UNIVERSITY OF OXFORD

ANALYSIS OF THE BRAINSTEM AUDITORY EVOKED POTENTIALS IN NEUROLOGICAL DISEASE

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To the memory of my father

ILLUSTRATIONS

1. Acoustic waveform of click

2-3. Ipsilateral-contralateral differences

4-21. Click polarity effect

22. Click intensity

23. Inverse effect of click intensity on amplitude

24. Delay of input to brainstem?

25-27. Click intensity

28. Click polarity effect

29. Acoustic waveform of click

30. Differences between montages

31-33. Click polarity effect

34. Progression in MS

35. BAEP oscillations

36-49. Resonator filter

50. Simulation model

51. Simulation of effect of click polarity

52. Simulations

53-64. Spectral density estimate

65. Relation between cochlea and BAEP

66. Deafness and wave I

67-70. Differences between montages

71. Click polarity effect

72-78. Unsustained oscillations

79-80. Low frequency BAEP

81-89. Planar vectogram

90. Multiple peaks

91-99. Variability between runs

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ABSTRACT

Many phenomena in the BAEP are difficult to explain on the basis of the accepted hypothesis of its origin (after Jewett, 1970). The alternative mechanism of origin to which these phenomena point is summation of oscillations. Therefore, simulation of the BAEP by a mathematical model consisting of the addition of four sine waves was tested. The model did simulate a normal BAEP as well as variations in the waveform produced by reversing click polarity.

This simulation gives further clues to the origin of the BAEP. The four sine waves begin simultaneously; corresponding BAEP oscillations must, therefore, originate from a single structure. These oscillations begin in less than half a millisecond after the click. This suggests that the structure from which they arise is outside the brainstem.

This alternative mechanism indicates that wave latencies do not reflect nervous conduction between discrete nuclei, and interpretation of BAEP abnormality need to be reconsidered. It also implies that mathematical frequency analysis is more appropriate, but this could be applied only when these methods have been perfected.

Meanwhile, through visual analysis and recognition of oscillations, abnormality can be detected and described in terms that may have physiological significance.

INTRODUCTION

The value of evoked potentials (EP) in neurological disease largely depends on knowledge of their origin. Such knowledge is essential to the understanding of the mechanisms of abnormality that may cause them, e.g. demyelination, ischaemia, wax in the ear. Abnormality, otherwise, becomes an expression that is clinically useless.

It is worse, of course, when the origin of the EP is thought to be known, but is, in fact, not. Misleading conclusions would be inevitable:"No data are better than wrong data".

The increasing use of the brainstem auditory evoked potentials (BAEP) in the investigation of brainstem disease depends on the assumption that the generators, at least of some of the waves, are known. In describing the potential in the cat (1970) Jewett postulated that discrete auditory brainstem nuclei, individually or in combination, generate the component waves. And together with Williston (1970), Jewett carried over the same postulate in the first report on the potential in man. Successive investigators examined this postulate using mainly three methods: they compared BAEP waves with potentials recorded directly from the brainstem (Wada and Starr 1983), in animals and in man; they made lesions in the brainstem of animals; and they studied the BAEP in patients with known pathology (as much as can be known clinically, radiologically and postmortem).

The following are examples of these methods: Hashimoto et al. (1981) recorded directly from the human brainstem and thalamus. Møller et al. (1981) and Møller and Jannetta (1982) also recorded directly in man, from the auditory nerve and from the inferior colliculus. Velasco et al. (1982) studied the origins of waves IV - VII, employing electrical stimulation and recording multiple unit activity with implanted electrodes, in man. Garg et al. (1982) speculated on the origin of wave II on finding it delayed in hereditary motor-sensory neuropathy. Corwin et al. (1982) studied the BAEP in the shark, gar, frog, turtle and dove. Maurer and Mika (1983) made lesions in the cerebellopontine angle of the rabbit. Wada and Starr (1983a,b,and c) made lesions in the brainstems of cats and guinea pigs.

Thus it is now generally agreed that the BAEP is generated by post-synaptic potentials in each of a successive series of brainstem nuclei, by action potentials in fibre tracts connecting them, or both. Table 1 shows the structures proposed by different authors for the origin of the BAEP.

This hypothesis implied that wave latency is a function of impulse conduction velocity and of the rate at which synaptic activation is reached. Wave amplitude, on the other hand, is a function of the number of axons conducting the impulses, the synchrony with which this conduction proceeds and the number of neurones activated in a synapse. On extrapolation, latency difference between successive peaks would reflect conduction time

Table 1

Origin of the BAEP

Wave	Hashimoto (1981)	Buchwald (1983)	Chiappa (1983)	Wada & Starr (1983)
I	VIII nerve	Cochlear nerve	Cochlear nerve	Cochlear nerve
II	VIII nerve + pons	IIA: Cochlear nerve IIB: CN	Cochlear nerve or CN	CN
III	pons (contra.)	SOC (bilateral)	SOC (mainly ipsilateral)	SOC (contralateral)
IV	pons (contra.)	VNLL (bilateral)	Unknown	Tegmentum of pons
V	IC (contra.)	IC (bilateral)	LL or IC (laterality not mentioned)	Tegmentum of pons
VI	MGB (contra.)	Not discussed	MGB (laterality not mentioned)	Not discussed
VII	Not discussed	Not discussed	Auditory radiations	Not discussed
VIII	Not discussed	Not discussed	Not discussed	Not discussed

CN: cochlear nucleus; IC: inferior colliculus; LL: lateral lemniscus; MGB: medial geniculate body; SOC: superior olivary complex; VNLL: ventral nucleus of lateral lemniscus

between their generators. Thus, the concept of central (or brainstem) transmission time (BTT) emerged.

Robinson and Rudge (1981), argued against the validity of central conduction time. They based their argument on the uncertainity of generators (of waves III and V, in their example) and on the possibility that more than two structures may be involved in the generation of a peak. In later work (1983), however, they speak positively of the generators of waves III and V as being the superior olivary nuclei and the colliculi, alluded to in their earlier work as a conclusion of misconception. And based on impeded transmission between these generators, which are anatomically at successively higher levels, they explain the more frequent delay of wave V (compared to that of wave III) in VIII nerve tumours. They also accept (1982) that an effect of demyelination is delay of wave V. The concept of central transmission time (between two generators or more) is, therefore, endorsed. In fact, the only condition for dismissing the validity of BTT, (assuming that the current hypothesis on the origin of the BAEP is correct) would be if impaired conduction results in decrease, as well as increase, in latency of any of the waves. This they did not find.

Thomas (1984) interpreted the generation of the BAEP in a different way. According to his analysis, all the waves are generated by a single repetitive component, with the exception of wave V. This wave is formed by a component, probably arising from the contralateral inferior colliculus, after a delay of about 5 msec. The latency and amplitude of wave V, he concludes,

are most useful in the analysis. Thus, the measure of conduction time between successively higher brainstem levels, is again asserted.

The concept of central transmission time has had a major influence on recording, analysis and interpretation of the BAEP. Latencies and amplitudes became cornerstones. Thus, with the rationale of stressing conduction and synaptic function in the auditory pathways, Pratt et al. (1981) and Elidan et al. (1982) used fast click rates. Their results were conflicting.

The effect of the click phase on the BAEP is perhaps the best example of how conception of the origin of an EP dictates the way it is recorded. This influence merits detailed study. Thus, until recently, investigators gave little attention to the effect that reversing the click phase may have on the waveform. Indeed, up to now, reports on its effect on the BAEP are conflicting, and the mechanism of this effect (however described) is not explained. The reason for this may be that Jewett (1970), having found no effect (except for the cochlear microphonic) on the BAEP waves (in cats), neglected this factor in the first description (1970b) of the BAEP in man. Indeed, given his speculation that the BAEP represents travel of auditory information through the brainstem, he would have no reason for anticipating that change in the phase of a sound stimulus--a change subjectively imperceptible--should produce any differences. Added to that was the suggestion that for brief click stimuli, click phase is unimportant (Stockard and Stockard 1983). Many of the investigators, therefore, did not

even mention this condition. Indeed, had it been not for the need* to reduce the stimulus electrical artefact, by alternating click polarity, this neglect might have continued even longer.

Another reason for encouraging indifference to the click phase is that some authors observed that it had no effect on the waveform (e.g. Robinson and Rudge 1981) or only little effect (Stockard 1979) and no effect (Thomas 1984) on wave V, the wave almost universally regarded the most important of the waveform. Other authors were convinced of a general agreement that the effect occurs during the first 4.5 msec.

Furthermore, when significant effects were recognized, the hypothesis of discrete brainstem generators made explanation so perplexing that Stockard (1982) called it Pandora's box, whereas Thornton (1982) concluded:

> "At present time it cannot be conclusively demonstrated whether the evoked potential to a single polarity stimulus is more simple or more complex than the response to an alternating stimulus."

As for analysis, computing techniques were developed to improve wave peak detection (Kobayashi and Yaguchi, 1981, Fridman et al., 1982); Ogleznev et al. (1983) suggested measuring the latency of a peak at the middle of its front, instead of its top;

* This again stemmed from the belief that the BAEP provided a measure of central conduction, making it important to use any method that helps this end. Thus, Stockard (1980) describes wave I as "the electrophysiological landmark from which more proximal conduction must be assessed."

Wada and Starr (1983b) stressed importance of dividing a wave into positive and negative halves (on their assumption that each half may have a different generator) for the purpose of latency and amplitude measurements, and different forms of statistics are used to define normal limits of latencies and amplitudes (Thornton 1976, Ciganek et al. 1984). Even in such analyses as wave area (Anthony et al. 1979) and the vectogram (Pratt et al. 1983), latencies and amplitudes form the major determinants.

Clinical interpretation of the BAEP also depends on latency and amplitude. An increase in latency implied processes impeding conduction, such as demyelination or ischaemia. Reduction in amplitude or distortion of the waveform indicated dysynchronized transmission. And since the generators of the BAEP are thought to be known, such interpretations extended to localization of the lesions.

Thus, on the basis of origin of waves III and V, Robinson and Rudge (1983) speculated on the mechanism of brainstem deformation by VIII nerve tumours. Hopf and Maurer (1983), finding delay of wave I, concluded that the peripheral part of the acoustic nerve is affected in MS. Chiappa (1983) states that

> When there is an abnormal III-V interpeak latency--(the interpretaion might read:)'This abnormality suggests the presence of a conduction defect in the brainstem auditory system between the lower pons and the midbrain'.

And, with an upper limit of error unlikely to exceed 1 cm, he continues, localization of generators is sufficiently accurate for most clinical purposes.

On the same theme, Levine and McGaffigan (1983), finding, in normal persons, right-left asymmetries in the BAEP, suggested that cerebral asymmetries for language are related to asymmetries in the brainstem auditory system.

Interpretation of BAEP differences between men and women is another example of inference based on Jewett's hypothesis. In women, interpeak latencies are shorter. Stockard et al. (1979) and Allison et al. (1983) attributed these differences to brain size. And Del Pozo (1982) measured the distance between the cochlear nucleus and inferior colliculus in fresh post-mortem specimens; he did find it longer in men, although differences were not statistically significant. Yet these authors do not to explain the close similarity between the time scales of the BAEP in man and in animals with as small a head size as that of the rat (Discussion p.11).

Central conduction time also influenced investigators in selecting diseases in which BAEP were examined. For example, with the hope of detecting occult brainstem demyelination, the technique was applied to the diagnosis of multiple sclerosis. On similar grounds, investigators used the BAEP in the study of a variety of neurological diseases: mental retardation (Squires et al., 1980), leukodystrophies (Markand et al., 1982), Friedreich's ataxia (Amantini et al., 1984), chronic paint sniffing (Metrick and Brenner, 1982), diabetes mellitus (Verma et al., 1984), closed head trauma (Scherg et al., 1984), cerebellopontine angle tumours (Robinson and Rudge, 1983), pontine haemorrhages,

alcoholism, meningitis (Chiappa, 1983). Had it not been for its assumed ability to reflect brainstem conduction, the BAEP may not have had such a wide application.

Likewise, the concept of conduction time meant that the BAEP can be used to observe the effect of disease, and drugs, on brainstem function. Thus Amantini et al. (1984) advocated the use of the BAEP to monitor the progression of Friedreich's ataxia. Green et al. (1982) finding prolonged waves I-V interval, concluded that phenytoin slows central conduction. Squires et al. (1980) finding little effect of fast click rate on I-V interval in Down's syndrome, concluded that both peripheral and central auditory processing disorders may contribute to retardation; Peled et al. (1983) investigated brainstem dysfunction in sleep apnoea. Their findings were "surprising"; BAEP remained stable during the various phases of apneic episodes; Sohmer et al. (1982, 1983 and 1984) studied the effects of hypoxia, hypercapnia and ischaemia and Deutsch et al. (1983) investigated those of hypoglycaemia on the brainstem by using measures of BAEP latency. In all these studies, BAEP findings were paradoxical (according to Jewett's hypothesis). Convinced of this hypothesis, however, the authors made remarkable inferences on the function of the brainstem.

Work for this thesis began with the aim of studying the effect of drugs in multiple sclerosis, as reflected in the BAEP. In a double-blind crossover trial, ten patients received the calcium antagonist prenylamine. This drug may improve conduction

in demyelinated axons (Sherratt et al. 1980). Should this happen, latencies of BAEP waves might decrease and amplitudes increase.

Similarly, the effect on the BAEP of changing core temperature, as measured from the vicinity of the tympanic membrane, in patients with multiple sclerosis, was investigted.

These BAEP were studied with measures of latency and amplitude. No consistent differences were found. This was not surprising; drug dosage was small,and no clinical changes were observed. Some latency changes, in fact, were paradoxical, assuming the hypothesis of discrete brainstem generators to be true.

In addition, and to obtain a visual impression of differences between BAEP, subtraction was also used. Results often appeared as wavy lines and were dismissed as artefacts. And because both click polarities, separately, were used, and seeing that the BAEP differences between them were always striking, always out of proprtion to what is described in the literature, subtraction was also used to see what these differences looked like. Results were surprising. Differences often looked like sine waves. And when digital filtering was also applied, results showed that most of the BAEP can be broken down into oscillations of different frequencies.

The accepted hypothesis of the generation of the BAEP did not appear to explain the observed phenomena and alternative theories were therefore explored.

METHOD

BAEP were recorded from 27 normal hearing healthy persons (18-37 years of age,mean 28, 17 males) and from 160 patients with definite or suspected neurological disease.

Subjects reclined in a comfortable chair, to reduce neck-muscle artifacts, in a quiet, dim-lit, but not sound-proofed room. Silver cup electrodes (10 mm diameter, chlorided and disinfected by immersion for 20 minutes in 1:2 Chloros solution), were placed, with surgical adhesive tape and after cleaning the skin with 70% methylated spirit, on the vertex (active), mastoids and chest. Ground electrode was placed on the forehead. Electrode cup cavity was filled with conductive jelly and electrical contact enhanced by scarification of the scalp underneath the elctrode with a blunt large-bored needle. Interelectrode impedance was maintained below 2Kohms. For this purpose an SLE impedence meter, delivering 14 Hz AC voltage across electrode pairs. (On some occasions, this frequency was changed to 700 Hz, as this would be closer to that of the BAEP. This showed, however, that less scarification was needed for a given impedance reading).

Digitimer D-160 differential amplifiers were set to a gain of 50,000 and filter limits (cutoff frequencies) of 53-3000Hz (3 dB points). A Digitimer D-200 8 bit microprocessor averaged 10 msec interval of the amplified signal, starting 1 msec after click onset, at 40 usec sampling rate (Nyquist frequency = 12.5 KHz, giving a resolution of 6 KHz). The leading edge of the square

wave pulse producing the click (click onset) triggered the sweeps. Averaging runs consisted of 1024 sweeps (2^{10} - 10*3dB=30dB improvement in S/N), and at least two runs were made for any set of recording conditions. Automatic artefact rejection (amplitude) was used.

Clicks were produced by a 0.2msec square wave pulses, delivered to an RS cushioned headphone, at a regular rate of 10 Hz. Sometimes a rate of 9.09 Hz was also used to check for the possibility of an integral factor of mains interference affecting the averages--no such effect was found. Monaural and binaural stimulation was used, with rarefaction and condensation clicks delivered separately. The acoustic waveform of the click (Fig.1) was viewd on an oscilloscope to check for headphone wiring so that both sides produced the same click phase. Click-hearing threshold was determined by the method of limits reliability within 5dB) and clicks were delivered at 65 dBSL hearing level (unless otherwise stated).

Algebraic subtraction between different BAEP was performed in the averager.

Except for a few instances (indicated), the convention followed in the illustrations is as follow:

(1) Traces are 10.2 msec long, start 1 msec after click onset and have the same amplitude scale

(2) Positivity at vertex is upwards

(3) Click polarity is shown on the right of records as "R" for rarefaction and "C" for condensation

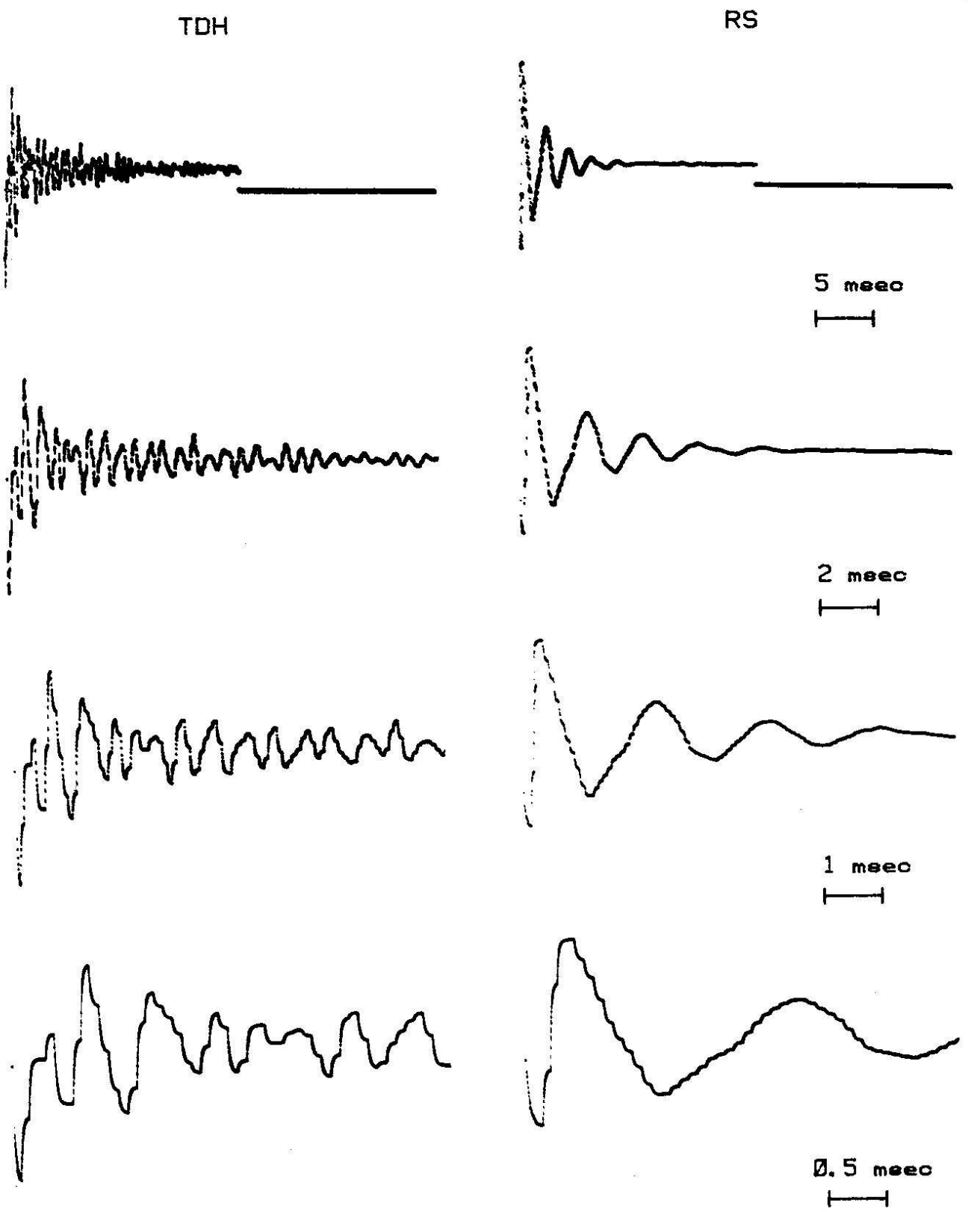


Fig. 1

Acoustic waveform (at different time scales) of click produced from headphones TDH (left) and RS.

(4) Traces are ipsilateral channels, to 65dBSL monaural clicks

(5) Result of digital subtraction, of a lower trace from an upper, is plotted at the bottom

Vectogram

Planar vectograms were constructed by plotting the values of all points (from 2 to 9 msec) of the ipsilateral channel on the vertical axis, against corresponding points of the contralateral channel on the horizontal axis. Triangular axes (Szelenberger, 1982) were also used (on the assumption that the vertex-ipsilateral and contralateral mastoid derivations are at an angle of less than 90°), but the vectogram pattern did not form a continous loop, and offered no practical advantages over that of the perpedicular axes. In plotting, time between successive dots is fixed: thus wider spacing indicates faster inscription.

Digital filtering

Smoothing filter:

Before plotting or applying further digital filtering, vectogram or performing frequency analysis, the BAEPs were smoothed in the averager by the following algorithm:

$$\text{After one smoothing } N_{x,t+1} = \frac{N_{x-1,t} + 2 * N_{x,t} + N_{x+1,t}}{4}$$

Filter of first-order differencing:

This filter is used to "...remove a trend [and] ...attain apparent stationarity...[of a waveform]" Chatfield (1980). It was applied to the BAEP before using the FFT.

It has the following formula:

$$y_t = x_{t+1} - x_t$$

where $[y_1,\ldots,y_{n-1}]$ is the new series, formed from the original series $[x_{t+1},\ldots,x_n]$.

Resonator filter:

Francis R. Pettit, former head of Oxford University's Computing Teaching Centre, kindly provided in a BASIC programme the following digital filter:

```
For L = 1 to 4
 m = 2↑L
 m2 = 2*m

   For n = 1 to 256

    Y(n) = 6*Y(n)-4*(Y(n-m)+Y(n+m))+Y(n-m2)+Y(n+m2)

   Next n

Next L
```

Simulation

The model runs on a BASIC microcomputer programme:

```
For N= 1 to 230
  W(1) = sin (( N + P1 )/ F )
  W(2) = sin (( N + P2 )/ ( F * 0.5 ))
  W(3) = sin (( N + P3 )/ ( F * 0.25 ))
  W(4) = sin (( N + P4 )/ ( F * 0.125 ))
     Y = W(1) + W(2) + W(3) + W(4)
Next N
```

where W(1) is the 120 Hz sine wave, P(wave no.) is the phase factor in pi radians, F (=36)is the frequency factor, and Y is the resulting simulated waveform. W(4) is linearly damped by a factor of 1.1, after N=160.

The model may be written in the following form:

$$Y_t = \sum_{i=1}^{4} A_i(t)\sin(W_i t + \phi i)$$

where: A is the amplitude factor:

$$A_1(t) = A_1$$

$$A_2(t) = A_2$$

$$A_3(t) = A_3$$

$$A_1 = A_2 = A_3$$

$$\text{And} \quad A_4(t) = \begin{cases} A_4 & t=1,\ldots,160 \\ A_4 \, (1.1)^{t-161} & t=161,\ldots,256 \end{cases}$$

Frequency (doubles for each successive sinusoid) is determined by W, and phase (variable) is determined by ϕ .

Method 6

Fequency analysis

This was kindly performed by Javier Alagon, D.Phil. student at the Department of Biomathematics, University of Oxford. The Blackman-Tukey method, using the Fast Fourier Transform algorithm for taking the Fourier transform of the windowed (Bartlett) autocorrelations, was used. The algorithm is represented by the formula:

$$f(w) = \frac{1}{2\pi}\left[C_o + 2\sum_{k=1}^{M} W_k C_k \cos W_k\right]$$

where M = 200 (number of autocorrelation lags), L = 400,

$W_k = 1-k/M = 1-k/200$ (Bartlett window)

C_0, C_1, C_2,...,C_{199} are the autocovariances of of the BAEP at lags 0,1,2,...,199

$$C_0 = 1/n \sum_{t=1}^{256} (x_t-\bar{x})(x_t-\bar{x})$$

$$C_1 = 1/n \sum_{t=1}^{255} (x_t-\bar{x})(x_{t+1}-\bar{x})$$

$$C_2 = 1/n \sum_{t=1}^{254} (x_t-\bar{x})(x_{t+2}-\bar{x})$$

.
.
.
etc.

where n = 256 (number of points in the BAEP), $x_1, x_2, \ldots, x_{255}$ are the values of the 255 points and $\bar{x}$ is their mean

$$\bar{x} = 1/n \sum_{t=1}^{256} x_t.$$

RESULTS AND DISCUSSION

In the following, the methods used to test Jewett's hypothesis will be discussed. But because an alternative mechanism is proposed in this thesis, some emphasis will be given to the limitations of these methods.

