standard deviation of 1.05. Salamy *et al.* (1982) reported a mean of 2.13 and a standard deviation of 1.26. A ratio below 1.0 is considered abnormal and indicative of a neurological disorder. The problem with the amplitude ratio is that the distribution is skewed and therefore the meaning of standard deviation is somewhat ambiguous.

7.2. Normative values in neonates and infants

7.2.1. Latency distributions at 60–70 dB nHL. Extensive studies by Salamy and collaborators have resulted in a wealth of normative data. Recently we (Eggermont and Salamy, 1988) elaborated on these data to extract normative time courses and distributions, an example of which is shown in Fig. 10. This histogram shows the distribution of wave V latency values in a group of 144 full term babies tested within a day after birth. The mean latency for wave V at 40 weeks post conception is 7.14 ms, the standard deviation is 0.43 ms. The distribution is slightly skewed. Compared to the normative data in adults we observe that the mean value is considerably longer and that the standard deviation is more than double the value in the adults.

7.2.2. The central conduction time. The I–V delay in full-term neonates as well as in premature born healthy babies at the conceptional age of 40 weeks show a normal distribution. The distributions are not statistically different and the mean value is 5.14 ms with a standard deviation of 0.40 ms, also this parameter is therefore considerably longer than in the adult. In Fig. 11 both distributions, for full-term and premature infants, are shown.

7.2.3. The wave V – wave I amplitude ratio. In the neonate wave I is more pronounced than in adults, as a result the wave V – wave I amplitude ratio is generally somewhat smaller. This is illustrated by the histogram of these ratios (Fig. 12), note that the amplitude classes are logarithmically increasing.

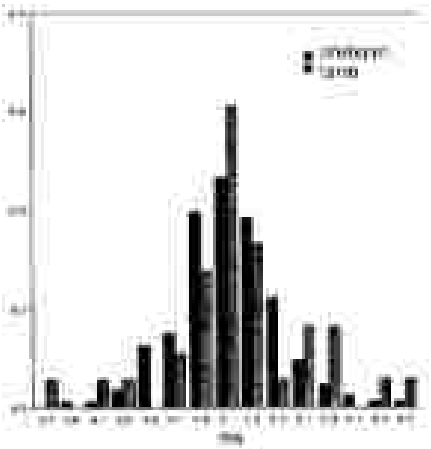


Figure 11. Distributions of the I–V interval for both preterm and full-term at 40 weeks conceptional age. One clearly notices that the distributions are similar.

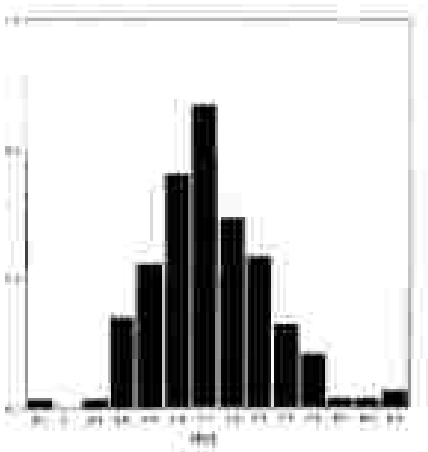


Figure 12. Distribution of the wave V– wave I amplitude ratio for full term, a logarithmic representation of the ratios is used to cope with the very large range of values.

One observes that the ratios cover a range from 0.32 to 7.57, with the most frequently occurring values around 0.95. The distribution is approximately log-normally distributed.

7.3. Normative values in the elderly

This is a difficult subject because barely any normative values exist. In addition if values are published which one should be taken as normative? Those without hearing loss an increasingly smaller population – or those obtained in subjects with varying amount of hearing loss? Rosenhall *et al.* (1986) studied 209 elderly persons, old subjects with slight sensorineural hearing loss had longer latencies (around 0.2 ms for wave V) and a slightly longer I-V interval. Subjects with moderate hearing loss had considerable prolongation in their latencies as well as prolonged I-V intervals. Subjects with pronounced high-frequency hearing loss had longer I-V intervals only for the females, both females and males had prolonged peak latencies. Prolongation of the I-V delay was always largest in the female population (as compared to a normal, young female population) than in the male population (also compared to a young male population). The differences increased from light to severe hearing loss: 0.18–0.21 ms for the female subgroup, and stayed around 0.10 for the male subgroup.

8. Clinical use of ABR

8.1. The ABR in audiology

8.1.1. Threshold and audiogram determination. Audiogram determination by ABR is only possible when stimuli are used that allow a frequency-specific evaluation of the threshold. Such stimuli include tone-pips, tonepips or clicks combined with notched noise, or tone pips or clicks combined with high-pass noise. When clicks are used without any form of additional masking one can only obtain a crude estimate of an average hearing threshold and of the audiogram configuration. Various studies (e.g., Van der Drift *et al.*, 1987) have shown that the click-ABR (wrsinok) correlates best with the mean threshold at 2 and 4 kHz. The correlation coefficient is usually high (around 0.9), and the slope of the regression line of click threshold on audiometric threshold in the 2–4 kHz range can approach 0.9 as well. This suggests that the click-ABR threshold is a reliable estimator of the threshold in the 2–4 kHz range.

Correlation with lower audiometric frequencies or with 8 kHz is usually poor and an estimate of the shape of the audiogram requires additional information. Such information can be provided by the slope of the latency-intensity function (e.g., Gorga *et al.*, 1985). The usefulness is, however, limited since in mild high frequency hearing loss the slope is still in the normal range. Only for average hearing losses in the 1–4 kHz range that exceed 46 dB a

more shallow slope results. In addition low frequency hearing losses, with say the thresholds for 2–8 kHz in the normal range, can never be detected on basis of click-ABR.

The overall picture indicates that the use of clicks results in a rather quick and for most clinical purposes sufficient indication of the average hearing level in the frequency range of 2–4 kHz. No detailed information about the audiogram can be obtained: small localized regions with hearing loss will be missed, and diagnosing a low-frequency hearing loss is impossible (Don *et al*, 1979). In other words, click ABR tells us the same about the hearing of the patients as a whispered-speech test: it is a screening test and is not likely to give detailed information. A way out of this problem, without the expense of a large increase in recording time, may be estimation of a two point audiogram. One point is given by the unmasked click, estimating the 2–4 kHz range, another point may be found by determining the click threshold in the presence of a 1-kHz high-pass noise. Care should be taken that the slope of the high-pass filter is at least 96 dB/octave. This combination can distinguish between rising-, flat-, or falling audiograms.

Alternative ways are the use of tone-pips of various frequencies. Kodera *et al* (1977) showed that the use of 5 ms fixed rise and fall time tone-pips with frequencies of 500, 1000, and 2000 Hz resulted in ABR thresholds that were close (about 10 dB) to the audiometric thresholds for hearing losses in the range of 5–70 dB. On basis of our experience in electrocochleography it can be predicted that using tone-pips with 2 periods rise and fall times will result in reliable ABR thresholds for the frequency range of 1 kHz and above (Eggermont, 1976, 1983). The use of clicks in the presence of high-pass noise and estimation of so called derived responses (Fig. 13) results in

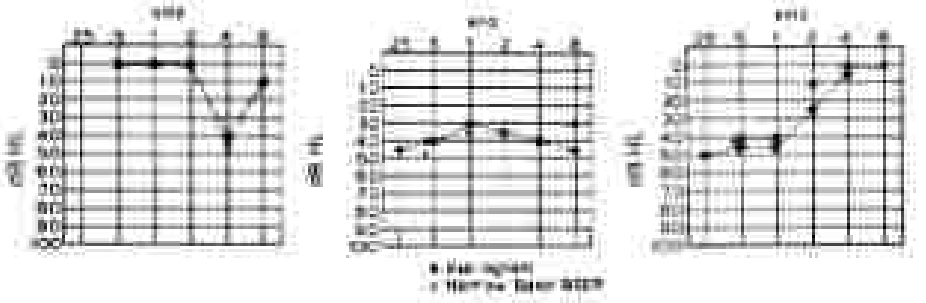


Figure 12. Three audiogram estimations with click and high-pass noise masking. Using clicks in the presence of masking noise high-pass filtered at 4, 1, 2, 4, and 8 kHz with a filter slope of 96 dB per octave, and thereby obtaining one-octave-wide ABRs one can accurately estimate audiograms. Shown are a flat hearing loss, a 4000 Hz 'acoustic', and a low frequency hearing loss. Note the close correspondence with the same audiograms. It is also noted that the click threshold without masking noise in the low frequency hearing loss case was normal, as was the latency-intensity functions. This type of hearing loss can therefore not be diagnosed on basis of the standard click ABR (From Don *et al*, 1979).

excellent estimates of the audiometric thresholds from 500 Hz and above (Don *et al.*, 1978). The often heard comment that this technique is difficult and time consuming is exaggerated. The method requires only one extra measurement per series at a fixed intensity level and the major evaluation is off-line and can be done with any averager capable of subtracting and storing wave forms.

Using tone-pips in the presence of high-pass or notched noise does not require subtraction and is the method of choice, although evaluation for the lower frequencies still may pose some problems in the hands of the inexperienced (Klapetek *et al.*, 1995).

8.1.2. Differentiating between conductive and cochlear hearing loss. Differentiation between retro-cochlear and other sources of hearing loss is made on basis of the I-V delay, details will be presented in the next section. Differentiation between conductive and cochlear hearing losses will be discussed here.

Following conventional audiometric procedures, the use of bone-conducted sound vs air-conducted sound is a major issue in the diagnosis of conductive vs sensorineural hearing loss. The current practical application has been limited. Mauldin and Berger (1979) were among the first to use bone-conducted ABR recently followed by among others Beauvais *et al.* (1983) and Finitzo-Hieber and Friel-Patti (1985). While the combination of air- and bone-conducted ABR is of course the best approach to determine the amount and type of hearing loss, most emphasis has been placed upon the attenuating effects of an impaired middle ear upon the ABR parameters as a function of stimulus intensity. The expectation is that amplitude-intensity and latency-intensity curves shift to higher intensity values with an amount representing the conductive hearing loss (Chaiklin and Hecox, 1977). There are, however, limits in employing this method. It has been observed that the range of intensity values at each particular latency value for normal ears is about 20 dB. The implication is that the minimum pure conductive hearing loss that can be detected on this basis will be 20 dB, and in addition the inaccuracy in the estimate of the amount of conductive hearing loss will also be 20 dB. An additional complication arises when wave I is absent in the ABR recording. In such cases there is no control upon the amount of wave V delay attributable to an increased central conduction time, e.g. resulting from a delay in brainstem development. Especially in infants this can frequently be accompanied by a conductive hearing loss. If an abnormally long I-V delay due to brainstem abnormality is not corrected for, then the amount of conductive hearing loss can be greatly over estimated, in particular if not the entire latency-intensity curve is obtained.

Latency-intensity functions in recruiting ears (due to cochlear hearing loss) either fall within the normal range or show elevated latencies at near threshold values which is usually reported as increased slope of the latency-intensity function (Gorga *et al.*, 1985). When clicks are used the influence of the audiogram

shape upon the latency-intensity function is marked. Claims have been made that mixed hearing loss are characterized by normal latencies at high intensities and increasing difference with normal latency at lower intensities. The same shift, however, is observed in pure high-frequency sensorineural hearing loss when the audiogram has a slope steeper than 50 dB per octave. Differentiation of mixed hearing losses of up to 30–50 dB into a conductive and sensorineural component on the basis of click-ABR alone seems to be mainly based on inspired guesses. A way out of this problem is again the estimation of the two point audiogram as indicated in the previous section and the estimation of the latency-intensity functions for both stimuli.

The general 'recipe' to distinguish, with some success, between conductive sensorineural and mixed hearing loss is: (1) use frequency-specific stimuli or clicks combined with high-pass noise; (2) determine the slope and shift of both the latency- and amplitude-intensity functions and compare these with normative data; and (3) be aware of the confidence region around the estimated values.

For more detailed information on the use of ABR in audiology consult the books edited by Moore (1983) and Jacobson (1985).

8.2. The ABR in neurology

8.2.1. When is the ABR abnormal? In the section on normative values we have basically presented all the ingredients to determine when an ABR is normal or abnormal. In terms of decreasing importance these factors are: (1) the presence of the major peaks, when earlier waves are present and later ones are not then this is a clear indication for an abnormality; (2) When all peaks are present an abnormally long I–V delay and/or an abnormally small wave V to wave I amplitude ratio are indicative for an abnormality; (3) when only the later waves such as III and V are present an abnormally long interwave V latency difference is suspect for an abnormality; (4) when the ABR morphology is disrupted for clicks presented at a rate of about 50 per second then an abnormality may be present; (5) large differences between the ABRs evoked by condensation and rarefaction clicks usually points to a steep high frequency hearing loss; and (6) general abnormalities in morphology as quantified by a template matching test using either cross-correlation or time-warping can be used as an indicator for abnormalities.

8.2.2. Acoustic neuroma and Cerebello-pontine-angle tumors. Site of lesion testing using ABR requires high level stimulation and low repetition rate since one wants to be assured of clear wave I responses. This application of the ABR has, even in skilled hands an extremely low false negative rate. More troublesome, however, is the number of false-positives, and reducing this number requires a detailed knowledge of the impact of cochlear hearing loss and conductive loss on the parameters of the ABR.

As general diagnostic in the detection of acoustic neuroma the early reports

(for a review see Eggermont, 1984) and the ABR morphology (cf. Fig. 2 for some representative tumor ABRs), later on more quantified as either ratios between wave amplitudes, correlation coefficients between waveforms and templates and general indices concerning repeatability. The more quantitative diagnostic procedures comprise the use of the absolute wave V latency with reference to a normative data set. The latency differences introduced by stimulation and recording equipment, gender and age of the patients started the practice to use the patients' other, hopefully normal, ear as a reference. The interaural wave V latency difference, generally indicated as IT_d, was introduced by Selters and Brackmann (1977). They empirically found a correction rule to account for latency increase in the tumor ear due to hearing loss at the higher frequencies. This criterion also proved to be very successful in other hands.

Ideally peripheral effects upon the latencies of the various ABR waves can be removed from the diagnostics by using the *delay* between waves I and V (Eggermont *et al.*, 1980). However, this delay still varies appreciably and some diagnostic improvement can be obtained by using the interaural difference in the I–V delays. This, however, requires the presence of waves I and V, a condition not likely to be found in more than half of the cases. A more practically useful procedure will be to combine IT_d with the I–V delay.

Whatever the diagnostic criterion, results have been strikingly good for ABR testing of acoustic neuroma and cerebello-pontine angle (CPA) pathology.

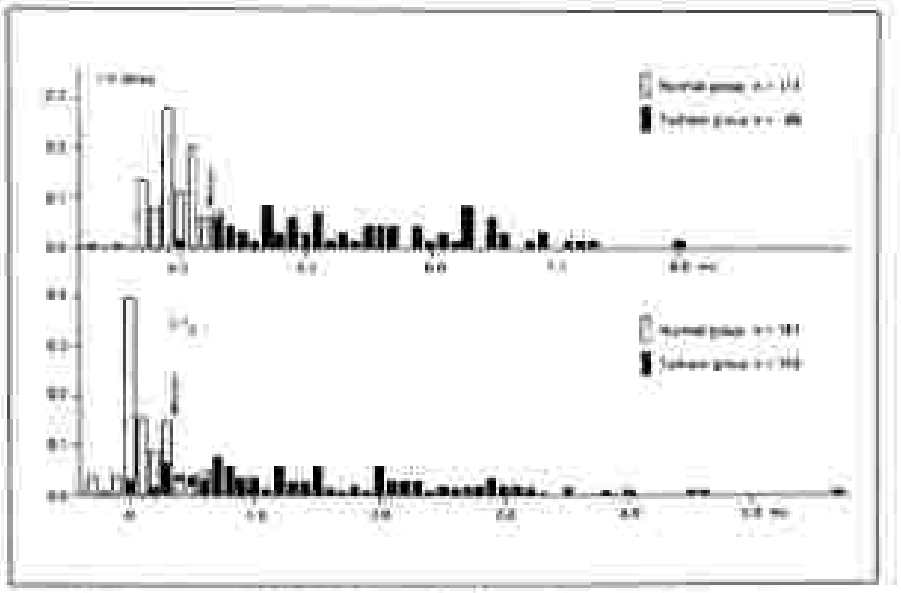


Figure 14. Comparison of the I–V delay and the IT_d as diagnostic tool in acoustic neuroma cases. The criterion values in both cases are indicated by the arrows (From Eggermont, 1984).

Two diagnostics are most popular in testing CPA pathology: the I-V delay and the CI_{1}. As can be seen from Fig. 14 where data from various reports are combined, using the I-V delay with a criterion value of 4.32 ms (about 2 standard deviations) results in a test-sensitivity (the percentage of correctly diagnosed abnormalities) of 98.5%, and a test-specificity (the percentage of correctly diagnosed peripheral losses) of 93%. For the CI_{1} these values are somewhat lower and are 89.5 respectively 88.5%. Differentiating the mixed tumors toward tumor size (Eggermont et al., 1988) indicates that tumors of 0.5 cm in diameter remain undetected in about half of the cases on basis of the ABR. Tumors larger than 1 cm in diameter will be detected without to much trouble.

8.2.3. Pons tumors. Lower pons tumor cases are to be suspected when the I-III delay is prolonged with preservation of the wave I. Most abnormalities are found on the ipsilateral side. When the I-III delay is normal but the III-V is delayed the lesion will be located in the upper or middle pons, maybe extending into the caudal midbrain. In these cases one may observe a contralateral effect, i.e., the ABR evoked by stimulation of the contralateral ear will show some abnormalities for the later waves. In general, however, pons tumors are not very specific in their effect on the ABR.

8.2.4. Demyelinating diseases. Multiple sclerosis (MS) can produce nearly all the abnormalities in the ABR listed under 8.2.1. Chiappa et al. (1980) in a study of 202 patients with MS found in about 13% that the only abnormality was an increased I-V delay, mostly the result of a delay in III–V. In 55% of the cases the only abnormality found was a reduction in the wave V amplitude. In 33% of the cases both an effect on the I-V delay and the wave V amplitude was seen. This means that in MS an effect on the I–V delay can be expected in less than half of the cases, on the other hand a reduction in wave V is far more common and found in nearly 90% of the cases. In some cases an abnormally long wave I latency has been reported and interpreted as a sign of peripheral demyelination.

Abnormalities show up more readily when increased click rates are used, at least according to some authors while others dispute this. Schmes (1983) sees a likely cause for this discrepancy in the level of stimulation that is used, and predicts that at lower stimulus levels, i.e. below 60 dB, the effect will be more pronounced.

8.2.5. Intoxications. Abnormalities encountered in barbiturate overdose and alcohol intoxications usually consist of prolonged I-V delays only.

8.2.6. Comata and brain death. The ABR can be used to indicate the site of the lesion responsible for the Coma. If one or more waves are absent there will be a lesion in the brainstem, if the ABR is normal the coma is probably due to a cerebral lesion. Prognosis is usually bad if there are

abnormalities in the ABR.

In case of brain death one obtains a flat EEG, usually the ABR waves are initially present but then gradually disappear with the highest numbered waves first. Brain death (then usually is called when only wave I is present. In case also wave I is missing one cannot be sure whether this is caused by the brain death or by failure of the inner ear.

8.2.7. Missing waves and related pathology. It is instructive to review the gross abnormalities found in the ABR and relate them to pathology that is found in such cases. The following survey is based on both Schwartz (1983), Chiappa (1983) and Starr and Hamilton (1976) and illustrated in Fig. 35.

Absence of waves IV/V and VI: this is usually found in conditions affecting the pons, such as pontine glioma, stenosis or occlusion of the basal artery, and intra-pontine hemorrage.

Absence of waves III through VI: this usually to diffuse brainstem lesions and cerebello-pontine angle tumors.

Absence of waves II through VI: that is correlated with wide spread diffuse brainstem damage such as arachnoiditus, enlarged ventricles, herniation of the cerebellar tonsils, cerebello-pontine angle tumors, posterior fossa tumors, and braindeath due to severe and prolonged anoxia.

Absence of all waves: this is always the case in wide spread brainstem damage that is accompanied by brainstem edema, in mental acoustic neuroma that have completely shut off the cochlear bloodflow, and in brainddeath.

It is noteworthy that in supratentorial disorders the ABR is mostly normal, sometimes there is a slight reduction in the amplitude of the later waves.

For detailed information of the use of ABR in neurology consult Chiappa's (1983) book and relevant chapters in Moore (1983) and Jacobson (1985).

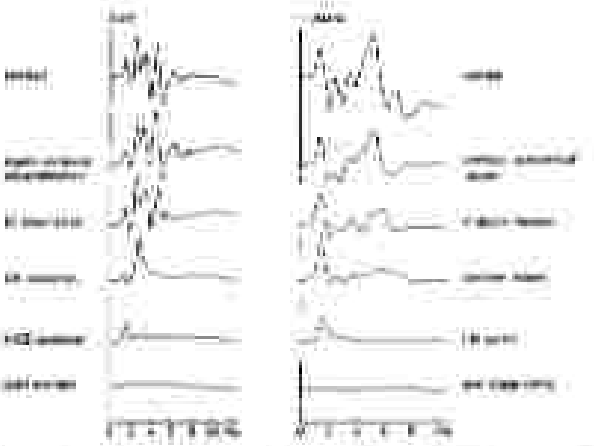


Figure 35. Some of ABRs representative of gross lesions in the brain (After Starr, 1976).

6.3. The ABR in neonatology and pediatrics

As a result of a number of factors (e.g. hyperbilirubinemia, hypoxia, respiratory distress, acidosis, and aminoglycoside therapy) premature born babies are at increased risk for hearing loss, for suffering metabolic disorders, and for delayed myelination (Gorga *et al.*, 1985). All of these factors can have an effect on the maturation of auditory evoked potentials. The influence of these conditions on the auditory brainstem response (ABR), have been well documented in adults and case studies of neonates and infants have also been reported (Durieux-Smith and Picton, 1985). In the case of hearing loss, either conductive or involving the cochlea, one expects an overall delay in the ABR latencies, whereas the interpeak-intervals (i.e., the I-V delay) are not affected or are slightly shorter. Metabolic disorders in neonates mainly affect myelogenesis, and together with delayed myelin deposition due to other sources will alter the peak-latencies as well as the interpeak intervals; the result is longer values than in the healthy full term at the same conceptional age. In neonates the latencies of the various waves (I, III, V) and the I-V interval (the so called central conduction time) constitute the primary ABR parameters studied (e.g. Rotteveel *et al.*, 1987). Only occasionally are amplitudes taken into account (Sininger *et al.*, 1989). One can argue that preterm babies are never normal, but quite often it is assumed that the maturation in healthy preterm infants proceeds such that at 40 weeks post conceptional age (i.e., term delivery) there is no difference with that of a term born baby (Eggermont, 1985a, 1986). Evidence for a different maturational pattern can also be studied on the basis of the variability in the ABR parameters in premature born babies. It has been observed that in term babies the variability in ABR latencies is larger than in older infants (Morgan *et al.*, 1987), as one might expect an even larger variability among the prematurely born. If the extrapolation from preterm age groups to full term age groups can be justified then it will be possible to construct a developmental profile that will have equal validity regardless of the conceptional age at birth. It has been shown (Eggermont and Salamy, 1988b) that with respect to the I-V interval as well as the wave V to wave I amplitude ratio the preterm infants develop in the same way as the full terms. However, for the absolute latencies of waves I and V, significant differences were found to exist up till about two years of age, the preterm population latencies being significantly longer than for the term population at the same conceptional age. This can be accounted for by the higher incidence of conductive hearing losses due to the prevalence of otitis media in the preterm infant.

The data given in the normative values section can be used to assess retardation in development in infants and children. However, of potentially more importance is the screening for hearing loss in the at-risk group of newborns. These can be defined as those with neonatal Asphyxia, Bacterial meningitis, Congenital infections such as cytomegalo virus, herpes virus, toxoplasmosis, syphilis, and rubella virus; Defects of the ear nose and throat;

Elevated bilirubin; a *Family* history of childhood hearing loss and family members affected with hearing loss; and less than 1500 Gram birth weight. This sequence is commonly referred to as the ABC...of the high risk register (e.g., Fria, 1965). If more than one factor is present the newborn is at risk for hearing impairment. In an overview of several studies covering about 3000 newborn that fulfilled these criteria the ABR failed about 10-19%. Follow up testing revealed an incidence of hearing loss of 2-9% in the various studies. Thus the screening procedure results in about 15% of false positives. With an emphasis on the fact that detection of all the hearing impaired outweighs the expense of an increased false positive rate this can be justified. For more details consult the relevant chapters in Jacobson (1985).

Part of the discrepancies between the initial ABR test and the follow up assessment are due to the fact that, rightly, the click-ABR is a screening method for hearing loss and not much more than that. Considerable improvement in its predictive value will be obtained if one expands the method to at least a two-point audiogram estimate as described above (Section 8.1.1.).

8.4. The ABR in intraoperative monitoring

Several features make the ABR an adequate tool to use in operative monitoring. The resistance of the ABR against pharmacological agents and anaesthesia make it the preferred method to monitor changes produced by the surgical interference itself. Applications so far are in surgery of the posterior cranial fossa and in cardiovascular surgery. Details and practical considerations are given in Kileny and McIntyre (1985).

9. Examples of ABR in daily practice

1. This patient noted at age 28 a sudden hearing loss in the right ear when using the phone, feels that it is progressive, and complains since six weeks about dizziness and sometimes vertigo. The audiogram on the left side is normal, on the right side is a low frequency hearing loss, speech discrimination on the right is 90%. Is this a case of Menière's disease?

Figure 16 shows the ABRs for right (full lines) and left ear (dashed lines) stimulation superimposed for intensities of 80 down to 60 dB HL. One observes that the wave one on the right side has a normal appearance but that the later waves are abnormal. This is suggestive for a retrocochlear involvement and rules out Menière's disease. A subsequent CAT scan revealed a small acoustic neuroma on the right, measuring about 0.5 cm in diameter.

2. This patient, age 49, has a hearing loss on the left side that gradually progressed over the last 6 months. The audiograms show a normal right ear, and a left ear that only responded to intensities above 60 dB 500 Hz and 85 dB 250 Hz. No response could be obtained at any of the other

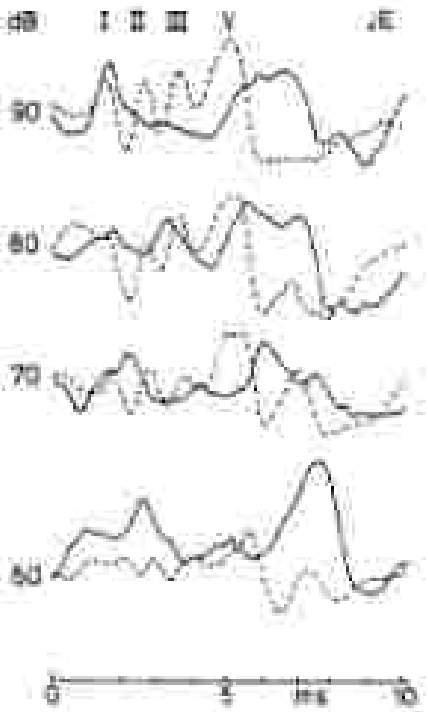


Figure 16. Normal (dashed) and pathological ABR (full lines) in a case called acoustic neuroma case

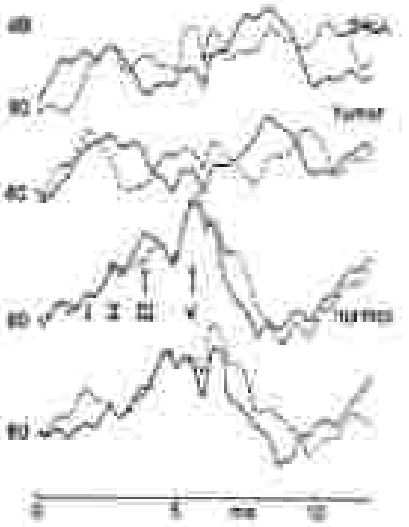


Figure 17. Comparison of the normal ear ABR (lower two recordings) and the pathological ear (upper two recordings) in case of a large cerebello pontine angle tumor. The dashed and full traces indicate repeated runs.

audiometric frequencies, there was no speech understanding at 100 dB.

The ABR on the problem side is not very reproducible (Fig. 17), but around 5-6 ms some response can be noted. At the normal ear a more or less normal looking ABR was obtained with much better replication. The fact that on the problem side with hardly any hearing at all still some response replication could be obtained, suggested that some information was passing into the brainstem and was not indicative for a cochlear hearing loss. CAT scan revealed a large tumor in the cerebello pontine angle, which upon surgery turned out to be a large (2.5 x 4 cm) vascular meningioma.

3. This patient, age 42, noted a slight hearing loss on the left following a blow on her face, this improved but was followed by tinnitus, there was no vertigo. The audiogram on the right was normal, on the left a flat 30 dB hearing loss was found.

The ABR (Fig. 18) was abnormal on both sides: on the left there was only a replicable wave I, on the right all peaks were present but the III-V interval

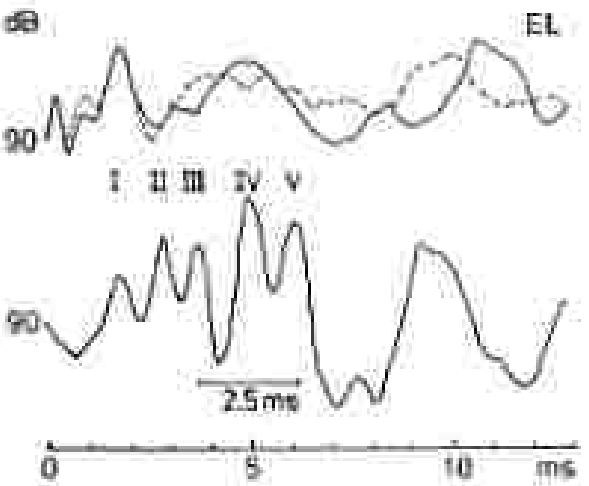


Figure 19. ABR in case of nasal myxoma. The upper set of traces shows responses to the left ear, the lower trace an ABR for the tumor (cymbal sign) on the right ear. Note the relatively large wave I for the relatively small and ill defined wave V complex for the left ear. This results points to a retrocochlear confirmation of the episodic neurosis in Fig. 16).

was prolonged. This is suggestive for a large tumor on the left displacing the pons. The CAT scan revealed a left cerebello pontine angle tumor of about 3.5 cm in diameter. Upon surgery this tumor turned out to be a large acoustic neuroma.

References

1. Antón Castelo F. and Klemp WTS. Ca... activity underlying the N. precedal. In: Pasquin HF and Fernandez C (eds) Evoked electrical activity in the auditory nervous system. Academic Press, New York, 1978, pp 165–189.
2. Bergman DGF, Kaplan H, Viney SL and Sm... AM Comparison of the latencies between bone and air conduction in the auditory evoked potential. Electroencephal clin Neurophysiol 1963, 56: 708–715.
3. Buchwald JS. Generators for Basis of auditory brainstem responses. Grune and Stratton, New York, 1983, pp 157–169.
4. Chiappa KH. Evoked potentials in clinical medicine. Raven Press, New York, 1983.
5. Chiappa KH, Harmon JL, Brooks EB, Young RR. Brainstem auditory evoked responses in 200 patients with multiple sclerosis. Ann Neurol (1980) 7: 135–143.
6. Don M, Eggermont JJ, Brackmann DE. Reconstruction of the audiogram using brainstem responses and high-pass noise masking. Ann Otol Rhinol Laryngol 1979; 88 (Suppl 57): 1–20.
7. Dolinsky-Smith A, Pilon LW, and Noble... Hearing assessment by auditory brainstem response: the Canadian experience. J Otolaryngol 1985; 14 (Suppl. 14): 3–18.
8. Eggermont JJ. Electrocochleography. In: Keidel WD, Neff WD (eds) Handbook of sensory physiology, Vol V/3B. Springer Verlag, Berlin, 1976, pp 625–705.
9. Eggermont JJ. Audiogenic disorders. In: Basis of auditory brainstem responses. Grune and

Sciatica, New York, 1993, pp 287–318.
10. Eggermont, J.J. Use of electrocochleography and brainstem auditory evoked potentials in the diagnosis of cerebellopontine angle pathology. Acta Oto-Rhino-Laryngol Belg 46: 9–47–50.
11. Eggermont, J.J. Physiology of the developing auditory system. In: Terkott SE, Aymonier R (eds), Auditory development in infancy. Pergamon Press, New York, 1988a; pp 23–49.
12. Eggermont, J.J. Peripheral auditory adaptation and fatigue: a model oriented review. Hearing Res 1988b; 34: 57–74.
13. Eggermont, J.J. Evoked potentials as indicators of auditory saturation. Acta Oto-Laryngol (Stockholm) 1990; Suppl 471: 41–47.
14. Eggermont, J.J. Auditory evoked potentials: windows on the brain, in: Proceedings of the 5th congress of the federation of audiological societies of Europe, edited by H. Scherz Cottbus, Leipzig, 1993; pp 161–170.
15. Eggermont, J.J., Don, M. Mechanisms of neural synchronization: tone prolongation in brainstem auditory evoked potentials. Acta Neurol Scand 1986; 67: 116–120.
16. Eggermont, J.J., Don, M., Brackmann, D.E., Electrocochleography and auditory brainstem electric response in patients with pontine angle tumors. Arch Otol Rhinol Laryngol 1980; 89 (Suppl 71): 1–26.
17. Eggermont, J.J., Salamy, A. Maturational processes in the ABR. II. prenatal and full term infants. Hearing Research 1988a; 35: 23–44.
18. Eggermont, J.J., Salamy, A. Development of ABR parameters in a preterm and a term born population. Ear and Hearing 1988b (in press).
19. Elberling, C., Auditory electrophysiology. The use of template matching and time-correlation functions in the analysis of brainstem potentials. Scand Audiology 1979; 8: 187–190.
20. Elberling, C., Don, M. Quality estimation of averaged auditory brainstem responses. Scand Audiology 1984; 13: 187–197.
21. Elberling, C., Parker, J. Reference data for ABRs in otoneurological diagnosis. Scand Audiology 1987; 16: 49–55.
22. Fischer-Hieber, I., Fjord-Pedi, S. Conductive hearing loss. In: The auditory brainstem response, edited by JT Jacobson, College-Hill Press, San Diego, 1985, pp 133–177.
23. Fria, T.J. Identification of conductive hearing loss with the auditory brainstem response. College-Hill Press, San Diego, 1985, pp 347–384.
24. FitzGerald, R.C., Lenox, R.A., Hecox, K.E., Elberling, C. Binaural interaction of click and tone-burst brainstem auditory evoked potentials. Scandinavian Audiology, 1987; 16: 165–175.
25. Galambos, R., Hecox, K., Clinical application of the brainstem auditory evoked potentials. Prog clin Neurophysiol 1977; 2: 1–19.
26. Gelfer, P.H., Jerger, A., Doyling, J.C. The developing human brain. J Wright, PSG Inc Boston, 1983.
27. George, M.P., Southington, D.W., Richard, J.R., Bergeron, R.A., Goldfarb, D.L., Some comparisons between auditory brainstem response thresholds, latencies and the pure-tone audiogram. Ear and Hearing 1987; 8: 305–312.
28. Jacobson, J.T. (ed.) The Auditory brainstem response. College-Hill Press, San Diego, 1985.
29. Kileny, P., McArdle, J.W. The ABR in the assessment of hearing. In: Jacobson JT (ed), The auditory brainstem response. College-Hill Press, San Diego, 1985, pp 237–261.
30. Kimura, K., Yamada, H., Yamada, O., Suzuki, J.I., Binaural response asymmetry as spatial perception. Audiology 1977; 16: 448–459.
31. Mackling, L., Jerger, J. Auditory brainstem evoked responses to time-condensed speech. Arch Otolaryngol 1978; 104: 666–686.
32. Moore, E.J. Basis of auditory brainstem responses. Grune and Stratton, New York, 1983.
33. Moore, JK. The human auditory brainstem: A comparative view. Hearing Research 29: 1–32.
34. Moore, JK. The human auditory brainstem as a generator of auditory evoked potentials. Hearing Research 29: 33–43.
35. Morgan, DE., Zimmerman, MC., Dobie, RA. Auditory brainstem evoked response abnormalities

in the full-term newborn infant. Ann Otol Rhinol Laryngol 1987; 96: 187–192.
30. Picton TW, Hunt M, Mowery R, Rodriguez R, Maru J. Evaluation of brainstem evoked potentials using dynamic time warping. Electroencephalogr Clin Neurophysiol 1983;
31. Reid A, Thornton ARD. The effects of interaural and monaural post-stimulus click maskers on the auditory brainstem response. Br J Audiol 1985; 19: 153–163.
32. Rosenhall U, Bjorkman G, Pedersen K, Kyle A. Brainstem auditory evoked potentials in different age groups. Electroencephalogr Clin Neurophysiol 1985; 62: 426–436.
33. Rosenhall U, Pedersen K, Donald M. Effects of presbyacusis and other types of hearing loss on auditory brainstem responses. Scand Audiology 1986; 15: 179–185.
34. Rosenhamer HJ. Observations on specific brainstem responses in conventional hearing tests. Scand Audiology 1977; 6: 179–196.
35. Rowland H, de Groot JS, Colon EJ, Bilger RC, Visser SW. The maturation of the central auditory conduction: a postnatal and two month follow-up study. II. The auditory brainstem responses (ABR's). Hearing Research 1985; 20: 1–15.
36. Salamy A, Mendelson T, Tooley WH. Developmental profile for the brainstem auditory evoked potential. Early Human Development 1982; 6: 331–338.
37. Salamy A, Mendelson T, Tooley WH, Caughlin SB. Differential development of brainstem evoked potentials in healthy and high-risk infants. Science 1980; 210: 553–555.
38. Schorg M, Von Cramon D. A new perspective on the generators of BAEP waves 1–5: Results of a spatio-temporal dipole model. Electroenceph clin Neurophysiol 1985; 62: 290–299.
39. Schwartz DM, Berry GA. Normative aspects of the ABR. In: The auditory brainstem response, edited by JT Jacobson, College-Hill Press, San Diego, 1985, pp 65–87.
40. Selters WA, Brackmann DE. Acoustic tumor detection with brainstem electric response audiometry. Arch Otolaryngol 1977; 103: 181–187.
41. Selters D. Neurologic disorders. In Basis of auditory brainstem responses, edited by EJ Moore, Grune and Stratton, New York, 1983, pp 717–744.
42. Stapells DR, Picton TW, Perez-Abalo M, Read D, Smith A. Frequency specificity in evoked potential audiometry. In: The auditory brainstem response, edited by JT Jacobson, College-Hill Press, San Diego, 1985, pp 147–177.
43. Stein A, Hamilton AE. Correlation between confirmed sites of neurological lesions and abnormalities of far-field auditory brainstem responses. Electroenceph clin Neurophysiol 1976; 41: 939–948.
44. Stein A, Selgin R. Localization of auditory brainstem potentials over the scalp and nasopharynx in humans. Ann NY Acad Sci 1982; 388: 427–442.
45. Stockard JE, Stockard JJ. Recording and averaging. In: Moore EJ (ed.), Basis of auditory brainstem responses. Grune and Stratton, New York, 1983, pp 253–280.
46. Stockard JJ, Stockard JE, Sharbrough FW. Nonpathologic factors influencing brainstem auditory evoked potentials. Am J EEG Technol 1978; 18: 177–209.
47. Vander Drift JFC, Brocaar MP, Van Zanten GA. The relation between the pure-tone audiogram and the click auditory brainstem response threshold in cochlear hearing loss. Audiology 1987; 26: 1–10.
48. Wood MH, Wolf MB, Jacobson JT. Response electric responses from selected frequency stimuli. J Am Acad Sci 1979; 9: 156–163.

Middle and long latency auditory evoked potentials

T. J. ROTTEVEEL

Introduction

Since Dawson (1947) described the summation and averaging technique by means of photographic superimposition (25), and Abe (1954) applied the method to analyse auditory evoked activity [1], interest and research in evoked potential technology has grown exponentially. The method found general acceptance predominantly by audiologists for the detection of hearing in non-cooperative subjects (22). The auditory brainstem responses, the ABRs, introduced in the 1970s, proved more useful for this purpose, though middle and long latency auditory evoked responses (MLRs and ACRs) can be elicited in the absence of ABRs (113). The information regarding the central processing of auditory input remains however limited to the brainstem. The MLRs and ACRs are generated at and above the level of the mesencephalon and are therefore of interest for neuro-audiology regarding the perceptual and developmental aspects of audition. Therefor the general and developmental features of the MLRs and ACRs will be described in this chapter as well as the anatomy of the central auditory afference.

Auditory evoked responses (AERs) reflect changes in the electrical activity over the auditory pathways in the central nervous system, elicited by acoustical stimuli. Single responses are hardly discernable in the spontaneously ongoing EEG activity. Signal averaging is necessary to identify the responses.

The AERs are subdivided according to their latency, i.e. the time from stimulus onset to a specific potential complex, into short latency (0-12 ms), middle latency (10-100 ms) and long latency or cortical components (50-1000 ms) (Fig. 1).

Evoked responses are also classified according their transiency. A discrimination has been made between continuing and on-responses. Continuing responses are among others the sustained cortical potential and the contingent negative variation. In this chapter we discuss the MLRs and ACRs as on-responses. Cortical long latency responses contain components which are endogenously elicited or even cognitive (ERPs) (P165, N2, P3). These are dependent on psychological variables as attention, anticipation and other

E. J. Costa and T. J. Visser (eds), Evoked potential manual, pp. 79–116.
© 1990 Kluwer Academic Publishers.

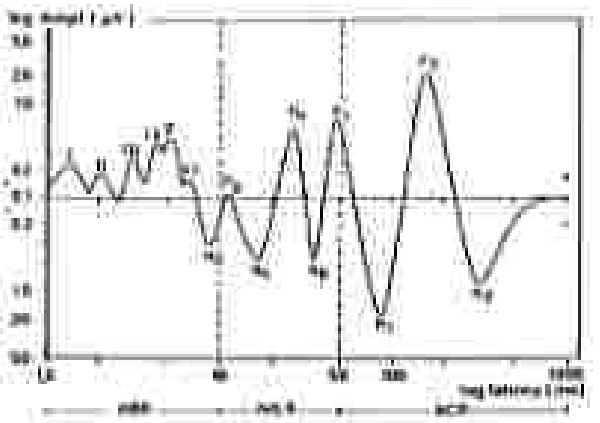


Figure 1. Diagrammatic representation of the ABR and ACR components, together called the BMAC ABRs (brainstem, middle latency and cortical auditory evoked responses). The components are plotted on logarithmic scales. (Redrawn after Picton (1990).

cognitive processes. The components of the ERPs vary with the stimulation paradigm. In this chapter the ACRs will be described, as far as they are stimulus refated or stimulus locked (N1, P2). The SERPs or stimulus related ACRs relate primarily to the physical characteristics of the eliciting stimuli and reflect thus more explicitly the quality of the auditory afference.

2. Anatomy of the central auditory pathways

All parts of the peripheral and central auditory system play their role in the propagation of the sound signals. The capacity of the peripheral components determine the quality of the central input (2, 58) (Chapter on the ABR, J.J. Eggermont).

The central auditory system consists of sequential and parallel rhombencephalic, diencephalic and telencephalic centres and fibre systems (Fig. 2). The rhombencephalic cell masses are the cochlear nuclei, the superior olivary nuclear complex and the nuclei of the lateral lemniscus. The mesencephalic relay is the inferior colliculus. The diencephalic or thalamic centre is the medial geniculate body. The telencephalic auditory areas are located in the temporal lobe.

2.1. Thalamic centres

All the stations mentioned above are interconnected by fibre bundles. The inferior colliculi (IC's) project via the brachium colliculi inferioris towards the ipsilateral medial geniculate body (MGB) and hence to the ipsilateral temporal lobe by the auditory radiation. The auditory thalamic relay is the

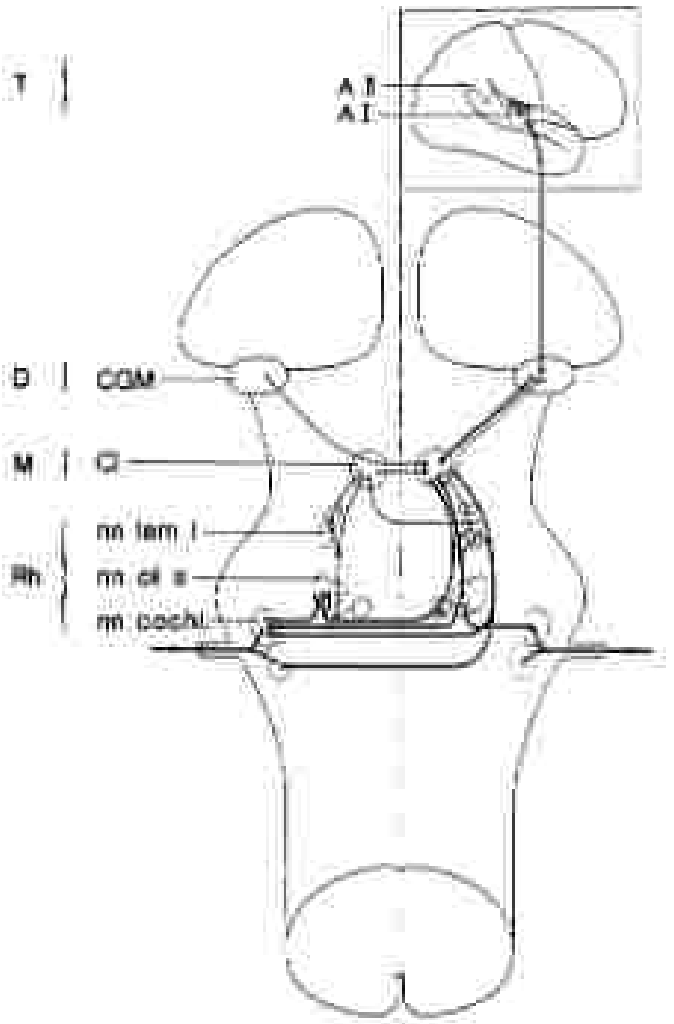


Figure 2. A dorsal view of the central auditory system. The transverse sections of the brain are depicted perpendicularly in space. T = telencephalon; D = diencephalon; CGM = corpus geniculatum mediale; M = mesencephalon; Cl = colliculi (inferiores); Rh = rhombencephalon; nn lem l = nuclei lemnisci lateralis; nn ol s = nuclei olivares superiores; nn cochl = nuclei cochlearis; AI and A II = primary and secondary auditory cortex. (With the courtesy of R. Nieuwenhuys [66])

MGB. It consists of a ventral, dorsal and medial division (143). The inferior colliculi project afferent tonotopically to the ventral division, the principal auditory nucleus. The dorsal division is composed of a 'deep dorsal', 'dorsal' and 'suprageniculate' nucleus. The dorsal nucleus receives exclusively auditory input and projects to the deep dorsal nucleus. The suprageniculate nucleus receives visual and auditory afferent input. The medial division of the MGB receives a multisensory input.

The nuclei of the MGB project to and receive fibres from the auditory cortex. Accordingly are the single unit responses of the MGB of different types. The majority is time locked (locksen), the minority is loosely synchronized (groupers) or do not show any time lock (special responders). The lockers are predominantly involved in the generation on evoked response components (12).

The MGB plays an important role in normal auditory behavior, in view of the integration of multisensory information which occurs in the MGB and the adjacent posterior thalamus (48).

2.2. *Telencephalic centres*

The auditory cortex is a sensory cortex and consists of six layers. The layers II, III and IV are densely populated with principal neurons, the pyramidal cells, and with intrinsic neurons, the stellate or granular cells. Layer V is less numerously populated. A sensory type cortex contains high density granule cells and is labeled accordingly 'koniocortex' which means 'dusty cortex'. The pyramidal cells have apical and basal dendrites. The apical dendrites branch in the superficial molecular layer. From the axons of the pyramidal cells horizontally oriented collateral's arise, which ascend to different levels. Intrinsic neurons remain in the local region. The size of the neurons relate more to the length of the axons than to the complexity of their function (124).

The bulk of the auditory region is positioned in the Sylvian Fossa on the upper surface of the temporal lobe (Fig. 3). This region is one of the most complexly folded in the human brain with a considerable interindividual and right versus left variability. The primary auditory cortex which can be characterized as a koniocortex, is surrounded by transitional cortex and parakoniocortex or the association fields (48).

The parakoniocortex of the association areas varies in architecture. The parietal operculum contains parakoniocortex with input from the MGB and other parakoniocortical fields. Stimulation of this area results in musical hallucinations.

The ventral parakoniocortex receives input from the caudal portion of the MGB. A complete representation of the auditive frequency spectrum in this area is found in the monkey. A tonotopic architecture has been found in the temporoparietal area. Callosal connections from the contralateral auditory region project by the splenium of the corpus callosum in this area. A role in language function has been postulated.

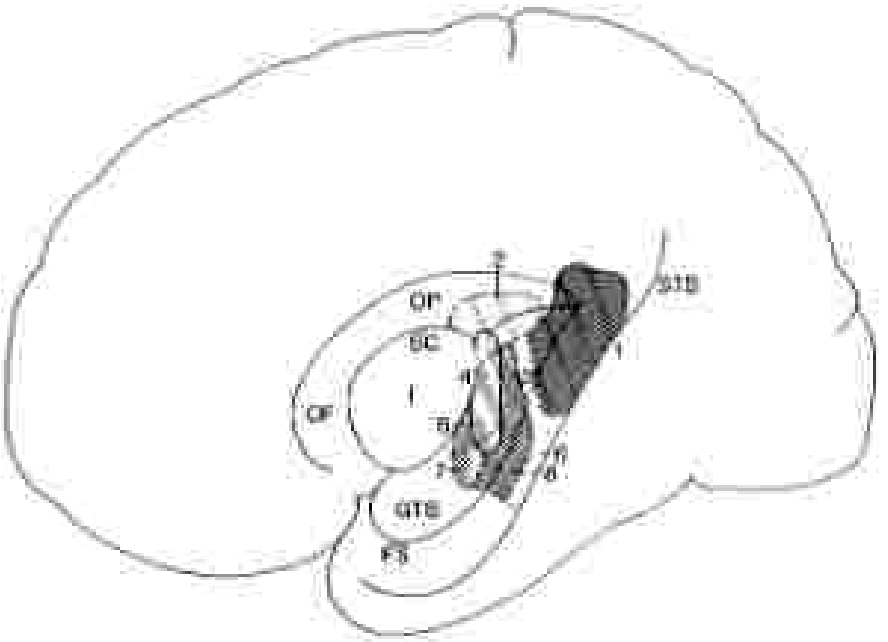


Figure 2. Schematic representation of the auditory cortical fields in the Talbot [sic]. Abbreviations: FS = fissura Sylvii, GTB = gyrus temporalis inferior, I = limbic, OF = operculum frontale, OP = operculum parietale, SC = sulcus centralis, STB = sulcus temporalis superior. Cortical fields: 1, transitional cortical structure to the supragranular cortex; 2, ventrolateral parakoniocortex; 3, lateral parakoniocortex; 4, nodal koniocortex; Heschl's gyrus; 5, parakoniocortex; 6, ventral parakoniocortex; 7, ventral parakoniocortex; 8, lateral koniocortex (Redrawn after Galambos (35)).

The auditory cortex receives its input in the koniocortex from the ventral division of the MGB. The dorsal multisensory division of the MGB projects to the principal cortex, the insular and the temporal areas. The medial multisensory division of the MGB projects to the adjacent auditory cortex, a multisensory cortical area. Cortico-cortical connections are not entirely diffuse and may exhibit a topographic order (35). No cortico-cortical connections have been demonstrated between the auditory and the visual or somatic cortices. The MGB apparently provides for such multisensory integration. The primary koniocortex and adjacent parakoniocortex and transitional cortical areas are interconnected heavily (48).

The neurons of the auditory cortex are oriented in columnar clusters (121). Among the columns a tangentially dendritic connectivity provides a manifold of possible response combinations as a result of the coupling of the columnar cell clusters. The ascending auditory signals probably flow from layer IV to layer II-III and down to layer V and to the cortico-cortical fibres (124). Layer V and VI provide feedback circuits to higher layers and to corticofugal

projections. The horizontal connectivity propagates signals between the 'columns' (38). The degree of overlap is greater in the association areas than in the primary cortices.

3. Methods

3.1. Test parameters

Depending upon the audiological or neurological purposes of the application of the ABRs, specific requirements have to be fulfilled (21, 22). In view of the frequency contents of the different signals, specific requirements apply for the analysis time and the mode of stimulation.

The example of the test protocol as listed in Table I is in use in our laboratory.

Table I. Test parameters.

		MLP	ACP
Stimulation			
click duration	μs	999	999
intensity*	dB	70	70
rate	Hz	8.7 or 6.7	appr. 8.5
mode (ipsilateral)		regular	random
AD/AS		exchangeable	exchangeable
Recording			
sensitivity	$\pm$ μV	25 or 50	50 or 125
high pass filter**	Hz	1	
low pass filter	Hz	250	30
Analysis			
sweep time	ms	100	1000
20% growth, time	ms	25	250
channels		4	4
sweeps		256 or 512	64 or 128
sample points		256	256
sample frequency	kHz	2.56	0.256
Electrode positions (10-20 system, Jasper 1958)			
active (ref)		Cz, C4', C3'	Cz, C4', C3'
reference		A2+A1 linked	A2, A1
ground		Fz	Fz
derivations		Cz - (A2A1)	Cz - A2
		C4'-C3'	Cz - A1
		C4' - (A2A1)	C4' - A2
		C3' - (A2A1)	C3' - A1

* Zero dB setting = 30 dB (post equalization SPL).
** Filter roll-off 12 dB/octave.

It is aimed to record in newborns and young infants. Sequentially we firstly obtain the ACRs twice by binaural stimulation, preferably in awake state. Subsequently the ABRs are recorded including an intensity series monaurally and finally the MLRs, both in quiet or sleep state.

3.2. Test conditions

The records are obtained in a certain preferential state. The awake state for the ACRs is chosen in view of the certainty of the state and its stability. Also because the generation of the various AR components depends on the awake or sleep state (22, 139, 142). A change in state results in changing latency values and complex composition. During the premature stage of development of the ACRs we only noticed small parameter value changes due to the state of vigilance. Those differences are probably due to a larger response jitter or fatigueness dependent on the state. The sleep state was chosen for the MLRs especially to avoid myogenic artifacts.

3.3. Electrode positions

Potentials measured at the surface of the scull are generated within the skull.

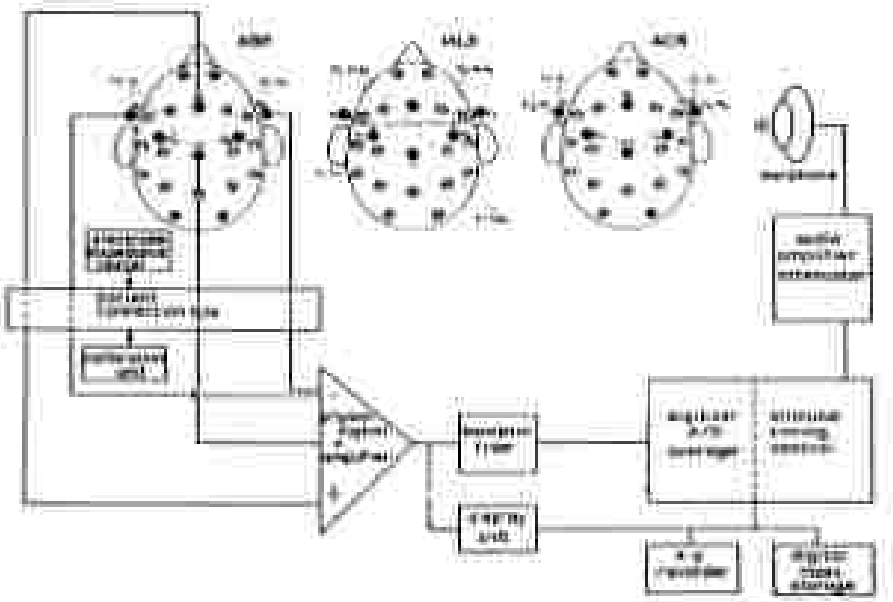


Figure 4. Block diagram of the evoked potential system in combination with the schematic drawing of the derivations as used in the BMC AR protocol. The electrode positions are determined according to the international 10-20 system (73). The locations C3' and C4' are located at half the distance between Cz'ic A1 and A2 respectively.

The contents of the skull is being a volume conductor which conducts electric current fairly well. Generators close to the skull require exact positioning of the electrodes. We are using miniature silverchloride electrodes which are attached to the prepared skin with collodion glue. The interelectrode impedance is kept below 3 kOhm.

The reference electrodes are positioned at the preauricular sites A1 and A2, in view of the convenience of that position in infants. For the MLR a linked A1A2 reference is used. This results in a decrease of myogenic artifacts. Linkage of reference electrodes is common for the recording of late slow potentials. The central temporal positions C3' and C4', half way Cz to A1 or A2 are stable and easy to define (Fig. 4).

3.4. Instrumentation

A common mode rejection (CMR) provides a suppression of interference signals, such as mains interference, stimulus artifacts and muscle activity. Symmetry in electrode impedances enhances the CMR.

The bandwidth of the filter specifies the frequency range of the recording. All frequencies outside the specific region are attenuated. The issue of proper filtering is of major concern in evoked potential recording (53, 64, 69, 114, 138). Filters do not only influence amplitudes, but may also induce phase shifts of AR components. This of course has an impact on the identification of the components and the measurements of their latencies. The MLR bandpass should be chosen in view of the signal frequencies in the MLR domain, 30-300 Hz. The ACR has a frequency content from 0.1 to 70 Hz. Because of the different filter settings for the MLR and the ACR, it is difficult to compare the MLR components with the late ABR or the early ACR components.

3.5. Stimulation parameters

An acoustic stimulus widely in use is the unfiltered click, which provides an efficient synchronization of the action potentials of the axons. The click, a square wave stimulus, contains frequencies which are appropriate to stimulate the full length of the basilar membrane, which is the determining factor for the reactivity to external stimuli (31, 71). Latency measurements of response components elicited after stimulation with broad band clicks are unequivocal. Most empiric experience is acquired with click stimulation by rectangular electric pulses to the speaker or earphones. The drawback of the use of unfiltered clicks is the uneven distribution of the energy in the acoustic spectra of the stimuli. The click duration of 1 ms is effective in obtaining the MLRs and ACRs and is consistent with the stimulation rate and time base (32). Rarefaction or positive polarity is considered to be more effective than condensation or negative polarity of the stimuli (128). The stimulation rate for the MLR is 4.7/s regularly and 0.5/s irregularly for the ACR. The stimulation intensity of 70 dB HL is usually sufficient. A intensity series with the ABR informs

about the hearing threshold. The stimulation for the MLR is performed monaurally to detect asymmetries. Bilateral stimulation enhances the ACR responses [23].

3.6. Averaging and signal processing

An averager improves the time record signal/noise ratio by adding successive sweeps together, as discussed in the chapter on evoked response technologies. The sample frequency, the number of samples to take from the sample per second, must be high enough to represent satisfactorily the fastest components (the shortest events) in the signal. A usual rule of thumb is to take the sampling frequency of about 5 times the low pass filter setting. A good visual resolution is then obtained. The assumption behind the principle of averaging is that the same evoked potential is elicited as an addition to the non related background activity (random noise). The signal to noise ratio (SNR) improvement increases approximately with the square root of the number of averaged responses. The number of sweeps in an average is limited in practice because little improvement is obtained when the number of stimuli is increased over a certain number of sweeps. Too long a recording period may even result in degrading the response wave forms. Fluctuations of the response due to pathological or immature features of the anatomical substrates or changes in the state of vigilance cause a response jitter which itself causes loss of amplitude and change in latency measurements.

The synchronization problems are more serious for the fast action potentials, than for the slow dendritic responses of the vertex response. However, at each synaptic relay from the cochlear nucleus onward some degree of temporal integration occurs, which decreases the effect of the jitter [24]. The response runs at each higher level slower than at the lower levels. The result is a relatively low sensitivity to the response jitter. So can be understood that ACRs can occur in the absence of ABRs.

3.7. Recording analysis

The measurements in the MLR and ACR concern the latency and amplitude values of the peaks and troughs of interest. The latency of a particular wave form is defined as the time difference between the onset of the stimulus and the occurrence of a peak maximum or trough minimum. The latency can be measured by means of a cursor on the display screen. The amplitudes of waveforms are measured with respect to the baseline. Long term baseline drift may occur due to a variety of technical factors. This influences the amplitude values and adds to the variance of the amplitude measurements. The labeling of EPs has not yet been internationally agreed upon. The suffixes "P" or "N" refer to the positivity or negativity of a complex component and the additional character the position of the wave.

Artifacts occur in a variety of ways. Many interferences cannot always be

avoided, but with careful shielding of the power source, its influence can be reduced or eliminated. Bioelectric artifacts such as muscle activity, spontaneous EEG and EMG activity can largely be eliminated by proper filtering, but this is not completely possible for the MLR And ACR. Activity from eye movements can usually be rejected. Skin potentials can be avoided by using a sufficiently low electrode to skin impedance.

The acquisition of duplicate recordings in subjects under the same conditions and superimposition of the traces enable a cross comparison of the identical wave components within one subject. The use of summated evoked responses for a whole group of individuals, the composite group average, provides an additional tool for the comparative identification of wave form components. Group averages cancel out interindividual recording differences. We examined the group averaging method for intrinsic influences on the latency values but we did not find significant differences between the calculated means and the values of the individual records.

The use of a pretrimulus interval gives an impression of the background noise. The visual identification of the stimuli is a good but subjective method and requires training.

4. The auditory middle latency response: MLR

The MLR has already been described by Geisler in 1958 (27). Because of the controversy concerning the generation since initiated by Bickford in 1964 (10, 36, 49, 63) the application has been rather *limited* (23, 62, 85).

The MLR occurs in a time domain which is not clearly defined (10–100 ms after acoustic stimulation). The distinction with the ABR is determined by the appearance of the sonomotor response at about 10 ms after stimulation above 60 dB SPL. The MLR contains myogenic and neurogenic activity. The "Sonomotor Response" within the latency domain of the MLR is considerably larger in amplitude and is dependent on muscle tone, especially that of the neck. It can largely be dismissed by artifact rejection and relaxation (76). The transition of the MLR into the ACR is less discrete. The P50 is sometimes considered as a middle latency component and sometimes as being an early long latency component. The frequency contents of the ABR, MLR and ACR differ and each require its own filter settings. Hence, the overlapping components of the MLR with the ABR and ACR have not necessarily identical characteristics.

The MLRs in adults, and to a lesser extent also in young children, are reported to be remarkable stable and to be rather insensitive for changes in the state of vigilance and age (66, 81, 82).

4.1. Method

An increasing stimulation intensity results in a latency decrease and amplitude

decrease [41, 73, 123]. A stimulation rate less than 9 per second with 256 to 512 stimuli is usually sufficient [79]. In small infants we found the number of stimuli necessary for an identifiable response to be dependent on the state of vigilance. We often noticed a waxing and waning of the MLR components during the averaging procedure [109]. Whether this is due to 'fatigueability' or to changes in sleep state remains to be ascertained. The appropriate stimulus duration for MLRs is determined by the temporal integration, which is about 15 ms [24]. Recording with coupled ear references decreases the artifacts but causes also uncertainty about potential artifact origin & process. Visual analysis of the recordings can be done by inspection of the duplo records and their summation, and by comparison with the group averages obtained in a control group [109]. Measurements can be performed at the middle of the waveforms to be determined. The amplitudes are measured with respect to the baseline voltage and the latencies from the onset of the stimulus.

4.2. MLR waveform

The waveforms of the adult MLR complex and in a 3 months old infant are depicted in Figs 5 and 6. The various components are denominated. The preceding positivity is called P0 and the subsequent peaks and troughs Pa, Nb, Pb, Nc etc. In individual records the components are discernable to

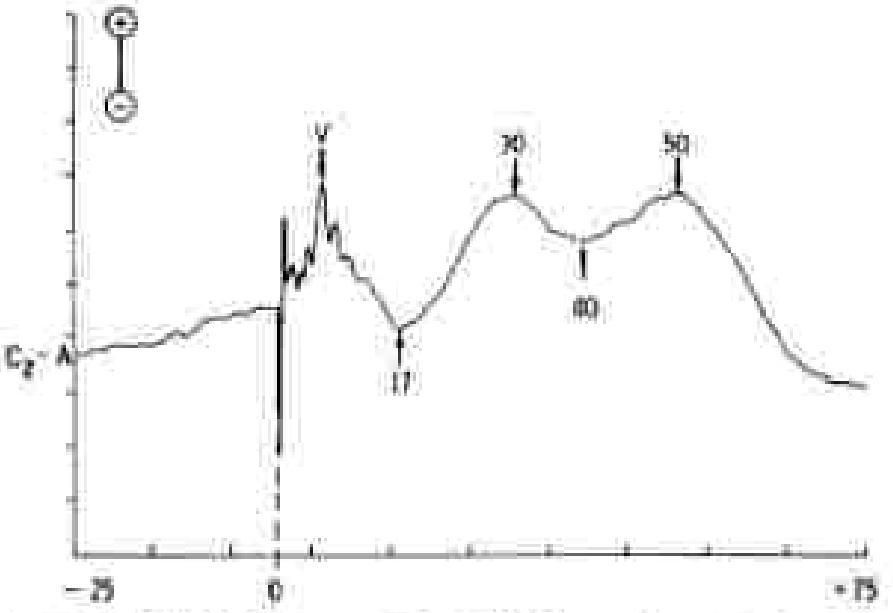


Figure 5. Adult MLR. Methods: monaural (r) 70 dB nHL, 0.1 ms rarefaction click, rate 4.3/s, BP: 3–3000 Hz. Normal values [ms]: V: 5.0 – 9.0; N_a(Na): 12.9 – 19.7; P_a(Pa): 25.3 – 31.7; N_b(Nb): 32.5 – 44.5; P_b(Pb): 34.7 – 48.5

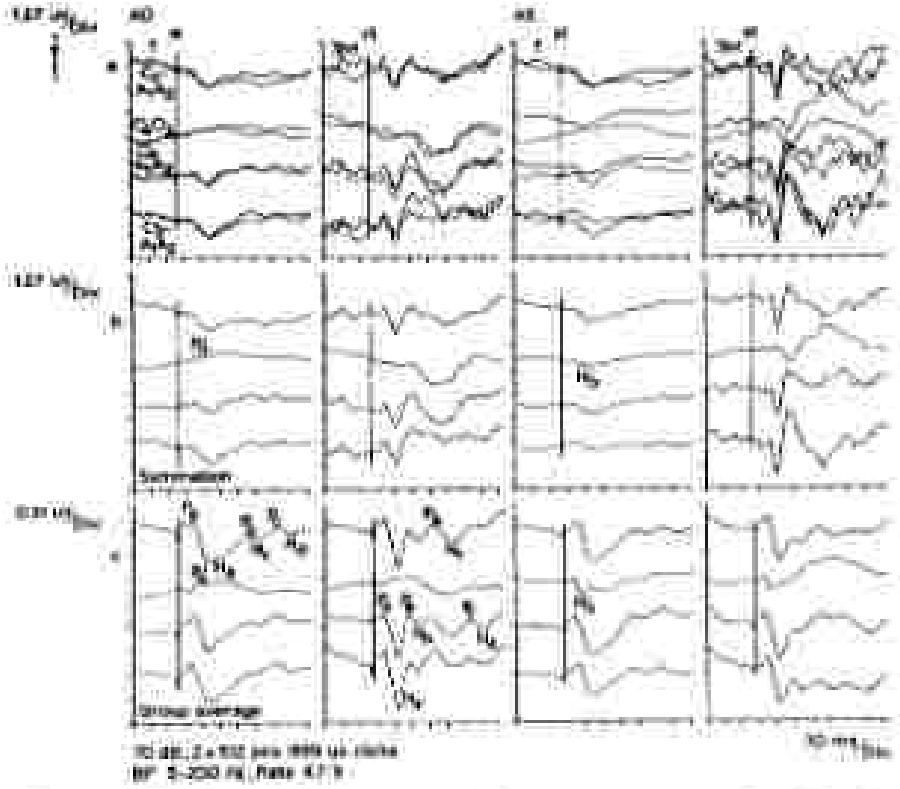


Figure 8. Middle latency auditory responses obtained in a representative newborn (T) with a follow-up at 3 months (M) after right ear (AD) and left ear (AS) stimulation. The upper records (a) show the duplo traces registered in C3–A1A2, C4'–C3', C4'–A1A2 and C3'–A1A2. The C4'–C3' derivation obtained after AD or AS stimulation is run reversed in gain after changing the side of stimulation. Subsequently the C4'–C3' traces show reversed curves. (b) Summation of the summations of the duplo records. The group averages, obtained from the summation of the individual records of all infants, and the demonstration of the various peaks and troughs are depicted in (c).

varying degrees. PO and Na constitute a better landmark in the analysis of the wave complexes than does Pa.

The waveforms in adults and infants are similar. The components are denominated by the suffix "P" or "N" with an additional suffix for the order in the complex.

4.3. Detectability

The components PO, Na and Pa are the most reproducible components of the MLR. The later components are less identifiable, especially in young infants. In early developmental stage the components tend to be fused. This results

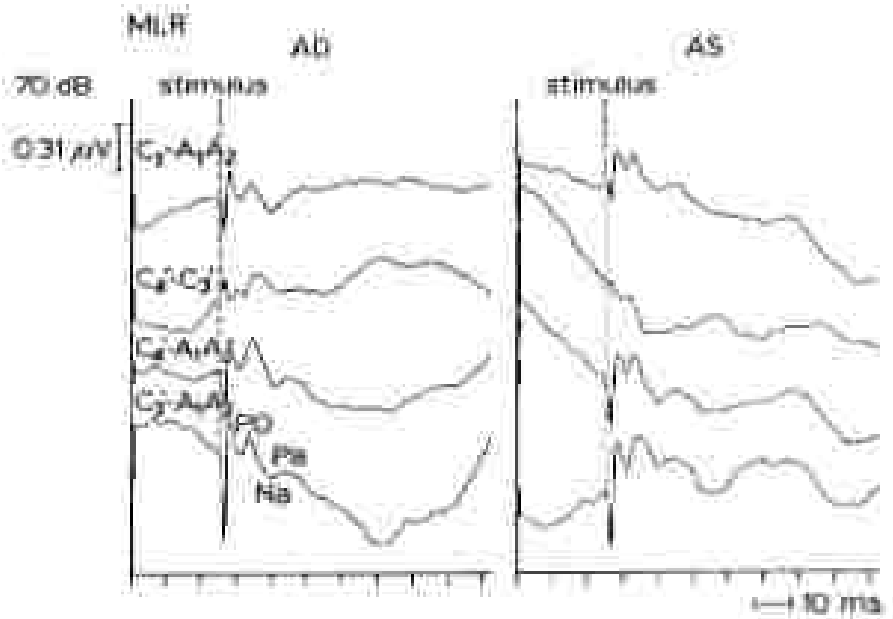


Figure 7 MLR in a preliminated infant.

in shallow waveforms with related measurement problems.

In sleep Pa is reported to be often hard to recognize. Yet, Pa is not purely myogenic as can be shown in patients who are paralysated (Fig. 7). PO shows in term infants slightly lower detectability in awake state compared with sleep. Pa shows a better detectability in awake state. Na is present in all states (90, 110).

Detectability rates show an age dependency. An increasing age results in an increasing detectability. Na is the first trough which can be recognized (from 30 weeks conceptional age (CA) onwards in 90% of the records. Pa reaches 50% at 7 months post term date. Generally, Na is detected to a greater extent than Po (62, 110). The detectability is not determined by the electrode positions. PO, sometimes considered as the equivalent of the ABR peaks V and VI, shows a detectability similar to Na.

The filter and stimulation rate influence the detectability. Filtering with a high bandpass of about 15 Hz and a stimulation rate of 2/s enhance the responses (33). The side of stimulation does not influence the detectability.

The influence of the ABR threshold on the detectability rate of the MLR results generally in a higher rate for ABR thresholds below 35 dB.

4.4. Latency and amplitude values

The side of stimulation does not influence the latency and amplitude values. The means and standard deviations of the latencies of the most important

Table 2. Comparative survey of MLR latency values [36].

MLR Components		PO	Na	Pa	
Adults					
Mendel	1969	16.7–40.8	26.6–27.3	40.2–41.3	50 dB click, BP 10–996/1500 Hz
Mendel	1977		19.1	29.2	60 dB (100 Hz pulse-train), BP 10/1500, 2V 155
Goff	1969	10[Pa]	15[N(b)]	25[P(b)]	45 dB click
Picton	1973	12	16	25	60 dB click
Vivion	1977	9.1–10.4	16.1–17.3	29.8–25.5	10/30 dB click 1,2,4,8,16/s
Musiek	1983			27.5–33.0	BP 30–100 Hz, 6/s
Celesia	1983		16.5	32.5	50 dB click, 11/s, BP 16–250
Recovery and infancy					
McRandle	1974	11.0±1.0	17.2±3.2	28.2±3.4	55 dB click, 4.3–9/s, BP 30–1250 Hz
Mendel	1977		16.3	34.3	60 dB sinusoids, BP 1/500, 25/1750 Hz
Wolf & Goldstein	1978		24		
Menkhorst & Rowland	1981	10.9±0.3	22.5–24.8		60 dB click, 9.7/s, BP 30–175 bisexually
Infancy					
Rommel	1987	8.6±0.6	18.7–21.5	25.1±3.0	75 dB HL click, 6.7/s, BP 5–250 Hz

components are listed comparatively in Table 2. A major problem in the comparison of the reported results in the literature however are the differences in the recording parameters and the subsequent labeling of the components.

The latency and amplitude values are reported to be remarkably stable for the different age groups [81, 82, 83, 155]. However, we found a significant latency decrease in preterm infants as a function of increasing conceptional age (Fig. 8). That finding is consistent with the suggestion of Galambos that the MLR constitutes a primitive function, laid down very early in development [56].

The influence of the ABR threshold on the MLR latency and amplitude values is slight if at all present. The state of vigilance has a small influence on the latency and amplitude parameters. We found in term infants a lower voltage for Na in sleep state compared to the awake and transitional state. Pa shows a lower voltage in sleep state which is in agreement with the lower detectability in that state.

4.3. Topography

Topographic differences in latency and amplitude values reflect the orientation

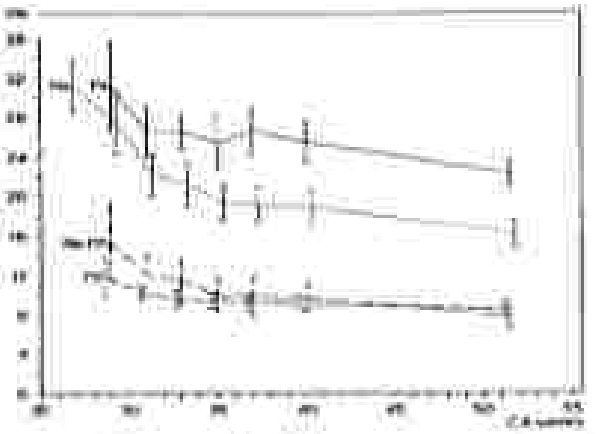


Figure 8. Means and standard deviations of the MLR latency parameters (ms) at the 8 consecutive age levels, obtained in the series derivation.

of the derivations towards the generation site. Latency differences for Na and Pa are hardly found ipsi- and contralateral to stimulation. PO shows ipsilateral to stimulation a longer latency compared with contralateral. Some consider PO to be similar with peak V of the ABR (66, 86). However, the latency differences with respect to the side of stimulation are opposite for PO compared with V (107).

Amplitudes are more dependent on the side of stimulation. PO in preterm infants shows initially a lower amplitude, but from term age onwards a higher amplitude ipsilateral to stimulation. Na has a larger amplitude contralateral to stimulation (110). In adults, Pa is the most prominent at the vertex and equally large over the temporal lobes (95, 146). In infants Pa appears the largest ipsilateral to stimulation.

4.8. Maturation of the MLR

The MLRs are obtainable as early as 25 weeks conceptional age. The development of the MLRs in waveform does not show important changes in the complex morphology (Fig. 9).

A latency decrease of the MLR components PO, Na and Pa occurs between 27 weeks conceptional age to 3 months after term date. After term date only small changes occur (110, 130). The largest latency decrease occurs predominantly in the period before term date. The most prominent latency decrease for Pa however takes place between term date and 3 months thereafter (Fig. 8).

Amplitude changes as a function of age in infants are only found between the early age levels versus the term or post-term age levels for Na and Pa. For PO no amplitude trend is established.

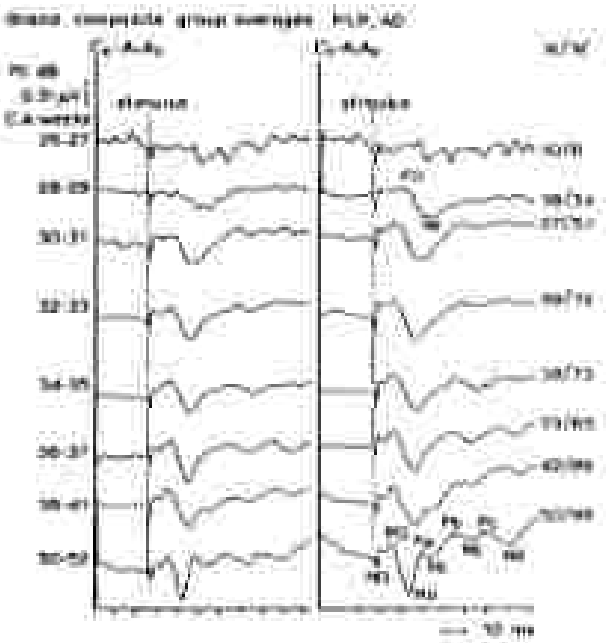


Figure 9 The grand component group averages of the MLR obtained after right ear (AD) stimulation. The side ipsilateral to stimulation is shown on the left side (C4'-A1&2), contralateral to stimulation on the right side (C3'-A1&2). The times are given for the different conceptional age levels. N: the number of infants; W: the number of contained records.

The influence of the degree of prematurity in preterm infants of different gestational age at term date is negligible. No clear developmental delay or acceleration as a result of preterm extrauterine life is found.

4.3. Generation of the MLR

The limitation of the AR technology is that only adequately synchronized generator activity can be detected. Precise knowledge of the generator would enhance the clinical value of the ARs. Many studies have been performed concerning the generation sites of the ARs. The ABRs are the best, the MLRs are less and the ACRs are the least delineated. Methods to study the generator sites include animal studies applying depth, cortical surface and scalp surface recordings. In man, the accessibility is limited. Scalp mapping studies, intracranial recordings during neurosurgical procedures, clinical cases and developmental studies throw some light on the issue.

The early waves in the MLR are associated with activity arising from the auditory thalamus and from the sensorimotor response (10). The 5N-10 slow activity, which may coincide with NO preceding PO, is not myogenic (34). Pharmacological agents also reveal properties determined by the site of

generation of AR components.

Neuromuscular paralyzing agents do not inhibit the neurogenic components of the MLR and dismiss the myogenic components (Fig. 7) (47). Hashimoto contributed NO, PO and Na to postsynaptic activity from the inferior colliculi, recording intracranially in neurosurgical patients (69).

In animals, the first positivity which is associated with the human Pa, is more prominent contralateral to stimulation suggesting a contralateral source. Lesion studies in animals with recording from the surface of the temporal lobes suggest an origin in the contralateral primary auditory cortex (55). Buchwald suggested on the basis of animal studies an origin in the reticular thalamic system, the caudal rostral midbrain reticular formation, the intralaminar thalamic nuclei and centrum medianum (11).

Clinical case studies support the theory of differential sources for the MLR from the auditory cortex and/or the thalamic radiation. Parving observed a normal Pa in a patient with auditory agnosia due to a temporal lobe lesion (97). Kraus reported normal Na and Pa components in patients with unilateral temporal lobe lesions but an abolition or amplitude reduction in patients with bitemporal lobe lesions (91), which also has been noted by Ozdamar (94).

Intracranial recordings in humans show a similarity between surface and cortically obtained records (112), although discrepancies has been reported as well (14). Goff postulated a subcortical positivity at 12 ms and cortical positivity at 25 ms (40). Recordings obtained from the surface of the temporal lobe compared with those from the scalp show a positivity at about 30 ms, which is attributed to the posterior part of the superior temporal gyrus, the parietal and frontal operculum (14).

Celesia found a potential field reversal at the level of the temporal plane for Pa using a coronal electrode chain, suggesting a dipole source for Pa at that level (17).

In a meticulous comparison between the ipsi- and contralateral records, Woods concluded that various MLR components are generated differently. Contralateral to stimulation Na showed a greater amplitude and shorter latency than ipsilateral. This was not the case for Pa and Nb (146).

The pattern of maturation of the subcortical and cortical structures involved in the acoustic signal propagation in the preterm infant and of the early components of the MLR, mainly determined by latency, suggests a subcortical generation (116). A cortical generation would result in more dramatic waveform changes in association with the huge anatomical changes in the cortical mantle in the timespan of the sixth to ninth month conceptional age. Topographic differences especially for the amplitude values of PO, Na and Pa between the sides ipsilateral and contralateral to stimulation can be consistent with a paired generation of these components.

5. The auditory cortical response: ACR

The ACR, also called the LLAEP or long latency auditory evoked potential, constitutes the third level of the auditory evoked response complex, following the ABR and MLR (Fig. 1). The ACR complex consists of relative low voltage fast waves, called the primary complex, and of high voltage slow potentials thereafter, the secondary complex. The waves occur within 1000 ms after stimulation. The ACR is an unresponse, appearing by any sudden change in an acoustic stimulation. The responses can be elicited during waking and sleep states. Partly the slow waves are determined by the physical properties of the stimuli (stimulus related), partly they are determined by cognitive processes, endogenous potentials which are event related or stimulus paradigm dependant (see Chapter on Event related potentials).

5.1. Waveform

The mature ACR waveshape has a P50-N90-P180-N250 configuration (21). The numbers relate to the mean latency values in ms of the peaks and troughs.

The response is enhanced by alertness and depressed by drowsiness. The amplitude after binaural stimulation is larger and is also dependent upon the interstimulus interval (ISI) and the stimulus intensity. Above 20 dB the amplitude increases rapidly.

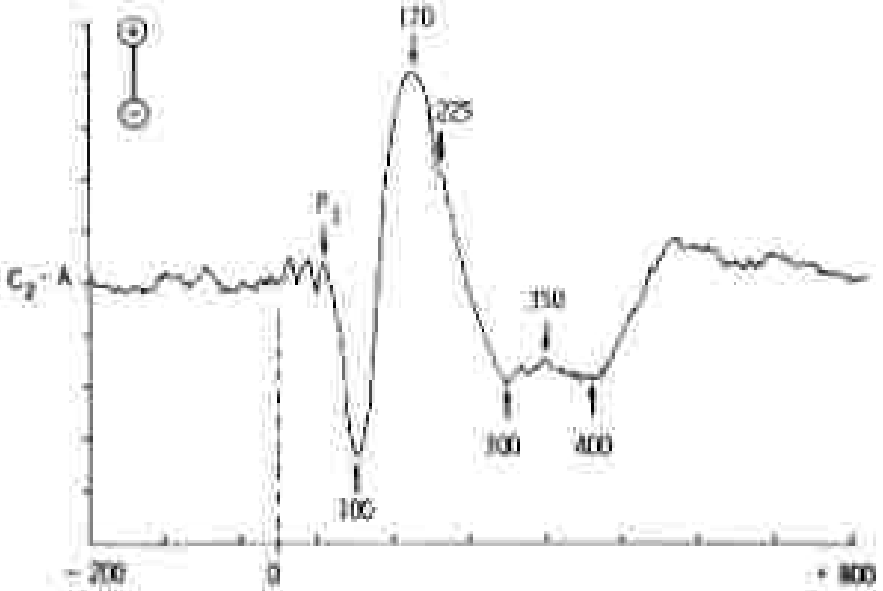


Figure 10. Adult ACR. Methods: monaural, 70 dB (ATE 0.1 ms doppler rectifying click, 0.25/s, BP: 1–250 Hz. Reversal values (ms): P_1 (not sufficiently reproducible); N_{1a} (N1): 75–115; P_{2a} (P_2): 145–195; P_{2b}–$\downarrow$ 350–380 (N_2, N_{2b}): 230–320; P_{3a} (P_3): 290–415; N_{3a} (N_3): 370–510.

The most effective stimulation rate is 1 to 2/s. Stimuli with a spectrum in the frequencies 1000 – 2000 Hz show the largest and sharpest responses. Stimulation with a frequency less than 0.5/s is less effective. Random stimulation results in a larger response. These features concern the awake recording.

Davis, who first described the vertex Potential (P180-N250) or cortical response in 1939, considered the response in sleep state as being different from the one obtained in awake state (18, 19). Asleep the response has a P280-N300-P600 configuration. The generation of the awake complex is considered to be different from the complex during sleep (21). In sleep stage 2 and 3, N600-800 appears, which coincides with increasing slow wave activity in the EEG. Davis did not note latency differences between the ipsi- and contralateral to stimulation.

Composite group averages reflect sufficiently intragroup stability of the responses in order to show consistent waveform components. The group averages serve as a template for the visual inspection of the individual records and their duplicates (Fig. 11).

Numeral latency suffixes indicating the components in the ACRs of preterm or young infants are misleading. Therefore arabic characters (primary complex) and roman numerals (secondary complex) are used to show the sequence of the components in the AR complex. In the primary complex the low voltage components consist of Na, Pa, Nb, P1 and N1; in the secondary complex the high voltage components P2, N2, P3, N3 and P4. In young infants P2 and N2 are the hallmarks in the analysis of the recordings.

The premature waveform is characterized by its morphology changes between 27 weeks conceptional age and 3 months post term. Because of this morphology changes the components of the premature waveform are labeled by means of an additional suffix "p" (Fig. 12).

5.2. Maturation of the ACR

The vertex potential has its mature morphology some weeks after term date (20). The ontogenesis of the ACR, thus of the central reactivity on acoustic stimuli, takes place when the ear canal is still closed, the middle ear not well ossified, the inner ear only partially developed and when the subcortical pathways are in the process of their anatomical maturation (28). As mentioned, the most outstanding feature of ACR maturation is the change in the waveform of the ACR complex rather than latency and/or amplitude changes as it were in the development of the ABR and MLR (109, 110) (Fig. 12).

After the appearance of the ACR at about 22 weeks conceptional age three developmental stages can be recognized. The premature stage up to about 36 weeks conceptional age, characterized by a negativity N2p and subsequent positivity P3p. This stage is followed by the transitional stage, in which mainly low voltage records can be obtained in which the components are difficult to identify. Finally the adult wave form appears gradually between term date

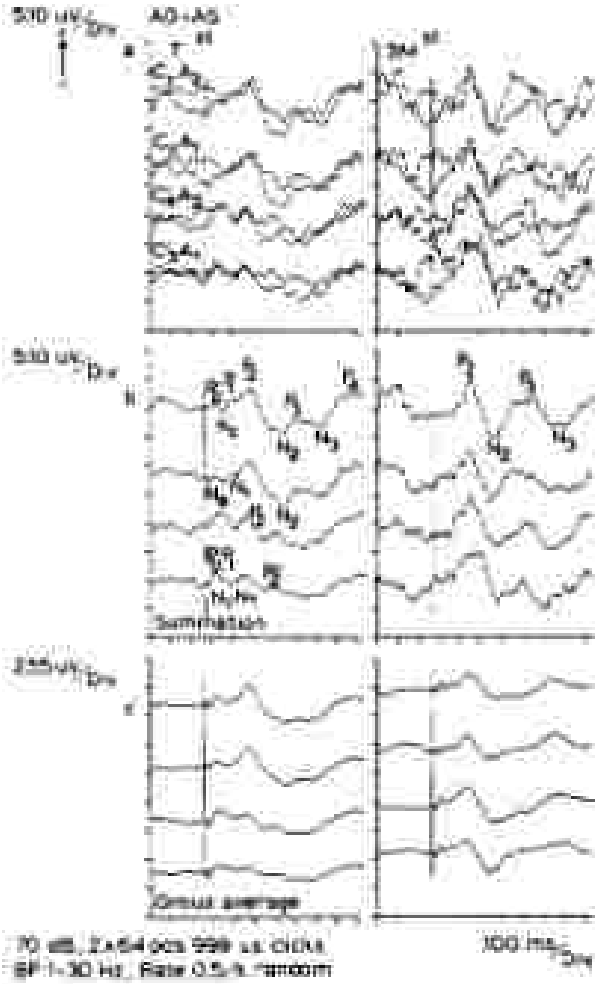


Figure 11. Duplex traces of the recording of the auditory cortical response of a representative normal healthy newborn at term (T) with a follow up at 3 months (3M) after binaural stimulation (ears at 25% of the analysis time (800 ms) (B) superposition of the duplex recording in (a) with decomposition of the subsequent peaks and troughs (c) complete group averages of the normal newborns at term date and at 3 months of age. The different cortical and cortical temporal derivations are denoted in (d).

and 3 months thereafter. In the primary complex the fast negative component Na preceding PbP1 is the most consistently present in all 3 stages. When P2 becomes more prominent, also N1 becomes distinguishable. Before 30 weeks CA P2p is not more than a notch in the descending negativity N2p which follows PbP1. At term date P2 is often hard if recognizable at all. This fits well the multiple source theory for the generation of P2.

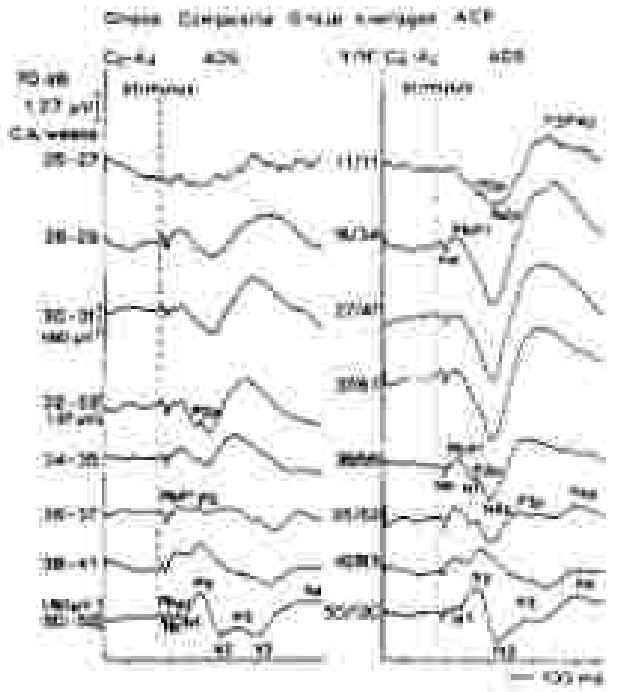


Figure 22. The grand computer group averages of the AEP, obtained after binaural stimulation at 8 CA levels. Upward deflections mean positivity. The derivations from the vertex and central temporal area referred to A2 are shown. CA = conceptional age, ADS = right and left ears, N = number of infants, N = number of maximum records.

3.3. Topographic maturation

Topographic differences of the ACEs are found comparing midline anterior and posterior derivations (141). Comparison of vertex and central temporal derivations shows consistent differences throughout the development towards the adult waveform. Latency and amplitude differences are largely dependent on the waveform changes. The primary complex shows amplitude differences to a greater extent than latency differences. In very preterm infants Na is less negative at the vertex and PbP1 more positive. After term date Pb becomes more positive central temporally. The secondary complex shows significant topographic differences for various components central temporally compared to the vertex. In the premature stage of development N2p is more negative at the vertex. P2 is in the transitional and mature stage more positive at the vertex (108, 111).

3.4. Detectability

The detectability is not dependent upon the derivations. With increasing age,

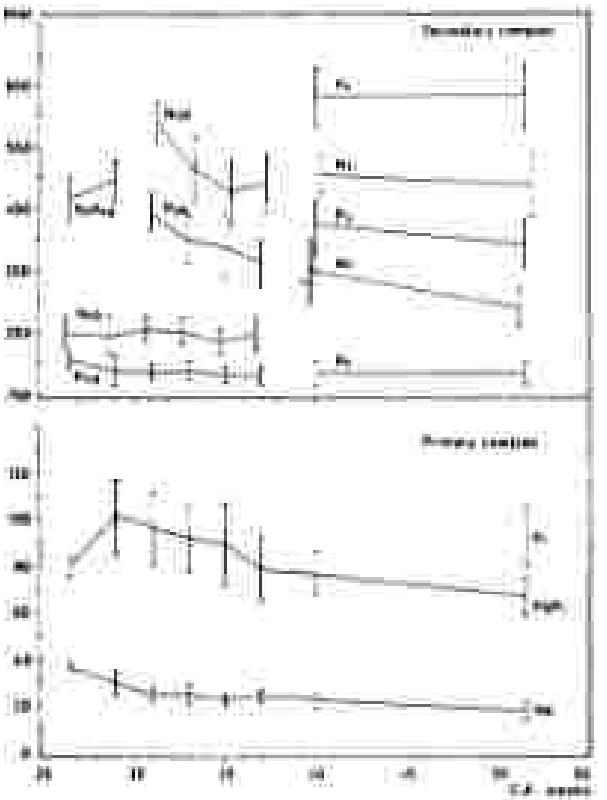


Figure 11. Means and standard deviations of ACR latency values measured in 4 CA levels obtained in the neonatal intensive care unit.

detectability increases. Sleep stages influence the detectability also. A decrease is seen in transitional sleep stage, especially with respect to the secondary complex. In young infants the detectability of the most stable components Na, P2, N2 and P3 in single records does not exceed 80%. If one performs repeat records, a detectability rate can be achieved of 100%. Generally the major ACR components are equally detectable as the prominent peak and troughs of the ABR and the MLR.

5.5. *ACR parameter values*

The latency values for the adult ACR are tabulated under Fig. 11. Developmentally the largest changes occur at the infantile stages. The latency decrease at the different stages of development are shown for the most important components of the primary and secondary complex in Fig. 11. The amplitude values of the primary complex do not change significantly, but do for the slow late components as discussed in the paragraph on the topographic

differences. An amplitude increase can be found especially in the temporal derivations for P2 and N2.

The primary complex shows developmental features such as latency decrease for Na and PbP1 and separation of fusion components. Being MLR components, the ACR test protocol is less suitable to study the primary complex than the special MLR protocol.

The influence of the degree of prematurity on the development of the ACR latency parameters is small, if present at all. Kurtzberg using tone bursts and speech sounds as stimuli observed a maturational delay of the term waveform in preterms compared with mature newborns (67). Such differences are described for the maturation of the visual evoked responses (119). It seems that maturational delay due to prematurity opposite to the extrauterine life depends upon stimulus modality and type of stimulation.

Another factor influencing the ACR parameter values is the state of vigilance. In active sleep the late slow components show intraindividually a decrease of latency and amplitude values compared with awake state (8, 70). The interindividual variation however is such that the influence of the sleep state is submerged in that variability (51, 67, 140). Akiyama did not observe any sleep stage determined interindividual latency differences but he found higher voltages in quiet sleep than in active sleep 3].

The influence of the background EEG does not have a significant effect on the amplitudes of N1P2. It appears that the decrease of the variability with increasing age occurs with the collateral changes in the spontaneous EEG-morphology as an expression of common electrophysiological maturational denominators (43).

3.6. The ACR generation

The ACRs, although first detected by Davis in 1939 as a vertex response, are the least delineated with respect to their generation. The reports concerning the generation of the ACRs are difficult to compare in view of the differences in approach and the protocol designs. Recent literature contains studies in animals and in man, from the scalp and the cortical surface as well as from depth probes.

Chatrian recorded responses to clicks from the cortical surface to the ongoing EEG. The response was found to be rate dependent. With increase of stimulation rate, the nature of the response showed features of an on-response, a following response and off response (18). Celesia recorded also slow wave reactions N60-P120-N220 from the surface of the cortex (15). Extension of this observation with depth electrodes resulted in different wave sequences obtained from the primary auditory cortex compared with the perisylvian areas. The primary auditory cortex A1 showed a P15-N20-P32-P62-P120-N220 sequence, the perisylvian areas P40-N62-P96-N142-P261-N328-P360. The early components proved to be more stable. The responses from the lateral surface of the superior temporal gyrus, the frontal and parietal operculum were variable

unit small. Monaural stimulation showed contralaterally a larger response than that ipsilaterally to stimulation. The wave forms were comparable with those observed in other primates. The response properties of the primary and the secondary cortex show a tonotopic order (147). In cat this was shown by Schreiner (118). Sterniechneider recorded from the scalp and simultaneously multiple unit activity in monkeys (123). He concluded that the slow waves of the ACRs were volume conducted potentials of deep origin.