1. Lesion studies:

Extensive work has been done along this line, and indeed, the strength of support for Jewett's hypthesis derives from lesion studies. For this reason, examples of this method, together with the conclusions derived from the results will be given for each of the major BAEP waves; (for a comprehensive review, see Buchwald [1983], who herself has done substantive lesion work).

a) Wave I This wave remained, while the succeding waves disappeared, when the VIII nerve was cut in the cat (Buchwald and Huang, 1975) and in the mouse (Henry, 1979) or inactivated with KCl, in the guinea pig (Legouix and Pierson, 1974), at its central end. This finding was, therefore, taken to support the origin of wave I from the auditory nerve (Buchwald, 1983).

b) Wave II (i)In the cat, section of the central end of the VIII nerve (Buchwald and Huang, 1975), or partial or complete destruction of the ipsilateral cochlear nucleus (Gardi et al., 1979 and Achor and Starr, 1980b) resulted in marked reduction or complete loss of this wave. (ii) Bilateral separation of the cochlear nucleus from the brainstem, in the cat (Buchwald and Huang, 1975), led to the disappearance of all the waves after II, which, together with I, was unaffected. (iii) Waves I and II, in the cat, were also unaffected, whereas the subsequent components were markedly reduced, when lesions were made in the dorsal, intermediate, and ventral acoustic stria. (iv) Extensive lesions of the superior olivary complex affecting the adjacent trapezoid body fibers, in the cat (Achor and Starr, 1980b), had no effect on either waves I or II. These findings have been taken to suggest that wave II is generated mainly by the cochlear nucleus (Buchwald, 1983).

c) Wave III (i) Extensive rostral lesions including the inferior colliculus and lateral lemniscus but sparing the superior olivary complex, as well as lesions in the dorsal and intermediate acoustic stria, in the cat (Gardi et al., 1979 and Achor and Starr, 1980b), had no effect on wave III. On the other hand, midsaggital section through the dorsoventral part of the trapezoid body (Buchwald and

Huang, 1975), markedly reduced or abolished wave III. Extensive unilteral lesions in the superior olivary complex in the cat, destroying most of the medial superior olive as well as the decussating fibers of the trapezoid body (Achor and Starr, 1980b), also abolished wave III, but mainly to ipsilateral stimulation. Smaller unilateral lesions in the superior olivary complex and adjacent trapezoid body led to the attenuation, but not absence, of wave III to both ipsilateral and contralateral clicks. These results have been interpreted as indicating the origin of wave III from both uncrossed and crossed input to the superior olivary colliculi (Buchwald, 1983).

d) Wave IV (i) Bilateral aspiration of the inferior colliculus in the cat (Buchwald and Huang, 1975 and Gardi et al., 1979), or extensive lesions in that structure in the cat (Achor and Starr, 1980b) and mouse (Henry, 1979), had no effect on this wave. (ii) Lesions in the decussating trapezoid body, however, (Achor and Starr, 1980b) caused marked attenuation of wave IV. (iii) Also in the cat, unilateral lesions of the ventral lemniscus (Buchwald and Huang, 1975) as well as focal cooling caudal to the lateral lemniscus (Stockard and Sharbrough, 1980) affected wave IV, but not the earlier waves. Accordingly, the origin of this wave is thought to be postsynaptic potential activity in the ventral nucleus of the lateral lemniscus (Buchwald, 1983).

e) Wave V Complete transection of the brainstem rostral to the inferior colliculus, in the cat (Buchwald and Huang, 1975) and mouse (Henry, 1979), had no effect on this wave. Local cooling including the medial and lateral lemnisci on both sides, in the cat (Stockard and Sharbrough, 1980) produced delay of waves IV and V. Also in the cat, lesions in the colliculi, or restricted lesions in the dorsal lateral lemniscus (Achor and Starr, 1980b), the negativity preceding wave V was reduced. Bilateral lesions, including the lateral and ventral parts of the inferior colliculi (Buchwald and Huang, 1975) led to reduction or loss of wave V. These results have been interpreted as suggesting the generation of wave V in the deep ventrolateral portion of the inferior colliculus (Buchwald, 1983).

Nevertheless, lesion studies have important limitations. For example, the ideal experiment, as described by Starr (1982), is making a lesion that affects only one particular structure. Robinson and Rudge (1982), on the other hand, maintain that even "a discrete lesion can cause considerable disruption of more than one component". Not surprisingly, therefore, up till now the ideal experiment has not succeeded. An example is the elaborate lesion study in guinea pigs and cats, where Wada and Starr (1983a) injected procaine HCl into the trapezoid body. The advantage of this method is reversibility. But the local anaesthetic spread to adjacent structures, making interpretation of results difficult. They also made surgical sections and

electrolytic coagulation, but findings were again ambiguous so that they concluded that the generators of the components affected by the lesion are structures receiving input from, not the sectioned structures themselves.

Notwithstanding, even if the ideal lesion is ever made, it would still be unlikely to define the anatomical region of wave generation, as Robinson and Rudge (1982) and Wada and Starr (1983c) themselves admit.

2. Direct recording:

Wada and Starr (1983a) also concede, in interpreting their lesion experiments, that potentials recorded directly from brainstem structures are not necessarily the same as those recorded at the surface. This limitation is best illustrated by the following controversies:

a) The first example is found in Jewett's first paper on the BAEP (1970). One of the observations from which he infers that the first positive wave of the BAEP (P1) reflects eighth nerve action potential is the synchrony of P1 with N1 (the negative potential recorded at the round window). He also cites the theory that, in a three-dimensional medium, action potentials moving toward or away from an electrode are recorded as positivity whereas only those passing an electrode are seen as negativity. Therefore, given that action potentials at the round window propagate

away from that area, N1 should have been positive. He explains this contradiction, however, as due to "some distortion of the fields in the vicinity of the complex anatomy of the cochlea".

b) In 1980, Achor and Starr made lesions in the brainstem of the cat to examine Jewett's hypothesis that each BAEP peak has a single generator. But they concluded that individual peaks receive contributions from more than one structure. Three years later, Wada and Starr (1983b) made lesion studies in the cat and guinea pig to reexamine the same issue. They concluded (1983c), however, that individual BAEP waves receive contributions from only a single brainstem structure.

c) Hashimoto et al. (1981), recording from the inferior colliculus in man, concluded that it generates wave V. Møller and Jannetta (1982), on the other hand, recording from the same structure, concluded that it is waves VI, VII and VIII this structure generates, not wave V. And in correlating their findings to man, Wada and Starr (1983c) concluded that the inferior colliculus generates none of the BAEP components.

3. Studying the BAEP in disease:

An example of these studies is the work of Garg et al. (1982). Finding delayed or unidentifiable* wave II in hereditary sensory motor neuropathy, they speculated that this wave originates from the intracranial extramedullary portion of the eighth nerve. But this inference is not sound because it presupposes that the origin of other waves is established.

The study of Hari et al. (1981) offers another example. Finding wave I only--records in their paper do contain succeeding waves, although at small amplitude--in the BAEP of a young man with alpha pattern coma, they suspected brainstem infarction, which autopsy confirmed. But autopsy also showed thrombus totally occluding the basilar artery. Thus, blood supply to the internal ear and acoustic nerve was jeopardized. By itself, this latter finding is enough to explain the BAEP abnormality if, as suggested in this thesis, all components of the BAEP are likely to originate in a peripheral structure.

Furthermore, bearing in mind the caveat that potentials recorded directly from brainstem structures are not necessarily the same as those recorded synchronously at the surface, an

* Wave II is occasionally absent in normal persons on one click polarity. These authors used alternating polarity.

important limitation common to all these methods is that these investigators recorded from or made lesions in brainstem structures they already suspected to be generators (after Jewett's hypothesis). It is, therefore, necessary to turn back and trace the evolution of that hypothesis.

Jewett (1983) describes that twenty years earlier, Dr. Galambos (in whose laboratory Jewett had just begun to work) encouraged him to investigate how auditory evoked responses in animals had been recorded in nonauditory brain areas. Dr. Galambos had expressed his hope that this work might demonstrate transmission of information through the brain.

Thus, having recorded throughout the brain of anaesthetized cats, short latency waves evoked by sound, having found that the first of these waves is synchronous with N1 potential of the round window, and having recognised that these waves are neural potentials, Jewett related them to the flow of information through the auditory pathways in the brainstem. The main theme of this hypothesis continues to prevail.

Thomas (1984) had a different view of BAEP origin. He proposed that all the waves, except wave V, are generated by a single repetitive component; wave V is generated by a delayed component, probably originating in the inferior colliculus. A third, slow background wave, gives the BAEP its sloping shape.

For the reasons discussed below, however, this hypothesis is not valid. Thus apart from polarity, he does not set fixed parameters for the behaviour of the slow background component, which he alters in shape loosely to account for different waveforms. For certain BAEP, for example, this component assumes the frequency of the repetitive wave (Figs. 2 and 3). Moreover, it is unlikely that a single group of neurones oscillating at 850c/s provide the only sinusoidal contribution to the BAEP. The occasional presence of several peaks in a wave indicates this. It also does not account for the following phenomena: the marked condensation-rarefaction differences, especially where wave V is also affected and the occasional absence of wave II on one click phase--Thomas studied BAEP to alternating click polarity--or the inverse amplitude relation between waves I and III on different click phases; decrease in amplitude or delay of wave V on increasing click intensity and on using different types of headphone.

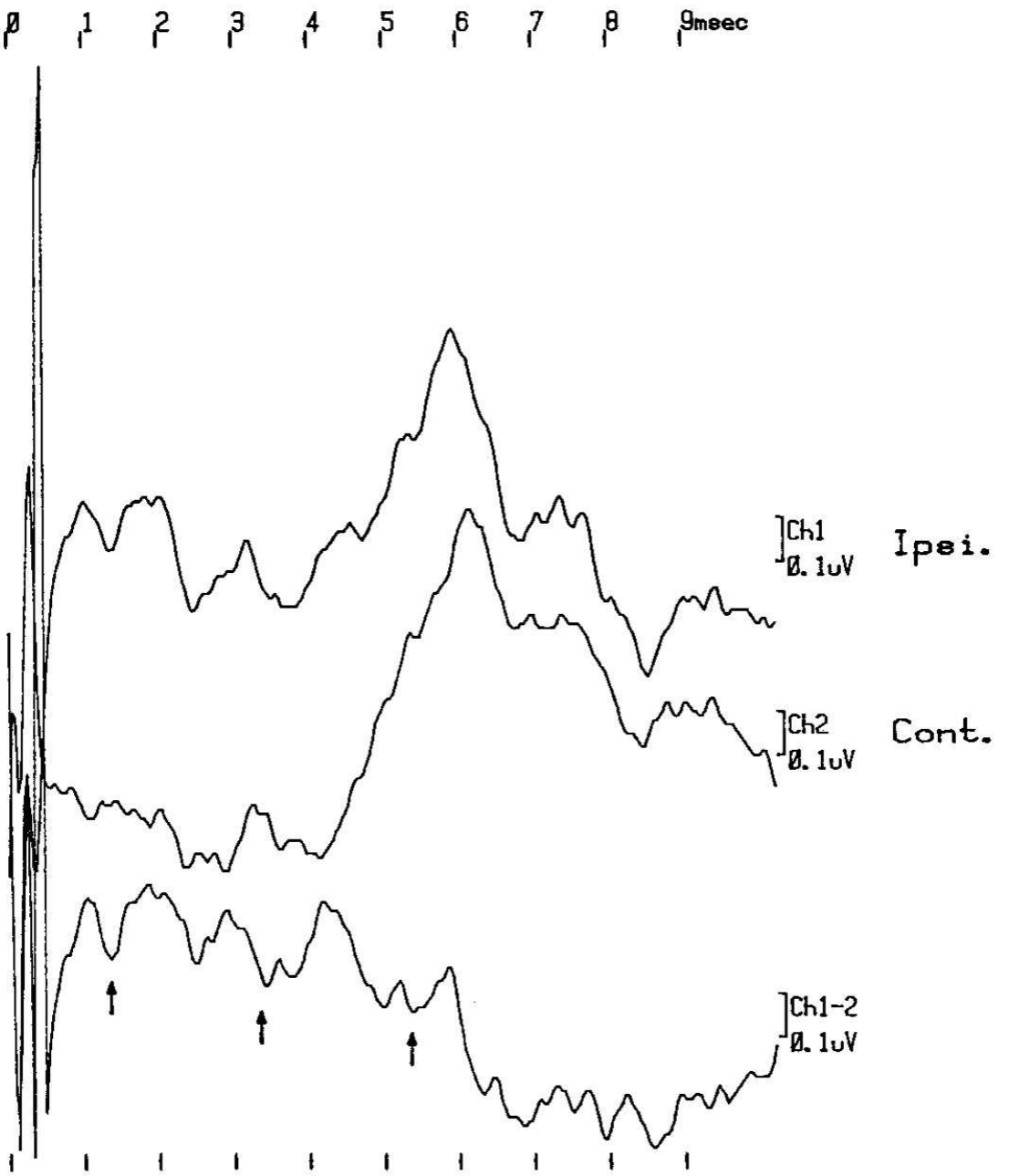


Fig. 2 Ipsilateral-contralateral differences

Healthy man,34. Right-sided rarefaction records. Subtraction shows sinusoidal pattern of mainly 480 (arrows) and 960c/s. Thomas (1984) observed this difference due to low frequency background component.

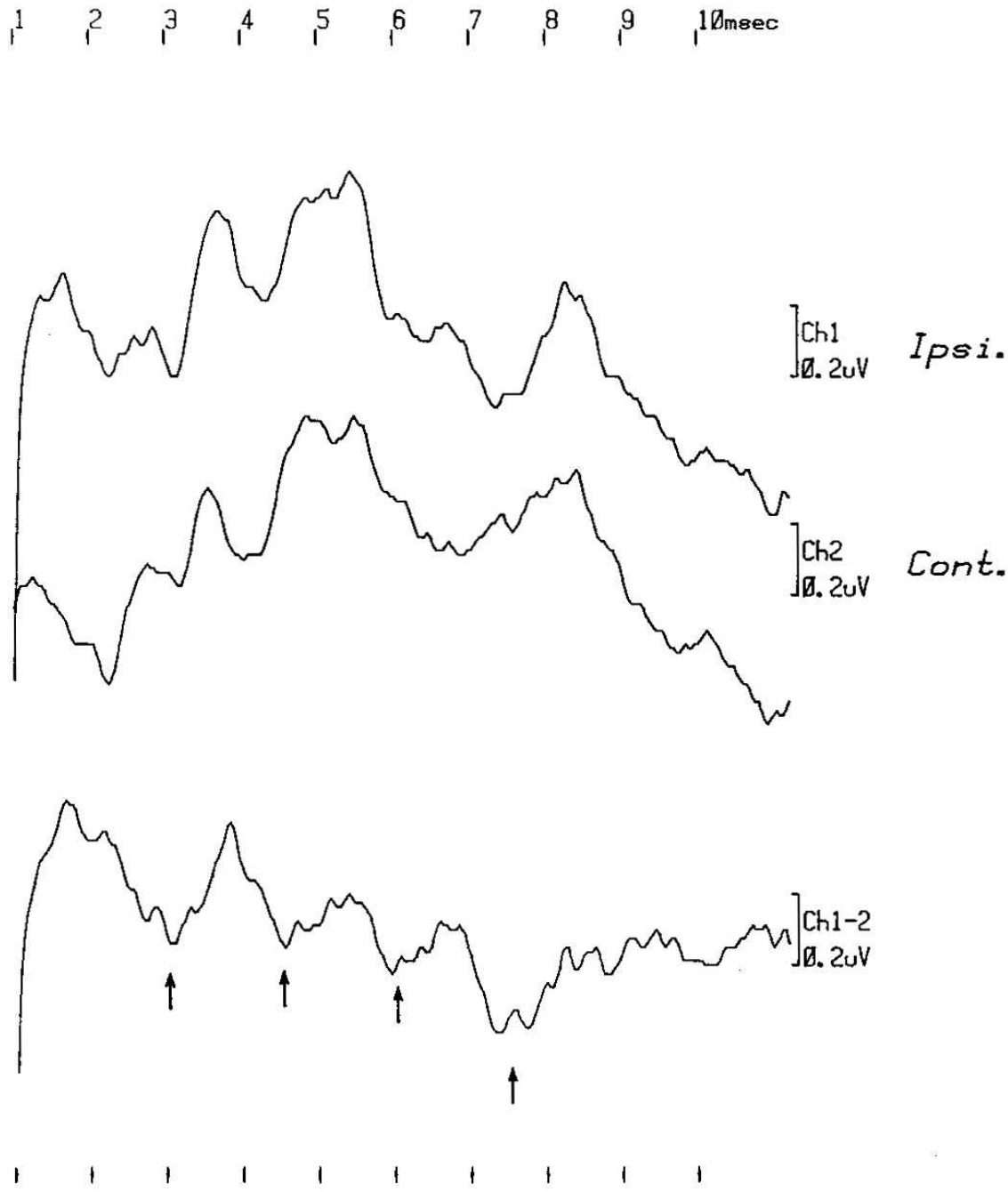


Fig. 3 Ipsilateral-contralateral differences

Healthy woman (MR),26. Left-sided rarefaction records. Differences due to change in 660c/s oscillation (arrows). This contradicts Thomas' (1984) analysis.

Having discussed the limitations of these hypotheses, in the following discussion these limitations will be substantiated by pointing to phenomena difficult to explain on the basis of discrete brainstem generators and that, alternatively, suggest the composition of the BAEP from superimposed oscillations:

1. The waveform of the normal BAEP, especially its first half, is sinusoidal: it can be visually analysed into three or four sine waves (Fig. 4). It is unlikely that summation of activity in discrete brainstem nuclei and fibre tracts, according to Jewett's hypothesis, should result in such a patterned waveform.

2. Differences (subtractions), between BAEP to different stimulus and recording conditions (click polarity, click intensity, type of headphone, time) often show a sinusoidal pattern: oscillations extending variably across the 10 msec. (Figs. 4-25). This is best seen with different click polarities, where all waves are affected, but the effect is more marked for waves II,IV and VI. Subtraction between these BAEP shows a pattern consisting mainly of 480 and 960c/s oscillations. This strongly suggests that the changes in all these waves are mediated by a common mechanism: change in charateristics of oscillations. By extrapolation, the mechanism of their generation is likely to be similar. Further support for this inference is presented shortly.

Other observations on the effect of click polarity cast more doubt on the conventional hypothesis of BAEP origin. It

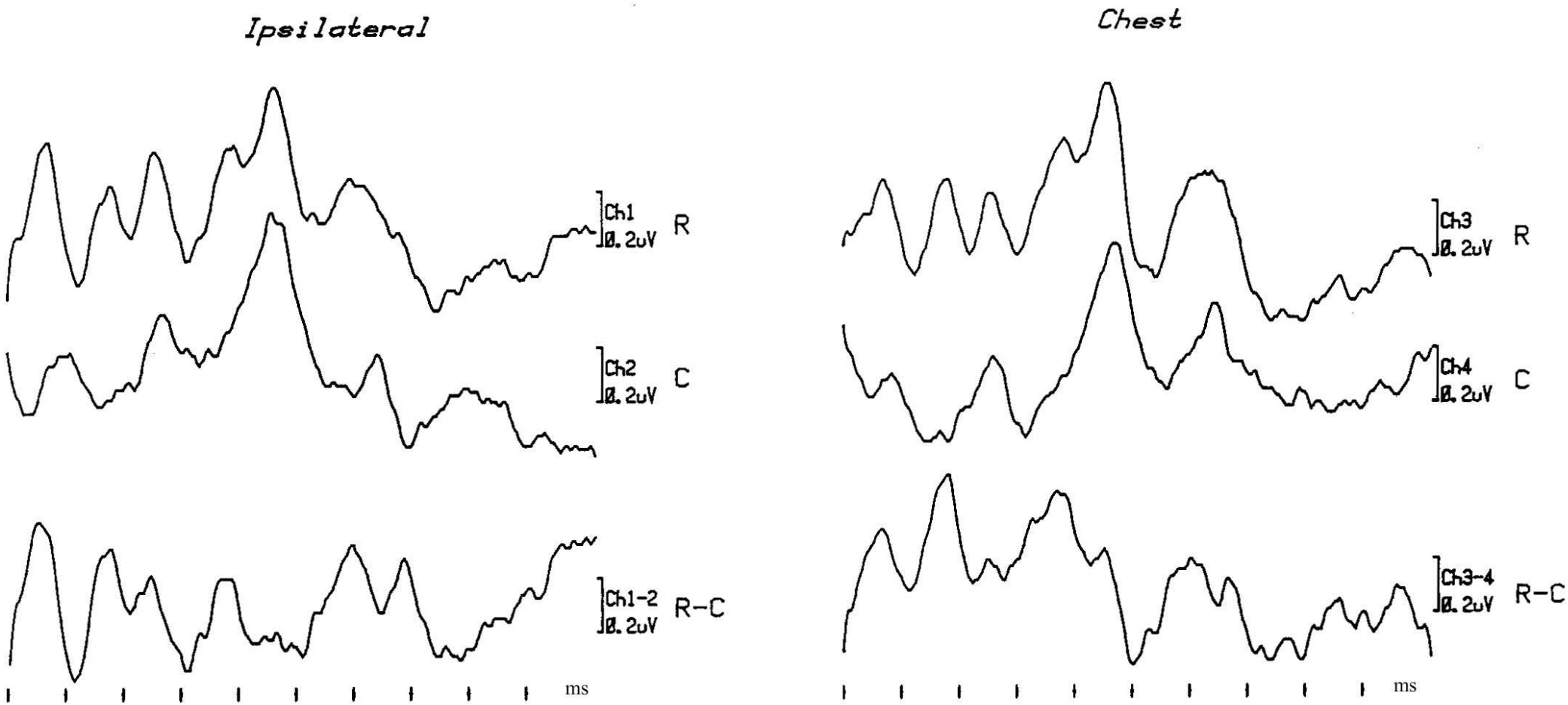


Fig. 4 Click polarity effect

Healthy woman (LR),31. Right-sided records showing effect on waves II,IV,VI and VII and sinusoidal pattern in subtraction.

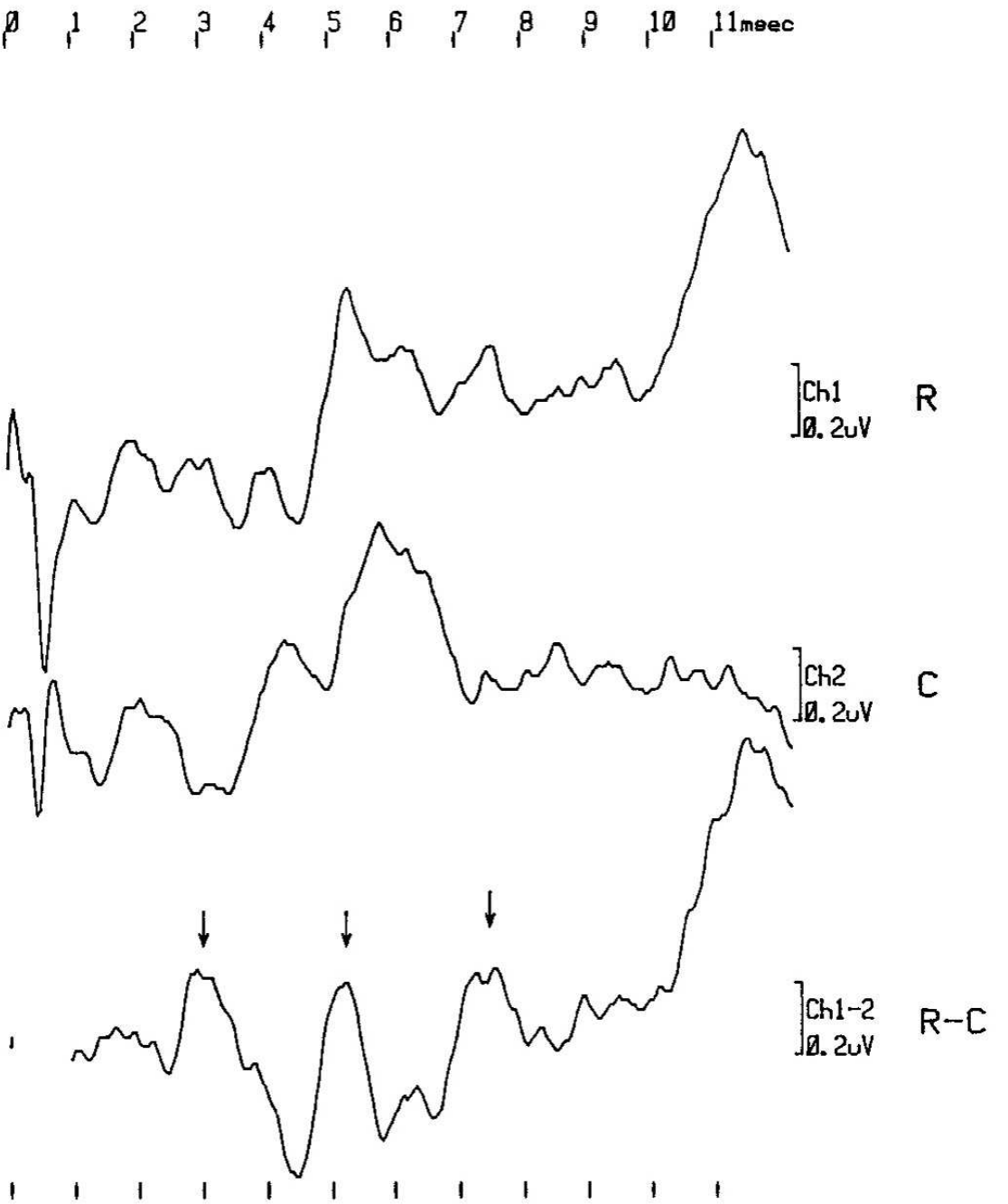


Fig. 5 Click polarity effect

Healthy woman,31. Right-sided BAEP showing effect on all waves. II and VI absent on condensation.
Change in 540c/s oscillation (arrows) explains effect and shows link between waves II and VI.

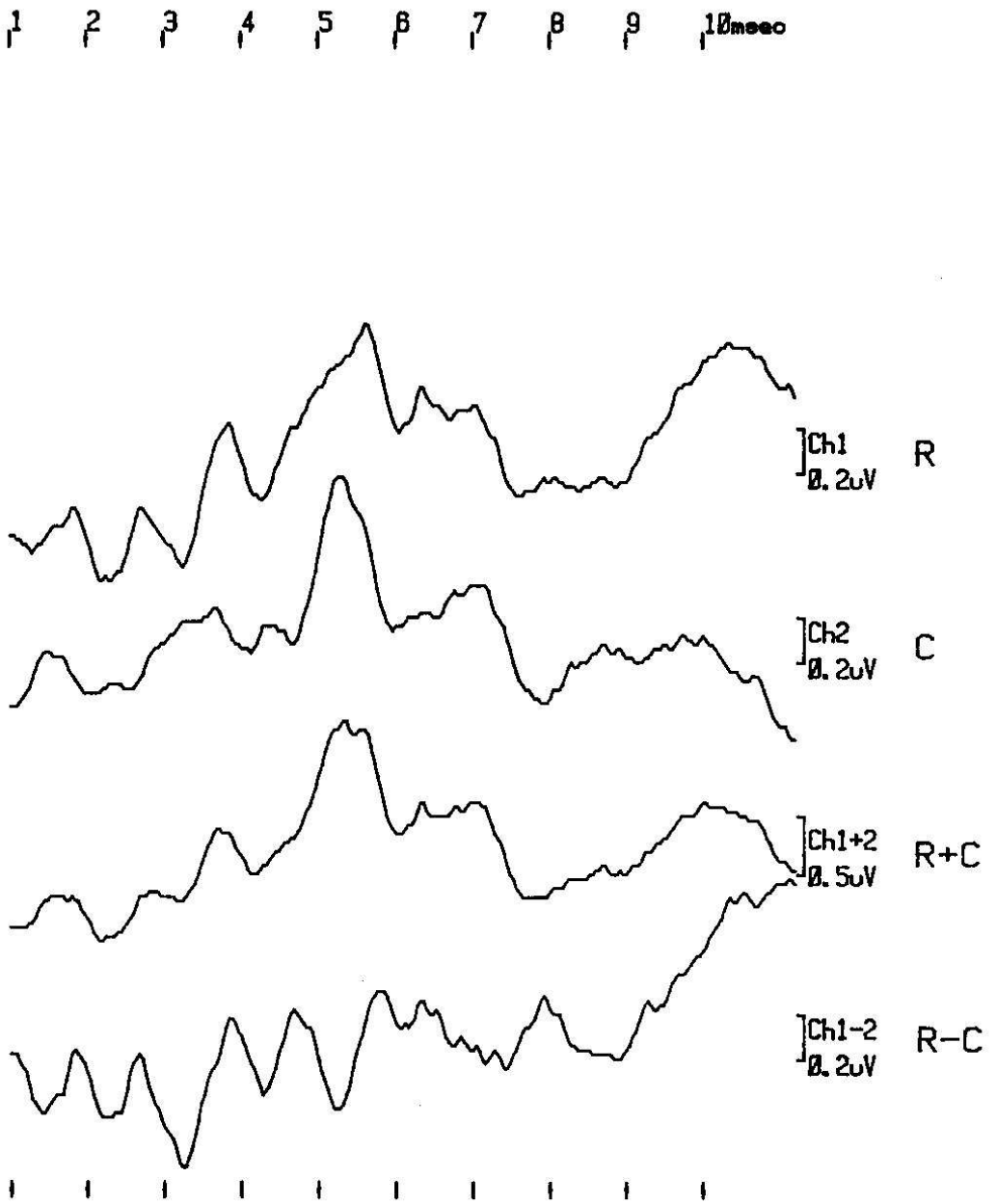


Fig. 6 Click polarity effect

Healthy man (PC),31. Right-sided records (upper two traces). Effect on all waves, particularly fusion of II and III and mirror images of IV/V (which are masked on addition [R+C] to simulate alternating click polarity) accounted for by change in 480 and 960c/s oscillations (subtraction).

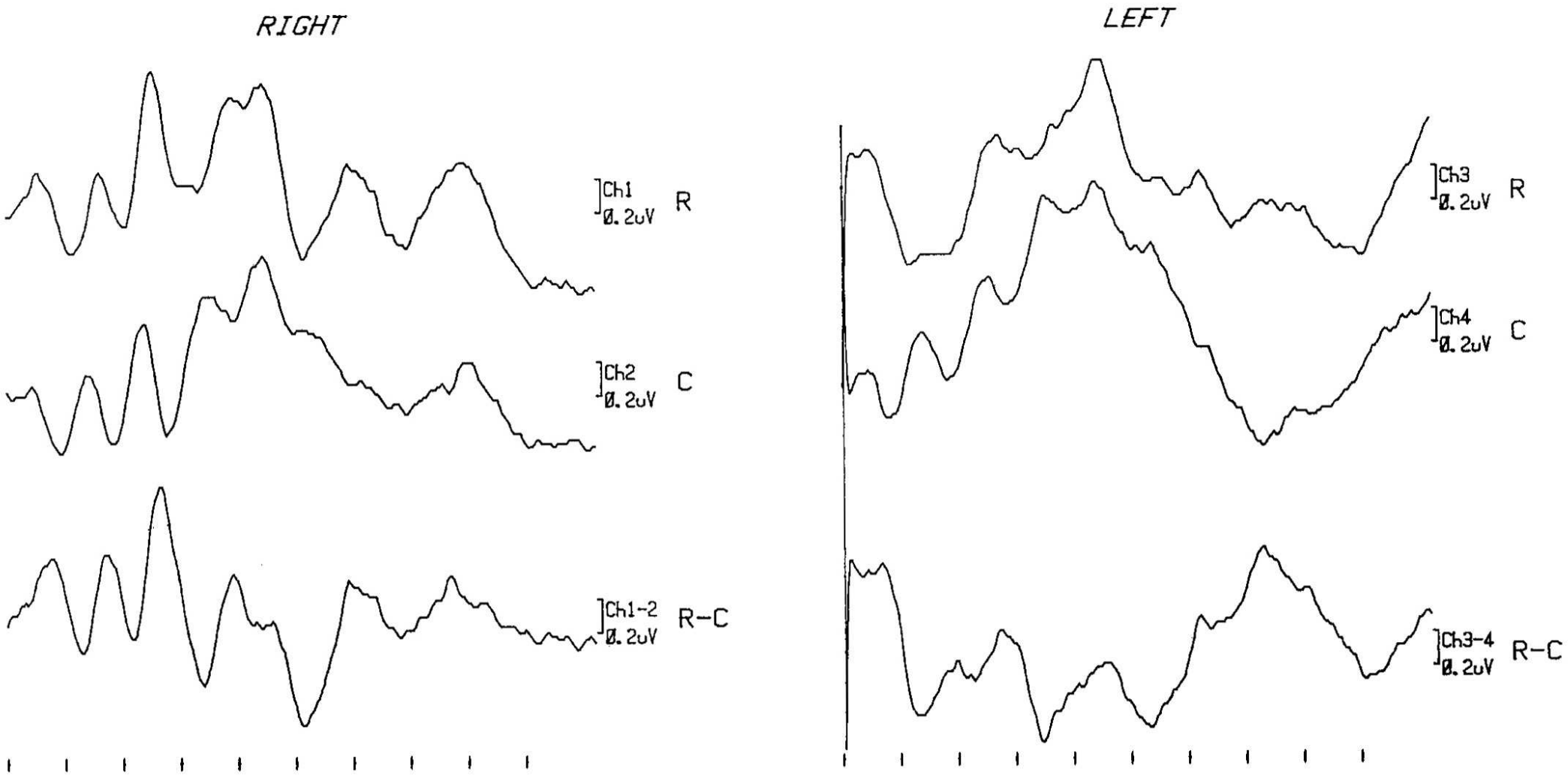


Fig. 7 Click polarity effect

Healthy woman,30. All waves affected; II absent on rarefaction on left. Sinusoidal patterns in subtractions show mainly 120 and 240c/s on right and 480 and 960c/s on left. Absence of wave VI (right, condensation) which is regarded as normal inconsistency of that wave, is linked by changes in oscillations to click polarity effect on other waves.

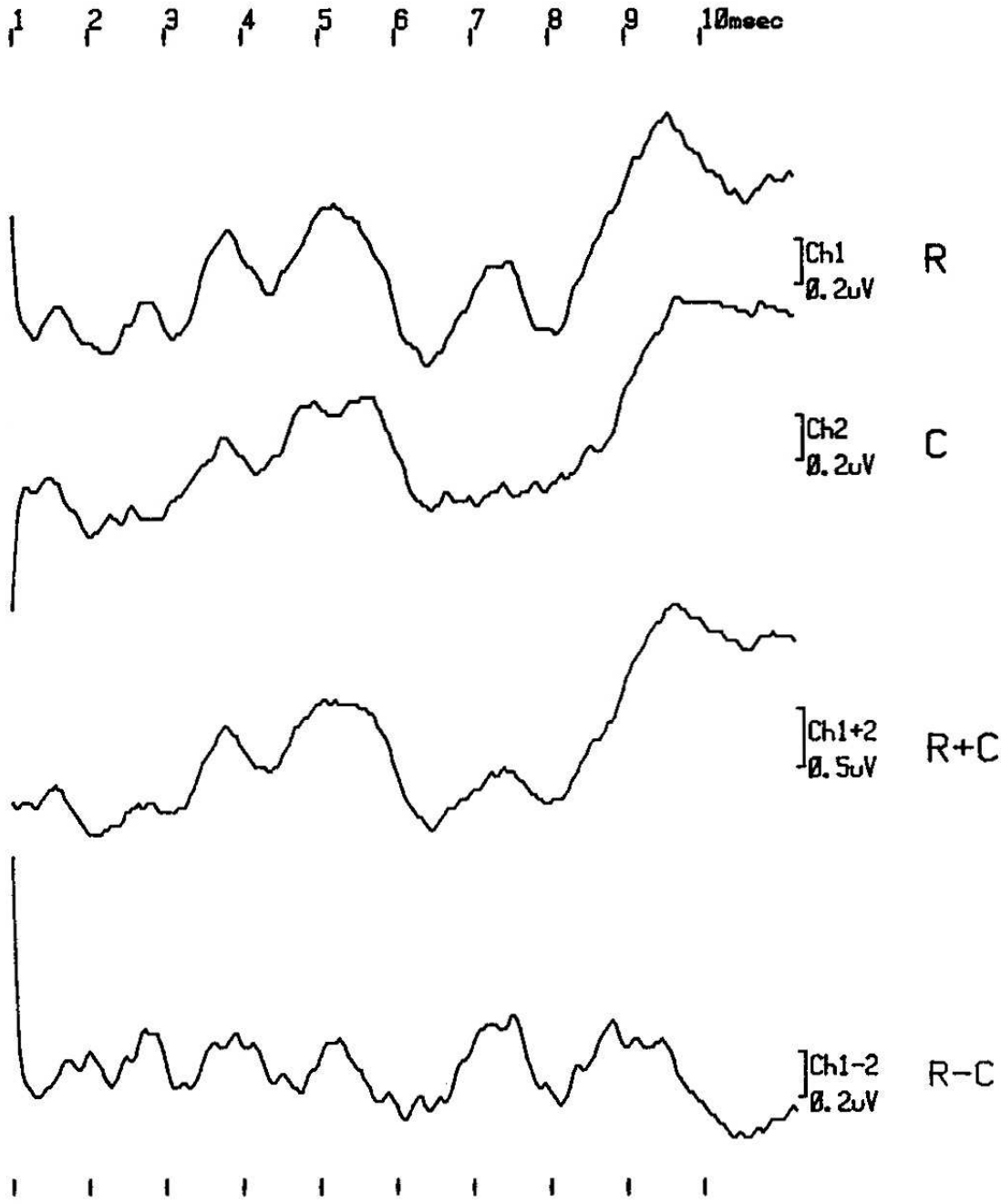


Fig. 8 Click polarity effect

Healthy man,37. Left-sided records (upper two traces). Click polarity markedly affects waves II,IV and VI. Subtraction shows sinusoidal pattern extending throughout BAEP.

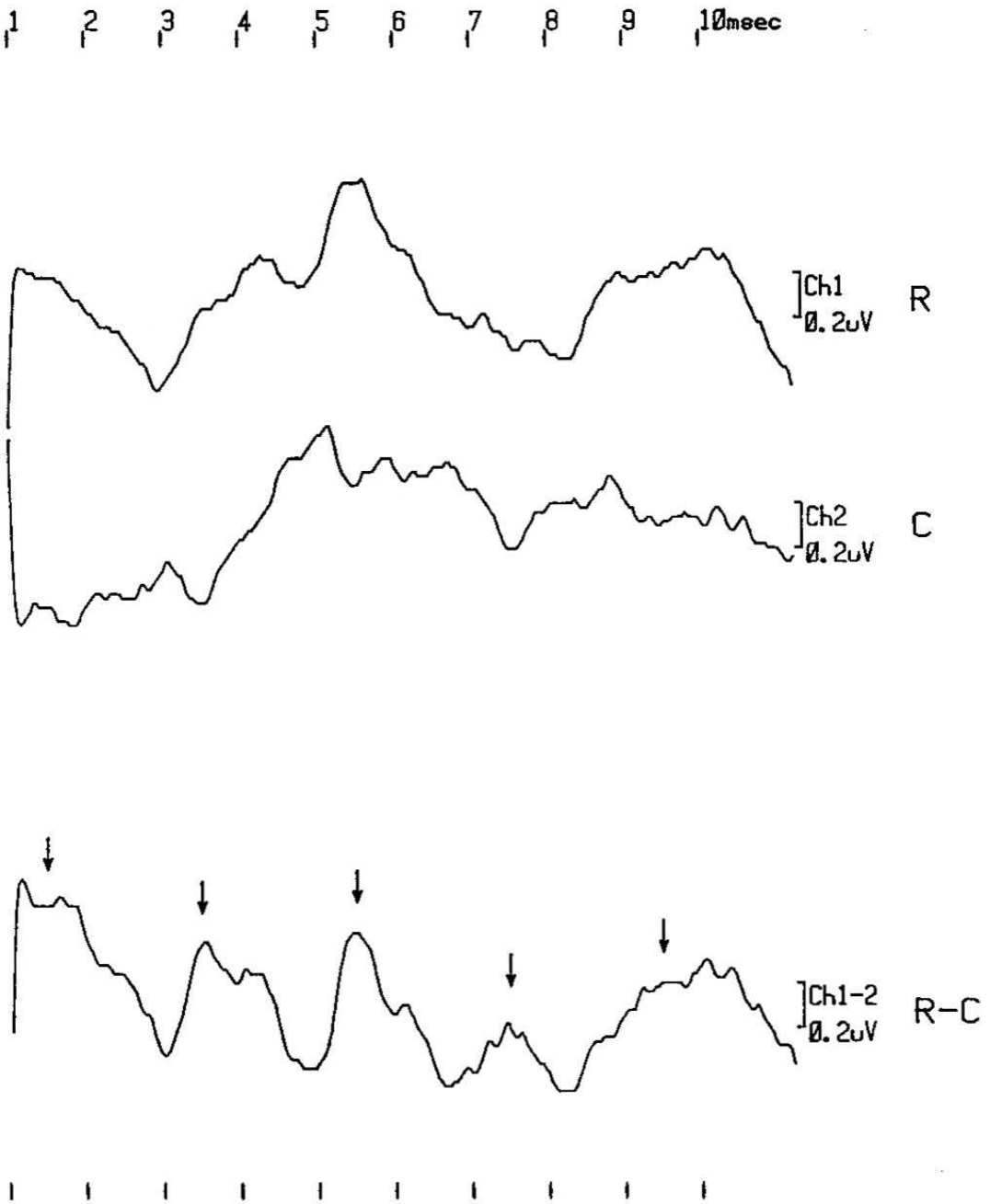


Fig. 9 Click polarity effect

Healthy man (SN),30. Chest channels of left-sided records. Subtraction shows effect on all waves, especially V, explained by changes mainly in 480 (arrows) and 960c/s (extending halfway through BAEP) oscillations.

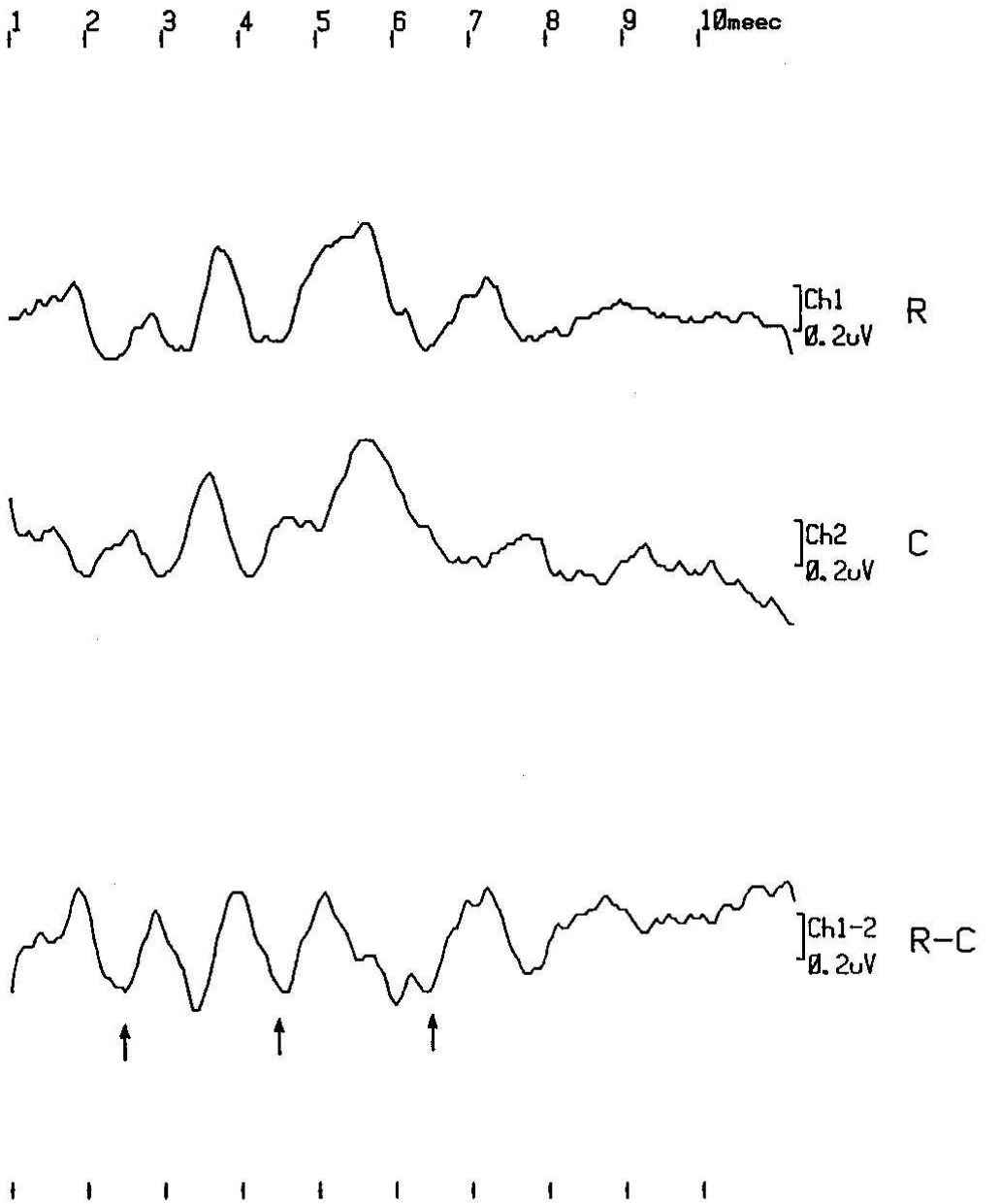


Fig. 10 Click polarity effect

Healthy man (JT),27. Right-sided records.
Effect on all waves explained by change in 480 (arrows) and 960c/s oscillations (subtraction).

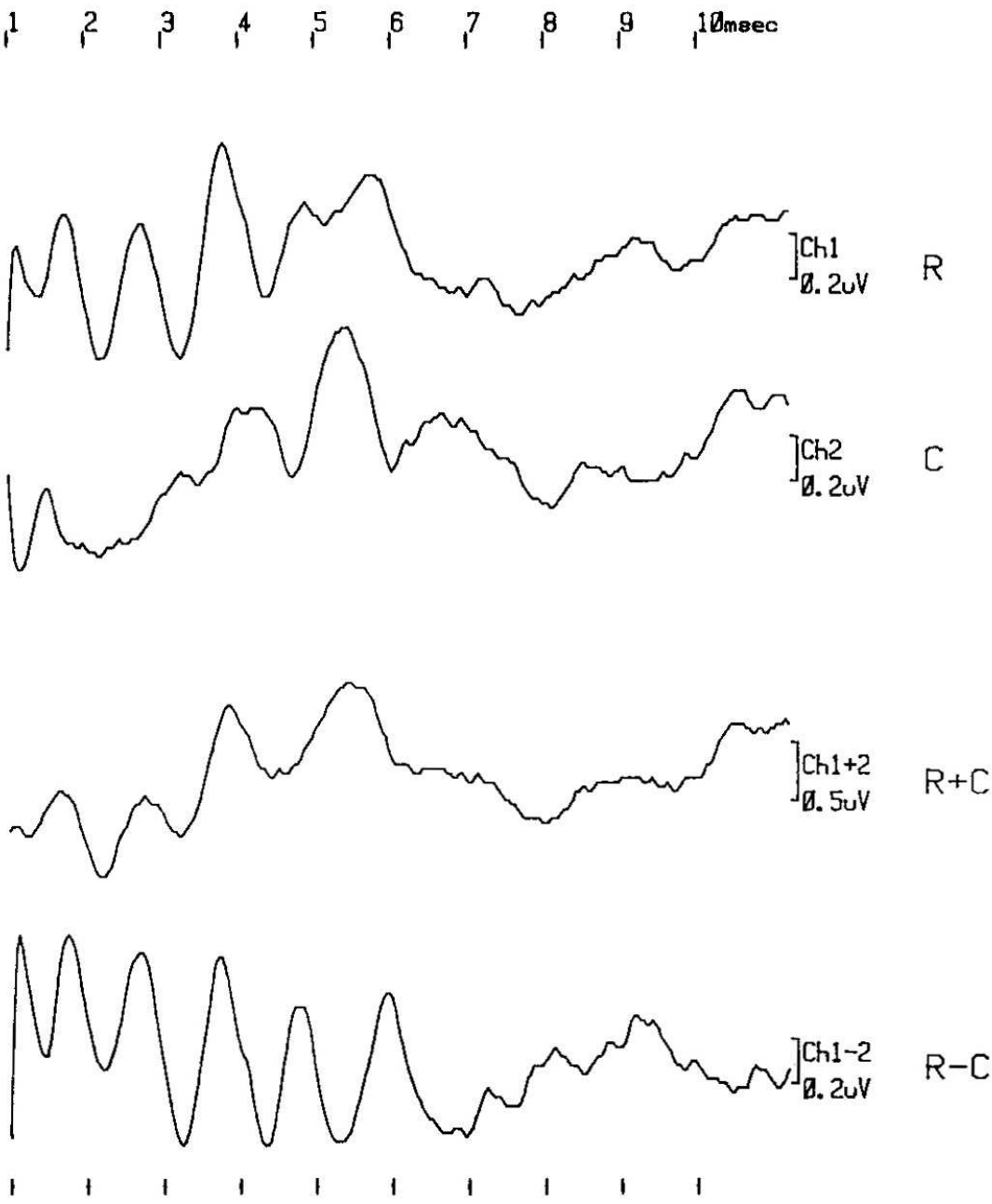


Fig. 11 Click polarity effect

Healthy man (SC),18. Left-sided records to 75dBSL clicks. Marked effect on all waves explained by change in 960c/s oscillation (subtraction).