Scalp recordings are applied in human in mapping studies (145), maximal field power studies (70) or just phenomenologically by description of the peak and trough properties of the ACR. The study of Vaughan and Ritter is classic (134). By using a multiple electrode array they found a N20-P40-N60-N100-P200 wave sequence. A potential reversal over the supratemporal plane suggested a generation of the primary components and P200 in that area. The use of irregular stimulation resulted in a clear P300, probably from the parietal temporal cortex. Knott, using a different reference, repudiated the conclusions of Vaughan (60). Smith found a field reversal between the applied nasopharyngeal and scalp electrodes and suggested a deep dipole source for the components between 120–400 ms (126). Components with a latency shorter than 120 ms do not show such reversals. Goff separated the myogenic and the neurogenic components of the ACRs. Myogenic activity over the different areas of the scalp could be found during the first 90 ms after stimulation dispersed between the neurogenic activity. The neurogenic vertex potential N115-P180 occurred maximally at the vertex. The P190-N200 components were attributed to the temporal lobe and might well be modality specific, though usually overpowered by the vertex potential (40). Wolpaw using a balanced non cephalic (hand, knee) reference found the components between 20 and 90 ms originating from the (superior temporal) plane. The components between 60 and 250 ms are generated by multiple sources from different brain regions (144). Mathematical analysis of the records, obtained by a coronal chain, led Perronet to the conclusion that single sources cannot explain the ACR changes as a function of derivation (98). On the basis of a theoretical dipole model, applied also to the results of Vaughan and Perronet, Scherg came to a similar conclusion (115). In the dipole model uni- and bilateral, vertically and horizontally oriented dipoles can be simulated. The vertex response can be understood as being generated by such vertical and horizontally oriented dipoles. The data analysis of Vaughan and Perronet showed that the waves between 60–250 ms match a generation of two bilateral sources within the temporal lobe. The sequence of the components fits a sequential activation of the primary and secondary auditory cortices.

The developmental wave form changes in preterm infants and the vertex versus central temporal differences point also to a differential development and generation of the ACRs components (111). The secondary complex of the ACRs can be considered to reflect the integrated influence of the auditory cortical and partially subcortical levels. The potentials recorded from the scalp stem from currents generated by among others activated neuronal elements.

During the ontogenesis of the ACRs huge changes occur parallel to the morphological substrates. The lateral surface of the temporal lobe is smooth until 23 weeks conceptional age and the delineation of the middle and posterior superior parts coincide with the appearance of the premature ACR. The transverse temporal Heschl 's gyrus appears between 28 and 31 weeks CA. During the last trimester of gestation gyri and sulci become deeply folded with a subsequent development of secondary and tertiary gyri and sulci at term date and the month there after. Simultaneously the cortex shows a prominent stratification (28). The late development status as the ACR waveform obtains its mature shape.

The premature ACR can be understood from a short circuit between the deep and more superficial cortex, due to a higher water content of the immature brain (98). In premature the spatial orientation of the cortex surface is thus relatively unimportant with respect to the electrical field orientation. At term date, as the tertiary gyri appear, the mature waveform becomes identifiable. The cortex itself probably generates most of the ACR activity and the orientation of the gyri should now contribute to the "W" shaped ACR. P2, however, appears earlier and is disturbed at term date more prominently over the vertex. A deeper source for P2 should therefor be postulated. Functional correlative studies also support a different generation for the ACR components. So postulated Eisenberg for P2, which appeared more prominently over the vertex than temporally, a generation by an alerting reaction. Other processes in audition are associated with N2 (29).

8. Clinical application

8.1. *Neuroaudiology*

Auditory evoked potentials can help to detect lesions of the auditory pathways, not only in the lower brainstem but also in the acoustic thalamus, radiation and cortex.

Lesions in the acoustic radiation cause a reduction or loss of the initial temporal middle latency activity with preservation of the late cortical components (116). Lesions in the auditory cortex cause unilateral reduction of both the middle and late components. Bitemporal cortical lesions result in loss of Pa and late cortical components in the presence of normal ABRs (42), though normal MLRs are reported as well (97).

8.2. *Cerebrovascular disease*

Generally event related potentials are applied to the detection of dysfunction and functional recovery after cerebro vascular accidents. Combinations of event and stimulus related potentials have also been used. Papanicolaou illustrated the role of the right hemisphere in the recovery of language in aphasics.

The frontal cortex, if lesioned, shows an amplitude increase of the potentials after contralateral stimulation (96). Unilateral temporal parietal lesions the amplitude of N1 without changes of P2 (59).

6.1. Tumors

MLRs and ACRs are applied rarely in patients with intracranial space occupying lesions. Tumors in the cerebello pontine angle cause in 50% MLR abnormalities. MLR abnormalities are even more strongly supporting the presence of a intracochlear lesion than ABRs do (105).

6.4. Head injuries

Normality or abnormality of the Pa in the MLR and of the ACR are reliable in the prediction of the outcome in patients with severe head injuries and seem to be even more reliable than other instrumental data as CCT scanning and EEG (57, 72, 92).

6.5. Coma

Preservation of MLRs and ACRs in comatose patients is related to survival, but not the preservation of the MLR alone. The pattern of MLR preservation is not related to the quality of survival (106). Kaga, however, found the MLR clearly a predictor for survival in comatose patients (50).

6.6. Hydrocephalus

A variety of abnormalities of evoked responses in hydrocephalic children are described (136). Investigations by means of MLRs and/or ACRs are sparse compared with those by means of the ABR and numerous case reports.

6.7. Huntington disease (HD)

Patients with Huntington Disease have been investigated by means of multimodality evoked potentials. Compared with matched controls, HD patients show a longer latency for N100 (N1) in the ACR. Amplitudes are generally reduced. The early components are usually normal (54).

6.8. Friedreich's Ataxia (FA)

Although abnormal ABRs are found in FA patients, cortical ARs appear essentially normal. Progressed stages of the disease are accompanied by latency prolongation attributed to dying back pathology by spinal cord and dorsal root ganglion degeneration (4). In the ACR, only an increase of the amplitude of N85 suggests cortical dysfunction (131).

6.8. Demyelinating disease

A large body of reports exists with respect to visual, somatosensory and brainstem auditory evoked responses in varying combinations in multiple sclerosis and degenerative diseases of the white matter, the leuko dystrophies. MLRs and stimulus related ACRs however are hardly studied in these diseases.

6.10. Perinatal disorders

Normalization of abnormalities in appearance or latency values of ACRs, found in acute stages of cerebral distress, correlate well with a normal outcome of these infants. Slow recovery of the abnormalities within 2 to 3 months are predictive for sequelae as cerebral palsy and/or mental retardation. If abnormalities persist beyond 6 months of age, the infants show more severe neurological damage (44). In infants with intracranial hemorrhage, the polygraphic accuracy EEG proved to be more valuable with respect to the prognosis than ACRs, although cortical ACRs were closely correlated with a favorable outcome (137).

In young children with cerebral palsy the ACRs show a latency increase for N1, P2 and N2, reflecting abnormal signal propagation in the auditory system (77).

Barnet reported abnormalities in ACRs in infants with marasmus, even persisting after treatment (9). Malnutrition apparently has long lasting effects on developing brain dysfunction.

6.11. Mental retardation

An increase of ACR amplitudes has been noted in mentally retarded patients. This has been attributed to a deficit of inhibitory mechanisms, which normally results in response habituation (6, 7, 122). However, audio-visual evoked responses show a much lower amplitude than would be predicted from unimodal stimulation. This has its implications on the views on attention and inhibition in retardates (125).

Normally, ACR amplitudes decrease with increasing older age. This phenomenon does not occur in Down syndrome (13).

6.12. Psychopharmacology, neurotoxicology, anesthesiology

Generally it is reported that depressant drugs diminish the amplitudes of the components of the ACRs. Such changes can be used as a measure for central psychotropic drug effect. However, many drugs have multiple actions. The contribution of the ACRs in drug evaluation remains to be investigated (68). Antipsychotic drugs tend to increase the ACR amplitudes (129).

Barbiturates have different effects on the auditory afference. Except for peak 1 augmentation no effects occur in the ABR during barbiturate coma.

The MLR ipsilateral and contralateral Pa, but Pa reappears with the emergence of brainstem neurologic signs (45).

Effects of anesthesiological agents can be investigated similarly. The depth of isoflurane anesthesia, for example, can be followed by the amplitude reduction and latency increase of the MLR waves and Nb (50).

The special characteristics of ACRs to complex auditory stimuli, such as phonemes or words, make ACRs suitable to assess the effects of neurotoxicants, such as lead, on complex stimulus encoding mechanisms involving higher order cortical processes (7, 93).

Usually multisensory evoked potentials (EPs) are applied for experimental purposes regarding neurotoxicology (104) and degenerative neurological diseases as Huntington disease, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis, dementia and cognitive dysfunctions as learning disabilities.

8.13. *Psychiatry*

The event related potentials, the P3 or P300, the contingent negative variation or CNV and the cortical slow potentials are used for research and clinical psychiatric purposes. Stimulus related potentials are applied to a lesser extent. Shagass found in chronic schizophrenics high amplitudes for the early ACR components, but low amplitudes for the ACR components after 100 ms. Topographically, larger amplitudes are found for the early components, predominantly in the posterior leads. ACR amplitudes deviate in neurotics in an opposite manner compared with schizophrenics (123). Voltage attenuation for the early components P1, N1 and P2, however, is also reported in schizophrenics. Pfefferbaum studied schizophrenics and found normal ABRs, higher voltages for P1 and P2 but a smaller negativity for N1. The latency for P2 was decreased (98). Acutely ill schizophrenics show a shorter latency for N1, which normalizes after haloperidol with concurrently a latency increase for P2 and N2 and an amplitude increase for P2-N2. This has been attributed to an overarousal state in schizophrenia (117).

In studies on attention and attention deficit disorders it appears that N120 is closely linked to selective attention (101).

In a group of normal, autistic and retarded children, auditory and visual evoked potentials differentiate between pathological groups and normal children, but not between autistic and retarded children (74). ACR studies have been performed in autistic children by Ornitz under varying conditions. During REM sleep the amplitude of N2 are larger than in normal children, both in ocular quiescent and eye movement burst phases of REM sleep. This was attributed to a vestibular dysfunction in autistic children (91).

8.14. *Sleep disorders, epilepsy*

The MLR and ACR have not been investigated systematically in epilepsy. Prosiman examined sleep deprived controls and narcoleptics. Sleep deprivation

induced an increase of the P2–N2 and N1–P2 amplitudes compared with non sleep deprived controls and narcoleptics. The amplitude for N2 is conversely related to the level of alertness. The N1–P2 amplitude depends on attention and decreases by emotional activation. Narcoleptics show an increase of P2–N2 in naps, not containing REM sleep and ACR amplitudes in REM sleep were even smaller than in wakefulness. The small ACR amplitudes preceding REM might be an sign of pathologically increased REM in narcolepsy (102).

6.13. *Language disorders*

Middle and late cortical evoked potentials have been applied in children with motor speech and language disorders.

The MLR can be used to test neural activity around the level of the auditory thalamus and the primary cortex in the temporal lobe in patients otherwise hard to test for central hearing. The slow components of the ACR test the cortical auditory association areas in the temporal and parietal lobes with respect to speech and language perception. The ACR and the event related potentials are independent of culture and audiometric procedures. The slow components reflect directly the activity of the substrates for perception and performance and are also sensitive for cerebral lateralization (128).

The amplitudes of the MLR in motor speech disturbed children are larger at the mastoid and temporal electrode sites. The ACR shows larger amplitudes at the vertex in motor speech disturbed children, which has been attributed to underactivity of the cortical inhibitory system. The ACR in language disordered children exhibit an abnormal left temporal hemispheric dominance (75).

6.14. *Clinical application: Remarks*

The MLRs have found only limited clinical application compared with the ABR and to some extent the ACRs also. Clinical application was limited primarily to the detection of the hearing threshold and to the obtaining of frequency specific audiometric information by using various stimulus modes such as clicks, tone pips, tone bursts and filtered clicks (22, 84, 85, 103). The audiological application of the MLR seems useful in the determination of the thresholds for low frequencies (500–1000 Hz). For audiometric purposes the MLRs seem less useful than the ABR and SSR (23, 78).

The MLR, as link between the ABR and the ACR in the auditory signal propagation might be of importance in the analysis of the quality of the auditory afference. Clinical studies however are thus far limited to the investigative level in cortical deaf or language impaired patients, as also mentioned above and with respect to the generation discussion (61, 62, 94, 97). The fact that MLR studies mainly have been performed in patients with telencephalic lesions might well be the reason for the lack of unequivocal clinico pathological correlations with 'abnormalities' in the MLR. In comatose patients a good

correlations has been found (45, 46, 56). For general application of the MLR as a diagnostic tool, further investigations with respect to the generation sites of the MLR components with respect to neurological and audiological dysfunctions are needed.

The clinical application of the ACR in the diagnosis of central auditory dysfunctions are very limited, because of the lack of sufficient clinico pathological correlative studies. The ABR has replaced the ACR for audiometric purposes. For the purpose of neurological, psychiatrical and psychophysical investigations event related potentials are more in use than the stimulus related ACRs.

References

1. Aby M: Electrical responses of the human brain to acoustic stimulus. Tohoku J Exp Med 1954; 60: 47–58.
2. Adrian EM, Ivanov DBT, Webster WR: Central mechanisms of hearing. In: Gregor HR (ed.): Handbook of Physiology. Am Physiol Soc Bethesda, Maryland, 1958, sect. 1, vol III, part 2, chapt 16, pp 675–737.
3. Akimoto Y, Ishida FJ, Schulte MA, Pierce JE, Allen AC: Auricular evoked responses in premature and full term newborn infants. EEG Clin Neurophysiol 1968; 25: 511–519.
4. Antinoro A, Rossi L, de Sessions G, Bindi A, Pagni P, Zappoli R: Auditory evoked potentials (early, middle, late components) and audiological tests in Friedreich's Ataxia. EEG clin Neurophysiol 1968; 38: 37–47.
5. Arieti JC, Samson R, Blanchet RE: Evoked potentials in the assessment of neurotoxicity of isoniazid. Neurobehav Toxicol and Teratol 1985; 7: 299–306.
6. Barrett AR, Lodge A: Click evoked EEG responses in normal and developmentally retarded infants. Nature 1967; 214: 252–255.
7. Barrett AR, Ohlrich ES, Shanks BL: EEG Evoked Responses to repetitive auditory stimulation in normal and Down's syndrome infants. Develop Med Child Neurol 1971; 13: 321–329.
8. Barrett AR, Ohlrich ES, Weiss IP, Shanks B: Auditory evoked potentials during sleep in normal children from ten days to three years age. EEG clin Neurophysiol 1975; 39: 29–41.
9. Barrett AR, Weiss IP, Serafin MV, Ohlrich ES: Abnormal auditory evoked potentials in early infancy malnutrition. Science 1978; 201: 458–459.
10. Bickford RG, Jacobson JL, Cody DTR: Nature of averaged evoked potentials to sound and other stimuli in man. Ann NY Acad Sci 1964; 112: 204–223.
11. Buchwald JS, Huang C, Norman RF, Hayes CM, Brown KA: Middle- and long-latency auditory evoked responses recorded from the vertex of normal and chronically hemiplegic cats. Brain Res 1981; 205: 91–109.
12. Caffaul MB: The potential area of the medial geniculate body of the cat defined by the auditory response gradients of single units. J Neurosci 1983; 3: 2350–2360.
13. Calder DA, Overton RE, Madson JA, Scharnberg T, Beck EC: Life-span changes in the averaged evoked responses of Down's syndrome and non-retarded patients. Am J Mental Deficiency 1976; 82: 588–605.
14. Calvin GG, Broughton RJ, Kamimura T, Branch C: Auditory evoked responses from the exposed human cortex. EEG clin Neurophysiol 1968; 24: 458–468.
15. Calvin GG: Organization of auditory evoked responses from the human brain. Brain 1970; 93: 401–414.
16. Chiarenza GH, Petersen MC, Lassen JA: Responses to clicks from the human brain: Some depth electrographic observations. EEG clin Neurophysiol 1980; 17: 479–489.
17. Celesia MM: Cortical topography of 40 cps auditory evoked potentials (MLAEPs)

of man. EEG clin Neurophysiol 1982; 53: 27–236.

18. Davis H, Davis PA, Loomis AL, Harvey EN, Hobart G. Electrical reactions of the human brain to auditory stimulation during sleep. J Neurophysiol 1939; 2: 500–514.
19. Davis PA. Effects of acoustic stimuli on the waking human brain. J Neurophysiol 1939; 2: 494–499.
20. Davis H, Osterle S. Mechanisms of auditory evoked potentials. Semin Audiol 1980; 1: 29–35.
21. Davis H. Responses and other responses in electric response audiometry. Ann Otol 1976; 85: 1–14.
22. Davis H. Principles of electric response audiometry. Ann Otol Rhinol Laryngol 1976; suppl 28.
23. Davis H, Hirsh SK, Shelnutt JL, Bowers CD. Frontal midline responses in electric response audiometry. Ann Otol Rhinol Laryngol 1973; 82: 206–218.
24. Davis H, Hosh BR, Pujadas GB, Pinedo C. Response sensitivity and thresholds of local stimuli suitable for electric response audiometry. Acta Otol 1984; 25: 50–54.
25. Dawson GD. Cerebral responses to electrical stimulation of peripheral nerve in man. J Neurol Neurosurg Psychiatr 1947; 10: 137–140.
26. Dunling EC, Chi JG, Gilles FH. Tricomputic development: changing gyral patterns. In: Gilles FH, Leviton A, Dunling EC (eds). The Developing Human Brain. John Wright PSG Inc, Boston, 1983, pp 94–104.
27. Duncan RF, Cullum DA. Cortical evoked response and cognitive dysfunction in concussion and Down's syndrome individuals. Arch J Mental Def Disord 1978; 83: 301–307.
28. Eggermont G. Development of hearing and response behavior in visual stimuli: behavioral studies. In: Development of Auditory and Vestibular Systems. Romand R (ed). Acad Press, New York, 1983, pp. 311–336.
29. Eisenberg RB. Development of hearing in children. In: Development of Auditory and Vestibular Systems. Romand R (ed). Acad Press, New York, 1983, pp. 259–272.
30. Elimpoos RF, Dansky T, Nelson R, Lathrop GH. Variability of auditory evoked potentials in human newborns. EEG clin Neurophysiol 1974; 36: 155–162.
31. Engel R. Early waves of the electroencephalic auditory response in neonates. Neuropädiatrie 1971; 2: 147–154.
32. Ertan RF, Buchwald JS. Midlatency auditory evoked responses: Differential recovery cycle characteristics. EEG clin Neurophysiol 1984; 58: 417–423.
33. Filer RC, Jerger JF, Noll DM. Effects of stimulus rate on MLR and BRD in neonates. Am Speech Hear Ass 1980; 26: 110.
34. Fria TJ, Saad MM, Doyle WJ, Carvalho JJ. Slow negative evoked potentials in the rhesus monkey (macaca mulatta): Exogenic versus endogenic influences. EEG clin Neurophysiol 1984; 58: 61–65.
35. Goldsmith A, Saunder F. Cytoarchitectonic organization of the human auditory cortex. J Comp Neurol 1986; 190: 957–970.
36. Gottardi R. Maturation of the auditory evoked potentials. In: Clinical application of evoked evoked potentials in peripheric medicine. Ed. Gu Casereta & Prpkopczyczak Exc Medica, Amsterdam, 1982.
37. Gruhle CD, Pantlingl LR, Rosenblith WA. Dynamical responses in somatic cells in man. Science 1956; 126: 1213–1214.
38. Gibbon CD. Hormonal programs in the mammalian. Trends in Neurosci 1985; 8: 160–165.
39. Graf WR, Allison T, Lyons W, Pinedo JC, Cruse R. Origin of short latency auditory evoked potentials in man. In: Dawson M (ed). AEPs in man. Psychopharmacology committee of IPs. Karger, Basel, Progress in Neurophysiol 1977; vol 2, pp 59–80.
40. Graf WR. The long latency components of the auditory evoked potentials. In: Naunton RF, Fernandez C (eds). Evoked electrical Activity in the auditory Nervous System. Academic Press Inc 1978; pp 505–524.
41. Goldstein R, Rodman LB. Early components of averaged evoked responses to rapidly repeated auditory stimuli. J Speech Hear Res 1967; 10: 697–705.

42 Graham J, Greenwood R, Leahy J: Cortical deafness. J Neurol Sci 1980; 48: 35–49.
43 Grattan LJ, Kohl J, Cooke RG, Cooper JR, Wellman HN: The maturation and interrelationship of EEG patterns and auditory evoked responses in premature infants. EEG clin Neurophysiol 1974; 36: 367–375.
44 Hirakawa S, Watanabe K, Hara K, Miyoshi S: The evolution of visual and auditory evoked potentials in infants with prenatal disorder. Brain Dev (JE); 3: 159–166.
45 Hall JW III: The effects of high-dose barbiturate on the acoustic reflex and auditory evoked responses. Acta Otolaryngol 1979; 88: 347–348.
46 Hall JW, Brown DP, Mackey-Bolgiano JR: Positive applications of otoacoustic emissions and middle latency evoked myogenic recordings. Int J Ped Otorhinolar 1985; 9: 201–218.
47 Hecker LA, Hecox K, Nunn RJ, Morris MD: Effects of middle component auditory evoked potentials. Arch Otolaryngol 1977; 103: 133–137.
48 Hetherton JM, Howe ME, Anatomy of the adhesive auditory apparatus system of mammals. In: Handbook of Sensory Physiol 1979; Vol 5, Coupon S, Kuifel WD, Neff WD (eds). Springer, Berlin.
49 Hoshimoto I: Auditory evoked potentials from the human midbrain: slow brainstem responses. EEG clin Neurophysiol 1982; 53: 652–657.
50 Houghton CHH, Thornton C, Rosenhall M, Jones JG: Effects of influenza on the auditory evoked response in man. Br J Audiol 1987; 21: 257–262.
51 Hrbek A, Hrbkova M, Linnell MH: Somatosensory, auditory and visual evoked responses in newborn infants during sleep and wakefulness. EEG clin Neurophysiol 1969; 26: 597–602.
52 Jasper HH: The ten-twenty electrode system of the international federation. EEG clin Neurophysiol 1958; 10: 371–375.
53 Jerger J, Chmiel R, Chase D, Frost JD: Rise and fall dependencies of the middle latency response in infants. Audiol 1987; 26: 209–283.
54 Jonkman EJ, Stegeman C, Marcelli HL, Brouwer RA: Auditory and visual evoked potentials in Huntington's disease. 1982 and Clin Neurophysiol 1984; 57: 515–518.
55 Kaga K, Hink RF, Tsuzuki T, Suzuki J: Evidence for a putative auditory origin of a middle latency auditory evoked potential in rats. EEG clin Neurophysiol 1980; 48: 254–260.
56 Kaga K, Kagan T, Tokumori K, Marsh RR: Auditory short, middle and long latency responses in auditory evanescent patients. Laryngoscope 1985; 95: 52–55.
57 Kaiser DH, Marshall LF, McCarthy CB, Klauber MR, Bickford RG: Localizing and prognostic value of auditory evoked responses in coma after closed head injury. Neurol 1982; 12: 299–302.
58 Kiang NYS: Peripheral neural processing of auditory information. In: Geiger SR (ed), Handbook of Physiology. Am Physiol Soc, Bethesda, Maryland, sect 1, 1984, vol III, part 2, chapt. 13, pp 639–674.
59 Knight RT, Hillyard SA, Woods DL, Neville J: The effects of frontal and temporal parietal lesions on the auditory evoked potential in man. EEG clin Neurophysiol 1980; 50: 112–124.
60 Kurtzberg A, Tipton AC, Marshall RE: Peripheral and brainstem contributions of the vertex components of the human auditory evoked response: a comparison. EEG clin Neurophysiol 1971; 31: 166–168.
61 Kraus N, Ozdamar O, Hier D, Stein L: Auditory middle latency responses (MLRs) in patients with cortical lesions. EEG clin Neurophysiol 1982; 54: 275–287.
62 Kraus N, Smith DI, Reed NL, Stein LK, Cartee C: Auditory middle latency responses in children: Effects of age and diagnostic category. EEG clin Neurophysiol 1985; 62: 343–351.
63 Kraus N, Smith DI, Reed NL, Wagner E, Cowan J: Auditory habituation and middle latency responses in the human premature. Hear Res 1985; 17: 13–23.
64 Kraus N, Smith DI, Mahoney T: Reticular formation influences on developing middle latency responses. Audiology 1987; 26: 257–268.
65 Kraus N, Reed N, Smith DI, Stein L, Cartee C: Hyperactive brain settings affect the generation

of MLRs in humans. EEG clin Neurophysiol 1967; 18: 234–236.
66. Kappenman B. Manifestations of the early middle response. Scand Audiol 1980; suppl 13: 145–148.
67. Kraus N, Ozdamar O, Stein L, Reed N. Absent auditory middle latency response(s) in profoundly retarded children. Int J Neurosci 1984; 22: 159–163.
68. Kraus N, Ozdamar O, Hier D, Stein L. Auditory middle latency responses (MLRs) in patients with cochlear hearing loss. Otolaryngol Head Neck Surg 1982; 90: 406–412.
69. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
70. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of stimulus and recording parameters. Ear Hear 1985; 6: 307–311.
71. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
72. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: maturational effects and diagnostic potential. Scand Audiol 1985; 14: 27–30.
73. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
74. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
75. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
76. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
77. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
78. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
79. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
80. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
81. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
82. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
83. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
84. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
85. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
86. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
87. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
88. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
89. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
90. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
91. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
92. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
93. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
94. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
95. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
96. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
97. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
98. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.
99. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses and evoked potentials for stimuli of short duration. Electroencephalogr Clin Neurophysiol 1985; 60: 390–397.
100. Kraus N, Smith DI, Reed NL, Stein L, Cartee C. Auditory middle latency responses in children: effects of age and diagnostic category. Electroencephalogr Clin Neurophysiol 1985; 62: 343–351.

89. Hinojosa-Rios R. Anatomy of the auditory pathways with emphasis on the brain stem. Adv Oto Rhino Laryngol 1984; 34: 25–38.
90. Ikeno T. Middle component of the auditory evoked response in young children. Sound Audiol 1984; 13: 83–86.
91. Ornitz EM, Ritvo ER, Panman LM, Lee YH, Carr EM, Walter RD. The auditory evoked response in normal and autistic children during sleep. EEG clin Neurophysiol 1968; 25: 624–635.
92. Orsini T, Abouloir G, Cudennec AB, Tremplot S, Paladini G. Auditory brain-stem (ABR) and Middle Latency Auditory Responses (MLRs) in the prognosis of severely head-injured patients. EEG and clin Neurophysiol 1990; 77: 186–202.
93. Otto DA, Bourgon TR, Miller RE, Barnet CN. Effects of age and body head height on CNS function in young children. I. Scalp auditory potentials. EEG clin Neurophysiol 1981; 52: 229–236.
94. Özdamar Ö, Kraus N, Curry F. Auditory brainstem and middle latency responses in a patient with cortical deafness. EEG clin Neurophysiol 1982; 53: 224–238.
95. Özdamar Ö, Kraus N. Auditorily evoked potentials over evolution of rat's components. Laryngoscope 1983; 77: 806–822.
96. Papanicolaou AC, Moore BD, Loring DD, Eisenberg HM. Evoked potential correlates of right hemisphere involvement in language recovery following stroke. Arch Neurol 1987; 44: 323–324.
97. Pelizzi S, Salomon G, Ellerizg C, Lauwe R, Lauwe YA. Middle components of the auditory evoked response in bilateral temporal lobe lesions. Scand Audiol 1980; 9: 161–167.
98. Perrault T, Giard MH, Bertrand O, Pernier J. The temporal component of the auditory evoked potential: A neuropsychological EEG study. Biol Psychol 1986; 19: 67–71.
99. Picton-Bachrach A, Horwitz EB, Roth WT, Tinklenberg JR, Kopell BS. Auditory and cortical evoked potentials in schizophrenia. Psychiatry 1980; 18: 209–222.
100. Picton TW, Hillyard SA, Krausz HI, Galambos R. Human auditory evoked potentials. I: Evaluation of components. EEG clin Neurophysiol 1974; 36: 179–190.
101. Picton TW, Hillyard SA. Human auditory evoked potentials. II: Effects of attention. EEG clin Neurophysiol 1974; 36: 191–199.
102. Pratorius MR, Spelman A-L, Pollak CP, Weinman JD. Long latency auditory evoked responses during sleep deprivation and in narcolepsy. Sleep 1982; 5: 147–156.
103. Rapin I, Schimmel H. Assessment of auditory sensitivity in infants and in neurologically handicapped children by using the two components of the average auditory evoked potential. In: JE Desmedt, Prog clin Neurophysiol. 1977, vol 2, pp. 79–92. Karger, Basel.
104. Kelsey CS. Multisensory evoked potentials in experimental and applied neuroimmunology. Neurobehav Toxicol Teratol 1983; 5: 559–573.
105. Robinson K, Rudge P. The differential diagnosis of cerebello-pontine angle lesions. J Neurol Sci 1983; 59: 1–13.
106. Rosenberg C, Wegerman R, Starr A. Auditory brainstem and middle- and long-latency evoked potentials in coma. Arch Neurol 1984; 41: 823–828.
107. Rotteveel JJ, Colon EJ, de Groot, Notermans SLH, Beuzinga GBA, Visser Y. The normal auditory conduction at term date and four months after birth. II. Middle latency responses (MLRs). Scand Audiol 1986; 15: 75–84.
108. Rotteveel JJ, Colon EJ, Notermans SLH, Beuzinga GBA, de Groot, Visser YM. The normal auditory conduction at term date and four months after birth. IV. Auditory Cortical Responses. Scand Audiol 1986; 15: 85–93.
109. Rotteveel JJ, Colon EJ, Stegeman DF, Visser YM. The maturation of the central auditory conduction in preterm infants and three months post term. I. Computer group averages of brainstem (ABR) and middle latency (MLR) auditory evoked responses. Hear Res 1987; 26: 11–26.
110. Rotteveel JJ, Stegeman DF, Graaf de R, Colon EJ, Visser Y. The maturation of the central auditory conduction in preterm infants and four months post term. III. The middle latency

auditory evoked responses (MLR). Hear Res 1987; 27: 245–256.
111. Rowland JL, Colon EJ, Stegeman DF. Vitex S. The interpretation of the normal auditory potentials in perinatal asphyxia and brain necrosis postnatum. V. The auditory evoked responses (AEP). Hear Res 1985; 17: 45–71.
112. Rosen H, Walker JC. Acoustical evoked potentials in man. Mediators of early components. Laryngoscope 1967; 77: 408–422.
113. Salas-Mora S, Wolpaw JR, Cuaco AT, Sevilla CA. Late auditory evoked potentials can assist seizure focus localization. EEG clin Neurophysiol 1987; 66: 304–310.
114. Schieg M. Detection of the middle latency auditory response produced by analog filtering. Scand Audiol 1982; 11: 97–101.
115. Schieg M, D e Cramon. Two different sources of the late AEP as identified by a spatio-temporal dipole model. EEG clin Neurophysiol. 1985; 62: 32–44.
116. Schieg M, D e Cramon. Psychoacoustic and electrophysiologic correlates of central hearing disorders in man. Eur Arch Psychiatr Neurol Sci 1986; 236: 30–40.
117. Schlee KH, Meiser HW, Horn S, Rieger H. Schizophrenia, psychiatric, neurologic and auditory evoked potentials. Pharmacopsychiat 1983; 16: 287–296.
118. Schramm DR, Cynader MS. Rapid functional stabilization of neonatal auditory cortical field (A1) of the cat. J Neurophysiol 1984; 51: 1208–1302.
119. Schulte FJ, Hummel C, Wolfrand H, Tichy W, Lipsett HG. The contents of sensory perception in premature infants. Eur J Pediatr 1977; 126: 213–224.
120. Seitz MR, Weber BA, Jacobson JT, Mayerhofer R. The use of averaged electroencephalographic response techniques in the study of auditory processing related to speech and language. Brain and Language 1980; 11: 261–284.
121. Sellon JH, Structure of human auditory cortex. I. Cytoarchitecture and dendritic distributions. Brain Res 1981; 229: 277–294.
122. Shagass C, Roemer RA, Straumanis JJ, Josiassen RC. Intelligence as a factor in evoked potential studies of psychopathology. V. Comparison of low and high IQ subjects. Biol Psychiatry 1981; 16: 1067–1078.
123. Shagass C, Roemer RA, Straumanis JJ. Psychiatric diagnosis correlates of evoked potential topographic factors. Adv Biol Psychiat 1982; 9: 84–99.
124. Shepard GM. The Synaptic Organization of the Brain. Oxford Univ Press, NY 1975, 2nd ed.
125. Shipley T. Evoked brain potentials and sensory impairment in the retarded child. Am J Mental Deficiency 1978; 34: 717–725.
126. Smith DB, Lui ME, Soliman WD, Mayer R. Morphological phase invariance of cerebral evoked potentials and theoretical fault implications. EEG clin Neurophysiol 1975; 38: 454–458.
127. Sokhomeridze M, Arutiun A, Shagoyan HG. Phase-locked cortical responses to a human speech sound and low-frequency cross-modal stimulation. Brain Res 1986; 398: 75–84.
128. Stockard JE, Wannamaker BB, Tachdjian O. Information in the recording and interpretation of the brainstem auditory evoked potential for neonatal neurologic diagnosis. Adv Clin EEG Technol 1984; 21: 3–54.
129. Straumanis JJ, Shagass C, Roemer RA. Influence of antipsychotic and antidepressant drugs on evoked potential correlates of psychosis. Biol Psychiatry 1982; 17: 1103–1122.
130. Suzuki T, Hirabayashi M. Age related neurological changes in auditory middle latency response. Audiol 1987; 26: 322–329.
131. Taylor MJ, McMorrow JB, Aschenbach E, Wagers GV. Electrophysiological investigation of the auditory system in Friedreich's ataxia. Can Journal Canadien des Sciences Neurologiques 1982; 9: 133–137.
132. Thier P, Ammann D, Gaedke R. Scott brain potentials and psychomotor in depression. EEG and clin Neurophysiol 1981; 51: 575–581.
133. Thornton AR, Mendel MI, Anderson CV. Effects of stimulus frequency and intensity on the middle components of the averaged auditory electroencephalic response. J Speech Hear Res 1977; 20: 81–94.

134. Vaughan HG, Ritter W: The sources of auditory evoked responses recorded from the human scalp. EEG clin Neurophysiol 1970; 28: 360–367.

135. Vivion MC, Goldstein R, Wolf KE, McFarland WH: Middle components of human auditory averaged electric cortical response: waveform variation during averaging. Audiology 1977; 16: 23–35.

136. Yinger M de, Stahlegle E, Speidbrenner JHM: Visual evoked potentials, auditory evoked potentials and EEG in choroid hydrocephalus children. Neuropad 1981; 42: 55–61.

137. Watanabe K, Hara K, Miyauchi S, Takahashi K, Kamijyngi M, Nakamura S, Yamada H: The value of EEG and cerebral evoked potentials in the assessment of nontraumatic intracerebral hemorrhage. Eur J Pediatr 1981; 137: 177–184.

138. Wood JPC de, Kap H: Spectro-temporal representation and time-varying spectra of evoked potentials. Biol Cybern 1981; 41: 215–222.

139. Weitzman ED, Kremen H: Auditory evoked responses during different stages of sleep in man. EEG clin Neurophysiol 1965; 18: 65–70.

140. Weitzman ED, Fishbein W, Graziani L: Auditory evoked responses obtained from the scalp electroencephalogram of the human newborn during sleep. Ped Res 1965; 33: 458–462.

141. Weitzman ED, Graziani LJ: Maturation and topography of the auditory evoked response of the prematurely born infant. Develop in Psychiatr 1968; 1: 79–89.

142. Williams HL, Tepas DI, Morlock HC: Evoked responses to clicks and their correspondence to stages of sleep in man. Science 1962; 136: 402–404.

143. Wood JA: The human evoked potential in brain. Hear Res 1984; 15: 225–247.

144. Wolpaw JR, Wood CC: Scalp distribution of human auditory evoked potentials. I: Evaluation of reference electrode sites. EEG clin Neurophysiol 1982; 54: 15–24.

145. Wood CC, Wolpaw JR: Scalp distribution of human auditory evoked potentials. II: Evidence for overlapping sources and involvement of auditory cortex. EEG clin Neurophysiol 1982; 54: 25–30.

146. Woods DL, Clayworth CC: Click sound position influences middle latency auditory evoked potentials (MLAEPs) in humans. Electr clin Neurophysiol 1985; 60: 122–129.

147. Yingling CD, Nethercut GE: Evoked responses to frequency-shifted tones: Scotomyta and temporal discriminators. Intern J Neuroscience 1985; 25: 107–118.

PART THREE

Visual evoked potentials

Electrodiagnosis by luminance and pattern stimulation

F.C.C. RIEMSLAG and H. SPEKREIJSE

Introduction

Stimulation in order to obtain VEPs has been performed in many different ways. The responses to the different stimuli usually are analysed in terms of their temporal components and their spatial distribution. We shall discuss both descriptions of responses in a more or less extensive manner, covering both research data and those that are currently in use in clinical routine. When we come to present some pathological conditions in a later part of this chapter it will become clear which of the vast set of possible stimuli preferably should be used in a certain pathological condition.

The most simple and classically used stimulation is the delivery of a short duration high intensity flash at a relatively low rate (eg once per second). Flash VEPs contain several components at different latencies, which have been associated with different functions of the visual system and/or different locations of the brain. Cigánek (1961) distinguished three major components, based on the frequency content of the response at different latencies following the flash. Furthermore, Hammond (1969) found with multiple recording electrodes that these components appeared maximal at different locations on the skull.

Note that already at that early stage of VEP research the basic tools, which up to now provide most information in the analysis of responses, were available and applied. Most commonly in use in the clinical routine are now the measures of amplitude and latency of the various components (peaks) in the time averaged responses. In general the latencies are the more reliable parameters in VEP measurements. Amplitudes are highly variable and, what is more important, very dependent on their definition (peak-to-peak, peak to ground-average referred, or peak to average level of 40 ms preceding stimulation). They can be influenced by many parameters which are not under control, such as the retinocortical projection and the location of the brain with respect to the skull. VEP amplitudes therefore convey, in comparison to the more reliable amplitude measures in electroretinography less often useful information. As mentioned, the discrimination of the components in the flash EP is firmly

E. E. Celesia and E. E. Daly (eds), Handbook of electroencephalography, pp. 127–139.
© 1990 Elsevier Scientific Publishers.

based on their different frequency behaviour and topological distribution on the skull. Since the different components in the flash EP differ in their frequency content, the use of stimulation at different temporal frequencies, using sinewave modulated light and analyzing the responses in terms of (Fourier-) spectral components, is indicated. Better suited to the study of the topological distribution of the individual components seems to be the combination of a source (equipotential mapping) density derivation technique and principal component analysis. Each of these two techniques therefore will be discussed in this chapter in order to tailor the specific properties of the responses to the clinical questions at hand.

Both techniques have been applied equally successfully to the responses to luminance – as to pattern stimulation. And it is pattern stimulation that is currently used most often in the clinic. Therefore an extensive description of available pattern stimulation techniques will be given.

The various types of stimulation evoke specifically responses from different parts of the visual field. On the other hand the stimulation of various parts of the visual field will reveal the functioning of these parts in a more specific manner. The properties of this specific manner of distinction (macular- versus peripheral-, left field versus right field, or even quadrant stimulations) will be discussed in a separate section.

In order to be able to understand the physiological substrate underlying these responses, first we will summarize some anatomical and physiological data from the literature.

1. Anatomy and physiology

1.1. Anatomy

The visual system is fully confined to the Central Nervous System. Even the retina, which constitutes the peripheral part of the system is autogenetically a full part of the CNS. This retina, which is involved in the transduction of light into electrical signals that the brain can process, basically consists of five neuronal layers (Fig. 1), each with its own specific function.

The receptors (rods and cones) catch the light quanta and as a result respond with a gradual potential change (hyperpolarization) that is passed to the bipolar cells. These bipolars pass the signals directly to the ganglion cells which transform the analog signals into nerve impulses that are sent up the brain. However this information stream 'vertically' through the retina is regulated by the many connections within two layers that process the signals in 'horizontal' directions, that is within the plane of the retina itself: the horizontal and the amacrine cells. It should be noted that most of the ocular pathologies that affect these layers clinically are tested by recording of the Electroretinogram. Some basic principles therefore of clinical electroretinography will be discussed before we go into detail about the recording of VEPs. Obviously,

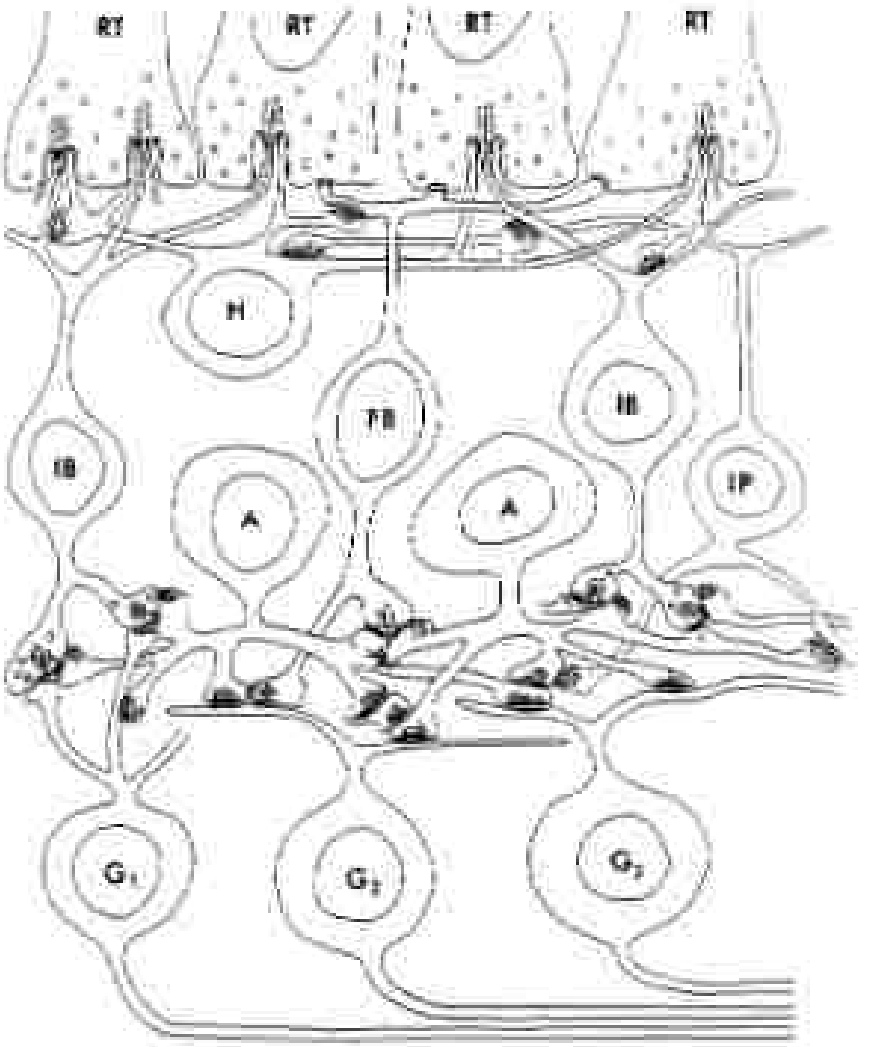


Figure 1. Summary diagram of the arrangements of synaptic contacts found in the vertebrate retina. Five neuronal layers can be distinguished. Receptors (RT: only the terminals are represented), Horizontal cells (H), Bipolar cells (IB or FB), Amacrine cells (A) and Ganglion cells (G). Not shown in the scheme but important for the ERG are the Müller cells that extend through all layers, from the Ganglion cell layer to the receptor layer; glial cells that guarantee the functioning of the neurones by supplying them both with glucose (from Dowling, 1987).

changes of the functioning of these layers, will influence the VEP and should always be considered when alterations of the VEP have been found.

The fibres of the ganglion cells leave the eye and form the Optic Tracts, that enter the skull through the foramen opticum. At the Optic Chiasm part of the fibres, the ones that subserve the nasal retinal half fields cross over

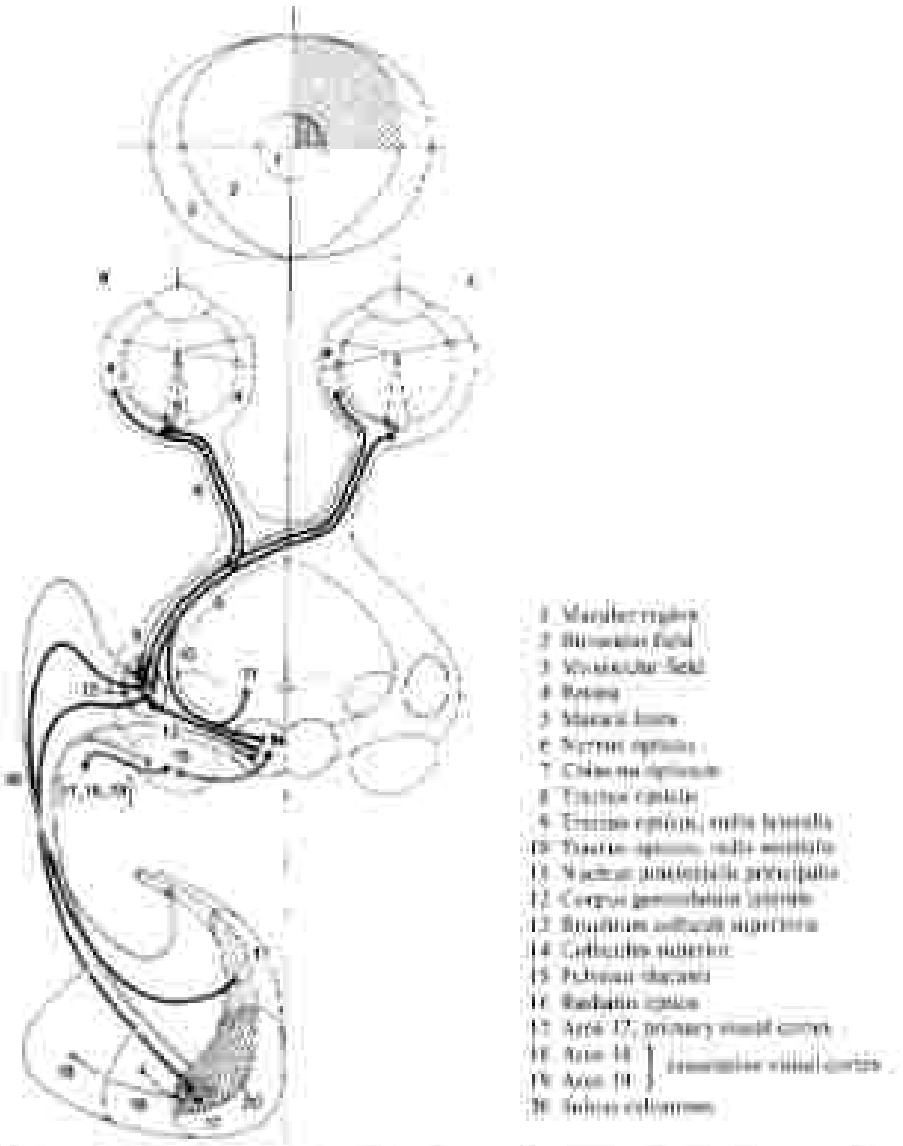


Figure 2. Schematic overview of the visual pathways and the topographic representation of the visual field (from Vanneste[ijen, 1979]).

to the contralateral side of the brain (Fig. 2), whereas the cells that subserve the temporal retinal half fields send their fibres to the ipsilateral side. The so formed Optic Nerves reach the Lateral Geniculate Nucleus, where the signals are relayed through to the fibres of the Optic Radiation. The Optic Radiation finally reaches the visual areas of the cortex: areas 17, 18 and 19 of Brodmann,

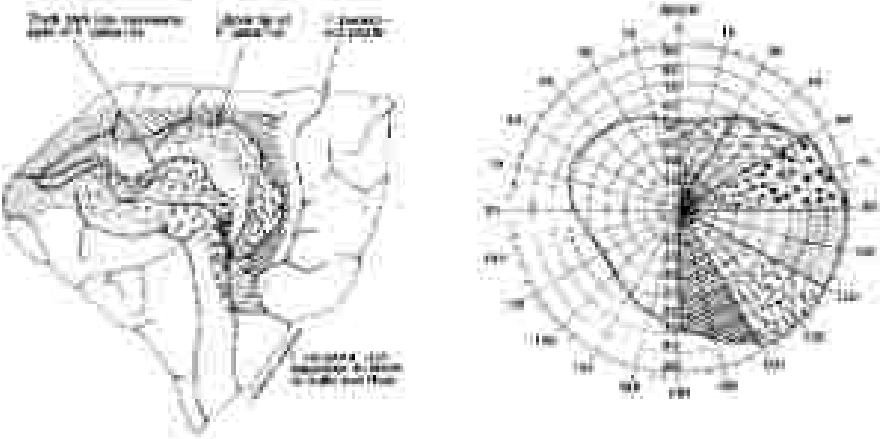


Figure 3. The mapping of the visual field on the occipital cortex (from Holmes, 1945)

or alternatively the striate and extrastriate areas. By this layout the different parts of the visual field are projected to specific regions of the visual areas, such that left half fields of the visual fields of both eyes are projected to the right hemisphere and vice versa. For the striate region the projection of the fovea is to the exterior part of the occipital lobe. The more peripheral part of the visual field is projected to the gyral banks fanning inwards into the Calcarine Fissure (Fig. 3).

The pathway described here is called the primary visual pathway, suggesting that several other areas of the brain probably are activated from the retina. However in VEP context they do not play a role of importance. This description of the visual system furthermore is confined to the strictly neuronal part of it. It neglects the fact that a very complex optical imaging apparatus is present in the eye, of which the functioning especially is important with respect to pattern VEPs. It furthermore neglects the fact that along the pathway several support tissues are present that supply the metabolic substances required by the neurons (Müller cells, Retinal Pigment Epithelium the retinal and choroidal arteries, the cortical and chiasmal blood supply). By being the eventual result of the processing along the complete pathway, the VEP might be unable to test either of these subsystems discretely. However, more direct methods for many of these functions are available (RPE: Electro-oculogram, Retinal flow: Doppler, fluorescence-angiography, etc.). Nevertheless, the critical interpretation of VEP data in connection with these techniques probably serves to enhance the reliability of diagnosis. The discussion of these other techniques is however considered outside the scope of this chapter.

1.2. Physiology

Transmission of the signals from receptor level to the ganglion cells, taken

the passage of at least two synapses. The time required to do so can be estimated to be of the order of about 20 ms, on the basis of single cell research in primates (Creutzfeldt and Kuhnt, 1973). The spikes travel along the myelinated fibres with a speed varying with the diameter of the fibres in the range of 20–50 m/s (McDonald, 1977). With an average speed of 40 m/s this accounts for a transport time along the optic nerve for the fastest signals of about 10 ms, including the synapse passage in the LGN. These numbers lead to an estimate of the earliest onset latency of the first cortical phenomenon or the cortical arrival time of about 30 ms. However, the fibres contained within the optic nerve/tract have been classified in different types according to their function. At present two parallel channels are commonly assumed: the parvocellular and magnocellular pathways which process independently but also interact with each other. The first subserves the spatial and colour coding; the second encodes gross features like motion. The types have different fibre diameters and therefore different conduction velocities. It is anticipated therefore that with different types of stimulation different onset latencies will result. None that onset latency also changes with body temperature. For the flash ERs a reduction of 3 ms per °C temperature rise was established (Rees *et al.*, 1941).

1.1. The electroretinogram

In the clinical routine the electroretinogram is usually recorded upon the delivery of a bright flash of very short duration, presented for instance once every two seconds. The intensity of the flash critically determines the waveform of the response obtained.

Basically the observation is as follows: upon a low intensity flash, delivered to the dark adapted retina a broad positive wave is found: the b-wave (b2). Its onset latency can be as long as 60 ms, its peak latency ca. 115ms. Then, upon the increase of the intensity the amplitude increases and the peak latency gradually decreases, until a negative wave preceding the b-wave is seen: the a-wave (a2). The amplitude of this negative deflection increases and at high intensities is preceded by another negative peak (a1). At this highest intensity also the b-wave is split into two peaks, b1 and b2. The first a- and b-wave (a1 and b1) generally are identified with the photopic system, whereas the second waves (a2 and b2) are identified with the scotopic system. a-waves are attributed to receptor activity, the b-waves reflect probably Muller cell activity, as a result of their activity of supplying potassium to the active bipolar cells. On top of the ascending limb of the b-wave in the bright flash response little wavelets (approx. 125 Hz) can be observed: the Oscillatory Potentials (OPs, Fig. 4). In the raw recordings they are frequently only barely visible, and the distinction between one of the OPs and the b1 component is generally very difficult. The OPs can be made clearly visible with appropriate high pass filtering (cut-off at 100 Hz, see Fig. 5). Note that for bright flashes almost coinciding with the corneas (Fig. 4), another response, the Early Receptor

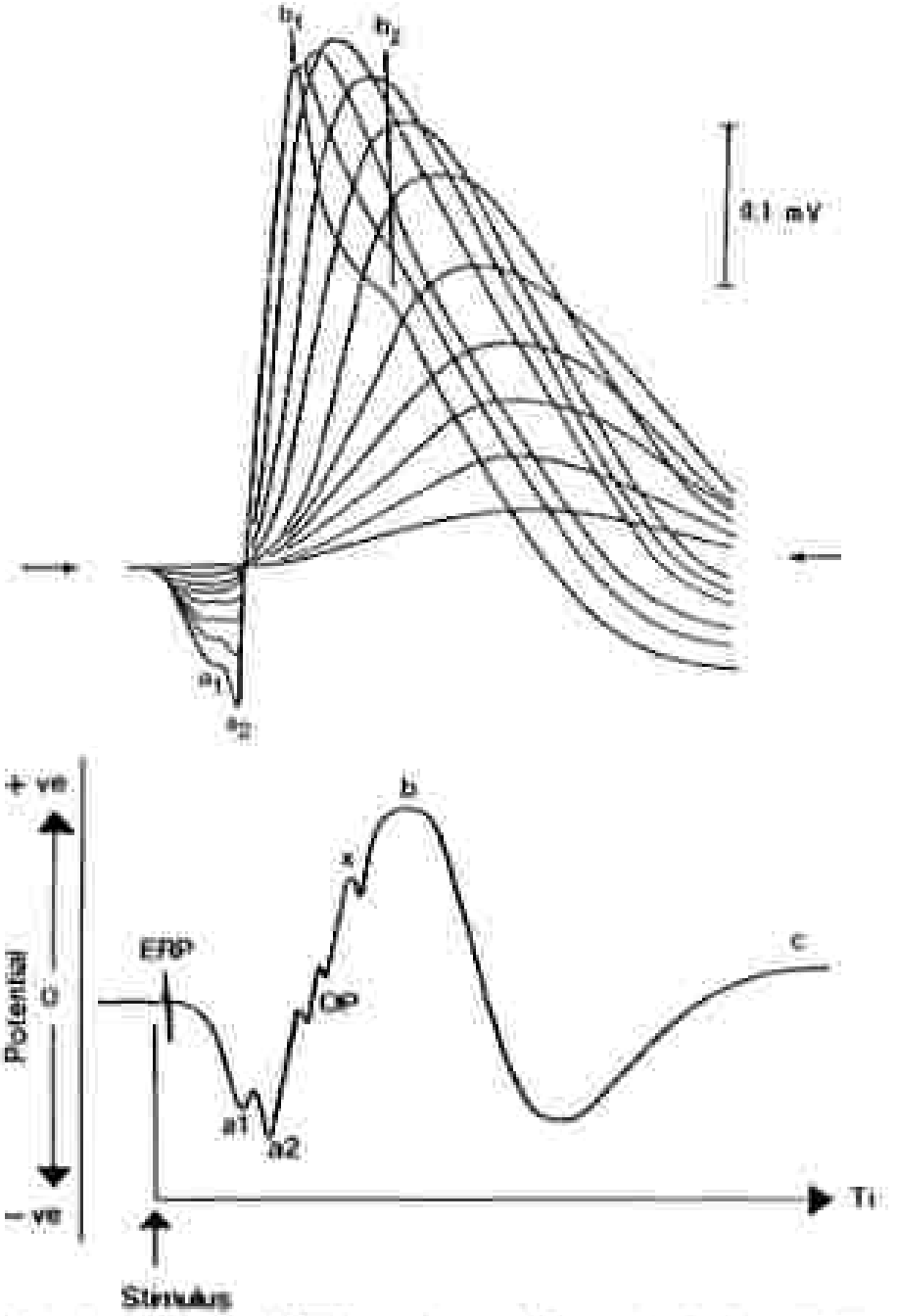


Figure 6 a. Superposition of 12 ERGs to various stimulus flux densities (bright set out). From Armington, 1953. b. Schematic representation of the human ERG.

Potential (ERP), can be recorded, which is due to the outer segment activity of the receptors at the absorption of quanta. The ERP is however not used in clinical routine, mainly because stimulus artifacts coincide with this small response.

For clinical purposes a standard for electroretinography, comprising the minimum requirements for clinical electroretinography, has been published recently by the International Standardization Committee of ISCEV (Marmor *et al.*, 1989). It has been proposed that at least be recorded five different responses (see Fig. 5): 1 a rod response (low intensity flash, dark adapted); 2 a mixed rod- and cone response (high intensity flash, dark adapted); 3 oscillatory potentials (high intensity flash, dark adapted); 4 a cone response (high intensity, light adapted) and 5 high frequency flicker responses (high intensity flash, light adapted, 30 flashes per second).

Mainly to illustrate the features of these responses three clinical examples of ERG recordings are reproduced below. The responses of Fig. 6 are those of an achromat. The low intensity flash in the dark adapted state produced a normal response. The high intensity flash in the dark adapted state produced only the later (scotopic) components. In the light adapted state no significant response was found for the brightest flash.

The responses of a Rod dystrophy patient are depicted in Fig. 7. Only photopic components for the high intensity flashes, both in the dark- and light adapted state are found. It should be noted however that for this example the latency of these components is prolonged, indicating that also the cone

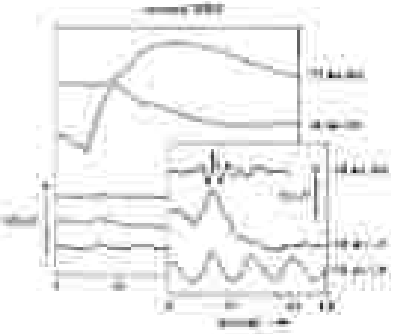


Figure 5. a. Normal ERG as specified by the ISCEV standardization committee. The upper curve is the dark adapted Rod response. The second is a mixed response of both the rod- and the cone pathway to a bright flash in the dark adapted eyes. The last three curves are recorded with increased sensitivity only. b, c, d. Oscillatory Potentials, the bright flash ERG in light adapted state and the response of the light adapted retina to 30 flashes/second.

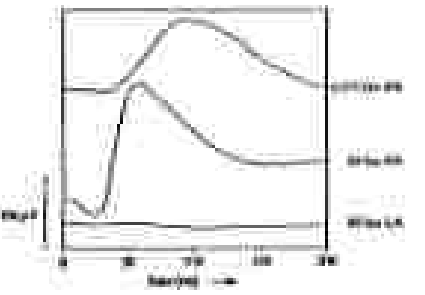


Figure 6. ERG of an achromat. The low intensity flash produced a fairly normal response (upper curve), where the high intensity flash in the dark adapted eye is revealed only in the late (scotopic) components (middle curve). The light adapted retina did not produce a significant response (lower curve).

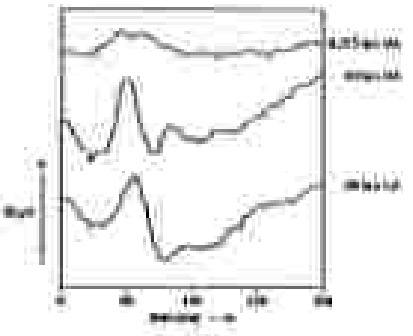


Figure 7. ERG of a Red Dystrophy patient. Only the photopic components both for the dark- and the light adapted state are present. The photopic components here are prolonged in latency, indicating that also the cone system is involved in the pathological process.

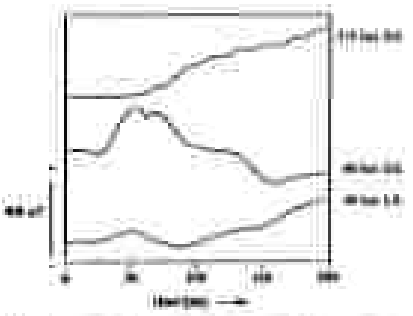


Figure 8. Responses of a very rare example of cone (rod) dysfunction. These responses mainly show scotopic characteristics. There was furthermore no response to red and a good response to blue flashes. The pattern (foveal portion) fails adaptation and good color discrimination.

system is involved in the pathological process.

The patient of Fig. 8 was a very rare example of cone (rod) dysfunction. His responses showed mainly scotopic characteristics for the dim flash fairly normal responses, but weaker than for the achromat, were present and for the bright flash only a small retinidy early b-wave could be seen. This behaviour was further established by recording of the responses to red and

Figure 9. ERG (flash) and VEP (pattern) retinal responses of a patient with retinitis pigmentosa (myopia) compared to the normal response. This pathological process in the beginning stage mainly affects the peripheral retina. The ERG therefore is absent while the VEP is normal.

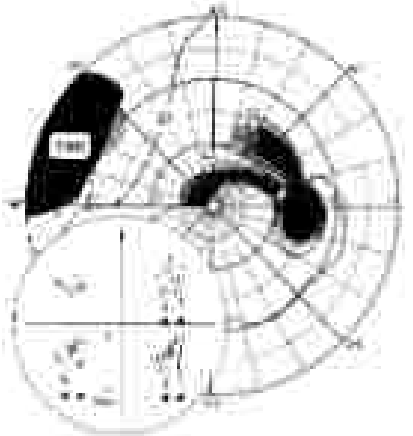


Figure 10. Quadrant field pattern retinal responses (system 4 results) of a glaucoma patient with depressed visual field loss. Only in the quadrant where the scotoma reaches the very center of the field is the VEP abnormal.

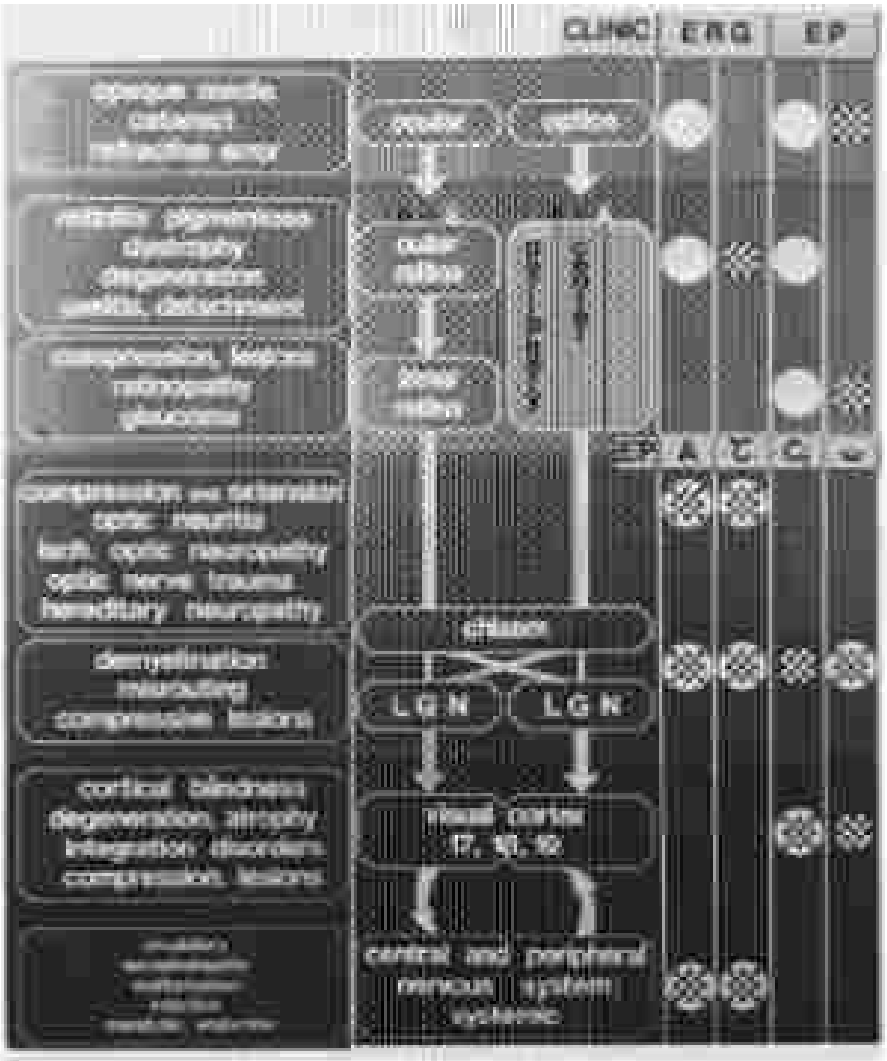


Figure 11. Clinical disorders and their electrophysiological approach. In the left most column lists a number of clinical disorders that can be tested with electrophysiology. The middle column depicts the stages of visual processing. The checkerboard pattern and/or the pattern on a homogeneous background in the right column indicates the proposed stimulus, i.e. pattern reversal or luminance flash stimulation. The responses to be used are Amplitude (A), Latency (time) for the most distal stage (ERG), and these two and added are the component specific (C), and retinal topography (—) for the proximal stage in the visual system.

blue coloured flashes. The blue flash response compared the white flash response, whereas the red flash response was absent. Since their latencies were shorter than for the achromat under similar conditions, it was concluded that some cones still were functioning. This was in line with the normal (!) dark adaptation and good colour discrimination this patient had. We have included this example to stress that sometimes the sensitivity of the recording channels should be increased when small responses are expected (see also the insert of Fig. 5) and that coloured stimuli can be required for differential diagnostic purposes.

It should be obvious at this point that most of the pathologies presented in an eye clinic, can be tested with the ERG. However it should be as obvious that all of these pathologies will have their result in the VEP. Both techniques are valuable and complementary in ophthalmic diagnostic routine. In the ERG the mass activity of the whole retina is recorded, so that pathology that affects the peripheral visual field causes serious changes in the ERG. The VEP on the contrary can be relatively unaffected (Fig. 9). The VEP is only affected by pathology that approaches the central visual field very near, as can be

Figure 12. a. Schematic representation of the flash evoked retinal potential according to Ogden (1984). Note that the time scale is varying in order to represent the three components (primary-, secondary- and late negative component) on their own appropriate scale.

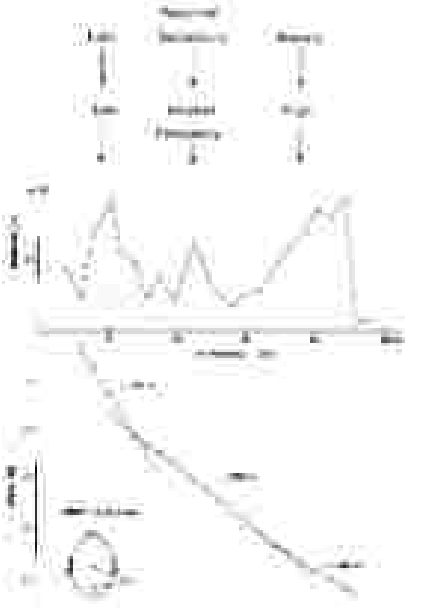


Figure 12. b. Amplitude and phase characteristics of the VEP obtained with sinusoidal stimulation. Filter properties can be directly assessed on the basis of these characteristics. Note that the high frequency system can be associated with the primary component and the medium frequency system with the secondary component.

seen in the glaucomatous visual field defect of Fig. 10.

An indication on which electrophysiological technique, which stimulation and which analyses should be applied in the different pathological conditions is depicted in Fig. 11. Clinical disorders that may be evaluated with electrophysiology are listed in the leftmost column. The center column schematically shows the stages of visual processing that probably are involved. At the right the advisable stimulus, pattern and/or luminance flash is depicted. The corresponding response parameters are given at the top of this column: Amplitude (A) and Latency (tau) of the various peaks of the ERG for the most distal stage, and added in these two components specificity (C) and cortical topography (...) for the proximal stage, i.e. the EP of the visual cortex. The center column also indicates that the ERG does not give information about the inner retina and thus the EP gives mainly information about the processing mediated through the central retina.

In the context of this book on evoked potentials we leave the electroretinogram for what it is and discuss in more detail the VEP.

2. Stimulus characteristics

2.1. Luminance stimulation

The VEP to a short duration high intensity flash contains at least three components of different cortical origin. The first of these is a short latency negative deflection with minimal inter-individual variability of its onset latency and a maximal amplitude just anterior to the inion. Due to overlap by the first complex the onset latency of the second complex is more difficult to determine, its amplitude is maximal more anteriorly. The third late and even more variable complex (latency more than 135 ms) is maximal even more forward.

In the top left of Fig. 12a the red flash EP is depicted and in the center the various time components on a varying time scale as presented by Cigánek (1961) in his Ph.D. thesis. This operation along the time axis is in practice impossible to obtain. The various components can be split up better by sine wave stimulation (Fig. 12b).

When the human visual system is stimulated with sine wave modulated light, the behaviour of the fundamental component in the response (i.e. the component at stimulus frequency) strongly suggests that at least three independent systems are involved in the generation of the VEP: a high frequency (35–60 Hz) a medium frequency (15–35 z) and a low frequency (7–12 Hz) system. Both the latency estimations from the phase characteristics and the topological distribution of the responses to various frequencies seem to identify the high frequency system (35–60 Hz) to the primary short latency component of the flash response, the medium frequency system (15–35 Hz) to the medium latency and the low frequency system (7–12 Hz) to the long-latency component.

The primary response, which has been identified with the high frequency subsystem (35–60 Hz), has been suggested to originate in the primary receiving area of the visual fibers of the optic radiation in the visual cortex (Brodmann's area 17; 1961; Reits, 1975; Spekreijse *et al.*, 1977). Recently the combination of dipole source modeling and principal analysis has verified this adequately (Maier *et al.*, 1987).

The variability across subjects of the latency of this primary component, whether its onset or its peak, is relatively low, its amplitude is usually very low, hampering its identification in the response. Now that its origin is so well established, it seems, however, a good candidate to judge conduction across the optic pathways in conditions where pattern stimulation is not appropriate, and especially so since for its recording only a minimal cooperation of the subject is required. Absence of the component, on the other hand, cannot be interpreted reliably as a pathological condition. In Fig. 13 such an example is depicted. The absence of the early component in the flash response might be misinterpreted as a delay in eye conduction. In that case pattern stimulation is indicated to establish whether the striate response is present. In this example taking during the acute phase of optic neuritis the absence of the pattern reversal response of the left eye is indicative for the absence and not for delay of the primary component in the flash EP. There is still discussion as to the origin of the secondary response, identified with the medium frequency system. It has been suggested, its origin is to be found in area 18 or 19. On the other hand recent topographical data suggest the medium frequency system to be maximal on foveal stimulation just near the latter. Since there seems to be no sequential link between the high frequency system and the medium frequency system (Regan *et al.*, 1976), a parallel pathway leading into area 18 or 19 has been hypothetized to be responsible for the generation of this secondary component (see also Fig. 13). The latency of this secondary component is highly variable (90–130 ms) and cannot be used

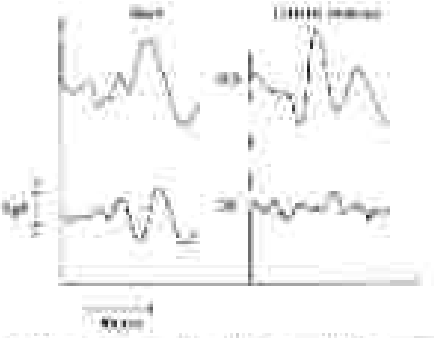


Figure 13. The flash and pattern reversal EPs of a monocular scotoma patient. Comparison of the flash EPs of the two eyes suggests a latency increase for the primary response. The absence of the pattern reversal response indicates that there is no response at the retinal level. Therefore the remaining flash response (here LE) interpreted as a secondary component only.

to detect pathology. Its amplitude on the contrary is large, rendering identification relatively easy. Therefore this secondary component can be used, as it is often in young children, to evaluate the eventual arrival of a signal at cortical level. It can be difficult to estimate the latency accurately, even when latency is determined from the phase characteristics, since the frequency trajectories of the long- and short-latency system overlap that of the secondary component (Dawson and Spekreijse, 1979).

The third late component in frequency content coinciding with the α- band does not seem to originate in the visual cortex, is notoriously variable across subjects and is rarely used in clinical circumstances.

2.2. Pattern stimulation

2.2.1. Introduction. Another type of stimulation is obtained when the luminance is not only modulated temporally, but also spatially, i.e. a structure of black and white elements is introduced within the visual field. In such a pattern equal area is covered by each of the two (black and white) sets of elements, and it is relatively easy to change the contrast (e.g. reverse it) without changing the luminance reaching the eye. The obtained response clearly can be distinguished from the luminance flash response in which total luminance is the only varied parameter. It should be noted however, that even if total luminance is constant, local luminance is modulating, and can evoke, apart from contrast evoked components, luminance specific components in the response. This holds especially when the spatial elements are large.

Reports on the use of various types of patterns can be found in the literature, as there are bars, sine wave gratings, isolated squares, dots, diamonds, checkerboards, etc. Although bars and sine wave gratings have received a fair amount of attention, it is the checkerboard pattern that is currently used most often in clinical routine. Checkerboards evoke larger responses than comparable bars or sine wave gratings, and are felt to fit best into the initial circular symmetry of receptive fields along the visual pathways. Polygons of higher order of course would fit in even better, but then such polygons have more than four neighbours, and contrast modulation without net luminance modulation would be impossible to obtain.

2.2.2. Technique. Several ways to produce these patterns have been introduced (Arden *et al.*, 1977) each with its own advantages and disadvantages, and each with its own limiting properties and consequently response latencies. Of importance for the clinical routine have appeared only two: the TV display and the slide projector galvanometer method. The slide projector method uses a translucent screen onto which the pattern is projected through a mirror, mounted on a galvanometer. By suddenly moving the mirror such that one full check of the pattern is traversed over the screen, a relatively fast (within 5 ms) pattern reversal can be made. Note that essentially movement is present within this stimulus, and it has become clear that movement determines part

of the response (see for details 2.2.3.1). Pattern jumps are the only type of stimulation that can be made with the galvanometer system, and for each checksize the jump step has to be adjusted if reversal is required. Contrast and luminance can be controlled only in a limited sense. Therefore TV display sets have nowadays replaced these mechanical devices.

It is essential that the frame rate of the TV set, the presentation of a new image and the averaging process are accurately time locked, in order to prevent trigger jitter to interfere with the registration (Arden *et al.*, 1977; Van Lith *et al.*, 1978; Van der Heijde *et al.*, 1982). Secondly the non-linearity of the voltage/luminance relation of the Z-axis of the TV display has to be compensated for, in order to make accurate variation of the modulation depth available. Finally the pattern should be built up symmetrically around the centre of the screen in order to obtain equal area (frame) coverage across the screen (de Waal *et al.*, 1983), again to guarantee pattern exchange without net luminance changes.

Provided these criteria have been met the TV display comprises a reliable and convenient pattern stimulator that very easily variables checksize and/or type of stimulation, frequency of stimulation, modulation depth, etc. Among its disadvantages are a relatively long pattern built up time (20 ms) and a relatively limited resolution. Resolution however can be increased by increasing the subject to screen distance, when very small checks are to be used. Only the most central part of the macula contributes to the response for small checks, and therefore only a small stimulation field is needed. In this condition however accurate fixation is required which obviously is not always available, typically in not cooperative subjects like children, and it is especially in this group where relatively small checks are used to obtain an objective estimate for visual acuity.

Since there exists a large variation in the extent to which all these requirements have been met in the commercially available TV display units, it is imperative that each laboratory "calibrates" its own system by testing a normal population. Stimulation through a diffusing screen/pupil should be part of this normative protocol, in order to detect possible artefacts not only from luminance stimulation but also from electric crosstalk. We deal with subject variability and normative data in a later part of this chapter, but we feel this point cannot be stressed enough and want to state that the mentioned normative values can only serve as a guideline and have no absolute meaning.

2.2.3. Pattern reversal. The most commonly used pattern stimulation is the one in which black and white checks are exchanged abruptly: the pattern reversal. The response to pattern reversal delivered at a low rate (e.g. 2 per second, so called transient recording) consists of a negative-positive complex of which the positive component (P100) is most prominent (see for example Fig. 9). Its peak latency varies only little among subjects and a good separation between normal and pathological response latencies can be found.

Relatively large checks (>30', most common 50') at high contrast levels

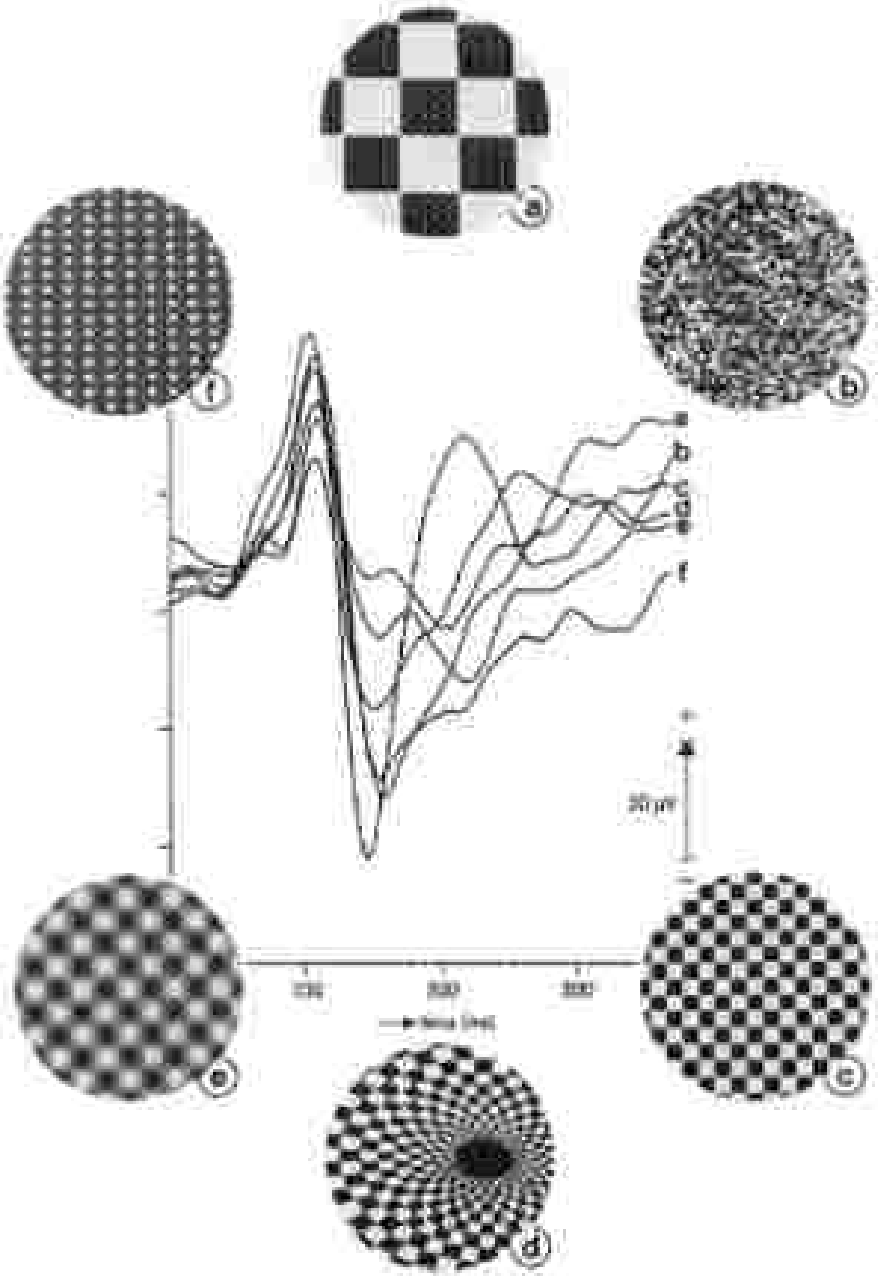


Figure 14. Responses are shown obtained with six quite different pattern reversal stimuli as shown in the inserts. Note how sensitive the P100 to late components show much more variability. For that reason they are not used in clinical routine.

(>80%) are used frequently in routine patient examinations is logical choice considering the insensitivity of the response to defocus, scatter (which reduces the contrast), etc. And even the choice of the specific pattern configuration does not seem to influence the response very much (given of course equal area coverage by the two sets of elements).

The response seems to be largely determined by the motion present within the stimulus. It should, however, be noted that especially for the larger pattern elements the local luminance modulation within the respective elements determines the response to a significant extent.

In the transient recording condition stimuli should follow each other at such a low rate, that the response has been completely terminated before the next stimulus is delivered. In the transient recording condition P100 amplitude can be small in some subjects and identification may be hampered a.o. by the presence of additional components. It is for this reason that an objective method of measuring this response at higher reversal rates (steady state recording) has been proposed. In the steady state recording condition stimuli follow each other at such a high rate, that the response is still going on when the next reversal is delivered. At these high rates the responses obtain a sinusoidal shape and can be analysed in terms of amplitude and phase of the stimulus frequency (i.e. the reversal rate) (Millar *et al.*, 1974; Dawson and Spekreijse, 1978; Regan*g et al.*, 1982). Since information about waveform is lost, steady state responses do not give additional information where a recognizable transient response is available. However, steady state recording gives a good estimate of latency where the transient response cannot be identified. The amplitude characteristics obtained in steady state conditions suggest that optimal signal-to-noise can be obtained at rates between 7 and 12 reversals per second (see Fig. 24).

The character of the reversal response has only been revealed partly yet. As mentioned the contours within the pattern do not seem to be important for this response, as is the case for the contrast or luminance of the pattern (see also Paragraph 5). There is however good evidence that the pattern reversal response is related to motion of the pattern across the retina. Firstly the amplitude of the response varies monotonously with the size of the displacement of the pattern, up till the step coincides with the width of the check (Spekreijse *et al.*, 1985) (Fig. 15).

Secondly they found that the latency of the late negative component increased with the duration of the movement, indicating that the response can be considered to be composed of at least two components: one evoked by motion onset, the other by motion offset (Spekreijse *et al.*, 1985). This finding, by the way, stresses the importance of the fact that only responses produced technically the same (same image display time) can be compared adequately, since obviously the duration of the switching over of the pattern will cause different interaction between the components mentioned. Thirdly, motion across the retina is the prime parameter since the same response is obtained, irrespective of whether the movement is caused by pattern movement or by eye movement

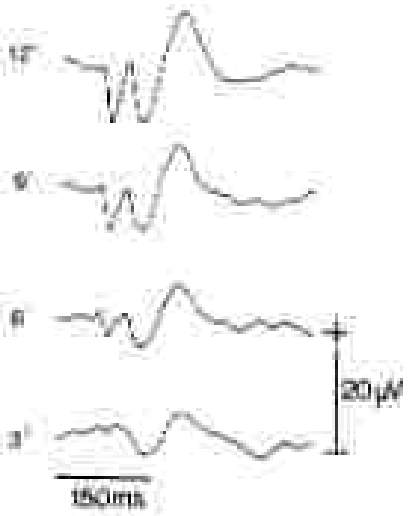


Figure 11. Eye recorded in the absence of a 12' checkerboard pattern. Displacement steps are indicated at the right of each trace. The stimulus used to obtain the trigonal response is identical to the pattern reversal stimulus.

(Armington, 1972; Riemslag *et al.*, 1987).

Principal component analysis proved that the P100 in the reversal response originates from striate cortical areas (Maier *et al.*, 1986).

2.2.4. Pattern onset. An alternative type of stimulation that evokes a more pattern related response, is pattern onset: the pattern is made to appear abruptly from a homogeneous field by increasing the "white" elements of the pattern as much in luminance as the "black" elements are reduced simultaneously. Again no net luminance change is the result, where the contrast changes considerably and independently. It should be noted again that, as for the pattern reversal condition, contrast change is produced by local luminance modulation within the checks.

TV displays always should be checked for net luminance changes, because of their non linear *x-y-z* luminance-voltage characteristics. This can be done relatively easy by observing the TV screen through a diffusing screen/paper, or observing the reflected light by a diffusing screen/paper placed at angles with the TV display. A pattern onset with ca. 10 presentations per second should by used, because psychophysical flicker sensitivity of the normal observer is good at 10 Hz. Thus very low overall luminance modulations, as low as 1% can be detected easily, and should be corrected for.

The response to pattern onset is critically dependent on pattern parameters as checksize, contrast, etc. For 10' to 20' checks, which are optimal to evoke the largest responses, the response consists of a Positive Negative Positive complex of which the respective peaks have been termed C1(P95), C1(N120)

Figure 10. Pattern appearance (A) - disappearance (D) response of the right (solid line) and left (dotted line) eye of a portable VS pattern (20' checks, 4° × 4° field, 100% contrast, 64 cd/m²). The pattern appeared during 300ms of every 600ms. The three components C1, CII and CIII are indicated with arrows.

and CIII(P388) (Jeffreys and Axford, 1972a, b). This alternative notation (C1, CII, CIII) for pattern onset has been used in literature and will be in this chapter in order to clearly distinguish these peaks from the pattern reversal peaks.

The latencies of these peaks all show a considerably larger variability across subjects than the latency of the pattern reversal P 100. This increased latency variability renders this type of stimulation less adequate in conditions where latency estimation is the purpose of the examination. This is not so for intrasubjectual examinations where the interocular latency differences (3 ms SD) of the pattern onset responses for fully corrected eyes should not exceed 10 ms, a value that is comparable to that for the pattern reversal response.

Peak-to-peak amplitudes are usually larger than for pattern reversal. The response therefore can be discriminated more easily in conditions, where the response is small by pathological and/or extraneous causes. Since, furthermore, the pattern configuration seems to be of minor importance for the pattern reversal response (indeed motion can be perceived without seeing detailed contours), where it is critically so for the pattern onset response, this type of stimulation is the more adequate when visual acuity is to be tested objectively. It is especially the CII peak that seems to be pattern specific: it decreases rapidly with defocus, dominates the response when only the borders of the checks are presented and is suppressed when the borders of the checks are superimposed by high contrast lines (Spekreijse *et al.*, 1973). Finally, the CII selectively is reduced in pathological conditions like amblyopia, and is not present in the neonate (Spekreijse, 1983). The C1 peak is suggested to be evoked by the local luminance modulation, whereas CIII is enhanced in binocular versus monocular condition.

The origin of the C1 and CII peaks has been studied extensively, but with conflicting results (striate and extrastriate respectively, or the reverse; Jeffreys and Axford, 1972a, b; Lemoyne and Joseph, 1979; Dinsdale, 1980). Jeffreys (1980) and Lemoyne and Joseph (1979) mentioned that none of the peaks in the pattern onset response appeared to have to be the result of only one active dipole source, and more specifically showed that the source responsible for CII is already

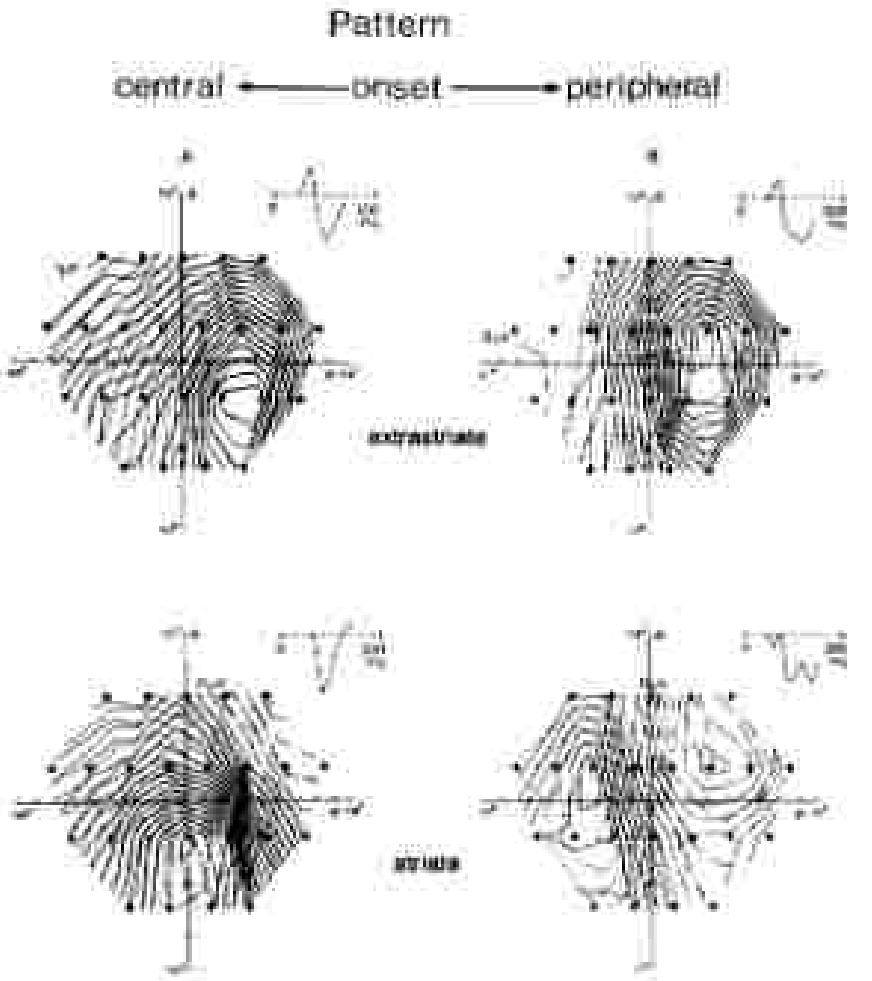


Figure 17. Equipotential maps derived from the recordings to the appearance of 15′, 30% contrast checkerboard in the central (A) and peripheral (B) part of the visual field. In each figure the upper map is derived from the extrastriate component and the lower from the striate component. The spacing between the lines is 2 μV. In each plot the shape of the principal component is shown in the insert in the upper right corner.

active at the time of C1. Principal Component Analysis especially is developed to answer such questions: how many components are required to explain a specific activity? And it is PCA that decomposes the pattern onset response in at least two in time overlapping activities: one of striate (area 17) and another of extrastriate (supposedly area 18) origin. These results yield the conclusion that the C1 or local luminance peak is part of a bigphasic wave of extrastriate origin: a positivity followed by a late negative wave. As a result

CII is due to both striate and extrastriate activity. The first part of CII or the pattern specific part is a negative only wave to be located in the striate area.

These results also directly support what we already mentioned before: there probably is not a sequential link between the two areas, again suggesting parallel pathways feeding into the two areas, since activity of both areas overlap considerably in time. Therefore the two principle components should be considered to convey independent information about the functioning of the system.

Recently also the origin of the CIII component has been determined (Oosterhlok and Spekreijse, 1990). CIII has also an extrastriate origin but does not show the retinotopic projection as the CI does and is therefore assumed to originate from area 19.

Pattern onset responses usually are being recorded at relatively low repetition rates, i.e. such that the response has finished when the new stimulus appears. This is done since the alteration of pattern and blank field yields different responses. The response to pattern onset generally can be clearly distinguished, also in its dependence on stimulus parameters, from the pattern offset response (when the pattern is abruptly exchanged by the homogeneous field, see for example Fig. 16). Therefore the use of higher rates (steady state) for this type of stimulation does not seem to be appropriate. There is however one condition in which such an interaction between pattern onset and offset is accepted tacitly. This is when the pattern is made to appear for a very short period (say 40 ms every 500 ms) (Jeffreys and Axford, 1972). Then the responses to onset and offset overlap and probably interact, although the offset response may be relatively small due to the short onset duration.

Brief pattern onset presentations are used relatively frequently since they evoke the largest responses and are perceived as the least disturbing stimulus, especially when the attention of the subject is to be attracted by means of

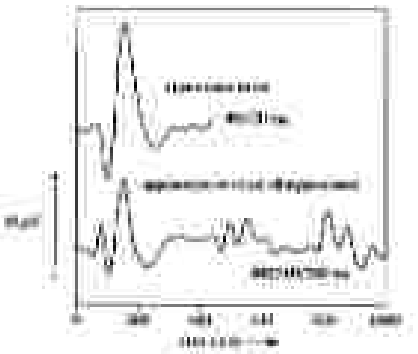


Figure 16. Normal VP to the short (40ms) presentation of a 12' checkboard pattern, and to the appearance-normal disappearance (450ms/50ms/500ms). The peak-to-peak amplitude for the short presentation is usually much larger, most of CIII latency both the appearance and the disappearance seem to generate positive [illegible]

e.g. simultaneous projection of cartoons (children). In conditions however, where attention of the subject is guaranteed, long pattern presentations (30s on every second) are preferred, such that the onset and the offset responses can be studied separately, and especially such that the offset response does not interfere with the onset response. The offset response is generally small, and often difficult to be identified. In clinical routine pattern offset is seldomly studied systematically.

3.3. Colour

Both luminance and contrast VEPs represent the eventual output of the scotopic and photopic visual system involving in principle the four types of light receptors normally present within the retina. The contribution of the rod system to the response can be studied in isolation at scotopic luminance levels (van der Tweel and Spekreijse, 1973). The contribution of the three cone systems to the response is more difficult to untangle.

Classically the two colour adaptation technique (Stiles, 1939; De Vries, 1948; Wald, 1964) has been applied to obtain selective stimulation of a single cone system. For the red, green and blue system each response components of different latencies have been reported: red P100 and P190, green P120 and P200 and for the blue P150 and P240 (White *et al.*, 1977). It will be appreciated from these data that the separation between "red" and "green" components is very difficult to obtain, probably because of the extensive overlap of spectral sensitivity between the two mechanisms. A better separation between the two long wavelength systems is obtained with the method of spectral compensation or silent substitution (Estevez and Spekreijse, 1974). In this method the ratio of modulation of two coloured lights is adjusted such that alteration of the stimuli comprises no modulation for one of the two cone systems. For the other mechanism then, because of its different spectral sensitivity curve the alteration of the two lights cannot result in complete cancellation and comprises a "perceived" luminance modulation (Spekreijse *et al.*, 1977). The data obtained from this type of stimuli and especially when applied in pattern stimulation, seem to suggest that the contrast evoked potential is generated by a single cortical contrast mechanism that can receive input independently from either of the long wavelength channels. The independent stimulation of one of the two systems yields responses that do not saturate for modulation depths as high as 50%. However the white (yellow) light activation of the cortical contrast mechanism already saturates at 10-15% modulation depth. It appears that once one of the two mechanisms is activated at a certain level, the contrast mechanism effectively blocks the input of the other cone system. To activate the blue cone system optimally, lower stimulus frequencies and coarser checks are needed (Estevez and Spekreijse, 1974).

For practical purposes in clinical circumstances the method provides an objective way of estimating spectral sensitivity in colour anomalies. However, the procedure requires a lengthy recording time, whereas a psychophysical

test based on the same principle of silent stimulation can be done rather quickly (Estevez *et al.*, 1983).