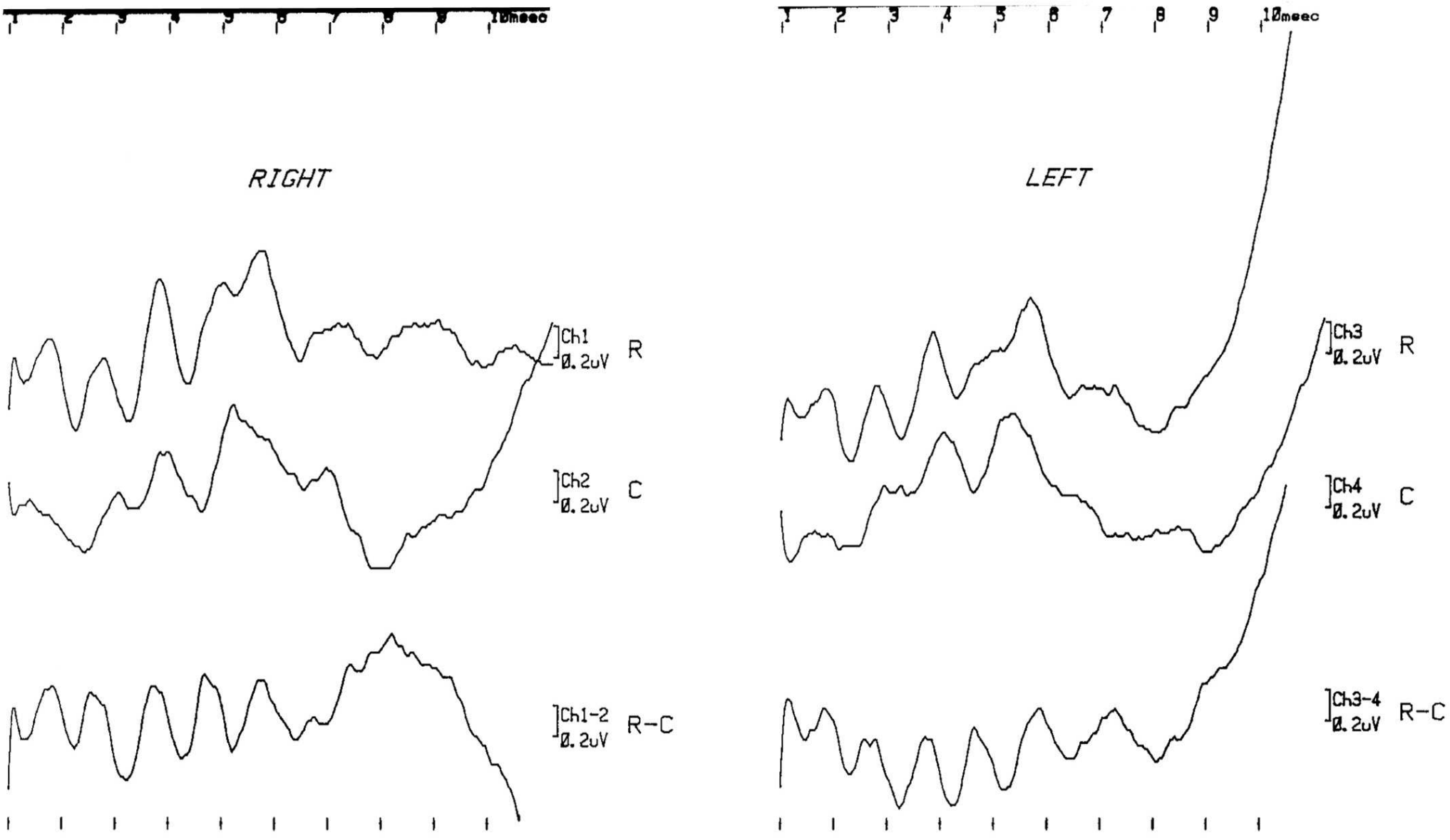


Fig. 12 **Click polarity effect**

Healthy man (SC),18. Effect on all waves, particularly IV and V, explained through change of mainly 960c/s oscillation (subtraction).

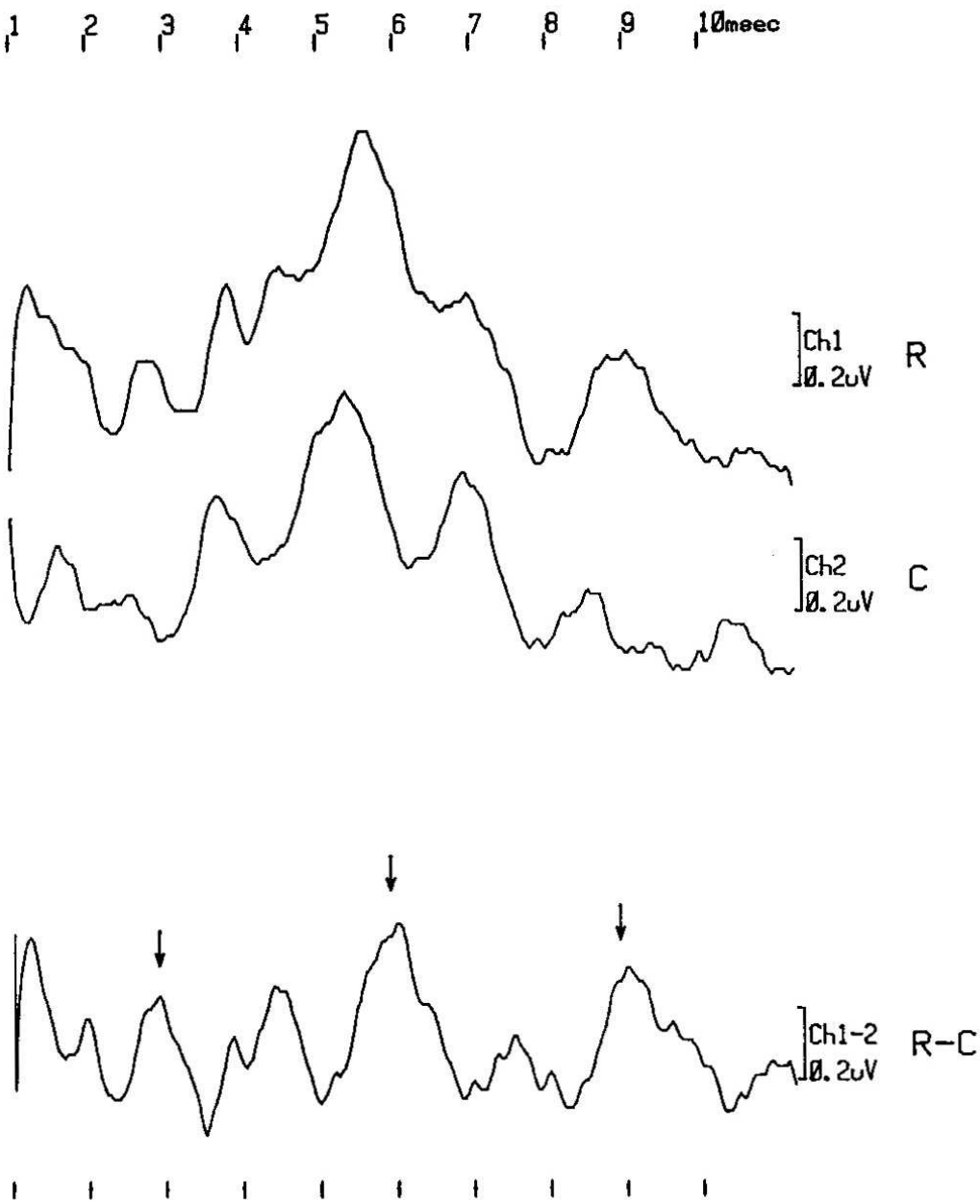


Fig. 13 Click polarity effect

Healthy man (AF),18. Right-sided records showing effect in all waves explained by change in 330 (arrows)and 660c/s oscillations.

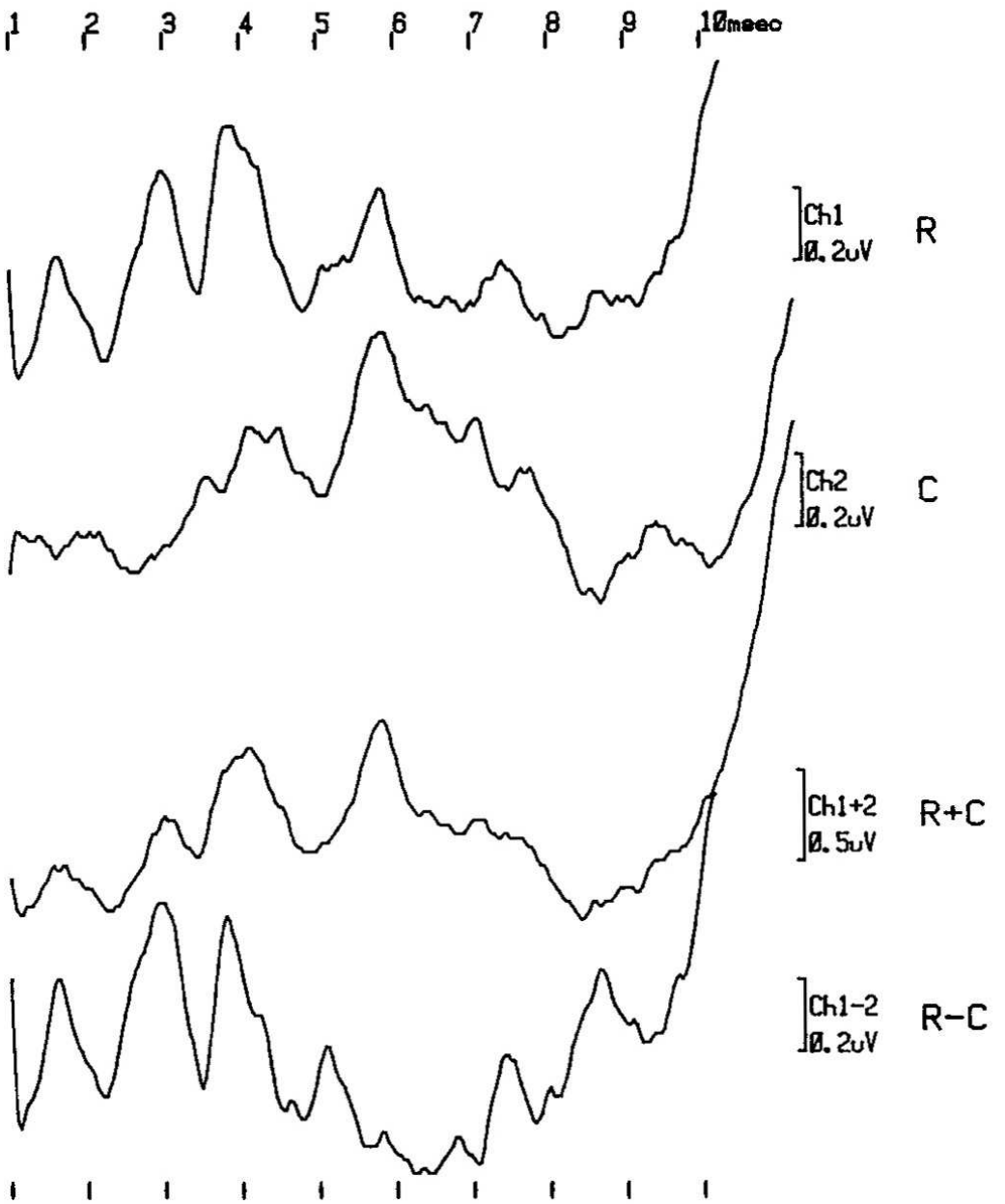


Fig. 14 Click polarity effect

Healthy man (SD), 30. Right-sided records (upper two traces) showing marked differences between two click polarities. Wave II absent on condensation. Adding these traces to simulate alternating click polarity (R+C) masks differences.
Subtraction shows sinusoidal pattern.

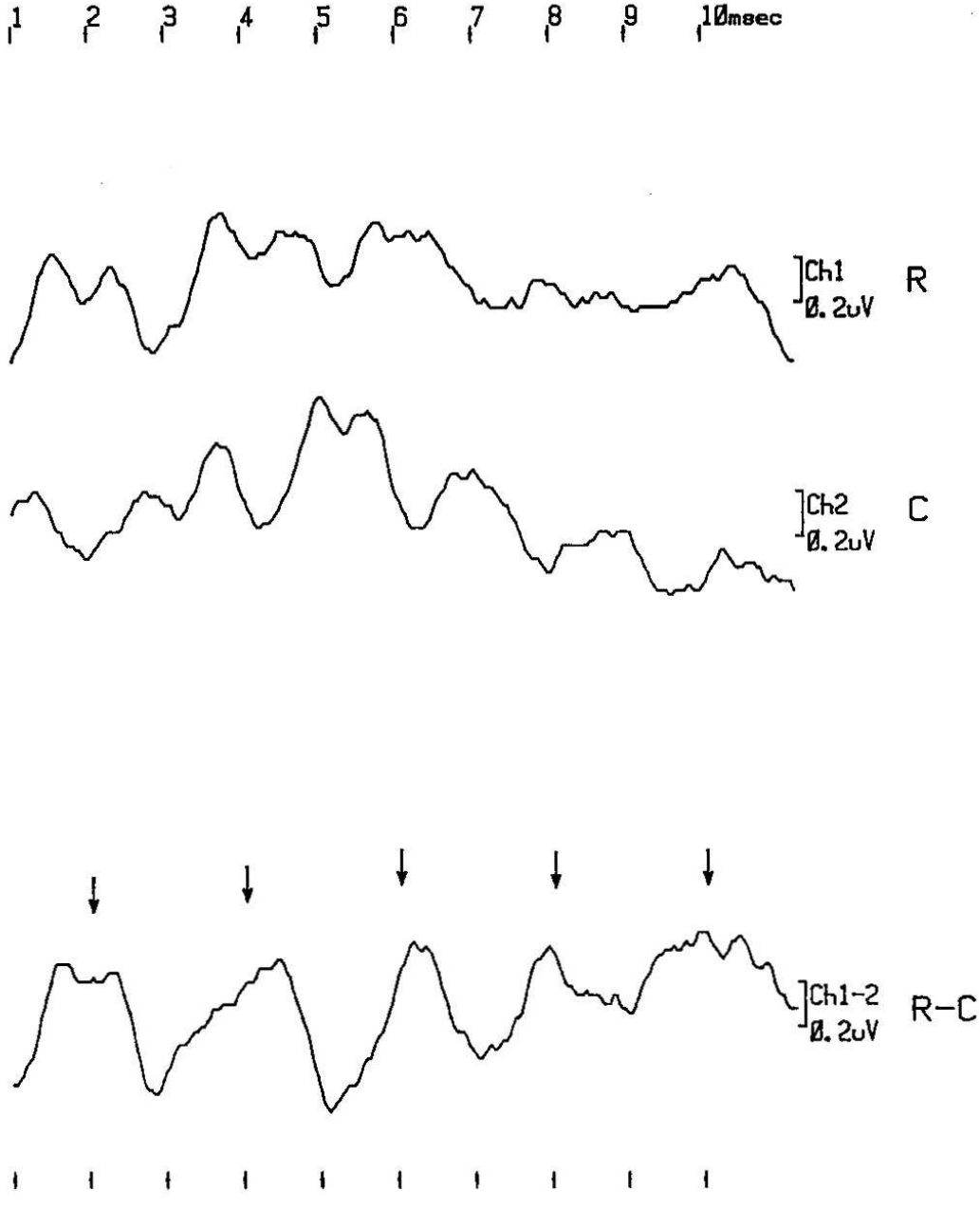


Fig. 15 Click polarity effect

Woman (LS), 62, with differential diagnosis of brainstem vascular event and labyrinthitis. Right-sided records showing marked differences accounted for mainly by 500c/s oscillation (arrows).

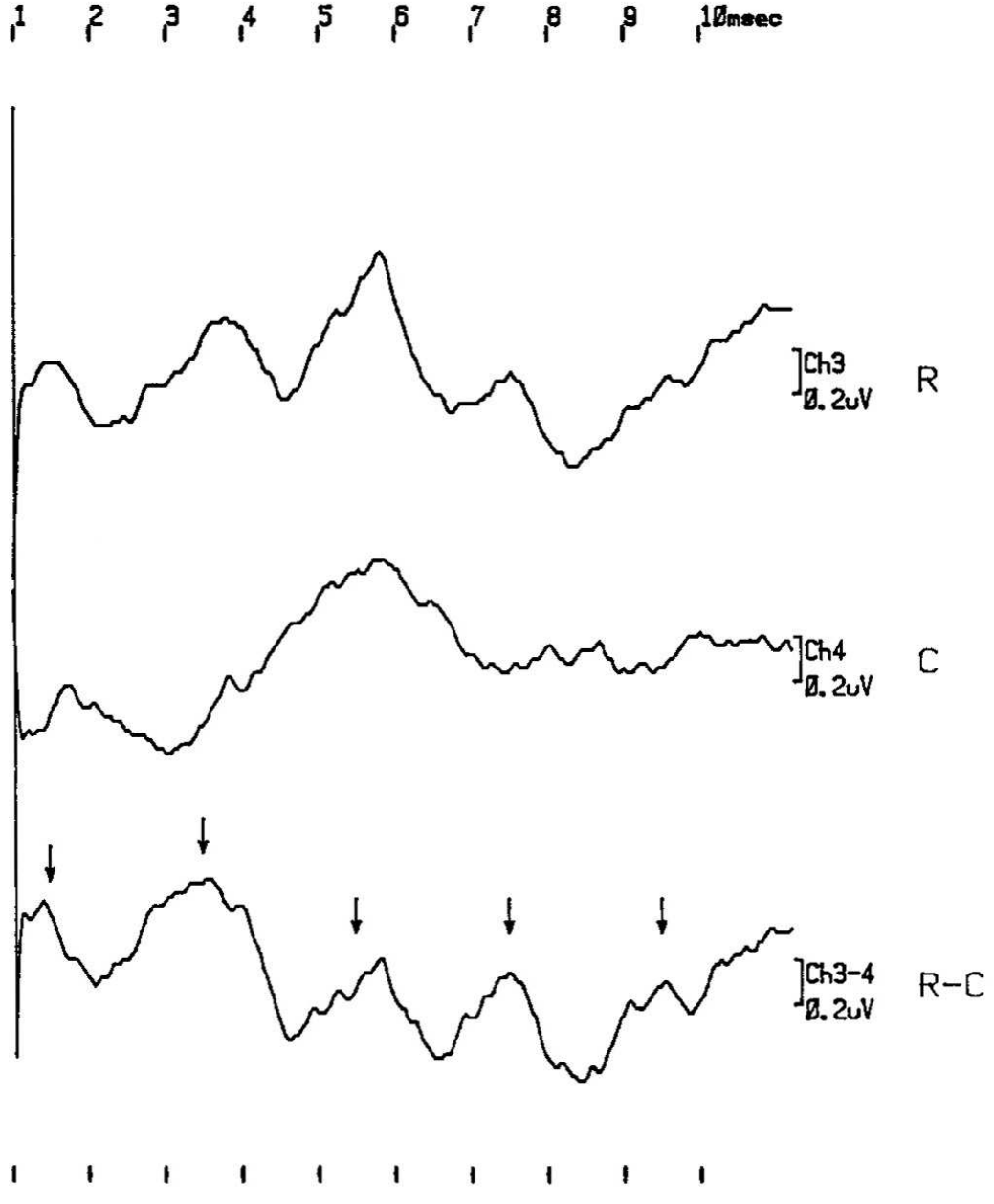


Fig. 16 Click polarity effect

Woman (ER),36, with atypical presentation of MS. Left-sided records.
Indistinct peaks on condensation explained by change (absence?) mainly of 500 c/s oscillation (arrows).

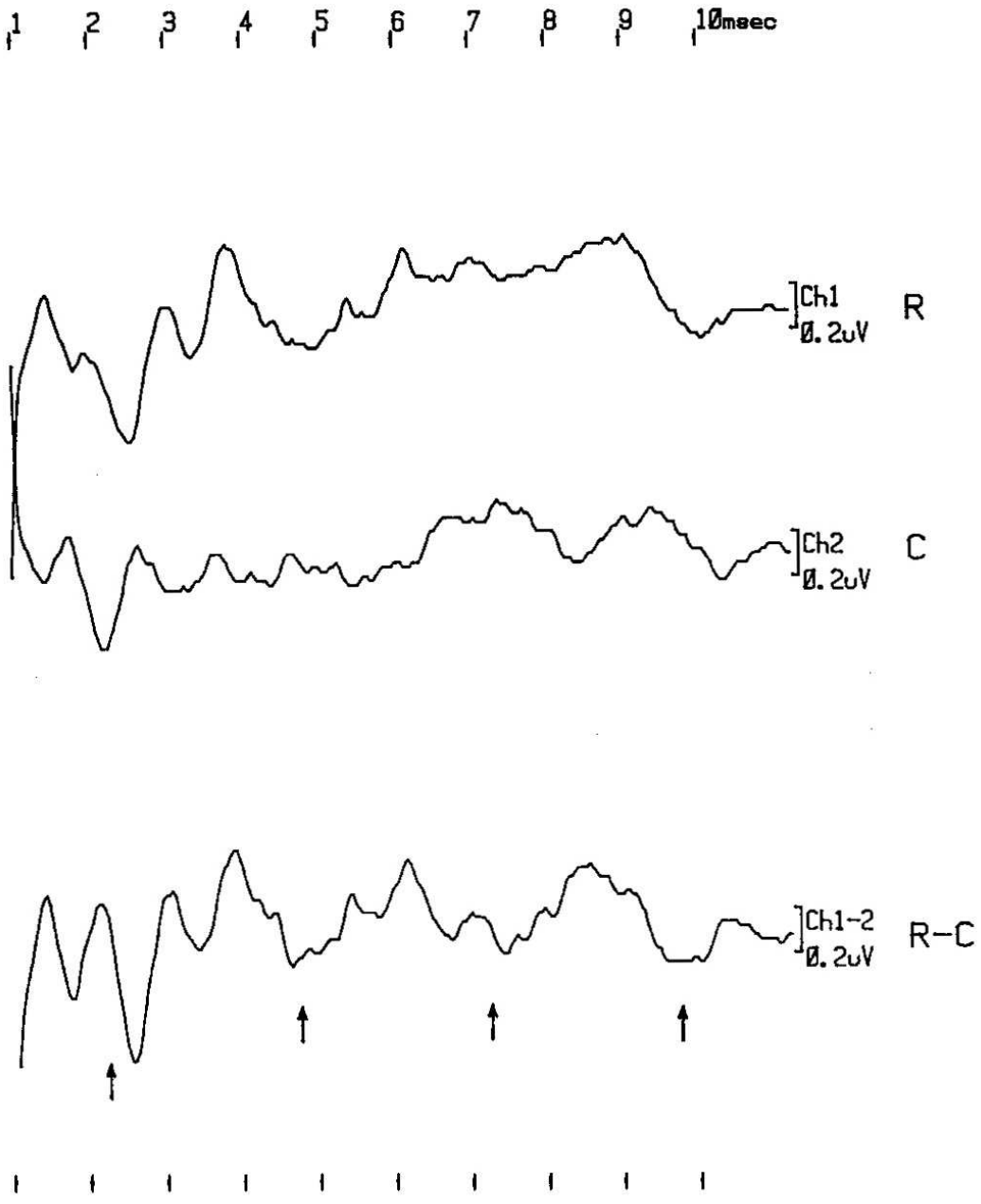


Fig. 17 Click polarity effect

Woman (AP),29, with probable MS. Right-sided records to 75dBSL clicks.
Subtraction shows 400c/s oscillation (arrows) and 960c/s oscillation, prematurely damped at 4msec. Compare Fig. 11.