Monochromatic stimulation, and especially with the aid of red LEDs has been proposed in a number of clinical studies (Purves and Lees, 1976; McInnes, 1977; Nilsson, 1979; Mladenov and Franck, 1981), with however varying success. From the saturation behaviour and the interaction of the red and green mechanisms described above it might be anticipated that differential stimulation should provide more reproducible results than the white light activation. But the red light stimulates the green mechanism considerably since isolation is not very efficient. Furthermore, since there is an saturation, the response becomes more dependent on optical parameters. In routine clinical studies the colour stimulation is unsatisfactory. The ways stimulated coloured patterns were produced technically were very complex until the Personal Computer systems came available recently. The development of PC colour graphics has made available a feasible way of producing equiluminant coloured patterns that can be easily used in clinical settings (Gunduz, Arden and Perry, 1988). The technique awaits a normative database, both psychophysically and in evoked potentials, which will probably come available in the near future.

3. Stimulus location

By discussing the data obtained from equipotential mapping and the Principal Component Analysis (2.2.4.) we have implicitly introduced the use of multi electrode recordings and localized (very) field) stimulation. It is only by the use of half field or even quadrant stimulation that unequivocal conclusions could be reached as for the origin of the specific components.

Localized *luminance* stimulation is in principle not straightforward to obtain. Since scatter within the media of the eye redirects a considerable part of the stimulus light, it is only when applied amidst a strong surrounding field (i.e. at or above stimulus level) that it can be guaranteed that the responses obtained stem indeed from the directly stimulated field. Probably this is why high-intensity flash stimulation is not adequate in obtaining local responses of only part of the visual field (Vaughan *et al.*, 1963).

The discussion on how exactly specific locations of the field can be made to evoke responses at corresponding locations on the skull therefore is mainly on pattern evoked responses. The VEP is, as we already discussed in the paragraph on ERG, mainly determined by the foveal part of the visual field.

The topographic projection of the visual field onto the visual cortical areas does not leave much room for the recording of the responses of the peripheral part of the field (outside 10 degree). Firstly for the striate projection the cortical representation of the fovea is much larger than the peripheral part (so called cortical magnification factor, Drasdo, 1977), and secondly the peripheral part of the primary visual cortex is hidden to a great extent into the calcarine fissure, and is not in direct contact with the skull. Therefore, stimulation

of the peripheral field gives only rise to relatively small potential changes to be recorded at the skull. Since large peripheral fields are needed to obtain a reasonable signal to noise ratio, it is practically half field stimulation to ensure activation of one hemisphere only, that is described extensively.

The behaviour of the pattern reversal response to left and right half field stimulation has long remained a matter of debate. For instance, when recorded from a horizontal array of five electrodes with the central electrode 5 cm above the inion, it was reported that the P100 goes for large half field (radius 16°) stimulation was maximal above the ipsilateral hemisphere instead of above the contralateral one as would be expected on anatomical grounds (Barrett *et al.*, 1976; see Fig. 9 upper part). On the other hand, when recorded from an array 3 cm above the inion, and using a small field (0°30' radius) P100 was always maximal above the contralateral hemisphere (Chain *et al.*, 1982). Also the finding of maximal abnormality over the contralateral hemisphere in patients with hemianopia contradicted the earlier findings (Wildberger *et al.*, 1976; Holder, 1980; Harding *et al.*, 1980). The paradoxical disagreement was suggested to stem from differences in stimulation - and electrode configuration. Chain *et al.* (1982) mentioned they could turn contralateral positivity into ipsilateral positivity when switching to 'Halliday' conditions. Indeed, an important part of the parafoveal field is projected on the inferior medial surface of the calcarine fissure and results in a dipole orientation for large half field stimulation that appears to produce maximal activity above the ipsilateral hemisphere but that in reality originates in the contralateral hemisphere.

Thus, for large half fields (16° radius, 30° checks) one can distinguish an ipsilateral NPN complex of macular origin and a contralateral PNP complex of paramacular origin. This paramacular complex is the one that is left in conditions where the central part of the field does not generate a response: in normal subjects by covering the central part (Blumhardt *et al.*, 1978), in patients by central scotomata from e.g. toxic amblyopia (Kriss *et al.*, 1982) or hereditary optic atrophy (Harding and Crews, 1982). In these conditions the P135 of the paramacular PNP complex then can easily be confused with an increased latency P100 of the macular NPN. One can be guarded against this adequately by carefully studying the interpolation of the responses to half field stimulation (Halliday, 1982). It is imperative then, for this type of pathology, to use a horizontal array of five electrodes as a minimum electrode configuration.

The response of upper and lower half field generally shows opposite polarity at ca. 100 ms, a fact which is again the result of the specific cortical projection of the fields. The upper half field is projected inwards into the skull and generally produces smaller responses. In practical terms one can conclude that maximal amplitude for a full field pattern reversal can be found in a Cz-Oz derivation, i.e. is one electrode near the inion and another one ca 9 cm up. The fact that both half fields produce very different responses furthermore implies that it will be extremely difficult to localize pathology in one of the halffields (e.g. in glaucoma) since even interocular comparison

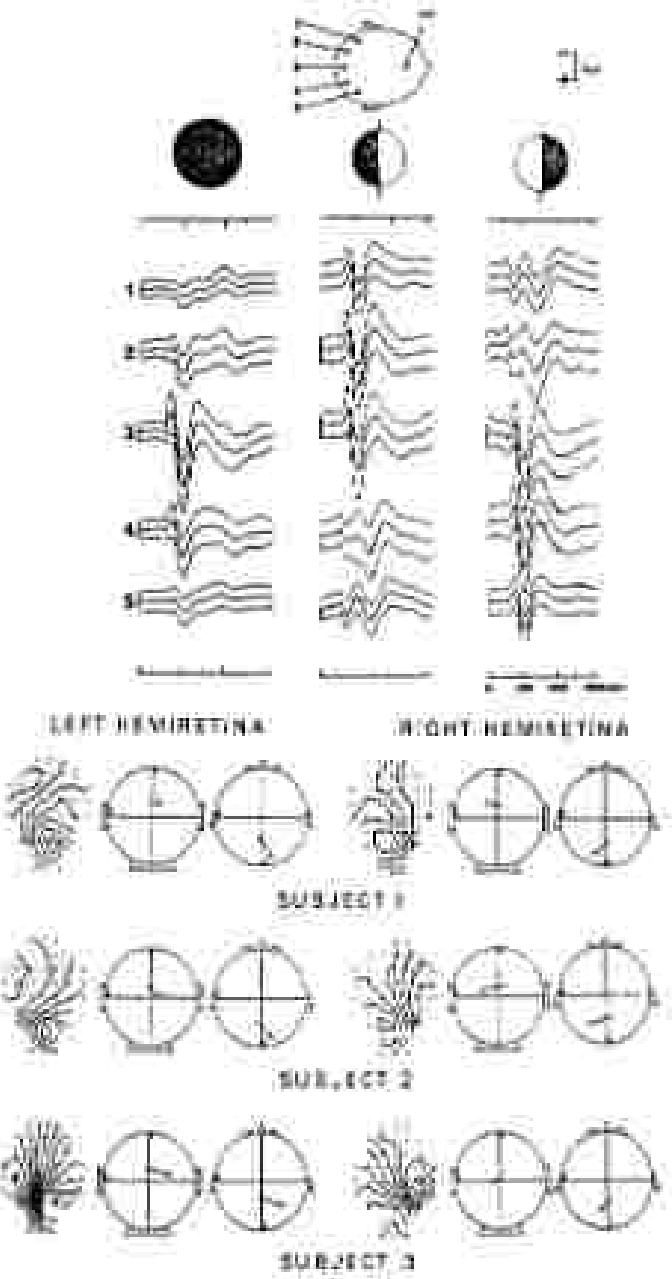


Figure 11. Upper: Distribution over the occipital scalp of the pattern reversal VEPs to full field (left column), left half field (mirror scheme) and the right half field (right column) (from Bobert *et al.*, 1976). Lower: Scalp distributions and dipole localizations plotted results for stimulation of the left hemifield (right visual field) and right hemifield (left visual field) (derived by Wood, 1982 from unpublished data of Halgren). While inspecting the lower part of this figure, please beware of the use of the words hemisphere and hemifield here in conjunction with those the words ipsilateral and contralateral have opposite meanings.

of halffields becomes meaningless. Interocular comparison however may be applied successfully.

The topographical distribution of the peaks of the pattern onset responses to half field stimulation is generally as would be expected on the basis of the anatomical layout. Upper and lower half field stimulation produces a polarity of each peak as for the P100 reversal component. Left and right halffield produce a clear C1 (P95) in the contralateral hemisphere. The CII (N120), on the other hand remains on the midline with halffield stimulation (Lascaro and Joseph, 1980; Draskic, 1980; Jeffreys, 1980).

Whereas these two conclusions were generally agreed upon already from their initial report, it left nevertheless room for different interpretations concerning the origin of these peaks. As mentioned above, principal component analysis and dipole source localisation seemed to settle this discussion recently. The C1 is mainly due to extrastriate activity, whereas both striate and extrastriate activity contribute to the CII peak.

These conclusions gave rise to recording procedures that can selectively enhance one of two (C1 and CII) peaks, as was originally proposed by Jeffreys. When for instance C1 is the peak of interest, half field (left or right) stimulation and a bipolar derivation (e.g. P3–P4) should be used. There the extrastriate component, as can readily be seen from the maps of Fig. 17, is sampled at maximal amplitude, whereas the striate component is sampled at almost the same equipotential line.

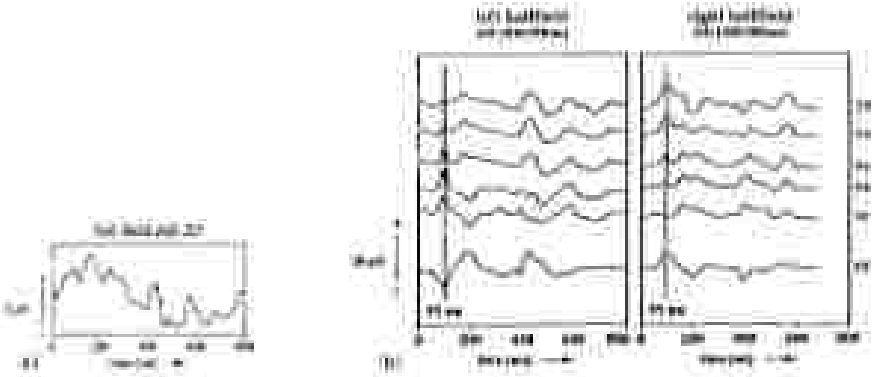


Figure 20. a: Full field pattern appearance-disappearance response of a male subject recorded 2.5 cm above the inion and referential to a midfrontal electrode. In this example the identification of components is difficult to establish. b: Left and right half field responses recorded from a row of five electrodes 2.5 cm above the inion and positioned symmetrically around the midline. The responses to the two half fields were obtained successively by using slightly different stimulation and averaging periods. Identification of especially the C1 component is unequivocally possible by its lateral representation in the left field to the right visual cortex and for the right half field in the left visual cortex/pla. In the lower channel (difference between the left and the right hemisphere) a clear polarity reversal between the two half field responses can be observed at the latency of C1 (95 ms in this subject). Show the use of half field stimulation and the recording of the topographic representation for the identification of components.

This method can be applied successfully when it is difficult to distinguish the C1 peak as for example in Fig. 20. In such a case a row of five electrodes and half field stimulation can be very helpful (Fig. 21).

Since C1 is a local luminance specific component that can be favoured with respect to C2 by the use of large checks, the use of large check stimulation, proved very successful in the detection of misrouting in albino subjects (Apkarian *et al.*, 1983; Apkarian and Spekreijse, 1985). In albino subjects the temporal half fields are differently projected, by crossing over to the

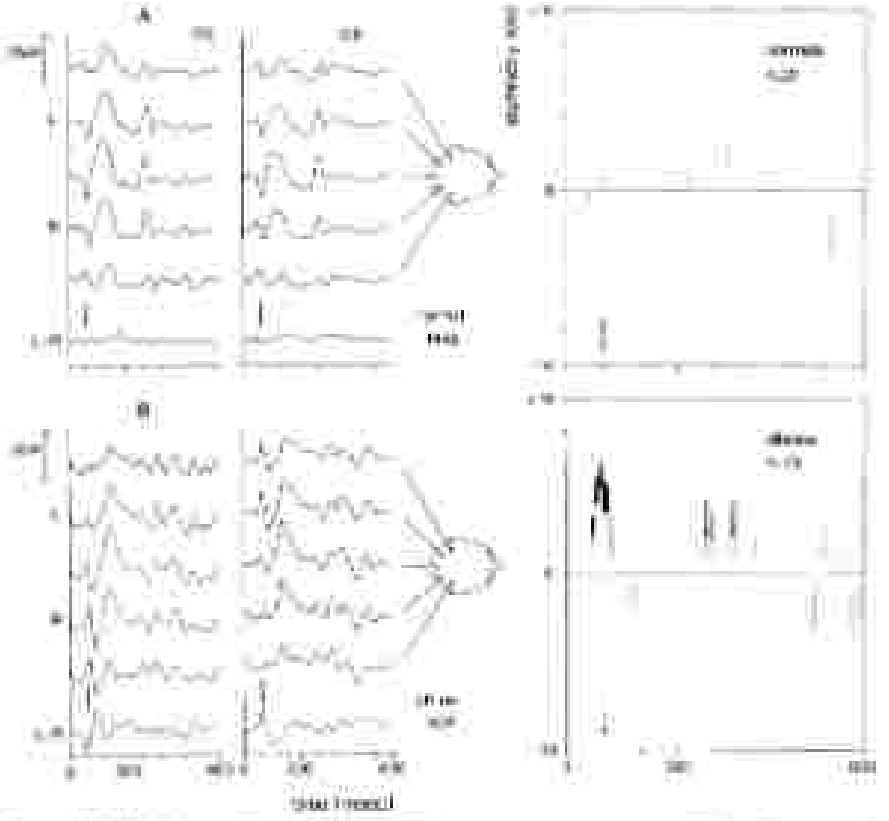


Figure 21. Left: Left eye (OS) and right eye (OD) responses to an apparently (300ms) disappearing (500ms) checkerboard pattern in a normal observer and an albino. Checksize was 55', fieldsize 20° (horizontal) by 15° (vertical), stimulus locally (0°)6. Recordings from a row of electrodes as in Fig. 20. The lower channels show the (split) "difference" between left and right hemisphere. There is no difference in the normal subject, suggesting a symmetric distribution, whereas in the albino there is a clear polarity reversal at ca. 100ms, suggesting an asymmetric distribution of the primordial (= full field) stimulation of the left and right eye. Right: Group average left minus right peak location for normal (open circles) and for albinos (closed circles) as a function of time. In albinos the peak latencies are significantly for a latency of ca. 100ms (After Spekreijse and Apkarian, 1986).

contralateral hemisphere. So the monocular full field responses in albinos resemble very much the half field responses of normal subjects. It is at CI latency that this asymmetry manifests itself the best. For practical purposes it is advised to use in addition to the usual 5 monopolar derivations a difference channel (P3–P4) between the left and the right hemisphere to visualize the effect immediately (Fig. 21).

Maximizing CII amplitude, when for instance visual acuity has to be tested objectively, can be obtained by full field stimulation with a monopolar derivation at the inion and referenced to another Fz (see also Fig. 17). The functioning of the different parts of the visual field cannot so easily be judged from this CII, since it contains activity from both the striate and the extrastriate regions.

4. Dissecting along the visual pathway

4.1. Early processing

In the foregoing we have confined ourselves to the responses to the classically used stimuli. The responses thus obtained generally have been assumed to originate in the primary and secondary visual cortical areas. We already pointed out that there is a priori no reason to assume a sequential link between the two systems, and hypothesized parallel pathways feeding into these areas. The VEP reflects the final output of the visual system, including the retina, anterior and posterior pathways, the chiasm, LGN and optic radiation. Although left and right half field responses comprise one way of localizing pathology along this pathway – a classical way, since it can be equally well applied in (psychophysical) visual field examination – no other way to do so is present in the techniques presented up to now. The techniques that specifically attempt to examine so to speak 'along the visual pathway' have to be mentioned here as current development.

Firstly there is the study of Visually Evoked Subcortical Potentials (VESP), that is based on classical methods: flash stimulation and coherent time averaging (Harding and Rubinstein, 1980; Rubinstein and Harding, 1981). Especially the combination of a simultaneous registration of the VEP, VESP and the ERG possibly could provide a valuable approach of the matter. However, we have seen that the VEP recorded to pattern stimulation produces the most consistent data, whereas for both the VESP and the ERG luminance flash stimulation is the most effective in attaining reproducible results.

A second approach to this problem comprises the sequential systems analysis (Spekreijse and Reits, 1982), in which the system is modelled by a so called "sandwich" system. The core of such a model is a non-linear element, this non-linear signal processing element is "sandwiched" between two linear processes. By astute choice of the stimulus signals it becomes possible to independently study the beginning and end part of the system. The stimuli

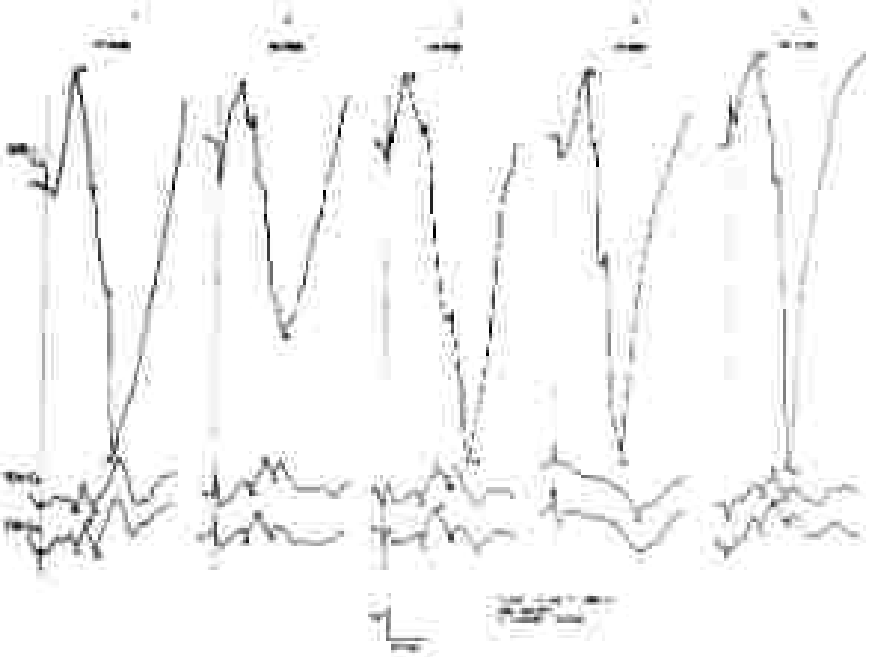


Figure 33 Simultaneous recordings of the corneal ERG and the VEP at five subjects. Clearly distinguished VEPs can be observed in (1), (2), (3) and (5). Subject 4 is atypical, though neurologically normal and with a normal ERG. (Fig. 3.13, PhD-thesis of M.P. Rubinstein, University of Aarau)

meant here are sinusoidal modulations, and especially the simultaneous presentation of two (or more) sine waves, that have no harmonic relation. The non-linear element in the system will, as a rule, cause intermodulation terms in the response, that is components that have a frequency equal to the sum or the difference of the input frequencies. The choice of a series of combinations which the difference frequency is constant each, will probe the early linear part of the system. Once the distal linear part is known, a series of stimuli in which the centrefrequency is varied systematically, but such that the constituting frequencies are very near to each other, will provide a probe for the later or proximal part of the system.

Especially attractive in this type of analysis is that it provides access to independent study of luminance (by superposition of the frequencies) and contrast (by presenting the two frequencies in neighbouring checkerboards) or even binocular (by presenting the two frequencies dichoptically) responses. Although already a fairly old concept (Spekreijse, 1966) its relatively complex analysis techniques has up to now hampered its application in the clinical routine.

4.2. Late processing

Several approaches have been brought forward to address the question of how binocularity could be tested. In a number of studies binocularity was merely tested by recording the responses in monocular and binocular conditions. The extent to which the binocular response then exceeds the monocular one or alternatively the sum (S) of both monocular responses is used as a measure for binocularity (Wanger, 1978; Sireno, 1978; Lennerstrand, 1978). The extent, however, to which the monocular responses can be summed to predict the binocular response is highly dependent on stimulus conditions. For instance at high stimulus contrasts the monocular response is saturated (Spekreijse *et al.*, 1972) and the binocular response can either be equal to the monocular or equal to the sum of both monocular responses, depending on the order of the saturating element and the binocular interaction element in the signal processing chain. By testing under a great number of stimulus conditions, varying both temporal and spatial frequency and stimulus orientation Apkarian *et al.* (1981) observed that the type of reaction for binocularity shows a large variability and a rather capricious dependence on the different parameters, rendering the application of this type of VEP measure for the assessment of binocularity in the clinic inadequate.

Another more recent approach to the problem of binocularity is the use of random dot stereograms and especially the dynamic version, in which the dot patterns are exchanged continuously at a high rate (50/60 per second). By presenting (Lehmann and Julesz, 1978; Hoffe-Wollmer, 1981) such patterns dichoptically and instantaneously (stimulating correlated patterns except but shifted a certain distance) a strong perception of movement in the depth is induced. The responses to such a stimulus as yet have not been studied extensively and unfortunately seem to be highly variable among subjects and very small in amplitude (Regan and Spekreijse, 1979; Odom and Chan, 1987). Nevertheless, technology to produce such stimuli develops rapidly and the method, that comprises a selective test of binocularity, will certainly come available for routine use in due time.

5. Dependence on physiological factors

The overwhelming variety of stimulus configurations used in the literature hampers the interpretation of variability to a great extent. We have in the foregoing already discussed the influence of a number of stimulus parameters to the response obtained, as there are (because of frequency of stimulation. However, a number of parameters have not been discussed yet, on purpose, since they are only partly under control by the equipment itself, but may be influenced by subject properties (luminance of the stimulus versus pupilsize, hue colour, cataract; modulation depth versus cataract, refraction). Establishment of these dependencies is to speak sets the working point of a certain

laboratory equipment and may reduce intersubject variabilities. The numbers thus obtained show a low variability in literature and thereby comprise a good calibration procedure for new laboratory equipment.

The dependence of P100 latency of the pattern reversal response on the luminance of the stimulus has been studied thoroughly (Cant *et al.*, 1978; Diener *et al.*, 1982; Halliday, 1982) and invariably showed a 12–15 ms increase per log unit decrease of the luminance, in the range of the routinely used luminances of 50–100 cd/m^2. Note that the effect can be considerably larger when an even further reduction of the luminance is effected (van der Tweel *et al.*, 1979; Spekreijse, 1980); a 5 log unit decrease produced a 140 ms increase of the CII peak latency of the pattern onset response. Note how invariant the shape of the pattern onset EP is for this 100,000 fold reduction of luminance, indicating again that cortical activity, and not the type of reception stimulated, determines the response.

It is in the context of the normal luminance dependence that the effect of pupil size on the latency of the response can be understood entirely (Sokol, 1981; Penne and Fonda, 1981). The latency difference observed for a reduction of pupildiameter from 8 mm to 2.5 mm, exactly corresponding with 1 log unit reduction, was 12–15 ms. So part of the normal subject variability may be understood from this phenomenon, and may be reduced by correction for it. In the same time, anisokoria easily can introduce an inter ocular latency difference that could be misjudged as being pathological, when not noticed by the examiner.

Obviously, more factors that determine the ultimate retinal illumination do exist, such as eg the colour of the lens can hardly be quantified and corrected for.

Analogously, but less systematically, is the response influenced by change

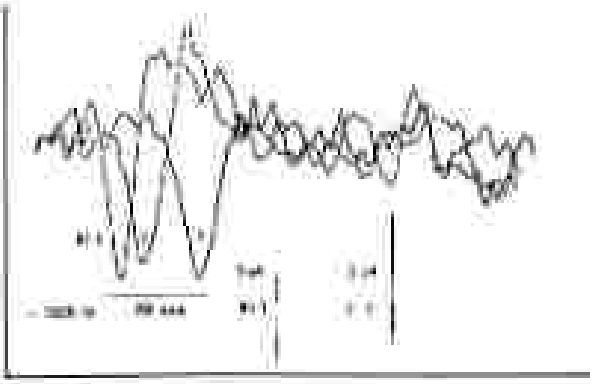


Figure 28. VEPs recorded to a checkerboard (30 checks, 4° lower half field appearance at different luminance levels. The sensitivity has been shifted in order to obtain equal amplitude deviations of the potential. The shape of the response is not dependent on (except when of the scotoma extension of photopic) the response is unaltered. Only its latency is and amplitude is changed.

of the modulation depth (contrast) of the pattern presented. It is well known that for contrasts above ca. 30% (both reversal and pattern onset) responses are saturated (Spekreijse *et al.*, 1972) that is their amplitudes remain constant irrespective of the modulation depth above 30%. At lower contrasts not only the amplitude decreases roughly proportional with log contrast, but also the peak latencies decrease. Probably this is one of the reasons why defocus delays the response and the more so the smaller the checksize (Sokol and Moskowitz, 1981). They observed for instance a latency decrease of ca. 15 ms for the P100 for 8D misfocus of a pattern of 48' checks. The effect however is by no means linear with the amount of defocus and the exact numbers are very difficult to interpret since the different components within the response (local luminance, pattern and movement) probably are affected to a different extent.

The examples presented here are meant to serve the purpose that they indicate that every VEP examination should be preceded by a meticulous ophthalmological examination of the subject, including the evaluation of the refraction, pupil size, clarity of the media and the like, since even a cylindric correction can change the pattern onset latency considerably (Spekreijse *et al.*, 1972). Note that the pattern onset is more sensitive for the quality of the retinal image than the pattern reversal response. Given these variabilities caused by variability of the quality of the image delivered at the retina there are two factors left that further influence (intersubject) variability: gender and age. The small but significant differences between the two sexes in the mean latency of the reversal P100 was first brought to attention by Stockard *et al.* (1979). The female response tends to be 3 to 5 ms earlier than the male. Furthermore an amplitude difference in the mean was found. Amplitude was up to 40% higher in the female responses (Halliday, 1982). Halliday suggested that the latency differences between sexes decline for subjects over 30 years of age, but already quoted his data as inconclusive about the point. Further study (Kriss *et al.*, 1984) showed the differences to persist even for the oldest subjects tested, and also established that the difference is found not only for pattern reversal but also for pattern onset stimuli. The gender differences were ascribed to differences in body temperature, skull thickness and headsize which however could not explain the whole difference fully.

Age effects on both latency and amplitude of the responses have been reported (Celesia and Daly, 1977; Allison *et al.*, 1979, Shaw and Cant, 1980, Halliday, 1982; Chiang and Hung, 1983; Kriss *et al.*, 1984; Sokol and Moskowitz, 1982).

Latency was shown to increase up to 10 ms for women above 50 years (Halliday, 1982), whereas others suggested a linear relation between age and latency for both male and female subjects, resulting also in a 10 ms difference between subjects of the age of 60 years and 20 years. The effect however was reported to be dependent on the luminance of the stimulus (Shaw and Cant, 1980), strongly suggesting that differences of the ultimate retinal stimulation to a certain extent can account for the effect. Indirect there is already a longstanding knowledge about the optical quality of the elder eye, reporting that its point spread function is much broader than its younger

equivalent (Vos, 1984), which results in a reduced image quality and a lower luminance level at the retina of the older eye. Furthermore, pupil size in older subjects in the mean is 1 mm smaller than the average younger pupil (mean 4 mm) resulting in a 44% reduction of retinal illuminance (Kriss *et al.*, 1984; Owsley *et al.*, 1983). It is most likely that the culmination of these effects produce the observed latency shifts.

Amplitude effects of age, however, are less straightforward, since an increase of amplitude with increasing age was reported for flash evoked VEPs (Dustman and Beck, 1969; Harding, 1982) and furthermore for two components of the pattern onset response (C1 and C11, Kriss *et al.*, 1984), whereas both the pattern reversal and pattern offset stimuli yielded smaller amplitudes in the older males, but not in the females. These effects, however, being only poorly significant, have not been reproduced yet and it remains to be established whether they may result from the way stimulation was performed. It can be questioned furthermore whether these amplitude effects, being only weakly significant, may encounter any clinical consequences.

6. Normative values

It is only within the limitations posed by the discussions above that we now reproduce normative data from the literature. It should be obvious that every laboratory that applies the types of stimulation and recording described in this chapter should start out and develop its "own" normative database. In the mean time the normative data from the literature can be of practical use both by way of reference for the local normative values, and for the intrinsic application of tests in clinical questions.

For the flash evoked potentials a vast number of peaks have been reported in literature. It is difficult to detect data since so many varieties of nomenclature to identify the peaks exist. We have already pointed out that only the latency of the onset of the primary complex is of importance when conduction is to be evaluated. Therefore, in Table 1 the onset latency of the primary component is quoted from the literature. The secondary complex, being quite large in amplitude, we stated, often is used to evaluate the eventual arrival

Table 1. Flash VEPs

Age	onset primary response P1 x ± SD	latency secondary component P2 x ± SD
Premature - 3days	NA	264 ± 68
0.5 - 1 months	27 ± 8	182 ± 32
6 months - 5 yrs	32 ± 12	189 ± 32
7 yrs - 49 yrs	38 ± 4	207 ± 10
59 yrs - 77 yrs	51 ± NA	227 ± 13

Table 2. Pattern reversal, checks > 20′.

Age	P100
4–9 months	135 ± 8
10 m–5 yr	108 ± 5
5 yr – 46 yr	103 ± 7

Note that for the Riemslag study, CnL includes the data of a relatively large number of infants, the P100 latency does not show a significant increase with age above 5 years.

Note furthermore that the variance of the latency of P100 in this study is relatively large; it includes a relatively large number of studies with various types of equipment used. Probably on a local normative database, these numbers can be made to very low, and then an age dependence as described by Rietz *et al.* (1988) might become significant.

of a signal at cortical level. The latency of the most prominent positive peak of this complex is given just to facilitate identification of the complex. These data depend on the age of the subject, the data, therefore, have been grouped into relevant age ranges (see Chubot and John, in the New Handbook of Electroencephalography and Clinical Neurophysiology 1986, for an extensive overview of these normative data). The values selected here are the values quoted as reference norms for individual patients. From the given means and SD values a 95% confidence interval can be constructed by adding/subtracting 1.96*SD ms from the means.

For the pattern reversal it is the latency of the prominent positive peak at ca 100 ms (P100 or P2) that is the relevant parameter. These data include those studies that used checks larger than 20′ of visual angle.

For the pattern onset stimulation the number of studies in literature is much smaller than the studies quoted on flash VEP or pattern reversal. The handbook provides no systematic evaluation of age on the three components C1, C11 and C111 for this type of stimulation. The data available suggest a much greater latency variability of the components, explaining its limited use in conditions where the latency is the parameter of interest. The numbers reproduced in Table 3 therefore serve a much more limited use. It is only to facilitate identification of the components that these numbers have been reproduced here. Indeed the pattern onset responses more often have been used in questions of objective visual acuity estimation, where the C11 amplitude is recorded as a function of check size: a relative measurement, that does not require a comparison to a normative database. Alternatively we have already seen application of the pattern onset in questions of the evaluation of the

Table 3. Pattern onset, 20′ checks.

Age	C1	C11	C111	
20–60 yr	70 ± 10	116 ± 15	173 ± 27	(Riemslag *et al.*, 1981)
70–85	89	136	197	(Celesia *et al.*, 1984)

topological distribution, where especially the CI was the most important parameter.

7. Applications

In a great number of ocular and neurological/pathological conditions the techniques indicated above can be applied and provide additional information. Even without attempting to be complete we intend to treat a selection of these in the following. The selection made has been aimed at the illustration of the different approaches to the questions encountered, rather than to provide a full coverage of diseases.

It is to be noted that certain aspects of the responses may indeed be altered in a very large number of pathologies. Therefore, none of the alterations observed in certain conditions can be considered specific for the disease. This argument reversed implies that VEP testing requires a precise delineation of the diagnostic question at hand. In other words the testing procedure which is to be adopted and the information which is to be gained from it, entirely depends on the referring physician's latter. Since we prefer to discuss methodological aspects rather than specific pathological entities, ophthalmological and neurological disorders will come across in a arbitrary order.

7.1. Latency increase

The first and probably most frequent application of VEPs is found in Multiple Sclerosis. Indeed, the objective establishment of a clinically silent lesion in the visual system, often constitutes a valuable piece of information to the neurologist when MS is considered in a diagnostic question. In such cases, i.e. not in exacerbation with the visual system involved, the responses of MS patients often show an increased peak latency without evident change of the waveform or amplitude. The examination procedure in MS therefore specifically should be aimed at the detection of a latency increase. Such an examination therefore should start with transient pattern reversal stimulation (2 rev/sec, 30' and 60' checks, field size $\geq 6°$), since the latency distribution of its prominent P100 shows the smallest variation in the normal population. As mentioned, sometimes it can be difficult to identify P100, since the response may be small and obscured by the presence of additional components. If therefore in this condition no recognizable response is obtained, the test should proceed with the recording of pattern-onset (pattern on 300 ms every 600 ms; 10', 20' and 30' checks) responses (for responses see Figs 16 and 25). For instance in patients with nystagmus by whatever cause, sometimes normal latency responses can be recorded, where no pattern reversal response can be identified. When this again should not produce recognizable responses a 'steady state' reversal rate of for instance 8 rev/sec should be applied. If this produces a response, an additional series of reversal rates (eg 7.1, 10 and 12.5 rev/sec) is to be applied

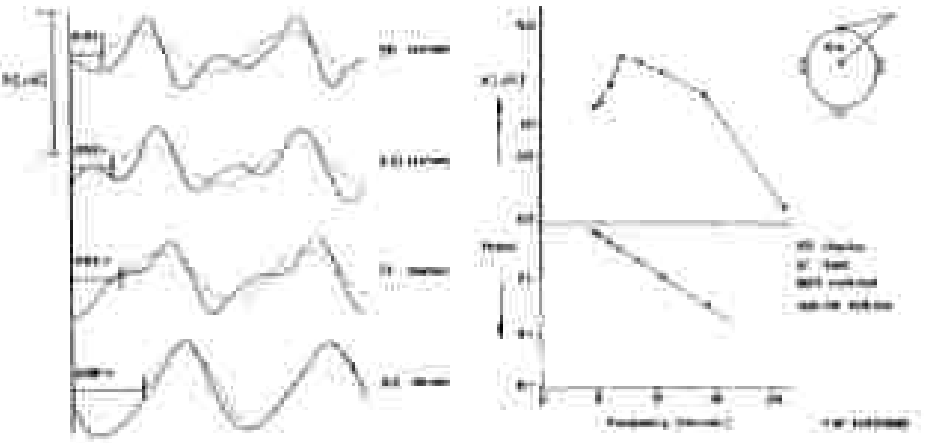


Figure 24. Analysis of steady state responses. On the left side responses to four different frequencies are shown. The dotted lines represent the first harmonic component (i.e. sinusoidal fit). The amplitudes and phases of these first harmonics have been plotted on the right side to give amplitude and phase characteristics. The phase is seen to vary proportionally with the frequency and from the slope of this phase characteristic an apparent latency can be obtained (After Riemslag *et al.*, 1981).

in order to be able to construct a phase characteristic (phases of the Fourier components at the reversal rate, as a function of that rate; Fig. 24). From the slope of this phase characteristic then, an estimation of the apparent latency of the response can be made.

The strategy obviously pursues a trade off between signal-to-noise ratio and examination time consumed, its main object being to obtain a recognizable response so as to be able to estimate its latency. In the context of MS diagnosis the amplitude of the EP is only indirectly relevant since it provides the prerequisite to enable latency estimation.

Also in cases of atrophy (Teschian 1975, Lewis *et al.*, 1978) the latency of the response may be increased; a condition which improves upon demodulation. Therefore accurate latency estimation carried out according to the procedure above, provides a valuable tool to monitor central nervous system function, in addition to EMG monitoring of the peripheral nerve system.

Latency may be increased in a number of disorders like compression of the pathways, Leber's atrophy, intoxications, optic disc edema, disc atrophy, etc. In many of these it is however only seemingly just a change of latency, since after careful evaluation of the response it is accompanied by amplitude- and/or distribution-alterations. For instance in cases of central scotomata (Leber's atrophy, intoxications) the seemingly present latency change of the pattern reversal response is a result of the absence of the central response. The parafoveolar P'N' response dominates of which the P135 is mistaken for the macular P100 (see also the upper part of Fig. 19).

7.2. Amplitude

Amplitude measurement we have already introduced in the section on stimulation, where we discussed the problem of amplitude distribution across the skull, and its dependence on the location of the stimulus within the visual field. This distribution was shown to be distorted in albino subjects. Or, reversed, this distribution can be used in order to diagnose albinism, which diagnosis is not as straightforward as considered classically. The question on amplitude variability in normal subjects has not been discussed in the section on normative data deliberately: amplitude variability is considerable and furthermore is even more critically dependent on specific stimulation and recording conditions. It is only when relative measurements can be made, referenced to comparable values within the same subject (other eye, comparable part of the visual field, etc.), that a meaningful measurement of the amplitude can be made.

Amplitudes may be reduced in various conditions, like acute retrobulbar neuritis, Leber's atrophy, disc edema, ocular circulatory disturbances, opacities of the media, blunt eye injury, etc. On the other hand variability of amplitudes in normals is very high and hampers correct interpretation of amplitude reductions. Usually in the named disorders, amplitude reduction accompanies a gross waveform alteration, which renders objective amplitude measurement even impossible.

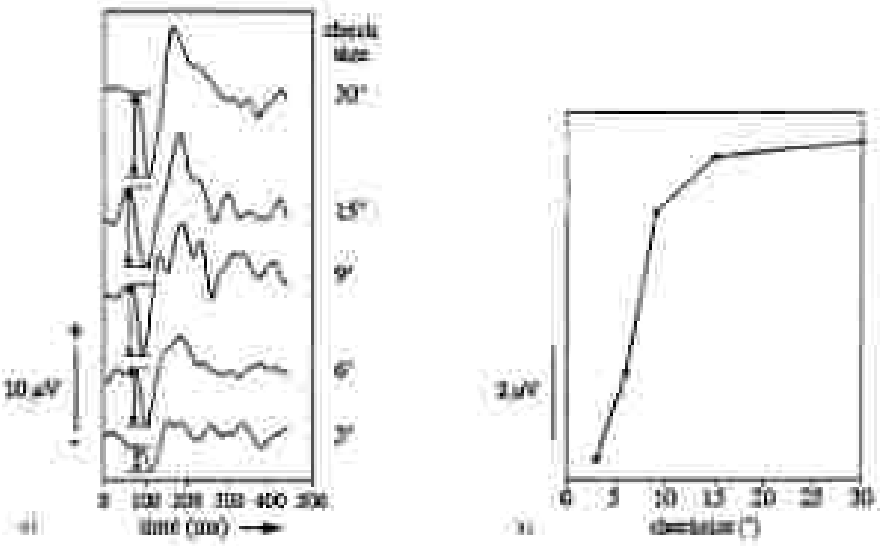


Figure 23. Objective assessment of visual acuity by means of pattern stimulation VEPs in a hysteric amblyopic patient. The responses to the standard 1 cpd at full contrast alternation in order to obtain an (under) estimate of the visual acuity (VA) amplitudes of the primary specific CH has been plotted as a function of checksize in a VEP scale. Extrapolation of the amplitude to zero yields an acuity estimate of better than 0.5

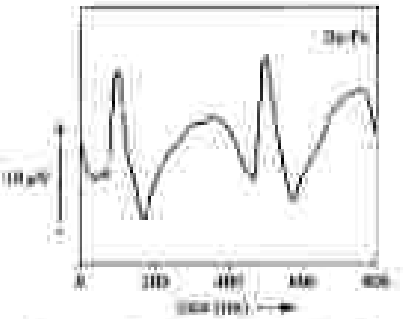


Figure 26. VEP pattern reversal response of a 6 month old boy (both eyes). The parents complained about 'a lack of eye contact'. From these normal responses it could be concluded that the primary visual system was functioning normally.

This is an unfortunate circumstance, since for instance in severe penetrating or blunt eye injury, it interferes with objective evaluation. In this case this would be a critical evaluation, since a decision has to be made between enucleation in connection with the risk of sympathetic ophthalmia and the chances of a very painful eye but with the prognosis of recovery of vision. (Crews *et al.*, 1978).

In amblyopia we already mentioned a selective reduction of CII of the pattern onset response. It thus comprises a gross waveform alteration. However, the interpretation in terms of components in the response, here helps to understand this alteration (Spekreijse *et al.*, 1972). Amplitude evaluation may be applied successfully, if an objective estimate of visual function is required, like in hysteric amblyopia, aggravation or uncooperative subjects (children). Such an evaluation is depicted in Fig. 25, giving the VEPs to a series of checkerboards of a 21 year old female patient complaining of reduced visual acuity by unknown cause. Hysteric amblyopia was suggested. The amplitudes of the CII-component were measured and plotted at the right against check-size. Extrapolation of this curve to zero amplitude yields a lower limit estimate of the visual acuity that does not differ from normal. Thus the diagnosis of hysteric amblyopia was confirmed objectively, especially since the CII component manifests itself so clearly in the response, whereas this component is usually reduced in amblyopia. Figure 26 finally gives the pattern reversal response of a 6 months old boy. His parents visited the ophthalmologist since they did not have 'eye-contact' with the boy. The normal responses, with high amplitudes, served to conclude that the primary visual cortex was functioning normally. (Caution should be observed in these cases, for even in cortical blindness evoked potentials may be recordable (Hoyt-Wilmer, 1977)).

In this application section we have concentrated on latency and amplitude measures since they are by far the most commonly used parameters in clinical routine. Application of topography and component specificity has been dealed with in the basic part of this chapter, where we discussed the origin of the different components and the resulting topographical distributions.

Acknowledgment

The authors wish to thank Dr. H.F.E. Vrabec Lamé, Mrs. A. Frens and Mrs L. Appel, of the Department of Ophthalmology of the Academic Medical Center of the University of Amsterdam for selecting the patient material.

References

Allison T, Goff T, Wood CC. Auditory, somatosensory and visual evoked potentials in the diagnosis of neuropathology: recording considerations and nomenclature. In: Lehmann D, Callaway E (eds) Human evoked potentials. Applications and problems. Plenum Press NY 1978; pp 1–16.

Aphamian P, Nakayama K, Tsuji CW. Bimodality in the human visual evoked potential: habituation, summation and opponency. Electroenc. C...n Neurophysiol 1981; 51: 490–504.

Aphamian P, Spekreijse H. The VEP and neuronal pathways in human albinism. In: Cracco RQ, Bodis-Wollner I (eds) Alan R Liss 80's 1982.

Aphamian P, Spekreijse H, van Dorp D. A realistic visual ophthalmological test for human albinism. Electroenc Clin Neurophysiol 1982; 53: 533–534.

Arden GB, Bodis-Wollner I, Barlow AM, Jeffreys JAX, Kulikowsky JJ, Spekreijse H, Regan D. Methodology of pattern visual evoked response: report of the Brussels Symposium of the Committee for Visual evoked potentials. In: *Visual evoked potentials in man: new developments*. Ed. JE Desmedt Clarendon Press Oxford 1977; p 1–11.

Arden GB, Faulkner DJ, Man CB. A versatile electronic pattern generator for visual evoked potentials. In Desmedt Clarendon Press Oxford; pp 99–109.

Armington JC. Visual cortical potentials and electroretinograms. Elicited by saccadic eye movements. In: JE Desmedt (ed) Visual evoked potentials in man, new developments. Clarendon Press Oxford 1977; pp 346–366.

Barrett G, Blumhardt LD, Halliday AM, Hall dey E, Kriss A. A paradox in the lateralization of the visual evoked response. Nature, London 1978; 261: 253–255.

Blumhardt LD, Barrett G, Halliday AM, Kriss A. The effect of experimental "sectioning" on the ipsilateral and contralateral responses to pattern reversal in one half field. Electroenc Clin Neurophysiol 1978; 45: 376–385.

Bodis-Wollner I. Visual association cortex and how to make pattern evoked occipital potentials in a blind boy. Science 1977; 198: 629–630.

Bodis-Wollner I. Selective stimulation reveals central components of the human visual evoked potentials. Electroenc Clin Neurophysiol 1981; 52: 204–207.

Bornschein H. Der Einfluss von Adaptationszustand und Reizvorgeschichte auf die Komponenten des menschlichen Potentialmusters. J Biol 1951; 103: 438.

Cant BR, Hume LR, Shaw NA. Effects of fixation on the pattern visual evoked potential in multiple sclerosis. Electroenc Clin Neurophysiol 1979; 47: 696–704.

Celesia GG, Daly RF. Effects of aging on visual evoked responses. Arch Neurol 1977; 34: 403–407.

Chalupa RJ, John RE. Event related potentials. In: FH Lopes da Silva, W Storm van Leeuwen, A Remond (eds) Handbook of Electroencephalography and Clinical Neurophysiology. Elsevier, Amsterdam 1986; pp 20–123.

Chiappa F, Greenberg M, Hirst JF, Libbey M. Ipsilateral delay of visual evoked potentials in patients with homonymous hemianopsia. In: *Evoked potentials*. F Blanquet, F Revol M. Advances in Neurology 32. Raven Press NY 1982; pp 51–70.

Cheung TR, Hong TF. Pattern reversal visual evoked potentials in normal subjects and patients with multiple sclerosis. J Formosan Med Assoc 1982; 81: 493–1500.

Cigánek L. Die elektroencephalographische Informationsanalyse der menschlichen Sinnesorgane. Ele-

society. Academic Med Rotterdam, 1981.

Creutzfeldt OD, Kuhnt U. Electrophysiology and topographical distribution of visual evoked potentials in animals. In: R Jung (ed) Handbook of Sensory Physiology VII/3. Springer-verlag, Berlin 1973; pp 595-646.

Cross S J, Thompson CWY, Harding GFA. The pRG and VEP in patients with severe eye injury. Doc Ophthal Proc Ser 1978; 15: 265-269.

Dawson HC, Kosh W, Dustgeb HC. The significance of hemianopsia on visual evoked potentials in diagnosis of MS. Arch Psych Neurol Sci 1962; 27: 149-154.

Dowling JE. The Retina. An approachable part of the brain. The Belknap Press, London 1987.

Dressler N. The neural representation of visual space. Nature, London 1977; 268: 344-349.

Dressler N. Cortical potentials evoked by pattern presentation in the visual region. In: C Barber (ed) Evoked Potentials. UPP Baltimore, 1980; pp 397-414.

Dumont AL, Spekreijse H. Latency of luminance and contrast evoked potentials in multiple sclerosis patients. Electroenceph Neurophysiol 1979; 47: 506-518.

Emmerson G, Spekreijse H. A spectral comparison method for determining the flicker characteristics of the human visual mechanism. Vision Res 1974; 14: 825-830.

Emmerson G, Spekreijse H, van Dalen JTW, Wytzgn Lunel HFE. The OSCAR colour vision test. Theory and evaluation of Objective Scanning of Colour Anomalies and Reductions. Am J Opt Phys Opt 1983; 60: 892-901.

Gunduz K, Arden GB, Perry S. Colour contrast sensitivity in laser operator's eyes. ISCEV 1988 in press 1988.

Halliday AM. Evoked potentials in clinical testing. Churchill Livingstone, Edinburgh 1982.

Halliday AM, Barrett G, Carroll WM, Kriss A. Problems in studying the normal limits of the visual evoked potential. In: J Courjon, F Mauguiere and M Revol (eds) Advances in Neurology 32. Raven Press NY 1982; pp 1-9.

Harding GFA, Crow SJ. The visual evoked potential in hereditary optic atrophy. In: J Courjon, F Mauguiere and M Revol (eds) Advances in Neurology 32. Raven Press NY 1982; pp 21-36.

Harding GFA, Rawstron MP. The scalp topography of the human subcortical potential. Int ophthal Vis Sci 1980; 19: 319-321.

Harding GFA, Smith GF, Smith PA. The effect of retinal eccentricity on the lateralisation of the VEP. In: C Barber (ed) Evoked Potentials. UPP Baltimore 1980; pp 213-218.

Heijde van der GL, van den Akker EJ, Aaftgarde CH. Comparison of RGD and VEP pattern stimulation. Doc Ophthal Proc Ser 1982; 31: 343-352.

Holder GE. Abnormalities of the pattern VEP in patients with non-organic visual field defects. In: Barber C (ed) Evoked potentials. UPP Baltimore 1980; pp 283-290.

Holmes G. The organization of the visual cortex in man. The Feeder Lecture. Proc Roy Soc B 1945; 132: 348-361.

Joynt GE, Bryan RL, Swanson JR. Electroencephalographic brain phenomena in diabetic ketoacidosis. Medicine & Cir, Edinburgh Psych, 1965.

Jeffreys DA. The nature of pattern VEPs. In: Barber C (ed) Evoked Potentials. UPP Baltimore 1980; pp 169-177.

Jeffreys DA, Axford JG. Source location of pattern specific components of human visual evoked potentials. I. Components of striate cortical origin. Exp Brain Res 1972a; 16: 1-21.

Jeffreys DA, Axford JG. Source location of pattern specific components of human visual evoked potentials. II. Components of extrastriate origin. Exp Brain Res; 16: 22-40.

Kavanagh RN, Darcey TM, Lehmann DM. The determinants of the human visual evoked potential EEG (in Neurophysiology 1976; 40: 933-944.

Kriss A, Carroll WM, Blankhorn LH, Halliday AM. Pattern and flash evoked cortical potential changes in toxic (nutritional) optic neuropathy. In: Courjon J, Mauguiere F, Revol M (Eds) Advances in Neurology 32. Raven Press NY 1982; pp 11-19.

Kriss A, Spekreijse H, Verduyn Lunel HFE, Rosenhall U, de Weerd BJ, Barrett G. A comparison of pattern onset, offset and reversal responses: effects of age, gender and duration. In: Noble RH, Barber C (Eds) Evoked Potentials II. Butterworth 1984; pp 355-361.

Lennox D, Davey TM, Skuse BJ. Luminance and angle fields revealed by horizontal checkerboard reversal, and mapping of cone driven ganglion. In: Costin J, Magalini F, Rizzo M (Eds) Advances in Neurology 32. Raven Press NY 1982; pp 41–48.

Lennox D, Jones R. Late-latent cortical potential evoked in humans by dynamic random-dot stereograms. Vision Res 1987; 27: 1285–1292.

Lindenmond G. Binocular interaction studied by cross evoked responses (VEP in normals with normal and unpaired anomalous retinal. Acta Ophthal 1978; 56: 626–633.

Lowyck N, Joseph JP. Modifications of the pattern evoked potential in relation to the retinotopic map of the visual field (cats) for the most probable origin of each component. Electroenc Clin Neurophysiol 1978; 45: 165–203.

Lowyck N, Joseph JP. Hypotheses concerning the most probable sites of origin of the various components of the pattern EP. In: Bagchi C (ed) Evoked Potentials, UPP Baltimore 1980, pp 159–166.

Lynch DG, Dunynne HE, Bola EC. Visual and somatosensory evoked potentials in patients undergoing lumbosacral and spinal surgery. Electroenc Clin Neurophysiol 1978; 44: 213–231.

Lim van GJE, van Mierl GW, Ten Mbu GJM. Variation in latency times of visually evoked cortical potentials. Brt J Ophthal 1978; 62: 220–225.

Maier J, Dagnelie G, Spekreijse H, Van Dijk BW. Principal components analysis for source localization of VEPs in man. Vision Res 1987; 27: 165–177.

Marmor M, Arden GB, Nilsson SE, Zrenner E. Standard for Clinical Electroretinography. Arch Ophthalmol 1989; 107: 816–819.

McDonald WC. Pathophysiology of conduction in central nerve fibres. In: Visual evoked potentials in man: new developments. Desmedt JE (ed). Clarendon Press Oxford 1977; pp 423–437.

Mehnert A. The visual evoked response in acute and acute chiasmal patients with suspected multiple sclerosis. Electroenc Clin Neurophysiol 1977; 43: 799.

Menthon L, Franck H. Apport des potentiels provoqués visuels à la diagnostique de la sclérose en plaques. Rev Oto-neuro-ophtal 1986; 58: 3–.

Miller RA, Regan D, Heron JR. Differential diagnosis of Multiple Sclerosis by visual evoked potential recording. Brain 1979; 97: 755–772.

Narsombhan R, Voigt and von Hal-Jan J. The human central nervous system. Springer Verlag Berlin 1978.

Nilson BY. Visual evoked responses in multiple sclerosis: comparison of two methods for pattern reversal. J Neurol Psychiatry 1978; 41: 495–508.

Odom JV, Chan GM. Dynamic movement: A comparison of electrophysiological and psychophysical measures. Inv Ophth Vis Sci 1983; 23: ARVO suppl 194.

Oosterhuis P, Spekreijse H. The retinotopic generators of the pattern onset E.P. A source localization approach. (Unpublished) 1990.

Owsley C, Sekuler R, Siemsen D. Contrast sensitivity throughout adulthood. Vision Res 1983; 23: 689–699.

Penn A, Kondo S. Influence of pupillary size on pERG latency times of pattern reversal VEP. Doc Ophthal Proc Ser 1981; 27: 255–262.

Perera SJ, Low MD. Visual evoked potentials in a moving pattern light emitting diode stimulator in normal subjects and patients with demyelinating disease. Electroenc Clin Neurophysiol 1978; 45: 93–102.

Regan D, Milner BA, Heron JR. Delayed visual perception and delayed visual evoked potentials in the spinal form of multiple sclerosis and its distribution in time. Brain 1978; 99: 43–66.

Regan D, Spekreijse H. Electrophysiological correlate of binocular depth perception in man. Nature 1970; 225: 93–94. Regan D. Evoked potentials in man produced by some modulated light. Physiol Hum. of Strasbo 1975.

Remond. Evoked brain potentials in relation to sensory information processing. Prentice Rev Prog Bull 1969; 2: 240–242.

Rijsdijk FCC, van der Heijde GL, van Dongen HMVM. Are the transient evoked potentials different from pattern reversal evoked potentials? Doc Ophthalm 1987; 66: 279–289.

Riemslag FCC, Spekreijse H, van Weelden H. Pattern reversal and appearance-disappearance responses of MD patients. Doc Ophthal 1981; 27: 213–221.

Riemslag FCC, Spekreijse H, van Weelden H. Pattern evoked potential diagnosis of multiple sclerosis: a comparison of various contrast stimuli. In: Cavallotti J, Mangiaterra P, Rizzo M (eds). Advances in Neurology 32. Raven Press, NY 1982; pp 417–428.

Rubinstein MP, Harding GFA. The visually evoked cortical potential: Is it related to the electroretinogram? Int Ophthalmol Vienna 1981; pp 29: 135–144.

Shaw NA, Cant BR. Age dependent changes in the latency of the pattern visual evoked potential. Electroenc Clin Neurophysiol 1980; 48: 237–243.

Sokol S, Moskowitz A. Effect of retinal blur on the peak latency of the pattern evoked potential. Vision res 1981; 21: 1279–1286.

Sokol S, Dumas A, Moskowitz A, Schauer E. Pattern evoked potential latency and contrast sensitivity in glaucoma and ocular hypertension. Doc Ophthal Proc Ser 1981; pp 27: 79–86.

Spekreijse H. Analysis of EEG responses to dense and to patterned light in humans. Thesis Junk Publ, The Hague, The Netherlands 1966.

Spekreijse H. Pattern evoked potentials: principles, methodology and pharmacology. In: Barber C (ed). Evoked potentials. MTP Publishing 1980; pp 25–34.

Spekreijse H. Comparison of acuity with cortical evoked potential versus the mechanism underlying cortical processing in man. Behav Brain Res 1982; 5(1): 107–117.

Spekreijse H, Dagnelie G, Maier J, Regan D. Flicker and luminance components of the pattern evoked response. Vision Res 1982; 23: 1287–1301.

Spekreijse H, Dawson AL, Porchaska Meyer EE. Cortical evoked potentials and psychophysics in multiple sclerosis patients. In: Human evoked potentials. Yehoram D, Calaresu F (eds). Plenum Press NY 1979; 315–381.

Spekreijse H, Estevez O, Reits D. Visual evoked potentials and the physiological analysis of visual processes in man. In: Desmedt 1977; pp 16–89.

Spekreijse H, Rhee LH, van der Tweel LH. A case of amblyopia: electrophysiology and psychophysics of luminance and contrast. The visual system. Archin GB (Ed), Plenum Press NY 1972.

Spekreijse H, Reits D. Sequential analysis of the visual cortical potential system in man: nonlinear analysis of a sandwich system. In: J. Bedin W, Otto (ed). Evoked potentials. Ann Acad Sci NY 1982; pp 388: 96–112.

Spekreijse H, van der Tweel LH, Zuidema T. Contrast evoked responses in man. Vision Res 1973; 13: 1577–1601.

Stelmach R. Visually evoked response , binocular facilitation and failure when binocular vision is disturbed. Acta Ophthal 1976; 96: 438–458.

Stiles WS. The directional sensitivity of the retina and the spectral sensitivity of rods and cones. Proc R Soc B 1939; 127: 64–105. Swanson JE, Hughes JF, Strebeigh JW. Visually evoked potentials in myotonic dystrophy myotonia: Lacunar syndrome with gender, age and technical factors. Am J EEG Technol 1978; 18: 171–254.

Tsuchui F. EEG and other neurophysiological abnormalities in uremia. Kidney Intern Suppl 1975; 2(4): 216–218.

van der Tweel LH. Pattern evoked potentials. Folia ant ophthalmol Plus 1980; ISCEV symposium 1979; pp 37–42.

van der Tweel LH, Estevez O, Cavanagh CR. Interaction of the retinal evoked potential with changes in retinal illuminance. Ocular res 1976; 18: 1263–1267.

van der Tweel LH, Spekreijse H. Basic optimetrics and electrophysiology of a test optometer. Doc Ophthalmy 1979; 2: 163–173.

Vaughan HG, Kaufman A, Taylor J. Abnormalities of visual evoked responses in the presence of homonymous field defects. Electroenc Clin Neurophysiol 1965; 19: 317–326.

Yee RI. Disability gives - a state-of-the-art report. CIE journal 1986; 5: 39–42.

de Vries H. The fundamental response curves of retinal and subjective adaptation and their mutual connection. Physica 1948; 14: 367–380.

de Weert RJ, Riem IA, Spierings H, Colombo GA. Implementation of a portable pattern stimulator and VEP/ERG recording system based on an Apple microcomputer. Doc Ophthal Proc Series. 1983; 37: 209–218.

Wald LO. The receptors of human color vision. Science 145: 1964; 145: 1007–1016.

Wolfe GA. The vertebrate eye. Hafner publishing company NY 1967.

Sharpe P. Visual evoked responses to primate neuronal activity with amblyopia and/or defective binocular function. Acta Ophthal 1979; 56: 517–527.

White CT, Kurtzberg D, Vaughan Jr. Color evoked potentials: development of a methodology for the analysis of the processing of red–green vision. In: Desmedt JE (ed), Visual evoked potentials in man: new developments. Clarendon Press Oxford 1977; pp 209–222.

Wildberger HGM, van Lith GHM, Wijngaarde R, Dirk-Mak GTM. Visually evoked cortical potentials before evaluation of homonymous hemispheric visual field defects. Clin Ophthalm 1978; 40: 231.

Wood CC. Application of dipole localization in clinical neurology: identification of human evoked potentials. In: J Roda-Wodlinger (ed), Evoked potentials. Ann Acad Sci NY 1982; 388: 139–155.

Visual evoked potentials in clinical neurology

A.W. de WEERD

Introduction

Visual evoked potentials (VEPs) have been used now for more than two decades. Reviews of methodology and clinical applications were published some years ago by among others Halliday, Chiappa, Sokol, Spehlmann and Lowitzsch [1-3]. Since those texts were written new fields of use have emerged, on the other hand areas of previous interest are thought less important nowadays.

After a summary of technical aspects of VEPs, this chapter will focus on new developments, in particular on those with clinical implications. Moreover, applications of VEPs which will probably be clinically important in the near future as well as new aspects of VEPs thought to be relevant for insight in functions of the nervous system, will be described.

Methods and normal values

Methods

Brain potentials can be evoked visually in many ways. It has been recognized after wide dispute that the universally applicable method does not exist. Stimulation and recording parameters should be tailored to the clinical problem and condition of the patient under study. For example, flash VEPs (FVEPs) will be preferred in the examination of young children, uncooperative patients and in the intensive care unit or operation room. Commercially available stimulator units allow a wide choice in methods for pattern VEPs for almost every laboratory. It is advisable to get optimal experience in one or two of them, but it should be remembered that other methods often have a higher diagnostic yield in special cases. Examples for this are VEPs to gratings in patients with Parkinson's disease and the combination of pattern VEPs and electroretinography in ophthalmologic disorders and detailed studies of demyelinating diseases. A description of all available methods in VEP studies is outside the scope of this chapter. Reviews can be found in the monographs

E. S. Calver and S. L. Visser (eds), Evoked potential manual pp. 101-208

Table 1. Recommended method for obtaining visual evoked potentials (checkerboard)

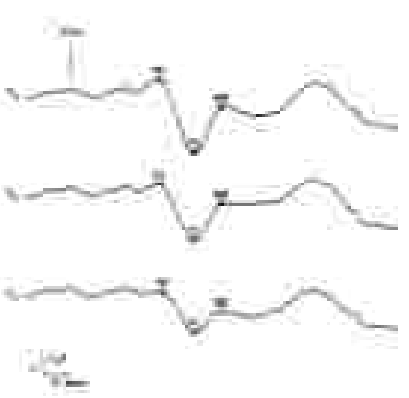
A. Full field stimulation	
Stimulation	
Check size	28–30 arc.
	> 92' arc.
Contrast	(Lmax - Lmin)/(Lmax + Lmin) > 80%
Field size	> 8° arc, with a central fixation point
Stimulus rate	< 2/sec.
Screen luminance	4.5–15 lx (in 100–300 lx) (~14lx)
Analysis time	250 – 300 msec
Averaging	100 – 200 trials
EO-montage and montage: Quasi Square System, i.e. midoccipital (5 cm above inion) MO, right/left occipital (5 cm lateral to MO) RO and LO, referenced to midfrontal (12 cm above nasion) MF or 1/2, O1, O2 referenced to Fz.	
Analysis: peak latencies, amplitudes of N75, P100 (N1,P) components and interocular difference for P100 latencies	
B. Half field stimulation	
Stimulation same as A	
Check size	> 90' arc
Field size	> 8° arc., fixation point at central to inner edge of pattern
Montage	Quasi Square System; i.e. MO referenced to MF, left and right temporal (10 cm lateral to MO) LT and RT referenced to MF or T6, T5. Or referenced to Fz. If more channels can be analysed use also 1O or O1 and 2O or O2 referenced to MF or Fz.
Analysis	latencies of the peaks (or N75, P100 and N145 components and the contralateral P75, N135 and P135 components, amplitudes of the P100 and N145 components. Other stimulus parameters and recording conditions as for full field stimulation.

These recommendations are in agreement with those by the ISCEV and American Electroencephalographic Society [6,7]

on evoked potentials mentioned above and in the contribution by Speckreyse and Riemslag to this book. Pattern evoked VEPs and in particular the checkerboard reversal method have found general acceptance and are considered as the method of choice in most situations. Unless stated otherwise, the studies mentioned in this chapter were performed using this way of generating VEPs. They will be referred to as PVEPs. Recommendations for stimulation and recording of (P)VEPs can be found in the "Standards in Clinical Neurophysiology" of the IFSECN [6] and in the publications from the American Electroencephalographic Society [7], (see Table 1 for a summary). The methods used in most studies referred to in this chapter are in accordance with these specifications.

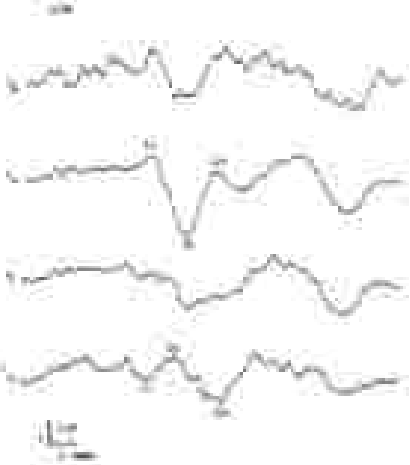
Normal values

Full field checkerboard pattern stimulation of one eye and recording from a row of electrodes at the backside of the head result in curves which for the first 200 msec after stimulation are characterized by a positive component



(a)

Figure 1a. Normal PVEP, full field stimulation. All electrodes referenced to Fz. NPM configuration in all derivations, and slightly asymmetric distribution of amplitudes over the stimulus localised electrodes. Latencies: N1: 96 msec; P1: 101 msec; N2: 124 msec. Right eye, woman, 29 years old.



(b)

Figure 1b. Normal PVEP, half field stimulation. All electrodes referenced to Fz. Stimulation of the right half field, right eye in the same woman of fig. 1a. Note the NPM configuration ipsilateral to the stimulated half field as well as the mid-occipital electrode, and the PNP configuration contralaterally. Inversion between both PVEPs at electrode 01. Latencies as indicated in the figure. The latency of the N105 component is shorter than that of the P100, which is considered to be a normal variant.

at approximately 100 msec (P100) and a maximal amplitude at the mid-occipital electrode. This positive wave is flanked by two negative peaks at about 70 and 145 msec. After monocular half field stimulation an asymmetric response appears which consists of a N70-P100-N145 complex ipsilateral to the stimulated half field and a contralaterally localised P70-N105-P135 complex. See fig. 1 for examples of normal full and half field PVEPs.

Even small variations in techniques of stimulation and in conditions during the recording result in changes in latencies and amplitudes of all components. Simple extrapolation of normal values from one laboratory to the other is not allowable due to the non-linearity of these external influences. Results of VEP registrations can be compared only when made under strictly similar conditions of stimulation and recording. Normal values for each laboratory remain a requirement in all VEP studies. Yet, comparison of normal values from a laboratory to those of others can be useful as a given insight in methodological errors. For this reason the normal values of the main component of the full field PVEPs from the laboratory of the author are given (Figs 2 and 3, and Table 2). These data should be compared with those published elsewhere (among others: [1, 2, 8–13]). All studies stress that the

age and sex of the patient (s) under study should be taken into account in the assessment of the PVEPs. The configuration of the curves after full and half field stimulation, reproducibility of the curves, latencies of the various components and interocular differences in latency of the P100 peak are parameters of importance in all studies. Large variations in absolute amplitudes even in normal subjects rise among others [14, 15] nearly always preclude the clinical use of this parameter, interocular amplitude ratios are mentioned sometimes. The latter is the only amplitude parameter that is used in the laboratory of the author. In normal subjects the upper limit for this amplitude ratio (amplitude at electrode 01/amplitude at electrode 02 or the inverse) is 3:1.

PVEPs have often been used in studies of the spontaneous course of disorders in the visual system and in trials of therapies for such diseases. Either improvement or worsening of pathologically changed functions of the visual system can be detected, the variability of PVEPs in the course of time should be known for normal subjects (Table 2) [16–21]. Even for the most stable (!) component of PVEPs, the P100, the upper limit of these changes over time is mentioned to be approximately 10–12 msec.

The values given in Figs 2 and 3 and in Table 2 are those for normal adults. VEPs are also obtainable in children of all age categories, even in extremely premature infants. Flashes and patterns can be used to evoke these potentials. The flash method (stroboscopy or LED's) [22] is preferred in most studies as it is thought to be most reliable and easy to perform. In the first year of life some differences between FVEPs and PVEPs exist; the configuration and development of the responses to both ways of stimulation however, are essentially similar [23–25]. It is recommended to record the VEPs in the awake child as the potentials are more variable in configuration, latencies and amplitudes in sleep [26–29]. Although variations occur, up to the age of one year the limits of normality in FVEPs can be defined within still useful margins.

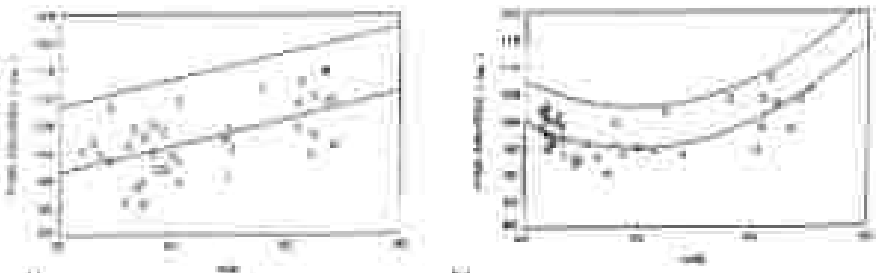


Figure 2. Normal values of full field PVEPs related to the age of the subjects. Check size 1° arc., field size 28° arc., luminance 100 cd/m², contrast 95%, bandpass Cp-Fz, 01-Fz, 02-Fz, filters 2–100 Hz (– 3dB), averaging of 8 100 trials. The lines in Fig. 2, 3 indicate the mean and upper limit of normal, i.e. the mean plus 2.5 SD. Latencies indicated in the figure as the mean of two eyes. Normal subjects, 37 women, 29 men. a. Latencies P100, women. Note the age limit subdivided in steps.

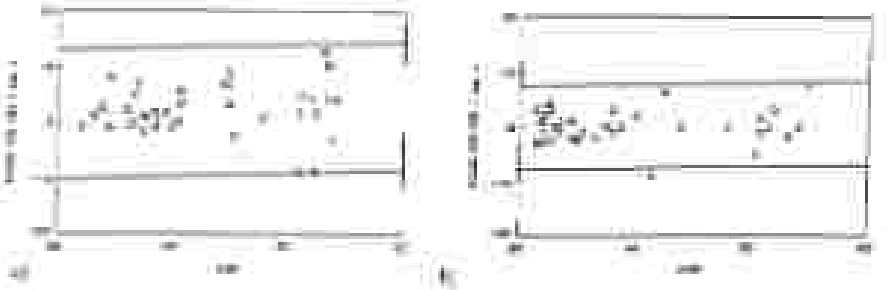


Figure 3. Normal values of P100 latency and P100 amplitude as a function of the subject's age.
Check size 15' arc, field size 20° arc, luminance 120 cd/m², contrast 97%, averages 64–128, 95–99% confidence limits 2–400 Hz bandpass, averaging of 100 trials. The lines in Fig. 3 indicate the mean and upper limit of normal (i.e. the mean plus 2.5 SD). Latencies indicated in the figure as the mean of two eyes. Normal subjects: 57 women, 39 men, a Interocular differences in latencies P100, mean, b Interocular differences in amplitudes P100, means. The lines in Figs 3a and 3b indicate the upper and lower limits of 'normality', calculated as the mean ± 2.5 SD.

This allows application of the method in the assessment of maturation of the visual system in an individual patient. Premature with a conceptional age (CA) of 25 weeks or less have no FVEPs. With increasing age negative wave with a peak latency of approximately 300 msec and high amplitude appears. Later on, positive components can be found flanking this negative one. The first of the positive waves is most important as it is considered to be the "precursor" to the P100 later in life. At a CA of 36 weeks this wave should be seen in nearly all "normal" premature (see Fig. 4) [28, 36].

Table 3

Normal values of PVEPs, half field stimulation

N = 10

Montages: O1, O1–Oz, O2–Oz (referential to Fz)

In all cases transition from an ipsilateral N70 – P100 – N145 complex to either a P70 – N105 – P135 complex or no PVEP at the occipital midline electrode (see Fig. 1). This reversal occurred in 75% between the contralateral occipital and temporal electrodes, in the other 25% between both occipital electrode positions.

Latencies (msec) ipsilateral P100: 101.2 ± 3.4
contralateral P100: 106.3 ± 7.2

Normal values, variability of P100

Full field stimulation

Average interocular between value: 106.4 ms
N = 57

Difference (ms) in between (msec)

	Mean	SD	Mean ± 2 SD
P100	4.1	4.3	−4.5 < 4.1 < 12.7

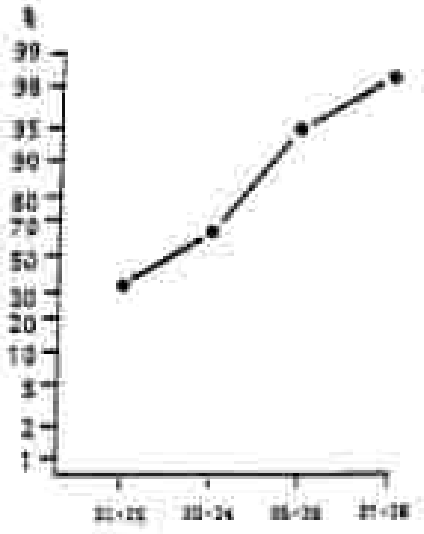


Figure 4. Percentage of PVEP recordings in which the major positive wave is present at each post conception age. After modification, reprinted (with permission from the authors and publishers) from Pharoah *et al* [23].

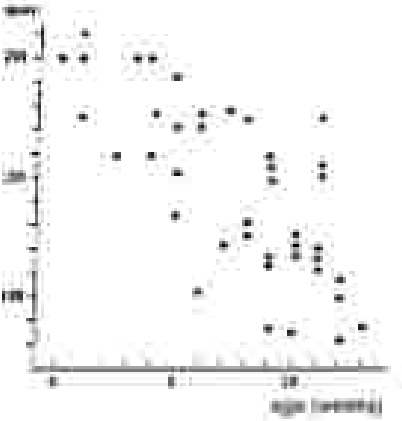


Figure 5. Latencies of the major positive PVEP components according to age in 41 babies. Reprinted (with permission from the author and publishers) from Harden [36].

323]. It has a latency of about 200 msec. Serial examinations in (extreme) premature show that PVEPs develop faster under extra-uterine conditions than cross sectional data suggest [31]. One could speculate on the influence of light in this respect. In the first months after term the PVEPs change considerably. Their configuration becomes more complex and the latency of all components, in particular that of the major positive one, decreases (Table 3, Fig. 5) [23, 24, 34-37].

For the PVEPs in the first 200 msec after stimulation the adult configuration and latencies of the various components are reached at an age of 2–4 years. The maturation of the long latency potentials takes about two years more [35]. After the age of six only minor changes occur, predominantly in amplitudes [38, 39]. Compared to (brainstem) auditory and somato sensory evoked potentials the maturation of VEPs seems to lag behind in time, possibly due to the relatively slow increase of synaptic density and myelination in the visual system [40].

The (sub)cortical structures underlying the various VEP components have been studied extensively in animals. A review of these data is outside the scope of this chapter. Studies in man are scarce and often limited to a few cases but seem to confirm the animal data by suggesting a cortical origin

Table 3. Normal values in children. Latencies (in ms) of the major positive components.

Age (months)	Latencies: N (SD)	
	PVEPs	PVEPs (60' checks)
0.5	(75 [4])	-
1	194 (36)	220.9 (32.5)
2	129 (27)	170.1 (22.8)
3	115 (23)	140.6 (19.1)
4	-	130.1 (7.2)
6	106 (4)	122.8 (7.1)
9	97 (4)	113.9 (6.7)
12	95 (2)	109.2 (3.8)
24	83 (19)	108.9 (8.6)
36	93 (38)	102.1 (5.1)

References (27,30)

for all clinically relevant components of PVEPs [41–48]. Practically, the most important result of the studies summarized above is the differentiation in macularly dependent components and those related to activity in parafoveolar parts of the visual system. The positivity at 135 msec which can be demonstrated best in half field studies is an example of the latter. Foveal stimulation results in a prominent P100 underlining the results of many studies which categorize this peak as a component generated in area 17, i.e. macularly dependent [43, 49–51].

The theoretical base of abnormal PVEPs

It is clinical practice to categorize abnormalities in the visual system in disturbances localized before, in or after the optic chiasm. As can be seen in patients suffering from multiple sclerosis with plaques in the optic nerve as well as in the occipital white matter this classification is sometimes an artificial one. However, for the sake of clarification of theoretical background of abnormal PVEPs it still will be used in this chapter.

Full field stimulation

Lesions of the eye or optic nerve will cause changes in the configuration and/or prolonged latencies of components of PVEPs, in particular the P100. In patients with dense central scotomata due to a macular lesion or selective damage to the core of the optic nerve the P100 which is largely dependent on good function of these structures, can not be generated. As can be seen in Fig. 6 full field PVEPs resemble the algebraic summation of the responses generated by stimulation of both half fields apart. In the case of dropout

of the macular P100 the summation of both preserved parafoveal P135 components gives a positive wave which otherwise can not be seen. This 'new' dominant potential at about 135 msec is of course abnormal but should be differentiated from a true P100 with prolonged latency (see also Fig. 11) [52, 53]. A low amplitude P100 and well developed P135 components can result in a mixture of positive waves, the so called 'pathological W configuration' of PVEPs. Any delayed or distorted P100 component, in particular if its latency has changed to about 135 msec has to be analysed further. This should be done at least with a full field study using laterally localised electrodes but best of all- with half field stimulation. Theoretically, a prominent negative wave in the frontal areas can falsely suggest an occipital positivity in the anterior-posterior derivations commonly in use for the recording of VEPs. Although rare, this situation does occur. It is highly confusing in cases with no P100 and a well developed frontal negativity at about 100 msec from the moment of stimulation. Half field recordings and the use of a non cephalic reference electrode may elucidate this problem [54, 55].

Monocular full field stimulation results in PVEPs with maximal amplitudes at the midoccipital electrode. As can be seen in Fig. 1 PVEPs can also be recorded from more laterally placed electrodes. These responses are similar to the midoccipital one in configuration but have lower amplitudes. Approximately in 60% of the cases the amplitudes of these lateral PVEPs are similar for the right and left occipital site. However, an asymmetry up to 3:1 is still regarded as normal in our laboratory (see also [1, 12, 13]). In patients exceeding

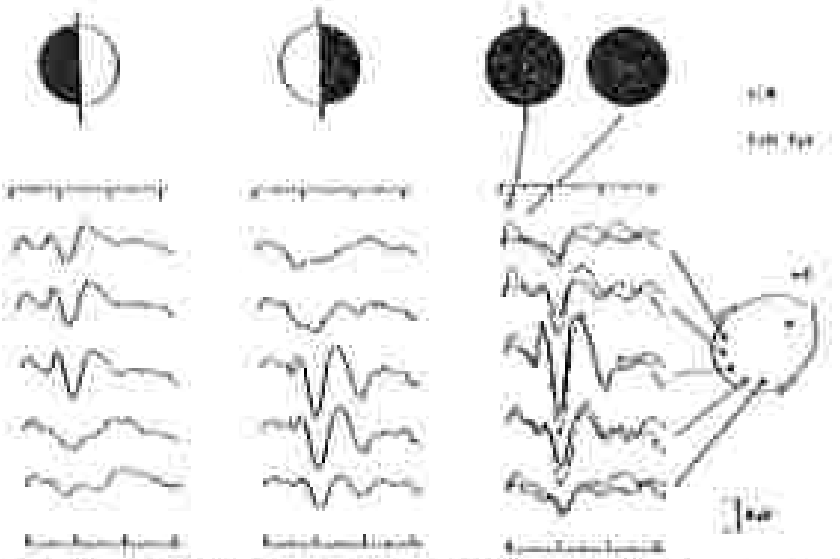


Figure 1. PVEPs after full field and half field (shown here) stimulation. The slightly lateralised amplitude of the monocular PVEPs after half field stimulation resemble the full field PVEPs. Reproduced (with permission from the authors and publisher) from Blankhuis et al. [51].

this ratio, one should be alert to lesions in or behind the chiasm. In the latter cases a so called uncrossed asymmetry can be observed, i.e. monocular stimulation of right and left eye results in a pathological amplitude ratio lateralized to the same occipital electrode. Due to the orientation of the preserved striatal generator the highest amplitude is paradoxically found at the side of the retro-chiasmatic lesion [28]. In extreme cases in the 'blind' half field the P100 can not be generated at all. In contrast to retrochiasmal lesions disturbances in crossing fibres in the midline of the optic chiasm result in a crossed asymmetry after full field stimulation. In these cases the pathological amplitude ratio is reversed when one switches to stimulation of the other eye (see Fig. 9 for an example).

Half field stimulation

Monocular half field stimulation evokes responses with a characteristic form. At the mid-occipital as well as at the occipital and posterior temporal electrodes ipsilateral to the stimulated field a N70–P100–N145 complex is recorded; a P70–N105–P135 complex can be seen at the posterior temporal electrode contralaterally to the half field. In between the latter site and the mid-occipital electrode the reversal from positive-negative-positive (PNP) to NPN complex occurs. This distribution of potentials is seen in most normal subjects. Sometimes the contralateral PNP configurated PVEPs can not be demonstrated at all. Both types of 'responses' should be considered as normal (fig. 7A).

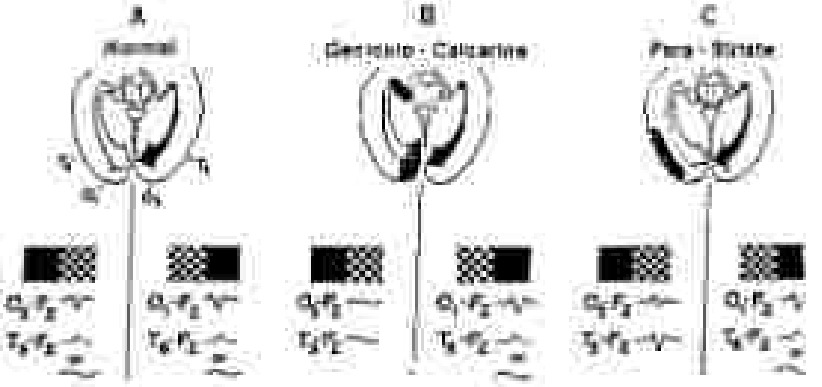


Figure 7. Normal half field PVEPs (panel A) the abnormal responses to hemifield stimulation in retrochiasmal lesions. Normal ipsilateral PNP and contralateral PNP complexes (in an unilateral response) in A. Large lesions of the geniculo-striatal pathway or the primary visual cortex result in some attenuation or abolition of the responses dependent on the 'blind' right upper half field (panel B). Parieto-basal or parietal lesions abolish the contralateral PNP complex resulting in a persistent NPN complex (panel C, right side) half field stimulations.
Note that in all panels the curves have the complete electrode spreading in the stimulated field and the contralateral temporal one are shown. Segmental (with permission from the authors and publishers) from Harrison and Halley [67].

A NPN complex at all electrodes upto the contralateral posterior temporal one suggests pathology in the secondary visual areas contralateral to the stimulated half field (Fig. 7C, right sided stimulation). This distribution of potentials is rare. Complete loss of vision in one half field due to a severe lesion in the geniculo-striatal pathway or in the primary visual cortex results in distorted responses or no responses at all when the 'blind' field is stimulated (Fig. 7B). PVEPs related to the intact half field ought to be normal.

Normally distributed PVEPs which are sometimes paradoxically seen after stimulation of an anoptic half field result from eccentric fixation not realized by patient and supervising technician. Stimuli in half fields with partially disturbed vision can result in PVEPs ranging from completely normal to no response at all. As yet, a close correlation in field defects disclosed in perimetry has not been established [1, 57–60]. PVEPs related to the intact half field ought to be completely normal.

Mutatis mutandis half field PVEPs in lesions which completely destroy the crossing fibres in the midline of the chiasm can be predicted theoretically. Stimulation of the anoptic temporal fields at best responses with an abnormal configuration. Partial loss of vision however, results in unpredictable PVEPs. As there is often extension of the lesion to or compression of surrounding parts of the visual system the various components evoked by stimulation of the "normal" half field can be delayed in otherwise normally configurated and distributed PVEPs.

Strategies in the use of PVEPs

PVEP examinations of patients suspected of lesions anywhere in the visual system start with monocular half field stimulation. Lesions of the optic nerve are demonstrated best using this technique and standard sized checks, i.e. seen in 25–30 minutes of arc in the visual field. For patients with multiple sclerosis it has been shown that larger checks have a lower sensitivity in the detection of demyelinating lesions [61]. Some authors claim a higher diagnostic yield in low luminance testing [62], others disagree with this statement. Normal PVEPs in adequately refracted patients nearly preclude anoptic lesions in the eye or optic nerve. So called 'silent lesions' in these parts of the visual system are probably detectable in most cases. This claim still lacks endorsement in a prospective anatomical study. Possibly, detailed magnetic resonance imaging (MRI) can solve this question. As described previously, the full field test should be followed by a half field examination in any uncertainty on the origine of a delayed P100 component. Combined full and half field studies are indicated for patients suspected of chiasmic lesions. The sensitivity of the test is high resulting in a role for these extended PVEPs as a meaningful adjunct to clinical examination and perimetry [57, 60, 63–66]. Lesions in the visual system localized behind the chiasm are suggested by uncrossed asymmetry in the distribution of amplitudes in laterally recorded full field PVEPs. This finding should always be verified in a subsequently performed half field

examination. However, the detection rate for retrochiasmal disturbances has been found rather low and—more important—unpredictable, precluding clinical use of the method in this respect [12, 57–60, 67].

Computer analysis of PVEPs and mapping

A first analysis of PVEPs results in a large amount of data on configuration, latencies, amplitudes, asymmetries, time differences between peaks, reproducibility etc. When recorded from multiple locations on the head the quantity of data becomes staggering. In the last ten years some ways of data reduction have been developed. Those which have gained general acceptance will be described briefly. 'Mapping' of PVEPs is commercially available and has been introduced in many laboratories. In its most simple form time-amplitude relations for each electrode position are presented in easily surveyable maps using color coded scales. Although attractive at first sight this method has major drawbacks such as the dominant role of the reference electrode(s), confusing effects of interpolation of "data" at locations between real recording electrodes, difficulties in the detection of artifacts and the suggestive power of color coding [68, 69]. Still, time-amplitude mapping seems to be meaningful as a method of first survey of complex (VEP) data. Its power would be more impressive when the method would be modified in order to meet some of its major criticisms. An important modification is the "reference free" method designed by Lehmann [70].

Other ways of analysis go beyond reduction of amplitudes in relation to

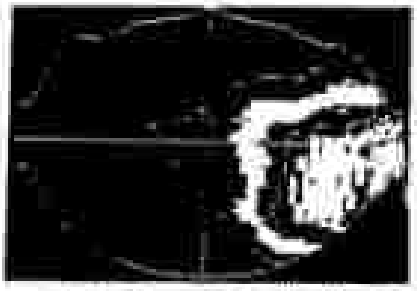


Figure 8a. Significance Probability Mapping using t-transformations against a large group of normal subjects of PVEPs data from an individual patient with a large parietal tumor-lesion at the right side. The degrees of significance are displayed in different colours (shades of grey in the reproduction). Reproduced (with permission from the authors and publishers) from Duffy *et al.* [71].

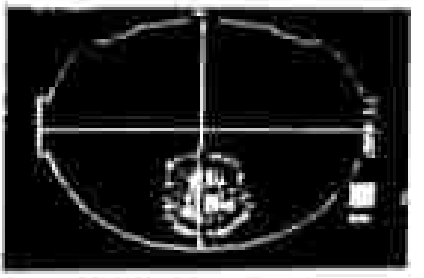


Figure 8b. Map of regional differences between groups of normal and dyslexic subjects for PVEPs data. The differences are based upon a two sample t-test statistic and are coded for significance into colours (for the sake of reproduction in white and black in this figure). The abnormalities in PVEPs in dyslexic children are located in the midoccipital region superficialized. Reproduced (with permission from the authors and publishers) from Duffy *et al.* [71].

time and mid (comparison of the data obtained in the patient(s) under study to a group of other patients or normal subjects. This procedure is often followed by mapping of the computed differences with display of the degree of their significance into colors. In its most simple form Student's t-tests are used to examine differences in relevant parameters (latencies and amplitudes in relation to their location on the head) between groups and Z-scores for the analysis of individual data (fig.8) [71–73]. The use of these otherwise attractive statistical methods implies denial of possible interrelations between data, for example between the latencies of N70, P100 and N145 components in one individual patient and the limited power of such univariate statistics in the handling of hundreds of parameters. At a chosen level of significance of 5%, chance alone would score one out of every twenty parameters as abnormal! Methods as designed by Bonferroni or Holms [74] can be used for the latter problem; the former could be (partially) solved with multivariate statistical analysis using Mahalanobis distances [75]. The results of these statistical studies are also fit for mapping. Their main disadvantage is the difficulty to get insight into which variable or combination of variables causes the significant differences from a 'normal' set of data. However, awaiting widespread commercial introduction of other methods as principal component analysis and cluster analysis [76], assessment of neurophysiological data based on the use of Mahalanobis distances seems to be the best method available at the moment.

Clinical applications and new developments

Preliminary remarks

Diseases of the eyes give rise to important changes in PVEPs. A complete review is outside the scope of this chapter devoted to the use of VEPs in clinical neurology; it can be found elsewhere (among others: [1]). However, some non-neurological disturbances of vision have a high prevalence and should be taken into account in every recording and assessment of PVEPs. Amblyopia ex anopsia, defined as loss of visual acuity due to misalignment of the eyes or severe refraction abnormalities in childhood, glaucoma in elder people and low visual acuity in general are most important in this respect. In amblyopia the configuration and latency of the major positive component are within normal limits if obtained after stimulation with a field larger than 10 degrees of arc and check sizes of 25 arc or more. In comparison to the normal fellow eye the amplitudes are low. Small field stimulation of the fovea discloses more important abnormalities seen as a delayed and distorted P100 component. In severe cases with a dense central scotoma this positive wave may have disappeared, giving way to the then dominant P135 component. The mechanism of this phenomenon has been described previously in this chapter. Patients suffering from glaucoma often have scotomata with implications for PVEP tests. Moreover, PVEPs are of the papilledema patients who are on medication

for this disease. Thus, an ophthalmological examination which is more than the usual search for refraction abnormalities should be done in such patients. Moderately diminished visual acuity, i.e. a vision of 0.4 or more, without further ophthalmological complications has no major influences on large field, high contrast PVEPs. However, optimal correction of refraction errors is mandatory for all PVEP studies.

Evoked potential techniques are often used to endorse the clinical suspicion of hysteria or malingering in patients with vague symptoms of sensory systems. A diagnosis of hysterical blindness is warranted in cases with normal PVEPs who nevertheless state a visual acuity of 1/6 or lower [77]. On the other hand, some people are capable of deliberately changing the results of a PVEP examination by choosing an aberrant, nearby fixation point [78]. To do so, the patient has to converge his eyes, a phenomenon which should be looked for by the technician who runs the test.

Tumors in the region of the optic nerve and chiasm

In patients clinically suspected of having tumors of the anterior parts of the visual system or compression hazard, perimetry and PVEPs are the functional tests of choice not only for the grading of already evident disturbances of visual function but also for the detection of subclinical ones. Lesions of the optic nerve and chiasm lead to an abnormal configuration of PVEPs and prolonged latencies of the remaining components. A crossed asymmetry of the laterally localized responses in full field tests and the absence of potentials after stimulation of the temporal half fields are the hallmarks of a complete lesion of the crossing fibres in the chiasm as has been outlined above (Fig. 9).

The sensitivity for a chiasmal lesion of the crossed asymmetry sign alone varies widely and can be as low as 25%. Half field tests enlarge the diagnostic power for such disturbances, but are often difficult to perform in these patients. In unselected groups the diagnosis was suggested by the combination of full and half field studies in single eyes in 50–100% of patients with a proven lesion of the chiasm and in 100% when combined with perimetry [57, 59, 60, 65, 66]. In the last ten years surgical intervention has lost part of its role in the treatment of hypophyseal tumors to medical therapy. Perimetry and PVEP studies combine to a powerful tool in monitoring these patients. Serial examinations with both techniques together allow the early detection of changes in the function of the chiasm and subsequent adjustment of the therapy.

Full field PVEPs are nearly always abnormal in tumors of the optic nerve itself and have a high sensitivity for compression, for example by an orbital tumor. The reliability of the method allows its use as monitor for (silent) optic nerve tumors in patients suffering from neurofibromatosis [79]. This role for serial PVEPs studies is comparable to that of brainstem auditory evoked potentials in the early detection of manifestations of the disease in

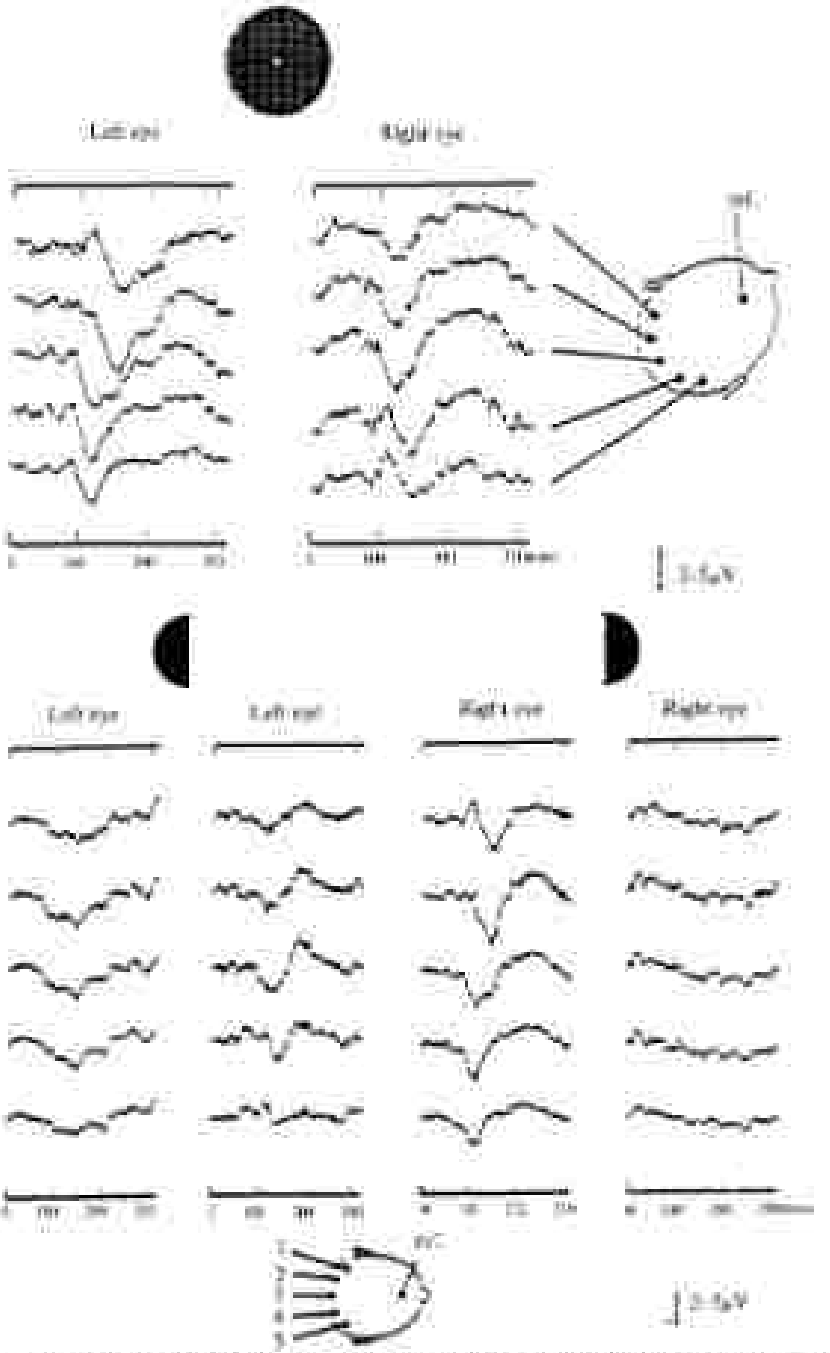


Figure 1. Half and full field (both temporal visual field) PVEPs in a patient with bitemporal hemianopsia due to chiasmal compression by a craniopharyngioma. Clearest asymmetry after full field stimulation. The P100 component can be seen at the midline and ipsilateral to the preserved visual fields in the left field test. The prominent contralateral positivity can be identified as a P135 by half field stimulation of the temporal half field. All the major features of the full field responses are arising from stimulation of the nasal hemifield of each eye, while the responses from the temporal field are relatively featureless. From Halliday [1], reproduced with permission from the author and publishers.

the pontine angle. Some patients with tumorous involvement of the optic nerve have lost all vision at the affected side. PVEPs are useless in the examination of such "eyes". However, a distinction between remnants of function, even if not detectable at clinical examination, or none at all is important in the decision to sacrifice the nerve or not during operative removal of the tumor. PVEP examination can be helpful in this respect [64].

Operations on (the anterior part of) the visual system jeopardize its function. An intraoperative monitoring device is highly wanted to prevent such disasters. Special purpose contact lenses allow flash stimulation of the eye without disturbing the operative field [80, 81]. However, the largely unpredictable sensitivity for anaesthetics precludes widespread use of this method [82–85].