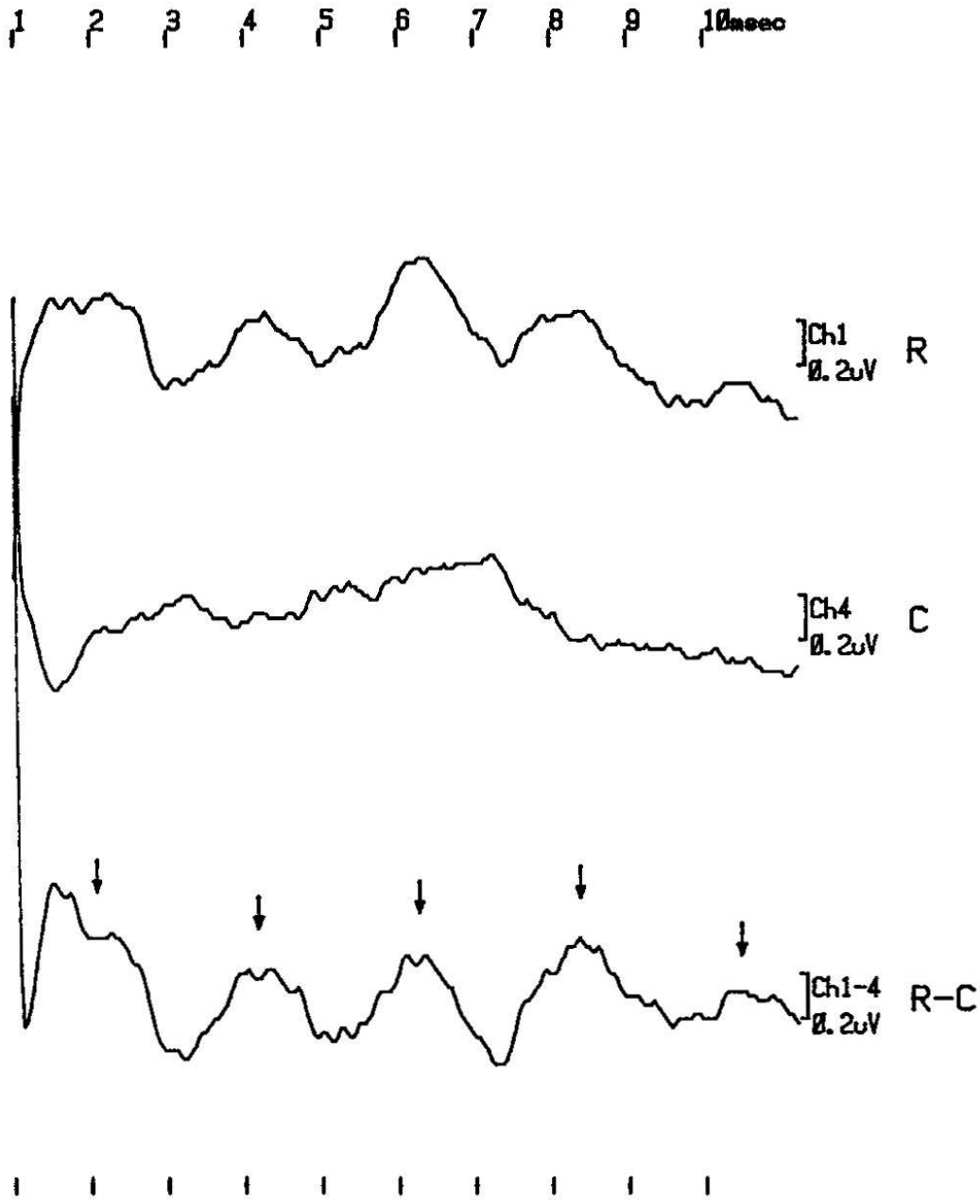


Fig. 18 Click polarity effect

Man (BA),33, with probable demyelination. Right-sided records.
Subtraction shows a 480 c/s oscillation.

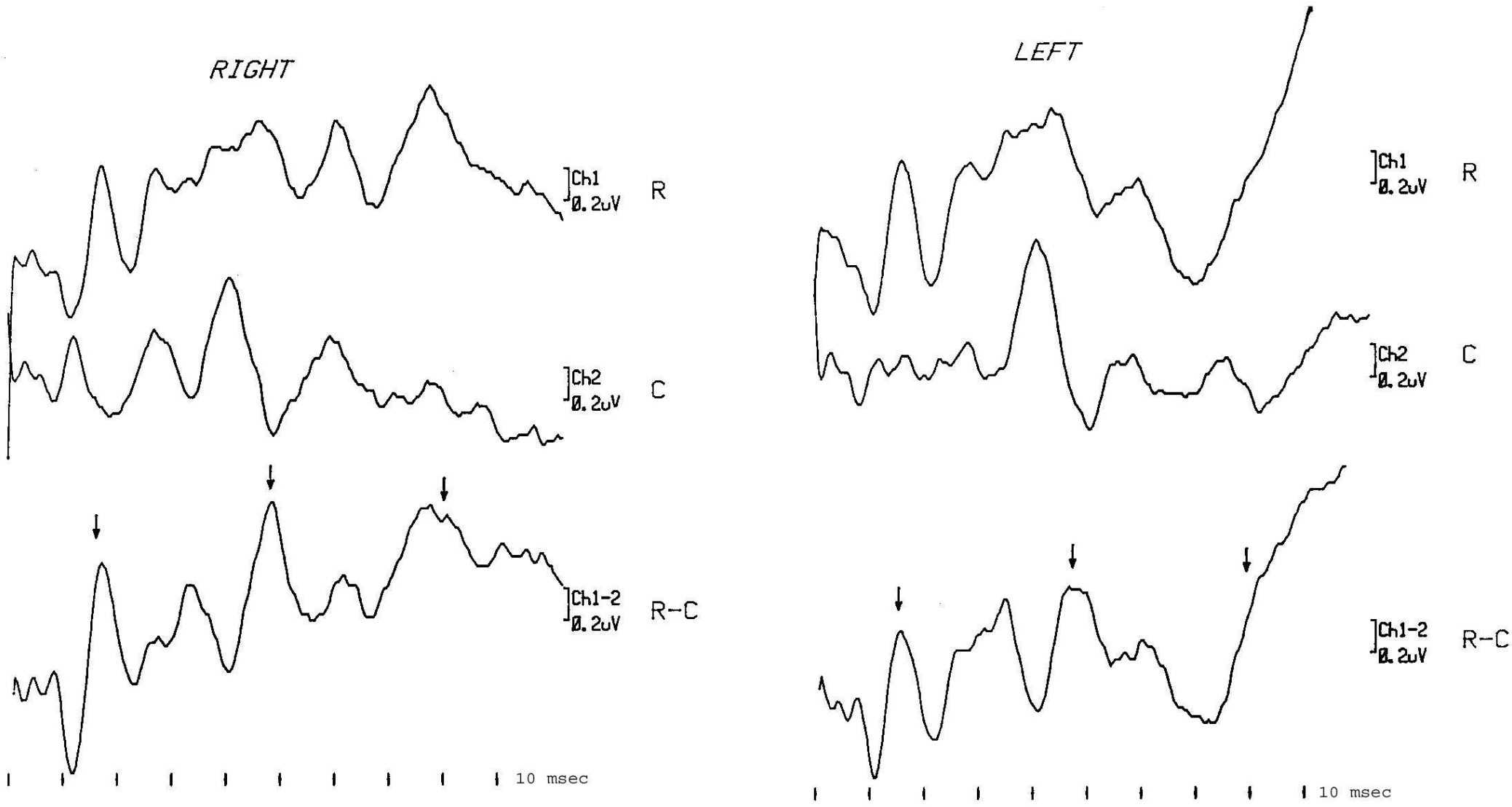


Fig. 19 Click polarity effect

Woman (AF),26, with probable MS. On condensation (left ear) waves II and III become "fragmented".
Subtractions show that despite apparently different click polarity effect, the mechanism is the same: changes in 300 (arrows) and 600c/s oscillations (subtractions).

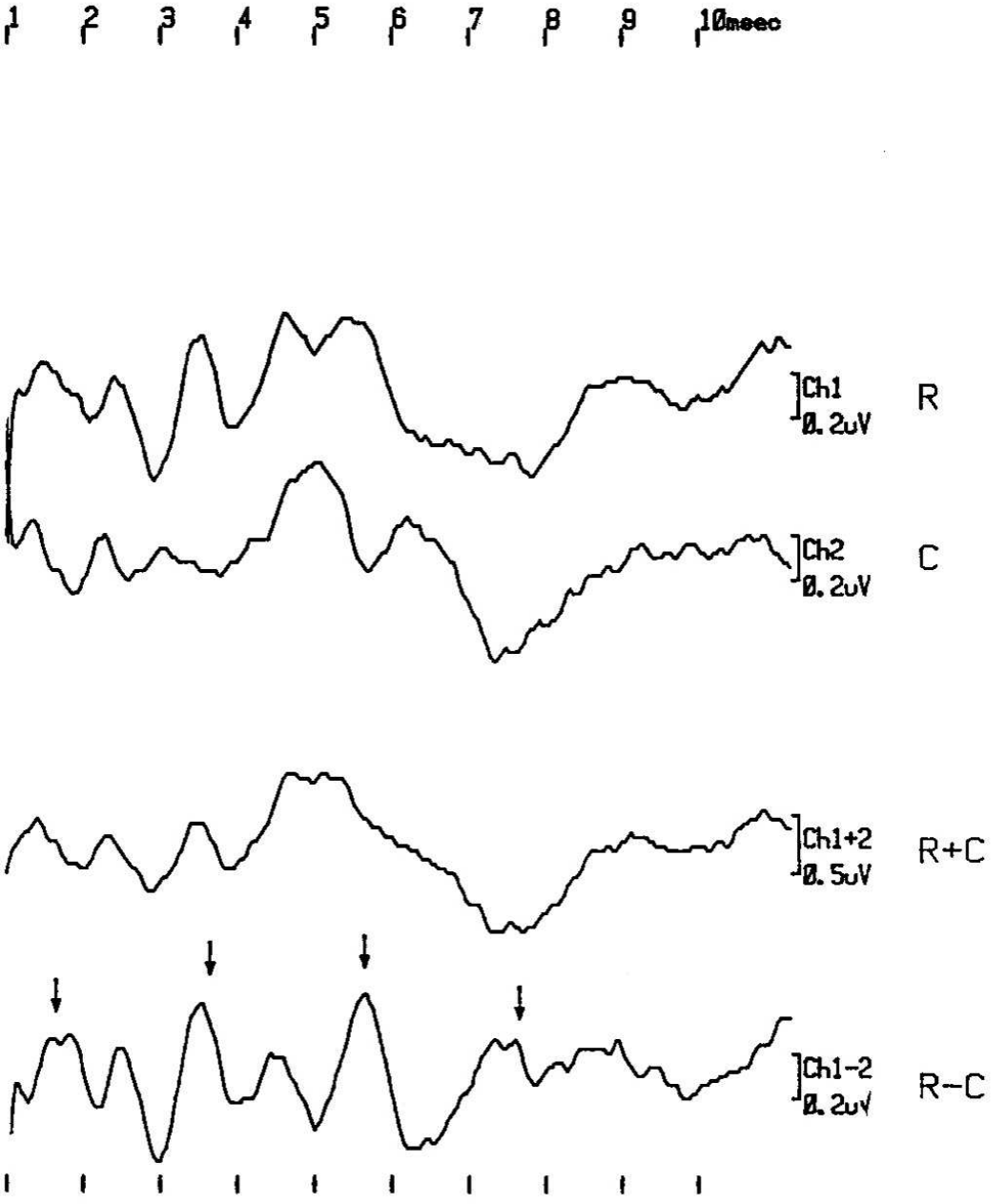


Fig. 20 Click polarity effect

Woman (JA),27,with MS. Right-sided records showing marked effect on all waves, particularly III,IV,V and VI. They also show the difficulty in determining wave peak, e.g. V, even on alternating click polarity (simulated in addition, R+C).
Subtraction shows effect an all waves explained by changes in 480 (arrows) and 960c/s (damped at about 5 msec) oscillations. The 480c/s oscillations accounts for differences in waves III, V, and late part of VI.

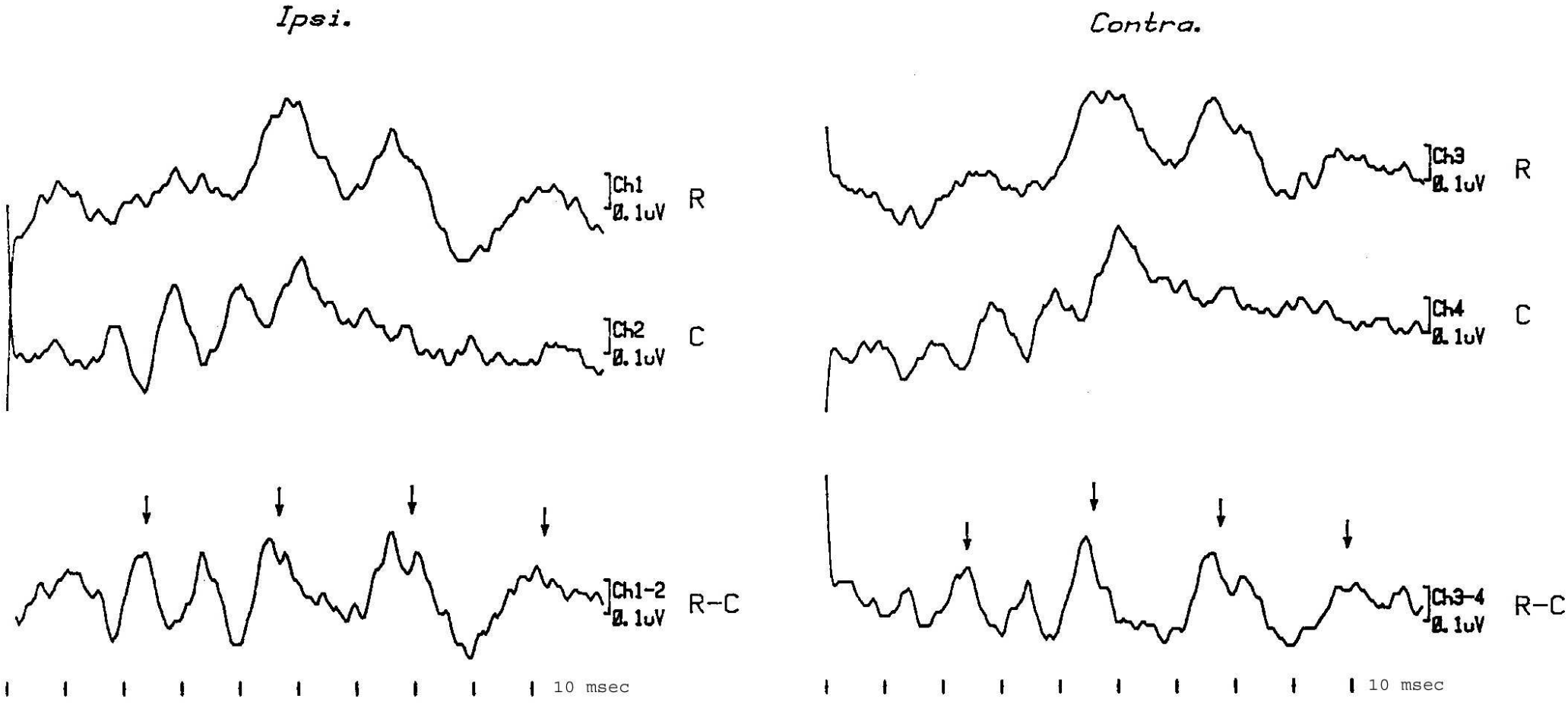


Fig. 21 Click polarity effect

Man (AK),44, with MS. Right-sided records to 75dBSL clicks. All waves are affectd. Waves II and III are indistinct on right while VI is large on rarefaction; opposite on condensation.
Subtraction shows mechanism of effect is change in 480 (arrows) and 960c/s (extending only halfway through BAEP) oscillations.

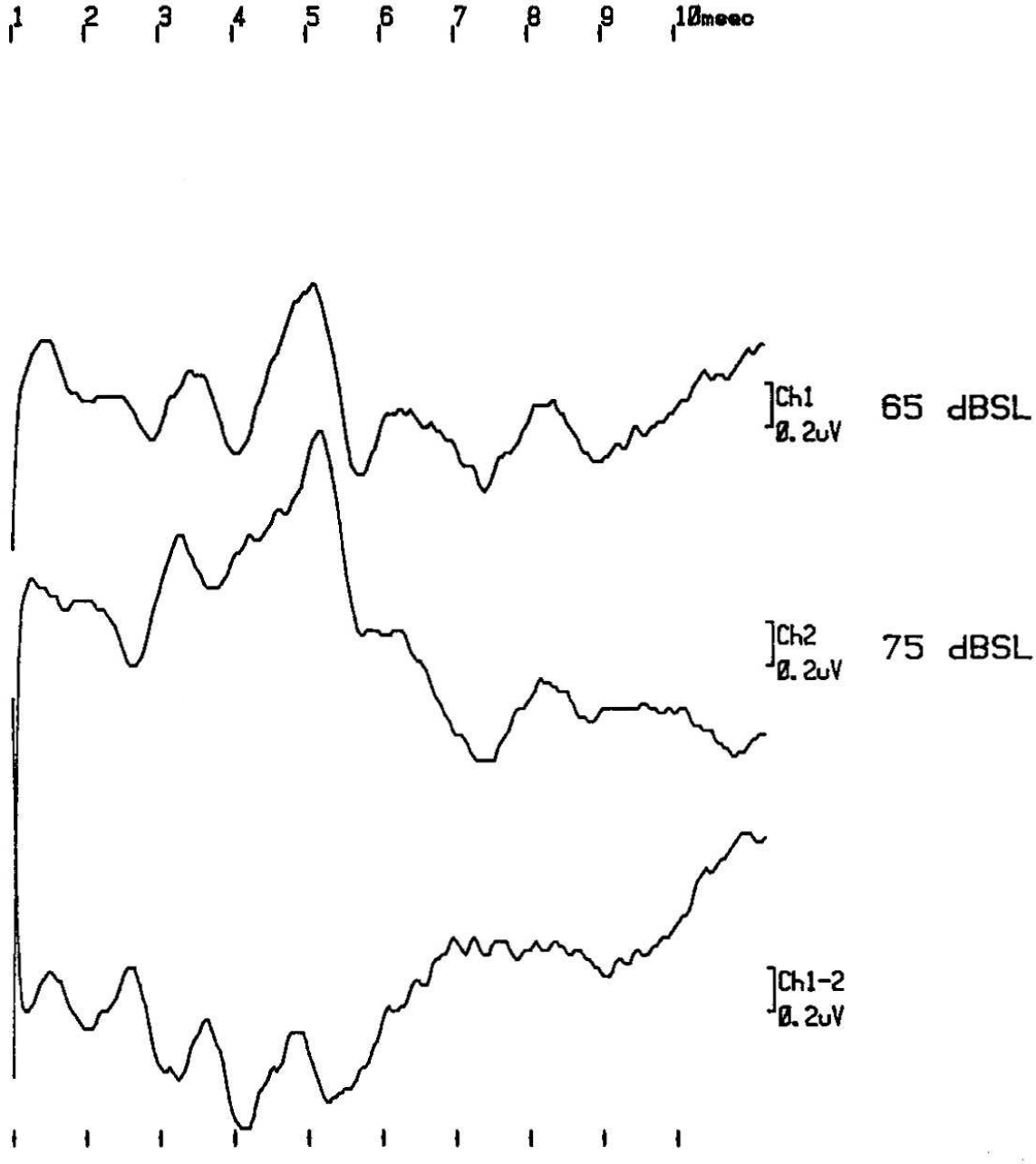


Fig. 22 Click intensity

Healthy woman (DP),21. Left-sided rarefaction records. Effects on waves I (paradoxical decrease in amplitude), II,III and IV explained mainly by 960c/s oscillation (subtraction).

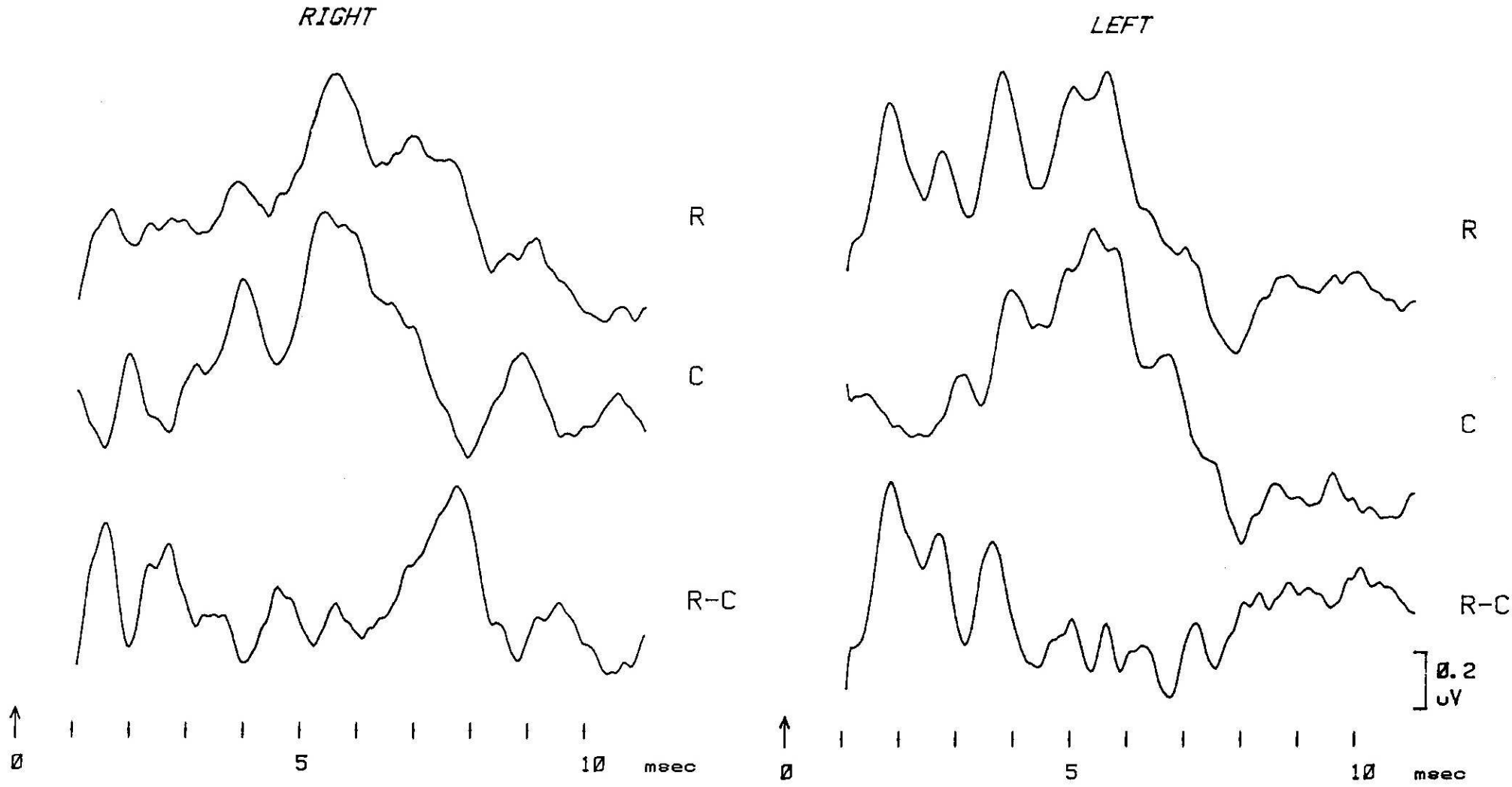


Fig. 23 Inverse effect of click polarity on amplitude

Healthy woman (AE),27. Monaural records. Amplitudes of waves I and III increase on condensation on right, but decrease on left.
Subtractions show sinusoidal pattern: 480 (arrows) and 960c/s oscillations.