Trauma to the eye or optic nerve

Traumatic disruption of the optic nerve is a relatively rare event. In such lesions decompression of malfunctioning but still viable structures can save vision in that eye. For a good surgical result a complete lesion should be differentiated from a partial one as early as possible. This distinction which requires a detailed ophthalmologic examination is difficult even in cooperative patients and is often made impossible by a concomitant cerebral contusion. Some authors have claimed a role for PVEPs in this respect. However, this method has a low reliability in the detection of optic nerve lesions due to the accompanying ocular trauma [86]. In another technique which is called visual electrically evoked potentials (VEEPs), flashes are replaced by low voltage electrical stimulation of the eye through special purpose contact lenses. In the absence of these responses the prognosis for functional recovery of that particular optic nerve is nihil with or without surgery. The operation is not a priori successful if these VEEPs can be generated, but should be tried [87]. This latter statement is applicable also for PVEPs which for most laboratories will remain the only method available. However, absent PVEPs early after a traumatic lesion of the optic nerve should not preclude surgical inspection.

Optic neuritis

The high diagnostic power of PVEPs in the detection of demyelinating disease of the optic nerve which has been demonstrated already in studies in the early seventies, is one of the main reasons for the widespread use of the method in all kinds of disease. The persistence of abnormalities in PVEPs after clinical recovery which allows verification of the patients history or detection of so called "silent" demyelinated areas in the nerve has attributed further to the popularity of the test. An example of the latter phenomenon is given in Fig. 10. For an overview of the results of some of the largest studies in patients with recent onset optic neuritis or a history of this disease see Tables 4 and 5. These tables also allow comparison between the diagnostic yield to demyelinating disease limited to the optic nerve and more generalized disorders of white matter.

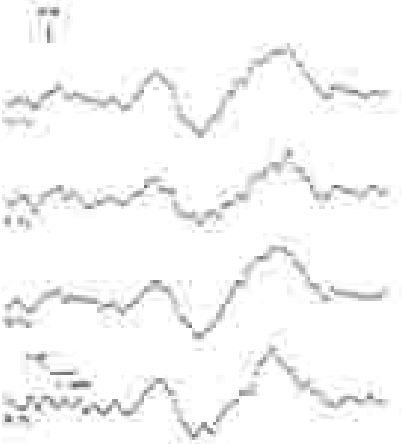


Figure 10. PVEPs after full field stimulation of the normal right eye in a patient with a history of optic neuritis in the left eye some years previously in the recording of the PVEPs. Visual acuity of the right eye 1.25. Normal total geometry of the responses, but a delayed P100 component of 123 msec. The presence of this component was confirmed in half field studies (not shown). As can be seen in the traces 1 and 4 the responses are symmetrical.

Foci of demyelination in the optic nerve can be demonstrated anatomically by MRI and in some cases with CT scanning. In clinically suspected optic neuritis the sensitivity of PVEPs is far larger than that of these imaging techniques. The rate of detection of asymptomatic lesions in the non affected *fellow eyes* is comparable (20–27%) for the ontogenetological and physiological methods [89] (see also the results of a similar comparison in multiple sclerosis in Table 7). Recovery of visual acuity is reflected in an increase in amplitudes of the PVEPs [90]. The latency of a delayed P100 component often shows some improvement. A return of all parameters to normal is exceptional. In particular the comparison of the affected eye and its healthy counterpart rarely

Table 4. Delayed or absent patterned retinal visual evoked potentials in eyes with optic neuritis

Author	Eyes with optic neuritis	Delayed visual evoked potential	Percentage
Halliday *et al.*, 1972	19	18/19	94
Miller *et al.*, 1974	1	1/1	100
Lowitzsch *et al.*, 1976	93	83/93	90
Matthews *et al.*, 1977	48	31/48	65
Shawkat *et al.*, 1978	59	52/59	87
Cringle *et al.*, 1980	83	78/82	96
Total (cumulative)	306	263/304	85.5

From Lowitzsch and Wolkenweg (1981), with permission of the authors and publishers. See the original publication for the full references.

always discloses significant differences in latencies and often also for amplitudes. Optic neuritis in childhood forms the exception to this general rule. A perfect recovery of clinical symptoms and PVEPs as well occurs in 55% of these cases [91].

PVEPs as a single test have little or no prognostic value for recovery of visual loss after demyelination of the optic nerve. It has been reported that combined recording of PVEPs and pattern electroretinography (PERG) can be used to predict the clinical course shortly after such an attack [92, 93], see also [94] for the prognostic value of PVEPs combined with quantified eye movements. Even in severely distorted PVEPs when recording of the PERG yields (nearly) normal results. This combination is seen in a predominantly demyelinating disorder. Disappearance of the latter response which is always accompanied by highly abnormal PVEPs probably represents axonal loss in a large part of the nerve and is considered as a prognostically unfavourable sign. In our opinion, the interpretation of PERGs is often difficult, prohibiting such unequivocal prediction of outcome in many cases.

Multiple sclerosis

The value of PVEPs in multiple sclerosis has been recognized as early as that for optic neuritis. However, the use of the test in generalized demyelinating disease is different from that in disease limited to the optic nerve. Its main application in multiple sclerosis is – as for all modes of evoked potentials – to demonstrate so called 'silent' lesions, which are relevant as evidence for the dispersion of the disease over multiple sites in the white matter. For the results of studies in some large groups of patients see Table 5.

Multiple sclerosis plaques can be located at all sites in the myelinated tracts in the visual system and sometimes also in the gray matter involved in that system. As the optic nerve is one of the preferred areas of demyelination, the PVEP examination is often limited to the study of this part of the visual pathway. One should be alert on foci at other sites and adapt the way of recording in order to detect these ones also. Full field PVEPs must be recorded from a mid occipital electrode and from lateral sites as has been described in the 'methods' section of this chapter. If (post) chiasmatic lesions are suspected from this first examination or doubts on the origin of the main positive component exist the full field study should be followed by recordings with half field stimulation.

In addition to the classical full field examination, i.e. a large field and check size 50-60' of arc, several other ways of stimulation have been tried in order to enhance the sensitivity of the method in multiple sclerosis. Different types of stimuli allow examination of more than only one of the parallel pathways in the visual system and as such enlarge the chance to find abnormalities. Various check sizes [61, 95, 96], gratings [97], pattern onset [98], stimulation of only the central field with small checks [99], repetitive stimulation and measurement of refractory periods [100-102], and diminished luminance of

Table 1. Delayed pattern reversal visual evoked potential in patients with multiple sclerosis with and without optic neuritis

Authors	No. of patients	Delayed visual evoked potential with optic neuritis	Percentage	Delayed visual evoked potential without optic neuritis	Percentage
Halliday et al., 1972	51	28/29	100	25/27	92
Asselman et al., 1975	51	15/15	100	19/36	53
Lesimouch et al., 1976	158	78/80	82	30/40	60
Matthews et al., 1977	110	30/36	83	40/74	53
Sherwin et al., 1978	149	58/67	87	31/82	38
Regan et al., 1978	104	38/55	69	5/49	10
Trontelj et al., 1979	50	19/20	95	16/30	53
Jacksonmaier et al., 1979	54	23/23	92	15/29	52
Dyken et al., 1980	88	27/31	100	21/57	37
Chiappa, 1980	349	169/178	97	92/221	42
Kraus, 1980	100	46/47	98	25/45	56
Lesimouch et al., 1982	427	192/229	84	97/243	40
Total (consecutive)	1555	914/1046	87	396/802	46

From Lesimouch and Wolkenstein [94], with permission of the authors and publishers.
See the original publications for the full references.

(for field [62]) are methods which have been tried in order to increase the sensitivity for demyelinated areas in the visual system. Although often some gain in power of the test was demonstrated, in particular for patients in less certain diagnostic classes of multiple sclerosis ('possible' and 'probable' categories), no single change in methodology has emerged as the most useful in this respect. Therefore, a choice is difficult. It is now common practice to perform a standard full field examination with check size chosen at 25–30' arc followed by full field stimulation with an other pattern (large checks, gratings etc.) and half field studies when necessary (see above). In the early days of the use of PVEPs a normal configuration but delayed response has been considered to be typical for demyelination in the optic nerve. This combination occurs but distorted PVEPs with a delayed major positive component are seen as often. This finding stresses again that none of the PVEP abnormalities are specific for demyelinating disease. Moreover, some of these so called typical demyelination PVEPs represent probably dominant P135 components in cases with loss of the real P100 due to a central scotoma (Fig. 11) [103].

In addition to PVEPs other methods have come available for routine use in the diagnostic work-up of patients suspected of multiple sclerosis. For the main ways of examination now in use, Tables 6 and 7 provide data on the sensitivity for lesions in the white matter, in particular for those categories of patients in whom the diagnosis is 'clinically possible or probable'.

Though these data clearly delineate the place of PVEPs in between other methods, some remarks on this subject still should be made. Somato-sensory evoked potentials (SEPs) obtained after stimulation of nerves in the upper and lower extremities together have a sensitivity comparable to that of PVEPs [2]. However, the latter test is easier to perform. The diagnostic yield of motor evoked potentials (MEPs) which can be recorded after electrical or magnetic stimulation of the motor cortex is also approximately similar to PVEPs (Table 6). In the period of first manifestations of multiple sclerosis MEPs seem somewhat higher, later on the situation reverses. Scrutinizing the data leaves that the methods have only partial overlap in the detection of disturbances which suggests a role for both, supplementary to each other [104, 105]. MRI has been added only recently to this list. Areas of altered diagnostic properties can be delineated on these scans in patients with multiple sclerosis. However, as in all the other methods mentioned, the abnormalities are not specific for the disease. As yet, already five major studies have been published which compare the relative diagnostic values of this new technique, examination of the cerebro-spinal fluid (IgG index and search for oligoclonal bands) and evoked potentials in the three main sensory modalities grouped together (BAEPs, SEPs and PVEPs; Table 7). As a single test MRI seems to have a sensitivity somewhat higher than the other two; large differences however, do not exist. Moreover, the functional tests for demyelination and the imaging technique give a higher diagnostic accuracy when used together. Evoked potentials and MRI were formally studied for their additional value. In a

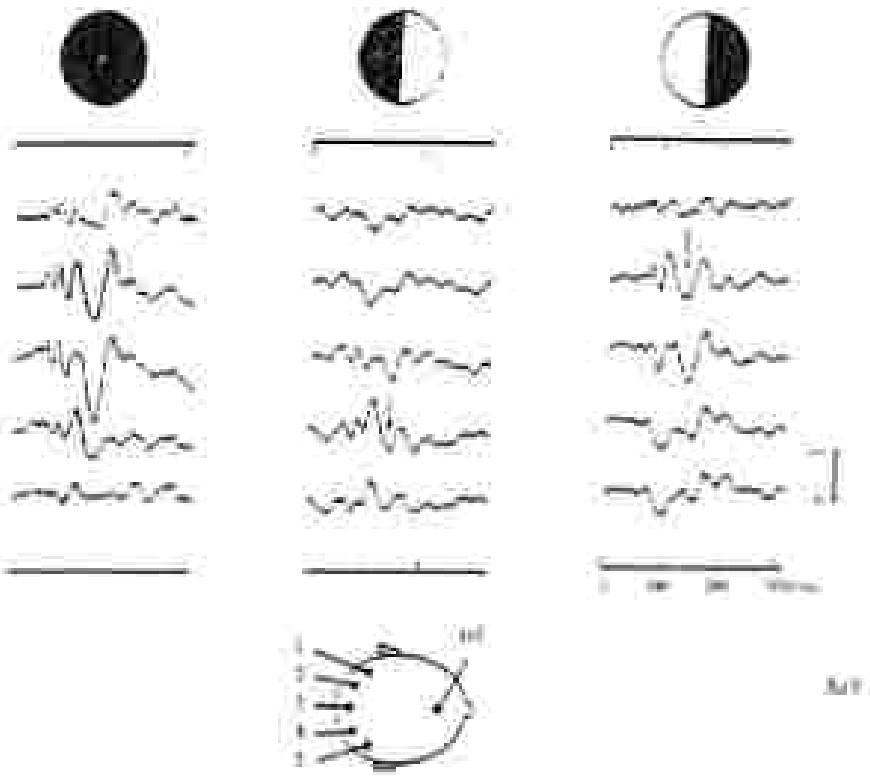


Figure 11. [illegible] PVEPs show an apparently delayed P100 component. Half-field stimulation shows this precisely to be the summation of the two contralateral P100 components (arrows) which are dominant over the low amplitude ipsilateral P100 potentials. Patient with a dense central scotoma due to multiple sclerosis. From Halliday [1], reproduced with permission from the author and publishers.

percentage up to 22% of the cases only one of them appeared to be abnormal [104, 110]. The sequence of examinations in a particular patient remains a choice which should be tailored to the case under study and should be adapted further to the local circumstances. As yet, evoked potentials and in particular PVEPs are meaningful in the diagnostic work-up of every patient in whom

Table 3. Comparison of sensory EP and motor EP [in %] of abnormalities

Reference	Sensory EP			Motor EP
	PVEP	SEP	BAEP	
Wilis et al. [108]	67	71		78
Hess et al. [107]	72	82	47	75

Table 7. Comparison of EP, MRI and CSF analysis in multiple sclerosis (Scotti [7] of the original)

Reference	n/p				All modalities	MRI	CSF
	PVEP	SEP	BAEP				
Evoking potentials and paraclinical data							
Bradley et al. (1981)					35	42	42
Cohen et al. (1977)	41	41	34		56	56	56
Tilikete et al. (1981)	87						
Evoking potentials, neuroradiology							
Halliday et al. (1984)	87		84	69	98	82	82
Lehtinen et al. (1984)	68	83					
Lesser et al. (1983)		83	69		85	85	85
Lesser et al. (1985)							
Lesser et al. (1987)	88	85				85	85
Rossi et al. (1983)	88	94				94	94
Shaw, Cant, Stewart (1984)	81						

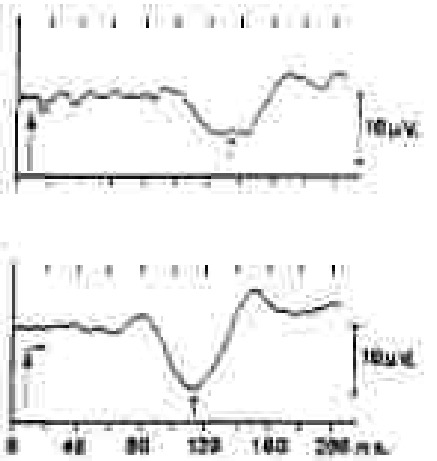


Figure 12. Same PVEPs in a patient with multiple sclerosis. In the upper trace a positivity at about 135 msec with pathological W configuration, possibly a dominant P135 component. Unfortunately, half field examinations to confirm this presumption were not done in this instance. In the lower trace PVEPs of the same patient 6 months later. In peripheral (extrafoveal) stimulation and with slightly prolonged latency of the major positive component.

multiple sclerosis is part of the differential diagnosis.

Serial recordings of evoked potentials provide information on changes in function of white matter tracts occurring in the course of time. Effects of therapy could be evaluated theoretically in such consecutive measurements. PVEPs have been used also for this purpose. In normal subjects the latency of the P100 component has a variability of about 10%, i.e. a upper limit of differences between recordings of 10–12 msec (Table 2). In patients with multiple sclerosis PVEPs show changes in the course of time exceeding those of normal subjects. Further disruption of the responses and increasing delay in the major components are often seen in serial examinations. Although rare, improvement still occurs in particular in patients who are followed for a long time (Fig. 12) [18, 20, 112–118].

Improvement and deterioration of PVEPs are positively correlated to the changes in visual acuity measured over the same time but show no parallels with the course of the overall clinical condition [18, 119]. The latter has been reason to doubt the clinical usefulness of such serial examinations. The anatomical substrate of these functional shifts has occasionally demonstrated by MRI but should be verified further. Nevertheless, in addition to clinical scores and parameters from the cerebro-spinal fluid, the quantification of (subclinical) changes in the function of an important white matter tract expressed in PVEPs, has played a role in many trials of therapy for multiple sclerosis. Hyperbaric oxygen [120–122], plasmapheresis [123, 124] and immunoregulating therapies [125–128] have been evaluated in this way. In general, no effects could be demonstrated, clinically nor on evoked potentials or biochemical parameters.

In addition to their role in the diagnosis and follow-up PVEPs can also give clues for the prognosis of an individual patient. For the prediction of recovery after demyelinating disorders of the optic nerve the possible role of combined recording of PVEPs and PERG has already been discussed. Patients with the so called "unpocused" form of multiple sclerosis in whom the diagnosis is uncertain due to the lack of signs of cerebral or visual disfunction, have to expect a more progressive course of the disease when their PVEPs are abnormal [129, 130].

The results of studies on the diagnostic and prognostic value of PVEPs have had important implications for the classification of multiple sclerosis. Categories of certainty of the disease which are based purely on clinical signs and symptoms have been abandoned now and have been replaced by the scales proposed by Poser *et al.* [131] (see Table 8).

So called 'paraclinical' signs such as roentgenological and evoked potential abnormalities and anomalies in the cerebro-spinal fluid on the one hand and clinical parameters on the other are all thought to be important and are summed up to classify the patient under study.

The last remarks on PVEPs in multiple sclerosis do not concern the patients self but their clinically healthy relatives. Significantly delayed P100 components have been demonstrated in sibs of patients [132]. Possibly, these abnormalities are only present in those who are HLA identical to their affected relatives. Preliminary MRI studies in twins seem to reveal similar results. These findings

Table 8. Diagnostic criteria for multiple sclerosis.

Category	Attacks	Evidence		CSF**	
		clinical		paraclinical*	
A. Clinically definite					
A1	2	2			
A2	2	1	and	1	
B. Laboratory supported definite					
B1	2	1	or	1	+
B2	1	2			+
B3	1	1	and	1	+
C. Clinically probable					
C1	2	1			
C2	1	2			
C3	1	1	and	1	
D. Laboratory supported probable					
D1	2				+

* Paraclinical evidence known to the author who means suggested by evoked potential techniques, psychophysiological procedures, neuropsychological assessment, CT, MRI or serological studies.

** Oligoclonal bands in IgG in CSF.

From: Poser *et al.* [131].

Table 4 Visual evoked potentials in hereditary disorders. Relative value of anomalies in the differential diagnosis.

Delay of P100 component		PVEPs		Asymmetry	SEP	BAEP	LHCN*
		Low amplitude	Abnormal configuration				
Friedreich's ataxia [133, 136, 139, 140, 141]	HP +	--	--		HP +	HP -	HP +
Charcot-Marie-Tooth disease [136, 139]	LP +	+	?		HP +	LP	HP +
Olivo-ponto-cerebellar atrophy [133, 139, 140]	LP +	+	+		HP +	HP +	LP +
Hereditary spastic paraparesis [131, 139]	LP +	+	+	+	HP +		LP +
Refsum's disease [141]	HP +	+	+				LP +
Chronic inflammatory demyelinating polyneuropathy [142]	HP +	+				LP	HP +
Multiple sclerosis	HP ++	+	+	++	HP ++	HP +	LP +

* LHCN: low nerve conduction velocities.
HP: high prevalence.
LP: low prevalence.
+, ++, ...: grade of abnormalities.
Blanks mean unknown.

could have impact on the assessment of otherwise puzzling abnormalities in PVEPs.

Hereditary diseases

In the continuum of diseases of the various parts of the central and peripheral nervous system evoked potentials have diagnostic value. For many of these disorders of which Friedreich's ataxia, olivo-ponto-cerebellar atrophy, hereditary spastic paraparesis and Charcot-Marie-Tooth disease are the most important, multiple sclerosis should be considered in the differential diagnosis. As in demyelination no specific abnormalities of PVEPs occur in the hereditary and degenerative diseases. However, in particular when combined with other clinical neurophysiological techniques, patterns can be encountered which are more or less typical for that entity (Table 9). The high prevalence of abnormal PVEPs in these patients who in general have no clinical symptoms or signs of visual disfunction should be noted again.

In the last years some studies on PVEPs in Huntington's chorea have been published. Patients with this hereditary disease show PVEPs with low amplitudes but normal latencies of the major components. Half field examinations are sometimes abnormal [144–147]. Although its use is ethically questionable, PVEPs are also abnormal in about half of the exposed relatives of patients who are (still) free of disease.

Ischaemia

Ischemia of the anterior parts of the visual system has influence on PVEPs, in particular on the configuration of the responses and the amplitudes. If recognizable, the various components have slightly prolonged latencies [1,2]. In monocular symptoms due to ischaemia the lack of anomalies in the PVEPs of the fellow eye can help in the differentiation from demyelination. One should realize however, that disorders which are often seen in association with ischemic disease, can also give subclinical disturbances of PVEPs. The best example in this respect is diabetes mellitus [148]. Cerebral ischemia often disturbs the function of retro chiasmal pathways and as such can result in abnormal PVEPs. Unproved asymmetry of the responses after full field stimulation and loss of potentials in half field examinations are the hallmarks of a complete hemianopia due to a lesion in the geniculo-striatal tracts of in the occipital region. Mainly multifocal, minor lesions are obtained in studies of patients with large tumors or vascular malformations in these areas. The theoretical base for these PVEPs anomalies has been described earlier in this chapter. In general, the sensitivity of the test is low for retrochiasmal lesions, this applies also for ischemic disturbances [12, 57–60]. Bilateral ischemic deficits in occipital regions with cortical blindness as clinical manifestation have been studied extensively with neurophysiological techniques. PVEPs are absent in most of these patients. In contrast, flash VEPs (FVEPs) can be recorded and

are often only slightly abnormal. The different results after pattern and flash stimulation which can also be found in patients with Alzheimer's dementia (see further on) can be explained in several ways. Different cortical generators for both VEP modalities, each with their own afferent vasculature and susceptibility to noxious influences, is the most attractive explanation. A pathway for flash evoked visual information outside the geniculo-striatal tracts has been postulated as an alternative [149–152].

Diffuse cerebral disorders

Low cerebral perfusion and hypoxia have influences on PVEPs [153–156]. The changes in the responses are limited for moderate ischemia. However, when a threshold of perfusion of about 20 ml of blood/minute/100 gram brain tissue is passed the VEPs change rapidly. These changes are still reversible up to a value of about 12 ml/minute/100 gram. These data which are derived partially from animal studies have been used as an argument for serial recordings of PVEPs as monitor of cerebral function in open heart surgery in humans [157]. As has been described before, anaesthetics cause profound changes in PVEPs, precluding the practical use of the method in the operation room. Monitoring by PVEPs has been done also for patients with severe cerebral trauma [158–163]. The application of PVEPs has gained only little acceptance and has been surpassed by somatosensory and auditory evoked potentials.

Intracranial hypertension per se causes only small changes in (P)VEPs. Even in cases with swollen optical discs the responses show minor anomalies, abnormal PVEPs occur only in severe compression of the optic nerve with consecutive atrophy of the discs. In these patients the responses are distorted and have low amplitudes. So called benign intracranial hypertension has also little influence on PVEPs except for severe and long standing cases [164]. For the value of VEPs in the clinical management of hydrocephalus see the paragraphs on the use of VEPs in children.

Patients suffering from (senile) dementia of the Alzheimer type (ft) DAT) have abnormal flash and pattern VEPs. The differences between the responses to both modalities are striking and are very interesting from a pathophysiological point of view. The PVEPs are normal up to the P100 component; the consecutive potentials are (partially) absent or have prolonged latencies [165]. For the same patients the late FVEPs components are abnormal as well, but in contrast to PVEPs the P2 components which also have a latency of about 100 msec, show significant delays [166–170]. When studied longitudinally this gap between the latencies of both positive waves is seen to widen further [171]. In pseudo-dementia due to senile depression both types of VEPs are normal [169]. The dissociation between the P100 and P2 components is thought to be connected to anomalies in cholinergic neurotransmitters which are probably important in the generation of early components of FVEPs and not so for PVEPs. This attractive hypothesis is endorsed

by the effects of anticholinergics and neuroleptic receptor blockers on PVEPs in normal subjects. These transient changes in normals are similar to those seen in SDAT patients. The PVEPs remained normal in these studies [172, 173].

Checkerboard PVEPs are normal in most patients with Parkinson's disease [174–176]. However, PVEPs after stimulation with gratings show significant delayes for the major positive component [177, 178]. This finding stresses again the existence of parallel running visual subsystems which seem to function independently in many respects, in particular for their main neurotransmitters. The differences between responses from right and left eye indicate variations in the impact of this (neurochemical) disorder on similar parts of the visual system [178–181]. In some studies positive correlations between the grade of PVEPs anomalies and duration of the course or clinical disability have been demonstrated; other authors deny these statements [177, 179, 182, 183]. In idiopathic Parkinson's disease and Parkinsonism due to the use of psychoactive drugs abnormal PVEPs often improve after therapy with DOPA. Such effects of dopaminergic stimulation do not occur in Parkinsonism secondary to diffuse cerebral ischemia [177, 178, 180, 181, 184, 185]. Blockade of the dopaminergic neurotransmission by haloperidol prolongs the latency of the components around 100 msec also in non Parkinsonian subjects [19, 177]. As yet, the localization of these dopamine dependent neuronal networks within the visual system is not clear. As the *electroretinogram* is often abnormal too, the retina is probably implicated, but at least one other part of the visual system, the geniculate bodies, have also major dopaminergic input [178, 183].

Diabetes mellitus may have profound effects on visual function, either through direct toxicity or as systemic complication of the disease. The localization of the disturbances is often difficult. Even in patients with no visual complaints and absence of retinopathy or cataracts, up to 80% of the cases has abnormal PVEPs with delayed major components and low amplitudes [148]. There are no clear correlations between these abnormalities and the duration of the disease or the efficacy of therapy. The high rate of abnormal PVEPs in diabetes mellitus precludes the use of the test in these patients for the detection of other disturbances in the visual system, for example due to multiple sclerosis.

Toxic influences

As yet, knowledge of effects of toxic substances and medicaments on (P)VEPs has gained only little attention in the literature. However, these influences, in particular those caused by medication may have major impact on the curves. An already long-known model for such changes in PVEPs is amblyopia due to alcohol and tobacco. The damage from these substances is clinically characterized by a dense central scotoma. Loss of the macular P100 component and replacement of this potential by the P135 are the consequences for the PVEPs as has been described in detail earlier in this chapter. In less severe

sometimes a true but delayed P100 component is still there [186, 187]. Similar effects can be demonstrated from tuberculostatics such as ethambutol and mesanburol [188, 189] and probably also from deferoxamine [190–192]. Long lasting exposure to organic solvents is known from industrial medicine and from studies of glue sniffers. These substances may lead to disturbances of visual functions which are rarely clinically evident but often can be detected in PVEP studies (Fig. 12) [193–197]. Table 10 provides an overview of the effects on PVEPs of toxic substances and medicaments for which human data are known. Obviously, the dose and duration of exposure are important for the grade of anomaly in the VEPs. Moreover, not all chemically induced changes in the responses are equivalent in every day clinical practice. For example, psychoactive drugs have their major impact on long latency components of the VEPs and have negligible influence on the potentials around 100 msec. For the details on changes induced by other substances, see the references mentioned in Table 10.

Endogenous intoxications as in anemia [213–216] or severe hepatic damage [217–221] have influences on the visual system similar to those from external substances. In these cases the point of impact is also unknown. The PVEPs

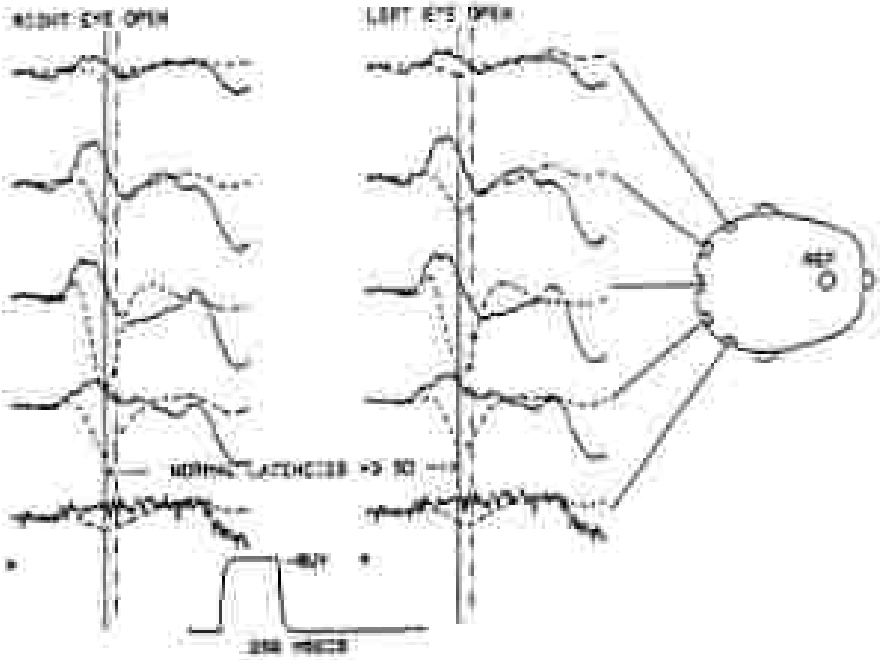


Figure 12. Full-field PVEPs from a glue sniffer (continuous lines) compared to the grand averages from a group of normal subjects (dotted lines). The patient had no visual complaints. The PVEPs were abnormal in respect to configuration and latencies of the major components. From Cooper [195], reproduced with permission from the author and the publishers.

Table IV. Substances known to have deleterious effects on VEPs

Substance	VEPs*	Effect**		Reference
		latencies	amplitudes	
Amphetamines	P	–	–	[198]
Anticholinergics	P	↑		[77]
Ether	P	–		[58]
Benzodiazepines	P		–	[199]
Chlorpromazine	P		–	[196]
Diazepam/Valium	P	↑		[100,193]
DOPA	P	–		[59]
Dormilux	P	↑	–	[189]
Ethanol(e)	P	↑		[198,199]
Haloperidol	P	↑		[58]
Halothane/Isoflurane	P	↑	–	[200,201]
Lithium	P		↑	[198,202]
Metrazol	P	↑		[198,199]
Neuroleptanalgesics	P	↑		[87]
Tricyclic anti-depressants	P	↑	–	[199]
Valproate	P	↑		[203,204]
Copper	P	↑		[205]
Lead	P,F	–		[206,207]
Mercury	P	↑		[208]
Mercury (organic)	P,F	↑		[209]
Alcohol	P,F	–	–	[87,196,210,211,212]
Marijuana	P	–		[198]
Solvents	P	↑		[196]
Toluene	P	–	–	[193,195,196,197]
Tobacco	P,F	–	↓	[196]

* F : FVEPs
P : PVEPs
** ↑ : increase
– : no effects
↓ : decrease

show a delay in the appearance of the major components and have low amplitudes. PVEPs may be abnormal before other signs of encephalopathy emerge. The usual biochemical parameters of hepatic and renal disease correspond only poorly to the severity of its neurophysiological abnormalities. In uremia the duration of the clinical course seems to be of more importance in this respect. This effect is not reversed in intermittent hemodialysis but may be counteracted by an unknown mechanism after transplantation [214, 215, 222].

For patients on medication with serious side effects on the visual system serial recordings of PVEPs are used in the decision to stop and eventually restart the therapy [189, 190]. Possibly, in the future a similar role for PVEPs can be expected in the management of encephalopathy due to renal or hepatic diseases [214, 223].

VEPs in young children

As described in the paragraphs on normal values, the "adult" configuration and latencies of flash and pattern VEPs can be observed already in young children. Depending on the component which is studied the maturation is completed at the age of 2–6 years. In the section abnormalities in VEPs in childhood and their relation to cerebral dysfunction will be described, in particular for children under the age of six years. In most of the studies that are mentioned flash stimulation was the method of choice. PVEPs can be obtained in this age category. They are used mainly for the estimation of visual acuity but have otherwise only limited application. In very young children VEPs are recorded for two major reasons which are testing of visual functions and providing help in the assessment of brain functions in general. Observation of the child's behaviour is the main approach for examination of the visual system at this age. Its results are endorsed and often supplemented by the more easily quantifiable VEP tests of visual acuity. For this purpose the responses to gratings or checks with sizes running from large to small, are recorded. Sudden changes in these VEPs give an indication for the maximal visual acuity of the child. If performed under optimal circumstances, the results of both the clinical and neurophysiological tests are comparable. Although some mutually additional value has been described, one successfully completed test suffices for a good estimate of visual capacity in case of failure of the other method [224, 225]. Cortical lesions are the main cause of visual handicaps at this age. The recording of VEPs provides insight in the extent of the damage and – if done serially – may give clues for the prognosis [226, 227]. The examination of normal children has shown that visual acuity develops quickly and reaches "adult" levels at the age of about one year, i.e. somewhat earlier than the final steps in the maturation of VEPs.

The other main application of VEPs in childhood is in neonatology, for prematures as well as for full term born children. Evoked potentials are a powerful tool in the assessment of the brain function in an individual child. In this respect VEPs are most useful in supratentorial lesions and auditory evoked potentials for brainstem disorders. The normal values of VEPs are well known for the various categories of conceptional age (see paragraphs on normal values). The presence and latency of the major positive component are thought to be the most valuable parameters. Anomalies in VEPs indicate disturbances in cerebral function and allow classification of the severity of the insult but give no clues for its cause. In Fig. 14 the impact of periventricular hemorrhage on VEPs in premature babies is shown. For asphyxia and neonatal infections comparable results have been obtained [226, 228, 229]. Even when combined with other neurophysiological techniques the disease specificity remains low.

The abnormalities in VEPs are often reversible. However, in most cases the improvement lags behind the clinical recovery. An exception to this general rule are VEPs in hydrocephalic children. In uncomplicated cases the responses

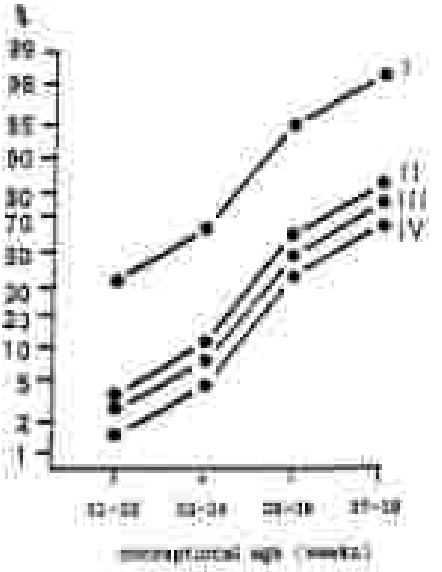


Figure 11. Maturation of VEPs in normal (I) and abnormal (II–IV) infants. The graph shows the percentage of EVEPs in which the major positive wave is present for each group at each conceptional age. Group I: normal. No pathological abnormalities at ultrasound scanning (PVH). Group II: hypotrophic, no PVH.
Group III: neurologically abnormal. PVH grades 1 and 2.
Group IV: neurologically abnormal. PVH grade 3 with ventriculomegaly.
From Pivnick *et al.* [29], reproduced with permission from the authors and the publishers.

should normalize quickly after drainage. If not so, permanent damage with implications for the further psychomotor development can be expected [230–233]. Studies on the prognostic value of VEPs in other neonatal diseases have not been done. On the long run VEPs appear to be a sensitive detector for late sequelae of perinatal neurological disease as was demonstrated in a VEP study of 5 year old children [234]. In contrast to their role in diseases in early childhood, VEPs seem to have only little application in older children. Most studies of children aged six years and older deal with learning disabilities, in particular dyslexia. Abnormal VEPs suggest aberrant visual input in some of these cases. However, the results of the various studies are not equivocal [235–239].

Inborn errors of metabolism

The differential diagnosis for patients suspected of neurometabolic disease is large. From the very nature of these disorders biochemical tests, if available, should give the final answer. VEPs, in particular when combined with EEG and electro-retinography (ERG), are a meaningful addition to the clinical signs in the choice of a pertinent metabolic examination. Table 11 gives an

Table 11. EEG, ERG and VEP in neurometabolic disorders (Lit. based)

	(P)VEP		EEG	ERG
	configuration	amplitudes		
1. neuronal ceroid lipofuscinoses				
infantile	–	low/abs.	+	+
late infantile	–	high	+	+
juvenile	–	low/abs.	+	+
2. global body hexosaminuria	+		+	
3. metachromatic leucodystrophy	+	low/abs.	+	
4. adrenoleucodystrophy	–	low/abs.	+	
5. Pelizaeus Merzbacher disease	+	low/abs.	+	
6. GM2 gangliosidosis	–	low/abs.	+	+
7. progressive neuronal degeneration childhood	–	low/abs.	+	–
8. infantile neuronal dystrophy	–	low/abs.	+	–
9. mitochondrial disease	+	low	+	?
10. Mucopolysaccharidoses	–	–	+	
11. Menkes disease	–	absent	+	+

\+ abnormal in all cases
\+ abnormal in less than half of the cases
– normal in all cases
low/abs. (progressive) decrease to amplitudes, sometimes to VEP absence
high(+) increased amplitudes

From Harden et al. [241–244] and Markand et al. [245].

overview of the occurrence of abnormal VEPs and disturbances in other neurophysiological tests in the major metabolic diseases of the brain. In addition to these quantitative data also the nature of the anomalies should be taken into account. The combination of a mildly disturbed background pattern of the EEG with some slow spike wave activity, low amplitude or absent ERG and initially well preserved VEPs which is thought characteristic for juvenile neuronal ceroid lipofuscinosis, can serve as an example for this statement. For other qualitative details on VEPs and in particular those in the EEG which are of utmost importancy in the differentiation between the various neurometabolic diseases, see the publications on this subject (among others: [240–245]).

Conclusion

In the twenty years after widespread introduction in neurology VEPs have gained a place in the diagnostic armamentarium. In some initially important fields the role of VEPs has been consolidated, for other diseases they are used less now. New applications have emerged which still have to endure

the test of time. The demyelinating diseases have remained the major field for the use of VEPs. Knowledge of anomalies of VEPs in other disorders is important as well, partly for the diagnosis of these entities, partly for their differentiation from demyelinating disease. VEPs have been found helpful in the prediction of the outcome in some of these conditions. Moreover, VEPs appear to have value for the detection and quantification of diffuse brain damage or intoxications. For this purpose in particular, computer analysis of VEP data seems essential. Ways to achieve this goal have been outlined in the last few years but still need to be developed further.

Acknowledgement

D.C.J. Pointvliet made a draft for the description of automatic analysis of VEPs. R.J. Widdershoven did the recordings and the analysis of the PVEPs in normal subjects. E.J. Jeekman and R.H. van Leeuwen read the manuscript. The work of Mrs. Wolthuis in the survey of the literature and preparation of the manuscript was indispensable. All advices and help of these members of the Research Unit for Clinical Neurophysiology MRL/TNO are gratefully acknowledged.

References

1. Halliday AM. Evoked potentials in clinical testing. Edinburgh Churchill Livingstone 1982, 73–126/ 149–202.
2. Chiappa KH. Evoked potentials in clinical medicine. New York, Raven Press 1983.
3. Sokol S. Visual evoked potentials. In: Aminoff MJ, Electrodiagnosis in clinical neurology. New York, Churchill Livingstone 1986; 441–464.
4. Spehlmann R. Evoked potentials primer. Boston, Butterworth Publishers 1985; 65–136.
5. Lowitzsch K. Visual evoked potentials. In: Lowitzsch K, Matern K, Hopf HC (eds). Evozierte Potentiale in der Klinischen Diagnostik. Stuttgart, Thieme 1983.
6. Halliday AM. Appendix II: Standards of clinical practice for the recording of evoked potentials. In: Recommendations on the practice of clinical neurophysiology. Amsterdam, Elsevier 1983; 69–80.
7. Recommended standards for visual system evoked potentials. J Clin Neurophysiol 1986, 3 (suppl): 54–70.
8. Celesia GG, Kaufman D, Cone S. Effects of age and sex on pattern electroretinograms and visual evoked potentials. Electroencephalogr Clin Neurophysiol 1987; 66: 481–492.
9. Allison T, Hume AL, Wood CC, Goff WR. Developmental and aging changes in somatosensory, auditory and visual evoked potentials. Electroencephalogr Clin Neurophysiol 1984; 58: 14–24.
10. Allison T, Wood CC, Goff WR. Brain stem auditory, pericentral visual, and short-latency somatosensory evoked potentials: latencies in relation to age, sex and brain and body size. Electroencephalogr Clin Neurophysiol 1983; 55: 619–636.
11. Sokol S, Moskowitz A, Towle VL. Age-related changes in the latency of the visual evoked potential: influence of check size. Electroencephalogr Clin Neurophysiol 1981; 51: 559–562.
12. Kuroiwa Y, Celesia GG. Visual evoked potentials with hemifield pattern stimulation. Their use in the diagnosis of retrochiasmatic lesions. Arch Neurol 1981; 38: 86–90.
13. Harnois IC, Paulay TA. Bilateral recordings of normal visual evoked potentials. I. Normal subjects. Electroencephalogr Clin Neurophysiol 1992; 84: 111–118.

14. La Marche JA, Dubois WR, Cobb NB, Daniels RE. Acquisition of visually evoked potentials in patterned stimuli: age and eye comparisons. Electroencephalogr clin Neurophysiol 1986; 65: 81–85.
15. Snyder EW, Dustman RE, Shearer DE. Pattern-reversal evoked potential amplitudes: life-span changes. Electroencephalogr clin Neurophysiol 1981; 52: 456–464.
16. Shaw EE, Arey JP, Brigell GS, Wright KW. P100 amplitude sensitivity of the pattern visual evoked potential. Electroencephalogr clin Neurophysiol 1991; 81: 318–328.
17. Dustman RE, Cleaphe KH, Gill E. Normal temporal variability of the P100. Electroencephalogr clin Neurophysiol 1987; 66: 151–156.
18. de Weerd AW. Variability of central conduction in the course of multiple sclerosis. Serial recordings of evoked potentials in the oculomotor of Onuphy. Clin Neurol Neurosurg 1987; 89: 9–13.
19. Riedo-Widmer I, Yalo MD, Mjlle I, Thomsen J. Dysmetropsia, dyslexia and delayed visual evoked potentials in lacunar. Acta Neurol 1992; 11: 479–483.
20. Dinse HCh, Schöbinger H. Follow-up studies of visual potentials in multiple sclerosis tested by checkerboard and Vernier stimulation. Electroencephalogr clin Neurophysiol 1990; 76: 486–496.
21. Mauguiere O, Kaiser L, Smolenski C, Lucas BF. Pattern reversal evoked cortical responses in normals. A study of different methods of stimulation and potential reproducibility. J Neurol 1979; 222: 43–53.
22. Madden J, Hogg CR, Dubowitz LMS, Ekstrand H, Arden GB. Visual evoked responses to light emitting diode (LED) photic stimulation in newborn infants. Electroencephalogr clin Neurophysiol 1984; 58: 317–325.
23. Barnet AB, Friedman SL, Stein IF, Oksenberg JB, Sharma R, Lodge A. VEP development in infancy and early childhood: a longitudinal study. Electroencephalogr clin Neurophysiol 1988; 69: 476–489.
24. Moskowitz A, Sokol S. Developmental changes in the human visual system as reflected by the latency of the pattern reversal VEP. Electroencephalogr clin Neurophysiol 1983; 56: 1–15.
25. Pieroni M, Shahidi I, Dubowitz LMS. Maturation of the visual evoked response and its correlation with visual acuity in preterm infants. Dev Med Child Neurol 1985; 27: 468–474.
26. Wright BH, Pearce JM, Taylor MJ. Changes in the VEP in preterm neonates with cranial scans, as assessed by EEG monitoring. Electroencephalogr clin Neurophysiol 1987; 68: 223–229.
27. Ellingson RJ. Variability of visual evoked responses in the human newborn. Electroencephalogr clin Neurophysiol 1976; 39: 10–18.
28. Hrbek A, Karlberg P, Olsson T. Development of visual and sensorimotory evoked responses in preterm newborn infants. Electroencephalogr clin Neurophysiol 1973; 34: 225–232.
29. Watanabe K, Iwase K, Hara K. Visual evoked responses during sleep and wakefulness in pre-term infants. Electroencephalogr clin Neurophysiol 1975; 39: 375–379.
30. Pryds O, Greisen G, Trippenbach W. Visual evoked potentials in preterm infants during the first hours of life. Electroencephalogr clin Neurophysiol 1989; 73: 257–265.
31. Kurtzberg C, Vaughan HG Jr. Preterm and post-term neonatal maturation of flash and pattern ERPs. In: Ogle VJ (ed). Maturation of the CNS and evoked potentials. Amsterdam: Elsevier Science Publishers, Excerpta Medica, International Congress Series 714, 1986; 9–15.
32. Stanley GB, Fleming PJ, Mulgan MH. Developmental wave form analysis of the neonatal flash evoked potential. Electroencephalogr clin Neurophysiol 1987; 66: 140–152.
33. Taylor MJ, Menzies R, MacMillan LJ, Whyte HE. VEPs in normal full-term immature neonates: Longitudinal versus cross-sectional data. Electroencephalogr clin Neurophysiol 1987; 68: 31–37.
34. Ellingson RJ. Development of visual evoked potentials and pseudo-sensory responses in normal full-term, low-risk premature and hypotrophic infants during the first year of life. Electroencephalogr clin Neurophysiol 1986; 63: 306–316.
35. Hrbek A, Karlberg PO, Vinge EL. The visual evoked potential in the first six years of life. Electroencephalogr clin Neurophysiol 1980; 48: 395–407.

30. Halliday A. Maturation of the visual evoked potential. In: Chiarenza GA, Papakostopoulos D (eds). Clinical application of cerebral evoked potentials in pediatric medicine. Amsterdam: Excerpta Medica 1982; 4–39.
31. Pratesi V. Temporal and spatial properties of the pattern-reversal VEPs in infants below 3 months of age. Human Neurobiol 1984; 3: 95–102.
32. Cobb WR, Kerbey J, Emmerson RY, Donovan BT. Pattern reversal evoked potentials, age, sex and hemisphere asymmetry. Electroencephalogr clin Neurophysiol 1985; 62: 366–405.
33. Fenwick PBC, Brown D, Hennessy J. The visual evoked response to pattern reversal in normal 4–14 year old children. Electroencephalogr clin Neurophysiol 1983; 55: 49–62.
34. Eggermont JJ. On the rate of maturation of sensory evoked potentials. Electroencephalogr clin Neurophysiol 1988; 70: 293–305.
35. Barber SR, Geraghty GA, Clark A, Hawkins RJ, Hopper JM, Smith KRH. Cortical generators of the C1 component of the pattern-reversal visual evoked potential. Electroencephalogr clin Neurophysiol 1997; 68: 216–25.
36. Dustal A, Pavo E, Maris EEM. Several generators of the visual evoked potentials: Intracerebral recording in awake humans. Electroencephalogr clin Neurophysiol 1988; 71: 88–99.
37. Kraut MA, Arezzo JC, Vaughan HG Jr. Intracortical generators of the flash VEP in monkeys. Electroencephalogr clin Neurophysiol 1985; 62: 300–312.
38. Lennox N, Joseph JP. Manifestations of the pattern-evoked potential (PEP) in relation to the individual part of the visual field. Electroencephalogr Neurophysiol 1978; 45: 183–202.
39. Colon EJG, Polegre RD, Halliday JE, Peckham RJ, Corby JR, Kregge RA. Visual evoked potentials and position emission tomography. Coupling of regional cerebral blood flow and evoked neuronal activity: Can the sensory potential generators be visualized? Electroencephalogr clin Neurophysiol 1982; 54: 240–253.
40. Mouguiere F, Guard MM, Hatwes Y, Pernier J. Cartes spatiales anatomiques des potentiels cérébraux provoqués par inversion de damier. Rôle générale comparé des modalités topographiques des evoked responses. Rev EEG Neurophysiol 1985; 15: 129–135.
41. Maier J, Dagnelie G, Spekreijse H, van Dijk BW. Principal components analysis for source localization of VEPs in man. Vision Res 1987; 27: 165–177.
42. Littmann D, Darrell TM, Scientific W. Intracranial and scalp fields evoked by interictal electrocortical normal and modeling of their dipolar generators. In: Cracco JJ, Mauguiere F, Rossi M (eds). Clinical applications of evoked potentials in neurology. New York: Raven Press 1982.
43. Wolkenstein HJ, Lyssenko E. Abhängigkeit der Parameterwerte des VEP bei Halbfeldreizung vom Reizort und Messpunkt. EEG-EMG 1988; 19: 123–127.
44. Blumhardt LD, Halliday AM. Hemisphere contributions to the composition of the pattern evoked potential waveform. Exp Brain Res 1979; 36: 53–69.
45. Blumhardt LD, Barrett G, Halliday AM. The asymmetrical evoked potential to pattern reversal and its significance for the analysis of visual field defects. Br J Ophthalmol 1977; 61: 454–461.
46. Fukui R, Kato M, Kamiwa Y. Effects of eyeball movements on pattern reversal visual evoked potentials in patients with multiple sclerosis and healthy subjects. Electroencephalogr clin Neurophysiol 1986; 63: 315–326.
47. Blumhardt LD. The theoretical pattern visual evoked response in neurology. In: Halliday AM, Butler SR, Paul R (eds). A textbook of clinical neurophysiology. Chichester: John Wiley and Sons 1987; 303–342.
48. Spehlmann MC, Emerson RG, Pedley TA. Dissociation of normal P100 from occipital P100 in pattern reversal visual evoked potentials. Electroencephalogr clin Neurophysiol 1986; 65: 165–169.
49. Shah PV, Amanoff MJ, Gonella CPK, Mayes MM. Effect of reference point on visual evoked potentials during scoliosis. Electroencephalogr clin Neurophysiol 1986; 71: 119–122.
50. Barrett G, Blumhardt LD, Halliday AM, Halliday E, Kriss A. A paradox in the lateralization of the visual evoked response. Nature 1978; 261: 253–255.

57. Blakemore JC, Pedley TA. Distal field pattern reversal visual evoked potentials. II. Lesions of the chiasm and posterior visual pathways. Electroencephalogr Clin Neurophysiol 1982; 54: 125–131.
58. Celesia GG, Meredith JT, Bodis R. Pyramidal, visual cortical potentials and visual evoked responses after hemispheric hemorrhages. Electroencephalogr Clin Neurophysiol 1983; 56: 15–30.
59. Maitland CG, Aminoff MJ, Raymond C, Hess WE. Evoked potentials in the evaluation of visual field defects due to abnormal of retrogeniculate origin. Neurology 1982; 32: 986–991.
60. Ghidoli M, Bodis-Wollner I, Miller L. Visual evoked potential diagnosis of field defects in patients with rheumatic and noninflammatic lesions. J Neurol Neurosurg Psychiatry 1982; 45: 298–302.
61. Ozdi M, Yilmaz T, Dursun OF, Kirnaz A. Visual evoked potentials by different check sizes in patients with multiple sclerosis. Neurology 2003; 35: 1683–1685.
62. Cant BR, Hume AL, Shaw NA. Effects of fixation on the pattern visual evoked potential in multiple sclerosis. Electroencephalogr Clin Neurophysiol 1978; 45: 496–504.
63. Kapoustin MI, Siegel IM, Carr RE, Rumbaugh C, Flamm E, Stokes E. Visual evoked potentials in chiasmal glioma in four adults. Acta Neurol 1981; 56: 462–465.
64. Greenwood Z, Klein A, Halliday AM, McDonald WI. Pattern- and flash-evoked potentials in the assessment and management of optic nerve glioma. J Neurol Neurosurg Psychiatry 1995; 48: 1125–1134.
65. Holder GE, Bullock PR. Visual evoked potentials in the assessment of patients with non-functioning hypothalamic adenomas. J Neurol Neurosurg Psychiatry 1989; 52: 31–37.
66. Steinhardt T, Reuther R, Riemann M, Krayat J. Value of visual evoked potentials (VEP) in compression of the anterior visual pathways, especially in the area of the chiasm. Nervenarzt 1995; 66: 560–567.
67. Holder GE. Pattern visual evoked potentials in patients with posterior visual space-occupying lesions. Doc Ophthalmol 1985; 59: 121–134.
68. Skaver MR, Jordan SE. The ectrophysiological and other spatial artifacts of topographic EEG mapping. J Clin Neurophysiol 1987; 4: 121–126.
69. Spitzer AR, Cohen LG, Tabaraes J, Hallett M. A method for measuring optimal interelectrode spacing for cerebral topographic mapping. Electroencephalogr Clin Neurophysiol 1989; 73: 355–361.
70. Lehmann D. Mapping and analyzing maps of evoked potentials. In: Barber C, Blum G, Johns D (eds). Evoked potentials III. Boston, Butterworths Publishers 1987; 91–99.
71. Duffy FH, Bartelfet JL, Lombroso CT. Brain electrical activity mapping (BEAM): A method for extending the clinical utility of EEG and evoked potential data. Ann Neurol 1979; 5: 309–321.
72. Duffy FH, Burnth PH, Bartelfet JL. Age-Related gender-linked by mapping. An aid in the topographic analysis of brain electrical activity. Electroencephalogr Clin Neurophysiol 1981; 51: 455–462.
73. Duffy FH, Denckla MB, Bartels PH, Sandini G, Kiessling. Dyslexia: Regional differences in brain electrical activity by topographic mapping. Ann Neurol 1980; 7: 412–420.
74. Dixon S. A simple sequentially sensitive outlier test procedure. Scand J Stat 1979; 6: 65–70.
75. John ER, Prichep LS, Isenni P. Normative data banks and neurometrics. In: Gevins AS, Rémond A (eds). Handbook of electroencephalography and clinical neurophysiology. Vol 1, Methods of analysis of brain electrical and magnetic signals. Amsterdam, Elsevier 1986.
76. Schieg M, von Cramon D. Evoked dipole source potentials of the human auditory cortex. Electroencephalogr Clin Neurophysiol 1986; 65: 344–360.
77. Howard IP, Ohmi M, Lai JS. Perceived potential in binocular and rivalry. J Clin Neurophysiol 1986; 3: 49–66.
78. Tan CT, Murray NMF, Sawyer D, Lorimer TBL. Differential alteration of the visual evoked potential. J Neurol Neurosurg Psychiatry 1984; 47: 518–523.
79. Jabbari B, Maitland CG, Merrill LM, Maddox J, Gandevia GH. The value of visual evoked

potential as a screening test in multiple sclerosis. Arch Neurol 1985; 42: 1072–1076.
80. Harding GFA, Smith VH, Yoshi HC. A cortical tuned photostimulator for surgical monitoring. Electroencephalogr clin Neurophysiol 1987; 66: 522–526.
81. Costa E, Silva L, Wang AH, Matson L. The application of flash visual evoked potentials during operations on the extradural visual pathways. Neurol Res 1985; 7: 11–18.
82. Cedzich C, Schramm J, Mengedoht CF, Fahlbusch R. Factors that limit the use of flash visual evoked potentials for surgical monitoring. Electroencephalogr clin Neurophysiol 1988; 71: 162–165.
83. Fenwick PBC, Slone SA, Barrowcliff S, Galambos D. Changes in the pattern reversal visual evoked potential as a function of implied screen angle of presentation. Electroencephalogr clin Neurophysiol 1988; 69: 178–183.
84. Sokol PS, Hjorth JT, Ingram DA, Effect of pattern scale on visual, auditory and somatosensory evoked potentials. Br J Ophthalmol 1982; 66: 1065–1069.
85. Rau W, Lasser V. Hauptsätze U. Zur Deutung der Neuropsychologie und der visuell evozierten Potentiale (VEP) der Menschen. Arzt Laborat 1985; 31: 335–336.
86. Nee HF, Gerhard L, Freyer M, Schurr HC, Reinhardt V, Jahn T. Optic nerve trauma. Clinical, electrophysiological and histological reports. Acta Neurochir 1987; 89: 15–22.
87. Halliday AM, Garwin M, Cornelis T, Lucie AA, Hawgood JF. Visual electrical evoked potentials. Evaluation of ocular injuries. Neurology 1987; 37: 825–828.
88. Lindenau K, Wolkenhauer H-J. Visual evoked potentials and computerized perimetry in optic neuritis and pituitary tumors. In: Barber C, Blom T (eds). Evoked potentials III. Boston, Butterworths Publishers 1987, 244–251.
89. Miller DH, Newton MR, van der Poel JC *et al*. Magnetic resonance imaging of the optic nerve in optic neuritis. Neurology 1988; 38: 175–179.
90. Skuse D, Regan D. Pattern visual evoked potentials and spatial vision in monocular uveitis and multiple sclerosis. Arch Neurol 1988; 41: 49–205.
91. Halliday AM, Kriss A, Carmichael P, François D, McDonald WI, Taylor D. Childhood optic neuritis. A study of pattern and flash evoked potentials. In: Galloni V (ed). Maturation of the CNS and evoked potentials. Amsterdam, Elsevier Science Publishers, Excerpta Medica, International Congress Series 716, 1986, 41–50.
92. Cohen JG, Kaufman D, Cant SH. Serial clinical recording of pattern electroretinography and visual evoked potentials in multiple sclerosis. Arch Neurol 1986; 43: 1247–1252.
93. Kaufman DI, Lessell IW, Wilson M, Way SH. The pattern shift electrodiagram. A long-term study of acute optic neuropathies. Neurology 1988; 38: 1767–1774.
94. MacFadyen DJ, Dennis SM, Douglas GR, Anderson EJ, Mawson DK, Rey HW. The retinal nerve fiber layer, neuroretinal dysfunction and visual evoked potentials in MS. Neurology 1988; 38: 1353–1358.
95. Novak GP, Wiesbeck M, Rattenborg D, Grauer BS, Vaughan HG. The utility of visual evoked potentials using Scintifed stimulation and cursor, cVMS type in the evaluation of suspected multiple sclerosis. Electroencephalogr clin Neurophysiol 1989; 73: 7–9.
96. Higher JR, Sakla H, Thiel H, Hart DA. Usefulness of different stimuli in visual evoked potentials. Neurology 1987; 37: 656–662.
97. Cohen J, Mykel LH, Bejda Wolkin L. The effect of monocular optimization on the visual evoked potential in multiple sclerosis. Ann Neurol 1983; 13: 532–539.
98. Aminoff MJ, Goin AL. Pattern-onset visual evoked potentials in suspected multiple sclerosis. J Neurol Neurosurg Psychiatry 1981; 44: 608–614.
99. Hennerici M, Wenzel D, Freund HJ. The comparison of sinusoidal, rectangle and checkerboard stimulation for the evaluation of delayed visual evoked responses in patients suspected of multiple sclerosis. Brain 1977; 100: 555–576.
100. Rizzolatti PCC, Spekreijse H, van Wezeman T. Abnormal pattern-evoked human potentials: Implications for the delayed evoked potentials in multiple sclerosis. Electroencephalogr clin Neurophysiol 1985; 62: 153–166.
101. Mitchell JD, Ramsey S, Mulgaus A, Campbell EW. The recovery cycle of the pattern visual evoked potential in normal subjects and patients with multiple sclerosis. Electroencephalogr clin

Neurophysiol 1963; 56: 108–112.
102. Gerhard H, Jörg J. Zur zeitlichen Abhängigkeit des VEP bei Normalpersonen und Patienten mit Multipler Sklerose. EEG-EMG 1982; 13: 37–41.
103. Hazelwood SR, Yiannikas C. Contribution of patient mental level and task difficulty to analysis of VEP abnormalities in multiple sclerosis. Electroencephalogr clin Neurophysiol 1986; 64: 103–110.
104. Wolf TEN, Gasser CO, Oechsle M. Zeitliche und räumliche Leitungsstörung bei Multipler Sklerose: Ein weglich nur visuell und somatosensorisch evozierte Potentiale in Abhängigkeit vom Verlaufstyp. Z. EEG-EMG 1988; 19: 247–256.
105. Ron CW, Mills KR, Murray NMF, Schiefer TW. Magnetic motor stimulation: Central motor conduction studies in multiple sclerosis. Ann Neurol 1987; 22: 786–792.
106. Fazekas MR, Markind OH, Edelman MK, Strauss JC, Kinkel OT. Multiple sclerosis. Magnetic resonance imaging, evoked responses, and spinal fluid electrophoresis. Neurology 1986; 36: 829–831.
107. Gozzo JM, Monje Argüello A. The sensitivity of multimodal evoked potentials in multiple sclerosis. A comparative with magnetic resonance imaging and cerebrospinal fluid analysis. Electroencephalogr clin Neurophysiol 1990; 76: 208–218.
108. Uhlenbrock D, Seidel D, Gehlen W, Hess HH, Hunn S, Dichgans J, Zeit T, Hopfe R. MR imaging in multiple sclerosis. Comparison with blood, CSF, and evoked potential findings. AJNR 1988; 9: 59–67.
109. Goldszmidt SS, Galpalshoff TO, Gumnit S, Krahe JE, Leech JT, Ames AM. The initial diagnosis of multiple sclerosis. Clinical impact of magnetic resonance imaging. Arch Neurol 1991; 13: 468–474.
110. Gosser BS, Kjeldberg K, Vaughan HG, Arezzo JC, Aine ME, Smith CR, LaBossa NG, Schelling LC. Extended evoked potentials compared with magnetic resonance imaging in the diagnosis of multiple sclerosis. Arch Neurol 1987; 44: 291–294.
111. Pery DW, Ogar JM, Kinkelhoff LF *et al.* MRI in the diagnosis of MS. A prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. Neurology 1990; 30: 166–185.
112. Matthews WB, Small DG. Some recording of visual and somatosensory evoked potentials in multiple sclerosis. J Neurol Sci 1979; 40: 11–21.
113. Matthews WB, Small M. Prolonged follow-up of abnormalities of evoked potentials in multiple sclerosis. Evidence for delayed recovery. J Neurology Psychiatry 1981; 40: 939–942.
114. Walsh JC, Garlick R, Cleeves J, McLeod JG. Evoked potential changes in clinically definite multiple sclerosis: A two year follow up study. J Neurol Neurosurg Psychiatry 1982; 45: 494–500.
115. Lowitzsch K, Wolkobinski HD. Normalisierung der VEP bei Multipler Sklerose? Verlaufsbeobachtung bei 50 von 500 MS-Patienten. ZEEG-EMG 1983; 14: 81–85.
116. Cruikshank C, Macquarrie P, Courtney J, Ahmad G, Dyers M. Course of visual evoked potentials in MS. In: Courjon J, Mauguière F, Revol M (eds). Clinical applications of evoked potentials in neurology. New York, Raven Press 1982; 305–310.
117. de Weerd AW, Jonkman EJ. Changes in visual and short latency somatosensory evoked potentials in patients with multiple sclerosis. In: Courjon J, Mauguière F, Revol M (eds). Clinical applications of evoked potentials in neurology. New York, Raven Press 1982; 327–334.
118. Celesia GN, Syndulko K, Hamoir E, Tourtellotte WW, Potvin AR. Variability on serial testing of visual evoked potentials in patients with multiple sclerosis. In: Courjon J, Mauguière F, Revol M (eds). Clinical applications of evoked potentials in neurology. New York, Raven Press 1982; 359–363.
119. Amtzoff M, Dinet SL, Pernoch HB. Serial evoked potential studies in persons with definite multiple sclerosis. Arch Neurol 1988; 45: 1267–1272.
120. Barnes GD, Sicks R, Bass BH, Bass MJ, Bell SB, Rees L, Noseworthy JH, Rae-Grant GD, Shen GC. Hyperbaric oxygen therapy in chronic stable multiple sclerosis: Double-blind study. Neurology 1990; 36: 980–981.

121. Barker MP, Bates D, Cartlidge NEF, Daniels JM, Shaw DA. Hyperbaric oxygen and multiple sclerosis. Final results of a placebo-controlled, double-blind trial. J Neurol, Neurosurg, Psychiatry 1985; 48: 1402–1406.

122. Anderson DC, Shaw CE, Mortensen R, Dreager MO. Evoked potentials in serial treatment of chronic multiple sclerosis. Arch Neurol, 1987; 44: 1127–1129.

123. Goodin PA, Carroll PH, Ebers WR, Jeffrey V, Marsh L, Mercier BL, Ommaid D, Warren KG. A double-blind controlled pilot study of plasma exchange versus sham apheresis in chronic progressive multiple sclerosis. Can J Neurol Sci 1985; 12: 96–98.

124. Rhind RO, McQuillen MP, Herrington GJ, Bischoff D, Richardson RG. Chronic progressive multiple sclerosis: Double-blind controlled study of plasmapheresis in patients using immunosuppressive drugs. Neurology 1985; 35: 1–2–319.

125. Martin J, Kappos M, Knight SC et al. A double-blind controlled trial of human interferon in the treatment of multiple sclerosis. First report. Lancet 1982; i (8): 551–554.

126. Compston DAS, Milligan NM, Hughes RE, Gibbs J, McDonnell V, Morgan BP, Campbell AK. A double-blind controlled trial of high dose methylprednisolone in patients with multiple sclerosis. 2. Laboratory results. J Neurol, Neurosurg Psychiatry 1987; 50: 917–922.

127. Beaver MR, Packwood EW, Myers LW, Elkins GW. Evoked potentials predict the clinical changes in a multiple sclerosis drug study. Neurology 1987; 37: 1754–1757.

128. Elkins GW, Myers LW, Mosley MR, Greene MK, Packwood WW, Beaver MR. Clinical experience with azathioprine. Ther proc Physiology 1986; 10 (Suppl 2): 20–23.

129. Jonsson J, Tranberg W. Follow-up investigation with serial evoked multiple stimuli. A clinical and electrophysiological study. J Neurol Neurosurg Psychiatry 1982; 45: 906–914.

130. Haas AL, Wiesman SD. Evoked potentials in suspected multiple sclerosis. Diagnostic value and prediction of clinical course. J Neurol Sci 1988; 83: 97–210.

131. Poser CM, Paty DW, Scheinberg L et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13: 227–231.

132. Beaver MR, Vanmiller RE, Packwood JW, Compston NS. Evoked potential testing in relatives of multiple sclerosis patients. Arch Neurol 1985; 2: 33–34.

133. Petersen L, Trojaborg W. Visual, auditory and somatosensory pathway involvement in hereditary cerebellar ataxia. Friedreich's ataxia and familial spastic paraplegia. Electroencephalogr clin Neurophysiol 1981; 52: 283–292.

134. Carroll WM, Jones SJ, Halliday AM. Visual evoked potential abnormalities in Charcot-Marie-Tooth disease and comparison with Friedreich's ataxia. J Neurol Sci 1985; 71: 125–131.

135. Carroll WM, Kriss A, Stockler M, Harris C, Halliday AM. The incidence and nature of visual pathway involvement in Friedreich's ataxia. Brain 1988; 103: 415–424.

136. Livingstone IR, Murnaghan FE, Ellis R, Howe JW. Visual involvement in Friedreich's ataxia and hereditary spastic ataxia. Acta Neurol 1981; 36: 75–78.

137. Rogers J, Civalos C, Romero S, Rogers A, Correa H, Bedrossian A. Visual evoked potentials and brain stem auditory potentials in Friedreich's ataxia: A longitudinal study. Can J Neurol Sci 1986; 13: 505–509.

138. Bell TD, Gange E. Pattern reversal visual evoked potentials. Studies in Charcot-Marie-Tooth neuropathy. Arch Neurol 1984; 41: 738–741.

139. Hammond CJ, Willis AJ. Delayed potentials in dysgammaglobulinaemic neuropathy. Arch Neurol 1983; 40: 366–369.

140. Nuwer MR, Perlman J, Lachmann V, Rabkhinov A. Involvement of somatosensory and visual pathways in late onset ataxias. Electroencephalogr Clin Neurophysiol 1985; 61: 218–221.

141. Sandrini G, Grimi C, Rossi V, Bisogni PL, Alessio E, Pecchioli C, Vitri AP, Saggi G. Electroencephalographic and visual evoked potential abnormalities in systemic cytolipin. Electroencephalogr clin Neurophysiol 1986; 64: 215–217.

142. Fukutake A, Drake Jr ME, Bowden RJ, Chaturvedi DW, Marshall JR. Evoked potentials in chronic inflammatory demyelinating polyneuropathy. Arch Neurol 1988; 45: 1014–1016.

143. Nuwer MR, Perlman SL, Packwood JW, Rice RAP. Evoked potential abnormalities in the spinocerebellar ataxias. Ann Neurol 1988; 23: 281–287.

144. Uemiseki M, Hamasaki Y, Lingo HW. Evoked potentials in patients with Huntington's disease and their offspring. II. Visual evoked potentials. Electroencephalogr Clin Neurophysiol 1985; 62: 167–176.

145. Johansen BC, Skagen C, Marstad EL, Reinvang R-A. Auditory and visual evoked potentials in Huntington's disease. Electroencephalogr Clin Neurophysiol 1984; 57: 215–218.

146. Cogan G, Ivens M, Tardos G. Visual (VEP) and somatosensory (SSEP) evoked potentials in Huntington's chorea. Electroencephalogr Clin Neurophysiol 1986; 63: 466–470.

147. Ellis AL, Stewart RM, Lishman WA, Leonard HCA. Evoked potentials in Huntington's disease. Arch Neurol 1986; 43: 379–382.

148. Paramanthan K, Devachandra G, Wong PK. Visual (evoked) responses in diabetes. J Neurol Neurosurg Psychiatry 1985; 48: 647–647.

149. Celesia GG, Archer CR, Kaiwiles S, Goldfader PR. Visual function of the extrageniculocalcarine system in man. Relationship to acuity and fixedness. Arch Neurol 1980; 37: 504–508.

150. Fraser V, Lewis F. Visual evoked potentials in the evaluation of 'cortical blindness' in children. Ann Neurol 1979; 5: 156–159.

151. Spillmann R, Gross RA, Hyl MS, Tavares JE, Sherman RA. Visual evoked potentials and psychometric findings in a case of cortical blindness. Ann Neurol 1977; 2: 531–536.

152. Barlow SL, Goodin DS, Aminoff MJ. Visual evoked potentials in the investigation of "blindsight". Neurology 1980; 30: 304–309.

153. Schmitt H, Pfeiffers S, Malaeke S. Multimodality evoked potentials in hypoxemia. Electroencephalogr Clin Neurophysiol 1986; 64: 529–533.

154. Kutsuna MK, Taylor MJ, Cohn JO, Pierce RJ, Rudnow FA. The use of VEPs for CNS monitoring during experimental cardiopulmonary bypass and circulatory arrest. Electroencephalogr Clin Neurophysiol 1987; 68: 281–290.

155. Sugar S, Buscaglione P, Moody RA. The effects of isovolemic hemodilution and reinfusion of packed erythrocytes on somatosensory and visual evoked potentials. J Surg Res 1978; 25: 532–537.

156. Reilly EL, Kondo C, Brantberg JA, Terry HB. Visual evoked potentials during hypothermia and prolonged circulatory arrest. Electroencephalogr Neurophysiol 1979; 47: 106–116.

157. Markand ON, Warren CH, Moorthy SS, Dawson JR, King RD. Monitoring of multimodality evoked potentials during open heart surgery under hypothermia. Electroencephalogr Clin Neurophysiol 1984; 58: 431–440.

158. Gomez T, Lassale T. EEGs and evoked potentials in comatose patients with severe brain damage. Electroencephalogr Clin Neurophysiol 1988; 69: 1–13.

159. Shahshahani B, Schwartz G, Greenstein M. Clinical relevance of long-latency SEPs and VEPs during coma and emergence from coma. Electroencephalogr Clin Neurophysiol 1982; 53: 88–89.

160. Andersen DC, Brandice S, Rockwood GL. Multimodality evoked potentials in closed head trauma. Arch Neurol 1984; 41: 969–974.

161. Greenberg RP, Becker DP, Miller JD, Mayer DJ. Evaluation of brain function in severe human head trauma with multimodality evoked potentials. Part 2. Localization of brain dysfunction and correlation with posttraumatic neurological conditions. J Neurosurg 1977; 47: 163–177.

162. Lindsay KW, Carlin J, Kennedy L, Fry J, McInnes A, Dundee GM. Evoked potentials in severe head injury – analysis and relation to outcome. J Neurol Neurosurg Psychiatry 1981; 44: 796–802.

163. Narayan RK, Greenberg RP, Miller JD, et al. Improved confidence of outcome prediction in severe head injury. A computerized analysis of the clinical examination, multimodality evoked potentials, CT scanning, and intracranial pressure. J Neurosurg 1981; 54: 751–762.

164. Verpaalen M, Kaufman DI, Pierce T, Yielding S, Kaltenbach D. Electrophysiologic versus psychophysical in the detection of visual loss in multiple sclerosis. Neurology 1988; 38: 1709–1713.

165. Visser SL, van Tilburg W, Hooijer C, Jonker C, de Rijke W. Visual evoked potentials

(VEPs) in senile dementia: clinical aspects and hemispheric lateralization in the elderly. Comparison with EEG parameters. Electroencephalogr Clin Neurophysiol 1985; 60: 115–121.

166. Wright CE, Harding GFA, Drasdo A. Perverse dementia. The use of the flash and pattern VEP to diagnose. Electroencephalogr Clin Neurophysiol 1984; 57: 405–415.
167. Harding GF, Wright CE, Drasdo A. Primary presenile dementia: The use of the visual evoked potential as a diagnostic indicator. Br J Psychiatry 1985; 147: 532–539.
168. Visser SL, Tuint PC, van Tellingen W, ep den Velde W, Blom IL, de Rijke W. Visual evoked response in senile and presenile dementia. Electroencephalogr Clin Neurophysiol 1978; 46: 393–402.
169. Wright CE, Harding GF, Drasdo A. VEP as a diagnostic indicator of dementia. Doc Ophthalmol 1986; 62: 89–90.
170. Wright CE, Drasdo N, Harding GF. Pathologies of the optic nerve and visual association areas: Information given by the flash and pattern evoked potential, and the temporal and spatial contrast sensitivity function. Brain 1987; 110: 107–120.
171. Drasdo A, Wright CE, Harding GFA, Rowan JC, Rolfe EB. Serial visual evoked potential recordings in Alzheimer's disease. Br Med J 1986; 293: 9–10.
172. Bordia H, Deutsch L. Changes in flash but not pattern evoked potential after subchronic application of a monoamine oxidase (MAO) type A inhibitor in man. Electroencephalogr Clin Neurophysiol 1985; 62: 77–81.
173. Bajalan AAA, Wright CE, van der Vlis VJ. Changes in the human visual evoked potential caused by the cholinomimetic agent physostigmine hydrochloride: Comparison with results in Alzheimer's disease. J Neurol Neurosurg Psychiatry 1988; 49: 153–162.
174. Tartaglione A, Pizzi N, Bini G, Spadoni-Gelli L, Fiorelli B. VEP changes in Parkinson's disease are stimulus dependent. J Neurol Neurosurg Psychiatry 1988; 51: 305–307.
175. Diener HC, Ludwig H, Pfaffenrath V, Lenard HP, Klehr G. Pattern evoked potentials (PEPs) in Parkinson's disease. Neurology 1982; 28: 430–433.
176. Hile AE, Stewart RM, Canfield NS, Leventhal NA, Strom. Checkerboard pattern reversal evoked potentials in Parkinsonism. Electroencephalogr Clin Neurophysiol 1982; 54: 316–326.
177. Oseltj M, Orlandi MF, Bassani M, Gatti S. Visual evoked potentials in Parkinsonism and dopamine blockade: could a stimulus-dependent dopamine function be hereditary? J Neurol Neurosurg Psychiatry 1986; 49: 1139–1150.
178. Bodis-Wollner I, Yahr MD. Measurement of visual evoked potentials in Parkinson's disease. Brain 1978; 101: 661–671.
179. Delwaide PJ, Mormont R, de Pasqua V. Les potentiels evoques visuels dans la maladie de Parkinson. Rev EEG Neurophysiol 1980; 10: 336–342.
180. Gauvil MJ, Dye P, Vincent S, Clifford Rose P. Visual and auditory evoked responses in patients with Parkinson's disease. J R Coll Neurosurg Psychiatry 1981; 44: 227–232.
181. Sedwick D. Influence of levodopa on pattern reversal VEP: Behavioral differences in primary and secondary Parkinsonism. Electroencephalogr Clin Neurophysiol 1985; 61: 256–263.
182. Nightingale S, Mitchell KW, Howe JW. Visual evoked cortical potentials and pattern electroretinograms in Parkinson's disease (abstracted subjects). J Neurol Neurosurg Psychiatry 1986; 49: 1266–1267.
183. Regenwirth MJ, Shukla P, Siegel IW, Lieberman A. Visual vector electrodiagnosis in patients with Parkinson's disease. Arch Neurol Arch Neurol 1982; 39: 284–286.
184. Gerbitz J, Schmidt E, Hefter W, Benecke W. Abnormal of visual evoked potentials and electroretinograms in Parkinson's disease. Electroencephalogr Clin Neurophysiol 1987; 66: 346–357.
185. Bhushan PA, Vanchilingam S, Brandon EA, Dimopoulos A, Cameron RA. Effect of L-dopa on visual evoked potential in patients with Parkinson's disease. Neurology 1986; 36: 1119–1121.
186. Klug A, Carroll WM, Blackburn LD, McBride AM. Pattern and flash-evoked potential changes in cone monochromatic sensitivity. In: Courjon J, Mauguière F, Revol M (eds)

Clinical applications of evoked potentials in neurology. New York: Raven Press 1982; 11–19.

187. Pinkhasova T, Visser SL. Visual evoked potentials and alcohol-related brain damage. In: Courjon J, Mauguière F, Revol M (eds). Clinical applications of evoked potentials in neurology. New York: Raven Press 1982; 189–55.

188. Petrera JE, Dedolfis HC, Trojaborg W. Serial pattern evoked potential recording in a case of toxic optic neuropathy due to chloroquine. Electroencephalogr Clin Neurophysiol 1988; 71: 144–149.

189. Tsimoklis C, Wyatt JC, Mitchell JG. Visual evoked potentials in the detection of subclinical ophthalmic effects secondary to chloroquine. Arch Neurol 1987; 45: 845–848.

190. Taylor MJ, Keenan NK, Cullum T, Yusuf B, Freedman MH, Logan WJ. Subclinical VEP abnormalities in patients on chronic dihydroxychloroquine therapy: Longitudinal studies. Electroencephalogr Clin Neurophysiol 1987; 68: 41–47.

191. Ellison NJ, Barlow JB, Chow E *et al*. Visual and colour discriminatory responsivity in patients receiving subcutaneous deferoxamine infusions. N Engl J Med 1986; 314: 869–875.

192. Fendrich MM, Snyder M, Taylor M, Yusuf B. Visual potentials associated with deferoxamine therapy. Teratology 1986; 49: 283–290.

193. Chang YC. Symptomatic effects of tobacco on the human central nervous system: Evoked potential abnormalities in tobacco pulmonologists. J Neurol Neurosurg Psychiatry 1987; 50: 269–274.

194. Seppäläinen AM, Sydysaari-Ilpo I. Neurophysiological findings among workers exposed to organic solvents. Acta Neurol Scandinav 1982; 66, (suppl 92): 109–116.

195. Casper R, Newton P, Reed M. Neurophysiological sign of brain damage due to glue sniffing. Electroencephalogr Clin Neurophysiol 1985; 60: 23–31.

196. Seppäläinen AM, Raitta C, Hanninen HK. Neurotoxic and therapy in visual evoked potentials and electroencephalogram of industrial workers. Electroencephalogr Clin Neurophysiol 1979; 47: 442–456.

197. Ehrlenius S, Gamberale F, Hindmarsh T *et al*. Exposure to organic solvents. Scand J Work Environ Health 1986; 6: 159–171.

198. Shagass C. Evoked potentials in senile psychiatry. In: Shagass CB, Wilson WP (eds). EEG and evoked potentials in psychiatry and behavioral neurology. Boston: Butterworths 1981; 166–210.

199. Rau W, Kornhuber W, Hammerle G, Wood J. [Evoked Potentials in Anesthesia and Intensive Medicine. Absorption (Wash. D) 1986; 13: 192–198.

200. Uhl RR, Squires KC, Bunce DL, Starr A. Effect of halothane anesthesia on the human visual evoked response. Anesthesiology 1980; 52: 255–259.

201. Schell JPS, Ingram DA, Flynn PJ, Rutherford CR, Rogers H. Evoked potentials during isoflurane anesthesia. Br J Anaesth 1986; 58: 388–393.

202. Fenwick PBC, Robertson R. Changes in the visual evoked potential in patients treated with lithium medication. Electroencephalogr Clin Neurophysiol 1983; 55: 538–545.

203. Harding GFA, Alford CA, Pokoff TT. The effect of sodium valproate on sleep, reaction times, and visual evoked potential in normal subjects. Epilepsia 1985; 26: 397–401.

204. Dieckhöfer AC, Orr LT, Arendshorst W, Dorrance M. Alterations in transient visual evoked potentials induced by clonidine and other agents. Neuropsychobiology 1985; 14: 39–41.

205. Chu NS. Sensory evoked potentials in Wilson's disease. Brain 1986; 109: 911–927.

206. Araki S, Murata K, Aono H. Central and peripheral nervous system dysfunction in workers exposed to lead, zinc and copper. A 3-E-system study of visual and somatosensory evoked potentials, and Arch Occup Environ Health 1987; 59: 177–191.

207. Thurgher BW, Mc Adams R, Lester M. Evoked potentials related to lead exposure and lead in children. Ann N Y Acad Sci 1984; 425: 384–386.

208. Eisert T, Regius U, Wilmers G, Hellbrügge B, Frig J. Somato-Neurographie, visuell und somatosensorisch evozierte Potentiale (VEP und SEP) an Meerschweinchen Kindern. Nervenarzt 1986; 57: 465–471.

208. Jones K. Neuropathologic studies of Marinesco disease in Niigata. In: Merigan W, Weiss B (eds). Neurotoxicology of the visual system. New York, Raven Press 1980; 165–178.

209. Jappinen AM, Savolainen R, Kuvaja T. Changes induced by xylene and alcohol in human evoked potentials. Electroencephalography and Neurophysiology 1981; 51: 148–55.

210. Chan FW, McLeod JG, Tuck RR, Walsh JC, Perry PA. Visual evoked responses in chronic alcoholics. Journal of Neurology, Neurosurgery and Psychiatry 1986; 49: 945–950.

211. Mitsuda HM, Asher L, Ryder K, Conard R. Delayed visual evoked potentials in chronic alcoholism. Journal of Neurology 1986; 233: 161–163.

212. Kitta M, Peregrin J, Vit F, Bachmova J, Svorad J. Pattern-reversal visual evoked potentials in patients with chronic renal insufficiency. Electroencephalography and Neurophysiology 1981; 51: 436–442.

213. Harrad R, Bonner JR, Ward JW, Tomkins PT. Visually evoked cortical potentials in renal failure. Transient potentials. Electroencephalography and Neurophysiology 1979; 46: 606–618.

214. Lewis EG, Dawson SE, Bush EC. Visual and somatosensory evoked potential characteristics of patients undergoing hemodialysis and kidney transplantation. Electroencephalography and Neurophysiology 1979; 46: 225–234.

215. Rossini PM, Pizzella M, Torrioni M, Garibbo G, Di Paolo R, Albertazzi A. Cerebrocortical central and cycle P100 in the renal and pseudo-renal subjects. Electroencephalography and Neurophysiology 1981; 52: 425–444.

216. Bonfenbrenner G, Gigli GL, Bernardi L, Feri R, Grassi C, Milan A. Visual evoked potential recordings in hepatic encephalopathy and their evaluation during branched chain amino acid treatment. Hepatogastroenterology 1985; 32: 3–7.

217. Sandford SL, Taylor BJ, Sukhani R, see Tani LH. Sensory information processing in patients with neurohepatic coma/pre. J Neurol Sci. 1987; 80: 269–276.

218. Lees LJ, Bolton RP, Losowsky MS. The use of the visual evoked potential (VEP) in detecting a form of subclinical encephalopathy. A comparison with the standard colorimetric test (SCT). J Hepatol 1987; 5: 211–217.

219. Sandford SL, Sims RS. Assessment of hepatic encephalopathy with visual evoked potentials compared with conventional methods. Hepatology 1988; 8: 1004–1008.

220. Zanoli MG, Pasetti G, Gallo G, Pinto A, Morreal J, Zoli G, Nevinny E. Visual evoked potential: A diagnostic tool for the assessment of hepatic encephalopathy. Gut 1984; 25: 294–300.

221. Brown JJ, Bolt RH, Stallings HW. Visual evoked potential changes following renal transplantation. Electroencephalography and Neurophysiology 1982; 53: 181–187.

222. Bonfenbrenner G, Gigli GL, Bernardi L, Feri R, Grassi C, Milan A. Visual evoked potential recordings in hepatic encephalopathy and their variations during branched chain amino acid treatment. Hepatogastroenterology 1985; 32: 3–7.

223. Marmor A, Dubowitz LMS, Levene M, Dubowitz V. The discrepancy of visual function in normal and neurologically abnormal preterm and full-term infants. Develop Med Child Neurol 1982; 24: 771–784.

224. Tyler CW. Assessment of visual function in infants by evoked potentials. Develop Med Child Neurol 1982; 24: 853–858.

225. Lapp E, d'Allen AM, Sallerin B, Orio C, Bonnah F. Le place des PEV et des BBG dans les encéphalopathies sévères de la période de la plasmaphérèse résultats de association et de leurs relans. Rev EEG Neurophysiol 1984; 14: 45–51.

226. Whiting S, Jan JE, Wong PK, Flodmark O, Farrell K, McCormick AQ. Permanent cortical visual impairment in children. Dev Med Child Neurol 1988; 27: 750–759.

227. Cracchiolo BR, Harding GFA, Durkin GV. Electrogram and visual recording of BAEPs and VEPs in premature infants with did or did not sustain intracranial hemorrhage and/or periventricular leukomalacia. In: Gilla V (ed). Maturation of the CNS and evoked potentials. Amsterdam, Elsevier Science Publishers, Excerpta Medica, International Congress Series 714, 1986; 306–401.

228. Gamble G, Rennie IPC, Alberin G, Richiuto D, Tredoli MG, Politou GC. Follow-up

of visual evoked potential in full-term and pre-term normal newborns and in subjects who suffered from perinatal respiratory distress. Electroencephalogr Clin Neurophysiol 1969; 26: 309–316.

230. McMurray JW, Walters CL, Herbert JD. Acute visual evoked potential changes in hydrocephalus. Electroencephalogr Clin Neurophysiol 1982; 53: 341–345.

231. Goldsmith GN, Schubert RA, Hirsch RP, Viner JK. Visual evoked potentials in hydrocephalus: Relationship to head size, shunting, and mental development. Neurosurgery 1988; 68: 283–286.

232. Ellis A, Shin F. Visual evoked potentials in adults with hydrocephalus. Neurology 1979; 29: 1541–1544.

233. Campbell KC, Cockerell OD. Visual evoked potentials, intracranial pressure and ventricular size in hydrocephalus. Dev Ophthalmol 1987; 16: 321–329.

234. Visser SL, Nicolaides CJ, de Rijke W. Neurological syndrome of Rett in relation to the EEG and VEP at the age of 3. Electroencephalogr Clin Neurophysiol 1983; 54: 476–484.

235. Sutton JP, Whitton JL, Tsuge M, Mendelsohn H. Evoked potential maps in learning disabled children. Electroencephalogr Clin Neurophysiol 1986; 64: 398–404.

236. Cohen J, Rinsler PW. Visual evoked responses in dyslexic children. Ann NY Acad Sci 1980; 425: 136–143.

237. Byring R, Davidenko T. Auditory and visual evoked potentials of schoolboys with spelling disabilities. Dev Med Child Neurol 1985; 27: 141–148.

238. Joliot EB, Prichep L, Abel H, Ermes P, Friedman J, Kaye H. Neurometric evaluation of cognitive dysfunctions and neurological disorders in children. Prog Neuropsychol 1981; 21: 279–290.

239. Andreasi MR. EEG and evoked potentials in learning disabilities. In: Hughes JR, Wilson WP, eds. EEG and evoked potentials in psychiatry and behavioral neurology. Boston, Butterworths 1983; 241–250.

240. Verma NP, Hart ZH, Vigni M. Electrophysiologic studies in neonatal adrenoleukodystrophy. Electroencephalogr Clin Neurophysiol 1985; 60: 7–15.

241. Bordier A, Pampiglione G, Battaglia A. "Bilateral occipital epilepsy" or arteriovenous disease? EEG, EMG, VEP studies in 11 patients. J Neurol Neurosurg Psychiatry 1982; 45: 627–632.

242. Markand ON, Garg BP, DeMyer WE, Warren C, Worth RM. Brain stem auditory, visual and somatosensory evoked potentials in holoprosencephaly. Electroencephalogr Clin Neurophysiol 1982; 54: 39–48.

243. Goto I, Kobayashi T, Amano Y, Tohyama S, Kuroiwa Y. Adrenoleukodystrophy and variants: Clinical, neuropathological and biochemical studies in patients and family members. J Neurol Sci 1986; 72: 103–111.

244. Harden A. Electroencephalography and evoked potentials in children with neurometabolic brain disease. Clin Neurol Neurosurg 1987; 89 (Suppl 1): 45–51.

245. Andreasi MR. EEG in mental retardation. In: Hughes JR, Wilson WP (eds). EEG and evoked potentials in psychiatry and behavioral neurology. Boston, Butterworths 1983; 231–273.

PART FOUR

Somatosensory evoked potentials

Introduction to SSEP

E.J. COLON

Somato sensory evoked potentials are potentials which are elicited by means of stimuli on the skin, organs of the sensory nerves. They are derived from the peripheral nerves or the central nervous system.

For the latter type a further subdivision can be made into spinal, brainstem and cortical evoked potentials, according to the structures from which the response derives.

Up until now, the origin of the different components of the somato sensory evoked potentials has been only partially known. However, the use of these potentials in the diagnosis of lesions in the nervous system has proven to be valuable. The value, especially of the somato sensory evoked cortical potential, in relation to the other evoked potentials, is seen in the fact that the SSEP is clearly composed of two distinct parts, of which the first is a stable one produced by the excitation of a very long myelinated pathway. Abnormalities in the myelinated pathway may therefore be found earliest by SSEP.

The later components are influenced by the functional state of the brain. In clinical neurophysiology the SSEP seems especially suitable for the differentiation between diseases in the myelinated system and global changes in the brain itself. There are, as will be demonstrated in this chapter, many other applications. The signal/noise ratio is poor in SSEP, which means that a relatively large number of stimuli must be given. Given the increased need for gathering information by means of the SSEP in clinical practice, an increasing interest developed towards methods that might decrease this number of stimuli to be given to reach an interpretable signal.

1. Anatomy and physiology

1. The skin and its sense organs (Figs. 1a and 1b)

The skin contains different well-known forms of sense organs as well as free nerve endings. Formerly these different sense organs or terminal corpuscles

E. J. Colon and E. J. Visser (eds), Evoked potential manual, pp. 267–325.

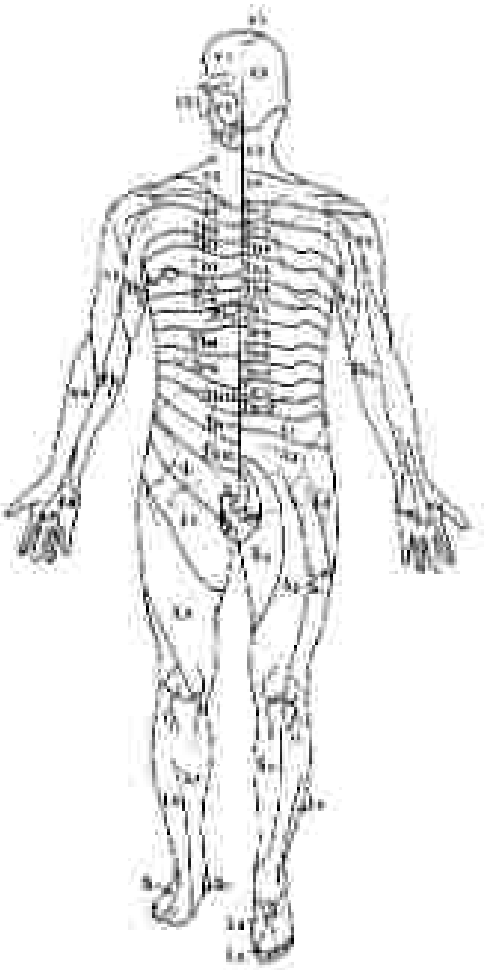


Figure 1a. Segmental sensory distribution in the human. Front and back.

were thought to have specific sensory qualities for touch, heat and pressure. The free nerve endings in the skin function in perceiving noxious stimuli.

It is clear however, from a physiological point of view, that they all transform the various kinds of stimuli, according to whether they are rapid or slow adapting, into electrical signals which travel along the afferent nerve fibres as action potentials.

Apart from the skin, from which all the exteroceptive impulses come, there is also input from sensory organs in the periarticular tissues and internal organs, giving information about posture and movement (called proprioception), and also from sensory organs and free nerve endings in the various visceral organs.

The skin is innervated by cutaneous nerves, most but not all these are branches from mixed sensory-motor nerves.

2. The peripheral nerve (Figs. 1a and 1b and Table 1)

There are pure sensory nerves, pure motor nerves and mixed nerves. In cutaneous nerves about 50% of the sensory fibres originate from so-called nociceptors, these are specialized receptors that after stimulation give rise to the sensation of pain.

The nerve fibre is formed by the axon of a nerve cell with its enveloping myelin sheath. This myelin sheath is formed by the Schwann's cells. On the other hand, there are also unmyelinated or naked fibres.

The thickest myelinated A-fibres vary from 1 μM to 20 μM in diameter. Their excitability threshold is low and their conduction velocity is high, up until about 100 m/sec (see Table 1).

The thin unmyelinated C-fibres have a high excitability threshold and their conduction velocity is as low as about 2 m/sec. All the nerve fibres of varying thickness are held together by connective tissue, of which fascicles of nerves fibres in turn are enclosed in a sheath called the perineurium.

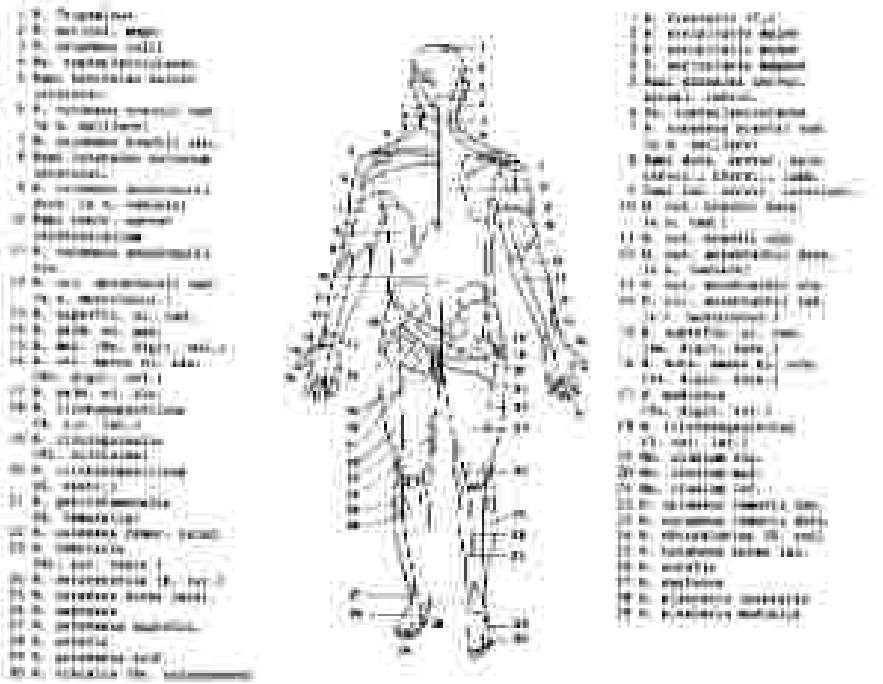


Figure 1b. Distribution of the sensory nerves over the skin, front and back.

Table 1. Different properties and parameters of the peripheral nerves.

Function	A		B and C		C	
	alpha motoneuron	delta nociceptive	autonomic pre- and postganglionic		unmyelinated dorsal root fibers, warmth, nociception	
Diameter μ	22	– 3	3	– 0.3	1.2	– 0.4
conduction velocity m/s	120	– 5	18	– 0.7	2.0	– 0.6
spike duration ms	0.4	– 0.3	1.2	– 2.0	3.0	
abs. refractory period ms	0.4	– 0.3	1.2	– 2.0	3.0	

The impulses or action potentials of each nerve fiber are conducted towards the dorsal ganglion in the dorsal root of the spinal nerve and then forward to the posterior horn in the spinal cord.