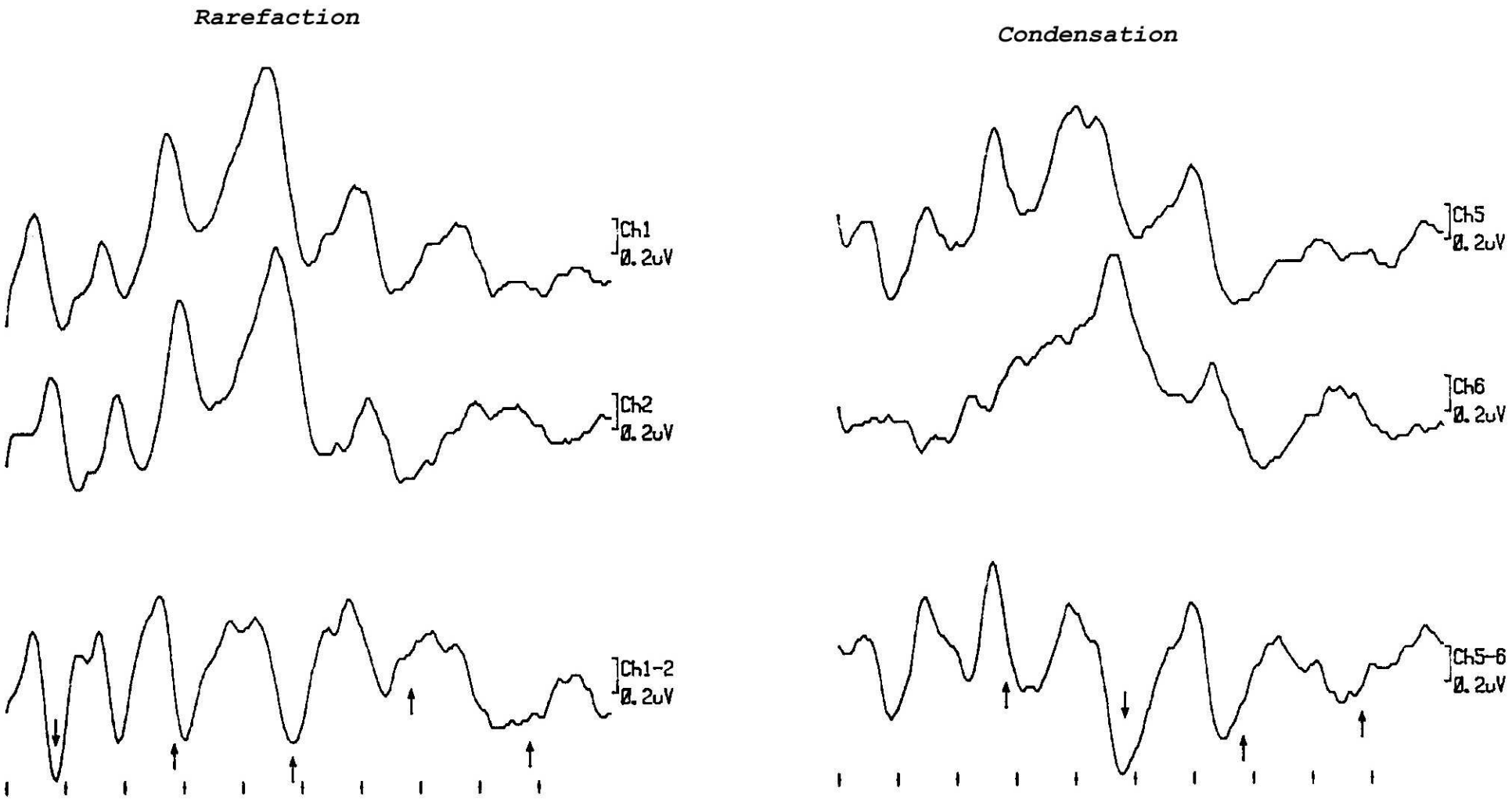


Fig. 24 Delay of brainstem input?

Woman,31, with MS. Right-sided records. In second run cotton wool ball placed in ear canal (to insulate thermistor probe). This is expected to muffle click and probably alter its waveform.
On rarefaction, waves are delayed but not reduced in amplitude (both expected according to Jewett's hypothesis). Delay, however, is not uniform; subtractions shows mainly 500 (arrowed) and 960c/s (damped at about 4msec) oscillations. If wave I represented input to brainstem, delay sould have been equal and subtraction would have shown pattern similar to original BAEP (presence of all oscillations). Similarly, effect on condensation would have been delay of waves with preservation of waveform, not distortion. Subtractions on condensation and rarefaction closely resemble each other.

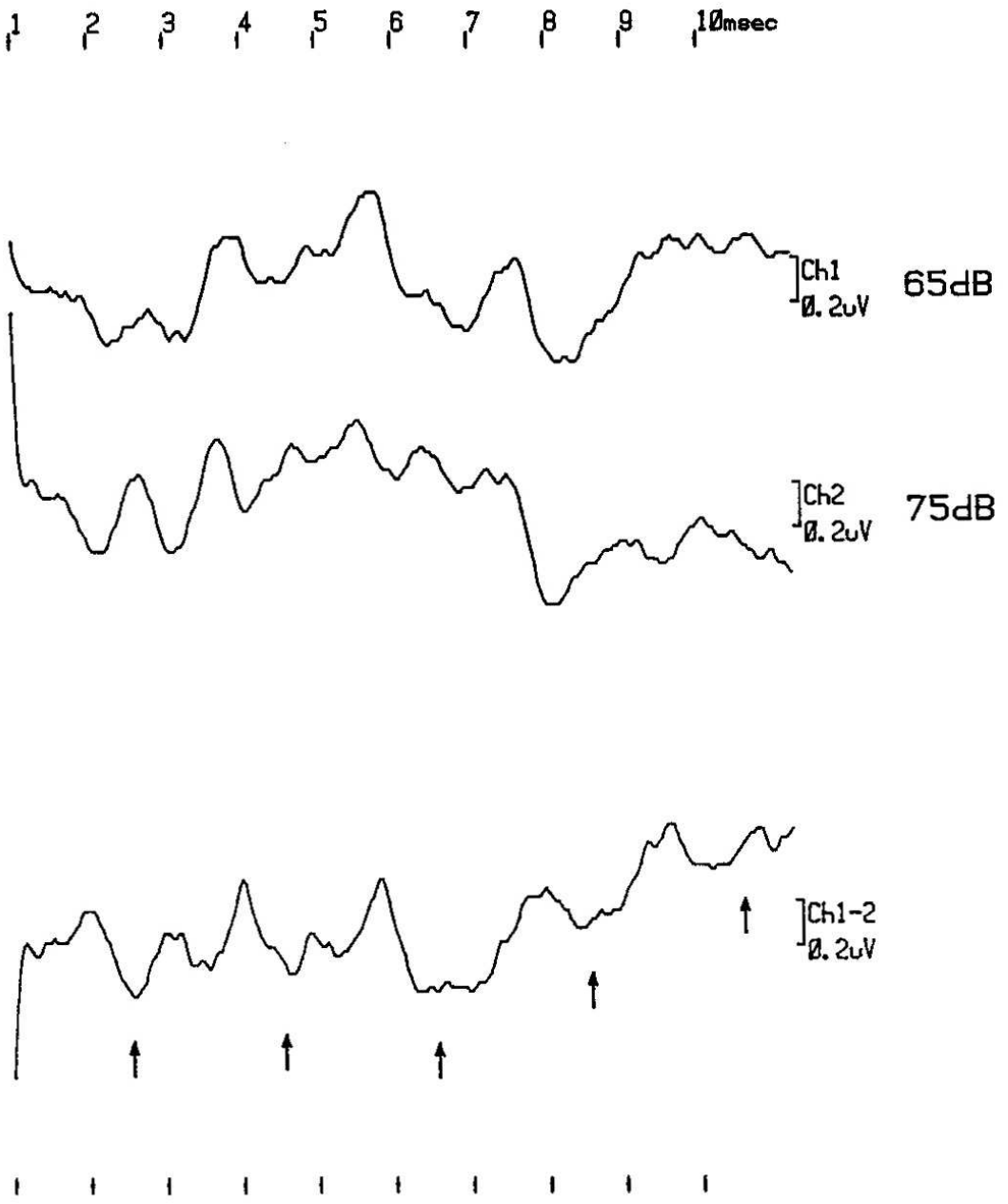


Fig. 25 Click Intensity

Woman (EM),59, with probable MS. Right-sided condensation records.
Among other changes produced by higher click intensity, wave V becomes (paradoxically) smaller.
Subtraction shows mainly two oscillations (480, arrows, and 960c/s, damped at 5msec) explaining changes in all waves.

is occasionally noted, for example, that in normal persons the waveform produced by condensation clicks appears "distorted" (Figs. 2 and 14). How could this be explained? Does it indicate desynchronization? In addition, click polarity may have a reversed effect: condensation, for example, affecting waves II and III on one side in a way opposite to that on the other side (Fig. 23). As seen from these illustrations, this phenomenon is better explained by superimposed oscillations.

3. Dissociation between latency changes: delay of early waves is not always accompanied by proportionate delay in succeeding waves (Fig. 24). This is difficult to explain if wave I represents input to the brainstem.

4. Dissociation between latency and amplitude changes. Robinson and Rudge (1982) and Chiappa (1983) maintain that both latency increase and amplitude decrease are produced by a common mechanism. Buchwald's (1983) hypothesis, on the other hand, allows independent mechanisms. According to the first view, reduction in amplitude of a wave is expected to accompany its delay. But this is not invariable. And neither view explains decrease in latency or increase in amplitude in disease. Squires et al. (1980), for example, found that in Down's syndrome the intervals I-II, III-IV and I-V were shorter than normal (which he described as "abnormally short central transmission time"), and that increasing click rate does not have the normal effect of prolonging latencies. Similarly, Wada and Starr (1983a) describe shortening of both

absolute wave IV and interwave latencies I-IV in experimental brainstem lesions. If impulse conduction along fibre tracts, or speed of synaptic polarization determine wave latency, this phenomenon constitutes a paradox.

5. Amplitude of wave I, in patients with MS, is sometimes larger than it is in normal persons (Elidan et al. 1982). Given Jewett's hypothesis, those authors had to offer an ambiguous explanation: demyelination of eighth nerve fibres causes poor synchronization and thus smaller waves from the upper brainstem, or demyelination in the olivo-cochlear bundle, whose normal function is thought to inhibit the neural activities of the cochlea. The phenomenon is better accounted for on the basis of oscillations: for example, absence of the lower frequency component (normally in negative phase in the region of wave I).

6. Occasional decrease in the amplitude of waves on increasing click intensity, on changing click phase or on using different headphone (Figs. 25-29). Similarly, Emmerson et al. (1982) observed the absence of wave V on stimulation at one intensity and its appearance at a lower intensity. While being difficult to explain on the basis of Jewett's hypothesis, on any of its variants, or on that of Thomas (1984), this phenomenon may be interpreted by changes in the oscillating characteristics of the BAEP, effected by different acoustic waveforms. And since differences in the acoustic waveform of the click are only differences in

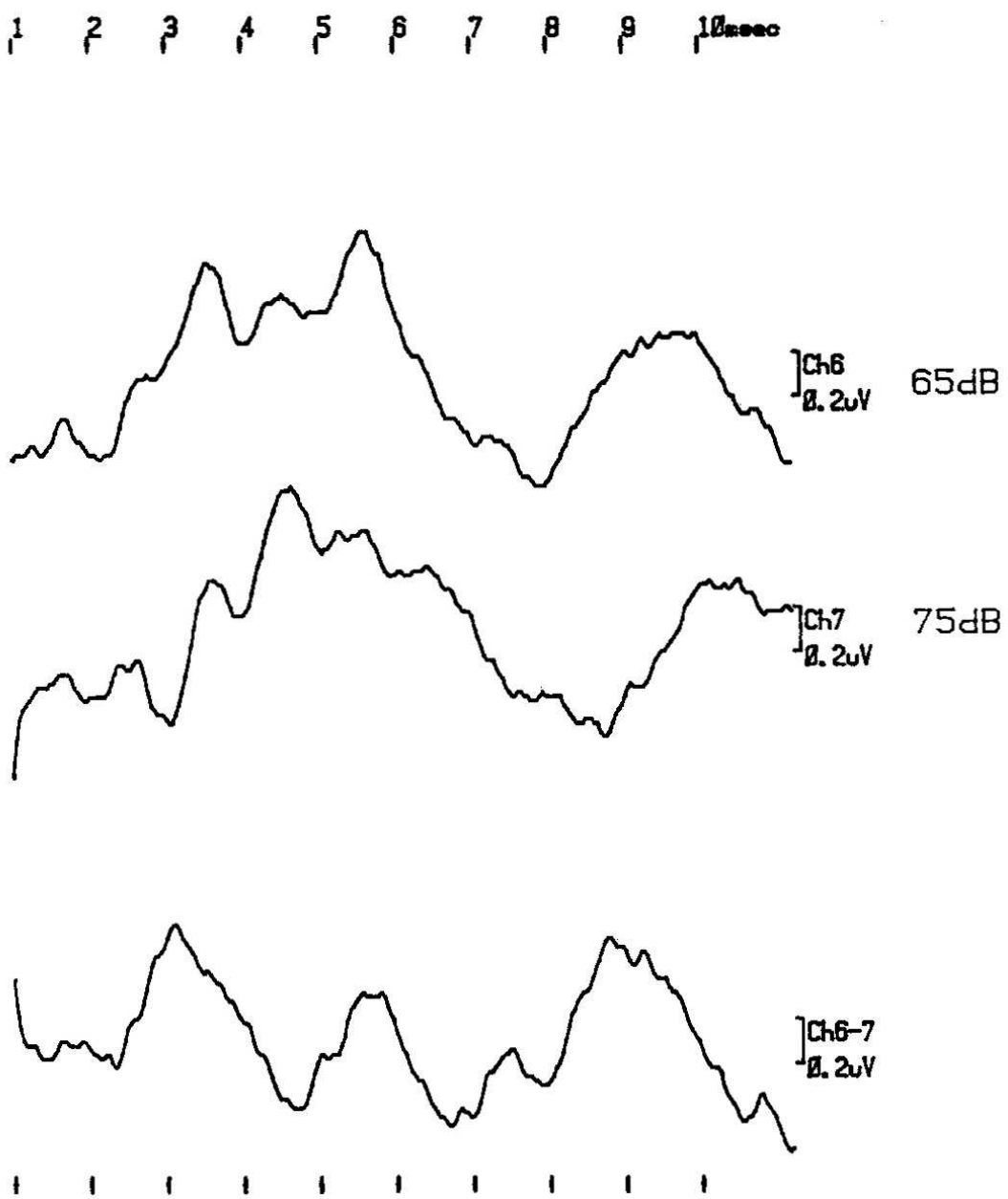


Fig. 26 Click intensity

Woman (ER),36, with atypical presentation of MS. Chest channels of right-sided records. Decrease in wave V amplitude (paradoxical), among other effects, explained by change mainly in 240 c/s oscillation (subtraction).

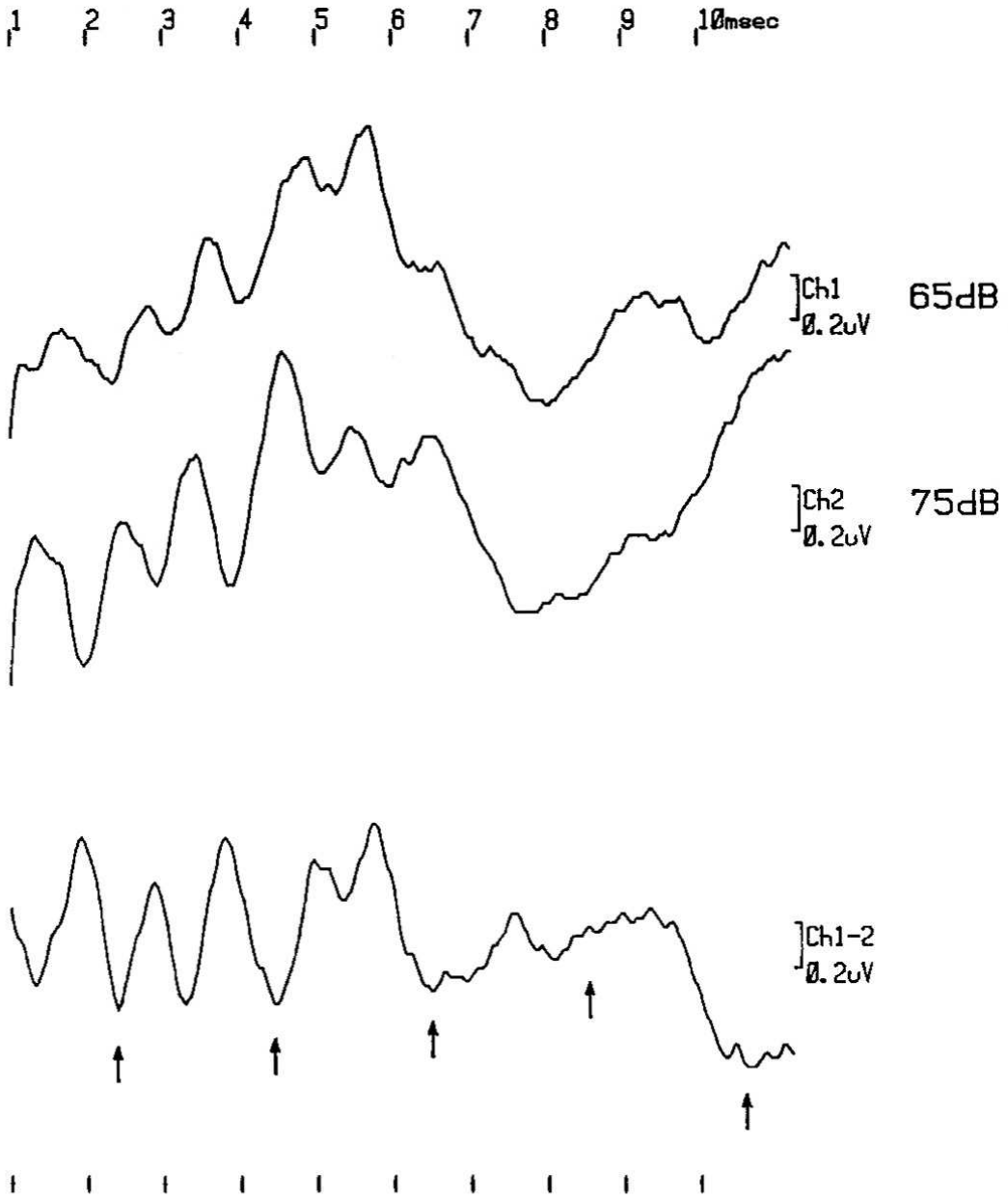


Fig. 27 Click intensity

Woman,34, with differential diagnosis of atypical MS and posterior fossa tumour.
Right-sided condensation records.
Subtraction shows reduction in amplitude of wave V on higher click intensity (paradoxical) due to change in 480 (arrows) and 960c/s (extending halfway through BAEP) oscillations.

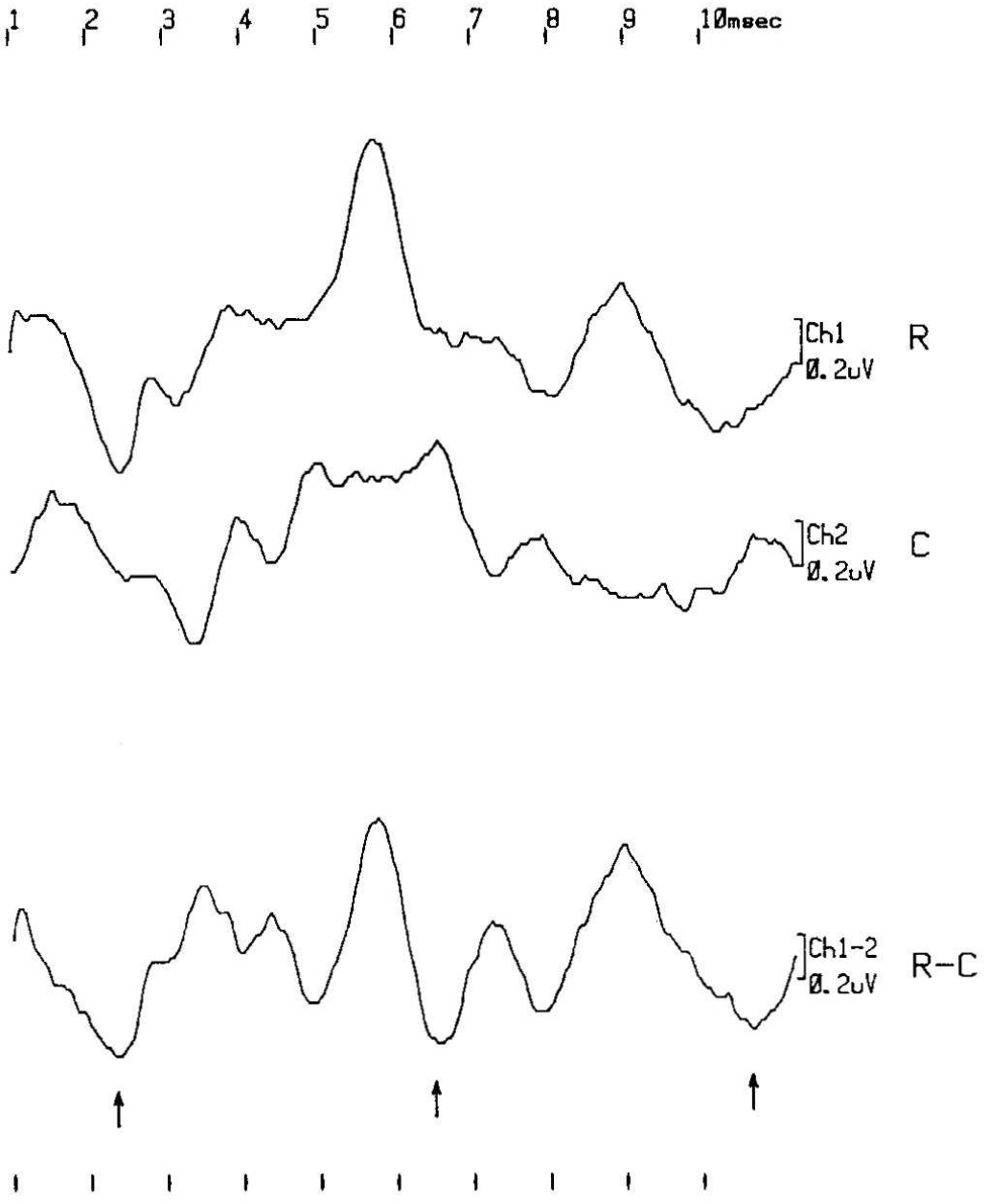


Fig. 28 Click polarity effect

Woman (AW),25, investigated for paroxysmal sensory disturbance and dystonia of right side, suspected to be due to MS. She also gives vague history of labyrinthitis two years earlier.
Chest derivation of left-sided records.
Subtraction shows changes in three oscillations (240, arrows, 480 and 960c/s) producing click polarity differences.