All these single fiber action potentials constitute the compound sensory nerve action potential (SNAP).

Because of the different conduction velocities, the SNAP becomes more dispersed, i.e. of lower amplitude and of longer duration as the distance between the site of stimulation and the site of recording increases.

To measure sensory conduction velocities on peripheral nerves one can use two methods. In the orthodromic method the stimulating electrodes are positioned at the distal end of the limb, where we generally find only sensory nerves. Then the cathode has to be placed proximal, generally on the mixed nerve.

The other possibility is the antidromic way, stimulating proximal and recording distally. In this case the cathode has to be placed distal of the anode. Both methods yield about the same conduction velocity, which for the upper extremity is 50–70 m/sec. At the lower limb the mean sensory conduction velocity is 45–60 m/sec.

If one stimulates a mixed nerve, for instance the median nerve at the wrist, then the compound action potential contains a volley of antidromically travelling motor nerve action potentials as well.

3. Transformation of the information on the segmental level

The dorsal roots (exclusively sensory nerve fibers) contain in their medial part mostly thick myelinated fibers which divide in an ascending branch in the dorsal column and a small descending branch.

The lateral part of the dorsal root is formed mainly by thin and unmyelinated nerve fibers.

For the conduction of impulses giving rise to evoked responses in the more rostral parts of the central nervous system, the dorsal columns are the most

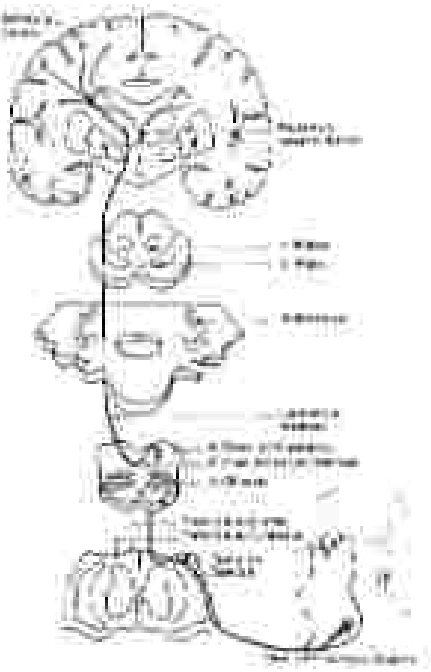


Figure 2 Pathways for the gracile somatosensory information from skin to the cortical centres

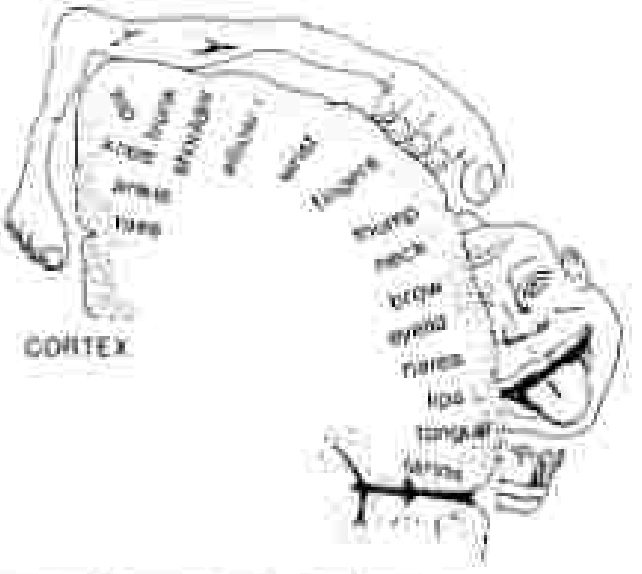


Figure 3 Localisation of the sensory input to the cerebral cortex

important pathways. The conduction velocity of these spinal fibre tracts is 60 m/sec.

In the clinical sensory examination, the sensory qualities of sense of posture, sense of movement and vibration sensation are mainly confined to these dorsal columns.

The information about the site of stimulation and the kind of stimulus, is mainly transported in the spatio-temporal pattern of the volley of impulses that reach the cell groups in the dorsal horn at the segmental level of the spinal cord.

4. The spino-cortical pathway (see Fig. 2)

The genetic information is transported mainly in the dorsal columns of the spinal cord. Information from the foot is located in the most medial part of this column in the tractus gracilis. Information from the upper extremity is transported over the most lateral part of the dorsal column, the so-called tractus cuneatus.

When reaching the brainstem, the information is transformed by means of a synapse in the nucleus gracilis and nucleus cuneatus onto the lemniscus medialis and transported to the thalamus on the hetero lateral side. This part of the tract for genetic information transport is defined as the "second neuron". The 'third' neuron is found in the last part of this pathway, when the information is brought from the N. ventro-lateralis of the thalamus transport to the specific sensory cortex.

There is a typical division of body representation over the sensory cortex, which means that for the analysis of the somato sensory evoked responses the active electrode must be located above the representing area of the stimulated part of the body. This representation is given in Fig. 3.

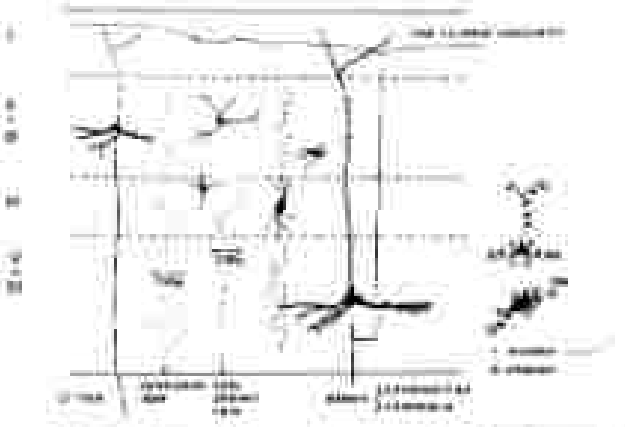


Figure 4. Schematic drawing of the cerebral cortex. Information reaches the cortex by association and specific afferent fibres and leaves the cortex by means of efferent and fibres.

1. *The brain*

Figure 4 gives a schematic drawing of the way in which information is received and distributed in the brain. The Thalamo-cortical tract ends in the layer IV of the cortex where synapses are found especially with stellate cells. From here the information is transported to the layers II and III and V and VI respectively. From the upper layers, the so-called U fibres emerge, making contact with adjacent areas.

From the lower layers large myelinated fibres emerge to the structures that are relatively far away as, for example, the cortex of the other hemisphere, crossing the corpus callosum.

From the basic work of Hubel and Wiesel (1962) we know that the cortex itself is built up by means of functional columns in which one exclusive function is located. These columns exist out of layers of neurons in such a way that in between different species these layer structures can always be found but are essentially different in their composition.

2. Method of stimulation and related problems

1. *Temperature*

The propagation velocity of action potentials in myelinated nerves is substantially influenced by temperature.

The dispersion of action potentials reaching the deriving electrode increases with decreasing temperature, which also gives rise to broadening of the compound action potentials. This means that it is only possible to compare normative data for amplitude and latency in populations as well as in individuals in a standard temperature condition.

For clinical use a skin temperature of at least 30 degrees C (86 degrees F) at the area of stimulation is needed. The temperature near the nerve is about 1 degrees C (1.4 degrees F) higher.

One must consider the fact that at higher temperatures the propagation velocity will also rise.

There are different ways in which we can measure skin temperature. The most suitable way is to place the area of stimulation in warm water or to place an infra-red lamp above this area. One must take care not to burn the skin, especially when using infra-red light. It is advisable always to stay near the patient during warming up. There are commercially available digital thermometers which measure skin temperature quickly and accurately. These thermometers are a must in the EP-room. In every EP experiment the skin temperature over the stimulated nerve must be measured.

2. The stimulus

For somato sensory evoked potential studies we need a stimulus that is clearly defined in time. This means that an electrical stimulus is preferable over tapping or pricking. Generally, a short electrical stimulus of 0.1 ms. (constant current) is applied to a sensory or mixed nerve.

For clinical use a frequency in between 1/4 and 10 Hz is generally used for somato sensory stimulation depending on the clinical application (see later). A higher frequency may give an unpleasant feeling, but will also give changes in latency of components. At low stimulus intensities, only a small part of the myelinated fibres of a nerve will be stimulated. With increasing intensity more and more nerves become active, and the derived compound action potential will grow to a maximum. This maximum is generally reached when the current, in humans, lies between 8 and 15 mA for skin electrodes. The most adequate way for establishing optimal reproducible intensity of the stimulus on the mixed nerve is to give such a current that small twitches are seen in the distal muscle. For pure sensory nerves the amplitude of the distal sensory nerve action potential (SNAP) should be measured and the current should be increased until this potential becomes maximal; one then reaches the supramaximal level.

For example, in studies of the cortical SSEP after stimulation of an index finger, one first analyses the median nerve sensory potential at the wrist. When with increasing intensity there is no increase of the potential, one diminishes the intensity until the moment that the potential also diminishes.

Just above this stimulation level is the optimal intensity (supramaximal), where most nerves are activated and the burden for the patient is relatively minimal.

In this case, one stimulates supramaximal in relation to the distal sensory potential. When stimulating at this supramaximal intensity the maximum voltage of the different components of the SSEP is always reached.

From our own experiments we know that at finger stimulation the N20 reaches its maximum amplitude at a stimulus strength of more than 10 mA, but this value may be higher in persons with a thick finger skin, or fatty tissues. The same holds true for the amplitude of the N20 and P200 components (see Fig. 5). In Fig. 5 the effect of the stimulation strength on the amplitude of the different components of the SSEP is given.

The pattern of stimulation may be regular or at random. It seems adequate always to give random stimulation for the long-latency components of the SSEP. Each human topic is bound to habituation, which in principle, always appears in repetitive stimulation. This may give rise to changes in amplitude and/or latencies. One can, to some extent, avoid this by using random stimulations.

When performing cortical evoked potential examination the late components have a limiting effect on the time in between which two stimuli may succeed. The recovery phase of the late components is very long (more than 5 s.),

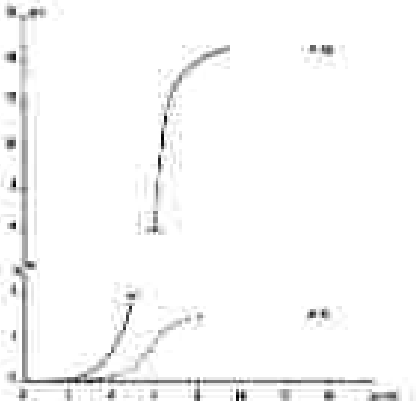


Figure 5. Relation between amplitude (in μV) of the initial N20 and P200 and stimulus strength (in mA) after stimulation of the index finger with ring-electrode

which means that the at random stimulus should be given with intervals in between 2 and 5 seconds.

One must consider the possibility of a CNV (Contingent Negative Variation) when using these long time lags in between two stimuli, which is an additional reason for random stimulation.

Alpha rhythm artifacts may also be diminished by random stimulation.

The number of stimuli to be given is highly dependent on the signal-to-noise ratio. For distal sensory nerve action potential measurements in arm or leg, a number of 16 stimuli is generally sufficient. For the study in adults of the EP in the neighbourhood of the vertebral column and for the specific cortical reaction, a number of stimuli in between 500 and 1000 may be sufficient. For the study of late components of the SSEP 100 stimuli generally give adequate results. In young children, aged under 1 month, a low stimulation frequency (0.5 Hz) and a low number of stimuli (maximal) is advised (Bongers *et al.*, 1989), for short latency SSEP elicitation. The electrodes used for the electrical stimulation are given in Fig. 6. The advantage of electrical stimulation is also found in the fact that triggering of these stimuli is easy. It is possible, of course, to connect a trigger system to a hammer. In this case, the EP is elicited by means of tapping, which in practice gives the same EP pattern as electrical stimulation. Besides the routine electrical stimulation of sensory or mixed nerves, other methods are used. Mechanical stimulation as tapping, pin-pricking and touch must be mentioned here. Also EP's after thermal and nociceptive stimuli and joint displacement have been described, but at this moment are not used in a routine clinical setting.

The human somato sensory system can also be driven by stimulus trains, this responses can be recognized at frequencies as high as 200 Hz. (Nuwer *et al.*, 1994).

3. Place of stimulation

There are three ways to choose a place of stimulation, which are highly dependent on the reason why the EP is done. The first way is segmental stimulation (performed when one wants to know where abnormalities are located in the spinal roots or in the spinal cord).

The second way of stimulation is direct stimulation of the mixed nerve (performed when one wants to know whether this nerve is abnormal).

With the third option one is especially interested in probable abnormalities of the sensory nerve itself, or in the processing of sensory information.

In this case only sensory nerves must be stimulated. For the positioning of the stimulus electrode one may consult Fig. 1, in which the different sensory segments of the body and the different sensory nerve localizations are represented. The most frequently used localizations are:

1. Median nerve on the index finger.
2. Median nerve at the wrist.

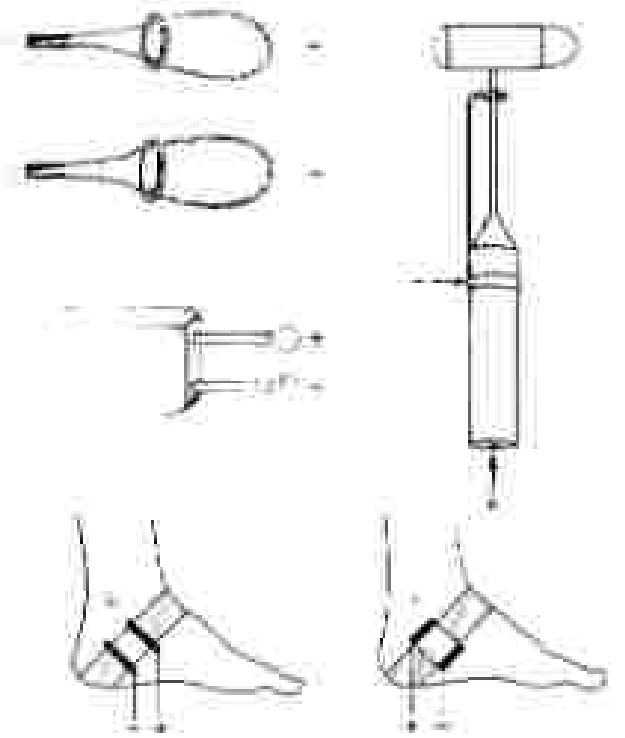


Figure 1. Example of different electrodes used for evoking sensory (electrical) or mechanical stimulation. For the mechanical stimulation the use of electrodes containing rubber may be preferable.

3. Peroneal nerve at the level of the head of the fibula.
4. Sural nerve at the ankle.
5. Segmental skin stimulation C5 until C8 in the arm and L3 until S1 in the leg.

The numbers 1 and 4 are exclusively sensory nerves and 2 and 3 are mixed sensory and motor nerves.

4. Problems of neck and head muscles, eye artifacts and alpha rhythm

The abilities of an evoked potential department are well reflected in the quality of the EP's produced. This quality is influenced, among other things, by the signal-to-noise ratio. Noise in SSEP examinations consists especially of muscle artifacts, and movement artifacts. For near field and far field SSEP in the neck and head region, the muscle artifacts from the head and neck may become a disaster. We can avoid, or at least diminish it by adequate, friendly patient care.

The attitude of the technician and the doctor are the highest promoters for rest or tranquility. When the patient lies on a couch or sits in a very comfortable chair the artifacts of neck muscles may also be diminished.

Muscle artifacts of the temporal muscles may be influenced by opening of the mouth.

Eye artifacts, as well as alpha rhythm, can be diminished by asking the patient to open his eyes and fixate, for example, on a painting which is not too close by.

Stimulation of peripheral nerves may provoke somato-motor responses over the scalp. These myogenic responses may interfere with the neurogenic SSEP. Myogenic potentials with latencies of 15 ms and 300 ms, are described as evoked potentials derived from the scalp. In general it is possible to minimize these potentials by relaxation. Take notice that these potentials may probably interfere especially in neurological patients and children.

5. Stimulus artifacts

These artifacts are sometimes very disturbing because of their amplitude and duration. The only way to reduce these artifacts is by proper grounding and a careful positioning of both the stimulating and recording electrodes.

6. Problems with noise and light

What is described in 4 also holds for too much ambient noise or light. These may provoke muscle tension in the patient. Rhythmical noise may provoke its own cortical reactions and may interfere with the SSEP. Light may not flicker for the same reasons. Too little noise and too little light however, may give changes in the alertness of the patient, which may influence the amplitudes of the late components.

7. The SSEP-room

In general, the demands for the SSEP room are the same as for the departments of clinical neurophysiology, where electroencephalography is done.

It must be possible to enter the room with a bed. The light must be such that it can be dimmed (no fluorescent lighting), while the curtains of the room must be of such material that the room can be made dark. In the room there should be a comfortable settee. An alarm signal must be available in case of emergency.

Because of electrical and magnetical influences it is advisable to locate the room at a distance of more than 25 metres from radiological, surgical and physiotherapeutic departments. Also elevators and some clinical laboratories may have disturbing influences. A separate electrical main supply with properly grounded system may be necessary.

8. The optimal configuration

The most optimal position for a patient to undergo a SSEP is, in general, when he is lying on a relatively soft mattress. On the ceiling a point (for example a picture) is indicated where the patient can fix his eyes on, in a more or less comfortable way. This fixation diminishes the eye-movement artifacts. The lights on the ceiling may be very tiresome when they shine in the eyes.

A technician must always be in the neighbourhood. Repetitive artifacts (muscle for example) must be avoided. The temperature of the room should be above 21 degrees C (or 69.8 degrees F) and if possible a direct heating system should be directed to the place of stimulation.

9. Mental state

The amplitude of the late components of the EP is dependent on the mental state of the patient. All normal values are referred to a certain state of alertness, generally with eyes open. Some medications may influence the mental state of the patient (especially psychotropic drugs).

Method of analysis

1. Equipment

For somato-sensory evoked potential examination the equipment must exist of a stimulating unit, some amplifiers, an averager and a display unit. For detailed information see Part One of the book.

2. Sweep duration and sample frequency

It is useful always to analyse a prestimulus interval. A prestimulus interval over a period of 25% of the poststimulus interval is adequate. For short latency SSEP (until 45 ms.) a sweep duration up to 100 ms. may be chosen, for the late components a sweep duration of at least 400 ms is necessary.

Sometimes these late components can be delayed up to 700 or 800 ms. The number of points on the sweep where the averaged signal is measured can best be chosen in such a way that the time difference between the two points is less than 4% of the measured time, which means that the measuring error will be less than 8%.

3. Peak detection

The latencies of the SSEP are measured as peak latencies. In general these peaks are indicated by means of visual inspection, which in itself gives, of course, an error. Automatical methods, as for example the detection of the point where the first derivative of the EP waveform crosses the baseline (after smoothing with an appropriate window) are generally not implemented in the various hardware equipment that is commercially available.

Localization of the various components

The SSEP may be elicited at different parts of the body. The so-called distal sensory potential is found near the place of stimulation. The proximal and spinal sensory potentials are found more or less on the vertebral column. The cortical SSEP is found at the skull, and is divided in short latency and long latency components. In Fig. 7 the form of the cortical SSEP is drawn in its most simple appearance. Many other components are described by different authors. The shape of this cortical SSEP (Fig. 7) is accepted by all of them. This cortical SSEP (until 45 ms.) is the short latency part and from 45 until over 300 ms. is the long latency part.

Figure 7. Cortical somatosensory evoked potential in its most simple appearance.

1. Distal sensory

a. At the wrist. Stimulation of the digital nerves with ringelectrodes (cathode proximally) causes a SNAP at the wrist, for the median nerve if the index finger is stimulated and for the ulnar nerve if the little finger is stimulated.

One can use subcutaneous needle electrodes placed near the median or ulnar nerve, or surface electrodes. These different techniques yield different normative values.

b. At the elbow. When monitoring the sensory nerve action potentials of the median nerve, the electrodes are to be placed on the skin in the cubital fossa.

The recording of the action potentials of the ulnar nerve can be done just below or above the olecranon in the ulnar sulcus.

c. At the ankle. Stimulation of the sural nerve behind the lateral malleolus will evoke a sensory nerve action potential.

2. Proximal sensory (see Fig. 8)

At Erb's point in the supraclavicular fossa one can record a compound action potential which originates in the brachial plexus. The potential has a peak latency for the negative peak of 9ms. after stimulation of the median nerve at the wrist. The indifferent electrode can be located on the mastoid bone behind the ear or at FPz.

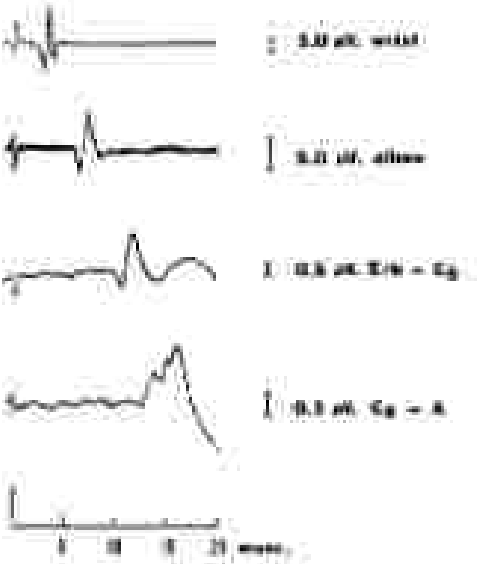


Figure 8. Schematic drawing of sensory nerve action potentials following stimulation of finger III, the action potential at Erb's point and the cervical sensory evoked potential.

Short latency somatosensory evoked potentials

L. GARCÍA-LARREA and F. MAUGUIÈRE

Evoked potentials (EPs) are the only non-invasive method available to assess in 'real time' the processing (sensory information) in the central nervous system in man. This low cost investigation can be viewed as a complement to clinical examination and most of its clinical success was due to its ability to disclose silent lesions in demyelinating diseases. In clinical practice SEPs may be used for four main purposes (but do not exclude each other): 1) to test sensory functions when clinical examination is not reliable (young children, comatose patients, suspected conversion disorder...); 2) to disclose asymptomatic dysfunction or to decide whether more sophisticated or invasive morphological investigations should be envisaged in patients with purely subjective symptoms; 3) to determine the lesion site or the extent to which an anatomically-proven lesion is disrupting sensory impulse transmission; 4) to understand the mechanisms that underly the neurological deficit, the evolution of the disease, or the functional recovery. These purposes directly address, among others, the question of the specificity and localizing value of the method, and the one of the pathophysiological interpretation of abnormal waveforms. Such questions will be discussed in sections A through C before envisaging the clinical use of SEPs.

A. Identification of normal SEP components

Since the report by Halliday and Wakefield (1963) of normal SEPs in patients with lesions of the spino-thalamic tract, cortical nervous system (CNS) potentials evoked in man by electrical, non-painful stimulation of peripheral nerves have been considered as specifically related to the activity of the dorsal columns system (DCS). Also in monkeys Cook *et al.* (1978) demonstrated that ablation of dorsal columns abolished SEPs, whereas mydotomy sparing selectively the dorsal columns left these responses virtually unaffected. Thus, potentials recorded over the cervical spine and scalp within the first 30 msec after a non-painful stimulus can be safely considered as dependent on lemniscal, DCS activation.

E. J. Colon and S. I. Visser (eds), Evoked potential manual, pp. 221–278.

If high-intensity stimuli are used other ascending tracts in the cord may also be stimulated, and especially anterolateral spinothalamic tracts (Powers *et al.*, 1982). For clinical interpretation purposes DCS selectivity should only be assumed when non-painful stimuli are delivered.

A.1. Upper limb stimulation (median or cubital stimulation at the wrist, or digit stimulation).

A.1.1. Peripheral components (N9, N9).

After stimulating a mixed nerve in the arm a compound action potential (CAP) corresponding to the peripheral ascending volley can be recorded at different levels, the most widely used electrode position for that purpose is the supraclavicular fossa (Erb's point, Fig. 1). At this electrode site a di- or triphasic potential (positive-negative-positive) can be obtained that reflects the activation of brachial plexus trunks. The latency of its negative peak being about 9 msec in normal conditions, this potential is usually named N9. The peripheral ascending volley can be recorded more distally over the traject of the nerve

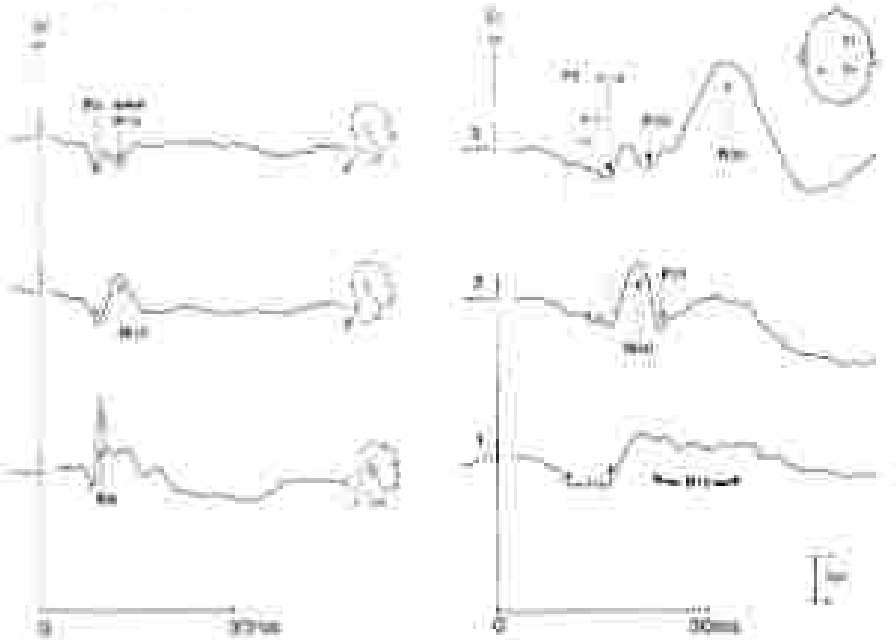


Figure 1. Normal SEPs to median nerve stimulation (unpredictable reference montage, stimulation of left median nerve at the wrist). This figure illustrates the early SEPs that can be routinely studied with a shoulder reference. Note that in the ipsilateral parietal region (1) there is a wide lasting negative shift that immediately follows the cortical positivities and corresponds to the widespread N30 potential. The cortical N20 component is picked up as P13 potentials by an anterior cervical electrode. Contralateral potential N20-P27 and frontal P22-N30 are essentially obtained in normal subjects (see text for details). (From Mauguière *et al.*, 1987, with permission of Butterworths Publishers).

at the elbow (N6). Both potentials are mixed motor and sensory responses, and thus qualitatively different from the purely sensory central SEP components.

4.1.2. Cervical components (N11, spinal N13/P13).

Most investigators use the frontal Fz scalp electrode as reference for the recording of cervical and scalp SEP components. This montage has proved to be efficient and reliable for a quick exploration in clinical routine (Jones, 1982; Chiappa, 1983) but has the disadvantage of mixing the activity picked up at the front with the potentials generated near the so-called 'active' cervical electrode (see Fig. 14). With the non-cephalic reference recording technique that by-passes this inconvenience a cervical electrode at Cv6 level picks up a distinct complex formed by 3 components, namely P9, N11 and N13 (Table 1 and Fig. 1). Convergent evidences detailed in Table 1 point to the respective origin of these potentials in the brachial plexus (P9), dorsal columns (N11) and dorsal horn of the spinal cord (N13).

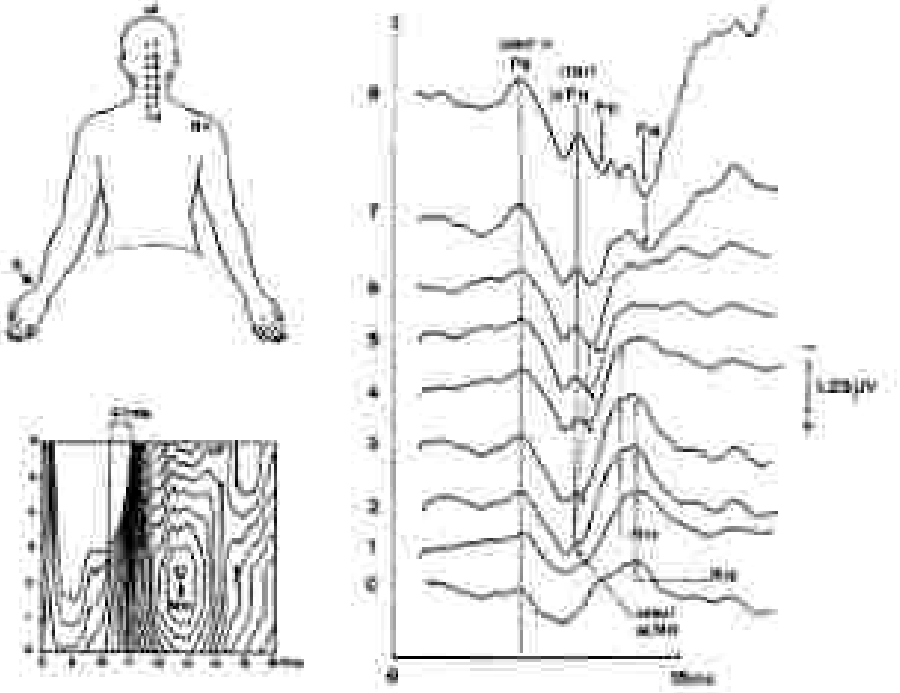


Figure 3. Topographic study of normal potentials with quasi-tangential single stimulation of the median nerve at the wrist. This recording shows a 0.7-ms shift of N11 onset latency from lower to upper neck. The N11 potential is present up only to the lower neck, and is not present in the supplementary position (electrode 6). P9 onset is the same in all traces (dotted vertical line). P11 onset at Fz (electrode 8) is synchronous with N11 onset at Cv6 (electrode 3). (From Mauguière et al., 1987, by permission of Butterworths Publishers.)

Table 2

Component	Optimal electrode	Origin	Rationale for origin assumptions		References	Pitfalls
N8	Erb's point (Supra-clavicular fossa)	Brachial plexus (CAP)	Recorded near plexus roots Normal in lesions proximal to dorsal ganglia	→	Jones, 1979	Brachial plexus discussion may return false amplitude reduction
N11	Posterior neck	Ascending volley in dorsal columns	Intracranial recordings Latency shift from C6 to C1	→ →	Iseki and Mayanagi, 1984 Desmedt and Cheron, 1981 Maugiere, 1982	May be partially occluded by N13 potential
			Abnormal in lesions proximal to dorsal ganglia	→	Jones et al., 1982?	
N13	Posterior neck (C5–C6)	Dorsal horn (post-synaptic)	No latency shift from C6 to C1	←	Desmedt and Cheron, 1980 Restuccia et al., 1984 Nuwer, 1984	In reversal or scalp montages N13 gets mixed with brainstem P14 picked up by the frontal 'reference' electrode
			Sense ('proprioceptive') recovery cycle	←	Hazewood, 1981 Gatica, 1982	
			Phase reversal (PTT) in anterior neck Normal in upper cervical lesions	→ ←	Desmedt and Cheron, 1981 Antonaki and Cracco, 1981 Maugiere et al., 1983	
Spinal P13	anterior neck (at laryngeal)	same as N13	Same topography as N13 Same clinical behaviour as N13	→ →	Desmedt and Cheron, 1981 Maugiere and Barker, 1985 Rothwell et al., 1986	Not to be confounded with scalp far-field P13-P14 components
P9	anywhere over the scalp, anterior or posterior neck	peripheral volley at or around axillary level	Slightly earlier than N8 Latency shift when shoulder moves Clinical behaviour as N8	→ → →	Cracco and Cracco, 1976 Desmedt et al., 1983 Nakanishi et al., 1983 Yamada et al., 1988	Amplitude very different with ipsi- or contralateral shoulder as reference (changes in P9/P14 ratio)

Table 1. Continued

Component	Optimal electrode	Origin	Rationale for origin assumption		References	Pitfalls
P13	anywhere over the scalp, and earlobes	ascending volley in dorsal columns	Widespread distribution over the scalp	→	Cracco and Cracco, 1978	Absent in about 20% of normals Its cortical dipole may be mistaken with P14
			Same onset as N13	→	Desmedt and Cheron, 1980 Iragui, 1984	
			Same clinical sensitivity as N13	→	Mauguière and Ibañez, 1985	
			Present in brain death	→	Buchner *et al.*, 1986	
P13-14 (or 'P14')	anywhere on the scalp (better at Fz)	Brainstem (P13 probably cortical)	Conduction time in normals	→	Desmedt and Cheron, 1980	Identical with opposite polarity to cervical scalp or normal ear lobe analogue
			Intracranial recordings	•	Halliwell, 1964	
			Abnormal in lesions of the cervicomedullary junction	→	Aminoff and Cracco, 1981 Mauguière *et al.*, 1982	
			Absent in brain death	•	Buchner *et al.*, 1986	
			Normal in thalamic lesions	•	Nakanishi *et al.*, 1979	
			P13 (but perhaps not P13) normal in parasellar/fossa lesions	→	Nakanishi *et al.*, 1983 Delorme *et al.*, 1986	
N18	ipsilateral parietal (near the end of the widely-interspersed by two electrodes)	cortical	Widespread on the scalp	→	Desmedt and Cheron, 1981	If low frequencies are not much filtered N18 can mimick ipsilateral N20
			Absent in cervical medullary lesions	→	Mauguière and Ibañez, 1985	
			Present in thalamic lesions	→	Mauguière *et al.*, 1983	
			Present if P13/14 present	→	Mauguière and Ibañez, 1985	
N20	contralateral parietal (P3-P4)	(perioral cortex)	Magnetic & potential recordings	→	Wood *et al.*, 1984	– If recorded with a frontal reference may be contaminated by pre-rolandic P22 – recording electrode must be quite posterior on the scalp to get maximal N20
			N20-P20 tangential dipole on scalp	→	Desmedt *et al.*, 1986	
			Abolished by selective removal of perioral cortex	→	Stoop *et al.*, 1981	

Table 1. Continued

Component	Optimal electrode	Origin	Rationale for origin assumption		Reference	Pitfalls
P22	Contralateral central (C3–C4)	frontal cortex	Magnetic & potential recordings Scalp field distribution suggests radial source	→	Wood *et al.*, 1984	May contaminate N20 in parietal P22 recordings
				→	Desmedt and Cheron, 1980 Dalbey *et al.*, 1986	
			Possibility of clinical dissociation between N20 and P22	→	Mauguière *et al.*, 1987	
			Proposed after selective removal of parietal cortex	—	Hume *et al.*, 1986	
P27	contralateral parietal (P3–P4)	parietal cortex?	Similar behaviour as N20, but lack of definitive evidence			
N30	Fz	frontal cortex?	Possibility of dissociation between N30–P27 and P22–N30 but lack of definitive evidence	→	Mauguière *et al.*, 1983	

- The *P9* component exhibits the same physiological and pathological behaviour, and has the same origin (in brachial plexus trunks) as its scalp far-field homologue (see section A.1.3).
- The nuchal *N13* component is recorded all along the posterior aspect of the neck, where it usually appears contaminating the ascending slope of N13. Its onset latency was found to increase from CV6 to CV1 spinal processes by 0.95 ± 0.15 msec and 0.89 ± 0.12 msec respectively by Desmedt and Cheron (1980 a) and in our laboratory (Mauguière, 1983). This shift of N13 onset latency can also be evidenced by spatio-temporal mapping (Fig. 2) and fits with the hypothesis that N13 might be generated by the ascending volley of action potentials in the dorsal columns of the cervical spinal cord.

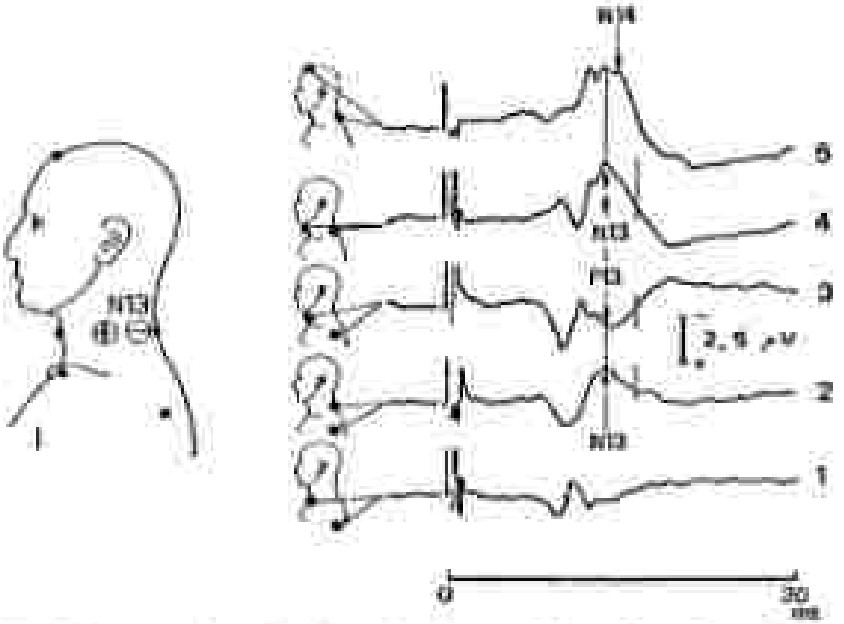


Figure 1. Comparison of several reference sites for spinal N13 recording. All recordings were simultaneously obtained on a single subject. In (a) 1 bipolar tracks active electrode (negativity up) was referenced to the shoulder contralateral to the stimulated one. The two upper traces show the waveforms resulting of a cervico-laryngeal (4) and a cervico-frontal montage (5). In supramaximal median-antebrachial stimulation (1) at x_3 and 9.9 msec. With a neck-to-shoulder montage (2) a spinal negativity (N13) is recorded that reverses polarity at cervical (laryngeal) shoulder derivation (4). Note that N13 recorded at Cv4 and P13 at anterior neck (traces 2 and 3) are usually in phase reversal, that is, associated with the occurrence of a dipole separation transversally disposed at the dorsal horn of cervical cord (figure at the left). Consequently, a transverse posterior-to-anterior neck derivation as chosen in trace 4 will cancel the segmental spinal component. If an IV reference is used (upper trace 5) a non-spinal potential is additioned to the waveform (N14 in the figure) which corresponds to the P14 brainstem potential recorded by the reference and inverted with opposite polarity. The montage chosen in trace 4 is thus enough selective to record reliable spinal components without supplemental electrode insertions.

As first mentioned by Cracco (1973) and illustrated in Figs 1 and 2 it may be difficult to differentiate the N11 from the following N13 component: this seriously hampers its utilization in clinical practice, which is actually very limited.

- The *N13* component is obtained at the nuchia, with a maximum amplitude at Cv5–Cv6 levels (Fig. 1) and decreasing at more rostral or caudal electrode positions. Conversely to N11, no clear latency shift is observed between Cv6 and Cv2 recordings in normals (Desmedt and Cheron, 1980a; Mauguière, 1983; Desmedt and Nguyen, 1984). This potential can be recorded with *opposite polarity* from the anterior aspect of the cord or neck (spinal P13 in Fig. 1), as it has been demonstrated with oesophageal (Desmedt and Cheron, 1981a), epidural (Cook and Meglio, 1986) or anterior cervical electrodes (Desmedt and Cheron, 1980a; Mauguière and Ibañez, 1985). The behaviour of spinal-P13 in neonates or patients, as well as its distribution along the cranio-caudal axis are the same as for the N13 component. Both spinal N13 and P13 are still present in cerebral death or in lesions at the cervicomedullary junction that abolish all brainstem and cortical components (Mauguière and Ibañez, 1985; Buchner *et al.*, 1986). A fixed dipolar source in dorsal horn, perpendicular to the spinal cord axis, could account for this spatial organization. In practice a transverse montage connecting electrodes located over the Cv6 spinal process and above the laryngeal cartilage is the most adapted for recording the spinal N13/P13 activity (Fig. 3).

4.1.3. Far-field positive scalp components (P9, P11, P14).

Three brief and widespread far-fields can be recorded on the scalp (Fig. 1):

P9. This potential reflects the peripheral afferent volley at the level of the axilla (Cracco and Cracco, 1978; Nakanishi *et al.*, 1981; Desmedt *et al.*, 1983). Absolute latencies are obviously highly dependent on, and should be corrected for arm length.

P11. The P11 potential is supposed to reflect the ascending volley in dorsal columns. Desmedt and Cheron (1980a) first reported that the P11 potential begins in synchrony with N11 at Cv6 cervical level (entry zone of roots into the cord): our data confirmed this finding by showing onset latencies of 10.2 ± 0.8 msec for both components (Fig. 2). Clinical use of P11 is hampered by its absence or lack of reliability in about 20% of normal controls; however, assessing its persistence is crucial in cases of absence of all subsequent potentials, as in lesions at the cervicomedullary junction (see Section C.3.1).

P14. The P14 far-field is constantly recorded in normals but presents some interindividual variations due to the presence in most subjects of a superimposed P13 potential. This gives rise to a P_{13-14} complex which shows different morphological variations in normal subjects. As it is illustrated in Fig. 4, both positivities may be of similar amplitude, so either of them may be the more prominent; in many instances P14 presents

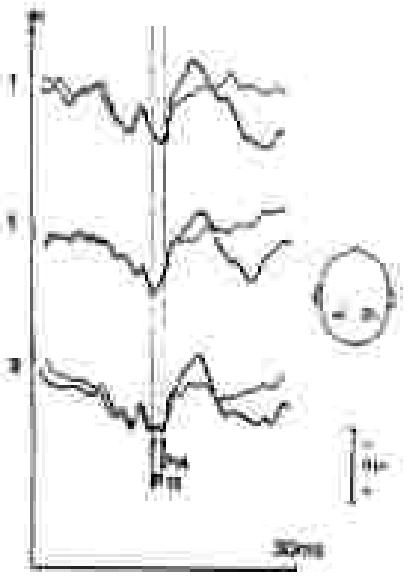


Figure 4. Inter-individual variability of the P13–14 complex. Recordings were obtained on left scalp–neck, after left (1) and right (2) median nerve stimulation at the wrist. Thirty traces corresponding to responses picked up by contralateral parietal electrodes, and superimposed in each case over those recorded on the ipsilateral parietal scalp. Reference point was at the shoulder for all recordings. P14 may be either of equal amplitude as P13 (bottom) or just a notch on its ascending slope (middle trace). *How* frequently P14 is the most positive peak of the complex (upper trace).

itself only as a notch on the ascending phase of P13. Occasionally the morphology of P_{13-14} shows some degree of intraindividual side-to-side variation, which may create some difficulties for interside latency comparisons if only the higher of the two positivities is considered. A cue for accurate identification of P14 is to compare its latency with that of cervical N13, since P14, but not P13, peaks always later than the cervical potential (Mauguière, 1983). The P_{13-14} complex is picked up at the earlobe but with a lower amplitude than on the scalp, for this reason it usually persists with a scalp–earlobe montage (Nakanishi *et al.* 1978; Yamada *et al.* 1980). All along this chapter the term 'P14' will be used, unless stated the contrary, as synonymous of 'P_{13-14}'.

Early SEP studies in patients with thalamic lesions showed that P14 had its origin at subthalamic level (Nakanishi *et al.* 1978, Anziska and Cracco, 1980a). Posteriorly, data from patients with well-delineated lesions at the cervicomedullary junction (Mauguière *et al.* 1983) as well as in brain death patients (Buchner *et al.* 1986) have demonstrated that the origin of P13-14 complex is situated *above the level of the foramen magnum*. The anatomical generator of these potentials is presumed to be the ascending volley in medial lemniscus fibres at the brainstem level (Desmedt and Cheron, 1980a). The

question whether both subcomponents correspond to different levels of the afferent volley at the lemniscus (Suzuki *et al.*, 1984), to different fiber populations or to qualitatively different kind of potentials has not yet been elucidated. Anecdotal reports of normal P13 coexisting with abnormal P14 in pons or mesencephalic lesions have been provided by Nukanishi *et al.* (1983) and Delattre *et al.* (1986), and this is also our experience (Chevers, 1988). This favors the hypothesis of a different brainstem level for each component; however, large series of SEPs in well-delineated brainstem lesions are still lacking, and P13–P14 dissociation is so rarely seen in clinical practice that both components must have indeed a very close anatomical origin.

A most important point concerns the differentiation between *spinal P13*, the anterior neck counterpart of cervical N13, generated at the cervical cord, and *brainstem far-field P13* of the P_{9-14} complex. In spite of their similar peak latency and polarity, both components have a very different origin and can be selectively affected not only in compressive lesions at the cervicomedullary junction (Mauguière and Desmedt 1985) but also in other conditions such as multiple sclerosis (MS) (Garcia-Larrea and Mauguière, 1988) (see Fig. 5).

A.1.4. The widespread N18 negativity.

This potential identified by Desmedt and Cheron (1981b) as a long-lasting negative shift which immediately follows P14. In normals N18 can be fairly individualized only in the parietal region *ipsilateral* to the stimulation, where there is no or minimal interference with later cortical components (Fig. 1). As illustrated in Fig. 8 this event is artificially shortened when low frequencies are cut by filtering and thus might be falsely interpreted as an ipsilateral cortical N20.

N18 persists with a widespread distribution on the scalp in patients with N20 abolition secondary to lesions of the ventro-postero-lateral (VPL) thalamic nucleus or of the centro-parietal cortex, including hemispherectomy (Mauguière *et al.*, 1983b; Mauguière, 1987 and Fig. 23). Moreover N18 disappears in all cases with cervicomedullary lesions causing absent or reduced P14. This indicates that N18 is generated below the thalamus and above the foramen magnum, perhaps by ancillary parallel fibers of the medial lemniscus, or brainstem structures connected with the dorsal column nuclei.

As illustrated in Fig. 7 three potentials are normally superimposed to N18, namely contralateral parietal P27 and central P22 and frontal P20 (vide infra, A.1.5). As a result of this interference there is some negativity which precedes the onsets of P20 and P22 in midfrontal and central regions respectively. This frontal and central negativities were considered as true cortical 'N17' and 'N19' components by Yamada *et al.* (1985); however superimposition of ipsilateral parietal tracts, where N18 is not contaminated by contralateral cortical components (Fig. 7) clearly shows that there is no actual scalp negativity other than N18 and N20 within the first 25 msec after the stimulus, and that frontal and central 'N17' and 'N19' merely reflect onset points of P20 (frontal) and P22 (central) components.

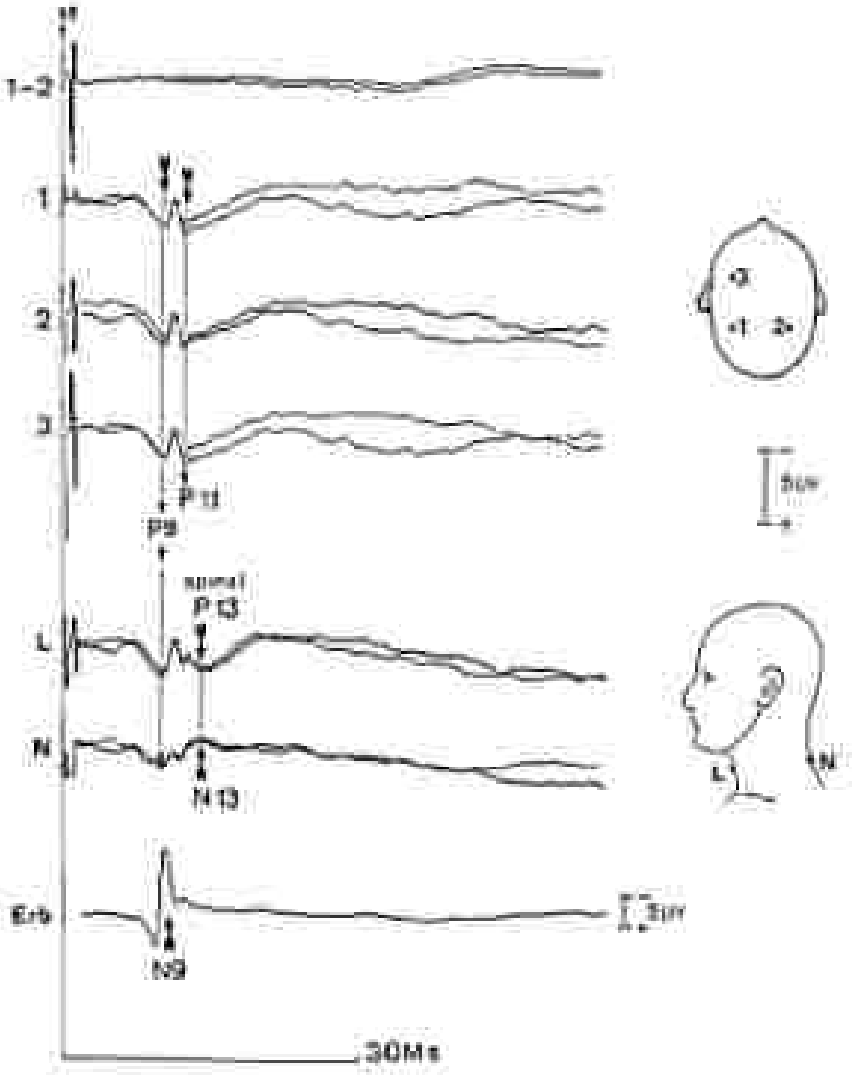


Figure 1. Dissociation between spinal N13/P13 and brainstem P11/14. This 20 year-old patient was referred because of sudden appearance of paresthesia of the right hand. Clinical examination disclosed hyperreflexia of the right upper limb without sudden deficit; subtle dysphonia was present, there was also right hand weakness. The rest of the examination was normal. SEPs to left median nerve were also normal, but after stimulation of the right median nerve peripheral N9 (and its far-field counterpart $P9_f$ down, inverted $P_{1'}$) and segmental spinal N13/P13 could be obtained, whereas brainstem P_{11}–$_{14}$ as well as all subsequent potentials were abolished. This indicates interruption of ascending somatosensory impulses high in the cervical cord or at the cervicomedullary junction, and clearly allows the existence of two separate generators for spinal N13/P13 and far-field P_{11}–$_{14}$. (From Cruccu, Cruccu & Manfredini, 1985; reproduced by permission)

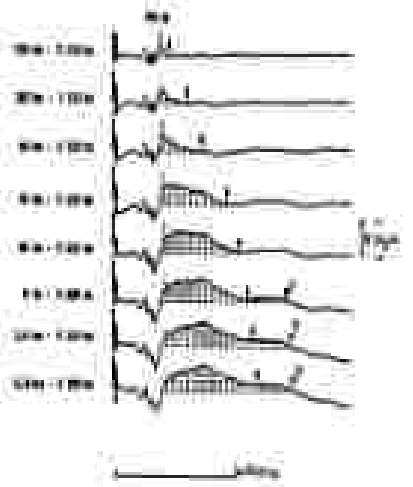


Figure 6. Effect of low frequency filtering on N14. Traces recorded on the parietal region ipsilateral to median nerve stimulation. Low frequency filtering at 80 Hz or more entails the creation of an artificial negative peak in the ipsilateral points, region that may be mistaken for a genuine cortical component. This kind of errors can be prevented with the use of a large bandpass (two bottom traces). (From Mauguière *et al.*, 1983, with permission).

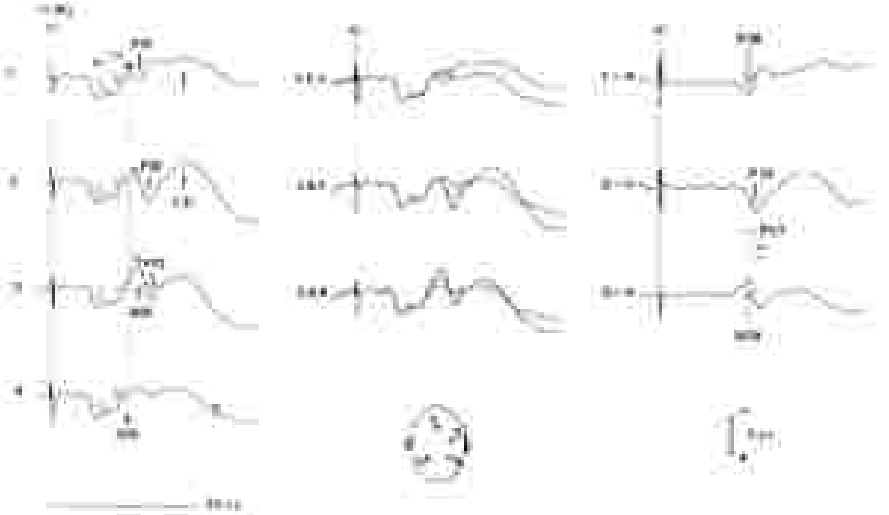


Figure 7. Identification of N20, P27 and P22 components. Left traces were recorded in the ipsilateral parietal (4), contralateral parietal (3), and central (2) regions, and at F3 (1), after stimulation of the median nerve at a normal output. Superimposition of the ipsilateral parietal response on other traces (arrows) allows identification of the cortical components and calculation of their amplitude. There is no apparent active N20 in the central and frontal regions (the small negativities apparently existing in these regions are all phase-reversed), corresponding to the diffuse N19 component accompanied by positive potentials P20 and P22. The traces on the right column were obtained by subtraction of the ipsilateral responses from the contralateral ones. Only parietal N20 emerges as an actual scalp negative peak in most conditions. The frontal P20 peaks in synchrony with parietal N20, whereas P22 peaks later. (From Mauguière *et al.*, 1983, with permission).

A.1.3. Early cortical components (N20, P27, P22, N30).

Two sets of early cortical potentials, each made of two components, are superimposed on the widespread N19 (Figs. 1 and 7). The first one is made of a N20-P27 complex located in the parietal region contralateral to the stimulation; the second is composed of the P22-N30 potentials which are recorded in the contralateral pre-rolandic region but often spread to the frontal region. These components are also present after finger stimulation and their spatial distribution on the scalp is not distorted in earlobe reference recordings. As it is the case with all SEP components, latencies after finger stimulation are increased by 2-3 msec compared to those obtained after median nerve stimulation because of finger to wrist conduction time. For sake of clarity the same labels have been used in figures to identify cortical potentials evoked by finger or median nerve stimuli. Spatio-temporal maps obtained after median nerve stimulation are illustrated in Figure 8 which shows the interindividual variability of field distributions obtained with a linear array of eight electrodes.

One of the most debated issues concerning identification of these cortical components was to determine whether a single tangential generator could account for both parietal N20 and central P22, or whether each of these two components had its own generating source. Early investigators favored the former hypothesis and proposed that a dipole-equivalent generator situated in the posterior bank of the rolandic fissure (area 3b) could be responsible for this negative/positive configuration (Broughton, 1968; Goff *et al.*, 1977; Allison *et al.*, 1980), but others argued that the latency shift existing between parietal and centro-frontal components precluded the existence of a common generator for both (Desmedt and Cheron, 1980, 1981; Papakostopoulos and Crow, 1980). According to these divergent views the label 'P22' was proposed by some to differentiate the fronto-central positivity from parietal N20 (Desmedt and Cheron, 1981; Mauguière *et al.*, 1983; de Weerd *et al.*, 1985) while others preferred to speak of a single dipolar N20/P20 with no independent P22 (Allison, 1982; Cohen *et al.*, 1984).

Data from our own experience in 15 normals studied with spatio-temporal maps (Fig. 8) showed that: 1) in the pooled group P22 began and peaked significantly later than N20; 2) the electrode site where P22 could be best individualized varied according to subjects, and consequently spatial mapping proved imperative for such latency studies; 3) even if P22 could culminate at the same time, or earlier than N20, P22 onset was never earlier than N20 onset.

In order to further document this finding we studied sequential spatial maps obtained after stimulation of each individual finger in 12 normal young adults (Deiber *et al.*, 1986). This study gave important informations concerning N20 and P22 spatio-temporal distributions: when N20 peaks there is indeed a positive P20 in the medio-frontal region (Fig. 9: latency 23.04 msec) thus confirming its dipolar configuration in normals. However, a later P22 potential also exists, with no dipolar negative counterpart and a very restricted scalp distribution over the central regions (Fig. 9: latency 26.46 msec). These findings

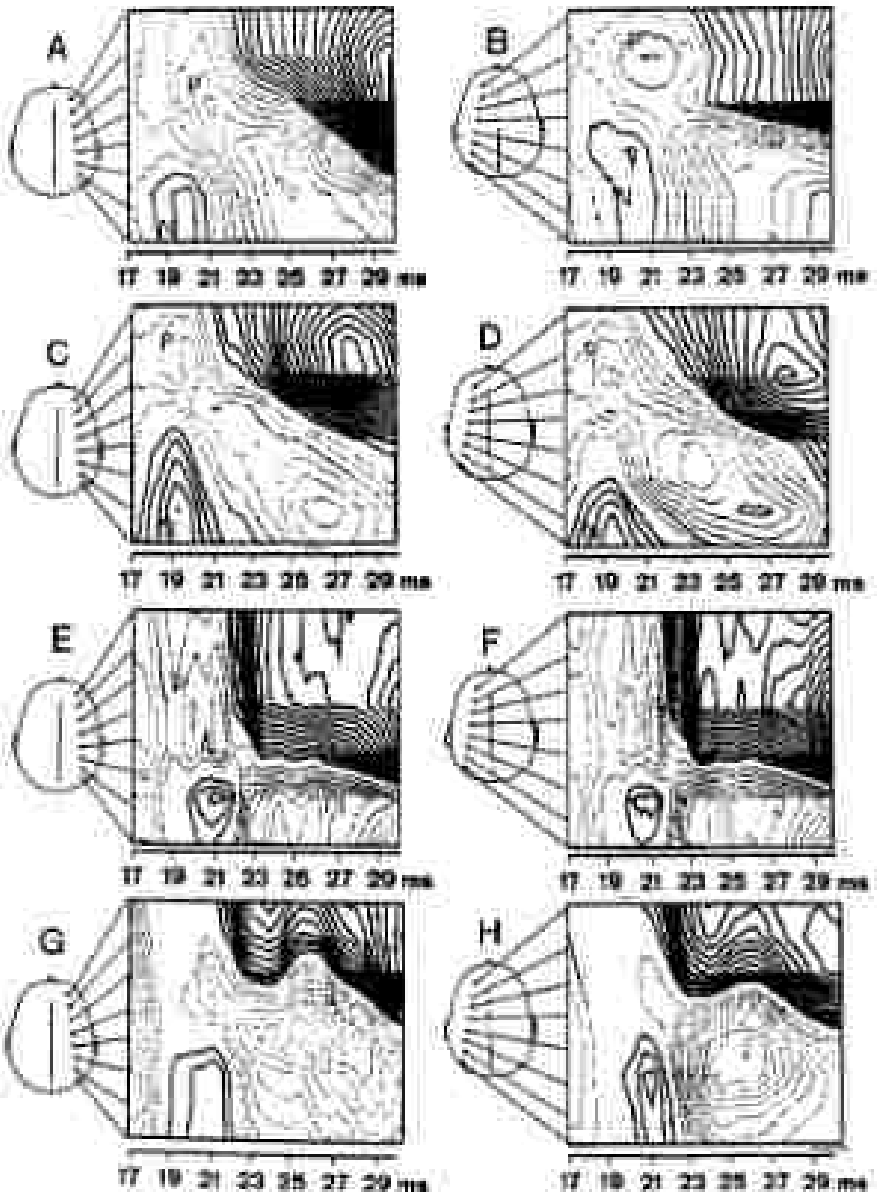


Figure 8. Spatiotemporal mapping of normal early cortical potentials to median nerve stimulation. Three maps were recorded in a normal subject after stimulation of the left (A,C,E,G) and right (B,D,F,H) median nerves. The earlobe contralateral to the stimulated side served as reference. Isovoltage lines are drawn for positivities and solid for negativities. Each map was calculated for latencies between 17 and 30 ms. Note that in all subjects the N20 maximum is in the parietal posterior region, whereas the topography and shape of the P22 peaks are more variable. (From Mauguière *et al.*, 1982; with permission)

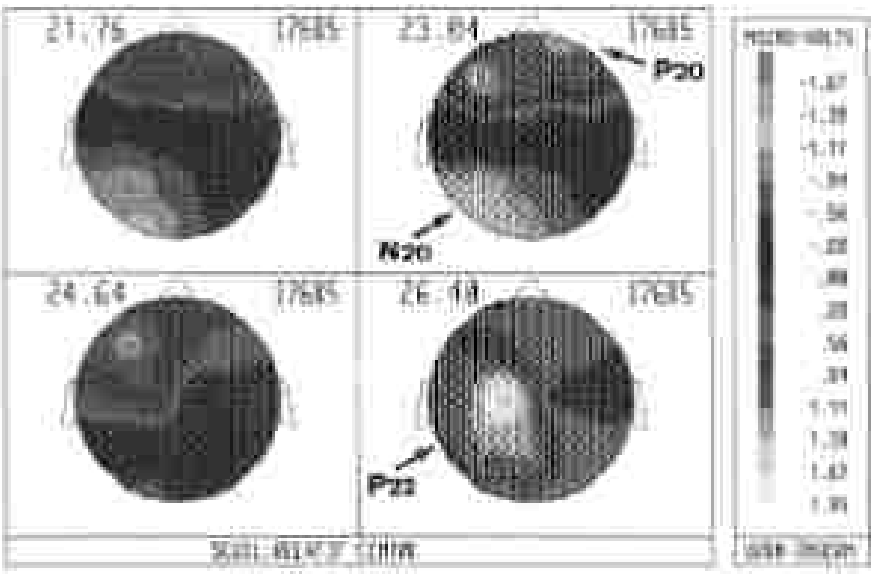


Figure 8. Sequential spatial maps of potential fields after finger stimulation. Three maps were obtained 21.75, 23.04, 24.64 and 26.40 milliseconds after stimulation of the right thumb of a normal subject. The mapping system is described with details in Dubois *et al.* (1984). The figure illustrates two different models of electric fields generated respectively by tangential (posterior parietal N20- frontal P20) and radial (frontal P22-) poles. This spatial distribution accounts for some divergent views concerning the origin of early SEP components by showing that these potentials might be generated by the activity of two distinct generators that partially overlap in a very short period of time.

favor the existence of *two separate generators* with distinct orientations for N20 and P22. The negative/positive configuration of the former, also identified by magnetic recordings (Broseus *et al.*, 1978; Okada *et al.*, 1984; Wood *et al.*, 1985), suggests a tangentially orientated dipolar generator in the posterior bank of the central sulcus, whose orientation was found to change according to the stimulated finger. Conversely, the concentric organization and the somatotopic distribution of isopotentials, even when P22 culminates, favors the hypothesis of a *radially oriented* generator for P22, anteriorly situated to N20-P20 source.

An additional argument favoring the hypothesis of separate generators for N20 and P22 has been recently provided by Shimp and co-workers (1986) who have shown the dissociation of both components after surgical removal of somatosensory cortex that completely abolished N20 but left unchanged P22.

Table I summarizes the main characteristics of SEP's components after upper limb stimulation, as well as literature references supporting their assumed anatomical origin.

A.2. Lower limb tibial nerve stimulation at the ankle

A.2.1. Peripheral component (N7).

A compound action potential corresponding to the activation of tibial nerve fibers running through the popliteal fossa (N7) may be bipolarly recorded at the posterior aspect of the knee (Fig. 10). As it was the case with upper limb N9 this is a mixed motor and sensory potential, classically useful to assess the integrity of the peripheral section of the pathway (Fig. 12).

A.2.2. Lumbar potential (N22).

Following posterior tibial nerve stimulation an electrode situated over the T12 or L1 spinal process records a negative potential culminating at about 22 msec in caucasian controls (Fig. 10) usually preceded by a small positivity peaking at around 17 msec. There is no consensus as to what standard label should be given to this lumbar negativity which has been named 'S' response (Delwaide *et al.*, 1985), N20 (Tsuji *et al.*, 1984), N21 (Small and Matthews, 1984), N22 (Lastimosa *et al.*, 1982; Jöllé *et al.*, 1984), N23 (Yamada *et al.*, 1982) and N24 (Desmedt and Cheron, 1981), such differences reflecting mainly filter settings and geographical origin (and thus height) of subjects examined.

The lumbar negative potential is segmentally originated in the spinal cord

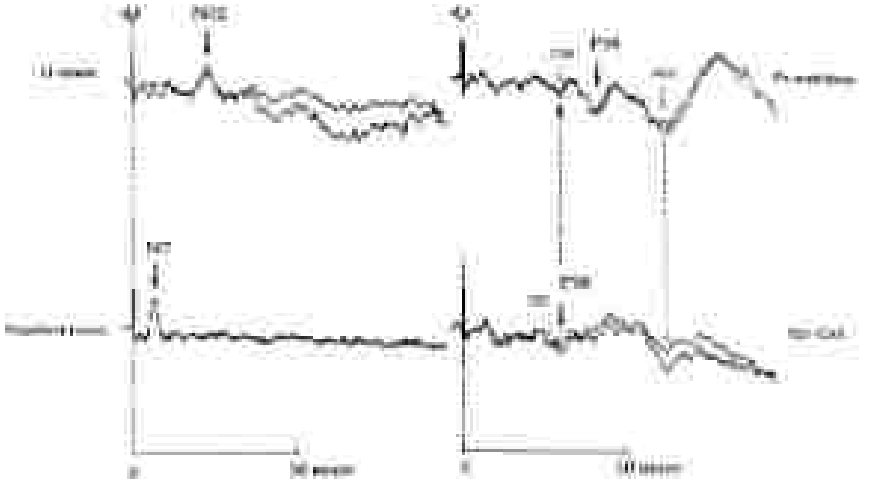


Figure 10. Normal responses to posterior tibial nerve stimulation. The 1 line channel montage shows the successive of peripheral (N7), segmental lumbar (N22), subcortical (P38) and cortical (P40, P23) responses after right or paramedian bipolar stimulation. Note that a small positivity (P27) precedes P40 on the Fpz-Cz derivation, the origin of this 'no field', which is not seen in all subjects, has not yet been clearly established but it is thought to arise from thalamic tissue (see A.2.3). In this subject P38 could also be seen in Pz-ear recordings, but in many occasions it is obscured by the descending slope of P38. This is not the case in 2pz recordings, since P38 is very nicely picked up at this location.

(Delbeke *et al.*, 1978; Jones and Small, 1978; Domićević *et al.*, 1979; Desmedt and Cheron, 1983; Lastimosa *et al.*, 1983; Small and Matthews, 1984; Tsuji *et al.*, 1984; Delwaide *et al.*, 1985) and it may be considered as equivalent to the N13 potential recorded after upper limb stimulation. Desmedt and Cheron (1983) demonstrated the existence of a positive counterpart of this potential which they were able to record with a pre-vertebral electrode. As it is the case with cervical N13/P13, the potential field distribution of the two lumbar components is consistent with a horizontally oriented dipolar source in the cord, probably corresponding to postsynaptic activity in the dorsal horn grey matter. Both posterior negativity and anterior positivity show maximal amplitude at T12-L1 vertebral level, decreasing without any latency shift at more rostral or caudal electrode positions.

The preceding positivity (P17) can also be recorded from the scalp if a non-cephalic reference is used (Yamada *et al.*, 1982). Its latency behaviour are consistent with those of a peripheral potential at or around the lumbar plexus or roots (Yamada *et al.*, 1982; Desmedt and Cheron, 1983).

4.2.3. Subcortical far-field potentials (P17, P27, P30).

With a non-cephalic reference several far-field positivities can be recorded over the scalp preceding the first cortical potential (Yamada *et al.*, 1982; Desmedt and Cheron, 1983; Kakigi and Shibasaki, 1983a). Only the last of these positivities is consistently recorded in normal controls, thus representing the only useful far-field contribution to the clinical application of tibial SEPs. As with all other components, the latency of this potential is heavily dependent on subject's height, and so it has been labelled P30 or P31 when recorded in caucasian volunteers (Yamada *et al.*, 1982; Desmedt *et al.*, 1983) but P27 or P28 when obtained in oriental oriented subjects (Kakigi *et al.*, 1982; Kakigi and Shibasaki, 1983). In this chapter we shall term it 'P30', according to our own normative data.

Although the exact generator of P30 has not been elucidated, evidence in normals suggests a brainstem origin (Yamada *et al.*, 1982; Desmedt and Cheron, 1983) and this potential could be viewed as the lower limb counterpart for the far-field P14 in the SEP to median nerve stimulation. Desmedt and Cheron (1983) calculated that the posterior tibial afferent volley could only involve the medial lemniscus at a latency in excess of 27 msec, so the mean latency of P30 in normals is not contradictory with the assumption of a brainstem origin for this potential.

In our experience, recordings of P30 are made easier if the active electrode is placed quite anteriorly on the scalp, on the sagittal line at Fz or Fpz (Fig. 10) where this component has maxima amplitude and contamination by subsequent potential is minimal. If electrodes are too posteriorly situated P30 may in some subjects be obscured by the descending slope of cortical P39. Considering technical difficulties to record far-field potentials with a hand or knee reference in many patients, the upper neck has been suggested as an optimal reference site for routine P30 recordings (Goyal *et al.*, 1983) since

it can be considered as virtually 'neutral' after lower limb stimulation (vide infra).

In young thin subjects and especially in children scalp-recorded P30 may be preceded by two other positivities, namely P17 and P27. The former is very rarely seen, it corresponds to the positivity preceding N22 in lumbar recordings and is generated at the lumbosacral plexus. P27 (see Fig. 10) has so far an unknown origin, but has been ascribed to the ascending volley as it travels in the upper dorsal (Desmedt and Cheron, 1983) or cervical (Yamada *et al.*, 1982) spine. Scalp P22 and P30 are recorded as 'negativities' in neck-to-scalp recordings, and can then be mistaken for genuine cervical potentials (vide infra, A.2.5).

A.2.4. Early cortical potentials

Electrical and magnetic recordings (Cruse *et al.*, 1983; Hari *et al.*, 1984; Huttunen *et al.*, 1987) support the view that the positive deflexion peaking at about 40 msec (P39 potential, Fig. 10) is the first cortical potential elicited by the stimulation of tibial nerve at the ankle. This latency is shortened by 6–7 msec with stimulation at the popliteal fossa, and is increased by about 3–5 msec with ulnar nerve stimulation.

P39 is usually recorded at Pz or Cz (midway between Pz and Cz) but frequently has maximal amplitude slightly *ipsilateral* to the stimulated limb (Cruse *et al.*, 1983). This may be explained by the anatomical disposition of the leg sensory cortical areas, medially in the parietal lobe and within the interhemispheric fissure. Field studies in animals (Cruse *et al.*, 1982; Seyal *et al.*, 1985; Desmedt and Bourguet, 1985; Kaltigi and Jones, 1986) have shown a dipolar oblique field distribution for this potential, with a constant positivity at the vertex (sometimes maximal at ipsilateral leads) and a concomitant negativity (N39) over the contralateral parietal region. Magnetic field studies (Hari *et al.*, 1984; Huttunen *et al.*, 1987) have also shown the existence of such a dipolar organization. The reason why the negative part of the dipole is not always present on the scalp could be explained by differences in the anatomical localization of the leg area (Brodal, 1969; Penfield and Rasmussen, 1950). As dipole fields arising from the activation of pyramidal cell layers are expectedly perpendicular to cortical surface, in cases with a very high leg projection in the fissure the dipole may be almost vertical and only its positive end will be seen, whereas in cases with a deeper leg area a horizontal fields may arise which can be recorded on the scalp (Seyal *et al.*, 1985).

In *Fz-ear* derivations far-field P30 can occasionally appear preceding P39 (see Fig. 10, upper right traces) due to the higher amplitude of P30 over the scalp than at the ears. It is important not to confound this subcortical potential with cortical P39. If any doubt exists, a Fpz-neck derivation allows to record P30 with no or little P39 contamination (see right lower traces on Fig. 10); alternatively a vertex-Fz derivation can also be useful to cancel P30 and ascertain the first cortical potential.

P39 may be sometimes poorly delineated at its usual recording site (Pz),

This is probably due to normal variations in the orientation of the equivalent P39/N39 dipole, but in some cases difficulties of interpretation arise and a subsequent normal P55 potential may be confounded with a delayed P39. In such cases it may be useful to record scalp potentials with an oblique derivation connecting the ipsilateral parietal region (Grid 1: P3 or P4) with a reference point at the *contralateral* frontal region (Grid 2: F3 or F4). This derivation tends to enhance P39 in cases with an oblique P39/N39 configuration.

4.2.2. The ascending volley along the spinal cord.

It is tempting to use spinal evoked potentials to lower limb stimulation to assess conduction velocity of the propagated volley along the spinal cord, but this has proved to be extremely difficult in clinical practice. Although several authors have reported the possibility of recording a dorsal column compound action potential (CAP) at progressively rostral levels over the spine (Yamada *et al.*, 1982; Kaji[gi] *et al.*, 1982; Seyal *et al.*, 1983; Desmedt and Cheron, 1983) these reports concern small and highly selected groups of young normal (presumably thin) volunteers, in whom very small potentials could be recorded up to the cervical level after 2000–6000 stimulations. Indeed, the amplitude of the spinal CAP drops dramatically (more than 60% from T12 to T6 level (Delbeke *et al.*, 1978, Seyal *et al.*, 1983) and responses at the cervical electrodes are, even in the best conditions, hardly reliable (Burwood, 1981; Desmedt and Cheron, 1983; Tsuji *et al.*, 1984). This is not surprising if we consider the degree of time-dispersion attained by the ascending volley at the cervical level after stimulation of lower limbs, as it has been evidenced using epidural electrodes (Jones *et al.*, 1982; Cioni and Meglio, 1986) and more recently by Jammoussi and co-workers (1988) directly recording over the dorsal columns in man.

Recording difficulties of dorso-cervical potentials explain that reports on them have been largely limited to studies in normals, no large series being available to assess their actual value in clinical settings. Indeed, quite pessimistic statements about the clinical usefulness of spinal potentials exist in literature (Tsuji *et al.*, 1984). Lueders *et al.*, (1981) using a cervical-to-vertex montage described a reliable negative potential which they considered originated in the cervical cord, but it was later demonstrated that "cervical" potentials in neck-to-scalp montages do not change in latency or amplitude from C1 to C7 spinal levels (Small and Matthews, 1984), and correspond most likely to far-field potentials picked-up by the reference electrode at the scalp (see A.2.3, and also Seyal *et al.*, 1983; Small and Matthews, 1984; Riffel *et al.*, 1984). Current EP techniques do not allow the obtention of accurate "spinal conduction times" in the clinical setting; nevertheless, a "transit time" from lumbar N22 to brainstem P39 (Small and Matthews, 1984) can be used in routine (see normative values).

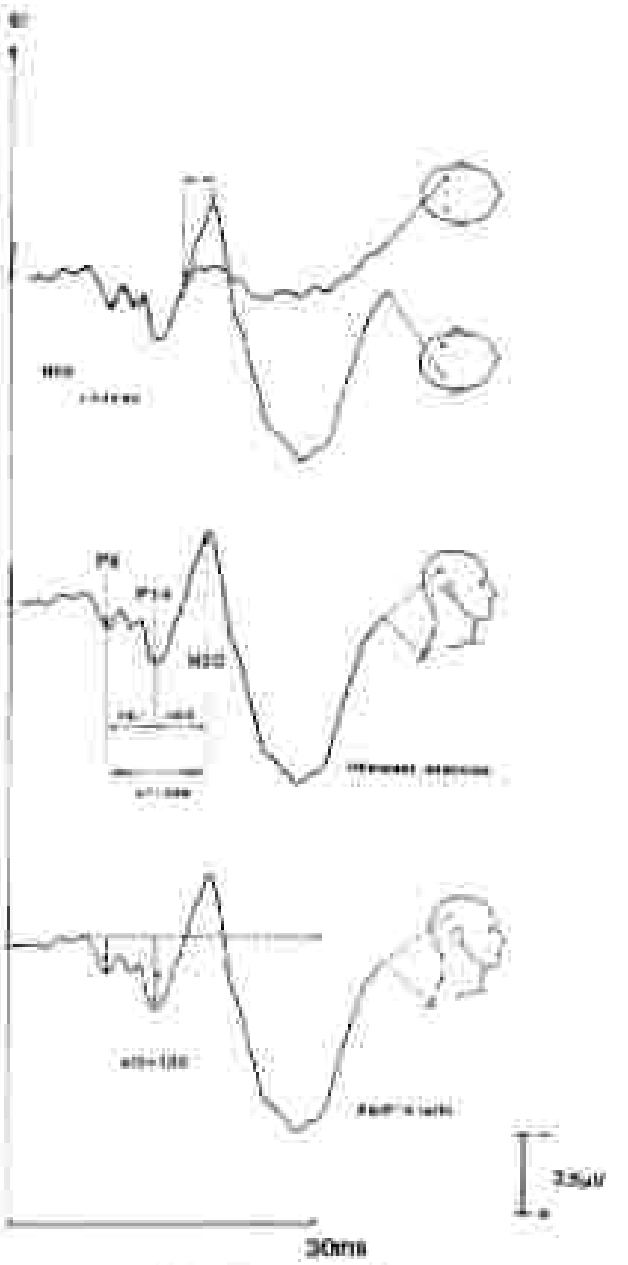


Figure 11. Normal responses to left median nerve stimulation (right parietal to right shoulder derivation). Measurements of P9/P14 amplitude ratio (bottom trace) and P9-P14, P14-N20 and P9-N20 interpeak latencies (upper trace). All (scalenic) reflex responses upper normal limits (mean value ± standard deviation).

B. Normative data

B.1. Latency, amplitude, morphology

SEPs are usually characterized in terms of latency and amplitude measurements. While latency values are usually normally distributed and show relatively small variance in normal controls, the establishment of normal values for amplitudes is hampered by their greater inter- and intraindividual variability that creates high standard deviations (SD), as well as by their frequent non-gaussian distribution preventing the use of parametric statistics. Amplitude ratios between components have proved to be useful to avoid some of this problems (see section on RAEPs) provided that both components on the ratio behave similarly under physiological conditions (and especially that both are similarly affected by background noise). The dispersion of the amplitude ratio distribution (as evaluated by SD/mean values) is frequently lower than that of each component's amplitude taken separately.

Other measurements that can be sometimes of utility are 'wave formation time' (interval between onset and peaking latencies, also called 'ascending time') and 'wave duration' (time between onset and ending of a component). In short-latency SEPs the former is usually easier to calculate and may be applied to N20 measurements (see Fig. 11).

Evaluation of morphology is a complex task involving the simultaneous recognition of several deviations from a 'normal pattern'. Waveshape is not easily defined in quantitative terms and so is more than each of the individual features from which it derives; therefore this parameter is far less used in clinical practice than amplitudes or latencies. However, it is sometimes possible to detect single features as the main determinant factors for a definite morphology. This may be accomplished by means of amplitude ratios, since they involve the simultaneous behaviour of two components. For instance, the characteristic shape of SEPs for field components is quite well described by the P8/P14 amplitude ratio, which has the advantage of being a quantifiable measure.

B.2. Absolute vs. relative latency measurements

Absolute latencies need to be corrected for arm's or leg's length before being interpretable in clinical practice. This implies a high number of normal controls to derive confidence limits and promote the use of interpeak latencies instead, which are not significantly affected by such variables. In Tables 2 and 3 normal values are presented for upper and lower limits in 38 and 20 control subjects respectively. Upper limits of normality can be taken as 2.5 or 3 SD over the mean. All far-field measures have been done on a contralateral parietal-shoulder derivation. N20 'ascending time' was calculated with a contralateral-to-ipsilateral parietal montage (Fig. 11).

Table 2a. Normative values for N9, P9, N13, P14 and N20 absolute and inter-peak latencies and P9-P14 amplitude (N. normal subjects, except 20 subjects for N13). (Measurements done on contralateral parietal/clavicular recordings for P9, P14, P14 & N20; on C4'-cheekbone for N13).

		Mean	SD	X + 3SD
absolute latencies (Msec)	N9	10.74	0.66	12.66
	P9	10.34	0.89	13
	N13	13.59	0.8	15.99
	P14	16.91	0.88	17.55
	N20	19.81	1.17	23.32
side-to-side difference (msec)	N9-N20	9.26	0.69	11.33
	P9-P14	4.56	0.32	6.11
	P14-N20	6.61	0.56	8.61
	N13-N20	6.62	0.69	7.62
side-to-side difference (msec)	N9-N20	0.3	0.26	1.08
	P9-P14	0.36	0.22	1.02
	P14-N20	0.25	0.32	1.21
P9/P14 amplitude ratio (from P9 onset)	0.66	0.22	1.31	

Table 2b. P30 measured on Pz-supra depression; P30 at Tpz-Cz(f); N22 on Ll-mast. Asterisks for P30 amplitude indicate the absence of clinical value of these measures.

	Positive (from next) (n=20)			
Latencies (ms)	N22	P30	P39	CCT
Mean	21.25	30.8	39.54	18.33
SD	1.83	1.15	1.81	1.66
X + 3SD	25.59	34.29	45.2	24.11
Amplitude (μv)				
Mean	1.38	*	3.82	
SD	0.7	*	1.36	

Table 3

Clinical findings	Cortical SEPs				
	All absent or reduced	Dissociated: Abnormal N20-P27	Abnormal P22-N30	Normal	Enhanced
Loss of tactile and joint sensations & hemiplegia	26	0	0	0	0
Asterognosis without motor deficit	5	11	0	0	0
Normal sensations & hemiplegia	0	0	5	8	2
Normal sensory & motor examination	0	0	0	10	7
Total	31	11	5	18	9
%	45 %	16.2 %	7.4	23.2 %	13.2 %

B.3. The measurement of 'central conduction time'

In patients with CNS diseases it has been proposed to measure the "central conduction time" from the summit of the cervical negativity obtained with a frontal reference to the peak of N20 (Rowe and Cant, 1978; Eisen and Odusote, 1980). However, the use of a frontal reference introduces a non-negligible degree of inaccurate as to the identification of the main cervical negative component (see A.1.2 and Fig. 14). For upper limb SEPs reliable conduction times can be measured with non cephalic reference recording using P9-P14 and P14-N20 intervals (Table 2).

Also after lower limb stimulation, some authors proposed a "cervical cord to cortex" conduction time defined as the time elapsed between the negative peak recorded with a cervico-frontal derivation and cortical P39. Since it has been demonstrated that cervical negativities after lower limb stimulation are mostly, if not only, derived from the scalp reference (see section A.2.3), this conduction time is indeed one between a presumably brainstem potential (P36) and the cortical positivity P39 (Shiraishi and Matthews, 1984; and see Fig. 10).

B.4. P9/P14 amplitude ratio

To by-pass difficulties inherent to amplitude measurements (see above) we described an amplitude ratio between a peripheral (P9) and a central component (P14) of upper limb SEPs (Fig. 11). This ratio proved to lack the variability of absolute amplitude measures and also to have a gaussian distribution in normal controls (Fig. 12). Its rationale is analogous to that of the BAEP I/V amplitude ratio (Stockard *et al.*, 1980) and it represents a sensitive index to assess and quantify amplitude decreases of the P14 component. In CNS demyelinating diseases, where P9 is preserved but central dispersion of somatosensory inputs entails amplitude reduction of P14, an increase of this ratio may be the first sign of abnormal conduction, before any latency measurement pathological values (Garcia-Larrea and Mauguière, 1988).

C. Ontogeny of SEPs

The process of somatosensory development from birth to adult life is dominated by two coexisting phenomena with opposite effects on SEPs. On one hand nervous system maturation (myelinogenesis, but also fiber diameter increase and synaptic efficiency modifications) entails a progressive increase in conduction velocities and synchronization of potentials. Body growth with concomitant lengthening of somatosensory pathways has the opposite effect, namely latency increase and desynchronization. Interaction of these two variables is responsible for the complex pattern of SEP development in children.

In spite of a number of published studies comparison of available data is still difficult due to methodological dissimilarities. Stimulation and recording

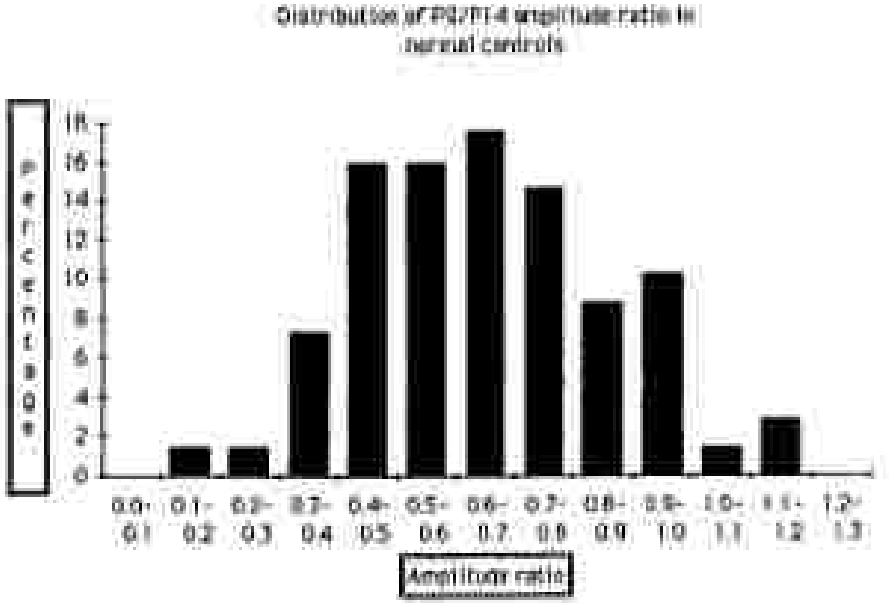


Figure 52. Distribution of P9/N14 amplitude ratio in 34 normal controls. Normality and symmetry of distribution allows the easy determination of confidence limits (for numerical values see Table 3).

sites, reference electrode and filter settings are so variable that preclude coherent comparison of reported values; moreover, studies done specifically to evaluate maturational changes concerned either subjects of different age groups or subdivided these age groups differently.

As a general rule we can say that during the first 4–5 years of life SEP evolution is dominated by maturational processes tending to progressively synchronize components and reduce their latencies (Desmedt *et al.*, 1976; Hashimoto *et al.*, 1983; Cadilhac *et al.*, 1985; Tomita *et al.*, 1986; Bartel *et al.*, 1987; Zhu *et al.*, 1987; Laureau *et al.*, 1988). Conduction velocity reaches adult values before the age of 3 in the peripheral nervous system (Thomas and Lambert, 1960; Desmedt *et al.*, 1973; Bouyon *et al.*, 1984) and at a slower rate in central somatosensory pathways (Desmedt *et al.*, 1973, 1976; Crocco *et al.*, 1979), spinal cord conduction after lower limb stimulation having been found to attain adult values at about 5–6 years of age by Cracco *et al.* (1979). From 5–6 years onwards (3 years for peripheral components) maturation effects begin to be obscured by body growth, and latencies increase up to adult values, reached at about 15–17 years of age (Allison *et al.*, 1986).

Establishing a bank of normative data for children requires normalization of values in order to eliminate part of their contingency. One of the easiest ways is to correct absolute latencies for height (or a height indicator) of the involved neural pathways; this can be accomplished by dividing latencies by

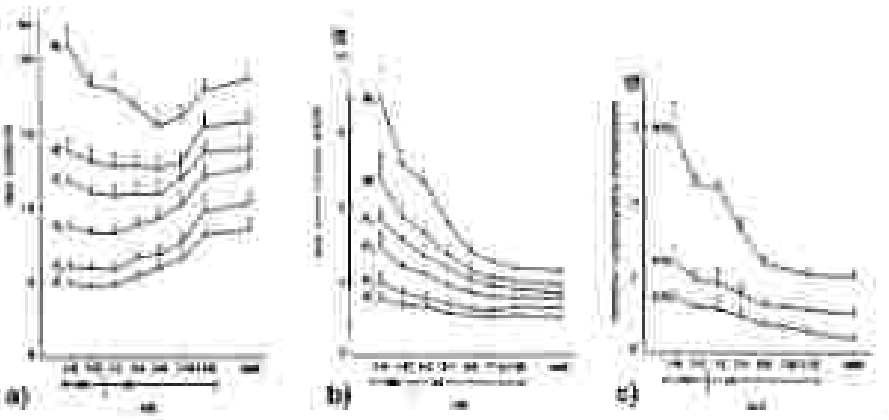


Figure 11. SEP latency changes from 1 month to 20 years of age, as obtained in a sample of 50 normal subjects. Labels P1, P2, P3, P4, N' and N1 correspond respectively to P9, P11, P13, P14, N18 and N20. In a, evolution of absolute latencies, showing the progressive increase from 2 years onwards for P1 to P3, and from 5 years onwards for the rest of components. In b and c absolute and interpeak latencies respectively corrected for body weight and head circumference. Data are seen to fit the chronological evolution of latencies as observed with this transformation, namely latency decrease from birth to adulthood. (From Tomita *et al.*, 1988, by permission)

arm's length or body height. This simple transformation makes all central SEP latencies decrease from birth to about 10 years of age, to stabilize thereafter (Tomita *et al.*, 1986; and unpublished data from our laboratory) (Fig. 13).

For central conduction studies and central interpeak latencies Tomita *et al.* (1988) proposed correcting latencies for head circumference, a variable that has been shown to be correlated with other growth parameters (Bartel *et al.*, 1987). Using this transformation they found that IPLs between P13, P14, N18 and N20 (P3, P4, N' and N1 in their nomenclature) decreased progressively from one month to 15 years of age, when they reached adult values. As it is shown in Fig. 13 this decrement is not steady, but steeper between birth and 4 years and slowing down thereafter. Only the P13-P14 IPL undergoes a further decrease between adolescence and adult life.

Zhu *et al.* (1986, 1987) studied the 'ascending time' of the first cortical potential after upper and lower limb stimulation. Conversely to what happens with latency measurements, N20 and P40 ascending time (from onset to peak) decreases steadily from birth to 16 years without any kind of data correction. This rises the possibility to devise some indexes of cortical SEP maturation seemingly *independent* of body height; unfortunately for practical purposes SEP interpretation in children usually needs knowledge of birth age and some indicator of neural pathway's height. Measures should be normalized as indicated (except perhaps for N20 or P40 ascending time) and limits of normality set at least at the 99% confidence level.

As an example we provide a nomogram extracted from Tomita and

researchers, the only authors having so far published data obtained with a non-cephalic reference from birth to adult life. These values are only indicative. As it was the case for adult SEPs every laboratory should create its own database, with at least 10 normal controls for each age.

D. Clinical use of SEPs

D.1. General remarks

SEP abnormalities reflect the degree, topography and sometimes the nature of neuronal damage, rather than its cause. However, abnormal patterns will be described that strongly suggest a definite pathology, or at least a pathogenic mechanism, if found in an appropriate clinical context. Schematically, demyelinating conditions tend to increase latencies, while axonal damage reduces amplitudes. However, focal dispersion due to demyelination also reduces amplitudes, and loss of fast-conducting axons may increase latencies. In general, we can accept that a reduction of conduction velocity greater than 40% is highly suggestive of a demyelinating condition (Cohen, 1966). Some attempts have been made to quantify time-dispersion of potentials as an early sign of demyelination (Rubens *et al.*, 1983) but their clinical utility is still to be proved.

A thorough neurological examination is imperative before a SEP recording is attempted, since number of channels, type of derivations and stimulating and recording sites are not standard for all conditions. As a general rule, good quality far-field potentials are essential for SEP interpretation in suspected lesions of the cord, brainstem or diencephalon, and thus a non-cephalic reference is needed in such instances. In cortical pathology, however, it is more important to have an estimate of the scalp distribution of cortical responses, and so several recording points on the scalp should be used, including contralateral parietal, frontal and central electrodes, as well as an ipsilateral parietal for comparison. Non-cephalic recordings are not imperative in these cases and an ear reference is a good alternative since it does not distort scalp potentials' distribution.

A single scalp recording site is enough when dealing with peripheral nervous system (PNS) problems. Since far-field potentials are seldom needed for interpretation in those cases, the reference point may be chosen on the scalp (ipsilateral parietal region, which is the most "neutral" site between 15 and 50 msec). Nevertheless, if radicular conditions are good an ear reference is always preferable.

Different stimulating sites are often needed for PNS assessment and special attention must be focussed to the segmental specificity of the stimulation in plexus or root pathology.

Good recordings of spinal N13 are important in most clinical problems. Only in thalamo-cortical or distal peripheral pathology its detection can be

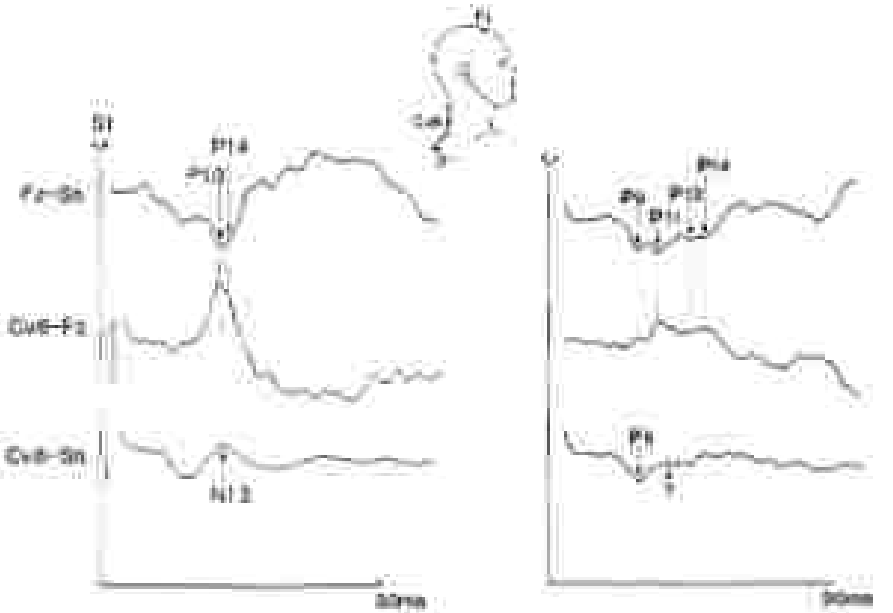


Figure 3A. Interpretative difficulties of the cervical complex due to the use of a midfrontal reference. In each set of traces the bottom and top channels are averaged to Cv6 and Fz electrodes referenced to shoulder; the middle trace depicts the neck-to-frontal derivation. *Left* shows normal cervical response at Cv6 shoulder, and a spurious 'N13' (likely P9-P11-P14 at Fz). The waveform in neck-frontal montage is clearly dominated by the N13 picked up by the reference electrode; neither of the negative peaks corresponds to actual spinal N13. *Right* traces illustrate an example of abnormal cervical response. No N13 is recorded with a shoulder reference, but biphasic P9-P11-P13 and P14 are visible at Fz. As a consequence, the Cv6-Fz montage (middle) records a waveform that exactly reproduces (inverted) the Cv6 response injected by the reference. What seems to be a N13 is indeed an inverted P13 (arrow). In the case of erroneous diagnosis of spinal N13 preservation (with probable "N14" vertebrobasilar) would have been done on the basis of cervical-frontal recordings alone.

safely skipped. Cervical-to-scalp montages must be *absolutely avoided* since they mix up spinal N13 and brainstem P_{CV7-9} and may prompt erroneous interpretation (see some examples at Fig. 14). Instead, a Cv6-anterior neck derivation allows for good quality recordings of a true spinal N13 with little muscle contamination (Fig. 3).

On the basis of a 4-channel EP device we suggest the following routine montages (the components studied in every derivation are written brackets):

Upper limb

PNS assessment:

1–bipolar peripheral recording at the elbow (N9)

2–Erb's point – Fz (N9, inverted P14)

3–Cv6-anterior neck (spinal N13)

4-contralateral parietal-ear (P14, N20) or cricto-to-ipsilateral parietal (N20/P27)

Diseases of cord, brainstem or subcortical structures (including MS studies):
1-Erb's point - *Fz* (N9, inverted P14)
2-Cv6 - anterior neck (spinal N13)
3-Contralateral parietal - shoulder (for fields P9, P11, P14; cortical N20/P27)
4-Ipsilateral parietal - shoulder (for fields P9, P11, P14; widespread N18)

Diseases of thalamus and cortex:
1-Contralateral parietal - ear (P14, N20, P27)
2-Contralateral central - ear (P14, P22, N30)
3-Contralateral frontal - ear (P14, P20, N30, sometimes P22)
4-Ipsilateral parietal - ear (N18 attenuated)

Lower limb
PNS studies
1-Bipolar recording at popliteal fossa (N7)
2-L1 - knee (or L1-T0) (N22 - difficult to obtain if pure sensory stimulation)
3-Pz - ear (P39, N55)
4-(Optional) Ipsilateral parietal - contralateral frontal (P39, N55)

CNS studies:
1-*Popliteal fossa* (N7)
2-L1 - knee or L1 - T0 (N22)
3-Fpz - Cv6 (P30) 4-Pz - *ear* (P39)

(in PNS studies subcortical *P39* is not needed for interpretation, and so it is safer to replicate the recording of cortical P39, which is sometimes the only reproducible potential in severe neuropathies)

D.2. Peripheral lesions

SEPs are useful for the evaluation of peripheral pathology in 3 circumstances:
a) Severe neuropathies with unobtainable sensory nerve action potentials.
b) Lesions situated in proximal segments of the peripheral pathways, inaccessible to conventional electroneurographic studies.
c) Diffuse conditions with both peripheral and central somatosensory troubles.

D.2.1. Peripheral neuropathies.
Early in the history of SEPs it was demonstrated that cerebral responses to peripheral nerve stimulation could be recorded in situations where a potential could not be obtained from the nerve itself (Calvin, 1964; Desmedt *et al.*, 1968). This is especially true in severe hereditary neuropathies such as Charcot-

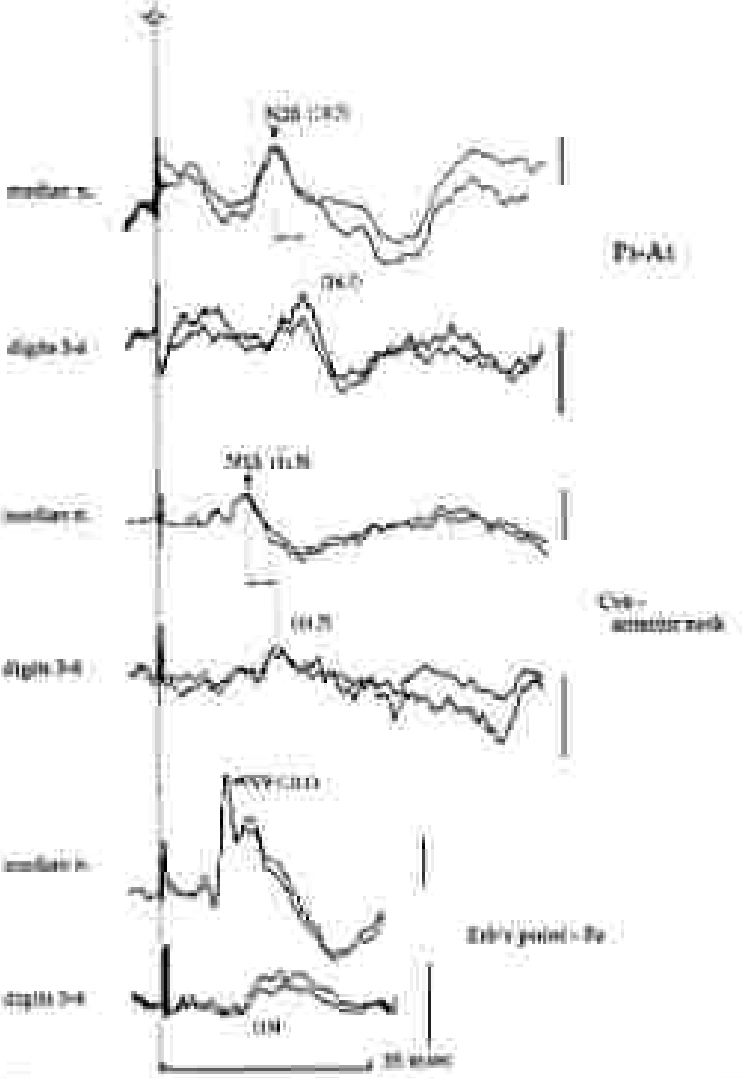


Figure 11 SEPs in a case of carpal tunnel syndrome. This patient had undergone a car accident after which neck pain and vertigo developed. After these symptoms had subsided the patient still complained from pain and paraesthesia at the hand and six digits of the right hand. Spinal CT scan and myelography were negative, and he was referred for SSEPs in search of a possible radiculopathy. SEPs to median or radial nerve stimulation were normal, but stimulation of right 3rd and 4th digits disclosed a desynchronized and delayed 9/8 (latency 10 msec) suggesting distal pathology. N9-N13 IPL for digits was normal and comparable to that obtained after median nerve stimulation (solid traces). The 3 cm delay between median and digits stimulation (normal = 3 ms) was maintained all along the pathway. Hint: N9 to N20 (upper traces). This suggesting the absence of root or CNS involvement. As alveolar or vascular pathology is very unlikely the cause of selective impairment of sensory fibers from only two digits, a diagnosis of median nerve compression at carpal tunnel was made, which was positively confirmed by conventional EMG studies. Note the possibility of recording reproducible spinal and cortical potentials even when peripheral responses are highly desynchronized and hardly evident.

Marie-Tooth or Déjerine-Sottas disease, but has also been described in acquired toxic or metabolic conditions (Parry and Antinoff, 1987) and even in carpal tunnel syndrome (Desmedt *et al.*, 1986). In all those cases, the difference in N20 latency elicited by stimulation of the nerve at 2 different sites can be used to estimate conduction velocity in the segment between the 2 stimulating points. For more accurate measurements it is preferable to measure onset rather than peak latencies. This can be done with a contralateral-to-epilational parietal derivation, which cancels far-field potentials without interfering with parietal N20.

When the severity of the process does not impede the recording of N13, P14 and N20 potentials, their IPL is normal (Fig. 15); otherwise, a combined central and peripheral condition must be suspected, and this may be diagnostically relevant (see Feinberg's ataxia, D.2.3.1). It must be reminded, however, that *peak* latency measures may be misleading in this respect: falsely increased central IPLs in peripheral conditions may sometimes be induced by dispersion of components (see Fig. 16), and also peak latencies shorter than normal may be found if axonal loss is important. In both instances onset, rather than peak latencies are helpful to avoid misinterpretations (see above).

D.2.2. Proximal lesions

D.2.2.1. Plexopathies. SEPs can be useful by establishing the topography of the injury, and also by demonstrating proximal axonal continuity when clinical examination fails to do so (Figure 18). One of the main concerns of surgeons in plexopathies is to accurately define whether the lesion is proximal or distal to dorsal ganglia. Microneurosurgical intervention can be helpful in this latter case, but not in root avulsion (i.e. complete lesion proximal to the ganglia). Since root avulsion can be misinterpreted on the basis of myelography only, electrophysiological studies are often asked for.

Persistence of a normal Erb's point potential (N9) with abolition of all subsequent components indicates avulsion of the roots corresponding to the stimulated nerve. It is a strongly reliable pattern, with a very poor prognosis of recovery. On the other hand, the absence of all components including Erb's point potential does indicate a complete lesion distal to the ganglia, but it impedes the demonstration of other possible proximal lesions. We then cannot conclude the absence of avulsion, for distal involvements may occlude proximal one.

When both peripheral N9 and spinal N13 potentials are reliably obtained, N13 attenuation reflects the total proportion of damaged fibers (pre and post-ganglionic) but N9 decrease reflects solely distal lesions. The relative participation of proximal and distal lesions can then be evaluated by comparing their respective degree of attenuation. Using this technique Jones et al. (1981) were able to correctly identify lesions in half of 16 patients for whom data from surgery was later available. In 3 cases there was major discordance between electrophysiological and surgical data, thus indicating that the technique

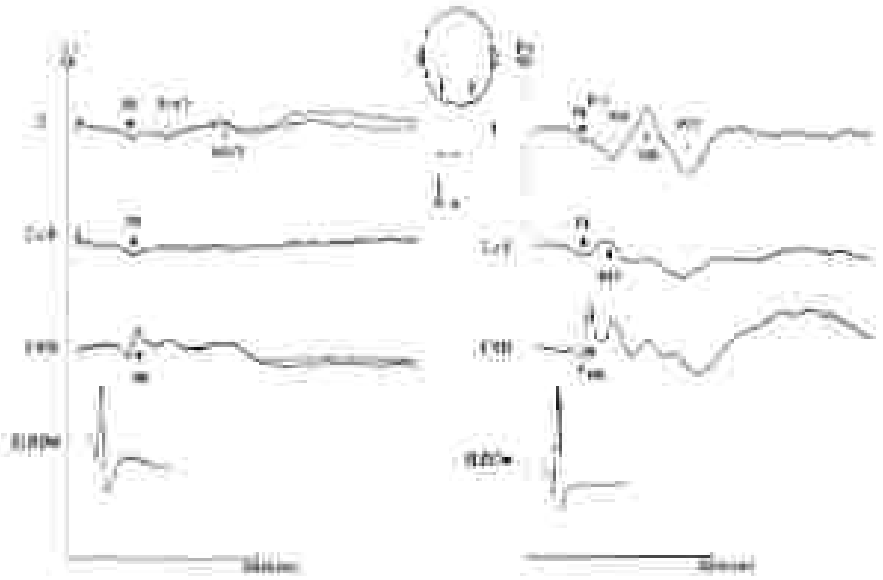


Figure 16. SEPs in a case of left brachial plexus injury. The patient sustained a motorbike accident after which a left brachial plexus lesion was clinically suspected. Left and right median nerve stimulation are respectively shown on left and right parts of the figure. Peripheral responses at elbow and Erb's point are well preserved after left side stimulation, but indicating a partial lesion distal to spinal ganglia. N13 consistently absent, and although P9–P14 IPL is symmetrical, P9–P14 amplitude ratio is abnormal for left stimulation. These signs suggest a lesion distal and proximal to dorsal ganglia, but further cervical sensory stimulation (digits) would have been needed to ascertain the exact level of the lesion and the real disproportion between N9 and N13 amplitude reduction. Nevertheless, as a rule, PDS is still recorded on the affected side a complete C5–C7 avulsion can be ruled out.

described is not 100% reliable. Reliability can be increased by measuring surfaces, and not only amplitudes of potentials, and by stimulating several nerves and/or dermatomes to distinguish between different plexular trunks, divisions and cords. Eisen (1986) has proposed stimulation of musculocutaneous, radial, median and ulnar nerves to thoroughly explore brachial plexus. Selectivity for lumbosacral plexular lesions is far more difficult due to greater overlapping of cutaneous innervations; no systematic studies have been attempted to assess the utility of SEPs in lumbosacral plexopathies.

SEPs can also demonstrate axonal continuity through the plexus when clinical data are difficult to interpret and peripheral potentials are not recordable. In this situation, recording of reproducible cortical potentials always indicates the absence of total denervation (neurotmesis) of the stimulated roots, being a favourable prognostic sign for later reinnervation.

Most of published reports have dealt with traumatic injuries to the plexus, but the utility of SEPs has also been demonstrated in metastatic involvement

of this structure (Symis and Cowan, 1983), a condition of difficult clinical diagnosis where conventional neurocyclic tests are often insufficient (Keet *et al.*, 1981).

D.2.2.2. Thoracic outlet syndrome. Only one study has so far reported *frequent* abnormalities of median and cubital SEPs in patients clinically suspected of this syndrome (Glover *et al.*, 1981), but evaluation of this report is hampered by the lack of abnormality criteria provided. In all other published studies, as well as in our experience, median and cubital SEPs have been normal in patients with only pain and paresthesiae (non neurogenic syndrome) and also in a substantial proportion of cases with objective neurologic signs. Thus, this technique cannot be considered as diagnostically useful in thoracic outlet syndrome, unless used to demonstrate the absence of other type of pathology in selected patients with difficult diagnosis.

In the few cases with well proven abnormal SEPs, these have been obtained to *cubital* nerve stimulation. Abnormalities consist of amplitude reduction or abolition of cervical components, either associated or not with N9 attenuation (Silvola *et al.*, 1979; Yamikas and Walsh, 1983).

D.2.2.3. Guillain-Barré syndrome (GBS). In this condition pathology is predominant in roots or proximal segments of nerves, in many cases inaccessible to conventional electroneurographic techniques. Distal conduction is often normal (Eisen and Humphreys, 1974), and although "F Wave" recordings can also assess proximal neural conduction, they are only recordable from a selected group of muscles, and give no information about sensory root disease.

In median nerve SEPs abnormalities consist in absent, delayed or dispersed N9 potential along with attenuated N13 and increased N9-N13 IPL. If lesions are confined to the proximal segments N9 may be normal, and all median SEPs are within normal limits in about half of the patients (Brown and Feasby, 1984; Walsh *et al.*, 1984; Rüppel and Chiappa, 1986). Tibial SEPs are more frequently affected, and then again peripheral nerve CAP (N7) may be normal or not whereas lumbar N22 is more frequently abolished or delayed (Rüppel and Chiappa, 1986).

There is controversy about the existence of Central Nervous System pathology in GBS. Anecdotal reports of increased central conduction time have been published (Rüppel and Marmarou, 1984) but no definite evidence exists from large series of patients.

SEPs are not a routine examination in GBS, since in most cases diagnosis is clear on clinical and peripheral electrophysiological grounds alone. SEP studies should be attempted when trying to evidence proximal conduction blocks not detected by F waves (Walsh *et al.*, 1984).

D.2.2.4. Proximal nerve lesions. SEPs are important in the evaluation of neural conduction along inaccessible proximal segments of nerves in the limbs. This

is especially true in meralgia paresthetica, where SEPs obtained by stimulation of femorocutaneous nerve (medial to the anterior iliac crest) clearly indicate the severity of involvement and prompt surgery if necessary (Synek, 1985). In cases of suspected retroperitoneal surgical lesions of the femoral nerve SEPs to saphenous nerve stimulation (at the lateral aspect of the knee) are absent or substantially delayed (Synek and Cowan, 1983). In both cases SEPs are probably the diagnostic method of choice.

D.2.2.5. Radiculopathies. Standard techniques involving mixed nerve stimulation in upper or lower limbs are seldom useful in radiculopathies due to their absence of segmental specificity (for instance, median nerve stimulation activates roots fibres from C6 through T1). As a consequence, dealing with isolated root problems most often deserves selective nerve (Eisen and Elleker, 1980; Eisen, 1986) or dermatomal (Scarff *et al.*, 1981; Aminoff *et al.*, 1985; Katifi and Sedgwick, 1987) stimulation. The first approach is technically easier and in our experience more reliable. Musculocutaneous nerve at the elbow can be stimulated for C5 radiculopathy, the thumb or first two digits for C6, the 3rd digit for C7 and the 5th and medial aspect of 4th digits for C8 (Foerster, 1933). Similarly, saphenous nerve at the knee may be stimulated for L3 segment, superficial peroneal nerve at the ankle for L5, sural nerve behind the lateral malleolus for S1–S2 (Fig. 37) and the dorsal nerve of the penis or clitoris for S3.

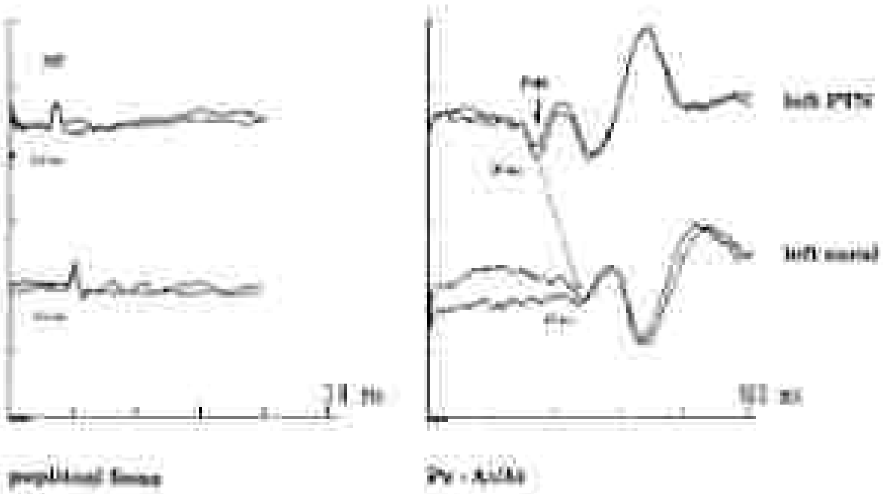


Figure 37. Left S1–S2 radiculopathy. Chronic injury to cauda equina in this 35 year-old woman caused delayed P40 after sural nerve, but not tibial nerve stimulation, thus indicating selective suffering of S1–S2 sensory roots. L5 preservation probably explains normal SEPs after posterior tibial nerve stimulation, which mainly activates sensory fibres from plantar skin entering the cord via L5 posterior root.

Dermatomal root innervation presents much overlapping and interindividual variations which make the above assumptions only approximative (Inouye and Bachtal, 1977); nevertheless, both dermatomal and cutaneous nerve stimulation have proved useful in the evaluation of radiculopathy, especially when only sensory symptoms (including pain) are present (Ehni *et al.*, 1965; Kanfi and Sedgwick, 1987).

Since recording of spinal and far-field potentials after either segmental nerve or dermatomal stimulation is difficult and time consuming, for most clinical studies on isolated radiculopathies a simple two-channel montage may be advised (peripheral CAP recording in channel 1, cortical N20 or P40 in channel 2), but this simplified montage should be *only* envisaged if cord pathology can be ruled *out (vide infra)*. Intervals latency and amplitude differences are preferable to absolute measurements. A scalp-to-scalp derivation (vertex-Fz for lower limb, contralateral-to-ipsilateral parietal for upper limb studies) should be preferred to improve signal-to-noise ratio, even if the price is cancellation of far-field potentials. Optimally, multiple nerves or dermatomes should be stimulated to obtain an electrophysiological scanning of the presumed affected roots.

It must be reminded here that clinical presentation of spinal cord tumors may include 'typical' radicular signs, including pain (Adams and Victor, 1985). If spinal cord pathology is suspected in a patient with radicular signs every effort should be made to assess central conduction time and segmental cord responses, and thus the 2-channel simplified montage just outlined will *no longer be accurate*. In the case of upper limb stimulation it is usually possible to obtain reliable N13, P14 and N20 potentials after digit stimulation (Fig. 15), thus making feasible the simultaneous assessment of radicular and cord lesions at cervical level. Unfortunately this is not the case for lower limb studies; consequently, if a spinal cord lesion is suspected as the origin of lumbo-sacral root symptoms segmental or dermatomal SEPs must be completed by mixed stimulation (preferably tibial nerve) so as to obtain the necessary components to assess dorsal integrity and central conduction time.

D.2.3. Diffuse conditions with central and peripheral involvement

D.2.3.1. Friedreich's ataxia. In Friedreich's ataxia (FA) it has been demonstrated that maximal sensory nerve conduction velocity is only moderately decreased, whereas the peak of the parietal N20, when obtainable, is delayed and desynchronized because of involvement of central somato-sensory pathways (Noël and Desmedt, 1978; Sauer and Schenck, 1977; Mastaglia *et al.*, 1978; Jones *et al.*, 1980; Pedersen and Trojaborg, 1981; Jubbari, 1982; Nuwer *et al.*, 1983; Taylor *et al.*, 1985). In our experience (Valeriani *et al.*, 1988) N9 and P9 are strongly attenuated or absent in all cases of FA. When obtainable, N9 latency is most often within normal limits and if P14 persists we have always found normal P9–P14 (or N9–P14) transit time; conversely P14–N20 IPL is almost *always* abnormal, N20 being delayed and desynchronized or totally absent (Fig. 18). In previous studies (Jones *et al.*, 1980; Pedersen and

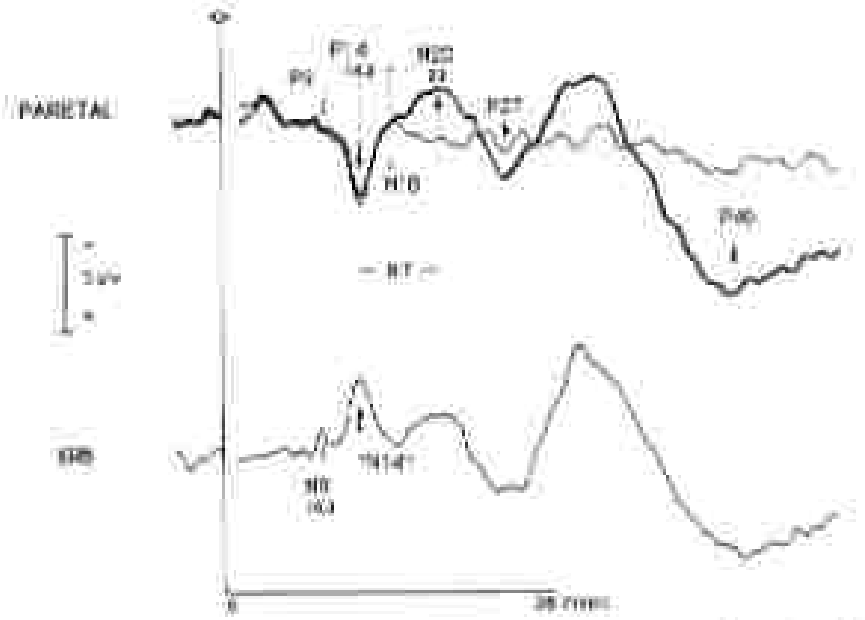


Figure 11. SEPs in a case of Friedreich's ataxia. Bifocal giant N9 potential is of very diminished amplitude but joint latency is only slightly delayed (about 0.5 msec). Upper recordings show contralateral parietal (Erb's) superimposed non-giant parietal responses, both against a non-cephalic reference. Conduction time between N9 and P14 is within normal limits, thus indicating the absence of somatosensory conduction deficits within the cervical spinal cord. Conversely, P14-N20 IPL is clearly prolonged (normal < 6.4 msec) and this suggests significant involvement of medial lemniscus or thalamo-cortical pathways in this patient. Note the existence of a "N14" recorded with the Erb's point-Fz derivation and corresponding to lowered P14 picked up by the reference (Fz) electrode. (From Valanne *et al.*, 1988, with permission)

Trojaborg, 1981) cervical potentials were shown to be present and of normal or near normal latency in a large proportion of FA cases. However, these recordings were done with a Fz reference which may create some problems of component identification since the waveform complex obtained in these conditions results both from a spinal cord generator (N13) and from a brainstem generator (P14) the activity of which is injected by the reference electrode as an "N14" in the cervical response (see sections A.1.2. and D.1.).

Non-cephalic recordings further elaborate the notion that in FA conduction velocity is unaffected up to the brainstem after stimulation of upper limbs (Valanne *et al.*, 1988). Amplitude reduction of N9 and P9 components can be accounted for by degeneration of large neurons in the posterior root ganglia and the resulting disappearance of large myelinated fibres in the peripheral nerves. The prolonged P14-N20 interval suggests brainstem, thalamus or thalamocortical radiations' pathology. Thalamic loss of neurons has been described in FA (Oppenheimer, 1979) and at least in one case ventroposte-

related nuclei were the most affected (Bouldin *et al.*, 1972); this could explain the N20 attenuation or abolition found in our patients, but not its delay. Central demyelination might explain such a slowing of central conduction velocity and demyelinating changes have indeed been reported in the medial lemniscus of FA patients (Lamarche *et al.*, 1984). However these changes were seen only in the ventral portion of the lemniscus, which conveys information from the lower limbs, whereas in our patients prolonged P14-N20 IPL as also seen after median nerve stimulation (Fig. 1B).

D.2.3.2. Other hereditary ataxias. SEPs have rarely been studied in hereditary ataxias other than FA (Pedersen and Trojaborg, 1981; Nowak *et al.*, 1983; Vanasse *et al.*, 1988) but might be useful in the future as an ancillary test for classification of this cerebrospinal group of diseases. In a recent work we compared somatosensory responses in a group of well defined FA patients with those obtained in patients affected by progressive early onset hereditary ataxias (PEOCA) different from FA (Vanasse *et al.*, 1988). There were clear differences in SEPs between FA and most PEOCA patients. Most of these latter had no peripheral or brainstem somatosensory involvement, as assessed by normal Erb's point and P14 potential; however, a delayed or absent N20 was found in all of them. In some patients abnormalities were reminiscent of those observed in FA, but hereditary pattern and/or presence of tendon reflexes discarded a diagnosis of FA. Most PEOCA patients had been classified on clinical grounds as "early onset cerebellar ataxia with retained tendon reflexes", a clinical entity defined by Harding in 1981; however, differences existed among them when studied from the electrophysiological point of view. This suggests that clinical homogeneity may in some cases hide pathophysiological differences relevant for diagnosis. Thus, we feel that systematic electrophysiological studies of ataxic patients can be useful in classification of progressive ataxias, in combination with clinical, biochemical and molecular genetics data.

D.2.3.3. Amyotrophic lateral sclerosis. Some authors have described central SEP abnormalities in this condition (Antoniades and Cracco, 1983; Machemer *et al.*, 1983) but others have not (Matthews, 1980; Okita and Chiappa, 1986). Since no definite correlation has been established between SEP abnormalities and severity or rapidity of evolution of this fatal disease, SEPs are not to be envisaged as a routine procedure in it.

D.3. Central nervous system (CNS) lesions

Conversely to that applying to peripheral conditions, in CNS pathology a non-cephalic reference is imperative for upper limb SEPs, since a correct assessment of far-field potentials may be crucial for interpretation.

B.2.1. Spinal cord diseases

B.2.1.1. Cervical spondylotic myelopathy. This is the most frequent type of myelopathy admitted to general hospitals (Adams and Victor, 1985); in this condition spinal cord injury may occur from compression or vascular compromise. Anatomical images from radiographic studies usually show multiple levels of possible cord lesion, and thus SEPs are useful to assess whether a significant impairment of dorsal funiculi exists, and if so which are the functionally affected levels in the cord. Assessing these two points may prompt surgery, which is effective in preventing progression. Additionally, SEPs may provide and ancillary means to survey progression after surgery.

As a general rule, tibial nerve stimulation yields a greater number of abnormal results when compared to median nerve SEPs (Noël and Desmedt, 1980; Yu and Jones, 1985; Pertik and Fischer, 1987) but in most studies cubital nerve SEPs have not been tested (El-Negamy and Sedwick, 1979; Gaines, 1980; Sirvola *et al.*, 1981; Emerson and Pedley, 1986). Diagnostic yield is improved by using both median and cubital SEPs to adequately cover cord segments as lower as T1 levels. Besides, even if lower limbs are more sensitive (probably due to greater temporal dispersion of the afferent volley) they fail to localize the level of the trouble. In this respect, median *and* cubital SEPs are often imperative to correctly study this condition.

Since most of these patients are aged, and peripheral neuropathies of different etiologies are not uncommon in them, it is important to rule them out by obtaining normal peripheral (N7) and lumbar (N22) responses for lower limb, as well as a normal Erb's potential for upper limb SEPs. Delayed N20 or P40 absolute latencies are not acceptable as the sole evidence of central conduction trouble in the elderly.

As is the general rule for compressive lesions in the cord, SEPs may be abnormal in the absence of any sensory loss (Emerson, 1986; *and vide infra*). For lower limb stimulation the only abnormal pattern consistent with cervical myelopathy is a delayed or attenuated P40 with normal N22. When obtained, P40 is also abnormal, but this component may be not recordable in some normal elderlies. Different abnormal SEP patterns can be found after median or cubital stimulation. A delayed spinal N13 in posterior-to-anterior neck montages is highly suggestive of associated root compression. Absence or marked reduction of this component suggests either cord distortion or associated pluriradicular radiculopathy. A normal N13 but increased N13-P14 IPL, or abnormal P9/P14 amplitude ratio, is indicative of pathology in the upper cervical cord or at the cervicomedullary junction. The outmost expression of this localization is the "cervicomedullary" SEP pattern, with absent P14 and N20 but normal N13, which is almost pathognomonic of a lesion at the medullary junction or in the upper segments of the cervical cord (Mauguière and Ibañez, 1985).

When P14 is present, the P14-N20 IPL should be normal; otherwise a brainstem dysfunction must be suspected that can be related with spondylosis itself (via vascular involvement of the vertebro-basilary system) or due to

independent additional conditions.

It has been stated that SEP abnormalities in spondylotic myelopathy are not related to the duration of symptoms (Yu and Jones, 1985), but other reports have recently challenged this view (Perrin and Fischer, 1987).

D.3.2.2. Tumors of the cervical spinal cord. SEPs can be normal in spite of impaired sensations when the cord is infiltrated by the tumoral process, whereas the inverse situation (i.e. absent or clearly abnormal P14 and cortical components with clinically normal sensations) may be encountered in extrinsic tumoral compression of the cord, as in spondylotic compression (Mauguière *et al.*, 1985, and *idem supra*). SEPs are known to be very sensitive to spinal cord compression (Schramm *et al.*, 1984); in patients whose SEPs are absent preoperatively a latency shift of P14 and later components can be observed long *after* surgical decompression and return of normal sensations (Fig. 19, Mauguière and Bathez, 1985).

When the dorsal horn of lower cervical cord is infiltrated by the tumor spinal N13 can be absent, but this component is unaffected by compression of dorsal columns due to extrinsic space-occupying lesions. One exception to the latter statement is seen when the radiculo-spinal junction is directly affected by compression at the segmental levels stimulated. Usefulness of non-cephalic reference recordings is best illustrated by what was coined as the 'cervico-medullary' pattern (Mauguière, 1987) in which far-field P9 and spinal N11 and N13 are normal whereas far-field P14 and later components are absent or abnormal (Fig. 19, Mauguière *et al.*, 1983; Mauguière and Bathez, 1985). When P14 is not completely cancelled the P9/P14 amplitude ratio is abnormally high in such patients. This SEP pattern means that the volley of impulses ascending in the cervical dorsal columns is blocked or dispersed at the cervico-medullary junction; it can also be observed in brain dead patients (Aminoff and Cracco, 1980b, 1982). In all cases with bilateral 'cervico-medullary' SEP pattern a persisting P11 scalp far-field positivity can be confused with a brainstem P14. The recording of the spinal N13 helps in making the distinction between since P11 peaks earlier and P14 later than N13.

D.3.3. Multiple sclerosis (MS).

In this condition SEPs are mainly used as diagnostic tool (see Jones, 1982; Chiappa, 1983; Spehlmann, 1986 for reviews) but a recent report suggests that they could also be able to predict clinical changes during therapeutic trials (Nieuwe *et al.*, 1987). Since MS diagnosis is established on the basis of dissemination in time (relapses) and space (different subsystems involved) SEPs are recorded to demonstrate subclinical lesions in sensorimotor pathways. In this regard, their diagnostic yield (i.e. the proportion of abnormalities in clinically unaffected patients) is greater than that of BAEP, but slightly lower than VEPs (Mantagliaet *et al.*, 1976; Trojaborg and Petersen, 1979; Chiappa *et al.*, 1980; Green *et al.*, 1980; Fischer *et al.*, 1988). Lower limb SEPs yield more abnormal results than upper limb's, but they fail to show characteristic

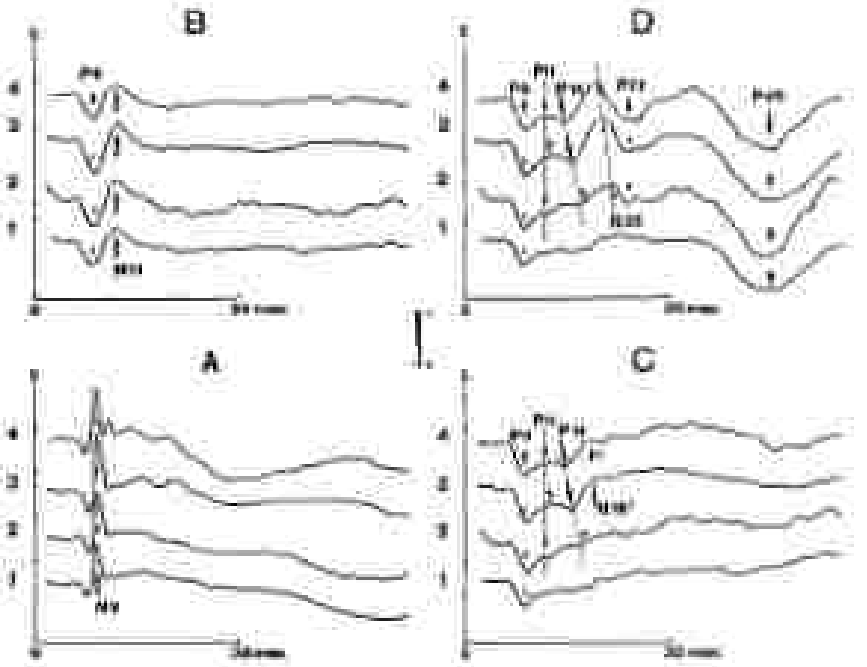


Figure 9. Intraoperative evolution of SSEPs in a patient with a neoplasm of the 3rd cervical cord. The patient was admitted with a Brown-Séquard syndrome under the left right dorsolateral right side hemiparesis, right tactile and pain/ position hypalgesia and arreflexia of the right hand, pain, impaired pain and thermal sensation [illegible] left side. Responses recorded at Erb's point are represented in A; those obtained at C6/C6 process are shown in B, and the ipsilateral and contralateral parietal responses are displayed respectively in C and D. Except for Erb's point tissue (frontal reference) all montages were obtained with a non-cephalic (mastoid) reference. Calibration marks represent 0.5 μV in A and 1 μV in B,C and D. For each derivation the numbered traces indicate the order of the successive records: 1A days after surgery; 2 months; 10 months and 4.1 years. In the first recording session normal responses were systematically obtained at Erb's point (peripheral N9) and at C6/C6 (spinal N13). On the scalp only the far-field P9 and the low cervical component P90 were present in the first session (1). Brainstem P14 and cortical N20-P27 were absent and only reappeared progressively, with delayed latencies and diminished amplitudes, from 2 to 10 months after surgery.

Montages recorded in session #1 correspond to [illegible] intramedullary SSEP patterns may indicate interruption of somatosensory impulses at the intramedullary level or very high in the cervical cord. Two particular points must be stressed (see (1) in Figure 9): (1) abnormal latencies can be observed long after surgical decompression of the cervical cord, and (2) late cortical components (in this case the P90 potential) may persist when all the subcortical or cortical responses are absent or altered. (From Mauguière & Hallett, 1985, with permission).

patterns of demyelination. Most previous reports give results in terms of percentage of abnormalities as a function of MS diagnostic class (see above references), but the actual relevant information to seek is the percentage of *diagnostically useful* recordings. Indeed SEPs are not useful in definite MS unless prognostic information is sought (Nuwer *et al.*, 1987); in possible and probable MS SEPs yield useful diagnostic indications when a) they demonstrate subclinical lesions in non-affected limbs, or b) when they show abnormalities suggestive of demyelination in affected limbs.

Typical SEP changes in MS are very similar to those seen in compressive pathology of spinal cord or brainstem, probably because in both cases the pathophysiology of waveform abnormalities is related to demyelination. Also in both cases abnormalities found in the absence of sensory symptoms. As a corollary of that it is not possible, on the basis of SEP studies alone, to distinguish between a compressive cord lesion and a demyelinating plaque.

In a series of 130 probable or definite MS patients studied with a non-cephalic reference (Garcia-Larrea and Mauguière, 1988) we found that far-field P14 was the most frequently affected component (more than 90% of abnormal SEPs). Using an ear reference Yamada *et al.*, (1986) also found that MS was the most frequent diagnosis in patients with abnormal P14. Abnormalities of P14 in MS usually consist of simultaneous delay and amplitude reduction, this latter parameter being quantified by means of the P9/P14 amplitude ratio (see normative data).

Combining latency measurements with amplitude ratios can result in a significant improving of the diagnostic yield. If only one criterion is being used, setting the limits at only 2SD over the mean implies that about 5% of normals will have abnormal values, which is unacceptable in MS. But if 2 criteria (non overlapping in normals) are used simultaneously it is conceivable to reduce the stringency of each one. It is then possible to consider abnormal the SEP if *both* latency and amplitude ratio measurements are beyond 2.5, or even 2 SD over the mean.

In about 70% of MS patients with abnormal SEPs attenuation and delay of P14 are simultaneously present, for temporal dispersion of afferent impulses is likely to desynchronize the potential. However, the degree of change of both parameters is not the same, and isolated P14 attenuation without latency shift can be seen (Fig. 20) as well as the reverse (Fig. 21). Figure 20 illustrates a case of isolated amplitude reduction of P14 which was followed one year later by the simultaneous alteration of latencies and amplitudes. Figure 22 depicts the most common kind of abnormal SEP found in MS patients, with normal P9, extremely desynchronized P14 and delayed N20. This pattern, when recorded in a patient with relapsing neurological symptoms, is highly suggestive of MS.

Although almost all kind of abnormal SEP pattern can be seen in this condition, some of them are infrequent enough to cast a doubt on this diagnosis. One of them is an abnormal or absent spinal N13 with *normal* far-field potentials and N20. This abnormality is seldom true of MS, but can

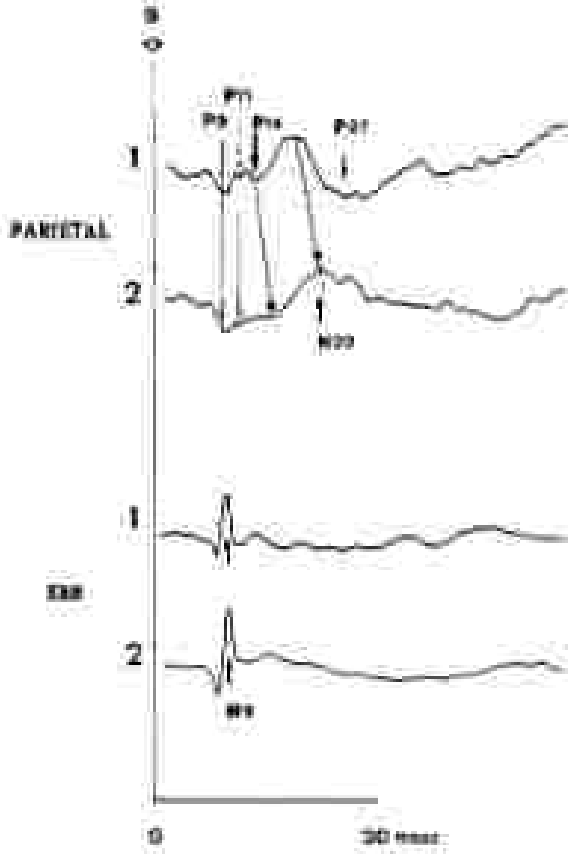


Figure 39. Evolution of SEPs in ML. [illegible] P14 amplitude decrease in amplitude and latency abnormalities. In the first recording session (1) P14 amplitude was decreased, but all interpeak latencies were still within normal limits. In the case of patient's MN, Peripheral stimulation one year later (2) disclosed that P14 was still of diminished amplitude, but P9-P14 and P14-N20 interpeak latencies had also become abnormal. (Reproduced from Garcia-Larrea & Mauguière, 1988, by permission)

be seen in infiltrating spinal cord tumors (Mauguière *et al.*, 1985). Also, MS should not be first choice diagnosis if signs of dorsal column dysfunction in one limb are not accompanied by SEP abnormalities at all.

Lower limb SEPs abnormal patterns in MS are a delayed P40 with absent or delayed subcortical P30. Lumbar N22 may or may not be recorded, depending on the localization of demyelinating plaques, but it is more frequently present than absent. Amplitude ratios for distal SEPs in MS have also been described by Delwaide and colleagues (1985), but their utility in large series of patients have not yet been established.

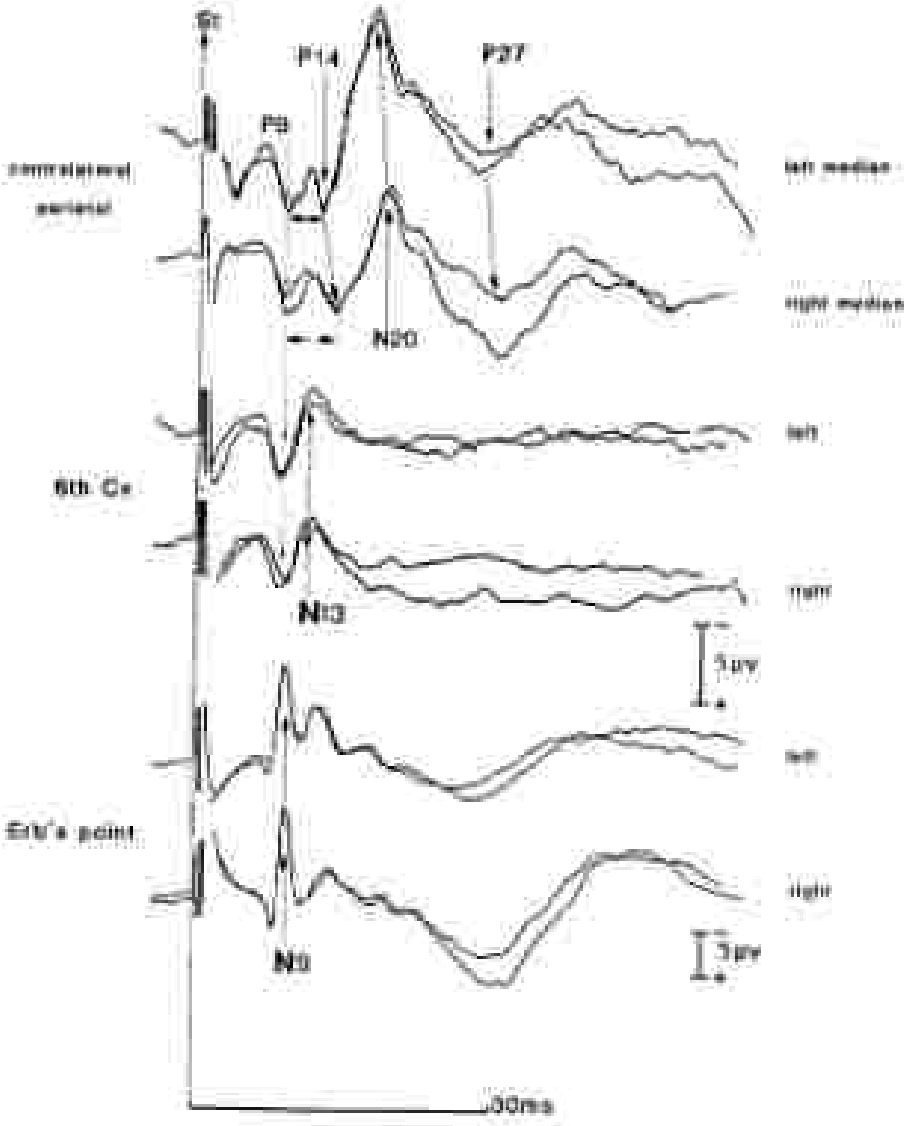


Figure 2. Delayed SEP components in MS. From bottom to top: Erb's point, left cervical and contralateral parietal responses to left and right median stimulation. The Erb's points had left cervical responses after right and left median nerve stimulation are mostly symmetrical, but there is a significant increase of the P9–P14 interpeak latency after left stimulation (top trace) with normal amplitude of P14. The P14–N20 interval is, however, only slightly modified, suggesting a normal thalamo-parietal connection. Although it is the earliest a P_{27-30} complex is seen, it has been labelled "P24" for clarity. (Reproduced from Garcia-Larrea & Mauguière, 1988, by permission)

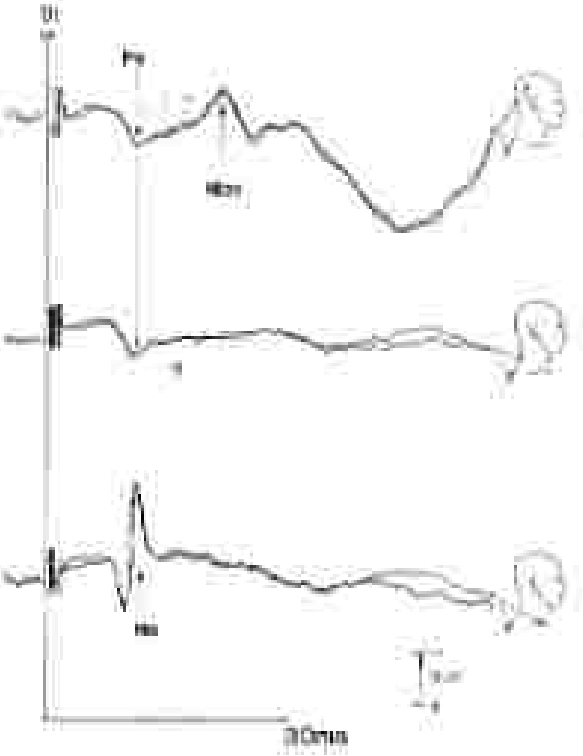


Figure 22. Abnormal latencies and amplitude ratios in a case of probable MS. Responses to left median nerve stimulation, bottom trace Erb's point, middle trace C#6 spinous process, upper trace contralateral parietal. Only the N9 and P9 potentials, reflecting the ascending volley in the brachial plexus are normal; the cortical negative wave N20, although delayed, is clearly delineated on two successive traces. In between the cortical response N13 is absent, and P14 is desynchronized with abnormal amplitude and latency. (Reproduced from Garcia-Larrea & Mauguière, 1988, by permission)

D.3.2. Brainstem lesions

SEP studies in brainstem lesions depend on a reliable assessment of $P_{(7-9)}$ potential. There are no large series of well-localized brainstem lesions studies with SEPs, most reports are anecdotal and have been devoted to establish the origin of SEP components rather than studying their clinical utility (Nakanishi *et al.*, 1983; Kaji and Sumitomo, 1985; Delastre *et al.*, 1986). From our own series of 25 patients with CT-proven brainstem lesions (Mauguière *et al.*, 1988) no definite electro-clinical correlations could be made between the aspect of the P14 potential and lesion site except that, in six patients, interruption of the spino-thalamic tract in medulla oblongata (Wallenberg's syndrome) did not modify P14 or N20, thus confirming the earlier data of Halliday and Wakefield (1963). From 16 patients whose lesion was located

in the pons or pedunculi 12 had ipsilateral cortical responses, but only in 5 of them it was found as abnormal or absent P14; this suggests that P14 must be generated, at least partly, in the lower part of the brainstem. Further conclusions from studies in patients would be risky at the present state of the art mainly because CT imaging of axial brainstem lesions are often not accurate enough to assess lesion site. Routine measurement of P9/P14 amplitude ratio combined with NMR studies are needed in the future; up to now there is only one report of one NMR documented pontine lesion with abnormal P14 (Delgado *et al.*, 1986).

D.3.4. Thalamic and capsulo-thalamic lesions.

In thalamic or capsular lesions interrupting the somatosensory pathways both parietal (N20, P27) and frontal components (P22, N30) are absent on the damaged side with preserved scalp-fixed-(left) positivities including P14 (Nakanishi *et al.*, 1978; Mauguière *et al.*, 1982, 1983b; Siditi *et al.*, 1983; Yamada *et al.*, 1985; Graff-Radford *et al.*, 1985). The N18 diffuse negativity persists in this condition (Mauguière *et al.*, 1983b; see Fig. 23). In our series of 90 cases we found that reduced or absent cortical SEPs were highly correlated to loss or impairment of tactile and joint sensations (Table 3) but much less clearly to vibration sensory loss and not at all to pain and temperature anesthesia.

Similarly the occurrence of spontaneous pains or paresthesiae was not associated to a peculiar SEP pattern (Table 4). This latter finding suggests that there is no simple relation between thalamic pains and deafferentation of area S1 evidenced by loss of SEP primary cortical components, and that study of later components, some of which have proved to be related to pain stimulation, will probably yield more insight in the field of deafferentation pain.

In patients with pure thalamic non-hemorrhagic stroke a fairly good correlation was found between SEP abnormalities and CT scan data. Cortical

Table 4. SEP findings and thalamic pain

	Parietal N20–P22			Frontal P22–N30		
Pain or paresthesia	Normal	Abnormal	Absent	Normal	Abnormal	Absent
Pain (n = 31)	10	7	11	6	2	11
Paresthesia (n = 14)	4	7	3	8	4	2
None (n = 35)	11	12	20	17	7	11
Total (80) (n = 80)	25	21	44	31	13	36
(%)	(27.8)	(23.3)	(48.9)	(34.4)	(14.5)	(51.1)

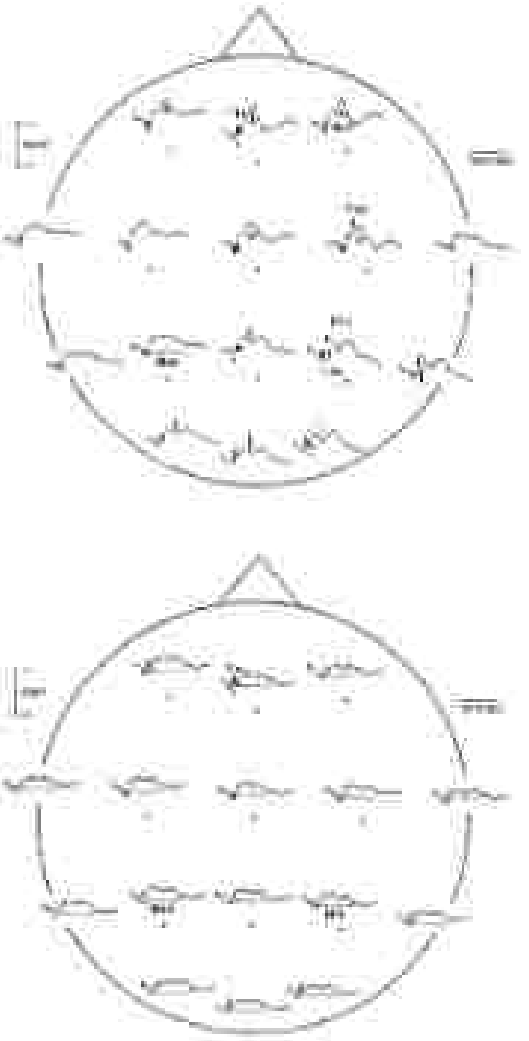


Figure 23. SEPs in a case of nonruptured hemorrhage. Several years after the neurological incident CT-scan showed a large hypodense area in the left parietal region. The patient presented a right spastic hemiplegia with loss of extension and abduction on the right side. After stimulation of the left median nerve SEP responses are normal (upper trace figure), whereas stimulation of right median nerve showed absence of a frontal component, with normal bi-field positivities and a persisting diffuse N18 negativity (lower trace figure). This SEP pattern, with complete abolition of all parietal and frontal components, indicates complete interruption of somatosensory impulses at the thalamic or thalamocortical radiations. (From Mauguière *et al.*, 1983, by permission).

SEPs were constantly absent or abnormal in postero-lateral infarctions of the geniculo-thalamic artery territory with loss of touch and position senses and they were normal in infarctions of other thalamic arterial territories. In capsular infarcts in the territory of anterior choroid artery (13 cases) or in thalamo-capsular hematomas (4 cases) we did not observe any clear correlation between CT scan and SEP findings. In such patients the degree of hemispheric somatosensory dysfunction cannot be accurately predicted from CT scan images. SEP investigation is of peculiar importance in patients with thalamic neglect (Watson and Heilman, 1979) since one of the criteria on which this concept is based is that both hemispheres are normally connected to peripheral sensory receptors. Minimal sensory loss, difficult to evidence even after a careful clinical examination, can be definitely ascertained by SEP recording in some of these patients.

D.3.3. Cortical lesions.

When the lesion is close to the cortex it may damage selectively pre- or post-

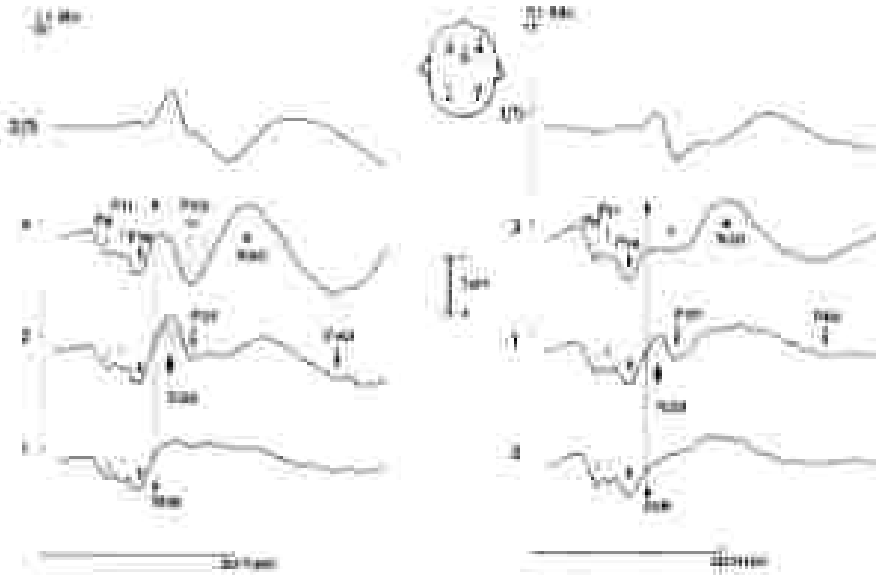


Figure 24. Loss of frontal P22 in a patient with a left infarction. This 76 year-old patient with a history of ischemic strokes of the right hand and arm presented a right hemiparesis without sensorimotor loss when SEPs were recorded. A small left hypodense lesion without mass effect was disclosed on CT scan and proved to be a grade I astrocytoma on biopsy. After stimulation of the left median nerve (left) a normal response was recorded, P22. After stimulation of the right median nerve (right) the frontal P22 is absent, parietal N20 is smaller than on the normal side but this reduction is not significant. Traces obtained with a parietal (or Fz) derivation (2, 3 and 1-2) only show an equivocal amplitude reduction of the responses. (From Mauguière et al., 1987; by permission).

rolandic cortex or thalamo-cortical fibres in the corona radiata. This dissociated loss of pre- or post-rolandic components is more likely to occur in this condition than in capsulo-thalamic lesions. Our initial observation of persisting frontal P22 and N30 with absent parietal N20 and P27 in parietal lesions causing astereognosis without hemiplegia (Mauguière *et al.*, 1983c) was recently confirmed by Shimp *et al.* (1986) who reported a similar observation after excision of the SI area in man. Dissociated findings were also reported during surgical monitoring at endarterectomy (Gigli *et al.*, 1987) and also in transient cerebral ischemia by de Weerd *et al.*, (1985), all SEP abnormalities in this latter work being detected in frontal, but not in parietal leads. These finding suggest that frontal and parietal potentials might be triggered via independent thalamo-cortical pathways, a conclusion which is also supported by the notion that frontal cortical lesions causing hemiplegia without sensory loss can reduce the pre-rolandic components without change of the parietal response (Fig. 24). Dissociated loss of cortical components was found in 16 patients from the group of 72 cases selected for this study. In the others, either the lesion spared the parietal and the perirolandic cortices and the responses were normal with no somatosensory loss, or it caused hemiplegia and hemianesthesia because of damage to the whole rolando-parietal region and SEPs were the same as in interruption of somatosensory pathways at thalamic level (*viz.* no cortical components at all, but preserved far-field and N18 over the damaged hemisphere.

After Bruetton's experiments on SEP recovery after middle cerebral artery occlusion in monkeys (Bruetton *et al.*, 1970) several investigators have reported a better vital and/or functional prognosis for stroke patients with persistence or partial recovery of SEPs (Crespi *et al.*, 1982; La Joie *et al.*, 1982; Parisi *et al.*, 1983). De Weerd and co-workers (1985) have reported that only one patient out of 18 with minor cerebral ischemia achieved complete SEP recovery in spite of good clinical evolution. This would suggest that SEP studies can detect subclinical abnormalities in patients suspected of having suffered from reversible stroke on account of their history alone.

D.3.b. Enhanced somatosensory responses.

Since the earliest description by Dawson in 1940 the relation between myoclonus-related EEG spikes and giant SEPs in patients with dyssynergia cerebellaris myoclonica, progressive myoclonic epilepsy or focal reflex myoclonus has not been fully elucidated (see Obeso *et al.*, (1985) and Shibasaki *et al.*, (1985 a and b) for recent reviews of the topic). A certitude is that, in patients with myoclonus, giant SEPs can be recorded in the absence of myoclonus-related spikes and vice-versa; moreover both abnormalities may be absent. Thus patients who apparently have similar clinical symptoms can show different SEP abnormalities. Shibasaki and Kuroiwa (1975) employed the technique of back averaging the EEG prior to the myoclonus (jerk-locked averaging) to establish that spontaneous myoclonus might be related to an abnormal cortical discharge even though the surface EEG showed no abnor-

mality. The giant SEP is made of a P25–N30 complex (Shibasaki and Kuroiwa, 1975). The interval between the peak of P25 on the back-averaged cortical spike and the onset of the myoclonus is in the order of 20 ms in the arm, consistent with rapid conduction from motor cortex to muscle down to a direct corticospinal pathway (Morton and Morton, 1980). This observation supports the view that in patients with cutaneous reflex, pure stretch or distal action myoclonus, who exhibit giant SEPs and myoclonus-related spikes the underlying disorder is an abnormal cortical response to afferent impulses ('pyramidal myoclonus' of Halliday, 1967); whereas in all other cases the pathophysiology of myoclonic jerks is different. Thus the finding of giant SEPs is of diagnostic significance in the management of myoclonus patients.

When it can identified the parietal N20 potential has normal latency and amplitude in most patients with myoclonus (Mauguière *et al.*, 1981; Rothwell *et al.*, 1984; Shibasaki *et al.*, 1985a; Obeso *et al.*, 1985). Similarly we found that P14 was normal in such patients (Mauguière *et al.*, 1981). The normal size of the N20 component indicates that the sensory input into the cortex as well as the primary cortical response itself are not grossly abnormal. The question whether giant SEPs correspond to enlarged components of the normal

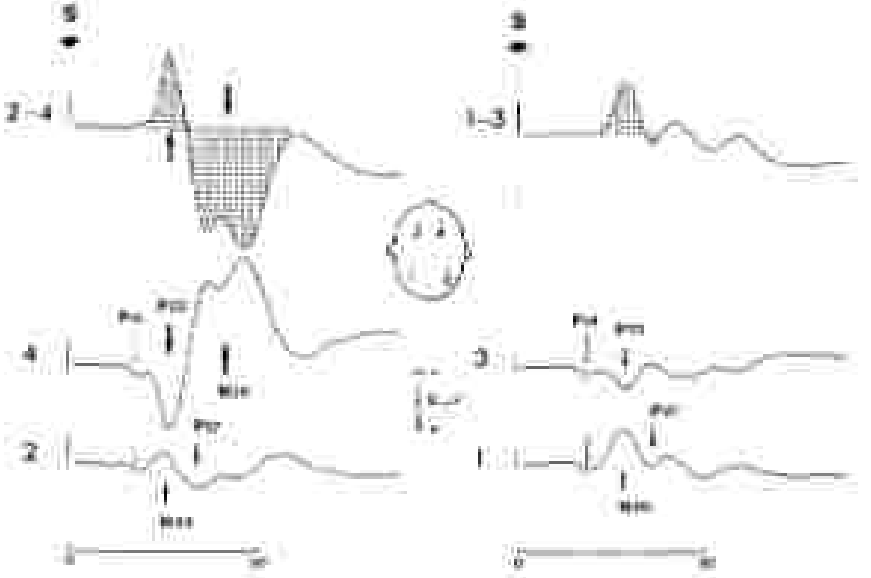


Figure 12. Selective enhancement of the precocious P22 and N30 components in a patient with a right midline, non-specific glioma. This figure shows that enhancement of SEP frontal components may be observed in other conditions than action myoclonus. The 57 year-old female patient had a progressive left hemiparesis but no seizures or myoclonus and no somatosensory loss. After stimulation of the affected left side (Left traces) only the frontal components are enhanced compared to those obtained on the normal side (Right traces). With the parietal to frontal derivation (2–4 and 1–3) it is not possible to know which of the pre- or post-rolandic components are enhanced on the damaged side. (From Mauguière et al., 1987) by permission.

response or to additional events which are not present in normal subjects has not been answered. Preliminary data from sequential spatial mapping studies of SEP to finger stimulation suggest that the spatio-temporal distribution of cortical SEPs is normal for both N20 and P22. This latter component however is immediately followed by the giant response which has a dipolar configuration.

Enhanced SEPs recorded over the damaged hemisphere in 9 of our patients with various cortical or cortico-subcortical lesions (3 tumours, 3 infarcts, 1 hematoma, 1 post-traumatic atrophy and 1 angioma). In all of these patients response enhancement was moderate and the usual cortical components could be easily identified. Myoclonus triggered by stimulations was observed in only one of them and none had somatosensory loss. In five cases only frontal P22 and N30 were enhanced (Fig. 25). Thus both electrophysiological characteristics and clinical context are very different for myoclonus-related giant potentials and enhanced responses due to focal cortical lesions. In these latter quite different phenomena, such as differences in medium conductivity or anatomical distortion of generators could be primarily involved.

D.3.7. Coma and brain death

Evoked potentials studies in comatose patients are usually undertaken for both diagnostic and prognostic purposes. In the present state of the art some conclusions may be safely accepted for routine application of SEPs in coma:

a) bilateral absence of parietal N20 is associated with a very poor prognosis, reaching almost 100% of death or persistent vegetative state (PVS) in published series (Greenberg *et al.*, 1977, 1982; Goldie *et al.*, 1981; Hume and Cant, 1981; Narayan *et al.*, 1981; Cant *et al.*, 1986). Presence of reliable peripheral potentials is imperative before attributing bilateral loss of cortical N20 to extensive brain damage. Anesthetic agents do not usually hamper SEP interpretation since short-latency evoked potentials (BAEPs and SEPs) have proved highly resistant to barbiturates at the doses currently used in ICU (Hume *et al.*, 1979; Sutton *et al.*, 1982; Drummond *et al.*, 1987; and see also chapter on BAEPs). Nevertheless, the recent observation of transient BAEP abolition in comatose patients under an anesthetic combination of lidocaine/thiopental (Garcia-Larrea *et al.*, 1988) suggests careful evaluation of drug levels, especially when using additive combinations, before establishing a prognostic on the basis of bilateral SEP abolition.

b) the mere preservation of N20 does not warrant a favorable outcome (Hume and Cant, 1981; Goldie *et al.*, 1981; Cant *et al.*, 1986). This is probably due to the fact that N20 is a primary cortical event that may persist in spite of large hemispheric damage. Evaluation of later SEP components (up to 200 msec) may prove useful to by-pass this limitation, and several authors have reported good correlation between the number of waves present within this period and both vital and functional outcome (De la Torre *et al.*, 1978; Lindsay *et al.*, 1981; Greenberg *et al.*, 1982). Unfortunately, both anesthetic drugs and body temperature variations are known to affect much more severely

late that early SEP components, and this may seriously hamper reliable interpretation of these potentials.

Early SEP studies in brain death were conflicting (Hume *et al.*, 1978; Anziska and Cracco, 1980b) mainly because of the lack of homogeneity in the parameters used for patient selection. When criteria include the presence of a flat EEG and absence of spontaneous respiratory effort (Goldie *et al.*, 1981; Bolsh and Chokroverty, 1987; Mauguière, 1987) cortical N20 is systematically absent. Brainstem P14 is usually absent in patients fulfilling these criteria but may be total or partially present if a part of the lower brainstem is still functional. Of course, persistence of a reproducible P14 potential is inconsistent with the diagnosis of brainstem death. In some cases a persisting P11 in non cephalic reference recordings can be confused with brainstem P14, since P11 peaks earlier than spinal N13, cervical recordings are useful to ascertain brainstem cessation of function in such cases (Buchner *et al.*, 1986; Mauguière, 1983, 1987).

Conclusions

SEPs are to be viewed as a complement to (not a substitute for) clinical examination. There is no standard recording protocol for them; stimulation site, number and disposition of electrodes and reference point are all strongly dependant on previous clinical history, neurological findings and purpose of the examination. Also, changes may be introduced in the recording protocol as a function of the results that are being obtained.

Every laboratory must create its own normative database. Interpretation on the basis of others' data is not acceptable since 'normal' limits of amplitudes and latencies depend on technical settings, especially filters and amplifiers. Besides this compulsory aspect, establishing a control data group is an excellent way to get familiar with recording techniques and equipment problems.

EPs are still an evolving field. Concepts underlying short-latency SEP interpretation have greatly changed over the past 10 years, and it would be presumptuous to think that a definitive knowledge of these responses has been achieved. What has been exposed in this chapter corresponds to current concepts on SEP origin and interpretation, supported by strong experimental evidence but also subject to change as any field in medicine. Continuous research in basic neuroscience, biophysics and modelization, but above all continuous learning from our patients and their clinical problems should create the basis for new insights in this field.

References

Aminoff B.O, Victor M, Principles of Neurology (2nd ed.), McGraw-Hill, New York, 1985.

Allison T, Goff WR, Williamson PD, VanGilder JC. On the neural origin of early components of the human somatosensory evoked potential. In: Desmedt JE (ed.), Clinical uses of cerebral, brainstem and spinal somatosensory evoked potentials. Progr Clin Neurophysiol Vol 7, Karger, Basel, 1980, pp 51–68.

Allison T. Scalp and cortical recordings of spinal somatosensory cortex activity in median nerve stimulation in man. Ann NY Acad Sc, 1982; 377–678.

Amantini A, Grassi B.W. Short-latency somatosensory evoked potentials. Studies in patients with focal neurological disease. Electroencephalo Neurophysiol, 1980a; 49: 227–239.

Amantini B, Grassi B.W. Short-latency somatosensory evoked potentials in brain dead patients. Arch Neurol 1980b; 37: 222–225.

Amantini A, Grassi B.W. Short-latency spinal somatosensory evoked potentials to median nerve stimulation in patients with diffuse neurologic disease. Neurology 1983; 33: 989–997.

Barral P, Gonnaud J, Boisseau C, Pialoux J, Rocher P. The relationship between median nerve somatosensory evoked potential latencies, cubitus valgus and growth parameters in young children. Electroencephalo Clin Neurophysiol 1987; 68: 190–196.

Bates DM, Chakravarty S. Short-latency evoked potentials in brain-dead patients. Electroencephalo clin Neurophysiol 1987; 68: 75–78.

Beaudet G, Gosselin A, Guillard A, Mikol J, Lacour P. Mylopathie du Friedreich avec anomalies spectroscopiques sus-médullaires, Rev Neurol 1992; 148: 443–450.

Brenner D, Lipton J, Kaufman L, Williamson SJ. Somatotopically evoked magnetic fields of the human brain. Science, 1978; 199: 81–83.

Brierley MM, Symon L, Copeland BR. Recovery of the cortical evoked response following temporary middle cerebral artery occlusion in baboons. Relation to local blood flow and PO_2. Stroke, 1978; 9: 2–8.

Bruhn S. Neurological anatomy. Oxford University Press, 1989 chapter 12.

Buchsbaum B.L. In: Daniels H, Daniels DR (eds), Average Evoked Potentials. U.S. Government Printing Office, Washington, DC, 1968, 59–84.

Bruno WP, Daube JT. Sensory evoked potentials in Guillain-Barré polyneuropathy. J Neurol Neurosurg Psychiat 1984; 47: 288–291.

Bruno AM, Chauchereau G, Bergé JC, Bory B. Valeurs de conduction sensitive nerveuse des nerfs médian et cubital chez l'enfant de la naissance à 15 ans. Rev. EEG Neurophysiol 1994; 14: 69–73.

Buchner H, Fetter A, Steg M, Hacke W. Evoked potential monitoring within acute Cerebrovascular Disease. Generators of BAEP and spinal SEP. In: Kunze K, Zangemeister WH, Aeri A (eds), Clinical problems of brainstem disorders, Georg Thieme Verlag Stuttgart New York, 1984, pp 139–151.

Cauhépé J, Pha V, Georgesco M, Rabineau B, Rondot M. La mensuration des potentiels évoqués somatosensitifs corticaux. Rev. EEG Neurophysiol 1985; 15: 1–11.

Caird BE, Hunt AL, Ashton JA, Shaw KA. The assessment of severe head injury by short latency somatosensory and brainstem auditory evoked potentials. Electroencephalo Clin Neurophysiol 1986; 65: 183–189.

Chiappa KH, Harrison JL, Brooks EB, Young PB. Brainstem auditory evoked responses in 200 patients with multiple sclerosis. Ann Neurol 1980; 7: 135–143.

Chiappa K. Evoked potentials in Clinical Medicine. Raven Press, Boston, 1983.

Conti B, Meglio M. Cortical neuralgia or thalamic sensory syndrome in the spinal cord by segmental, ascending and descending ischemia. Appl Neurophysiol 1985; 48: 315–320.

Cohen LF, Van Meenen E, Heimans GJ, Van Der Heyden BR, Dirven C. SSEP abnormalities in patients with multiple sclerosis. Acta Neurochir Suppl, 1988; 70: 31–41.

Courtois Ph. L'exploration des voies sensitives par les potentiels somatosensitifs provoqués dans les lésions de moelle cervicale. Thèse de Médecine, Université de St. Etienne, (France), 1989, 201 p.

Cracco JB, Cracco RQ. Somatosensory evoked potential in man: preliminary results. Electroencephalogr Clin Neurophysiol 1976; 40: 729–734.

Cracco RQ. Somatosensory evoked potential in man: far-field potentials. Electroencephalogr Clin Neurophysiol 1978; 44: 382–385.

Cracco RQ, Cracco JB. Somatosensory evoked potential in man: upper extremity. Electroencephalogr Clin Neurophysiol 1978; 45: 415–426.

Desmedt JE, Cheron G. Central somatosensory evoked potentials in normal and pathological man: modification of nerve input, skin temperature, electrode position, supramarginal lesions and sleep. Electroencephalogr Clin Neurophysiol 1980; 49: 221–254.

Desmedt JE, Cheron G. Central somatosensory evoked potentials in normal and pathological man. Ann Neurol 1981; 9: 394–413.

Desmedt JE, Cheron G. Somatosensory evoked potentials in normal aging man: precentral and postcentral components depend differently on peripheral conduction velocity, joint angles and muscular force. Electroencephalogr Clin Neurophysiol 1981; 52: 553–570.

Desmedt JE, Cheron G. Somatosensory evoked potentials to finger stimulation in healthy octogenarians and in young adults: wave forms, scalp topography and transit times of parietal and frontal components. Electroencephalogr Clin Neurophysiol 1981; 52: 624–644.

Desmedt JE, Cheron G. Prefrontal somatosensory evoked potentials in the primate brain: towards the physiological decoding of neurological disorders. Electroencephalogr Clin Neurophysiol 1981; 51: 253–266.

Desmedt JE, Cheron G. Central somatosensory evoked potentials in normal and pathological man: modification of nerve input, skin temperature, electrode position, supramarginal lesions and sleep. Electroencephalogr Clin Neurophysiol 1981; 52: 289–310.

Desmedt JE, Cheron G. Non-cephalic reference recording of early somatosensory potentials to finger stimulation in adult or aging man: differential effects of widespread N18 and contralateral N30 from the prerolandic P22 and N30 components. Electroencephalogr Clin Neurophysiol 1981; 52: 553–570.

Desmedt JE, Tomberg C, Tarantola J, Huguenin P. Precentral, thalamic and cervical components of human somatosensory evoked potentials dissociated by vibration and voluntary isometric effort. Electroencephalogr Clin Neurophysiol 1983; 56: 272–282.

Desmedt JE, Cheron G. Central somatosensory evoked potentials to finger stimulation in healthy octogenarians and in young adults: wave forms, scalp topography and transit times of parietal and frontal components. Electroencephalogr Clin Neurophysiol 1980; 50: 404–425.

Desmedt JE, Cheron G. Prefrontal somatosensory evoked potentials in the primate brain: towards the physiological decoding of neurological disorders. Electroencephalogr Clin Neurophysiol 1981; 51: 253–266.

Desmedt JE, Cheron G. Central somatosensory evoked potentials in normal and pathological man: modification of nerve input, skin temperature, electrode position, supramarginal lesions and sleep. Electroencephalogr Clin Neurophysiol 1981; 52: 289–310.

Desmedt JE, Cheron G. Non-cephalic reference recording of early somatosensory potentials to finger stimulation in adult or aging man: differential effects of widespread N18 and contralateral N30 from the prerolandic P22 and N30 components. Electroencephalogr Clin Neurophysiol 1981; 52: 553–570.

Desmedt JE, Tomberg C, Tarantola J, Huguenin P. Precentral, thalamic and cervical components of human somatosensory evoked potentials dissociated by vibration and voluntary isometric effort. Electroencephalogr Clin Neurophysiol 1983; 56: 272–282.

Desmedt JE, Cheron G. Spatial and far-field components of human somatosensory evoked potentials to proximal digital stimulation analysed with nonuniform dipolar and non-cephalic reference recording. Electroencephalogr Clin Neurophysiol 1983; 56: 635–651.

Desmedt JE, Nguyen TD. Bit-mapped colour imaging of the potential fields of propagated and segmental subcortical components of somatosensory evoked potentials in man. Electroencephalogr Clin Neurophysiol 1988; 69: 1–7.

Desmedt JE, Bourguet M. Colour imaging of parietal and frontal somatosensory potential fields evoked by stimulation of median or posterior tibial nerve in man. Electroencephalogr Clin Neurophysiol 1988; 69: 1–17.

Dimitrijevic MR, Lesser LE, Lehmann D, Rychewski A. Evoked spinal cord and nerve root potentials in humans using a multichannel recording technique. Electroencephalogr Clin Neurophysiol 1978; 45: 337–340.

Ebner A, Dietzel G. Prognostic and potential importance of subcortical SEPs: A comparison between pathological and pharmacologically induced conditions. Electroencephalogr Clin Neurophysiol 1988; 71: 170–176.

Evans A, Humphreys P. The Gilles-Barre syndrome: A clinical and electrophysiological study of 25 cases. Arch Neurol 1978; 35: 438–443.

Eisen A, Hilker G. Sensory nerve stimulation and evoked cortical potentials. Neurology 1980; 30: 1047–1100.

Eisen A, Odusote K. Central and peripheral conduction times in multiple sclerosis. Electroencephalogr clin Neurophysiol 1980; 49: 253–267.

Eisen A, Hutnik M, Moll A. Evaluation of radiculopathies by segmental stimulation and somatosensory evoked potentials. Can J Neurol Sci 1983; 10: 159–163. Eisen A. SEPs in the evaluation of disorders of the peripheral nervous system. In: Cracco RQ, Bodis-Wollner I (eds.), Evoked Potentials (Frontiers in clinical Neuroscience, Vol. 3) Alan R Liss Inc, New York, 1986; pp 409–417.

Emerson RG, Sayal M, Pedley T. Somatosensory evoked potentials following median nerve stimulation. I: The cervical components. Brain 1988; 111: 49–82.

Emerson RG, Pedley TA. Effects of cervical spinal cord lesions on early components of the median SEP. Neurology 1988; 38: 26–30.

Erwin C. Comparison on the human evoked spinogram recorded from the vertebral, epidural and subdural levels. Electroencephalogr Clin Neurophysiol 1978; 44: 688–696.

Feinleib G. The determination in post. Brain's 1977; 16: 1–36.

Gassel T. Somatosensory evaluation from and peripheral, cervical and cortical evoked potentials in patients with cervical spondylosis. J Neurol Neurosurg Psychiat 1980; 43: 691–698.

Gassel T. Exogenic and non-exogenic components of the human cortical evoked response. J Neurol Sci 1982; 55: 211–226.

Gómez-Larrea L, Mauguière F. Latency and amplitude changes of P14 in multiple sclerosis. Electroencephalogr Clin Neurophysiol 1988; 71: 185–186.

Gómez-Larrea L, Artés A, Bertrand O, Pernier J, Mauguière F. Transient drug-related abolition of BAEPs in coma. Neurology 1988; in press.

Gökün ZB. Somatosensory evoked potentials in healthy subjects and in patients with lesions of the nervous system. Ann NY Acad Sci 1986; 478: 43–142.

Gilliatt RW. Nerve conduction in human and experimental neuropathies. Proc Royal Soc Med 1968; 58: 899–901.

Grigg GL, Carmelo M, Maccioni MO, Zanelo F, Lassonde F, Rossi G, PM. Monitoring of subcortical and cortical somatosensory evoked potentials during craniocervical compression with steady pressure levels. Electroencephalogr Clin Neurophysiol 1987; 66: 424–432.

Grimes JL, Worth RM, Bonfiglio PJ, Hall PV, Maccard GM. Evoked responses in the diagnosis of thoracic outlet syndrome. Surgery, 1980; 89: 85–93.

Gulf GD, Mamourian V, Allison T, Goff WR. The scalp topography of human somatosensory and auditory evoked potentials. Electroencephalogr Clin Neurophysiol 1977; 42: 42–58.

Grubb WG, Chopra KH, Young RR, Symko EH. Anisotropy, auditory and short-latency somatosensory evoked responses in brain death. Neurology 1981; 31: 268–270.

Graf-Radford NR, Damasio H, Yamada T, Eslinger PJ, Damasio AR. Nonhaemorrhagic thalamic infarction: Clinical, neuropsychological and electrophysiological findings in four anatomical groups defined by computerized tomography. Brain 1985; 108: 485–516.

Cioni JD, Pratt R, Wardhaw NG. Short-latency somatosensory evoked potentials in MS. Comparison with auditory and visual evoked potentials. Arch Neurol 1988; 37: 630–633.

Greenberg RP, Mayer DJ, Becker DP, Miller JD. Localization of brain lesions in human severe head trauma with multimodality evoked potentials. J Neurosurg 1977; 47: 130–137.

Greenberg RP, Newton FG, Becker DP. The somatosensory evoked potential in patients with somatosensory head injury. Outcome prediction and monitoring of cerebral function. Ann NY Acad Sci 1982; 338: 453–469.

Halliday AM. The electrophysiological study of neurological man. Brain 1967; 90: 261–284.

Halliday AM, Wakefield GS. Cerebral evoked potentials in patients with demonstrable sensory loss. J Neurol Neurosurg Psychiat 1963; 26: 213–218.

Harding AE. Early onset cerebral ataxia with retained tendon reflexes. A clinical and genetic study of a disorder distinct from Friedreich's ataxia. J Neurol Neurosurg Psychiat 1981; 44: 565–568.

Hari R, Reinikainen K, Kaukoranta E *et al*. Somatosensory evoked magnetic fields from SI and SII in man. Electroenceph Clin Neurophysiol 1984; 57: 254–263.

Hashimoto I, Iguchi M, Hirata K, Ende S, Fukuda K, Tamura Y, Mori A, Miyao M. Short-latency somatosensory evoked potentials in children. Brain Dev 1983; 5: 389–396.

Hume AL, Cant BR, Shaw NA. Cortical somatosensory conduction time in comatose patients. Ann Neurol 1979; 5: 179–184.

Hume AL, Cant BR. Conduction time in central somatosensory pathways in man. Electroenceph Clin Neurophysiol 1978; 45: 361–375.

Hurtunen J, Kaukoranta E, Hari R. Cerebral magnetic response to stimulation of tibial and ulnar nerves. J Neurol Sci 1987; 78: 43–54.

Iannetti Y, Buchthal F. Segmental sensory conduction determined by potentials recorded from cervical spinal nerves. Brain 1975; 100: 721–748.

Iannetti P, Schwartz D, Chokroverty A, Feldman D. Somatosensory and brainstem auditory evoked response abnormalities in a family with Friedreich's ataxia. Electroenceph Clin Neurophysiol 1982; 53: 244–252.

Jeannerod D, Sedan M, Margairaz F. (in preparation).

Jeje WJ, La, Reddy NM, Mehta Z. Somatosensory evoked potentials: their predictive value in right hemiplegia. Arch Phys Med Rehab 1982; 63: 223–229.

Jones SJ, Small M. Spinal and intracranial evoked potentials following stimulation of the posterior tibial nerve in man. Electroenceph Clin Neurophysiol 1978; 44: 299–308.

Jones SJ, Barnaji M, Halliday AM. Peripheral and central somatosensory nerve conduction defects in Friedreich's ataxia. J Neurol Neurosurg Psychiat 1980; 43: 495–503.

Jones EJ, Wise Pacey CR, Lamb A. Diagnosis of brachial plexus traction by sensory nerve action potentials and somatosensory potentials. Injury 1981; 12: 356–362.

Jones SJ. Somatosensory evoked potentials. The abnormal waveforms in AM Halliday (Ed) Evoked Potentials in Clinical Testing. Churchill Livingstone 1982, pp 429–478.

Jones SJ, Edgar MA, Ransford AO. Sensory nerve conduction in the human spinal cord. Epidural recordings made during surgical operations. J Neurol Neurosurg Psychiat 1987; 50: 641–651.

Kakigi R, Shibasaki H, Hashimoto A, Kuroiwa Y. Short latency somatosensory evoked spinal and scalp-recorded potentials following posterior tibial nerve stimulation in man. Electroenceph Clin Neurophysiol 1982; 53: 402–411.

Kakigi R, Shibasaki H. Scalp topography of the short-latency somatosensory evoked potentials following posterior tibial nerve stimulation in man. Electroenceph Clin Neurophysiol 1983; 56: 426–437.

Kakigi R, Jones SJ. Influence of conscious attention on somatosensory evoked potentials following posterior nerve stimulation in man. Electroenceph Clin Neurophysiol 1986; 65: 118–129.

Kaji R, Sumner AJ. Bladder recording of short-latency somatosensory evoked potentials after evoked nerve stimulation. Neurology 1987; 37: 410–413.

Kanfi HA, Sednick EM. Somatosensory evoked potentials from posterior tibial nerve and lumbosacral dermatomes. Electroenceph Clin Neurophysiol 1981; 51: 248–259.

Kahn HA, Sedwick EM. Somatosensory evoked potentials in the assessment of MS disease diagnosis and results of treatment. In: Barber C, Blum T (eds.) Evoked Potentials III. Butterworths Boston 1987; pp 295–302.

Kurtzke JF, Hyllested K, Poser CM. Benefical plasma exchange in patients with chronic MS cases. Neurology 1981; 31: 45–58.

Lumsden JC, Lumsden JR, Low HB. The neuropathology of typical Friedreich's ataxia. Can J Neurol Sci 1984; 11: 535–548.

Lummis ACH, Ilan WF et al. Further spinal nerve and early cortical evoked potentials after tibial nerve stimulation: effects of filters on normative data. Electroenceph Clin Neurophysiol 1982; 54: 699–707.

Lusman E, Majkowski A, Rosenblatt R, Ricci F. A longitudinal study of short latency somatosensory evoked responses in healthy persons and adults. Electroenceph Clin Neurophysiol 1988; 71: 106–109.

Lindsay KW, Cuthe J, Kennedy J, Elsp A, McInnes A, Swaddle GM. Evoked potentials in severe head injury. Analysis and relation to outcome. J Neurol Neurosurg Psychiat 1981; 44: 796–802.

Lueders H, Acarturk S, Grant A, Wesley G, Lesser G. Origin of the N145 subcortical potentials evoked by stimulation of phalanges. Electroenceph Clin Neurophysiol 1981; 52: 346–348.

Mamoglu FL, Black IL, Collins DWE. Visual and spinal evoked potentials in the diagnosis of multiple sclerosis. Br Med J 1975; 2: 22.

Matthews WB. The normal somatosensory potential in diagnosis. In: Electroencephalography in clinical neurology. M Aminoff (ed). New York, Churchill Livingstone 1980; pp 431–467.

Mauguiere F, Barat J, Cinotti J. Lumbosacral cough somatosensory potentials due to discoid cervical disc with myelopathic progression. Rev EEG Clin Neurophysiol 1981; 11: 174–182.

Mauguiere F, Buisson AM, Echallier JF, Cinotti J. Early somatosensory evoked potentials in thalamocortical lesions of the somatosensory pathways in humans. In: Clinical Applications of Evoked Potentials in Neurology. Courjon J, Mauguiere F, Revol M (eds.). Advances in Neurology Raven Press New York 1982; Vol 32: 321–336.

Mauguiere F. Les potentiels evoques somatosensoriels corticaux chez l'homme. Analyse des aspects electrogenes utiles a leur interpretation en neurologie. Rev EEG Clin Neurophysiol 1983; 13: 259–272.

Mauguiere F, Courjon J. Dissociation of early SEP components in unilateral cerebral lesions of the lower medulla. Ann Neurol 1978a; 13: 309–313.

Mauguiere F, Desmedt JE, Courjon J. Neural generators of N18 and P14 far-field somatosensory evoked potentials studied in patients with lesions of brainstem or thalamus. Electroenceph Clin Neurophysiol 1983(b); 56: 283–292.

Mauguiere F, Desmedt JE, Courjon J. Astereognosis and dissociated loss of frontal or parietal components of somatosensory evoked potentials in hemispheric lesions. Brain 1983(a); 106: 271–311.

Mauguiere F, Hamy V. The dissociation of early SEP components in lesions of the cervico-medullary junction: a test for cortical interpretation of abnormal cervical responses to median nerve stimulation. Electroenceph Clin Neurophysiol 1985; 62: 418–428.

Mauguiere F, Hamy V, Fischer G. Somatosensory evoked potentials in intra-spinal tumors. Rev EEG Neurophysiol 1981; 11: 95–106.

Maugiere F. Short-latency somatosensory evoked potentials to upper limb stimulation in lesions of brainstem, thalamus and cortex. In: Halliday AM, (ed). The London Symposium. Elsevier Amsterdam 1987; pp 382–389.

Mauguiere F, Hamy V, Desbiez MP, Garcia-Larrea L. Somatosensory evoked potentials in non-demyelinating diseases. In: Evoked Potentials III, Harrison C (eds.). Butterworths Boston 1987; pp 43–55.

Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. Nature 1980; 285: 227.

Nakanishi T, Shimada Y, Sakata M, Tsuyuzaki K. The neural positive component of the scalp recorded somatosensory evoked potential in normal subjects and in patients with neurological

disorders. Electroencephalogr Clin Neurophysiol 1976; 41: 29–34.

Nakanishi T, Tanaki M, Suzuki K, Kubo R. Origin of 'non-cephalic' somatosensory far field potentials in man and cat. In: The Kyoto Symposia [EEG J Suppl No. 36]. Basic Mechanisms of Evoked Potentials. Proc. Amsterdam 1981; pp 356–368.

Nakanishi T, Tanaki M, Genki Y, Suzuki. Origin of short latency somatosensory evoked potentials in median nerve stimulation. Electroencephalogr Clin Neurophysiol 1982; 54: 34–45.

Nguyen BK, Greenberg RP, Miller JD, Finn JJ, Glen SC, Kinnier PS et al. Improved confidence of prediction in severe head injury. A comparative analysis of the clinical examination, multimodality evoked potentials, CT scanning and intracranial pressure. J Neurosurg 1981; 54: 751–762.

Noel P, Desmedt JE. Somatosensory pathways in Friedreich's ataxia. Acta Neurol Belg 1976; 76: 231.

Noren MR, Perrinn SL, Packwood JW, Kirk EAP. Evoked potential abnormalities in the various neuronal ceroids. Ann Neurol. 1983; 13: 26–27.

Noren MR, Packwood JW, Morris GW, Hixson GW. Evoked potentials predict the clinical changes in a multiple sclerosis drug study. Neurology 1985; 35: 1584–1587.

Olivier AA, Rothwell JC, Marsden CD. The treatment of cortical myoclonus from focal reflex seizures spontaneous motor epilepsy. Brain 1985; 108: 1043–1074.

Okada YC, Tomlinson R, Williamson SJ, Kaufman L. Somatotopic organization of the human somatosensory cortex revealed by neuromagnetic measurements. Exp Brain Res 1984; 56: 197–205.

Olson BR, Chiappa KH. Somatosensory evoked potentials in neurological diagnosis. In: Evoked Potentials (Frontiers in clinical Neuroscience, Vol. 3). Cracco RQ, Bodis-Wollner I (eds.). Alan R. Liss Inc. New York, 1986; pp. 379–395.

Oppenheimer DR, Brazil-Jacobs G, Friedreich's ataxia. Can J Neurol Sci 1979; 6: 173–176.

Papakostopoulos D, Cooper R. Direct recording of the EOR-Wave: the cerebral source of man and the differences between geniculate and postcentral potentials. In: Desmedt JE (Ed). Clinical Uses of Cerebral, Brainstem and Spinal Evoked Potentials. Prog clin Neurophysiol Vol 3. Karger, Basel, 1980; pp 15–30.

Pozzi AP, Ignazio D, Kaneshwari A. Diagnostic and prognostic value of somatosensory evoked potentials in acute cerebrovascular accident. Electroencephalogr Clin Neurophysiol 1983; 56: 3149.

Parry GJ, Aminoff MJ. Somatosensory evoked potentials in chronic acquired demyelinating peripheral neuropathy. Neurology 1982; 32: 113–116.

Penfield J, Rasmussen H. The Cerebral Cortex of Man. A Clinical Study of Localization of Function. McMillan, New York, 1950.

Pedroso L, Troiaburg W. Visual, auditory and somatosensory pathway involvement in hereditary cerebellar ataxia, Friedreich's ataxia and familial spastic paraplegia. Electroencephalogr Clin Neurophysiol 1981; 52: 283–297.

Perrin SJ, Fischer MA. Somatosensory evoked response evaluation of cervical spondylotic myelopathy. Muscle & nerve. 1987; 10: 405–409.

Powers SK, Bolger CA, Edwards MJR. Spinal cord pathways mediating somatosensory evoked potentials. J Neurosurg 1982; 57: 472–482.

Riffel B, Fisher M, Klimes I. Spinal and cortical potentials following stimulation of posterior tibial nerve in the diagnosis and localization of spinal cord disease. Electroencephalogr Clin Neurophysiol 1984; 58: 400–401.

Roberts EM, Lawrence PD, Enos A. Dispersion of the somatosensory evoked potentials in multiple sclerosis. EEG Clin 1983; 56: 261–264.

Rogger AH, Marsden A. Mechanism of pain relief in Guillain-Barré syndrome. Arch Neurol 1984; 41: 258–261.

Rogger AH, Chiappa KH. Evoked potentials in Guillain-Barré syndrome. Neurology 1986; 36: 587–591.

Rothwell JC, Obeso JA, Marsden CD. – On the significance of giant somatosensory evoked potentials in cortical myoclonus. J Neurol Neurosurg Psychiat 1984; 47: 35–42.

Sauer M, Schmid E. Elektrophysiologische untersuchungen an Friedreich patienten und an hereditary

motor and sensory neuropathy. Electroencephalogr Clin Neurophysiol 1977; 43: 623–

Schmitt HJH, Hess CW, Ludin HP. Somatosensory evoked potentials following nerve and segmental stimulation in man: results in normals and patients with sensory deficit. J Neurol Neurosurg Psychiatry 1980; 43: 182–197.

Schwartz J, Arezzo JC, Brodal M. Segmentally evoked preoperative and perioperative somatosensory potentials in spinal surgery. In: Hicks RM, Barber C (eds), Evoked Potentials II. The second International Evoked Potentials Symposium. Butterworth Publishers, Boston, 1986: 406–412.

Seyal M, Emerson RG, Pedley TA. Spinal and early subcortical components of the somatosensory evoked potential following stimulation of the posterior tibial nerve. Electroencephalogr clin Neurophysiol 1985; 62: 320–330.

Sherwood AM. Characteristics of somatosensory evoked potentials recorded over the spinal cord and brain of man. IEEE Trans Sci 26: 481–487.

Shibasaki H, Kuroiwa Y. Electroencephalographic evidence of myoclonus. Electroencephalogr Clin Neurophysiol 1978; 46: 455–463.

Shibasaki H, Yamashita Y, Neshige R, Tobimatsu S, Fujita R. Form perception of giant somatosensory evoked potentials in progressive myoclonic epilepsy. Brain 1989; 112: 905–920.

Shibasaki H, Neshige R, Hashiba Y. Cortical excitability after myoclonus: Jerk-locked somatosensory evoked potentials. Neurology 1987; 37(suppl 1): 76–6.

Simola J, Mylkilä VT, Salgi I, Hyökänen E. Facial nerve and auditory neurography in relation to surgical exposure. J Neurol Neurosurg Psychiatry 1979; 42: 1151–1159.

Simola J, Salgi I, Hämäläinen M. Somatosensory evoked potentials in diagnostics of cerebellopontine and hemiated disk. Electroencephalogr Clin Neurophysiol 1981; 52: 256–262.

Stamp JC, Tamas LB, Barker WC, Wylie AR. Somatosensory evoked potentials after removal of somatosensory cortical scar. Electroencephalogr clin Neurophysiol 1986; 65: 111–117.

Stegall M, Matthews WB. A method of subscalp spinal cord evoked potentials for monitoring in spinal nerve compression by spinal cord tumour and patients with spinal cord disease. Electroencephalogr clin Neurophysiol 1984; 59: 156–164.

Symington R. Evoked Potentials. Pitman Butterworths Publishers, Boston, 1980.

Stockard JJ, Stockard JE, Sharbrough FW. Brainstem auditory evoked potentials in neurology: Methodology, interpretation, clinical application. In: Aminoff M (ed.), Electrodiagnosis in clinical neurology. Churchill-Livingstone, New York, 1990: pp 370–413.

Stone M, Darbyshire J, Voigt K, Bantzer UW. The significance of somatosensory evoked potentials for localization of unilateral lesions within the cerebral hemispheres. J Neurol Sci 1983; 61: 49–63.

Sutton LN, Uzzman JT, Shutt R, Voigt J, Bruce DA. The effects of deep barbiturate coma on multimodality evoked potentials. J Neurosurg 1982; 57: 178–185.

Suzuki I, Matsuoka Y. Intracranial recordings of short-latency somatosensory evoked potentials in man: identification of origin of each component. Electroencephalogr clin Neurophysiol 1984; 59: 286–296.

Synek VM, Cowan B. Somatosensory evoked potentials in patients with metastatic involvement of the brachial plexus. Electroencephalogr clin Neurophysiol 1985; 61: 365–371.

Synek VM, Cowan JC. Segmental nerve evoked potentials and the assessment of [m]subdivided tissues in the forearm[/sm]. Muscle & Nerve, 1985; 8: 423–426.

Synek VM. Assessing sensory lesion location in lateral arch nerve lesions using somatosensory evoked potential techniques. Muscle & Nerve, 1985; 8: 71–77.

Taylor MJ, Chan-Lin WT, Logan WJ. Long latency evoked potential studies in hereditary ataxias. Can J Neurol Sci 1985; 12: 120–124.

Thomas JE, Lambert EH. Ulnar nerve conduction velocity and H-reflex in infants and children. J appl Physiol 1960; 15: 1–9.

Tomita Y, Nishimura S, Tomita T. Short latency SEPs in infants and children: Developmental changes and interpeak index of SEPs. Electroencephalogr Clin Neurophysiol 1986; 63: 339–343.

Trojaborg W, Pedersen E. Visual and somatosensory evoked cortical potentials in multiple sclerosis

J Neurol Neurosurg Psychiat 1979; 42: 323-330.

Thuy S, Lueders H, Lesser RP, Dinner DS, Klem G. Subcortical and cortical somatosensory potentials evoked by peroneal tibial nerve stimulation: normative values. *Electroenceph clin Neurophysiol* 1984; 58: 216-229.

Valeriani M, Garcia-Larrea L, Neuwirth-Riecker St, Dreyfus P, Mauguière F. Evoked potential studies in Friedreich's ataxia and progressive early-onset cerebellar ataxia. *Can J Neurol Sci* 1988; 15: (in press, to appear in August 88).

Van GA, Chiappa KH, Cooper RW. Scalp-recorded short-latency cortical and subcortical somatosensory evoked potentials to proximal nerve stimulation. *Electroenceph clin Neurophysiol* 1981; 52: 1-8.

Welsh JC, Tsuboyama C, McLeod JG. Abnormalities of proximal conduction in some idiopathic polyneuritis. Comparison of short-latency evoked potentials and F waves. *J Neurol Neurosurg Psychiat* 1986; 49: 987-998.

Watson RT, Heilman KM. Thalamic neglect. *Neurology* 1979; 29: 690-694.

Weerd AW de, Lucassen A, Vildhuizen RJ, Hulsbos AC. Somatosensory evoked potentials in motor cortical epilepsia: Diagnostic significance and changes in serial records. *Electroenceph clin Neurophysiol* 1985; 62: 43-55.