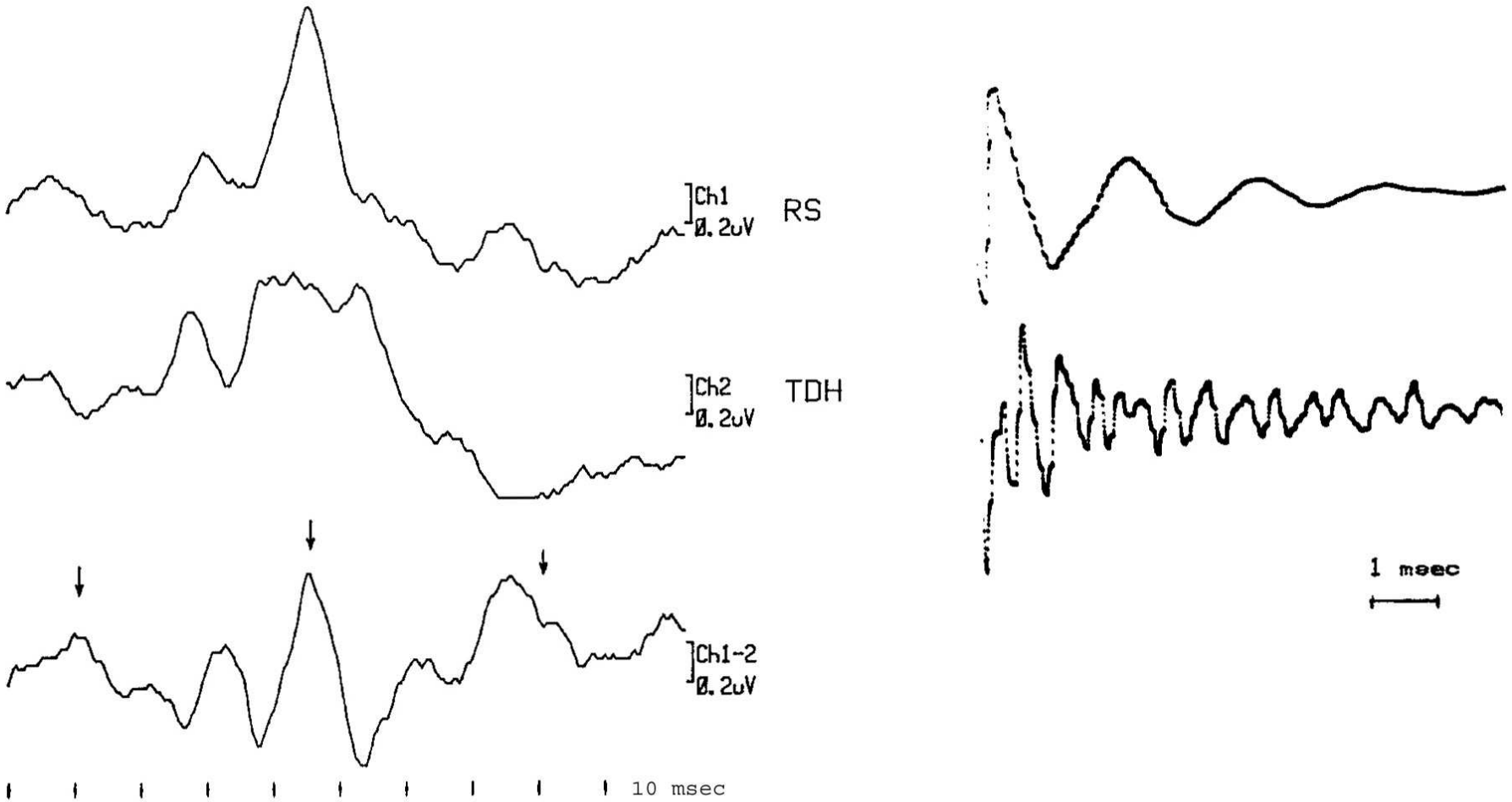


Fig. 29 Effect of acoustic waveform of click

Woman (TK),53, investigated for Meniere's disease. Right-sided records to different headphone (RS and TDH, acoustic waveform opposite).
Changes mainly in 290 (arrows) and 580c/s oscillations (subtraction) explain effect.

sinusoidal characteristics, this phenomenon provides strong support for the sinusoidal composition of the BAEP.

7. The occasional presence of wave I in the contralateral and chest channels (Figs. 4 and 30). The presence of succeeding waves in these montages is accepted, according to Jewett's hypothesis, on the grounds that they originate from structures close to the center of the head. So, if wave I originates from the action potential of the eight nerve, how could its appearance in the chest derivation be explained? In fact, this phenomenon is better explained if wave I, in common with all other waves, is formed by the superimposition of oscillations originating in a common structure. From that structure, these oscillations are volume-conducted to be picked up by the different electrodes. The differential damping effect of tissues--outside the nervous system--intervening between generator and electrodes, on these oscillations, cause the waveform differences between channels. Normally, it seems, this differential damping causes the absence of wave I from the contralateral channel. This selective absence of wave I, however, is apparent; in almost every case it occurs, succeeding waves are also affected, at least up to wave IV, and almost always*, the effect can be explained by changes in oscillations (Fig. 30).

* Artefacts distort the sinusoidal shape seen on subtraction.

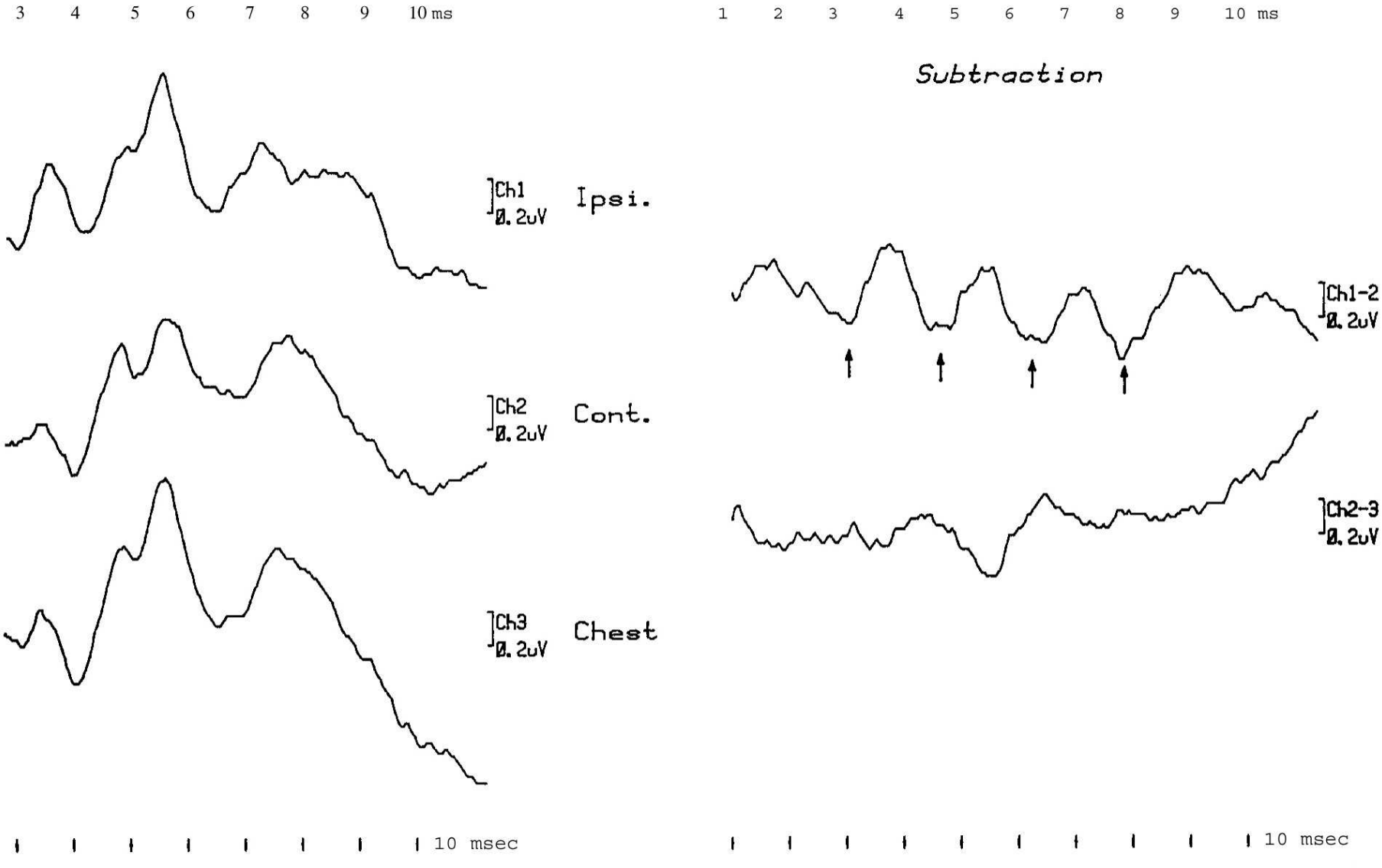


Fig. 30 Differences between montages

Healthy woman (RG),24. Left-sided records. Contralateral and chest channels closely similar, and difference from ipsilateral channel mainly due to change in 620c/s oscillation (arrows in subtraction). Wave I present in chest channel.

8. Absence of a wave (e.g. II) in normal persons (Figs. 31-33). This usually occurs on only one click polarity. Does this indicate that the nerve volley has missed a nucleus (or fibre tract) which generates that wave? In fact, this phenomenon is more easily explained through the interaction between sinusoids. It is also noted that changes in wave II are almost always accompanied by changes in waves IV and VI (Figs. 11-15 and 31-33). Simulation of the BAEP (discussed later) shows that wave II, together with waves IV and the first peak of VI, could be determined mainly by the 960 Hz sinusoid.

9. Inconsistency of waves VI, VII and VIII. Why should the "nervous volley carrying information of sound" unpredictably vary its course as it ascends the brainstem? And why should these late waves resolve better on using piezoelectric headphones (Hughes and Fino 1980). This, in fact, is best explained as variability in the oscillating time of components, affected by the acoustic waveform of the click.

10. Waves, in a normal BAEP, with more than one peak (Figs.2, 3 and 5). This also points to the generation of the BAEP by superimposed oscillations of different frequencies. Edwards et al. (1982) observed that extra peaks were occasionally accompanied by absence of wave IV or its fusion to wave V, and that these extra peaks were unrelated to the EMG. They inferred that this phenomenon may reflect subtle differences in the organization of the brainstem auditory pathways. Alternative explanations offered include double firing and

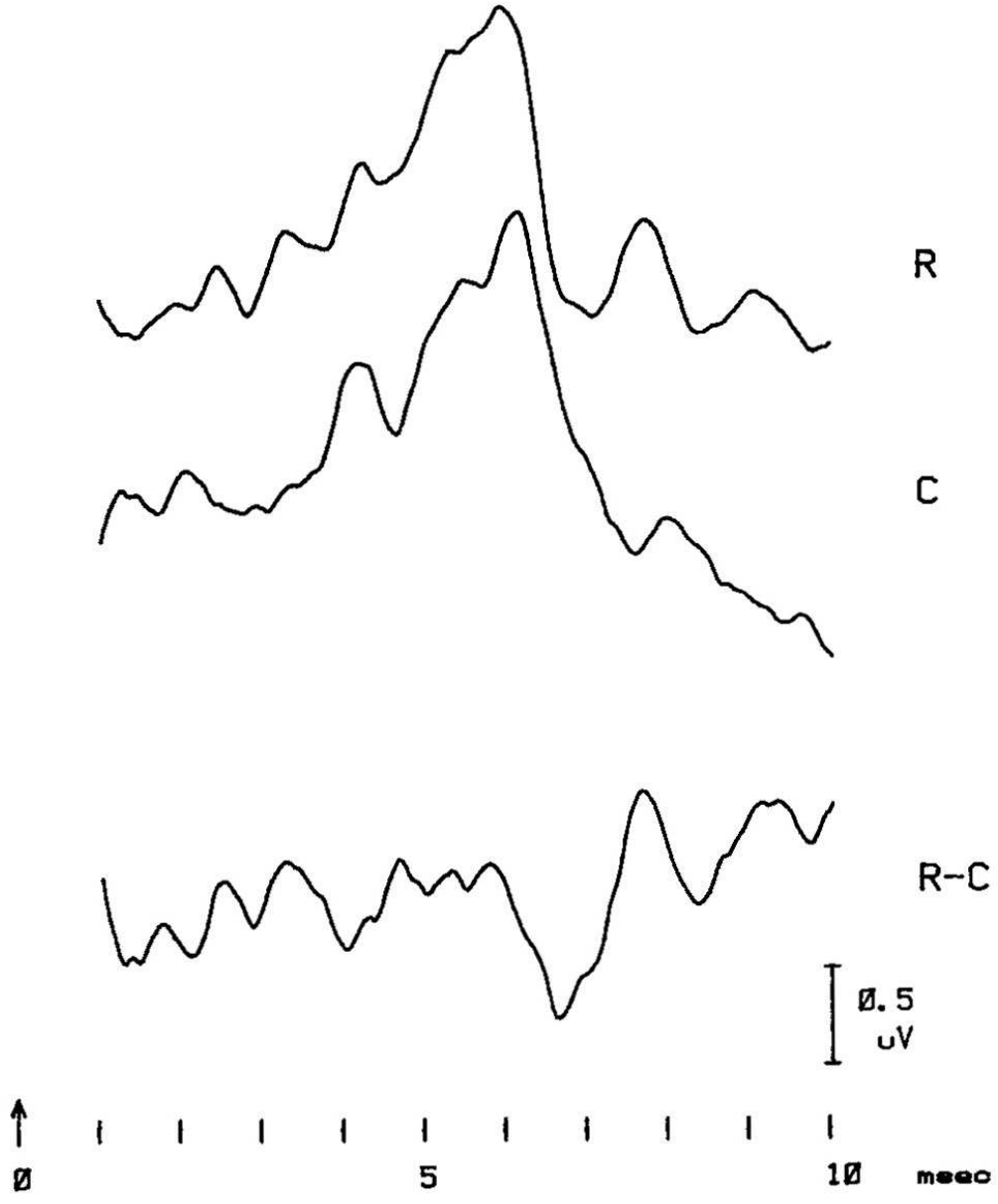


Fig. 31 Click polarity effect

Healthy man,31. Chest channels of binaural clicks. Wave II absent on condensation.
Subtraction shows sinusoidal pattern.

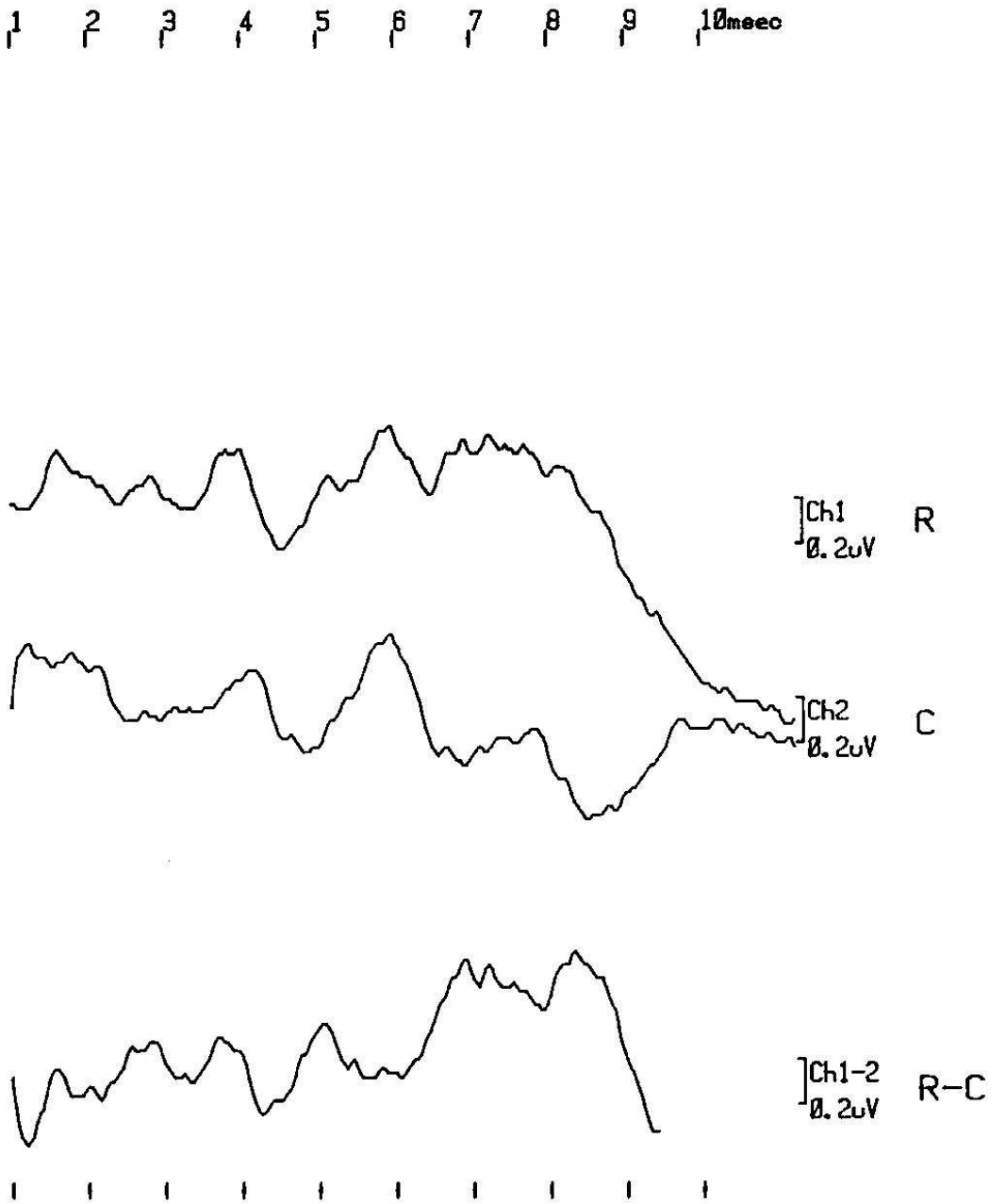


Fig. 32 Click polarity effect

Healthy man,23. Right-sided records showing marked effects on all waves; II absent on condensation.
Subtraction shows sinusoidal pattern.

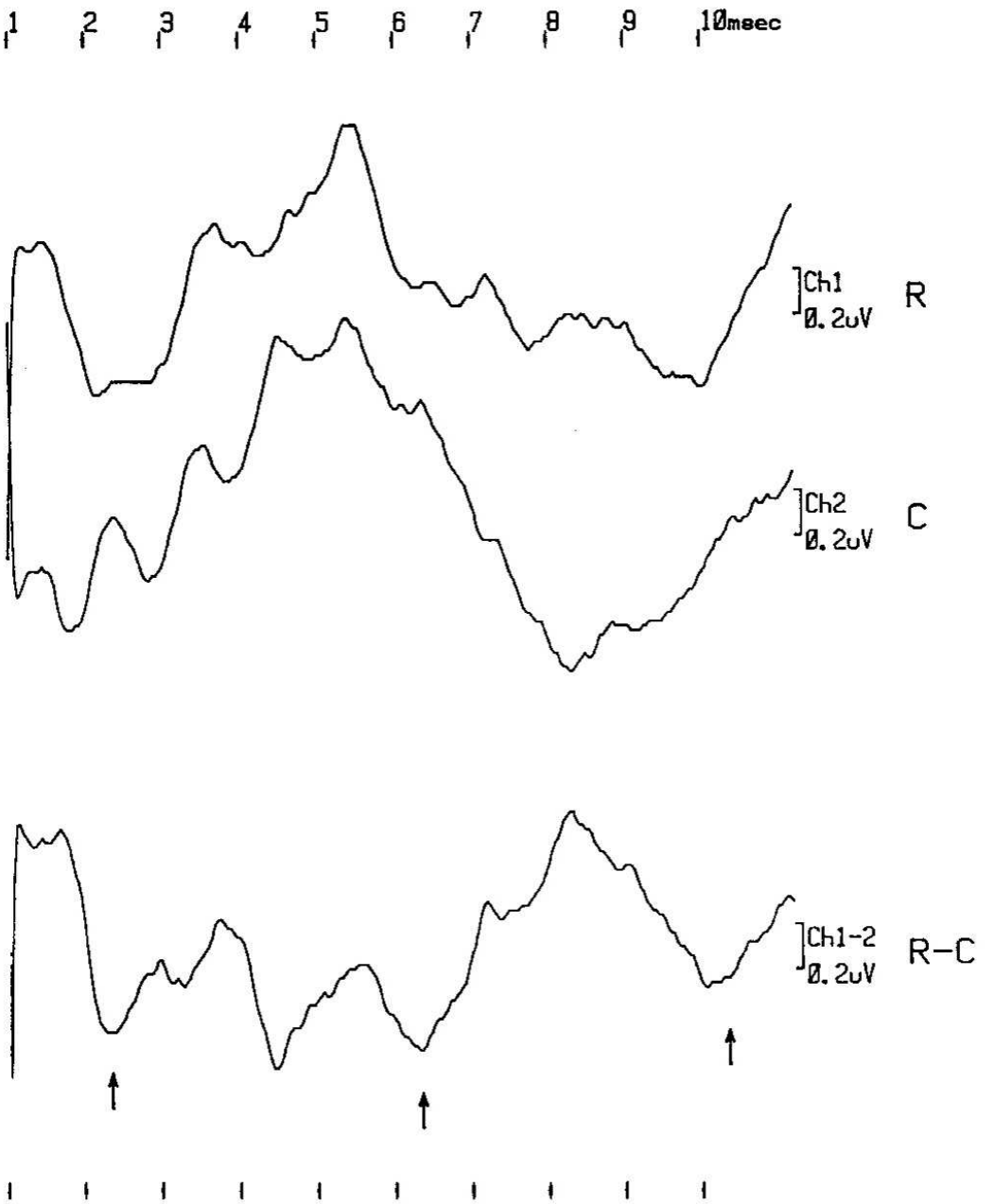


Fig. 33 Click polarity effect

Healthy woman (BS),30. Left-sided records showing marked effect on waves II,IV and VI; wave II absent on rarefaction.
Subtraction shows mainly 240 (arrows) and 480 c/s oscillations.

backfiring of post synaptic potentials, and abnormal synchronization (Barajas, 1982). The phenomenon, in fact, is better explained by the occasional presence of high frequency (>1000c/s) oscillations in the BAEP.

11. Double peak in wave I. Stockard et al. (1979) maintains that this represents latency jump or "amplitude dominance shift" from one peak to the other (to different click intensities), probably due to activity in neuronal populations, in the auditory nerve, with high and low thresholds. Hughes and Fino (1980), using piezoelectric earphones (which reduced stimulus artifact), recorded an "early peak I'" and called it a "new peak". They thought it is due either to repetitive firing of the eighth nerve, or probably "more specifically related to the postsynaptic potential arising in the afferent terminals of the eight nerve fibers in the response to the absorption of chemical transmitters from the hair cells....". Thomas (1984) attributes this first peak to the VIII nerve action potential, the second to a repetitive component. The simulation in Fig. 50 shows that the two peaks occurring in the first 2 msec after the click, belong to the four oscillating components.

12. Similarity in the BAEP time scale in animals with different head size. In the cat, for example, wave 4 (V in man) occurs at 5.2 msec (Fig. 2 in Jewett, 1970), and in the rat wave IV is at 3.8 msec (Fig. 1 in Church and Williams, 1984). Squires et al. (1980), it is noted here, found no correlation between

head size and I-V interpeak latency in man. This BAEP similarity in fact suggests oscillatory properties common to nervous systems in different species; the EEG has higher frequency of the occipital alpha rhythm in women (Kellaway, 1979).

Proposed site of origin of BAEP

Having proposed that the BAEP is unlikely to originate from discrete nuclei, the following discussion will deal with phenomena suggesting that the BAEP does not originate in the brainstem:

1. Dissociation between severity of disease and BAEP abnormality. For example, four children with no clinical evidence of brainstem dysfunction had markedly distorted BAEP (Worthington and Peters, 1980). On the other hand, MS patients with clinical involvement of the brainstem may have normal BAEP. Fig. 34 shows two records, two years apart, from a patient with MS. At the time of the first record (when symptoms had just begun and the BAEP was normal), this patient had more clinical signs of brainstem affection than she did two years later, when the BAEP became abnormal. But at the later date, she also had impaired hearing and hyperacusis, which were not present earlier. (Audiometry results were ambiguous, fitting neither cochlear nor retrocochlear impairment.)