Wood CC, Cohen D, Cuffin BN, Yarita M, Allison T. Electrical sources in human somatosensory cortex: Identification by combined magnetic and potential recordings. *Science* 1985; 227: 1051-1053.

Yamada T, Matloubi M, Kimura J. Paradoxical somatosensory evoked potentials after stimulation of the ulnar nerve. *Neurology* 1982; 32: 1151-1158.

Yamada T, Graff-Radford MR, Kimura J, Dawson DS, Adams HP. Topographic analysis of somatosensory evoked potentials in patients with lateralized thalamic infarctions. *J Neurol Sci* 1985; 68: 31-48.

Yamada T, Ishida T, Kudo Y, Kuroiwa Y-L, Kimura J. Clinical correlates of abnormal P14 in median SEPs. *Neurology* 1986; 36: 765-771.

Yu YL, Jones SJ. Somatosensory evoked potentials in cervical spondylosis. Correlation of median, ulnar and posterior tibial nerve components with clinical and radiological findings. *Brain* 1985; 108: 275-300.

Zhu Y, Georgesco M, Cuisiniac J. Normal latency values of early cortical somatosensory evoked potentials in children. *Electroenceph clin Neurophysiol* 1987; 68: 471-474.

Long latency somatosensory evoked potentials

E.J. COLON and G. COMI

Introduction

Although the long latency somatosensory evoked potentials were described before the short latency ones, only the latter have been used widely for clinical purposes. The limited utilization of long latency SEPs in practice is due to their probable large inter and intra individual variability and to the scanty knowledge of their generators. In this part, we will describe the SEP components that are generated in time after the short latency components.

Median nerve stimulation

The localization of the primary somatosensory area for the hand on the surface of the scalp made it easier to study upper arm SEPs, particularly from the median nerve (Desmedt, 1981; Mauguière *et al.*, 1983). After stimulation of the Median nerve, the first cortical components elicited are the parietal N20/

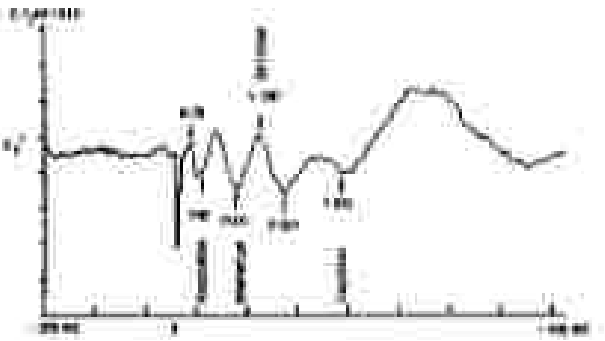


Figure 1. Example of a normal long latency SEP. The right median nerve is stimulated at wrist level, random stimuli, interval 3.1 s., analysis 0.5-150 Hz.

E. J. Colon and S. L. Visser (eds), Evoked potential manual, pp. 279–306.

P27 and the precuneatic P22/N30. Neither of these components is modified by psychological tasks, nor influenced by the stimulation of other sensory pathways (Desmedt *et al.*, 1983; Greenwood *et al.*, 1987). They are an expression of the activation of the specific thalamocortical projections (see pp. 212). After these two complexes, a positive wave, P40, is recorded contralaterally to the stimulated arm. This wave starts about 35 ms after the stimulus, in the parietal region, when the frontal area still shows the large negative wave N30. The positive P40 is followed by a negative one, N60, which also starts in the controlateral pre-rolandic area and diffuses to the fronto-polar and temporal regions. In some subjects, N60 splits into two waves, an earlier one with maximum in the pre-rolandic region and a later one with maximum more antero-laterally. Some scientists (Goff *et al.*, 1977; Colon *et al.*, 1980) called these negative waves N55 and N70, separated by a positive deflection P65 which has its maximal amplitude in the parietal region ipsilateral to the stimulated arm. N60 cannot be related to the same generator as P40 because of its different distribution. The components until P60 are ubiquitously distributed over the brain, the later components are seldom. The first of these components is the P100, widely diffuse, with an amplitude maximum in the

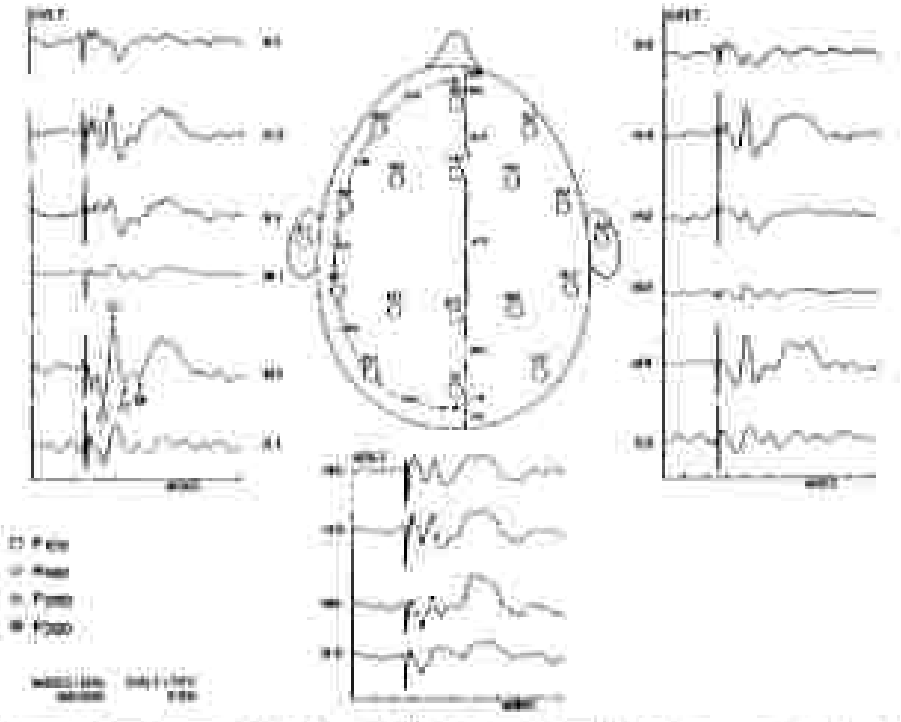


Figure 2. Grand average of long latency MEP in obtained from 16 adult volunteers after Right Median Nerve stimulation

frontal regions. This P100 is sometimes preceded by a small notch on an upward slope, the P80, which is more evident in the posterior areas, particularly on the ipsilateral side (Goff *et al.*, 1977). The following component the N140 is a large negative wave with maximal amplitude at the vertex. After N140 there is a positive deflection with two positive peaks P200 and P300, separated by the negative N260. This N260 is best seen in the occipital and lateral locations, while P200 and P300 have maximal amplitude at the vertex. After the P300 there is a large and diffuse negative wave N360 followed by two other components P420 and N490. An example of a normal SEP after median nerve stimulation is given in Fig. 1. In Fig. 1 the various long-latency SSEP waveforms over the skull is given. In Fig. 2 until 5 a representative set of topographic mapping of long-latency components is given and in Table 1 various normative values are summarized.

Table 1. Normal values of SEP after median nerve stimulation (amplitude of the main components)

	Lüders (1979) (N = 16; 40–90 years)		Yamada (1972) (N = 20; 9–19 years)	
	Mean	S.D.	Mean	S.D.
P40	44	9.9	42	6.3
N60	67	7.7	58	1.8
P100	105	4.7	88	5.5
N140	142	11.9	130	8.0
P200	229	8.9	202	8.9
N300	304	8.7	302	13.5
	Arezzo (1983) (N = 14; 18–33 years)		Celesia (1982) (N = 10; 28–30 years)	
	Mean	S.D.	Mean	S.D.
P45	44	4.4	40	5.7
N60	57	8.2	62	7.1
P100	80	11.0	97	16.0
N140	132	21.1	138	15.0
P200	187	31.0	227	17.0
N300	298	19.0	279	26.0
	Cooper (N = 15; 10–50 years)			
	Mean	S.D.		
P40	41	3.4		
N60	60	7.5		
P100	96	8.3		
N140	137	7.1		
P200	197	18.2		
P300	289	34.4		
N300	403	53.9		

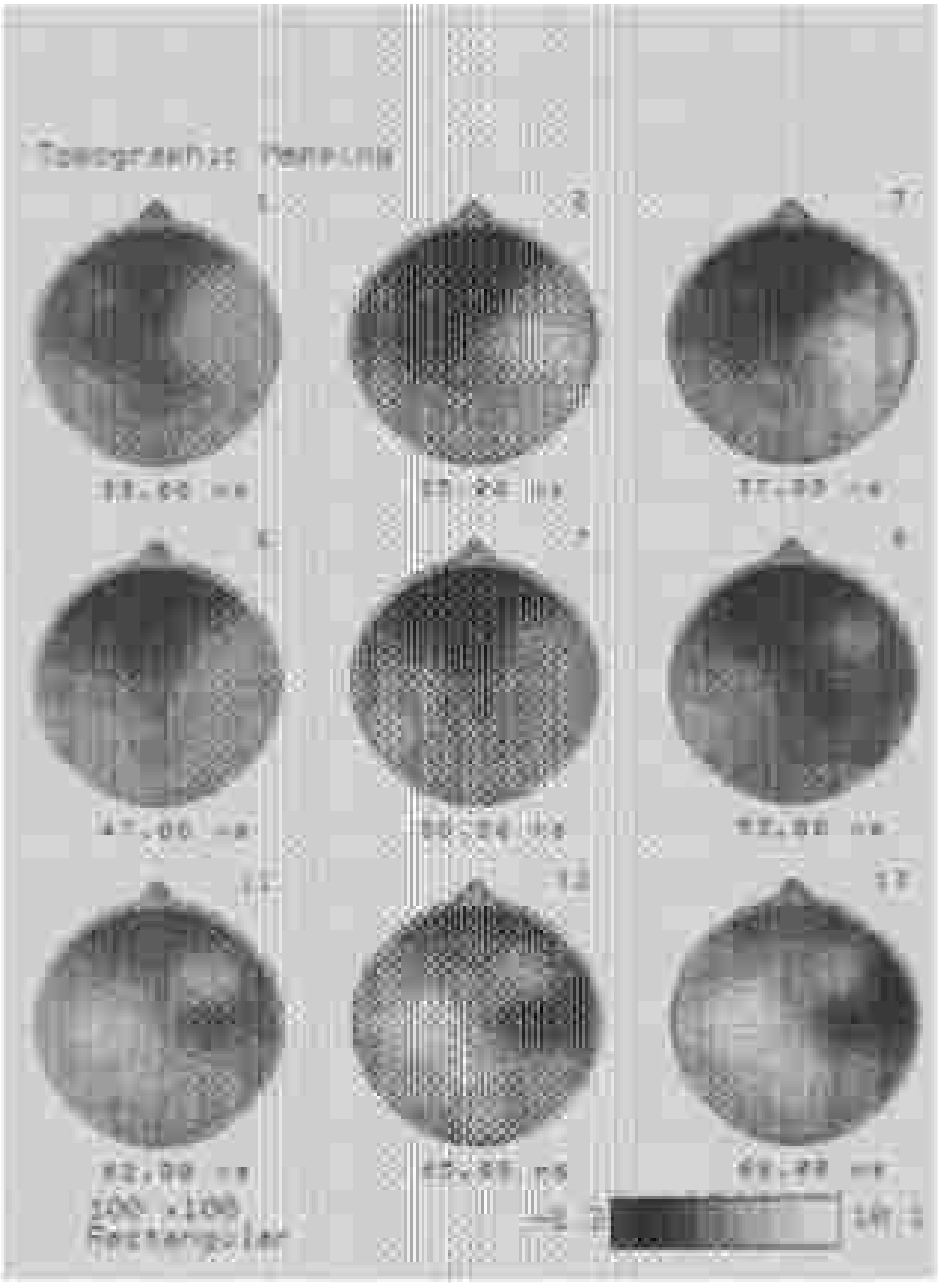


Figure 3. Spatio-topographical distribution of long latency components in a normal subject after left median nerve stimulation.

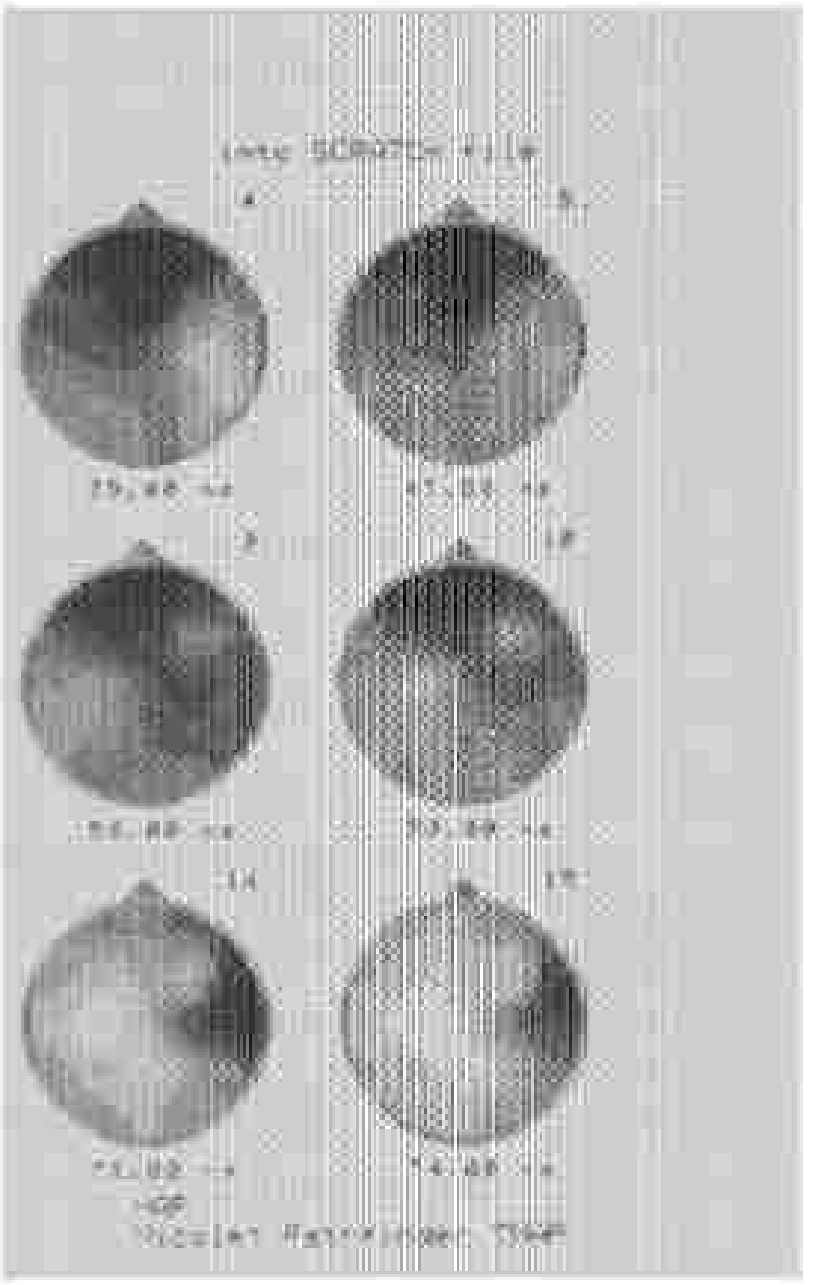


Figure 5 Continued

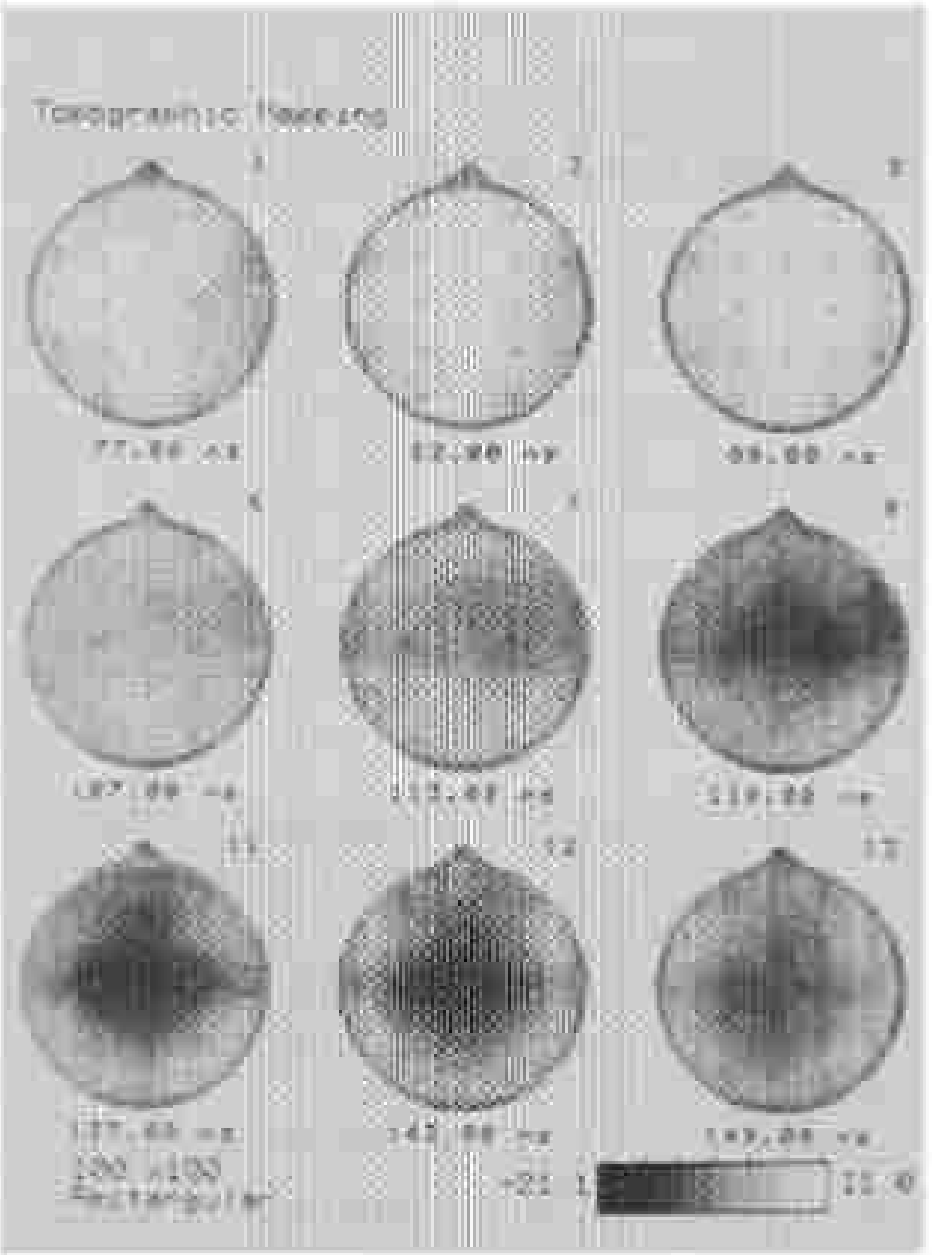


Figure 4. Topographical distribution of long latency components in a normal subject after left median nerve stimulation.

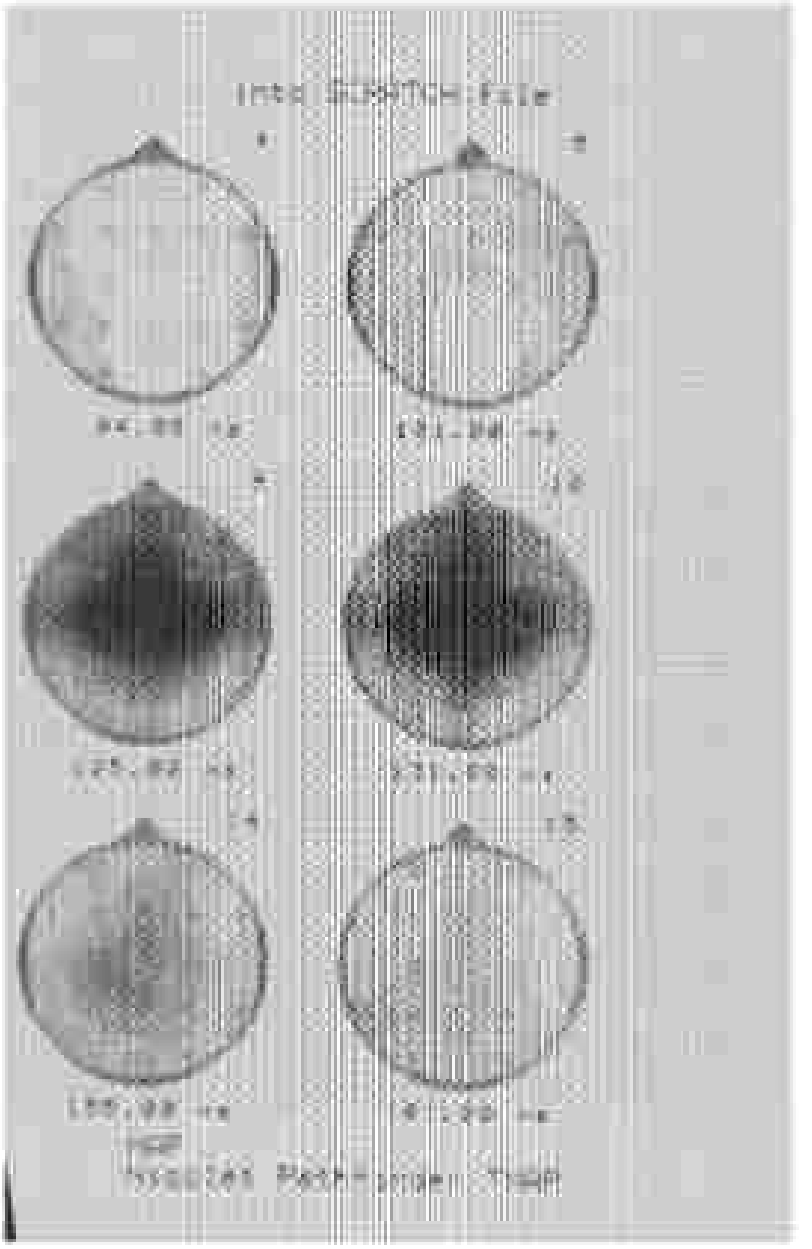


Figure 4 Continued

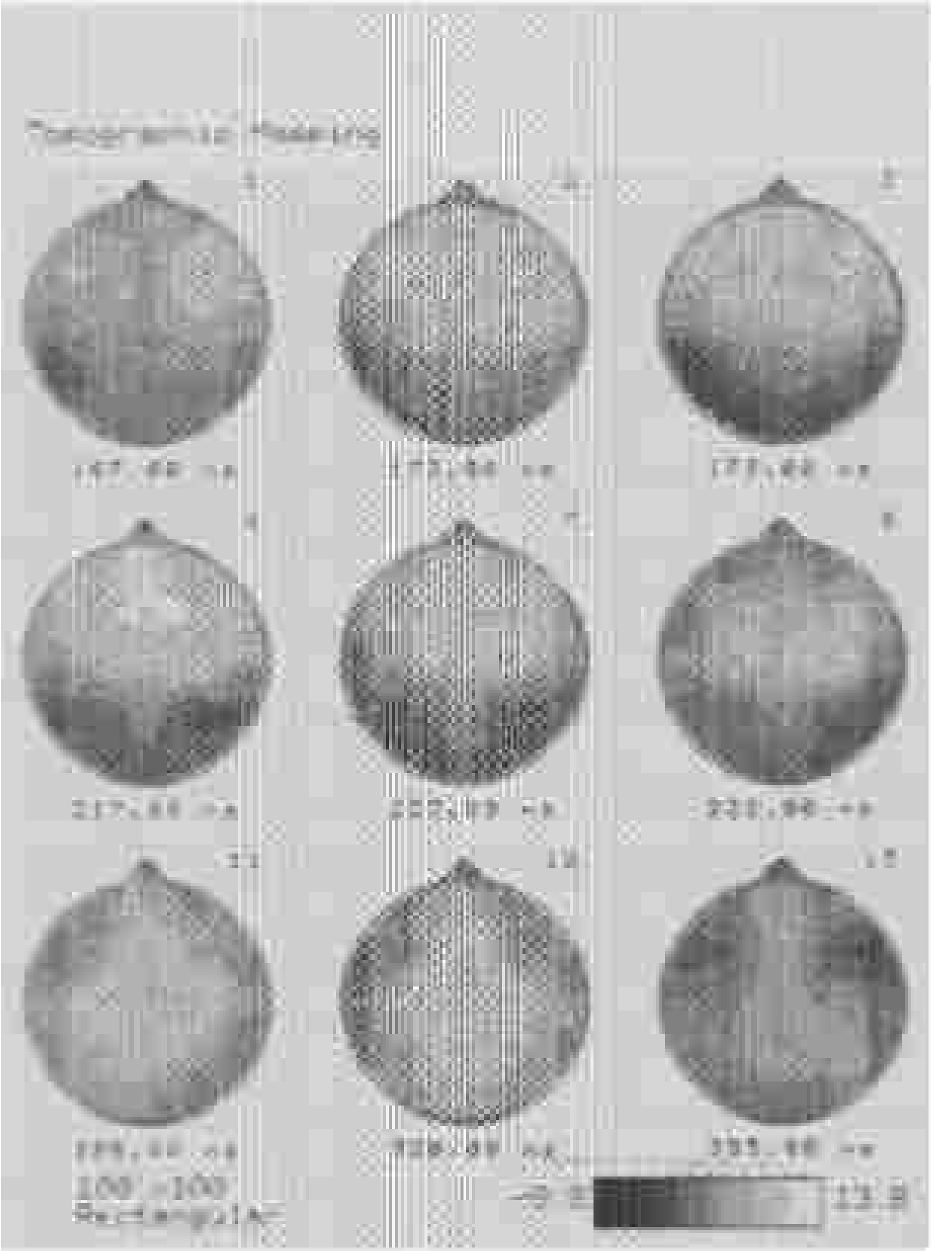


Figure 5. Spatio-topographical distribution of long latency components in a normal subject after left median nerve stimulation.

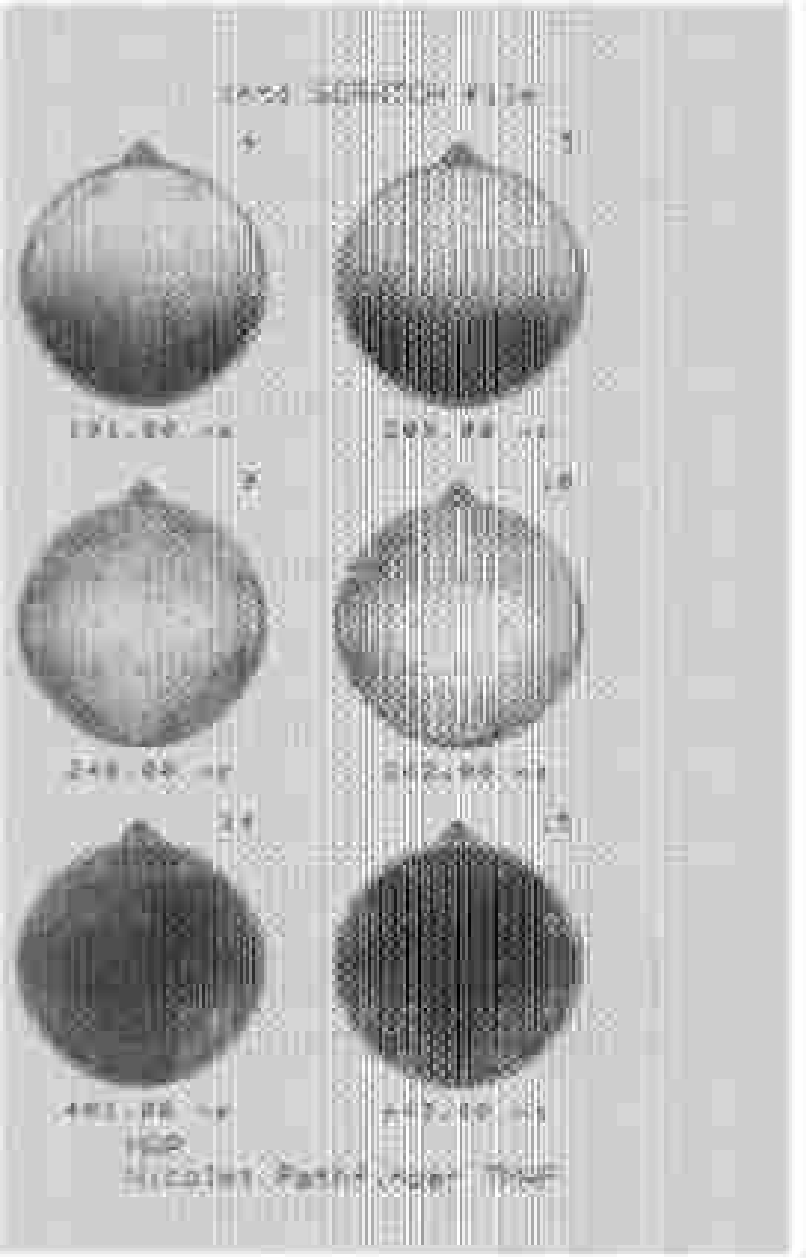


Figure 5. Continued.

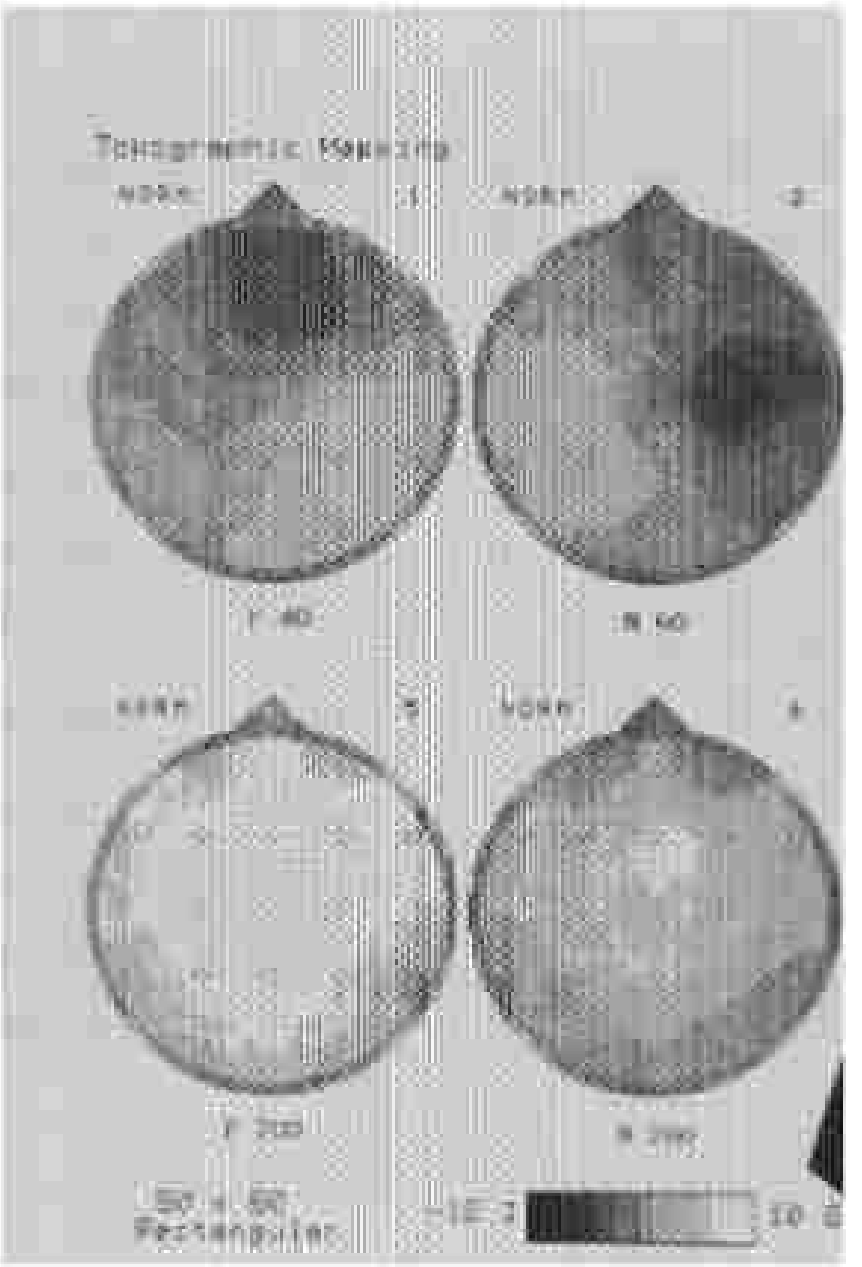


Figure 8. Grand averages of long latency SSEP after the stimulation of the left median nerve in 15 normal subjects. See text for display the spatial distribution of the main components.

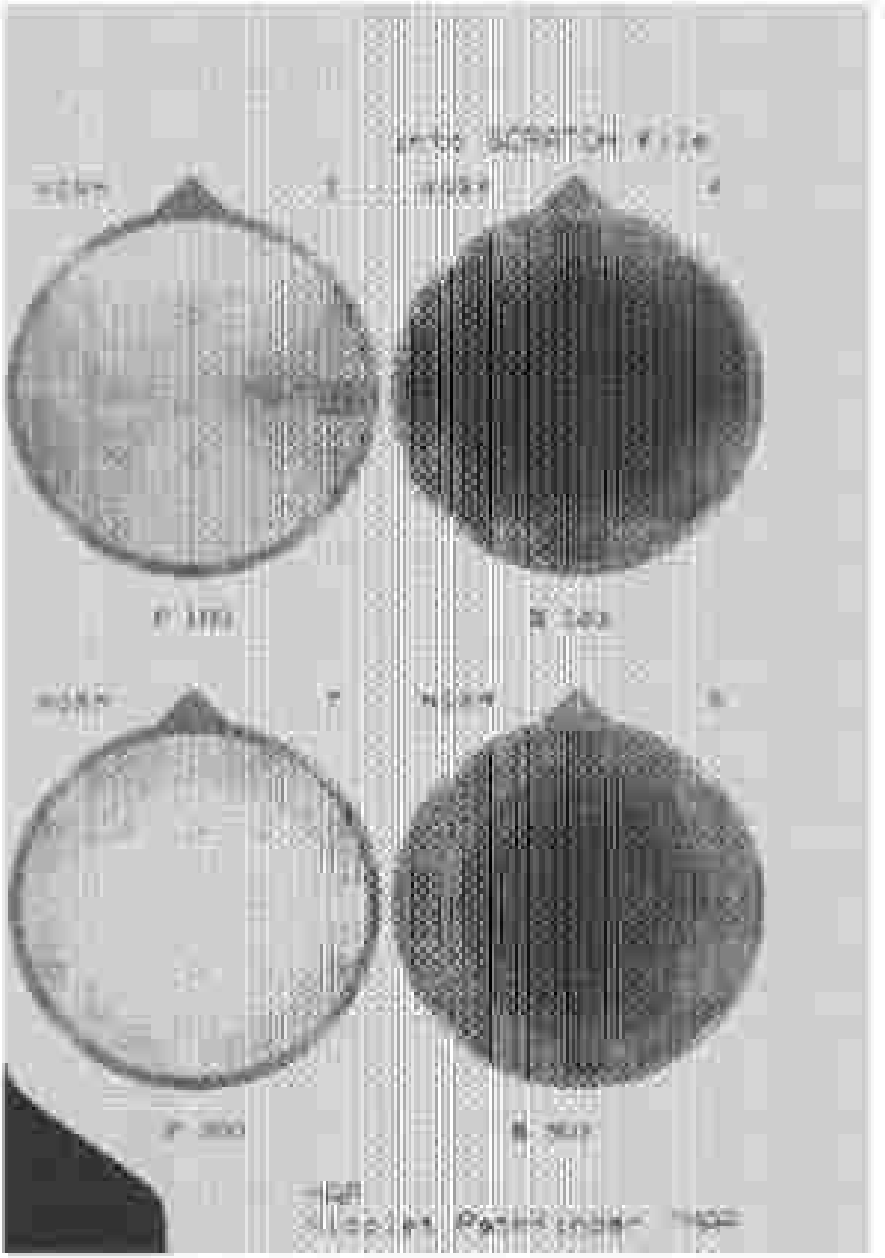


Figure 8. Continued

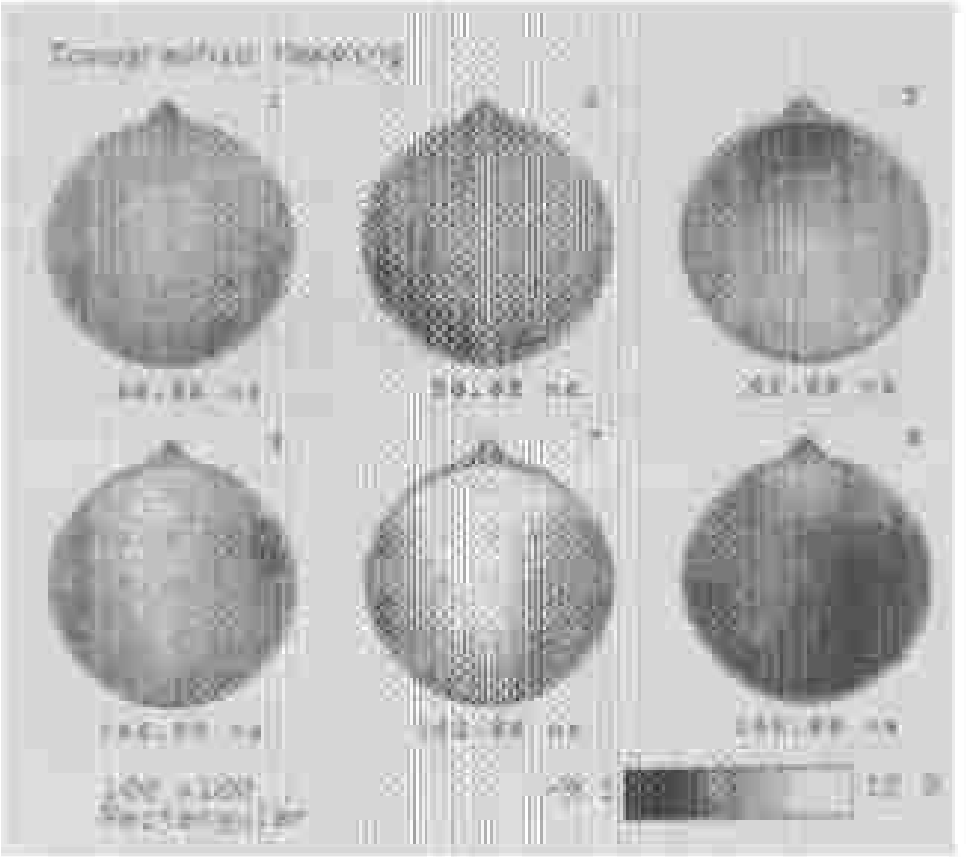


Figure 7. Long latency SEP after left tibial nerve stimulation in a normal subject. a. Topographic maps of the main components. Latencies values are reported at the bottom of each map.

Generators and physiological characteristics of long-latency SEPs after median nerve stimulation

There is very little information about the location of the generators of long latency components of the median nerve SEP. It has been suggested that the successive SEP components are generated in series of coupled units, where failure of one unit results in electrical silence, or altered neuronal activity in sequential units (Tsumoto *et al.*, 1978; Goff *et al.*, 1978). However, the modifications of some late components, particularly P40 and N60, observed in focal lesions of the Central Nervous System seem to contradict this interpretation. In thalamic lesions P40 and/or N60 could be abnormal where early SEP components could be preserved (Yamada *et al.*, 1995; Chu, 1996). On the other hand, absent early components can be associated with preserved late components (Yamada *et al.*, 1981; Colon *et al.*, 1984). These observations

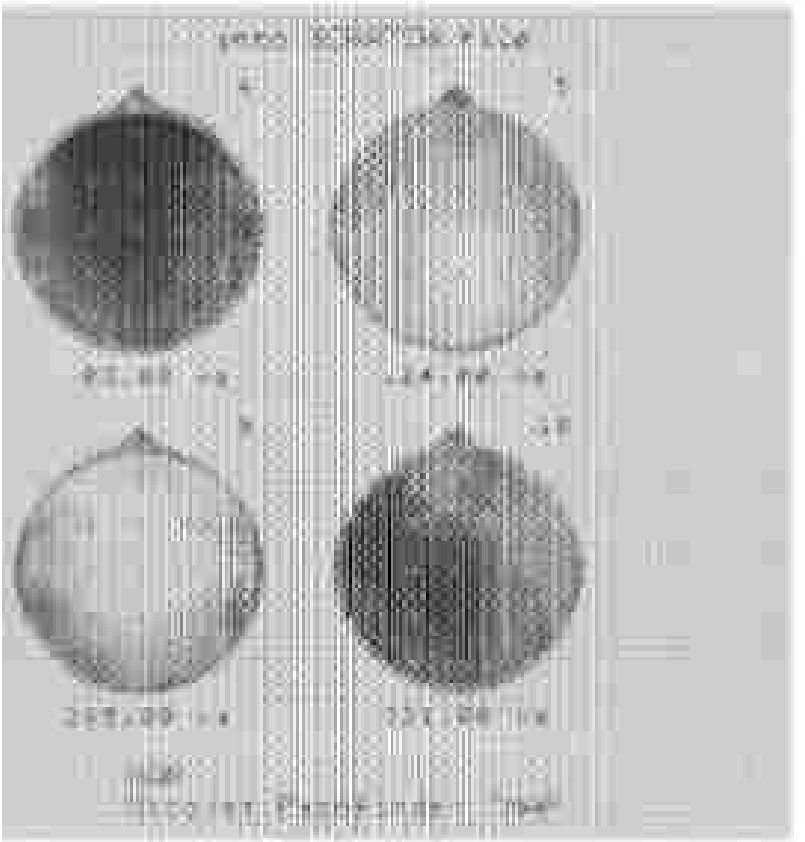


Figure 7.8. Traditional display of multitrigered round-up (1 first time subjects reference electrode (mixed ears bandpass 0.5–30 Hz. The number shown for different peaks: 1–P40; 2–N60; 3–P80; 4–N75; 5–P100; 6–N120; 7–P150; 8–N200; 9–P250; 10–N280.

suggest that P40 and N60 reflect projections of non-specific thalamic nuclei. Both P40 and N60 have cortical origins, but in different areas. P40 is generated in the parietal region and N60 in the pre-rolandic region (Mauguiere *et al.*, 1983; Goff *et al.*, 1978; Yamada *et al.*, 1983; Desmedt *et al.*, 1985; Colon *et al.*, 1985). The P40 and N60 are ameliorated, in most cases reduced or suppressed, during passive movement of the stimulated limb (Abbruzzese *et al.*, 1981; Angel *et al.*, 1985). The functional significance of the suppression of some SEP components remains unclear. One possible interpretation might be that this mechanism seems to shield ongoing movements against irrelevant afferent information (Cernenwich *et al.*, 1984). P100 could reflect a process of recognition of afferent stimuli, in the frontal region (Desmedt *et al.*, 1983). Based on the result of depth-electrode studies, the generators of the large amplitude vertex potentials, the N140/P200 complex, are assumed to be located

superficially, probably in the corpus callosum (Goff *et al.*, 1978; Goff *et al.*, 1980) or in the somatosensory associative cortex (Desmedt, 1981). The generators of the other components is completely unknown. P300 shows some bipolarity indicating a horizontal dipole located in the specific somatosensory area (Colon *et al.*, 1985), which might be caused by the local long lasting potential changes of glial cells.

Stimulation of other nerves

There is only a limited knowledge about long-latency SEPs arising after stimulation of nerves other than the Median nerve. After Tibial nerve stimulation at the ankle the following long-latency components can be observed (see Fig. 7) – P60 a positive wave that involves both parietal regions;
- N75 a large, widely diffuse wave;
- P100/N120/P150 a large and diffuse complex with two recognizable positive peaks, P100 an P150, separated by a small negative wave, N120;
- N190/P250/N320 a large complex, distributed diffusely over the scalp.

Comparable configurations of the late components have also been described after stimulation of Sural and Peroneal nerves (Tsumoto *et al.*, 1972; Nakanishi *et al.*, 1964; Colon, 1983).

The side of the generators of the late components of the SEP after stimulation of nerves in the legs is unknown, except for that of the P75 component, which resembles P40 as seen after Median nerve stimulation (Desmedt *et al.*, 1985).

Long latency SEPs after natural stimulation

Natural forms of sensory stimulation can be used to evoke somatosensory potentials in human beings. The advantage of using natural stimuli is the selective activation of specific groups of sensory receptors. With this kind of stimulation one can compare SEPs with subjective perception (Frances *et al.*, 1960). The disadvantages of natural stimulation are the difficulty of the quantification of the stimuli and the relatively low amplitude of the evoked potentials. For mechanical stimulation both manual taps with a hammer (Larsson *et al.*, 1970) and mechanical taps with an electromagnetically driven hammer (Dubecher *et al.*, 1984; Halliday *et al.*, 1964; Nakanishi *et al.*, 1973; Kakigi *et al.*, 1984) have been used. However, this type of stimulation may simultaneously activate several kinds of receptors. Air-puff stimuli selectively activate the rapidly adapting cutaneous mechanoreceptors (Johansson *et al.*, 1979; Shoppatt *et al.*, 1984). While the amplitude of early components of air-puff SEPs was on the average 30% of that of electrical stimulation, late components reached about 90% (Hashimoto, 1987). After mechanical stimulation of finger tips a P116, N106, P205, N245, P330 has been described (Johnson *et al.*, 1980). Tooth pulp stimulation causes a bilateral N80 and N140 in the

Table 2. Normal values of SEP after stimulation of nerves in the legs. Latencies of the main components.

	Tinazzi *et al.* (1992)* (N = 47; 19–34 years)		Fava *et al.* (1995)** (N = 54; 18–50 years)	
	Mean	S.D.	Mean	S.D.
P40	36	4.2	38	3.1
N75	74	5.0	75	5.4
P98	99	7.3	118	15.8
N120	126	13.0	–	–
P200	203	19.6	–	–
	Kakigi (1990)* (N = 20; 21–29 years)		Cruccu** (N = 11; 22–36 years)	
	Mean	S.D.	Mean	S.D.
P40	38	2.5	38	4.4
N75	83	2.8	89	8.2
P100	102	4.0	105	11.0
N120	99	6	115	13.8
P150	–	–	146	18.5
N190	–	–	187	23.0
P250	–	–	254	27.0
N320	–	–	321	36.4

* Proximal nerve at knee.
** Tibial nerve at ankle.

parietal regions and the midline components N42, P80, N145 and P250 (Booth *et al.*, 1985).

Mechanical stimulation gives a more or less similar reaction as is seen after electrical stimulation (Nakashita *et al.*, 1974).

Peripheral painful stimuli have been used as well (Chudler *et al.*, 1983; Weller *et al.*, 1985).

Methodology

Many endogeneous and exogeneous influences can affect long-latency SEPs. Hence, the circumstances under which the examinations are done should be standardized as much as possible.

Recording should be done in a sound proof and air conditioned room. To minimize the interferences, the examined subject should be relaxed, in a supine position, alert, with eyes open to reduce the influence of excessive alpha in the EEG and to avoid drowsiness. Gaze shifts can be reduced by asking the subject to look at a fixed point. The EEG should be continuously monitored to check muscle activity and other artifacts. The modality of

stimulation) is essentially equal to that for short latency SSEP. The intensity of the stimulus should be 2-3 times the subjective sensory threshold or twitch level. Because of the long refractory period of the long-latency evoked potentials, the choice of the frequency of stimulation is critical. The longer the latency of a component, the longer its absolute and relative refractory period is (Tsumoto *et al.*, 1972). With an interstimulus interval (ISI) of less than 4s, amplitudes of later components diminish rapidly and progressively with the shortening of the ISI (Colon, 1983; Desmedt, 1977), while the latencies show minor changes (Fig. 8).

For this reason, for adults, a frequency of stimulation of 25 Hz, or less is advised. Due to maturational changes, longer ISI should be used in neonates (Laget, 1982). Random stimulation is preferred for the elicitation of late components following N60 (Papakostopoulos *et al.*, 1980). Studies of long latency SSEP after mechanical stimulation have shown an even greater influence of the ISI (Pratt *et al.*, 1980; Roth *et al.*, 1981). Besides the relative refractory period, other mechanisms are also responsible for the decrease of the amplitude of the response during repetitive stimulation. Serial measurements of successive SSEP's produced by series of stimuli showed a sharp decrement following the first response (Angel *et al.*, 1985). This decrement is probably a form of fatigue (Bongers *et al.*, 1998) or of habituation, a basic adaptive phenomenon in the central nervous system. To study the unilaterally distributed P40–N60, bilateral stimulation might be preferable over unilateral, by excluding mid-to-mid differences (Yamada, 1983). Later components are evaluated better with unilateral stimulation. Most long-latency SSEP components are spread diffusely over the scalp, varying in amplitude from region to region. The best way to study these phenomena is the analysis of spatial distribution by means of mapping or topography. With mapping techniques the changes of SSEP component distribution, related to psychological or pathological conditions, can be followed. This technique requires complicated multichannel derivations.

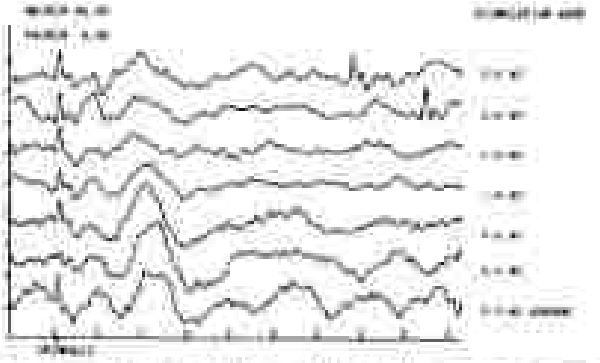


Figure 8. Influence of stimulus rate. Bilateral median nerve stimulation at the right wrist; derivation C3' contra lateral shoulder. Amplitude is diminished with the increase of the stimulus frequency; changes are more evident in later components.

Still there are many partially unresolved problems in the statistical analysis of the tremendous amount of data.

By SSEP-chrono-topographs only the normative spatial location of the maximal amplitude of the various components, combined with the location of its positive or negative counterpart, is summarized by isopotential maps (Colon *et al.*, 1985). This way an impression is reached about the direction of the hypothetical bipolar generators of the SSEP. These maps show the estimated area in which the maxima of component amplitudes are found in 50%, 75% and 90% of the population (Goff *et al.*, 1977; Colon *et al.*, 1984).

In Fig. 9 the normative SSEP-chrono-topographical distribution of long latency SSEP components is given. Using these normative distributions one can easily see whether the distribution of a certain component in a certain patient can be considered 'normal' (Colon *et al.*, 1986, 1985). Mapping and chrono-topography always require a previous detailed study of the conventionally displayed SSEP.

When these sophisticated methods of analysis are not available, long-latency SSEP can be evaluated in the usual manner, however simultaneous recording of at least four channels is advisable.

Because of the diffuse distribution of many components, a cervicephalic reference electrode is theoretically the best choice, however artifacts usually prohibit adequate recording. Chin or (linked) ear reference are the best alternatives. Long-latency SSEP's contain few high frequencies and low-pass filters can be set at 250 Hz. For the high pass filter a setting at 1 Hz or even 0.5 Hz is necessary. Many endogeneous and exogeneous influences affect long-latency SSEP's. Some influences have already been considered and other factors will be discussed in the next sections.

Influences on long-latency SSEP's

1. Age

There are important changes on the configuration of the SSEP's during maturation of the Central Nervous System. In newborns a thrompbasic long-

Figure 8. Chrono-topographical mappings of some late SSEP components. The area in which the maximal amplitude is found in 50%, 75% and 90% of the normal adult population.

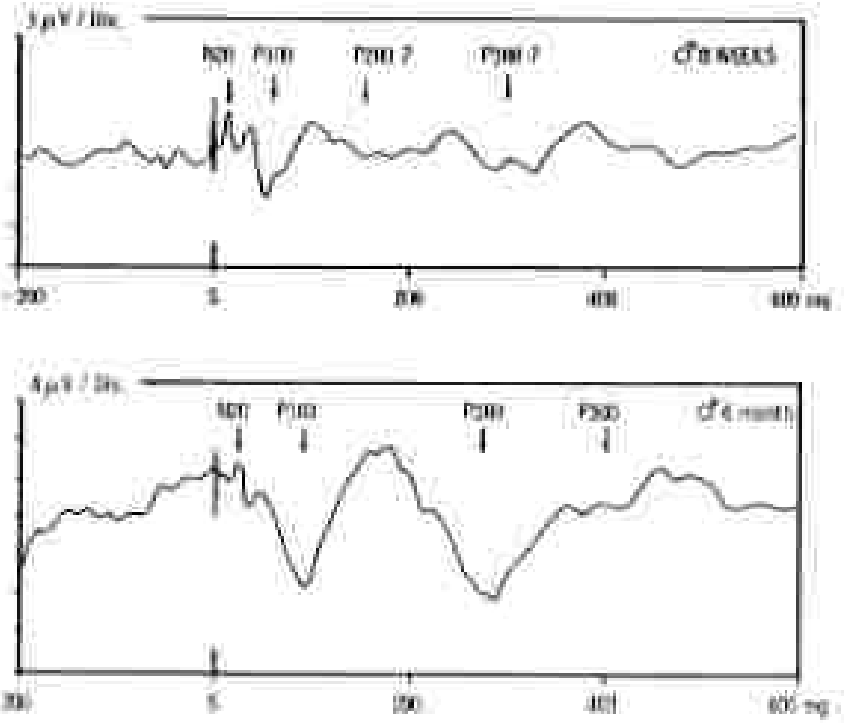


Figure 10. Example of a long-latency SSEP in a 6 weeks and a 6 months old boy.

latency SSEP is seen which changes slowly (Laget et al., 1976, 1982). Adult morphology, but not adult latencies, are reached at the age of three years (Laget et al., 1976); an example of the SSEP waveform in an 8 weeks and 6 months old boy is given in Fig. 10.

In middle the SSEP remains stable; in aged subjects the late SSEP components become larger and latencies are slightly prolonged (Kakigi et al., 1984; Noel et al., 1973). The development of the SSEP from the nerves in the leg in young children is more or less identical to the development of median nerve SSEP (Hirbek et al., 1973).

2. Temperature

Both hypothermia and hyperthermia induce progressive increase in latency and decrease in amplitude (Markand et al., 1984a; Dubois et al., 1981). Below a temperature of 25 C and above 39 C late components of the SSEP disappear.

In patients suffering from hypothermia an increase of their 'natural' temperature gives rise to a decrease in long-latency SSEP components latencies.

3. Sleep

As yet no extensive studies on the effect of sleep on the waveform and latency of the SSEP are done.

The configuration of long-latency SSEP's changes importantly during the different phases of sleep (Desmedt *et al.*, 1980).

The waveform in REM sleep resembles that in the waking state. In slow wave sleep, however, the configuration is essentially different. In children amplitudes are higher in slow wave sleep (Halliman *et al.*, 1978).

4. Attention and psychological factors

SEPs elicited after electrical stimulation can be modified by voluntary movement of the stimulated limb (Rushton *et al.*, 1981; Cooper *et al.*, 1972; Papakostopoulos *et al.*, 1975), or by mechanical stimuli (Abbruzzese *et al.*, 1981; Jones, 1981; Jones *et al.*, 1981). The amplitudes of the P80/N80 complex and of N140 were diminished by both passive and active movements of the stimulated digit (Rushton *et al.*, 1981; Abbruzzese *et al.*, 1981). This reduction was considered to be the result of a 'gating' process at the cortical level. Cognitive processing even of simple (somato) sensory events in serial selective attention tasks involves complex brain mechanisms that are likely to be reflected in the waveform of the SSEP. Up to at least 45 ms after stimulation, the SSEP is not influenced by mental activity. Later components are probably influenced. The P100 may index the sorting out and identification of input signals against templates in short time memory (Desmedt *et al.*, 1983). The N140 can be influenced by task performance and is considered to be a preselection component. The event-related P300 is the first postdecision potential (Desmedt, 1981 a, b). In Fig. 1 the components are indicated that are influenced by psychic processing.

Table 2. Effect of drugs on long-latency SSEP components in healthy volunteers.

Drug	latency	amplitude
Alcohol	0	0
Amphetamine	↓	↑↑
Anaesthetics	↑↑	—
Barbiturates	↑↑	—
Benzodiazepines	↑↑	—
Chlorpromazine	↑↑	↓↓
Lithium	0	
Neuroleptics	↑↑	—
Tricyclic antidepressants	↑↑	↓ or↑

↑ = increase.
↓ = decrease.
0 = no changes.

5. Drugs

Most drugs that act on the Central Nervous System induce changes in the late components. Benzodiazepines, barbiturates, neuroleptics and chlorpromazine increase late component latencies and reduce amplitudes (Saletu, 1977). Amphetamines increase amplitude and slightly decrease latencies (Shagass, 1983). Tricyclic antidepressants increase latencies and have variable effects on amplitudes (Saletu, 1977). Most anaesthetics reduce amplitudes and increase latencies. A summary of the effects of drugs on the long latency SSEP is given in Table 3.

Clinical applications

In clinical practice the long latency components are useful for the analysis of the integrity of sensory information processing within the cerebral cortex.

Late components are changed when the cortex itself is affected (Colon *et al.*, 1979; Goff *et al.*, 1980; Kazis *et al.*, 1982). Disturbances in the commissural fibers cause propagation defects of the late components to the hemispheres (Ferris, 1973; Goff *et al.*, 1980; Kazis *et al.*, 1982). So, diseases that are especially bound to the cortical gray matter and to the subcortical white matter cause changes in the late components of the SSEP. Especially in diseases where diffuse dysfunction of the cortical gray exists or begins, the late components seem to be more sensitive than the EEG. One of the advantages of the SSEP over the EEG is also the fact that SSEP has a relatively simple form and distribution, whereas it is rather easy to quantify this potential and to compare it with normative values. Therefore, long-latency SSEP's have been utilized to study both neurological and psychiatric disorders. Because of a supposed large interindividual variability of long latency components, the clinical applications are still rather limited. However, from the various normative data in Table 1 it seems that the interindividual variability is not exceeding those of most other biological parameters. The fact that the methodology for elicitation of late SSEP components is still not uniform in various laboratories might be the essential cause for the limited use.

Especially chronotopography and mapping, by enabling evaluation of SSEP's scalp distribution, could increase the clinical use of late SSEP components in the near future (Colon *et al.*, 1985).

1. Focal lesions of the central nervous tissue

Somatosensory evoked potentials after Median nerve stimulation have been studied extensively in neurological diseases in which there are discrete cerebral lesions. The majority of these studies have been concerned primarily with short latency components (Thomson *et al.*, 1973; Shahani *et al.*, 1980; Kazis *et al.*, 1982). A variety of abnormalities were observed, ranging from total

absence of components to subtle alterations of individual components in a localized area. In patients with brainstem lesions, alterations of late components are observed only when early components are abnormal (Noel *et al.*, 1975; Yamada *et al.*, 1975). With thalamic lesions, the characteristics of SSEP abnormalities were generally related to the areas involved. In patients with infarctions involving primary sensory cortex, all SSEP components after P14 were absent when the affected area was stimulated. Lateral thalamic lesions affected especially the Median N60 and P100. Medial thalamic lesions preferentially affected P40 and N60 (Yamada *et al.*, 1985; Chu, 1986; Graff-Radford *et al.*, 1985). Corona radiata infarcts produced SSEP changes similar to those for ventroposterior thalamic lesions.

In patients with parietal lobe lesions and sensory deficits in all modalities, both early and late SSEP components may be affected (Yamamoto *et al.*, 1973; Yamada *et al.*, 1985; Shiba *et al.*, 1983; Stoehr *et al.*, 1983). Whenever there is little or no sensory deficit the early SSEP components may have normal or slightly prolonged amplitudes and/or ciminished amplitudes, especially of P40 and N60 (Mauguière *et al.*, 1982, 1983; Yamada *et al.*, 1983, 1985; Shimasaki *et al.*, 1977). SSEP's are less reproducible on the affected side than on the other side (Wong *et al.*, 1982). Whether this is caused by changes in the "tangentness" of the cortex or by changes in conduction properties of the white matter is not clear. Another explanation might be erratic depolarization of malfunctioning neurons in the diseased cortex. In focal lesions of the Central Nervous System, the changes of long-latency SSEP's are partially dependent on the type of pathology. The abnormalities in patients with tumors are often less severe than those in patients with ischemic or hemorrhagic lesions of the same – anatomical – size. A minor neuronal damage in most tumors might be an explanation for this phenomenon (Shiba *et al.*, 1983). On the other hand one must keep in mind that the functional disturbance and the extension of lesions as imaged with CT or NMR might be larger than can be visualized. Evoked potentials are amongst others a reflection of function and not of anatomical damage.

2. Diffuse diseases of the central nervous system

a) *Intoxications.* The effect of drugs on the SSEP has already been described (see p. 298).

b) *Wilson's disease.* Most patients show prolongation or absence of the later SSEP peaks (Chu, 1986; Lüders *et al.*, 1984).

c) *Renal failure.* Prolonged latencies and abnormal low amplitude late SSEP components are often found. These abnormalities are only partially reversed after hemodialysis (Lewis *et al.*, 1978; Stoehr *et al.*, 1982).

d) *Reye's syndrome.* Both early and late components are markedly abnormal in the acute phase (Goff *et al.*, 1978). Progressive recovery of SSEP components later than P100 has a good prognostic sign. (Goff *et al.*, 1983).

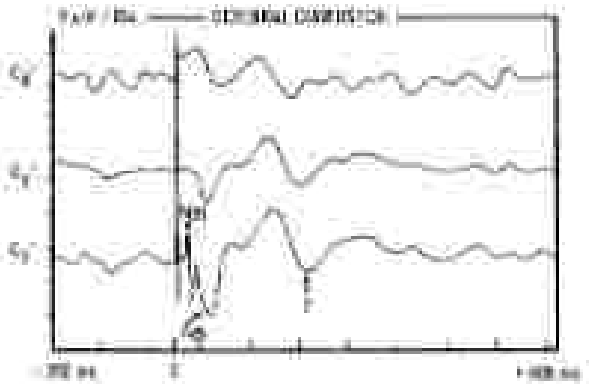


Figure 11. Long latency SSEP abnormality as can be seen after cerebral concussion. Most late components are delayed and the curve is distorted.

e) *Multiple sclerosis*. The midcortical complex P40-N60 may be affected without involvement of the earlier or later peaks (Colon *et al.*, 1964; Yamada *et al.*, 1982).

f) *Leucodystrophies*. The short latency components are selectively altered (Colon *et al.*, 1979; Markand *et al.*, 1982).

g) In *Huntington's disease* late components are delayed, distorted or absent. These abnormalities can also be observed in non-affected relatives (Depen *et al.*, 1981).

h) In *Carotid hypofunction*: absence, and delayed late components occur that are sometimes of high amplitude (D'Albuit *et al.*, 1982).

i) In *myoclonus epilepsy* a myoclonus related highly enlarged N35 appears. This abnormality is not seen in patients with a benign form of myoclonus epilepsy (Halliday and Halliday, 1980; Shibasaki *et al.*, 1980).

j) *Cerebral trauma*. Severe head injury results in relevant changes in SSEP's. The late components are more affected than the early ones. Alterations of long-latency SSEP's are correlated with the outcome (Greenberg *et al.*, 1977; Pfurtscheller *et al.*, 1985). In Fig. 11 an example of a long latency SSEP in a patient with mild cerebral concussion is given.

k) *Surgical monitoring*. Due to the cortical and subcortical depression that may result from anaesthetics late components of SSEP's are probably of minor importance in the operating theater (Saletu, 1977). Only the P40-N60 complex, which is relatively resistant to such influences, has been used to monitor cerebral function during surgery (Markand *et al.*, 1984b).

l) *Psychiatry*. The late components are a reflection of the functional state of the cerebral cortex. Therefore, especially in psychiatry we might expect the most intensive clinical uses of late SSEP components.

The more or less normal changes that are seen in elderly people can be found in a relative early stage of dementia. Severe changes in latencies

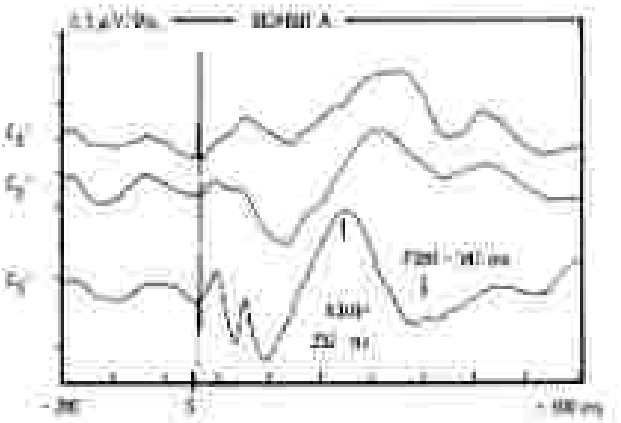


Figure 12. Long latency SSEP in dementia type SDAT, stage 4.

of SSEP components until N140 and a reduction or amplitude or abolition of the latest components are the most findings in progressing dementia (Shagass, 1979, 1983; Platonun *et al.*, 1985). In Fig. 12 an example of a SSEP in a patient with Alzheimer disease stage 4 is given.

Differentiation between dementia and depression is possible in groups of patients (Levy *et al.*, 1971). In schizophrenia, psychotic depression and manic psychosis amplitude reduction and instability of later components is established. In neurosis and personality disorders unstable long latency components are seen as well. The distribution of late components over the skull is disturbed in schizophrenia, especially *cf.* N40 where the maximum is located incorrectly in the frontal region. In depression the P100 is abnormal (see Shagass, 1979, 1983). A relation exists between the metabolites of neurotransmitters in the cerebrospinal fluid and the N140–P200 amplitude (Aegren *et al.*, 1985).

m) *Maturation and mental retardation.* The state of maturation of the brain of newborns can be established by evoked potentials. Hrbeck (1977) demonstrated that increased latency of long-latency SSEP and disturbed wave form is a characteristic pattern in asphyxiated children. A permanently abnormal wave form is a bad prognostic sign. In hemiplegic palsy Luget *et al.* (1976) found a positive correlation between the established changes and the affected side of the body. They concluded that SSEP produces more accurate and reliable diagnostic results than EEG. In the detection of diffuse cortical diseases in children the SSEP shows late component time delay (Calder *et al.*, 1979). In children with a mild mental retardation of unknown origin P200 is delayed and P300, which is related to cognitive aspects of performing tasks (Dirnes, 1982) is even absent in most children. All late components show abnormal dipoles with assumed radial generator in one hemisphere (Calder *et al.*, 1986). In retardates

the functional coupling of the two hemispheres seems to be disturbed. Changes in synapse activity may be the cause of this finding (Bodis-Wollner *et al.*, 1982).

References

Abrahamse G, Barle S, Fayade E, Abel-Aziz M. Hypercapnic modulation of somatosensory evoked potentials during acute or gradual Sigot hemodialysis in man. J Neurol Neurosurg Psychiatry 1981; 44: 945–8.

Angres H, Dannenberg R, Schlüter F, Fuccaro O. Diagnostic significance of somatosensory evoked potentials 1. Correlations between SEP and neurological findings in CSD. Biol Psychiatry 1983; 18: 635–46.

Anthonsen DC, Bodis S, Rinkenauer GL. Somatosensory evoked potentials in cervical head trauma. Arch Neurol Chir 1994; 67: 369–374.

Angel RW, Quick WW, Boyle CC, Weinert M, Buckalew RL. Detection of somatosensory evoked potentials during vertebral decompression. Electromyography Clin Neurophysiol 1981; 60: 535–42. Bodis-Wollner I, Vaky MD, Mylin L, Tzavaras J. Hypointergog deficiency and delayed visual evoked potentials in Parkinson. Ann Neurol 1982; 11: 479–483.

Bongers-Schokking CJ, Colon EJ, Hoogland RA, v.d. Brande JL, de Groot RJ. Somatosensory evoked potentials of normal infants: influence of their handposition, postural stress and number of stimuli. Brain and Development 1989; 11: 33–36.

Bruhn P, de Broucker T, Manyo P, Marinacci S, Wiet JC. Potentiels evoqués somesthésiques et douleur. 1. Etude des réponses corticales corrélées aux différents niveaux de la stimulation. Rev EEG Neurophysiol 1985; 15: 19–28.

Chu NS. Median and tibial somatosensory evoked potentials: changes in short and long-latency components in patients with lesions of the Gasserian and Retrogasserian rootlets. J Neurol Sci 1988; 76: 199–219.

Colon E, Stuart A. Abnormal somatosensory potentials evoked by Achilles tendon taps in humans. Electroencephalogr Clin Neurophysiol 1985; 62: 109–16.

Colon EJ, Reimer W, Galanda E. Propagation defects in somatosensory evoked responses in children. In: Lechner H, Aranibar A (eds.). EEG and clinical neurophysiology. Amsterdam, Elsevier North Holland 1979; 301–5.

Colon EJ. Somatosensory evoked potentials. In: Colon EJ, Visser SL, De Weerd J, Zonneveld A. Evoked potential manual. Boston, The Hague: Martinus Nijhoff Publishers, 1985; 245–317.

Colon EJ, van Mourcker F, Hommes OR, Bruijnes-v.d.Linden R, Dirven C. SSEP chronotopography in patients with multiple sclerosis. Acta Neurol Scand 1986; 69: 38–41.

Colon EJ, van Mourcker F, Hommes OR, Bruijnes-v.d.Linden R, Dirven C. SSEP chronotopography in patients with multiple sclerosis. Acta Neurol Scand 1986; 69: 38–41.

Colon E, Bruining v. d. Bastiaan R, Lipsay H v. d, Dirven C. Somatosensory Chronotopography: Normative values. Z. EEG-EMG 1987; 18: 206–210.

Colon EJ, van der Lende M, Dirven HO, Bruijnes-v.d.Linden R, Dirven C. Chronotopographical potential distribution of some SSEP components in cerebrovascular insufficiency. Eur Neurol 1985; 24: 33–40.

Colon EJ, Reimer W, Galanda E. SSEP topography in children. In: Galley V (ed.). Movements of the CNS and Evoked Potentials. Delgado Medical, Amsterdam, 1986; 141–148.

Colon EJ, Wiet AW. Long-latency somatosensory evoked potentials. J Clin Neurophysiol 1986; 3(4): 279–296.

Cuypers JM, Cochlovius M, Lenz MC. Modification des potentiels evoqués corticaux somesthésiques dûment dus mouvements actifs et passifs chez l'homme. Electroencephalogr Clin Neurophysiol 1972; 33: 295–306.

D'Albis AM, Lugli P, Rainaldi J. Visual pre-saccadic potentials in schizophrenia. In: Courjon J, Mauguière F, Revol M (eds.). Clinical applications of evoked potentials in neurology. New York: Raven Press 1982; 397–407.

Dubocovich A, Deyrolle JE. Les potentials evoques occipitaux et les potentials de scalp associes avec l'ouverture et l'fermeture des yeux chez l'homme. Electroencephalogr Motricite 1961; 8. Acta Neurol Bel 1968; 68: 1213–1244.

Desmedt JE. Scalp potential spatial mapping, pattern recognition, and muscle or nerve models of cognitive processing. In: Sidtis JJ, Weitzman ED, Wollman RD, Divenyi PL (eds.). The organization of the cerebral cortex. Cambridge, MA: MIT Press 1981; 441–71.

Desmedt JE, Huy NT, Bourguet M. The cognitive P40, N60 and P100 components of somatosensory evoked potentials and the earliest electrical signs of sensory processing in man. Electroencephalogr Clin Neurophysiol 1983; 56: 272–82.

Desmedt JE, Bourguet N. Color imaging of parietal and frontal somatosensory potential fields evoked by stimulation of median or posterior tibial nerve in man. Electroencephalogr Clin Neurophysiol 1985; 60: 1–17.

Desmedt JE. Some observations on the morphology of cerebral evoked potentials in man. In: Desmedt JE (ed.). Attention, voluntary contraction and event related cerebral potentials. Basel, Karger 1977; 1–36.

Desmedt JE, Brunko E, Debecker J. Maturation and cerebral origin of the somatosensory evoked potential. In: Desmedt JE (ed.). Clinical uses of cerebral, brainstem and spinal somatosensory evoked potentials. Basel, Karger 1980; 140–6.

Desmedt E. Brain and peripheral neural correlates following sigmoid sinus thrombosis in man. In: Barber C (ed.). Evoked Potentials. Lancaster, PA: MTP Press Ltd 1980; 215–22.

Dubow M, Coppola R, Rosenbaum MS. Late (80) somatosensory evoked potentials during whole body hyperthermia in humans. Electroencephalogr Clin Neurophysiol 1981; 52: 157–62.

Eimas GD, Siqueland ER. Evoked responses to speech and nonspeech. Electroencephalogr Clin Neurophysiol 1975; 39: 442. Halliday AM, Halliday E. Cerebral blood flow, oximetry and visual evoked potentials in different clinical forms of myopathy. In: Desmedt JE (ed.). Clinical uses of cerebral, brainstem and spinal somatosensory evoked potentials. Basel, Karger 1980; 292–310.

Fagerini D, Colombelli E. Cerebral response of psychophysical responses evoked by tactile stimulation in man. Ergebn Rev Physiol 1968; 1–18.

Goff GD, Matsumiya Y, Allison T, Goff WR. The scalp topography of human somatosensory and auditory evoked potentials. Electroencephalogr Clin Neurophysiol 1977; 42: 57–76.

Goff WR, Allison T, Vaughan HG. The functional neuroanatomy of event related potentials. In: Callaway E, Tueting P, Koslow SH (eds.). Event related brain potentials in man. New York, Academic Press 1978; 1–80.

Goff WR, Williamson PD, Van Gilder JC, Allison T, Fisher TC. Special origins of long-latency evoked potentials recorded from the depth and from the cortical surface of the brain in man. In: Desmedt JE (ed.). Clinical uses of cerebral brainstem and spinal somatosensory evoked potentials. Basel, Karger 1980; 126–45.

Goff WR, Rhoades RA, Goff GD, Rubinstein MA, Barrientos JG, Vance JL, Rothman PD. Somatic evoked potentials: exceptions of cerebral origin. Electroencephalogr Clin Neurophysiol 1980; 50: 301–06.

Graff-Radford SB, Damasio H, Yamada T, Eslinger PJ, Damasio AR. Nonhemorrhagic thalamic infarction. Clinical, neuropsychological and electrophysiological findings in four anatomical groups defined by CT. Brain 1985; 108: 485–516.

Grossberg JP, Becker DP, Miller JD, Mayer EJ. Localization of brain function in severe human head injury with multimodality evoked potentials. Part II: Localization of brain dysfunction and correlation with post-traumatic neurological conditions. J Neurosurg 1977; 47: 163–177.

Greenwood PM, Goff WR. Modification of midlatency somatic evoked potentials by prior median nerve, peroneal nerve and auditory stimulation. Electroencephalogr Clin Neurophysiol 1987; 68: 295–302.

Grunewald G, Grunewald-Zuberbier E, Schuppenies H, Mewald J, Mehl J. Somatosensory evoked potentials to mechanical displacement of gastrocnemius tendon in man: Gating of middle range components. Electroencephalogr Clin Neurophysiol 1986; 64: 525–36.

Halliday AM, Mason AA. The effect of hypnotic suggestion on cortical responses. J Neurol Neurosurg Psychiat 1964; 27: 300–312.

Hashimoto I. Somatosensory evoked potentials of cortical origin elicited by a new light-spot stimulation system. Electroencephalogr Clin Neurophysiol 1983; 55: 230–235.

Henderickson E, Levy R, Post F. Averaged evoked responses in relation to cognitive and affective state of elderly psychiatric patients. Br J Psychiatry 1979; 134: 604–610.

Hrbek AP, Kjellberg P, Kjellmer G, Olsson T, Riha M. Clinical application of evoked electroencephalographic responses in newborn infants. J Perinat Aesthetic Develop Med Child Neurol 1977; 19: 34–44.

Hussain UW, Pasha M, Haque U, Khan SL, Ar Rijhi W. Somatosensory evoked potentials in healthy volunteers and in patients with dementia. Clin Neurol Neurosurg 1995; 97: 11–16.

Johansson RS, Vallbo AB. Tactile sensibility in the human hand: Relative and absolute densities of four types of mechanoreceptive units in the glabrous skin. J Physiol (Lond) 1979; 286: 283–300.

Johnson D, Jannetta R, Kemeckey MH. Somatosensory evoked potentials and vibration. Arch Psychiat Nervenkr 1980; 228: 191–7.

Jones SJ. An 'interference' approach to the study of somatosensory evoked potentials in man. Electroencephalogr Clin Neurophysiol 1981; 52: 167–76.

Jones SJ. Surface distribution and normal ranges of somatosensory evoked potentials. In: Chiarenza GA, Papakostopoulos (eds.). Clinical application of cerebral evoked potentials in pediatric medicine. Europa Medica, Giannini; 1982; 103–113.

Jones SJ, Power CN. Scalp topography of [somatosensory evoked potentials] the effect of interfering tactile stimulation applied to the hand. Electroencephalogr Clin Neurophysiol 1984; 58: 23–36.

Kakigi R, Shibasaki H. Scalp topography of vibratory and electrically evoked somatosensory potentials in man. Electroencephalogr Clin Neurophysiol 1984; 59: 48–56.

Kalra A, Nicholas D, Papakostopoulos J, Papakostopoulos A, Ferguson D. Somatosensory evoked potentials in unilateral cerebral lesions. BMJ (Clin Res Ed) 1982; 285: 1681–1682.

Khechinashvili G, Thompson DR, Ellington RJ. Event related brain potentials across the life span. In: Calloway E, Tueting P, Koslow SH (eds.). Event related brain potentials in man. New York, Academic Press 1978; 11–30.

Lagos P, Ramseault J, D'Allaire AM, Jean-Guerrier R, Bastien J, Tanon-Perron G. La stimulation des potentiels evoques somatosensoriels chez l'homme. Electroencephalogr Clin Neurophysiol 1973; 40: 499–515.

Lagos P, Maniscalco M. Effects of the somatosensitive evoked potentials in normal children. In: Chiarenza GA, Papakostopoulos D (eds.). Clinical applications of cerebral evoked potentials in pediatric medicine. Amsterdam, Excerpta Medica 1982; 145–216.

Lamarre LE, Perez TS. Somatosensory response to mechanical stimulation as recorded in the human EEG. Electroencephalogr Clin Neurophysiol 1970; 28: 362–372.

Lee RG, White BG. Modification of the human somatosensory evoked response during voluntary movement. Electroencephalogr Clin Neurophysiol 1976; 39: 53–67.

Levy R, Jones A, Behrman J. Neurophysiological correlates of senile dementia. II. The somatosensory evoked response. Psychol Med 1971; 1: 159–63.

Lewis EG, Dahiotis BE, Beck EC. Visual and somatosensory evoked potentials in patients undergoing hemodialysis and kidney transplantation. Electroencephalogr Clin Neurophysiol 1979; 46: 223–31.

Lindsay KW, Carlin E, Reynolds J, Fry J, McLaren A, Tuttaba GM. Evoked potentials in severe head injury: clinical and electrophysiological correlations. J Neurol Neurosurg Psychiat 1981; 44: 780–787.

Ludwig H. The effects of aging on the wave form of the somatosensory cortical evoked potential. Electroencephalogr Clin Neurophysiol 1970; 29: 470–80.

Luders H, Klass M, Klawans Jr. Cortical evoked potentials in hyperkinetic dyskinesias. Electroencephalogr Clin Neurophysiol 1980; 27: 425–428.

Markand ON, Warren CH, Moorthy SS, Mencang RR, Hagi RD. Monitoring of multimodality evoked potentials during open heart surgery under hypothermia. Electroencephalogr Clin Neurophysiol 1984; 59: 432–48.

Markand ON, DeMyer WE, Wood RM, Warren C. Multimodality evoked responses in brainstem epilepsy. In: Courjon J, Mauguière F, Revol M (eds.). Clinical applications of evoked potentials in neurology. New York, Raven Press 1982; 409–19.

Markand ON, Daly RS, Moorthy SS, Warren C. Monitoring of somatosensory evoked responses during carotid endarterectomy. Ann Neurol 1984; 15: 375–8.

Mauguière F, Desmedt JE, Courjon J. Astereognosis and dissociated loss of frontal or parietal components of somatosensory evoked potentials in hemispheric lesions. Brain 1983; 106: 271–311.

Mauguière F, Buisson AM, Labadie JF, Courjon J. Early somatosensory evoked potentials in thalamocortical lesions of the hemispheral surface in humans. In: Courjon J, Mauguière F, Revol M (eds.). Clinical applications of evoked potentials in neurology. New York, Raven Press 1982; 321–39.

Matsumoto T, Shimada Y, Furukawa Y. Somatosensory evoked responses to mechanical stimulation in normal subjects and in patients with neurological disorders. J Neurol Sci 1978; 37: 209–16.

Nakanishi T, Takita K, Tagashira T. Somatosensory evoked responses to tactile tap in man. Electroencephalogr Clin Neurophysiol 1977; 34: 1–6.

Noel P, Desmedt JE. Somatosensory evoked potentials after cerebellar lesions of the hemisphere and dentate nucleus. Brain 1977; 99: 113–128.

Orgeas G, Desmedt JE, Thodeux V. Visual and somatosensory evoked potentials in Huntington's Chorea. Electroencephalogr Clin Neurophysiol 1981; 51: 666–679.

Papakostopoulos D, Cooper R, Crow HJ. Inhibition of cortical evoked potentials and sensation by self-initiated movement in man. Nature (Lond.) 1975; 258: 321–324.

Papakostopoulos D, Crow HJ. Event recording of late somatosensory evoked potentials from the cerebral cortex of man and the differences between preparatory and postmotor potentials. In: Desmedt JE (ed.). Clinical uses of cerebral brainstem and spinal somatosensory evoked potentials. Basel, Karger 1980; 17–26.

Pfurtscheller G, Schwarz G, Grienenberger K. Clinical relevance of long latency SEPs and VEPs during coma and emergence from coma. Electroencephalogr Clin Neurophysiol 1980; 62: 48–60.

Pratt H, Politoske D, Starr A. Multimodality and directionally evoked somatosensory potentials in humans: effects of attention and precentral cortex lesions. Electroencephalogr Clin Neurophysiol 1980; 49: 240–254.

Rushton DN, Rothwell JC, Craggs MD. Gating of somatosensory evoked potentials during different kinds of movement in man. Brain 1981; 104: 465–91.

Salem R. Cerebral evoked potentials in psychopharmacology. In: Desmedt JE (ed.). Auditory potentials in man. Psychopharmacology correlates of evoked potentials. Basel, Karger 1977; 175–207.

Shagass C. Evoked potentials in adult psychiatry. In: Hughes JR, Wilson WP (eds.). EEG and evoked potentials in psychiatry and behavioral neurology. Boston MA, Butterworth 1983; 169–210.

Shagass C. Sensory evoked potentials in psychosis. In: Buchsbaum M (ed.). Evoked brain potentials and behaviour. New York, Plenum Press 1979; 467–88.

Shagass C, Roemer RA, Straumanis JJ, Amadeo M. Spatial distribution of sensory evoked potentials in psychiatric disorders. In: Lesse (ed.), Callaway E (eds.). Brain evoked potentials. New York, Plenum Press 1978; 347–82.

Shimoji K, Bharucha BP, Capildeo RS. Comparative study of early and late somatosensory evoked potentials in patients with anoxaemia and/or hypotension. In: Barber C (ed.). Evoked potentials. Lancaster, PA, MTP Press Ltd 1980; 467–76.

Shibasaki H, Yamashita Y, Tsuji S. Somatosensory evoked potentials. Diagnostic criteria and abnormalities in cerebral lesions. J Neurol Sci 1977; 34: 427–36.

Buttgen M, Dejean A. Brief latency cortical potentials evoked by acute target stimulation of body and face in man. Electroencephalogr Clin Neurophysiol 1984; 58: 418–427.

Bühs N, Gerber Th, Thiagel R.N. Somatosensorisch evozierte kortikale Potentialkomponenten bei Hallux-Stimulation: durch overbeck Untersuchungsmethode Elektromyogr. Z Elektr Elektr 1983; 14: 196–203.

Starr A, Mc Kean R, Shaw N, Buchl D. Cervical potentials evoked by muscle stretch in man. Brain 1983; 106: 149–166.

Goode M, Dehgaan J, Voge K, Buettner UW. The significance of spontaneously evoked potentials for localization of unilateral lesions within the cerebral hemispheres. J Neurol Sci 1983; 61: 49–63.

Goode M, Dehgaan HC, Buettner UW. Evoked Potentials. Berlin, Heidelberg, New York, Springer Verlag 1982, 212–5.

Iinuma T, Hirose N, Nemoto S, Takahashi M. Cerebrovascular disease. Changes in somatosensory evoked potentials associated with unilateral lesions. Electroencephalogr Clin Neurophysiol 1973; 35: 463–473.

Tsumoto T, Hirose N, Nemoto S, Takahashi M. Analysis of somatosensory evoked potentials to lateral popliteal nerve stimulation in man. Electroencephalogr Clin Neurophysiol 1973; 35: 379–88.

Tsujimoto H, Yamashita Y, Kayama Y. The high amplitude somatosensory evoked potential in progressive myoclonic epilepsy, its relationship with the myoclonus-related cortical spike. In: Barbet C (ed). Evoked Potentials. Lancaster, PA, MTP Press LTD 1986; 475–84.

Willer JC, Simonet S, Maitre P, de Broucker T, Rondi P. Parietal evoked potentials in diabetic polyneuropathy: the sensation-independent cortical potential and the cortical N wave. Ann EEG Neurophysiol 1985; 15: 27–39.

Wong PKH, Gentleman CT, Mastaglia F. Somatosensory evoked potentials: variability analysis in intubated laryngectomy cases. Electroencephalogr Clin Neurophysiol 1982; 54: 266–74.

Yamada T, Graff-Radford MR, Kimura J, Dickins QS, Adams HP. Topographic analysis of somatosensory evoked potentials in patients with left hemisphere ischemic infarctions. J Neurol Sci 1985; 68: 31–46.

Yamada T, Tanner M, Kimura J. Thoracic outlet and somatosensory evoked potentials. Neurology 1981; 31: 1524–8.

Yamada T, Kimura J, Wilkinson JT, Kaminski R. Short and long latency median somatosensory evoked potentials. Findings in patients with localized neurological lesions. Arch Neurol 1983; 40: 215–20.

Yiannikas T, Kimura J, Young E, Powers M. Scalp potentials evoked by bilateral stimulation of the median nerve and its clinical significance. Neurology 1979; 29: 219–23.

Yiannikas T, Shiraishi E, Wilkinson JT, Kimura J. Short and long latency somatosensory evoked potentials at multiple sclerosis. Arch Neurol 1982; 39: 88–91.

Case histories of short latency and long latency somatosensory evoked potentials

E.J. COLON

E. J. Colon and J. L. Vitek (eds), Evoked potential manual, 307–317.

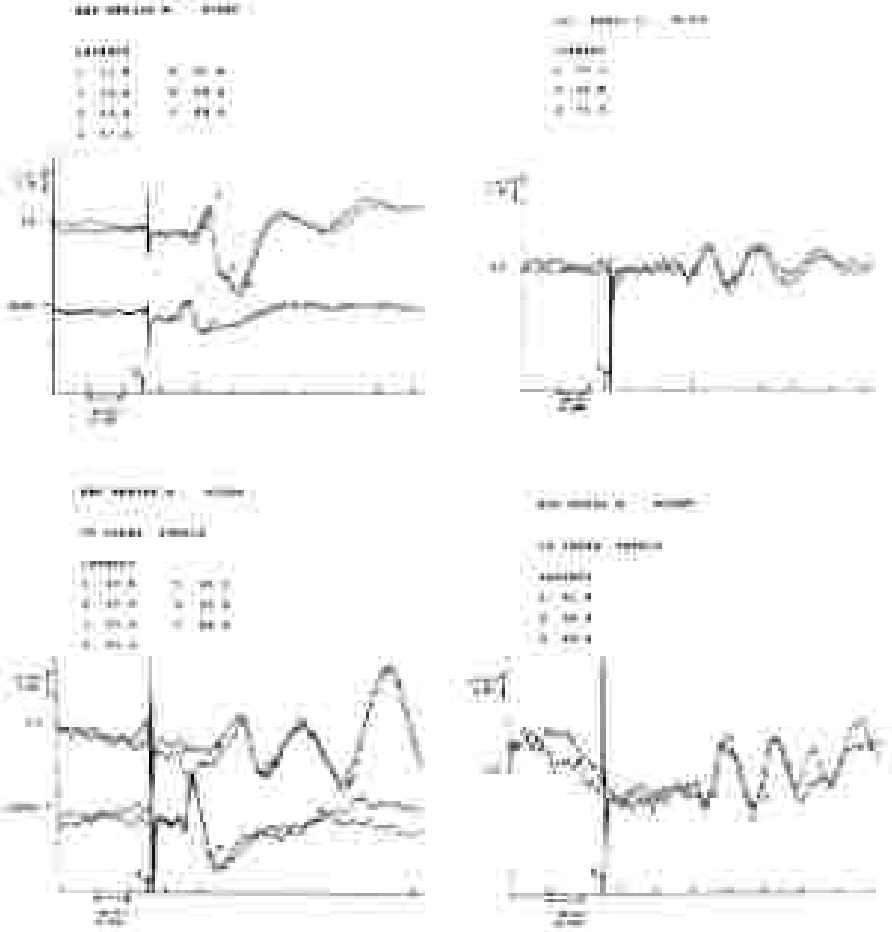


Figure 1

Case 1

Female 30 year

22 • Unilateral blurred vision.
• Complete recovery.
23 • Unilateral blurred vision and slight paresis of the right arm.
• Quite complete recovery.
27 • Ataxia and auditory impairment.
• Quite complete recovery.
30 • Progressive bilateral vision loss.

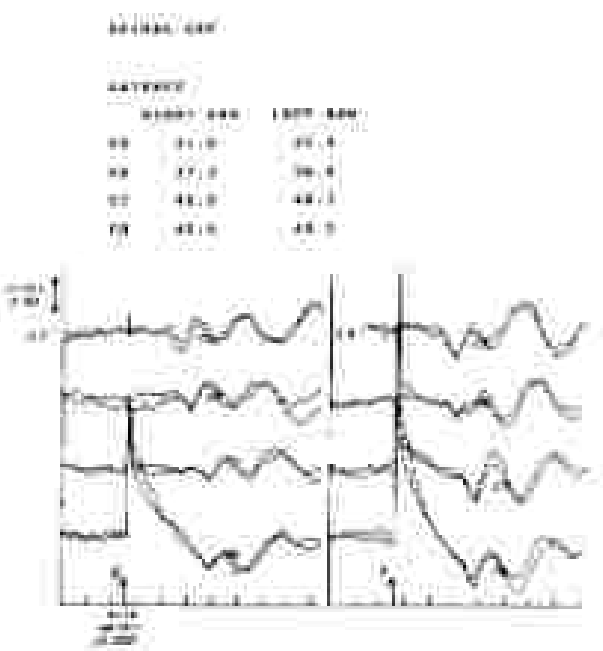
At admission
• Slight ataxia, slight pyramidal syndrome.
• Spinal fluid: Igg increased.
• EEG: normal.
• EMG: normal.
• CT: normal.

See Figure 1.

SSEP top
Example of a normal median nerve SSEP and example of a normal sural nerve SSEP.

SSEP bottom
• SSEP's of the patient.
• The median nerve SSEP is normal in the cervical derivation an delayed at the cortical (N20) level.
• the sural nerve SSEP is delayed.

Conclusion
Dysfunction of propagation of information over the white myelinated pathways in the central nervous system.



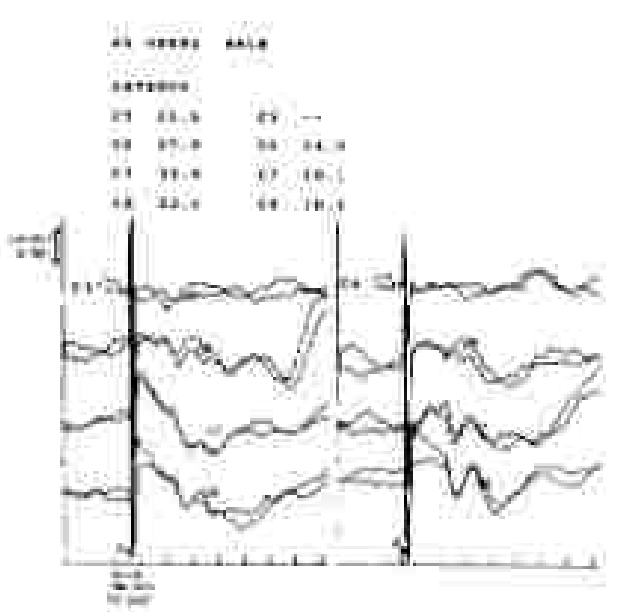


Figure 2

Case 2

Man 45 years

During recent years cervicobrachialgia on the left side.

At admission
- Disturbed abduction of the left arm.
- No other neurological findings.
- X-ervical region: foramen C5-C6 too small.
- EMG three weeks later: normal motoric and sensory velocities and fibrillations and positive sharp waves in deltoid and biceps muscle.

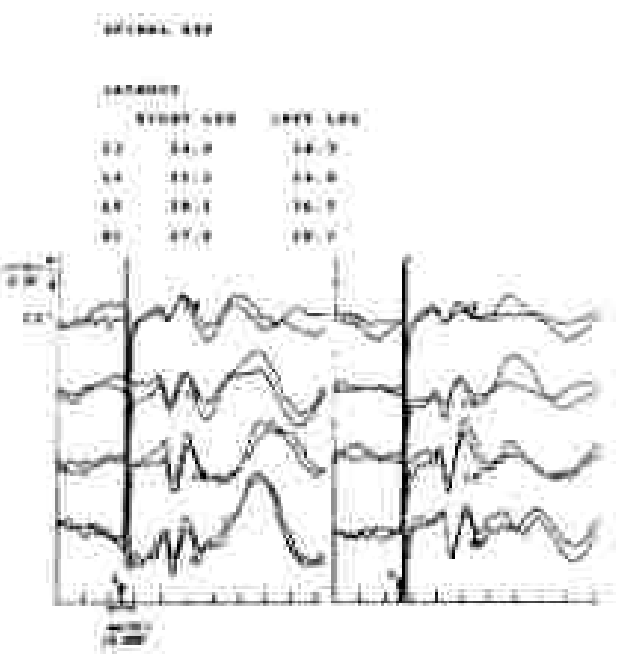
See Figure 2.

SSEP re-test
normal dermatomonal SSEP C5 until T101.

SSEP histogram
abnormal C5 SSEP on the left side.

Conclusion
C5 lesion on the left side.

Dermatomonal stimulation, 3 = stimulation level, 3/s, n= 200, bandpass 5–250 Hz, reference electrode at Fz.



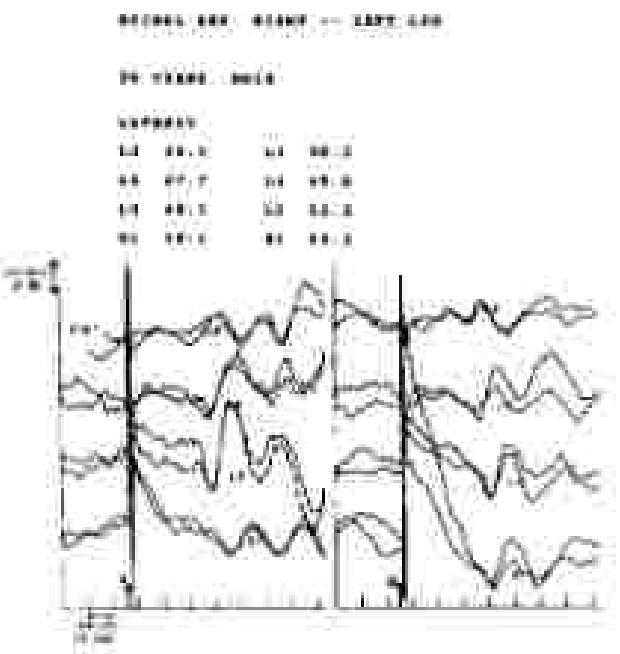


Figure 1

Case 3

Man 39 years

Since a number of years lumbosacral complaints, radiating into the right leg.

At admission:
- No neurological findings except hypaesthesia on the lateral side of his right foot.
- Myelography: normal.
- CT: normal.
- EMG: Normal H-reflexes over Soleus and Gastrocnemius muscle. Some denervation in the Gastrocnemius muscle (S1) on the right side.
- Normal motoric and sensory velocities.

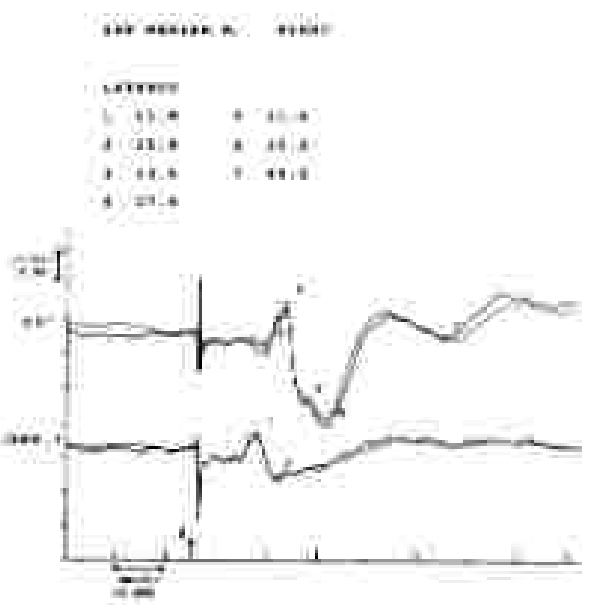
See Figure 3.

SSEP top:
Normal dermatomomal SSEP L3 and S1.

SSEP bottom:
Abnormal S1 SSEP on the right side.

Conclusion
S1 lesion on the right side.

Dermatomomal stimulation, 3 × sensation level, 3/s, = 200, bandpass 5–250, reference electrode at Fz.



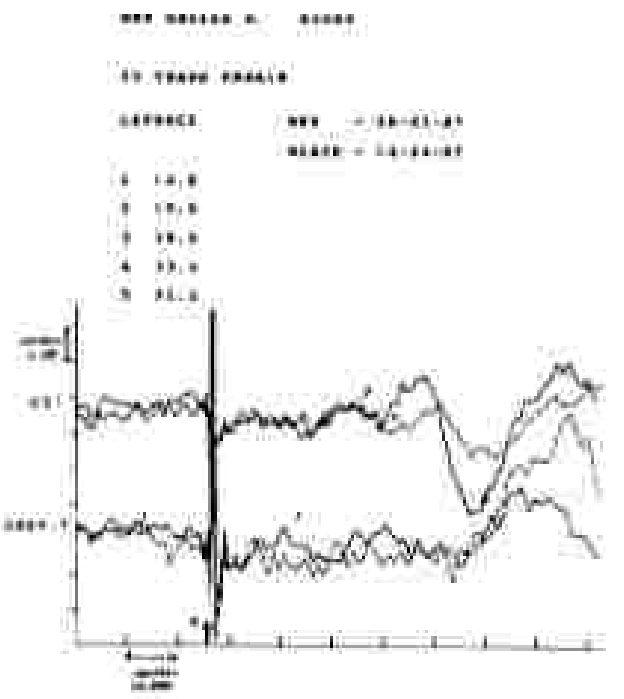


Figure 8

Case 4

Female 55 years

52y • Disturbed vision right eye (amaurosis fugax?).
• Complete recovery.
53y • Paresis right leg.
• Complete recovery.
55y • Again slight paresis right leg.

At admission
• Slight pyramidal syndrome right leg.
• Slight ataxia.
• Spinal fluid: IgG increased.
• EMG: normal.
• EEG: normal.
• NMR: normal.

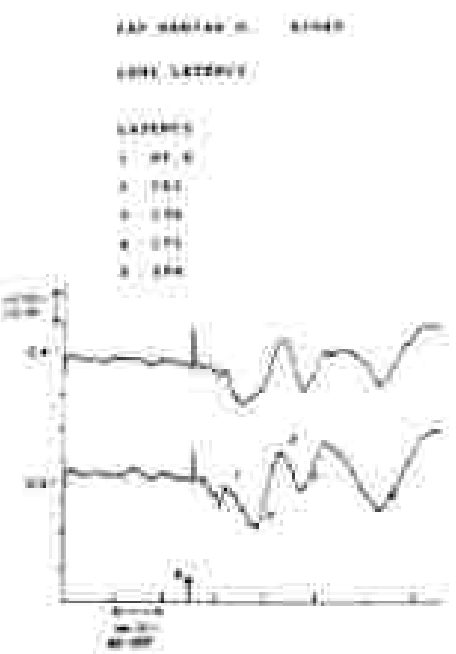
See Figure 4.

SSEP top:
Example of a normal median nerve SSEP.

SSEP bottom:
No cervical reaction and only P45 at the cortical level.

Conclusion
Dysfunction of propagation of information over the myelinated pathway in between median nerve and cortex. Rather typical reaction in patients with demyelinating disease.

Median nerve stimulation, 3/s, cortical level, regular, bandpass 5–2500 hz, reference electrode at A (ipsi).



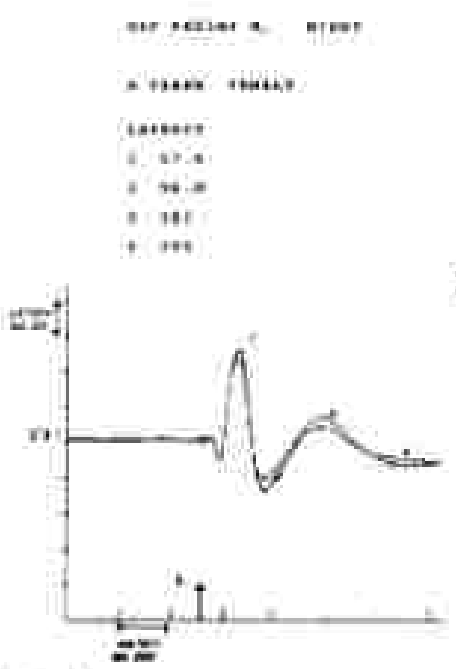


Figure 5

Case 5

Girl 8 years

- Language development disturbed.
- Pregnancy and labor normal.
- 3y: febrile convulsions.

At admission
- Normal weight and length.
- No physical abnormalities.
- CT: normal.
- Psychological examination: language development 2 years retarded.
- EEG: spike-slow wave complexes in both parietal areas. Amplitude of this complex in left cortex twice as high as in the right cortex.

See Figure 5.

SSEP top:
Example of a normal (long latency) SSEP.

SSEP bottom:
SSEP after right and after left median nerve stimulation.

Conclusion
Stimulation of the median nerve provokes spike and slow wave parietal area.

Median nerve stimulation, 0.3/3, random, switch level, bandpass 0.3 until 250 hz, reference electrode at Afpz.

Transcranial and transcord stimulation

E.J. COLON

Introduction

Noninvasive stimulation of the human cortex is possible by means of electrical and magnetic brain stimulation. In 1980 and later on in 1982 Merton and Morton described a low output impedance electrical stimulator, with which central motor conduction velocity can be measured. Stimulation of the motor cortex trough the intact scalp and skull by brief high voltage stimuli can give rise to brief muscle contractions, for example, in the hand (Marsden *et al.*, 1983).

Averaging of the response is not necessary. A single electrical stimulus activates, probably, pyramidal tract neurones to produce the fast descending volley in the corticospinal tract which is called the D-wave. At high intensity the pyramidal neurones produce later repetitive waves called I-waves (Kernell and Chien-Ping, 1967). The stimulation procedure can be used at the vertebral column either, where the proximal motor roots are activated (Mills and Murray, 1986). That way conduction studies over the various central or peripheral segments of the motorpathways are possible (see also Fig. 1).

The major disadvantage of this method is the local painsensation in the scalp in the area of high current density. Polson and Barker developed in 1982 a time varying magnetic field stimulator. With this stimulator the motor cortex can be stimulated easily with no discomfort at all (Barker *et al.*, 1982). Of course, this stimulator is more expensive in relation to the electrical one. However, magnetic stimulation proved to be noninvasive. Magnetic stimulation is considered to be safe. However, a history of epilepsy or a cardiac pace maker are relative contraindications. Therefore, we advocate this method in all other indications.

Method of stimulation

For cortical electrical stimulation the anode is placed on the motor area of the arm or hand. A point 7 cm below the interaural line from the vertex

E. J. Colon and S. E. Visser (eds), Evoked potential manual, 319–324.

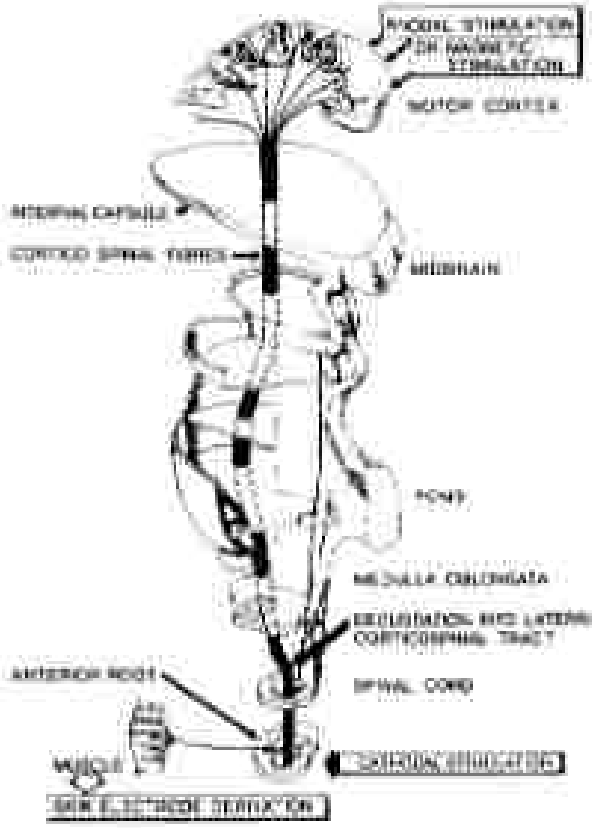


Figure 1. Schematic drawing of the methods of cortical nervous system stimulation.

and 1 cm anterior to that line is generally used. The cathode is placed 6 cm anterior to the anode. Stimuli from a low output impedance stimulator are applied with increasing voltage between 800 and 1900 Volts, decaying with a time constant of 50 mus, until a maximum amplitude response is obtained from the moderately contracted muscle (about 5%). Recently Hassan *et al.* (1985) reported a technical adjustment that allows electrical stimulation of the motor cortex by commercially available scalp electrodes. For unifocal stimulation a flat circular anode is placed on the scalp overlying the motor cortex. A flexible stainless steel belt cathode is wrapped around the head 2 to 3 cm above the nasion plane. The unifocal stimulation is performed with voltages between 100 and 300 μV. The response can be recorded by means of surface electrodes and displayed on a conventional electromyograph machine. Spinal root stimulation can be done by the same electrical stimulator. Here the cathode is placed between the spines concerned, the anode is on lateral to the cathode. For cortical magnetic stimulation a small flat circular

copper coil is placed above the vertex. Capacitors charged to a maximum of 3 KV are discharged through the coil. A brief magnetic field (at 150 mmV, 2.1 Tesla peak) generates and induces a current in the brain. Stimulation intensities of 20% above threshold are applied. A small voluntary contraction, or preinnervation, of the stimulated muscle may be useful to facilitate the response. That way a greater amplitude and shorter latency (Day., 1986) are obtained (1–2ms). Evoked responses after magnetic cortical stimulation have a significantly larger latency than after electrical stimulation. The average difference is 1.5 ms. Isolated high cervical tract stimulation exiting motoneurones of the upper extremity is often not possible since the excitation threshold of the motor roots is much lower than of the descending motor tracts (Meyer *et al.*, 1987).

Normative values

a) *Cortex stimulation*

C7/T1 interspace stimulation and correction form m. abd. digiti minimi (Hess *et al.*, 1986). Stimulation by means of magnetic induction above the vertex and electrical stimulation over C7/T1 interspace by means of low output impedance electrical stimulator

Cortex — M. abd. dig. min.:	latency	19.6 ± 1.4 ms
	amplitude	2.0 ± 6.8 mmV
C7/T1 — M. abd. dig. min.:	latency	13.6 ± 1.6 ms
	amplitude	3.5 ± 10.7 mmV

18 normal subjects, 21–38 Y, 14 men and 4 women, 22 sides.

b) *Spinal cord and cauda equina stimulation*

At C8, L1 and L4 muscle responses are recorded from the pelvic floor (intra anal surface electrodes) or from the tibial anterior muscle (Sakoda and Swash, 1985).

Motor conduction velocity C8 — L1: 67.4 ± 9.1 m/s
Motor conduction velocity L1 — L4: 57.9 ± 10.3 m/s

21 subjects, 22–73 years.

c) *Cortex stimulation, C7 root stimulation and cervix stimulation*

Stimulation by means of an electrical low output impedance stimulator. Response are recorded from the forearm flexor muscles (Mills and Murray, 1985).

Cord to axilla conduction: 4.1 ± 0.01 ms
Cortex to cord conduction: 4.4 ± 0.75 ms

15 subjects, 12 males between 19 and 37 years and 3 females between 19 and 34 years.

d. Cortex stimulation

Stimulation by means of an electrical low output generator (Thomson *et al.*, 1985, 1987).

Cortex to Biceps muscle	:	10.2 ± 0.6 ms
Cortex to Finger extensors	:	13.7 ± 1.4
Cortex to Thenar muscle	:	19.6 ± 1.1 ms
Cortex to Quadriceps muscle	:	21 ± 1.2 ms
Cortex to Tibialis ant. muscle	:	29.3 ± 1 ms
Cortex to Ext. Dig. Brev. muscle:		39.9 ± 1.9 ms

24 subjects, 23 males and 1 female between 26 and 58 years for the arm and 16 subjects between 28 and 34 years for the legs.

Clinical application

Up to now clinical applications are mainly on the field of demyelinating diseases, especially of MS (Cowan *et al.*, 1984; Hess *et al.*, 1986; Mills *et al.*, 1985; Rossini *et al.*, 1985; Snooks *et al.*, 1985; Thomson *et al.*, 1985; Hess *et al.*, 1987). In nearly all patients with definite MS the central motor conduction time (C.M.C.T.) has prolongated. The method is of value, especially when physical signs are equivocal in patients with probable multiple sclerosis.

Defects in motor conduction can also be demonstrated in patients with cervical cord trauma and myelopathy (Snooks *et al.*, 1985; Thomson *et al.*, 1985, 1987 a, b) and during scoliosis therapy (Boyd *et al.*, 1986). In some patients somatosensory evoked potentials failed to predict postoperative paralysis (Lesser *et al.*, 1986). Motor conduction time can likely help here. For intraoperative monitoring or the assessment of motor function in comatose patients one has to rely on normative values achieved without preinnervation (Hacke *et al.*, 1987). These normative values are in general increased with more than 2.5 ms after cortex stimulations. The latencies of the spinal stimulated muscle potentials are comparable for preinnervated as well as not preinnervated muscles.

Even in motor neuron disease an abnormal central motor conduction can be established (Ingram *et al.*, 1986; Berardelli *et al.*, 1987).

Vascular insufficiencies in the spinal cord (e.g. the spinalis anterior syndrome) especially affect the anterior part of the cord and here C.M.C.T. studies are more useful than SSEP (Boyd *et al.*, 1986; Levy *et al.*, 1984).

For clinical application the examination of transcephalic magnetic or electric cortex stimulation, or cord stimulation can quickly be performed. It is an easy and noninvasive method.

References

Berardelli A, Inghilleri M, Formisano R *et al.*, Spinal cord motor tracts in motor neuron disease. In *J Neurol Neurosurg Psychiatr* 1987; 50(6):772–777.

Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of the human motor cortex. *Lancet* 1985; 2(8437):1106–1107.

Boyd SG, Rothwell JC, Cowan JMA *et al.* A method of monitoring function in corticospinal pathways during scoliosis surgery with a note on motor conduction velocities. *J Neurol Neurosurg Psychiatr* 1986; 49:251–257.

Cowan JMA, Dick JPR, Day BL *et al.* Abnormalities in central motor pathway conduction in multiple sclerosis. *Lancet* 1984; 2:304–307.

Day BL, Dick JPR, Marsden CD, Thompson PD. Differences between electrical and magnetic stimulation of the human brain. *J Physiol* 1986; 378:34P.

Hauler W, Wachter H, Schrappeling H, Kartner Dr. Motor potentials following spinal and transcranial stimulation. Normative values of amplitude within a pronator muscle. *Z EEG-EMG* 1987; 18:173–178.

Hennerici MF, Rossini PM, Cracco RQ, Cracco JB. Vertexoid motor cortex activation by low voltage stimuli. In: Mortimer C, Rizzo PA (eds.). *Evoked Potentials: Neurophysiological and clinical aspects*. Elsevier, New York, 1985, pp 3–13.

Hess CW, Mills KR, Murray NMF. Measurement of central motor conduction in multiple sclerosis by magnetic brain stimulation. *The Lancet*, August 16, 1986, 335–336.

Hess CW, Mills KR, Murray NMF, Schriefer TN. Magnetic brain stimulation. Central Motor Conduction studies in Multiple Sclerosis. *Annals of Neurol* 1987; 22(6):744–752.

Ingram DA, Swash M. Central motor conduction is abnormal in motor neuron disease. *J Neurol Neurosurg Psychiatr* 1986; 49:475.

Kuroiwa Y, Celesia GG, Ping W. Symptoms of the premotor cortex in infarction of the patient's motor cortex. *J Physiol* 1987; 191:653–672.

Lesser RP, Kanazawa P *et al.* Functional neurological criteria may assist despite unchanged intraoperative somatosensory evoked potentials. *Anesthesiology* 1986; 19–22–25.

Levy WJ, York DH, McCaffrey, Dawson F. Motor evoked potentials from transcranial stimulation of the motor cortex in humans. *Neurosurgery* 1984; 15:287–302.

Merton CD, Morton PA, Morton HB. Direct electrical stimulation of corticospinal pathways through the intact scalp in human subjects. *Adv Neurol* 1983; 39:393–401.

Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. *Nature* 1980; 285:227.

Merton PA, Morton HB, Hill DK, Marsden CD. Scope of a technique for electrical stimulation of human brain, spinal cord and muscle. *Lancet* 1983; 2:597–600.

Mills KR, Murray NMF. Corticospinal tract conduction time in multiple sclerosis. *Ann Neurol* 1985; 18(6):682.

Mills KR, Murray NMF. Electrical stimulation of the human vestibulo-ocular system: which motor elements are excited? *Electroencephalogr Clin Neurophysiol* 1986; 17(2):65–67.

Polson MJR, Barker AT, Freeston IL. Stimulation of nerve trunks with time-varying magnetic fields. *Med Biol Eng Comput* 1982; 20:243–244.

Swash M, Kamil M. Motor conduction velocity in the human spinal cord: slowed conduction in multiple sclerosis and radiation myelopathy. J Neurol Neurosurg Psychiat 1985; 48:1135–1138.

Thomson PD, Day BL, Rothwell JPR *et al*. Central motor conduction in neurological disease. Electroencephl Clin Neurophysiol 1985; 61:68–78.

Thomson PD, Day BL, Rothwell JPR *et al*. The interpretation of electromyographic responses to cortical stimulation of the motor cortex in diseases of the upper motor neurons. J of the Neurol Sci 1987; 80:1–10.

PART FIVE

Event related evoked potentials

An introduction to methodology, psychophysiological significance and clinical applications

R. LICHT and V. HÖMBERG

Introduction

The goal of this chapter is to introduce the reader into the field of Event-Related Potential (ERP) research. To attain this goal different types of ERPs and methodological aspects of their registration and statistical treatment will be discussed. In addition, the major findings in the field of ERP research concerning the functional significance of different components as well as clinical ERP applications are reviewed.

In contrast to the early or 'exogenous' potentials following a stimulus, ERPs or 'endogenous' potentials are not related to the physical parameters of the evoking stimulus but reflect more elaborate, higher ordered perceptual and cognitive processes. Whereas the exogenous evoked potential components have been widely used to determine the integrity of primary sensory systems in various modalities (see preceding chapters), and have provided usefull information in a wide variety of neurological disorders, the diagnostic values of endogenous components or event-related potentials covers the field of more complex 'cognitive' functions. Hence they have been applied as tools in basic neurosciences, especially psychophysiology and cognitive psychology, and their clinical application has been devoted to devise electrophysiological techniques for assessment of cognitive functions in psychiatry and behavioural neurology.

To provide the reader with a systematic overview of the field, a distinction is made between potentials preceding and following events. Potentials preceding the actual presentation of a stimulus may reflect preparatory processes associated with motor behavior or preparation for stimulus evaluation. Potentials that precede the performance of a self paced motor act are called 'Bereitschaft Potentials' (BP) or 'Readiness Potentials' (RP) (*Kornhuber and Deecke, 1965*). Potentials preceding stimulus evaluation or motor responses in the interval between a warning stimulus and an imperative stimulus are called 'Contingent Negative Variation' (CNV) or expectancy waves (Walter *et al.*, 1964). ERP components following the onset of an event such as N2, N400 or P300 may reflect to the processing of stimulus information.

For potentials following stimulus onset a whole 'family' of different potential

E. J. Colon and S. L. Visser (eds.), Evoked potential manual, pp. 327–393

Table 1.

I. ERP dependent on contingent stimulus coupling.
CNV – contingent negative variation
1. preceding slow for motor reactions
2. preceding slow for sensory discriminations

II. ERPs preceding and following self paced motor activities
1. readiness potential (Bereitschaftspotential)
2. goal directed movement potentials

III. ERPs following an event
1. N200, N400
2. P300
3. slow wave

components has been described such as the N200, N350, N400, P300, P3A, P3B or slow wave. This plethora of different labels attached to these ERP waves under particular contextual or behavioral circumstances, illustrates that ERPs may reflect a wide variety of motor, perceptive or cognitive processes. The variety of different 'components' impose methodological problems for thorough analysis, which beyond 'classical' scoring procedures call for more elaborate ways for data presentation and statistical treatment. Table 1 presents a list of typical ERP waveforms preceding or following responses or stimuli, that will be discussed in the present chapter.

Methodological considerations

Exogenous potentials usually have relatively short latencies beyond 200 msec, are largely determined by physical stimulus properties (pitch, loudness, contrast, brightness) and show a modality specific topographical distribution with maxima over primary projection areas. Endogenous potentials (after 200 ms) are associated with the contextual properties of the eliciting stimuli. These can be interpreted as neurophysiological correlates or manifestations of stimulus evaluation, such as expectancy, processing strategies, tasks demands, etc. Usually endogenous potentials are not modality specific, albeit their latencies and scalp distributions may slightly change with various modalities. A good illustration of the 'endogenous' nature of these late potentials is the finding that they can be elicited by the absence of a physical stimulus in an otherwise regular series of regularly occurring stimuli ('emitted potentials': e.g. Ruchkin and Sutton, 1979).

Whereas exogenous components show fast phasic deflections, ERPs usually have a much slower time course which may exceed several seconds. This implies that for their appropriate recording DC-coupled recordings are optimal. As they are however often difficult to handle, long time constants (above 3 to

10 sec) are used. This is especially important for contingent negative variations and movement related macropotentials, but should also be used for recordings of N200, N400 or P300 type of potentials following events.

The use of long time constant or DC-recordings renders the registration of the brain activity more vulnerable to distortion by artifacts, especially eye movement-related artifacts, induced by a spread of activity originating from the ocular dipole. Another source of artifacts are mechanically induced DC-shifts, e.g. due to head or limb movements, and sudo-motor activity. For this reason, in recording ERPs care has to be taken to prepare the skin-electrode-coupling as well as possible in order to keep the electrode impedances as low as possible (optimally below 1 KOhm). In addition, concomitant recordings of eye movement activity by electro-oculography (EOG) is necessary to monitor eye movement related artifacts. Averages of EOG activity, both in vertical and horizontal directions, should accompany every ERP recording both to reject artifacts either online or during offline editing and to help to avoid misinterpretation of the resulting waveforms, which may be contaminated by extracerebral activity.

Another important methodological issue in ERP recording, due to their vulnerability by task demands and behaviors' content, is the necessity for concomitant recordings of behavioral data, such as reaction times, error scores, EMG activity or kinesiological data in movement tasks. Furthermore, the task demands should be clearly defined including definitions, to determine if the subject or patient involved followed the instructions imposed by the experimenter.

Depending on the type of ERP studied more or less comprehensive EEG-electrode montages are used. In general, it is feasible to use as many EEG-channels as possible to derive a better estimate of the entire scalp distribution of ERP waveforms. Recently the commercial availability of multichannel EEG-mapping devices have made such recordings easier, but generate large amounts of data imposing additional problems for their proper display and statistical treatment. Whereas a 4-channel midline montage can be sufficient to answer the question, Whether there is a delay of P300 latency in the assessment of dementia, the interpretation of CNV or movement-related macropotentials requires to record also from hemispheric electrodes.

Another problem is the selection of a proper reference. Ideally, this reference site should be not active and extracranial. In ERP recording most commonly linked mastoids or earlobes are used as references. Possible extracranial references include chest and nose. When more comprehensive electrode montages are used, the problem of reference site may be solved by using a 'common average reference', comprising all channels recorded.

With few exceptions, ERP recordings need averaging over consecutive trials similar to the conventional evoked potential techniques. For most ERP subtypes such as CNV, movement-related macropotentials or P300, between 20 and 50 trials are usually sufficient to derive a reasonable signal to noise ratio. ERPs in contrast to conventional short latency evoked potentials, have a higher

trial by trial latency variation in parallel to the variation in timing of the underlying cognitive or motor process. Hence averaging necessarily, due to the increased jitter of trial by trial latencies, results in a distortion of latency and amplitude information in the resulting average. On the other hand, it is rather complicated to derive unequivocal information on single trials, e.g. after using filtering techniques to reduce the overlying "noise" caused by ongoing EEG activity (Woody, 1967). As these filtering techniques usually require a lot of computation and are difficult to interpret, they have not been widely used in ERP work, especially not when it comes to clinical applications.

After averaging, the ERP is represented as a voltage-time diagram, which shows certain peaks and troughs in temporal relation to the evoking event. The most conventional approach of analysis is to take amplitude measures of these peaks, either in the form of peak to peak measures or by measuring against a 'baseline', estimated from a time period of 50 or 250 msec preceding the eliciting event. This type of measurement, either performed by scoring the data under visual inspection, e.g. using interactive cursors on the computer screen, or by using an automatic detecting algorithm looking for relative minima and maxima in certain latency ranges, results in a series of amplitude and latency measures of ERP elements or "components". These are mostly labelled according to their polarity (positive or negative) relative to the reference electrode and the latency at which this particular peak in the waveform has occurred. Typical examples of this are 'P300' or 'N200', referring to a positive component at 300 msec or a negative component at 200 msec. The situation is more complicated when instead of well defined maxima the waveform consists of longer lasting DC-shifts, e.g. in movement-related potentials preceding or following movement onset or in the CNV preceding the second stimulus (see Figs. 1 and 2). In this case, it can be more appropriate to derive 'area' measurements, i.e. an integral of voltages over a certain period of time, such as the last 200 msec preceding S2 in a CNV paradigm or the last 100 msec preceding EMG onset in a 'Bereitschaft Potential'. All these measurements are usually done at various scalp locations and can be compared across experimental conditions and electrode locations, using repeated measures analysis of variance (ANOVA) designs. In recent years, the availability of

Figure 1. Schematic CNV potential elicited in a two-stimuli paradigm. S1 and S2 represent the warning and imperative stimulus, respectively. O indicates the O(nset) wave and T indicates the T(ermination) wave (from Rösler, 1982).

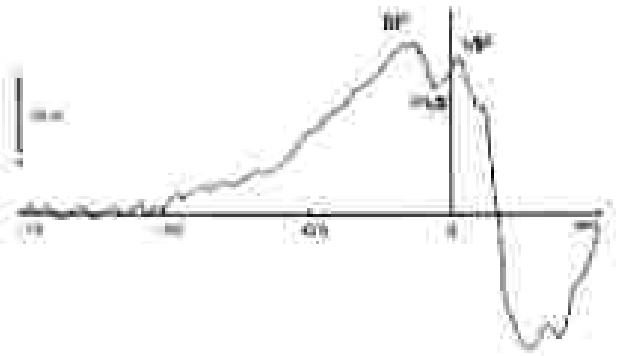


Figure 2. Schematic presentation of the spatial parameters describing Event-related Potential (ERP), Peak Motion Potentials (PMP) and Motion Potential (MP). Vertical line indicates response onset.

multichannel EG-recording systems allowing for colour-coded 'mapping' of isopotential lines has propagated different approaches for statistical treatment of these topographical data. The construction of these 'brain' maps is based on estimating additional 'pixels' between the actual recording sites using linear extrapolation. This results in a matrix of data points reflecting the topographical distribution. This 'inflated' matrix of data points is then often subjected to conventional statistical procedures, such as t-test statistics by making point by point statistical comparisons and mapping the resulting significance levels again as a statistical probability map, e.g. to compare two conditions or two groups in an ERP experiment or to compare an individual patient's data against the data base of a matched control group. This technique, inaugurated by Duffy *et al.* (1979), has been labeled brain electrical activity mapping (BEAM). The problem with the statistical treatment in this case is that hundreds and hundreds of individual statistical comparisons are made over correlated data, which may give rise to erroneous inferences about statistical significance (for a critical comment see e.g. Gasser and Chiappa, 1986). The advantage of these ERP-mapping techniques is to provide an easily communicable display of the complex topographical structure of an ERP component, readable similar to neuroimaging data. The statistical treatment however had to be handled carefully to avoid false conclusions.

Another problem with the statistical treatment of ERP data is, that the resulting waveforms obtained at various electrode locations never represent independent measures. For example, a positive component at around 300 msec may have a maximum amplitude over midline parietal electrodes, but is also recordable at frontal, central, and occipital as well as at hemispheric locations. Furthermore, there may be considerable overlap of independent elements or "components" in the waveform which are difficult to disentangle just using peak or area measurements. An often used statistical technique to account for overlap of ERP components is the Principal Component Analysis (PCA). This is a multivariate technique, described in detail for ERP applications by

Donchin and Heffley (1978): from the cross-correlation or cross-covariance matrix of ERP waveforms across electrodes, conditions or experimental groups, a factorial analysis is performed, resulting in a description of statistically independent "orthogonal" factors, which can be depicted in their time course (factor loadings). The underlying factor scores can be subjected to statistical treatment by ANOVA. The advantage of this approach is that it helps to describe in a non-experimenter biased way the variance in a set of ERP waveforms and helps to visualize the possible overlap between different "components". A disadvantage is that it may be cumbersome to interpret the resulting factor loadings in relation to the sequence of peaks and troughs in the original waveform and that information of latency variation between conditions is usually lost when this technique is applied. Furthermore, simulation studies have demonstrated misallocation of variance by PCA (Wood and McCarthy, 1984). Hence PCA also has to be used carefully.

Considerations for clinical applications

Whereas the clinical application of short latency evoked potentials follows a simple rationale describing abnormalities in the primary sensory projection systems, the application of ERP measurements in neurological and psychiatric disorders, must follow more elaborate considerations due to their "cognitive" nature. Basically three different aims for the clinical application of ERP measurements have to be considered:

1. ERP measurements can be used as a diagnostic tool to differentiate between various disease entities, i.e. as a tool to disentangle nosological subtypes of a disorder. A good example of this is the use of P300 recordings to differentiate between various forms of dementia or to differentiate neurotic from psychotic depression in psychiatry.
2. In a different approach, ERPs can be used to clarify the "cognitive structure" of abnormalities of information processing in neurobehavioral disorders. In this sense the aim for clinical application of ERPs would not be a diagnostic one but an attempt to clarify the cognitive "nature" of a supposed disorder in addition to behavioral or psychometric testing. An example of this would be to use the contingent negative variation (CNV) and P300 as indicators of motor preparation and stimulus evaluation, respectively, in order to analyse if attention and/or stimulus evaluation are impaired in schizophrenia or in dyslexia.
3. Finally, ERP measurements in clinical applications can be used as a tool to differentiate between "state" and "trait" variables in a diseased population. A "state" variable would describe the current status of a patient in terms of his cognitive abilities, whereas a "trait" variable indicates a supposed underlying genetically determined predisposition for a disorder. An example of ERP measurements to discover "trait" variables would be to use P300 recording in asymptomatic patients at risk to be gene carriers for Hun-

tington's disease or Alzheimer's disease. Here ERP measurements could be a tool for early diagnosis of a 'trait' variable.

Depending on which of these three major rationales for ERP usage in neurology and psychiatry is announced, the definition of an ERP protocol as 'test' will be different. The clinician who wants to use ERPs has to clarify beforehand which of the three lines he wants to follow. Subsequently, he has to design his ERP protocol accordingly and has to restrict his interpretation along the concept applied.

Contingent negative variation

In 1964 Grey-Walter and his associates at the Burden Neurological Institute in Bristol made the observation that a surface negative slow-potential shift could be recorded over the human vertex region in the inter-stimulus interval (ISI) between two successive stimuli (S1 and S2), with S2 functioning as a warning signal to respond as fast as possible to the second stimulus. This first observation of an electrophysiological correlate of a conditioning phenomenon likely to originate in human cortex has started the entire field of interest in ERPs as possible tools to understand human cognitive processes. Figure 1 schematically depicts the time course of a CNV. After S1, an evoked potential ensues which may have a topographical distribution according to the modality of S1. This evoked potential followed by a negative potential shift which most often has a ramp-shaped morphology increasing in amplitude until occurrence of S2. S2 again is followed by an evoked potential. The CNV generally has maximum amplitudes at the vertex with amplitudes up to 20 μV and diminishes in amplitude towards more lateral, anterior, and posterior directions. CNVs have been recorded using auditory, visual and somatosensory stimuli as warning and imperative signals. These studies revealed similar CNVs with only minor differences across modality (for a review see McCallum, 1979).

Whereas CNV initially was regarded as a unitary phenomenon, later studies using longer ISI (> 3 sec) demonstrated that the CNV could be broken down into two distinct components, which are also schematically illustrated in Fig. 1. The first component labelled the O-wave (i.e. 'orienting wave') seems to be associated with a process of orienting to S1, whereas the second component labelled the E-wave (i.e. 'expectancy' wave) seems to be related to motor preparation prior to S2 (Loveless and Sanford, 1975; Gaillard, 1980). The functional interpretation of these two different cognitive processes of the O- and E-waves is based on findings that the variation in the length of the ISI has no effect on the O-wave amplitude, but is associated with a decrease in E-wave amplitude. The O-wave in contrast seems to be related to the information delivered by S1 (e.g. Rohrbaugh and Gaillard, 1983).

In contrast to the 'classical' CNV paradigm in which S2 is imperative for a motor response with the E-wave being related to motor preparation, pure 'sensory' CNVs can also be elicited when S2 involves a sensory discrimination

(Grünewald *et al.*, 1981, 1984; Ruchkin *et al.*, 1986; Grünewald *et al.*, 1987; Besson and Diamon, 1988). The CNVs preceding a sensory discrimination are located more posteriorly than the CNV preceding a motor act and show interesting hemispheric asymmetries being larger over the parietal cortex of the non-dominant hemisphere. These asymmetries may indicate superiority of the non-dominant parietal lobe for processing of stimuli delivering manipulo-spatial information. This interpretation was also corroborated in left-handers, who showed larger amplitudes of these CNVs preceding sensory discrimination stimuli over their minor left hemisphere (Grünewald *et al.*, 1987).

Concerning the possible cerebral generators underlying surface CNV, it appears most likely that CNV activity is generated in frontal or parietal cortical areas, encompassing the premotor cortex, the supplementary motor area (SMA) for 'motor' CNVs and the parietal association cortex for 'sensory' CNVs. Looking at animal experimental data, there is a striking similarity in the envelope of discharge properties of premotor cortex neurons in monkeys when similar paradigms are used. These neurons show an increasing probability to discharge preceding the onset of an imperative stimulus in a forewarned reaction time experiment with a constant ISI between warning an imperative stimulus (Mauritz and Wise, 1985). In this context it is interesting to note that a similar time course of single unit activity can be found in monkey striatum preceding initiation of movements (Schultz and Romo, 1988). This may be of importance since the basal ganglia feed their information into the SAMA and the premotor cortex. Thus it may be possible that at least in motor CNV paradigms the E-wave reflects activity in neuronal circuits involving not only premotor cortex but also basal ganglia. These findings are similarly pertinent for movement related potentials, such as the Bereitschafts Potentials (readiness potential, which will be discussed in section 4.

In the motor CNV condition, the E-wave resembles properties of the Bereitschaft Potentials or readiness potentials, preceding self paced voluntary motor activity (Grünewald *et al.*, 1979), although they usually lack the typical asymmetry of readiness potentials immediately preceding movement onset. Nevertheless it is still appropriate to conclude that at least part of the E-wave encompass a readiness potential in preparation for a motor response to S2 (Loveless, 1983).

Although a lot of enthusiasm was created to use CNV as a possible tool to understand abnormalities of attention or motor preparation, also in neurological or psychiatric abnormalities, the clinical usefulness of CNV has remained fairly restricted. This is at least partly due to the fact that findings of CNV abnormalities across patient populations appeared to be unspecific, limiting their usefulness for nosological taxonomy. Furthermore, it also turned out that CNV was not particularly helpful in disentangling possible underlying cognitive dysfunctions in neurobehavioral abnormalities. Although there is a vast amount of publications on CNV recordings in neurological and psychiatric patients, the bottom line is that the same major pattern of changes in CNV phenomenology can be obtained across different pathology. In most

neurological disorders with circumscribed brain lesions, CNV amplitudes are decreased, irrespective of the type of lesion or its localisation (McCallum and Cummins, 1975; Cohen, 1975). Usually, CNV asymmetries follow the location of the lesion in one or the other hemisphere, although this has not been corroborated in all studies (e.g. Zappoli *et al.*, 1976). Reduction of CNV amplitudes have been described in patients with closed head injuries (Rizzo *et al.*, 1978; Curry, 1980). Rosenthal, Bigg *et al.* (1989), using a go-no-go unwarned reaction time experiment, demonstrated that in patients with closed head injury the modulation of CNV amplitude (being larger on 'go' than 'no-go' trials in normals) was diminished. The authors attributed this finding to primary damage to the frontal lobes and/or their connections, which was corroborated by concomitant changes in typical 'frontal lobe signs' on psychometry. Unfortunately, the authors did not provide neuro-imaging evidence for their localisatory statements.

In psychiatric patients reduction of CNV amplitude has been found in a variety of disorders, extending from dementia over schizophrenia to depression (for a thorough review see Ruth *et al.*, 1988). When long ISIs are used, early CNV (O-wave) seems to be more sensitive to schizophrenia than late CNV (e.g. van den Bosch, 1983). In neurotic patients CNV amplitude rather tends to be increased (e.g. Plooij-van Gorsel, 1981). Also in patients with specific phobias increased CNV amplitudes preceding phobiogenic S2 stimuli have been described (e.g. Lumsden *et al.*, 1980). High-amplitude CNVs have been reported in patients with psychosomatic disorders, such as asthma (Dongier and Kisielicka, 1970), and in migraine compared to tension headaches (e.g. Mauritsen de Noordhout *et al.*, 1986).

An interesting phenomenon, first described in patients with schizophrenia and mutism (Timsit-Berthier, 1970), is a prolongation of CNV negativity outlasting the occurrence of S2, which has been labelled as 'postimperative negative variation' (PINV). This phenomenon however, also is non-specific to a particular disease entity and can even occur in normals under conditions where prolonged processing of S2 is necessary, e.g. when response outcome has to be further evaluated (e.g. Rockstroh *et al.*, 1979).

In summary, there seems to be a continuity from missing or even positive going potentials in the S1-S2 interval, such as a 'contingent positive variation' in patients with severe Alzheimer's disease (Timsit-Berthier *et al.*, 1984), up to enhanced CNV amplitude preceding S2 and even outlasting S2 in patients with various forms of neurosis or psychosomatic abnormalities. Unfortunately, very few data exist to clarify the roles which neurotransmitter systems in the cortex are involved in the modulation of these CNV changes. Currently, it appears that both dopaminergic and cholinergic mediators rather enhance CNV amplitudes, whereas a reduction of CNV amplitudes may be related either to structural lesions or to circumscribed lesions in a projection system using a particular neurotransmitter, such as acetylcholine in Alzheimer's disease. In terms of the underlying psychophysiological processes across the various populations of patients mentioned, still the attention-related 'distrac-

tion arousal" concept, first proposed by Teice (1972), remains to be the most attractive. This model links CNV amplitude modulation with the allocation of appropriate arousal and attention towards stimuli. This may follow an inverse relationship, being optimally tuned at intermediate levels of arousal, while being diminished likewise both at low as well as inappropriately high arousal levels. This means that CNV amplitude will be reduced both in underaroused as well as in overaroused states.

In summary, it can be concluded that with respect to the possible clinical usefulness of CNV paradigms, CNVs are hardly suitable as a tool for neurological or localisational diagnostics, but rather seems to reflect the amount of exploitable attentional resources in a particular situation.

Movement-related potentials

In 1965 Kornhuber and Deecke made an ingenious invention, looking at brain electrical activity preceding a *self paced* voluntary motor activity. In those days it was still necessary to make an FM-tape-recorder running backwards, as no cyclic buffering computer storage devices were available, allowing to average activity originating in the past, i.e. preceding an event rather than following it. They described a ramp-shaped negative potential preceding the occurrence of a self paced voluntary index finger extension, by 1000 to 800 msec. The onset of EMG activity from the extensor indicis muscle was used as trigger point for this "backward averaging procedure". This for the first time illustrated that at a fairly long interval before onset of a voluntary self paced motor act the human brain prepared for the release of this particular discrete motor act. For good reasons this technique was looked upon as an avenue to study preparatory processes preceding motor activity. This was pertinent to one of the most interesting problems in motor neurophysiology, namely how motor programs are generated and stored in the brain and how they interact with attentional or motivational factors on one and the outcome-related EMG or kinesiological features on the other side. The technique turned out to describe which brain structures might be involved in programming of motor activity prior to area 4, the primary motor cortex, is activated to send the final commands to motor neuron pools. Kornhuber and Deecke labelled this type of activity the "Bereitschafts Potential", which was later on translated into "readiness potential". This implied that they felt that this activity was related to a preparatory process, making the motor system ready to issue a particular motor activity. As illustrated in Fig. 2, the typical readiness potential consists of a slowly emerging negative wave, starting at about 800 msec preceding movement onset, which gradually increases and reaches a maximum shortly after the initiation of the motor response. It is followed by a positive going wave after completion of this short motor act.

Later on it has been described that, when more complex "goal-directed" movements were used, the negative potential preceding movement onset

initiated movement onset and stayed negative until the completion of the entire goal-directed movement activity (Grünewald *et al.*, 1981).

Usually the 'Bereitschafts Potential' starts about 1 sec prior to movement or EMG onset. The maximum of this Bereitschafts Potential or N1-component (Vaughan *et al.*, 1968) is at the vertex. Shortly before movement onset an additional negativity, which has a maximum over the hand area contralateral to the moving limb, comes which has been labelled the 'motor potential' (Deecke *et al.*, 1976). This motor potential is asymmetrical distributed over the hemispheres according to the side of the limb used.

When more complex goal directed movements are executed, this lateralized 'motor potential' component exceeds movement onset and may outlast the entire execution of the goal-directed movement (Grünewald *et al.*, 1981). Hence there appear to be at least two different overlapping negative potentials preceding movement onset, one (the readiness potential) which has a clear maximum in its topographical distribution at the vertex and two a lateralized component the motor potential which is exactly lateralized according to the side of the moving limb, being larger over the motor area contralateral to the limb moved. Sometimes, preceding movement onset a short lasting positive inflection with parietal maximum can be obtained, which has been labelled 'premotion positivity' (PMP) (see Fig. 2).

A dissociation between the midline dominant non-specific and the lateralized component changing polarity with the hand used, has also been derived from studies in children with different abilities to concentrate (Grünewald-Zuberbier *et al.*, 1980). This study showed that whereas the unspecific vertex dominant component of goal-directed movement potentials was absent in children with lower than average ability to concentrate, similar to low amplitude CNVs in these children (Grünewald *et al.*, 1978), they still showed a lateralized component with maxima overlying the motor area, contralateral to the moving hand. This clearly demonstrated that the two components could be differentiated from each other in the sense that only the contralateral isometric component immediately preceding movement onset was a necessary counter part of motor activity, possibly originating in the motor cortex (area 4). In contrast, the unspecific vertex dominant component could be present or not, depending on the attentional resources of the children studied.

For lower limb, especially toe-movements, an interesting polarity inversion of the lateralized component has been described by Brunia (1980) and Brunia and Vingerhoets (1981). This could be attributed to the geometry of the underlying dipole in the foot representation of area 4, close to the sagittal midline in the human brain. Magnetoencephalographic recordings, providing a more accurate localization of the real sources of underlying activity, demonstrated that the underlying generators were located, also for foot-movements, in the hemisphere contralateral to the moving toes (Deecke *et al.*, 1981).

Concerning the functional significance of movement related potentials, a major line of argumentation, especially put forward by the group of Deecke,

has been that at least the unspecific vertex dextrinant component is indicative of activity in the supplementary motor area. This area, as has been alluded to already in section 4, has a pivotal position in interfacing processing between basal ganglia and motor cortex. This has created a lot of interest in how the movement-related macropotentials can be changed in patients not only with unilateral damage to motor cortex but especially with damage to upstream areas as the basal ganglia, such as in Parkinson's disease (PD). This disorder is characterized by a loss of dopaminergic input into the neostriatum, originating from the substantia nigra, with the rest of the intrinsic basal ganglia neuronal network remaining unchanged. Controversial findings have been reported on possible changes of movement potentials in Parkinson's disease. Early work by Deecke *et al.* (1977), Kornhuber and Deecke (1978), and Ikibasaki *et al* (1978) has suggested that there was a decrease in amplitude of the Bereitschafts Potential in PD, which in patients with unilateral signs of PD was restricted to the affected hemisphere (Deecke *et al.*, 1977). This has been contradicted later on by a study published by Barrett *et al.* (1986), demonstrating that there were no differences between healthy age matched subjects and patients with PD in waveforms of cortical potentials preceding index finger extensions. More recently however, other studies have again demonstrated that the Bereitschafts Potential is diminished in amplitude in PD (Simpson and Khuraibet, 1987; Dick *et al.*, 1989). The latter authors had claimed before that Bereitschafts Potentials were not significantly impaired in PD (Dick *et al.*, 1987), but they have changed their mind because when using different measurement techniques in the late part of the Bereitschafts Potentials, there are definite abnormalities in PD. These data indicate that the research on the differentiation between various subcomponents of motor potentials preceding and following motor activity is still rather ambiguous. Cortical recordings of motor-related potentials in a patient with chronically implanted subdural electrodes in the premotor area (Neshige *et al.*, 1988) demonstrated high amplitude negative shifts preceding voluntary movements by more than 1 sec, being strictly localized to the precentral hand motor area and the medial part of the sensory hand projection area.

In summary, it can be concluded that to date movement-related macropotential techniques have not been a useful tool to delineate abnormalities of motor control in patients with abnormalities in the basal ganglia or in the upstream premotor cortical areas (area 6, SMA). It has also not been decisively disentangled to which extent motivational and/or "pure" motor system-related structural abnormalities do affect these movement-related macropotentials. However, it remains, as discussed in section 4, that there is a good correspondence between single motor unit activity in subcortical as well as in cortical motor structures and movement-related macropotentials in humans. Hence, this approach has a potential heuristic value to clarify problems in the relative contribution of different cortical and subcortical structures in human motor control.

Late negative potentials

In the latency range beyond 200 msec, multiple negative and positive deflections can be detected depending on the contextual property in which a particular stimulus is embedded and on the processing demands imposed by task instructions. The N2-component is a late negative potential peaking at around 200 to 300 msec. It has been associated with responses to physically deviating stimuli interspersed into sequences of otherwise regularly occurring stimuli. This has prompted the label 'mismatch negativity' (MMN), put forward by Näätanen (1979). Such N2 waves also occur for unexpected infrequent stimuli, labelled as 'N2' by Courchesne (1978, 1983) or as 'N2b' by Duncan-Johnson and Donchin (1982). These negative potentials also seem to be related to the classification of stimuli into categories (classification N2: Ritter *et al.*, 1983). They also may occur when in a regular series of stimuli suddenly a stimulus is missing (missing stimulus potential: MSP: Simson *et al.*, 1976; Renault, 1983). The bulk of literature existing on these negative components shows that there may be considerable overlap of various components in this latency range, some of which have a modality-specific topographical distribution while others appear non-modality-specific.

In an even later latency range at around 400 msec, N400 waves have been reported by Kutas and Hillyard in series of experiments investigating ERPs to stimuli being *semantically* incongruent (Kutas and Hillyard, 1980a, 1980b, 1982). For instance, N400 waves have been found for the last word presented in a sentence, whenever this word was semantically inappropriate. In contrast, physically deviant but semantically congruent words at the end of a sentence were associated with increased positivity in the same latency range resembling a P300 potential, as discussed in section 7. Similar negative waveforms have been described by Polich (1985) in series of semantically related words. Neville *et al.* (1982) described N400 waveforms during word-reading in adults, whereas Stuss *et al.* (1983) reported similar negative waves occurring during *non-semantic* processing, suggesting that semantic processing is not a necessary condition for the occurrence of N400 waves. Recently Ritter *et al.* (1988) found that the duration of such negative potentials in the latency range between 200 to 400 msec was related to the amount of information processing required. These authors described at least three overlapping deflections, resulting into the overall negative waveform. The fact that it has not been possible to delineate clear cut functional significance for the majority of these negative potentials so far, has precluded their systematic application for clinical studies. However it appears that potentials in this latency range are susceptible for semantic processing, which may open an avenue to study them in more detail in patients with neurolinguistic problems such as aphasia or dyslexia.

Late positive components (P300, slow wave)

One year after Grey-Walter had described the CNV as the first macropotential phenomenon related to psychological processes, Sutton and his associates in 1965 reported on a long latency positive deflection which was associated with delivery of salient information rather than physical stimulus properties. This ERP component, labelled P300, has been analysed in hundreds of studies and turned out to be the most prominent candidate for ERP application, both in the fields of cognitive psychology as well as in clinical neurobiology. A plethora of different paradigms has been used to evoke and analyze P300 potentials to clarify its functional significance and its possible cerebral generators. It is far beyond the scope of this introduction to cover the entire field of psychological variables related to P300 modulation. A good review can be found in Rösler *et al.* (1986). We will here concentrate on some of the major lines for P300 interpretation, being pertinent for rationales of clinical usefulness.

Another issue, which cannot be addressed properly here is the wide variety of different, possibly overlying components in the latency range of late positive waveforms. Especially when PCA-techniques are used, several different subtypes of components in the P300 latency range can be identified, which show different surface scalp distributions and may be looked upon to have different generators. It was first shown by Squires *et al.* (1975) that more than one late positive waveform component was present in the P300 complex. This is even more prominent, when more complex stimuli or situations are used (e.g. Homberg and Schuhmacher, 1984).

Figure 3 schematically depicts the typical sequence of waveform components which can be found following an informative event. In adults the typical

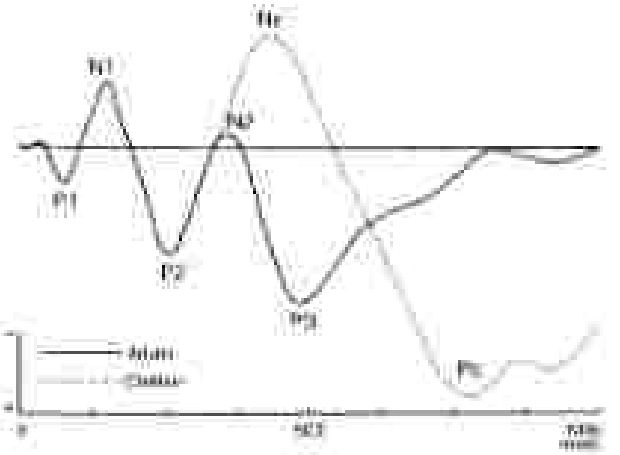


Figure 3. Schematic ERPs of adults and children showing negativities (P1, N1, N2) and endogenous (N2, P3, Ne and Pc) waves.

sequence consists of negative and positive N1 and P2 components in the latency range of exogenous potentials, followed by a variable N2 peak, which is followed by one or more positive going potentials (P3, slow wave etc.).

As can be observed in Fig. 1, the ERPs of young children differ qualitatively from those of adults in the epoch in which late negative waves occur. Children's ERPs are characterized by large negative waves around 300–500 msec (Symmes and Eisengart, 1971; Neville, 1977; Bakker *et al.*, 1980; Courchesne, 1978; Kok and Rooyackers, 1985; Licht *et al.*, 1986, 1988), while adult ERPs are generally dominated by a large positive potential (P300) that is preceded by a N2 wave in this epoch. Novel and out of focus visual stimuli elicited large negative waves around 410 msec (Nc) in children that were frontally distributed (Courchesne, 1978). Nc has been associated with the processing of meaningful stimuli and the detection of attention getting stimuli that need further processing. Licht *et al.* (1986, 1988) found two successive negative components (N360 and N550) during a word reading task in children. N360 increased, while N550 decreased with age. It was suggested by these authors that N360 and N550 amplitude effects reflect a change from more controlled processing (N550) in younger children to more automatic processing (N360) in older children during word recognition. In discrimination tasks with more simple stimuli quantitative differences in amplitude and latency between ERPs of children and adults have been found. Courchesne (1978) reported N2 waves around 410 msec for targets and background stimuli in children, whereas in adults similar N2 waves were found around 310 msec. P300 waves in children peaked around 700 msec while P300 in adults had a latency around 400 msec in the same task. Stamm *et al.* (1982) and Grünewald-Zuberbier and Grünewald (1982) found P300 waves around 400–500 msec in children during visual information processing. Hömberg *et al.* (1981) found positive potentials to visual stimuli in the latency range between 350 and 540 msec in children aged around 12 years, which showed amplitude variation with the amount of monetary payoff promised by the stimuli. These negative and positive waves in children seem to be functionally similar to those in adults, and differ only in amplitude and latency from adults. It has been suggested by Courchesne (1978, 1983) and Friedman *et al.* (1984) that qualitative differences in ERPs between children and adults are associated with differences in cognitive processing mode between children and adults. Quantitative ERP differences between children and adults seem to reflect similar cognitive processing modes but more efficient processing by adults.

Several typical paradigms have been used to elicit P300 responses. P300 waveforms can be elicited in 'guessing' paradigms following a feedback stimuli, indicating the outcome of a preceding guess. In signal detection paradigms larger P300 have been found for stimuli for which a more confident detection was possible (Hillyard *et al.*, 1971). Also in paradigms using stimuli delivering feedback, e.g. knowledge of results of a preceding cognitive or motor activity, P300 potentials have been obtained. But the most commonly used paradigm to elicit P300 responses is the 'oddball paradigm'. Here the subject's task

is to react, either with a motor response or just by silent counting, to a particular class of a "target" stimuli, embedded into sequences of otherwise irrelevant non-target stimuli. From all of this work it appeared that P300 potentials are usually larger in amplitude whenever a stimulus is relevant in a task context, e.g. being the target stimulus to be counted or to be reacted on, or when a stimulus is infrequent compared to other stimuli (Tueting *et al.*, 1970; Squires *et al.*, 1976). Large P300 potentials can also be elicited for stimuli which deliver salient, incentive or interesting information. It has been demonstrated that stimuli promising higher pay-off values to children elicit larger P300 responses (Hömberg *et al.*, 1981). Looking closer at the subjective experience of interest value as an explanatory variable for P300 amplitude modulation, it was demonstrated that the amount of "uncertainness" or "interest value" of a stimulus predicts P300 amplitude when using psychophysical estimates of interest value (Hömberg *et al.*, 1980; Begleiter *et al.*, 1983; Hömberg *et al.*, 1984; Hömberg and Schuhmacher, 1988). Many different possible cognitive processes have been claimed to account for the amplitude modulation of P300 responses. The bottom-line of this is, that the more information is delivered by a stimulus, either related to contextual properties or related to the emotional impact of the stimulus, the more it is prone to elicit larger P300 responses (Campbell *et al.*, 1979). This feature of P300 has also been applied for applications in the field of memory scanning tasks (Pratt *et al.*, 1989 a,b,c). A stimulus eliciting a larger P300 is also likely to be better remembered (e.g. Paller *et al.*, 1987).

Concerning the latency variation of late positive potentials in the P300 range, the most fruitful concept was that P300 latency could be related to "stimulus evaluation time" (Kutas and Donchin, 1977). This means that the latency of a P300 response may be indicative for the time needed in the central nervous system to analyse a stimulus to a level pertinent to elicit a behavioral sequelae such as counting or remembering it. Following this, it has been shown that latency values in the P300 latency range give additional information about mental chronometry, exceeding that obtained by reaction time measurements (McCarthy and Donchin, 1981).

The susceptibility of ERPs in the P300 latency range to cognitive function has prompted to search for cerebral structures being essential in mediating the observed cognitive modulations. To date however, there is still a controversy about which cerebral structures are likely to be the generator sources of P300 type of potentials. Data have been gathered from intracranial recordings in humans, having implanted electrodes with multiple recording sites to search for epileptogenic foci preceding surgery in medically non-treatable epilepsy. Using oddball tasks in these patients, intracerebral recordings in the P3 latency range show polarity inversions in midtemporal structures (hippocampus and parahippocampal gyrus) (Halgren *et al.*, 1980; Stapleton and Halgren, 1987; Wood *et al.*, 1984). Also a magnetoencephalographic study revealed evidence for a midtemporal generator for P300 responses in an oddball paradigm (Okada *et al.*, 1983). Furthermore, the hypothesis of a midtemporal

Table 3. Correlation of age and P300-latency in younger and older controls.

	N	DF_n	DF_d	r	Slope (ms/dec/y)
A: Younger age group (<45 years)					
Brown *et al.*, 1983 (<40 y)	22	384	22.7	0.193	0.53
Polich & Starr, 1984 (<40 y)	40	330	24.7	−0.042	−0.27
Syndulko *et al.*, 1982 (<45 y)	20	330	27.2	−0.032	−0.08
Goodin *et al.*, 1978 (<40 y)	28	308	22.8	0.614	1.69
Hömberg *et al.*, 1988 (< 50 y)	30	328	30.0	0.40	0.73
B: Older age group (>45 y)					
Brown *et al.*, 1983 (> 45 y)	24	342	46.5	0.720	3.10
Polich & Starr, 1984 (> 45 y)	30	456	35.0	0.435	1.96
Syndulko *et al.*, 1982 (> 45 y)	25	368	37.1	0.632	3.75
Goodin *et al.*, 1978 (> 45 y)	12	341	26.5	0.471	1.48
Hömberg *et al.*, 1988 (> 50 y)	28	369	29.0	0.46*	1.56

generator for P300 activity was supported by findings of single unit activity related to rare target stimuli in the hippocampus and the entorhinal cortex. This single unit activity corresponded in latency to the time course of simultaneously recorded P3 waveforms (Halgren *et al.*, 1980). Other studies however found evidence for generation structures of P300-like activity in the thalamus (Yingling and Hosobuchi, 1984; Allison, 1984) and in the frontal lobe (MacCarthy and Wood, 1985). These studies suggested that the scalp-recorded P300 may represent the summation of output activity in different generators (Johnson, 1986). In patients with unilateral temporal lobectomy no amplitude attenuation or scalp asymmetry of P300 activity could be obtained (Johnson, 1986). This also pointed against midtemporal structures as being the only generator of P300 activity. On the other hand, the presence or absence of P300 like activity in the temporal lobe of patients with intractable epilepsy during presurgical investigations can be used to predict which side is the pathological one (Puce *et al.*, 1995), as corroborated by post-surgery histology.

The most commonly used ERP paradigm for clinical application is the P300 oddball paradigm. The first description by Goodin *et al.* (1978) on abnormalities of P300-latencies in dementia has been followed by many studies on the

relationship between P300 and dementia, especially since dementing illnesses present a major health care issue.

For the interpretation of P300 it is important to take the physiological age-latency variation into account. Numerous studies have demonstrated that P300 latency increases with physiological aging (Goodin *et al.*, 1978a; Polich *et al.*, 1984; Syndulko *et al.*, 1982). Since this age-latency relationship is important to be considered for all clinical applications, the variability of this age-latency relationship across several studies has been summarized in Table II. It is certainly of importance to note, that at least under certain conditions the age-latency relationship may have a non-linear shape due to increased slopes and increased jitter in older age groups, as first described by Brown *et al.* (1983). Apart from this age dependency of P300 measures, P300 latency seems to be a well reproducible measurement in individual subjects as shown by Sklare and Lynn (1984). This was corroborated in a recent study, adding information about the topographical stability of P300 which appears to be very high for the target waveforms (Kutnuky and Blair, 1989). Beside being a stable measurement, the evaluation of P300 parameters appears to be attractive for clinical application, because the concept of P300 latency as being a measure of stimulus evaluation time (Kutas and Donchin, 1977) provides a clear rationale for interpretation. A prolongation for P300 latency has been obtained especially in subcortical forms of dementia including patients with Parkinson's disease (Hansch *et al.*, 1982; Goodin *et al.*, 1983), Huntington's disease (Rosenberg *et al.*, 1985; Hoenberg *et al.* 1986) or progressive supranuclear palsy (Pierrot-Deseilligny *et al.*, 1989). We have demonstrated that P300 latency and to a lesser extent that of the preceding N2 component is systematically related to the cognitive status of the patient as revealed by detailed psychometry (Hoenberg *et al.*, 1986). This study also demonstrated that in patients being asymptomatic but having a genetic risk to be gene carriers of Huntington's disease, abnormalities of P300 latency can be obtained in a small proportion of these at risk subjects. This indicates that P2300 latency can be used as a 'trait' variable to pick up abnormalities at an early preclinical stage.

Beside prolongations of P300 latency the second major abnormality is reduction of P300 amplitude which has been found in the majority of dementing disorders and in a wide variety of psychiatric abnormalities including schizophrenia and depression (Squires *et al.*, 1983). With few exceptions, patients with schizophrenia or depression have normal P300 latencies but reduced amplitudes. This may be related to the fact that the amplitude of P300 reflects the ability to handle information or to react effectively to a stimulus, whereas P300 latency as a measure of evaluation time. In this sense, this dissociation between abnormal amplitudes and normal latencies gives some insight into the underlying cognitive problem in these psychiatric disorders.

Novick *et al.* (1979) and Novick *et al.* (1980) also found severely reduced P300 amplitudes in autistic children. In other studies reduced amplitudes of late positive waves have been reported for reading disturbed children (Duane

et al., 1981; Holcomb *et al.*, 1985). In our own studies on reading disturbance (Bakker *et al.*, 1980) we found increased latencies for a positive wave (P310) and for a negative wave (N440) during word reading in dyslexic children. In addition, these children showed smaller and symmetric N440 amplitudes, while normal readers showed larger N440 amplitudes over the left hemisphere.

In summary, it has to be understood that P300 findings are unspecific for any particular diagnosis and are probably not helpful as a differential diagnostic tool but more as an early diagnostic tool. An exception may be that P300 can be helpful to differentiate between depressive pseudo-dementia and degenerative dementia (Vaughan *et al.* 1982). The most appropriate paradigm still appears to be the simple auditory or somatosensory oddball paradigm. Attempts to make P300 recordings more sensitive to subtle pathology, e.g. by increasing task demands or difficulty usually leads to an increase in variability also in the normal population (e.g. Pfefferbaum *et al.* 1984), which may render the delineation of pathology more difficult. This is due to the fact that multiple components appear in the P300 latency range which may be related to different strategies used by the subjects (e.g. Pritchard and Tarnitsky, 1980).

References

Ahlfors T. Recording and interpreting evoked potentials. In: E. Donchin (ed.), Cognitive Psychophysiology: Event-related potentials and the study of cognition. New Jersey: Lawrence Erlbaum; 1984.

Bakker DJ, Licht R, Kok A, Bouma A. Cortical responses to word reading by right and left visual normal and reading disturbed children. Journal of Clinical Neuropsychology 1980; 2:1–12.

Barrett G, Shibasaki H, Neville B. Cortical potential shifts preceding voluntary movement are normal in parkinsonism. Electroencephalography & Clinical Neurophysiology 1984; 57:346–348.

Begleiter H, Porjesz B, Chou CL. P3 and stimulus–response time. Psychophysiology 1983; 20:305–311.

van den Broek R. Contingent negative variation and psychopathology. Frontal-central distribution and association with performance measures. Biological Psychiatry 1985; 1:613–634.

Brunia CHM, Donald MW. Conditioning of the vertex maximum to apparent human EEG autonomic pulse in curarization. Brain & Language 1980; 9:226–248.

Brown WS, Marsh JT, LaRue A. Exponential electrophysiological aging: P3 latency. Electroencephalography & Clinical Neurophysiology 1983; 55:277–285.

Brunia CHM. What is wrong with hits in error processing? In: HH Kornhuber, L Deecke (eds.), Motivation, motor and sensory processes of the brain. Prog Brain Res 1986; 54:755–759.

Brunia CHM, Vingerhoets AJJM. Opposite effects of knowledge of feedback on premotor event-related potentials preceding foot and finger flexions. Biological Psychology; 1981; 13:201–209.

Brunia CHM, van den Bosch WKJ. The effects of response rate on the readiness potential prior to finger and foot movements: a period-key report. In: R Karrer, J Cohen, P Tueting (eds.), Brain and Information: Event-related potentials. New York: New York Academy of Sciences; 1984. (Vol. 425); pp 430–437.

Brunia CHM, Damen EJP. Distribution of slow brain potentials related to motor preparation

and stimulus anticipation in a time estimation task. Electroencephalography and Clinical Neurophysiology 1988; 69:234-247.

Campbell KB, Courchesne E, Picton TW, Squires KC. Evoked potential correlates of human information processing. Biological Psychology 1979; 8:45-68.

Chiarenza G, Papakostopoulos D, Giordana F, Guareschi-Cazzullo A. A developmental study of movement-related brain macropotentials during skilled performance. In: Karrer R, Cohen J, Tueting P (eds.). Brain and information: Event-related potentials. New York: New York Academy of Sciences, 1984; Vol 425; pp 438-448.

Cohen J. The CNV in cases of hemispheric cerebral lesions. Electroencephalography and Clinical Neurophysiology 1975; 38:547.

Courchesne E. Neurophysiological correlates of cognitive development: changes in long-latency event-related potentials from childhood to adulthood. Electroencephalography & Clinical Neurophysiology 1978; 45:468-482.

Courchesne E. Cognitive components of the ERP: changes associated with development. In: Gaillard AWK, Ritter W (eds.). Tutorials in ERP Research: Endogenous Components. Amsterdam: North-Holland 1983; pp 329-344.

Curry SH. Event-related potentials as indicants of structural and functional damage in closed head injury. In: Kornhuber HH, Deecke L (eds.). Motivation, Motor and Sensory Processes of the Brain: Electrical Potentials, Behaviour and Clinical Use. Progress in Brain Research; Elsevier, Amsterdam, 1980; Vol 54: 507-515.

Dainer KB, Klorman R, Salzman LF, Hess DW, Davidson PW. Learning-disordered children's evoked potentials during sustained attention. Journal of Abnormal Child Psychology 1981; 9:79-94.

Deecke L, Grözinger B, Kornhuber HH. Voluntary finger movement in man: Cerebral Potentials and theory. Biological Cybernetics 1976; 23:99-119.

Deecke L, Englitz HG, Kornhuber HH, Schmitt G. Cerebral potentials preceding voluntary movement in patients with bilateral or unilateral Parkinson akinesia. In: Desmedt JE (ed.). Attention, voluntary contraction and event-related cerebral potentials. Basel: Karger. Progress in Clinical Neurophysiology 1977; Vol 1 pp 151-163.

Deecke L, Kornhuber HH. Cerebral potentials and the initiation of voluntary movement. In: Desmedt JE. Attention, voluntary contraction and event-related cerebral potentials. Basel: Karger. Progress in Clinical Neurophysiology 1977; Vol 1 pp 132-150.

Deecke L, Boschert J, Weinberg H, Brickett P. Magnetic fields of the human brain (Bereitschaftsmagnetfeld) preceding voluntary foot and toe movements. Experimental Brain Research 1983; 52:81-86.

Desmedt JE. Some observations on the methodology of cerebral evoked potentials in man. In: Desmedt JE (ed.). Attention, voluntary contraction and event-related cerebral potentials. Basel: Karger. Progress in Clinical Neurophysiology 1977; Vol 1 pp 12-29.

Desmedt JE, Debecker J. Waveform and neural mechanism of the decision P350 elicited without pre-stimulus CNV or readiness potential in random sequences of near-threshold auditory clicks and finger stimuli. Electroencephalography & Clinical Neurophysiology 1979; 47:648-670.

Dick JPR, Cantello R, Buruma O, Gioux M, Benecke R, Day BL, Rothwell JC, Thompson PD, Marsden CD. The Bereitschaftspotential, L-DOPA and Parkinson's disease. Electroencephalography & Clinical Neurophysiology 1987; 66:263-274.

Dick JPR, Rothwell JC, Day BL, Cantello R, Buruma O, Gioux M, Benecke R, Berardelli A. The Bereitschaftspotential is abnormal in Parkinson's disease. Brain 1989; 112:233-244.

Donchin E, Heffley E. Multivariate analysis of event-related potential data: A tutorial review. In: Otto DA (ed.). Multidisciplinary perspectives in event-related brain potential research. Washington: Environmental Protection Agency, 1978; pp. 555-572.

Dongier M, Koninckx N. [illegible] neuropsychological models of mind-body interaction. Psychother Psychosom 1970; 18:123-129.

Duffy FH, Burchfiel JL, Lombroso CT. Brain electrical activity mapping (BEAM): A method for extending the clinical utility of EEG and evoked potential data. Annals of Neurology 1979; 5:309-321.

Duncan-Johnson CC, Donchin E. The P300 component of the event-related potential as an index of information processing. Biological Psychology 1982; 14:1–52.

Duncan-Johnson CC, Kopell BS, Squires NK. Effects of stimulus sequence on P300 and reaction time in schizophrenics: A preliminary report. In Kissin B, Gruzelier J, Starkey P (eds.), Brain and information: Event-related potentials. New York: New York Academy of Sciences 1984; Vol 425 pp 570–577.

Fein G, Turetsky B. P300 latency variability over the adult life span of paradigm and measurement technique. Electroencephalography & Clinical Neurophysiology 1989; 73:164–174.

Fischler I, Bloom PA, Childers DG, Roucos SE, Perry NW (1983). Brain potentials related to stages of sentence verification. Psychophysiology, 20:400–409.

Ford J, Dynowski GA, Pfefferbaum A, Roth WT. Language related potentials specific to human language versus nonlanguage stimuli. Science 1981; 212:353–355.

Friedman D, Cycowicz Y, Dziobek-Kreuzing I. Auditory evoked potentials as children at high risk for schizophrenia. In H Begleiter (ed.), Evoked brain potentials and behavior 1979, pp. 385–400. New York: Plenum Press.

Friedman D, Simson C, Vaughan HG, Ritter W, Dziobek-Kreuzing I. Cognitive brain potential components in adolescents. Psychophysiology 1984; 21(1):76–86.

Gaillard AWK. Central correlates of motor preparation. In Nicholson SS (ed.), Attention and performance VIII. Hillsdale NJ: Lawrence Erlbaum (1980) pp 75–91.

Galbraith GC, Squires N, Adair D, Childers DG. Electrophysiological assessment of normally retarded individuals. Paper presented to (place ?) Society Evoked brain potentials and behavior. New York: Plenum Press 1979, pp 229–246.

Gaillard LR. Analysis of concurrent potential components. In Desmedt JE (ed.), Attention voluntary contraction and event-related cortical potentials. Basel Karger (Progress in Clinical Neurophysiology 1977) Vol. 1, pp. 174–89.

Goodin DS, Squires KC, Henderson BH, Starr A. Age-related variations in evoked potentials to auditory stimuli in normal subjects. Electroencephalography & Clinical Neurophysiology 1978; 44:447–458.

Goodin DS, Squires KC, Starr A. Long latency events and components of the auditory evoked potential in dementia 1978b. Brain, 101: 635–648.

Goodin DS, Starr A, Chippendale TR, Squires KC. Sequential changes in the P3 component of the auditory evoked potential in confusional states and dementing illness. Neurology (NY) 1983; 33:1225–1230.

Grözinger B, Kornhuber HH, Kriebel J. Human cerebral potentials preceding speech production, phonation and movements of the mouth and tongue, with reference to respiratory and vocal cerebral potentials. In H Desmedt (ed.), Language and hemispheric specialization in man: Cerebral event-related potentials (Progress in Clinical Neurophysiology. Vol. 3), 1977, pp. 87–103. Basel: Karger.

Grünewald-Zuberbier E, Grünewald G, Rauche A, Metz J. Contingent negative variation and alpha adrenolytic response in children with callosal ability to concentrate. Electroencephalography and Clinical Neurophysiology 1978; 44:37–47.

Grünewald G, Grünewald-Zuberbier E, Hömberg V, Metz. Cerebral potentials during smooth goal-directed hand movements in right-handed and left-handed subjects. Pflügers Archiv, European Journal of Physiology 1979; 381: 39–45.

Grünewald G, Grünewald-Zuberbier E, Metz J, Hömberg V, Saletu G. Relationships between the late components of the contingent negative variation and the Benton hallucination test. Electroencephalography and Clinical Neurophysiology 1979; 46:535–545.

Grünewald-Zuberbier E, Grünewald G, Hömberg V, Schwarzacher H. Two components of slow negative potential shifts during manual goal-directed hand movements. In Kornhuber HH, Deecke L (eds.), Motivation, motor and sensory processes of the brain: Electrical potentials, behaviour and clinical use. Elsevier North Holland Biomedical Press 1980, pp 755–760.

Grünewald-Zuberbier E, Grünewald G, Runge H, Metz J, Hömberg V. 1981. Cerebral potentials during visible slow positioning movements. Biological Psychology 1981; 13:71–87.

Grünewald-Zuberbier E, Grünewald G. Event-related ERG changes in children with different

children to consonants. In: A. Rothenberger (ed.), event-related potentials in children. Basic concepts and clinical application 1992, pp. 295–316. Amsterdam: Elsevier Biomedical Press.

Gatzonis G, Gatzonis-Zaharias E, Hömberg V, Schönenberger M. Hemispheric asymmetry of feedback-related slow negative potential (fSP) in a processing assessment task. In: Karmos R, Cohen J, Hüttig P (eds.), Brain and Information: Event-related potentials 1984; vol. 425 pp. 470–476. New York: New York Academy of Sciences.

Gatzonis G, Gatzonis-Zaharias E, Dietzinger R, Mensah J, Schönenberger M. Hemispheric asymmetry of feedback-related potentials in a positioning task: Comparison of right- and left-handed subjects. Biological Psychology 1987; 24:209–223.

Halgren E, Squires NK, Wilson CL, Rohrbaugh JW, Babb TM, Crandall PH. Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. Science 1980; 210:803–805.

Hanisch EC, Spehlmann R, Cobbin SM, Goldring JJ, Peters AR, Fairchilds WW. Cognition in Parkinson's disease: An event-related potential investigation. Annals of Neurology 1982; 11:599–607.

Hanter MR, Ann C, Schroeder C. Hemispheric differences in the mental processing of stimulus location and type: effects of selective attention on visual evoked potentials. Neuropsychologia 1982; 20:421–438.

Hillyard SA, Squires KC, Bauer JW, Lindsay PH. Evoked potential correlates of auditory signal detection. Science 1971; 172:1357–1360.

Holcomb PJ, Ackerman PT, Dykman RA. Cognitive event-related brain potentials in children with attention and reading deficits. Psychophysiology 1985; 22:6, 656–667.

Hömberg V, Gatzonis G, Gatzonis-Zaharias E. The successive relief of stimuli and the P300 component of (auditory) evoked potentials. In: Koelbacher HH, Deecke L (eds.), Motivation, motor and sensory processes of the brain: Electrical potentials, behaviour and clinical use. Amsterdam: Elsevier Biomedical Press, 1980; pp. 629–632.

Hömberg V, Gatzonis G, Gatzonis-Zaharias E. The variation of P300 amplitudes as a measuring paradigm in children. Psychophysiology 1981; 18:1:256–262.

Hömberg V, Gatzonis G, Metz J. Category scaling of stimuli value of complex visual stimuli and late positive components of the evoked potential. In: Karmos R, Cohen J, Tueting P (eds.), Brain and Information: Event-related potentials. New York: New York Academy of Sciences 1984; Vol. 425 pp 218–222.

Hömberg V, Hofer H, Gatzonis G, Strauss W, Lange H, Hommel M. Event-related potentials in patients with Huntington's disease and relatives (1.0.0): a contribution to clinical psychiatric. Electroencephalography and Clinical Neurophysiology 1986; 63:352–360.

Hömberg V, Schuhlmacher H. Influence of late complex stimulus-related potentials to complex visual stimuli. Sex. Neurosci. Adv., 1988; 38, 1180.

Johnson R, Jr. A triarchic model of P300 amplitude. Psychophysiology 1986; 23:367–384.

Johnson R., Jr. Scalp-recorded P300 activity in patients following unilateral temporal lobectomy. Brain 1988; 111:1517–1529.

Karwoski W, Blair RC. Topographical and temporal stability of the P300. Electroencephalography & Clinical Neurophysiology 1989; 72:373–383.

Kok A, Looren de Jong H. The effect of repetition of infrequent familiar and unfamiliar visual patterns on components of the event-related brain potential. Biological Psychology 1989; 28:103–119.

Kok A, Rooijakkers JAJ. Comparison of event-related potentials of young children and adults in a visual recognition and word reading test. Psychophysiology 1985; 22:1, 11–23.

Kornhuber HH, Deecke L. Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente Potentiale. Pflügers Archiv 1965; 284:1–17.

Kornhuber HH, Deecke L. An electrical sign of participation of the mental supplementary motor cortex in human voluntary (ego) movements. Brain Research 1972; 159:473–476.

Kutas M, Donchin E. Augmenting mental chronometry: The P300 as a measure of stimulus evaluation time. Science 1977; 197:792–795.

Kutas M, Donchin E. The effect of handedness, of responding hand, and of response force on the contralateral dominance of the readiness potential. In: Desmedt JE (ed.). Attention, voluntary contraction and event-related cortical potentials. Basel: Karger (Progress in Clinical Neurophysiology 1977; Vol. 1, pp. 189–210.

Kutas M, Hillyard SA. Event-related brain potentials to grammatical errors and semantic anomalies. Biological Psychology 1980a; 11:99–116.

Kutas M, Hillyard SA. Reading senseless sentences: brain potentials reflect semantic incongruity. Science 1980b; 207:203–205.

Kutas M, Hillyard SA. The lateral distribution of event-related potentials during sentence processing. Neuropsychologia 1982; 20:579–590.

Lenz RS. The question of electrophysiological asymmetries preceding speech. In: Whitaker H, Whitaker HA (eds.). Studies in Neurolinguistics. New York: Academic Press 1977, Vol. 3, pp. 207–218.

Little R. Event-related potential correlates of word ambiguity in children. Doctoral Dissertation. 1986, Amsterdam: Free University.

Little R, Kok A, Bakker DJ, Bouma A. Hemispheric distribution of ERP components and word reading in preschool children. Brain & Language 1986; 27:91–120.

Little R, Bakker DJ, Kok A, Bouma A. The development of hemi-visual-field potentials (ERPs) related to word reading: A 6- or year longitudinal study. Neuropsychologia 1988; 26:3, 527–540.

Loveless NEC, Sanford AJ. The impact of warning signal intensity on reaction time and components of the contingent negative variation. Biological Psychology 1975; 2:217–226.

Low MD, Fox M. Scalp-recorded slow potential asymmetries preceding speech. In: Desmedt JE (ed.). Language and hemispheric specialization in man: Cerebral event-related potentials. Basel: Karger, Progress in Clinical Neurophysiology 1977; Vol. 3, pp. 104–111.

Lumsden J, Pearson GW, Howard RC. The contingent negative variation to fear related stimuli in acrophobia and claustrophobia. Biological Psychology 1980; 11:201.

Marrosu de Nervilliani A, Tyrer-Berthet M, Parisi M, Rimmaudo A. Contingent negative variation in headache. Annals of Neurology 1995; 19:74–80.

Mowrer RH, Wise SF. Premotor states of readiness and activity in anticipation of predictable environmental events. Experimental Brain research 1983; 6:229–248.

McAdam DW, Whitaker HA. Language production: electroencephalographic localization in the normal brain. Science 1971; 172:499–502.

McCallum WC, Cummins B. The effects of signal form on the contingent negative variation in attentional periods. Electroencephalography and Clinical Neurophysiology 1978; 35:445–456.

McCallum WC. Cognitive aspects of slow potential changes. In: Desmedt JE (ed.). Cognitive components in cerebral event-related potentials and selective attention. Basel: Karger, Progress in Clinical Neurophysiology 1979; Vol. 6, pp 121–137.

McCarthy G, Donchin E. Brain potentials associated with structural and functional visual encoding. Neuropsychologia 1979; 16:571–585.

McCarthy G, Donchin E. A metric for thought: a comparison of P300 latency and reaction time. Science 1981; 211:77–80.

McCarthy G, Wood CC. Intracranial recordings and endogenous ERPs in humans. Electroencephalography and clinical neurophysiology 1985; 59:101–107.

Näätänen P. Orienting and evoked potentials. In: Kimura D (ed.), van Der Eil, Oldenbeke JP (eds.). The orienting reflex in humans. Hillsdale: N.J. Erlbaum, 1979; pp 64–75.

Näätänen R. Processing negativity: an evoked potential reflection of selective attention. Psychological Bulletin 1982; 92:605–640.

Näätänen R, Gaillard AWK. The orienting reflex and the N2 deflection of the ERP. In: Gaillard AWK, Ritter W (eds.). Tutorials in ERP research: Endogenous Components 1983; pp 119–141. Amsterdam: North-Holland.

Näätänen R, Picton TW. N2 and automatic versus controlled processes. In: McCallum WC, Zappoli R, Denoth F (eds.). Cerebral Psychophysiology: Studies in event-related potentials

(EEG suppl. 39); 1986; pp. 169–180. Amsterdam: Elsevier Science Publishers (Biomedical Division).

Neville H, Lalwani H, Friedman L, Yabrick H. Recording of microvolt-related potentials from the human cortex. Annals of Neurology 1980; 54:439–445.

Neville J, Hillyard V, Grunewald-Zuberbier E, Grunewald G. Event-related changes of late (600msec) CNV activity in a positioning movement task. In: Kurtzberg R, Cohen J, Starling P (eds.). Brain and Information: Event-related potentials. New York: New York Academy of Sciences 1984; Vol. 425; pp. 463–484.

Neville H. Electrocorticographic mapping of cerebral specialization in normal and congenitally deaf children: A preliminary report. In: Segalowitz SJ, Gruber FA (eds.). Language development and neurological theory. New York: Academic Press 1977; pp. 121–131.

Neville H, Snyder E, Knight R, Galambos R. Event-related potentials to language and non-language tasks in patients with ideas without signifiés. In: Lehtonen O, Callaway E (eds.). Human evoked potentials: Application and problems. New York: Plenum Press; 1979; pp. 289–304.

Neville H, Kutas M, Schmidt A. Event-related potential studies of cerebral specialization during reading: (I) studies of normal adults. Brain & Language 1985; 16:300–315.

Novick B, Kurtzberg D, Vaughan HG jr. An electrophysiological indicator of auditory information storage in children (abstract). Psychonomic Research 1979; 1(10):310.

Novick B, Vaughan HG jr, Kurtzberg D, Simson R. An electrophysiological indicator of auditory processing defects in autism. Psychiatric research 1980; 3:107–114.

Okada YC, Kaufman L, Williamson SJ. The hippocampal formation as a source of the slow endogenous potentials. Electroencephalography and Clinical Neurophysiology 1983; 55:417–426.

Okon BE, Chiappa KH. Statistical limits concerning computerized analysis of Halstead-Reitan topography. Annals of Neurology 1980; Vol. 19, 3:283–294.

Otto DA, Boutgass VA, Ryan LJ, Linton LJ. Slow potential components of stimulus, response and preparatory processes in man: A multiple linear regression model. In: Desmedt (ed.). JE. Attention, Voluntary contraction and event-related cortical potentials. Basel: Karger. Progress in Clinical Neurophysiology 1983; Vol. 1; pp. 213–230.

Pallbo KA, Kutas M, Morris HH. Neural correlates of morphological processing paradigm. Electroencephalography and Clinical Neurophysiology 1987; 67:369–377.

Pfefferbaum A, Ford J, Wenegrat B, Roth WT, Kopell BS. Clinical applications of the P3 component of event-related potentials. I. Normal aging. Electroencephalography & Clinical Neurophysiology 1984a; 59:85–103.

Pierre-Dominique C, Jardi E, Pinet C, Lebrigand D, Rolin B, Chain F, Adid X. Increased wave P300 latency in progressive supranuclear palsy. Journal of Neurology, Neurosurgery and Psychiatry 1989; 52:656–658.

Pinsky SD, McAdam DW. Electroencephalographic and dichotic indices of cerebral laterality in stuttering. Brain & Language 1988; 33:2, 274–297.

Plinio Von Eiferd R. [3]Cardiac correlates of scrupulosity: a psychophysiological comparison of normotics and normal controls in relation to personality. Biological Psychology 1981; 13:147–156.

Polich J. Semantic categorization and event-related potentials. Brain & Language 1985; 26:2, 304–321.

Polich J, Howard L, Starr A. Effects of age on P3a and P3b subcomponents of event-related potentials from auditory stimulation. Journal of Gerontology 1985; 40:721–726.

Pratt H, Michalewski HJ, Barrett G, Starr A. Brain potentials in a memory scanning task. I. Modality and task effects on potentials in the probe. Electroencephalography and Clinical Neurophysiology 1989a; 72:407–421.

Pratt H, Michalewski HJ, Patterson JV, Starr A. Brain potentials in a memory scanning task. II. Effects of aging on potentials in the probe. Electroencephalography and Clinical Neurophysiology 1989b; 72:507–517.

Pratt H, Michalewski HJ, Patterson JV, Starr A. Brain potentials in a memory-scanning task. III. Potentials in the items being memorized. Electroencephalography and Clinical Neuro-

hysiology 1988; 73:41–51.

Puce A, Kalnins RM, Berkovic SF, Donnan GA, Bladin PF. Limbic P3 potentials, seizure localization, and surgical pathology in temporal lobe epilepsy. Annals of Neurology 1989; 26:377–385.

Renault B. The visual emitted potentials: clues for information processing. In: Gaillard AWK, Ritter W (eds.), Tutorials in ERP Research: Endogenous Components, 1983, pp 159–175. Amsterdam: North-Holland.

Ritter W, Simpson R, Vaughan HG Jr. Event-related potential correlates of two stages of information processing in physical and semantic discrimination tasks. Psychophysiology 1983; 20(2), 168–179.

Ritter W, Simson R, Vaughan HG. Effects of the amount of stimulus information processed on negative event-related potentials. Electroencephalography and Clinical Neurophysiology 1988; 69:244–258.

Rizzo PA, Amabile G, Caporali M, Spadaro M, Zanasi M, Morocutti CA. CNV study in a group of patients with traumatic head injuries. Electroencephalography and Clinical Neurophysiology 1978; 45:281–285.

Rockstroh B, Elbert T, Lutzenberger W, Birbaumer N. Slow cortical potentials under conditions of uncontrollability. Psychophysiology 1979; 16:374–380.

Rohrbaugh JW, Gaillard AWK. Sensory and motor aspects of the contingent negative variation. In: Gaillard AWK, Ritter W (eds.), Amsterdam: North-Holland, Tutorials in ERP Research: Endogenous Components, 1983, pp 269–310.

Rosenberg C, Nudleman K, Starr A. Cognitive evoked potentials in early Huntington's disease. Archives of Neurology 1985; 42:984–987.

Rösler F, Sutton S, Johnson R, Jr, Mulder G, Fabiani M, Plooij-Van Gorsel E, Roth WT. Endogenous ERP components and cognitive constructs. A review. In: McCallum WC, Zappoli R, Denoth F (eds.), Cerebral Psychophysiology: Studies in event-related potentials (EEG suppl. 38), 1986; pp 51–92. Elsevier Science Publishers B.V. (Biomedical Division).

Roth WT, Ford JM, Pfefferbaum A, Horvath TB, Doyle CM, Kopell BS. Event-related potential research in psychiatry. In: Lehmann D, Callaway E (eds.), Human evoked potentials: Applications and Problems. New York: Plenum Press 1979, pp 331–348.

Roth WT, Duncan CC, Pfefferbaum A, Timsit-Berthier M. Applications of Cognitive ERPs in Psychiatric patients. In: McCallum WC, Zappoli R, Denoth F (eds.), Cerebral Psychophysiology: Studies in event-related potentials, Biomedical division (EEG Suppl. 38) Elsevier Science Publishers B.V. 1986; pp 419–438.

Ruchkin DS, Glaser E. Simple digital filters for examining CNV and P300 on a single-trial basis. In: Otto DA (ed.), Multidisciplinary perspectives in event-related brain potential research. Washington: Environmental Protection Agency, 1978, pp 579–581.

Ruchkin DS, Sutton S. CNV and P300 relationships for emitted and for evoked cerebral potentials. In: Desmedt JE (ed.), Cognitive components in cerebral event-related potentials and selective attention. Basel: Karger, Progress in Clinical Neurophysiology 1979, Vol. 6, pp 119–131.

Ruchkin DS, Sutton S, Stega M. Emitted P300 and slow wave event-related potentials in guessing and detection tasks. Electroencephalography & Clinical Neurophysiology 1980, 49:1–14.

Ruchkin DS, Sutton S. Positive slow wave and P300: association and disassociation. In: Gaillard AWK, Ritter W (eds.), Amsterdam: North-Holland, Tutorials in ERP research: Endogenous Components 1983, pp 233–250.

Ruchkin DS, Sutton S, Mahaffey D, Glaser J. Terminal CNV in the absence of motor response. Electroencephalography and Clinical Neurophysiology 1986; 63:445–463.

Rugg MD, Cowan CP, Nagy ME, Milner AD, Jacobson I, Brooks DN. CNV abnormalities following closed head injury. Brain 1989; 112:489–506.

Schultz W, Romo R. Neuronal activity in the monkey striatum during the initiation of movements. Experimental Brain research 1988; 71:431–436.

Shibasaki H, Shima F, Kuroiwa Y. Clinical studies of the movement-related cortical potential (MP) and the relationship between the dentatorubrothalamic pathway and readiness potential (RP). Journal of Neurology 1978; 219:15–25.

Sanjose JA, Khusaiber AJ. Bradbrook potential of cortical area 4 preceding self paced movement in Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry 1987; 50:1384-1391.

Simson R, Vaughan HG Jr, Ritter W. The scalp topography of potentials associated with missing visual or auditory stimuli. Electroencephalography & Clinical Neurophysiology 1976; 40:33-42.

Sittiet DA, Lum GE. Latency of the P3 event related potential: Normative aspects and within subject variability. Electroencephalography & Clinical Neurophysiology 1986; 59:420-426.

Squires NK, Squires KC, Hillyard SA. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalography & Clinical Neurophysiology 1975; 38:387-401.

Squires KC, Wickens C, Squires NK, Donchin E. The effect of stimulus sequence on the waveform of the cortical event-related potential. Science 1976; 193:1142-1146.

Squires K, Goodin D, Starr A. Event-related potentials in development, aging and dementia. In: Lehmann D, Callaway E (eds.). Human evoked potentials. New York: Plenum Press. Applications and Problems 1979; pp 383-396.

Squires NK, Gollenith GC, Aine CJ. Event-related potential assessment of memory and cognitive deficits in the mentally retarded. In: Lehmann D, Callaway E (eds.). Human evoked potentials: Applications and Problems. New York: Plenum Press 1979; pp 397-414.

Squires NK, Hakerem S, Wilson CH, Crandall P. Human endogenous brain potentials: Cross-modality and depth/surface comparisons in epileptic subjects. In: Gaillard AWK, Ritter W (eds.). Amsterdam: North Holland. Tutorials in event related potential research: Endogenous Components 1983; pp 217-232.

Starr J, Birbaumer N, Lutzenberger W, Elbert T, Rockstroh B, Schleifer P. Event-related potentials during a continuous performance test vary with attention capacities. In: Birbaumer N (ed.). Event related potentials in children: Basic Concepts and Clinical Applications. Amsterdam: Elsevier Biomedical Press 1983; pp 253-264.

Stapleton JM, Harper E. Endogenous potentials evoked in simple cognitive tasks: Depth components and task constraints. Encephalography and Clinical Neurophysiology 1987; 67:44-52.

Stein DF, Pfefer FW. Neurophysiological correlates of human concept formation. Behavioral Biology 1978; 23:138-162.

Stern DB, Sanders FT, Lacey EC, Pfefer FW. Event related potentials during naming and mental rotation. Electroencephalography & Clinical Neurophysiology 1982; 54:133-146.

Symmes D, Chorpaut MA. Evoked cortical correlates of meaningful sound stimuli in children. Psychophysiology 1971; 8:768-779.

Synthelde R, Lindsley DB. Motor and sensory determinants of cortical slow potential shifts in man. In: Desmedt JE (ed.). Attention, Voluntary Contraction and event-related cortical potentials. Basel, Karger, Progress in Clinical Neurophysiology 1977; Vol. 1: pp 97-131.

Synthelde K, Hanuik EC, Cohen SS, Pfefer FW, Goldberg Z, Montana B, Tourtellotte WW, Pelvin AB. Longitudinal event-related potentials in normal aging and dementia. In: Courjon J, Mauguiere F, Revol M (eds.). New York: Raven. Clinical Application of Evoked Potentials in Neurology; 1982; pp 279-285.

Tallon J, Vaughan HG. Characteristics of visual and tactile potentials associated with speech production. In: Desmedt JE (ed.) Language and Hemispheric Specialization in Man: Cerebral event-related potentials. Progress in Clinical Neurophysiology 1977; Vol. 3.

Tecce JJ. Contingent negative variation (CNV) and psychological process in man. Psychological Bulletin 1972; 77:73-108.

Timsit-Berthier M. La variation contingente négative et les maladies mentales. Acta psychiatr. belg. 1976; 76:533-550.

Tueting P, Sutton S, Zubin J. Quantitative evoked potential correlates of the probability of events. Psychophysiology 1970; 7:367-396.

Vaughan HG, Costa LD, Ritter W. Topography of the human motor potential. Electroencephalography & Clinical Neurophysiology 1968; 25:1-10.

Vaughan HG Jr, Ritter W. The sources of auditory evoked responses recorded from the human scalp. Electroencephalography & Clinical Neurophysiology 1970; 28:360–367.

Walter WG, Cooper R, Aldridge V, McCallum WC, Winter AL. Contingent negative variation: An electrical sign of sensorimotor association and expectancy in the human brain. Nature 1964; 203:380–384.

Wood, CC., McCarthy G. Principal component analysis of event-related potentials: simulation studies demonstrate misallocation of variance across components. Electroencephalography & Clinical Neurophysiology 1984; 59:249–260.

Wood CC, McCarthy G, Squires NK, Vaughan HG, Woods DL, McCallum WC. Anatomical and physiological substrates of event-related potentials: two case studies. Annals of the New York Academy of Sciences 1984; 425:681–721.

Woody CD. Characteristics of an adaptive filter for the analysis of variable latency neuroelectric signals. Medical Biological Engineering 1967; 5:539–553.

Yingling CD, Hosobuchi Y. A subcortical correlate of P300 in man. Electroencephalography and Clinical Neurophysiology 1984; 59:72–76.

Zappoli R, Papini M, Bruni S, Benvenuti F, Pasquinelli A. CNV in patients with formaldehyde toxosis and mental disturbances. In: McCallum WC, Knott JR (eds.) The Responsive Brain. Wright, Bristol; 1976; 156–163.

Zimmerman GN, Knott JR. Slow potentials of the brain related to speech processing in normal speakers and stutterers. Electroencephalography & Clinical Neurophysiology 1974; 37:295–307.

Index of subjects