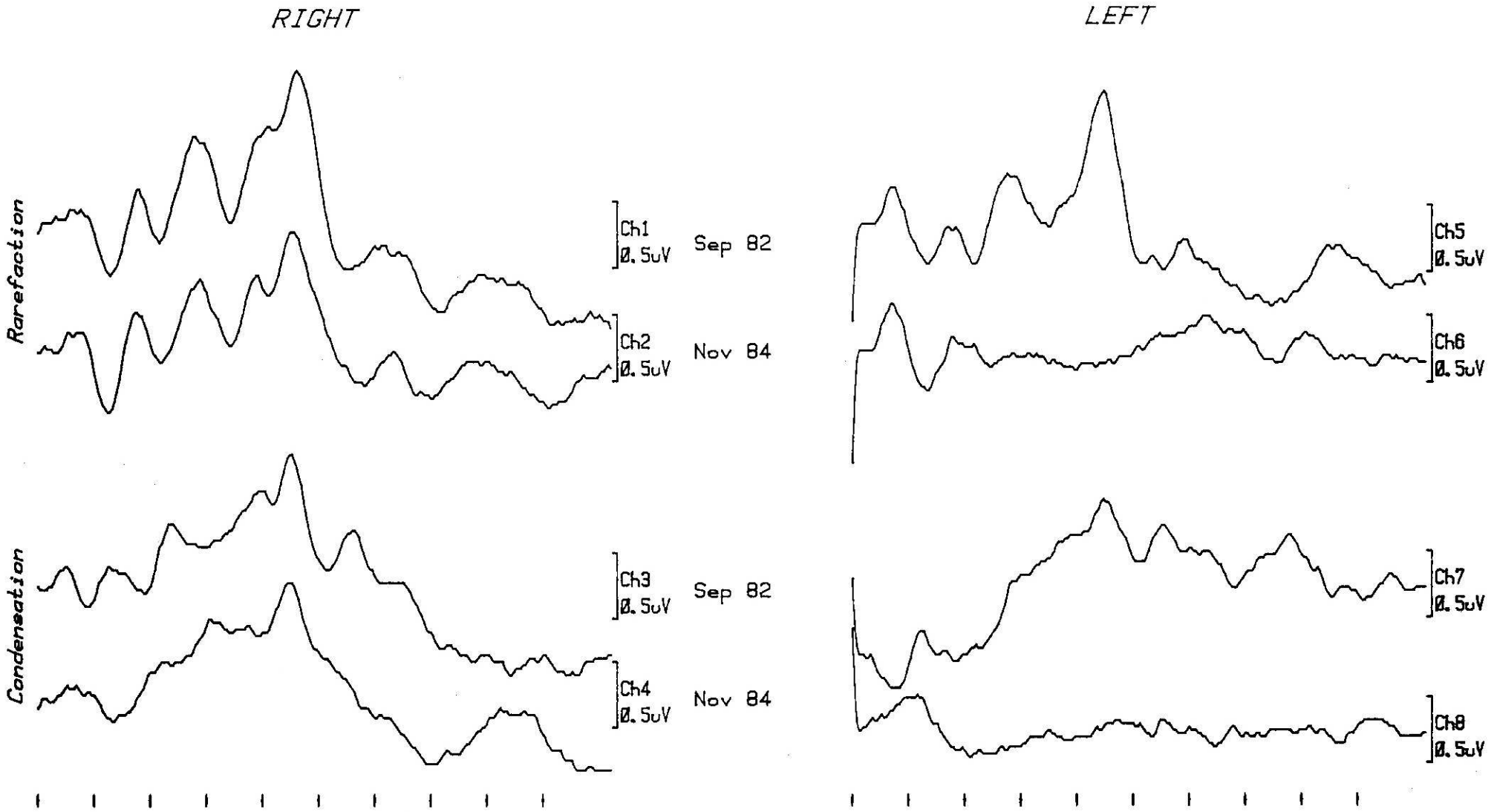


Fig. 34 Progression in MS

Woman (CO),37, with MS of two years duration.
In Sep 82 she had no hearing impairment; in Nov 84 she has hearing loss centered on 4000 Hz and phonophobia in the left ear (audiological tests failed to decide between cochlear or retrocochlear lesion). But in Sep 82 she had more clinical brainstem signs than in Nov 84.

Further examples of such discrepancy are provided by the following investigators: Sohmer et al. (1982, 1983 and 1984) found persisting BAEP despite marked brainstem hypoxia, hypercapnia and ischaemia, and Deutsch et al. (1983) found similar resistance of the BAEP during severe hypoglycaemia. Given the high metabolic rate of brainstem structures thought to generate the BAEP, these observations, as admitted by the authors, constitute a paradox. Similarly, during sleep apnoea where the brainstem is known to be affected, Peled at al. (1983) found normal BAEP.

2. Presence of normal late auditory evoked potentials, inspite of the absence of the BAEP (Satya-Murti et al., 1983). These authors proposed: (1) late potentials require less "precise synchrony" of conduction, (2) "...diminished transmission in brain stem auditory pathways could induce compensatory alterations at higher cortical levels, thus insuring the occurence of normal [late potentials]." and (3) separate pathways are resposible for the generation of the BAEP and late potntials. While the first two explanations are extremes, the third, based on anatomy, they admit, is the least likely. If one accepts, therefore, that late potentials reflect cortical activity, dependent on arrival of auditory information through the brainstem, then the BAEP is not related to such flow of information. An alternative explanation, however, although superficially close to the first of the above but depending on the idea of oscillations,

is that absence of the BAEP is due to unsustained oscillations of 240c/s and higher, while the lower frequency oscillations (at about 120c/s) continue long enough to produce the late potentials. Fig.35 shows analogous relation between the BAEP and middle latency potentials. This alternative explanation, however, also depends on the hypothesis that BAEP oscillations originate outside the brainstem.

3. Discrepancy between the high level of metabolism (reflected by local cerebral blood flow and glucose utilization) in the normal brainstem and the persistence of the BAEP under "extremely low" cerebral perfusion pressure (Sohmer et al., 1983). Similarly, Stockard et al. (1977) found that the BAEP persisted inspite of concentrations of isoflurane and barbiturates more than twice those required to abolish spontaneous EEG activity and clinical evidence of brainstem function in man and cat.



Fig. 35 Duration of BAEP oscillations

Healthy woman (LR),31. (Same record as in Fig. 50, but here it is averaged from tape playback.) A wave (?) at 14 msec is a continuation of the 240c/s oscillation (arrows). The 120c/s oscillation also appears to continue throughout the trace.

Filter

Application of the "resonator" digital filter (Method. p.4) shows how the BAEP is decomposed into oscillations of different frequencies (Figs. 36-46). It also shows how these oscillations together contribute to the formation of single peaks. Amplitudes of the different filtered oscillations, however, are arbitrary, and a leakage effect, different with different frequencies, occurs (Figs. 47-49).

Simulation

Simulation offers yet stonger evidence for the oscillatory origin of the BAEP.

Thus, the BAEP can be simulated by the addition of four sine waves of doubling frequency (lowest at 120 Hz, corresponding to the BAEP scale) but of the same amplitude (Fig. 50). They start simultaneously. Different waveforms are produced by phase shift of one or more of the simusoids.

This model was developed on trying to simulate a normal BAEP (Fig. 50), that can be visually decomposed into three sinusoids. Therefore, a BASIC graphics programme was written to generate and add three sine waves of equal amplitude but of harmonic frequencies. It soon became clear, however, that a fourth (120 Hz) sine wave was also needed and, through trial and error,

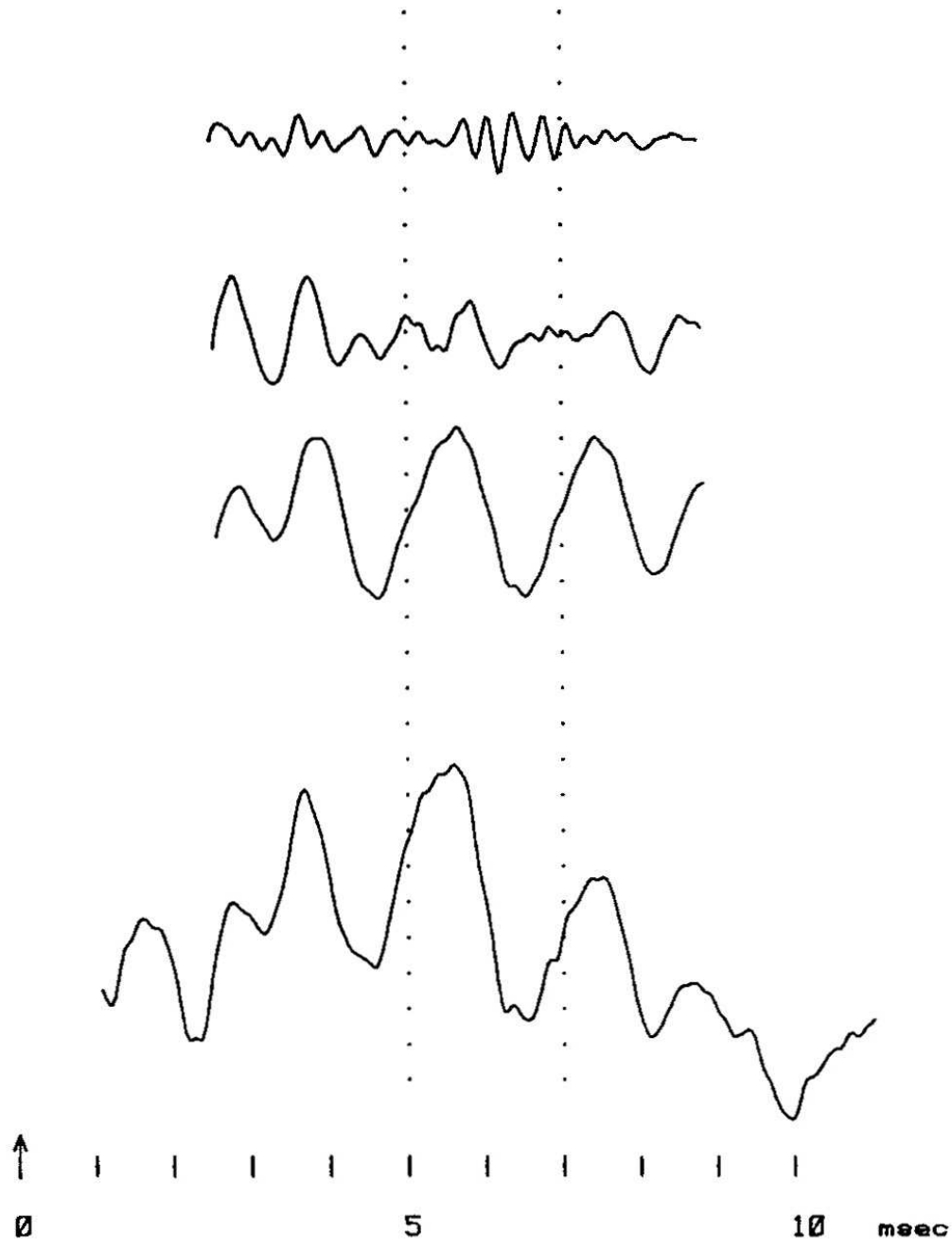


Fig. 36 Resonator filter

Healthy woman (RG), 24. Right-sided rarefaction record.

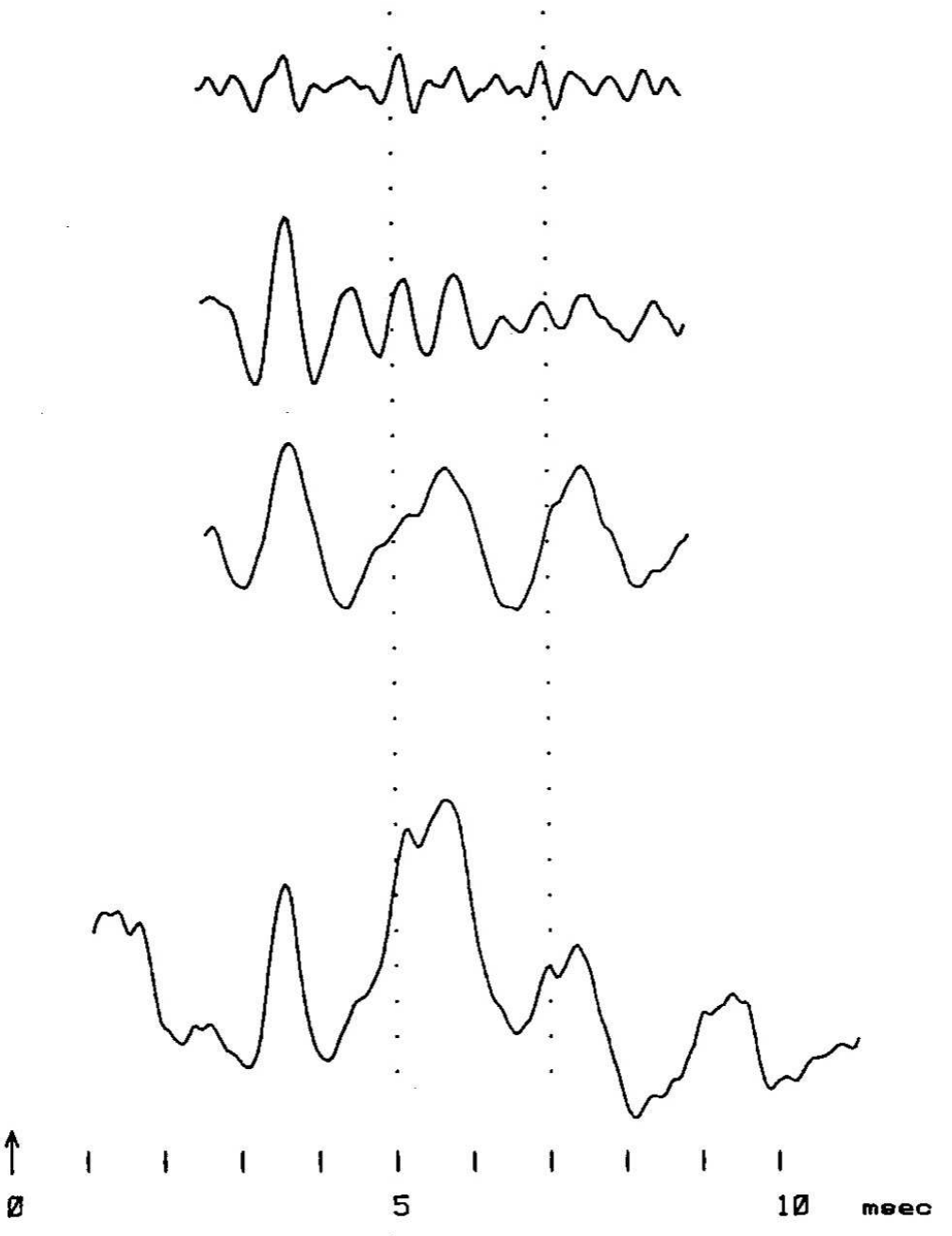


Fig. 37 Resonator filter

Same woman in previous figure. Right-sided condensation record.

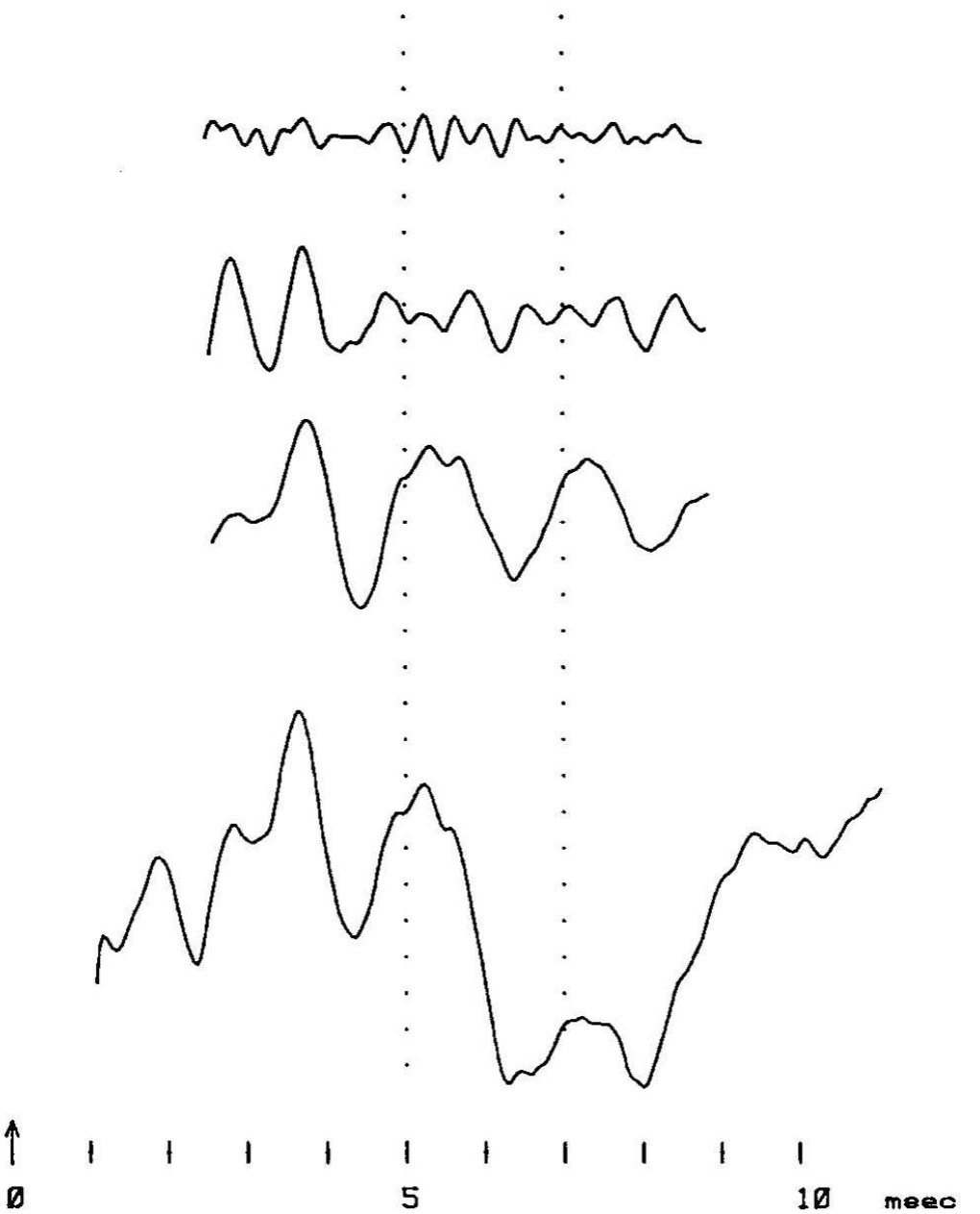


Fig. 38 Resonator filter

Healthy woman (LC), 24. Right-sided rarefaction record.

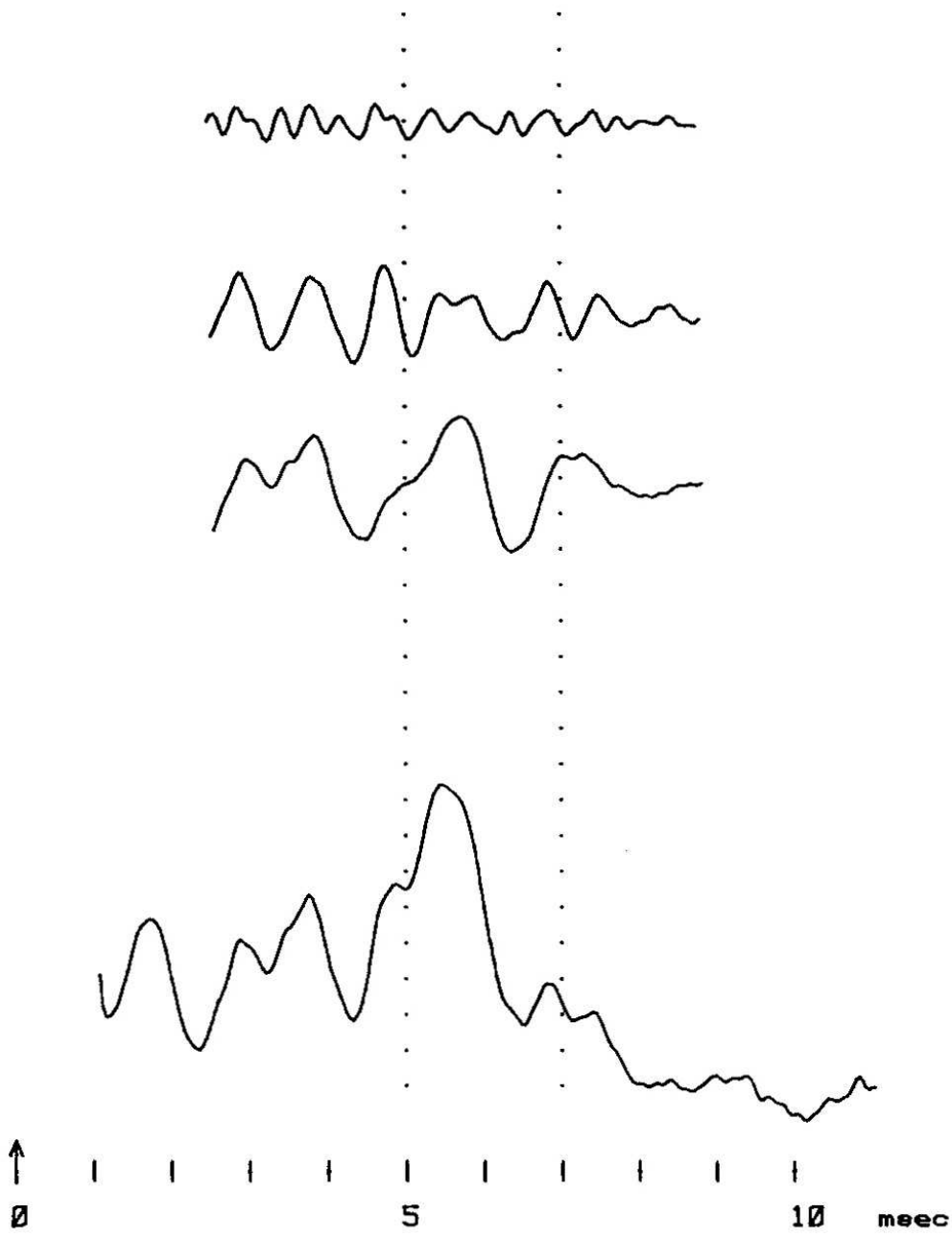


Fig. 39 Resonator filter

Same woman in previous figure. Right-sided condensation record.

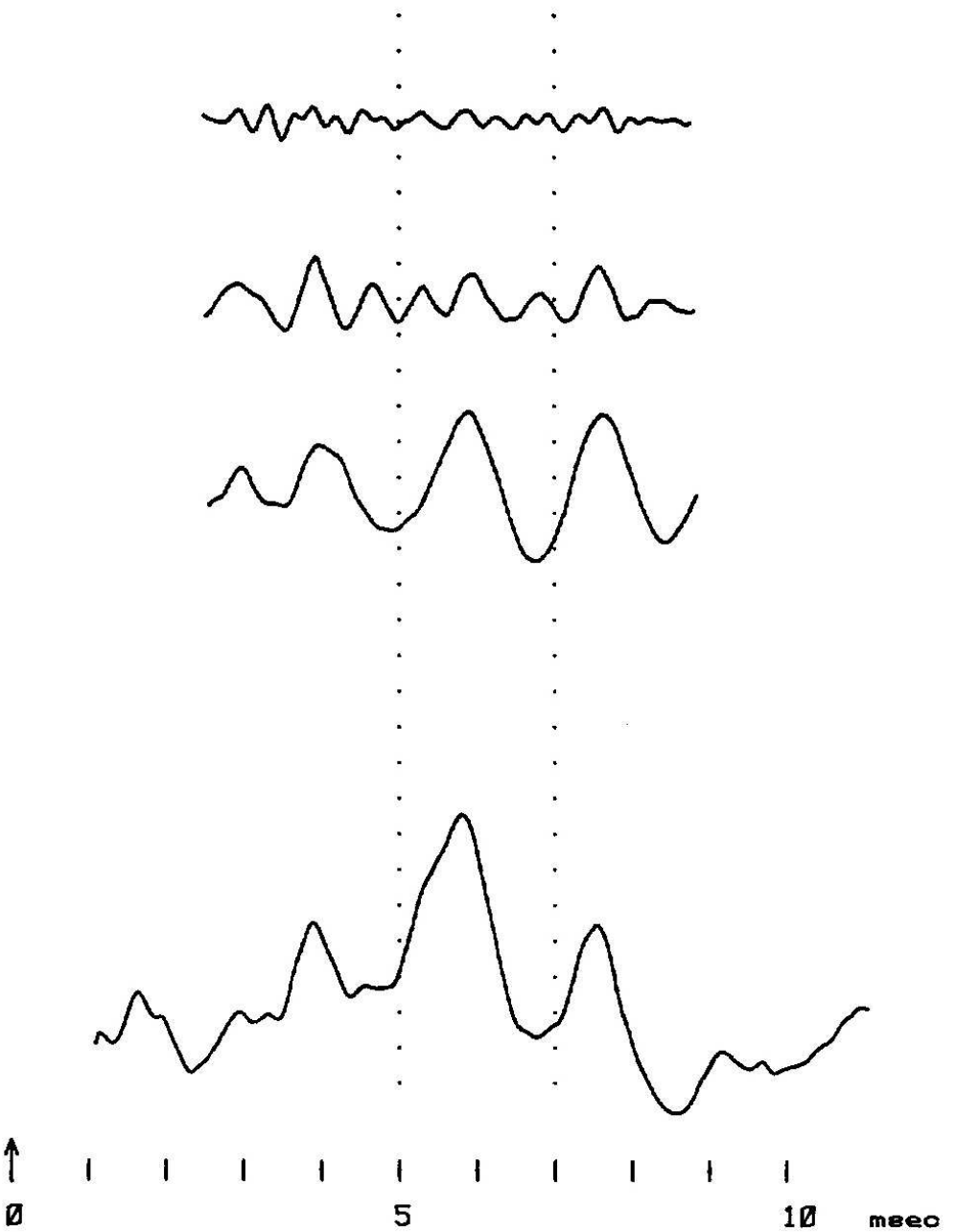


Fig. 40 Resonator filter

Healthy man (MD), 33. Right-sided rarefaction record.

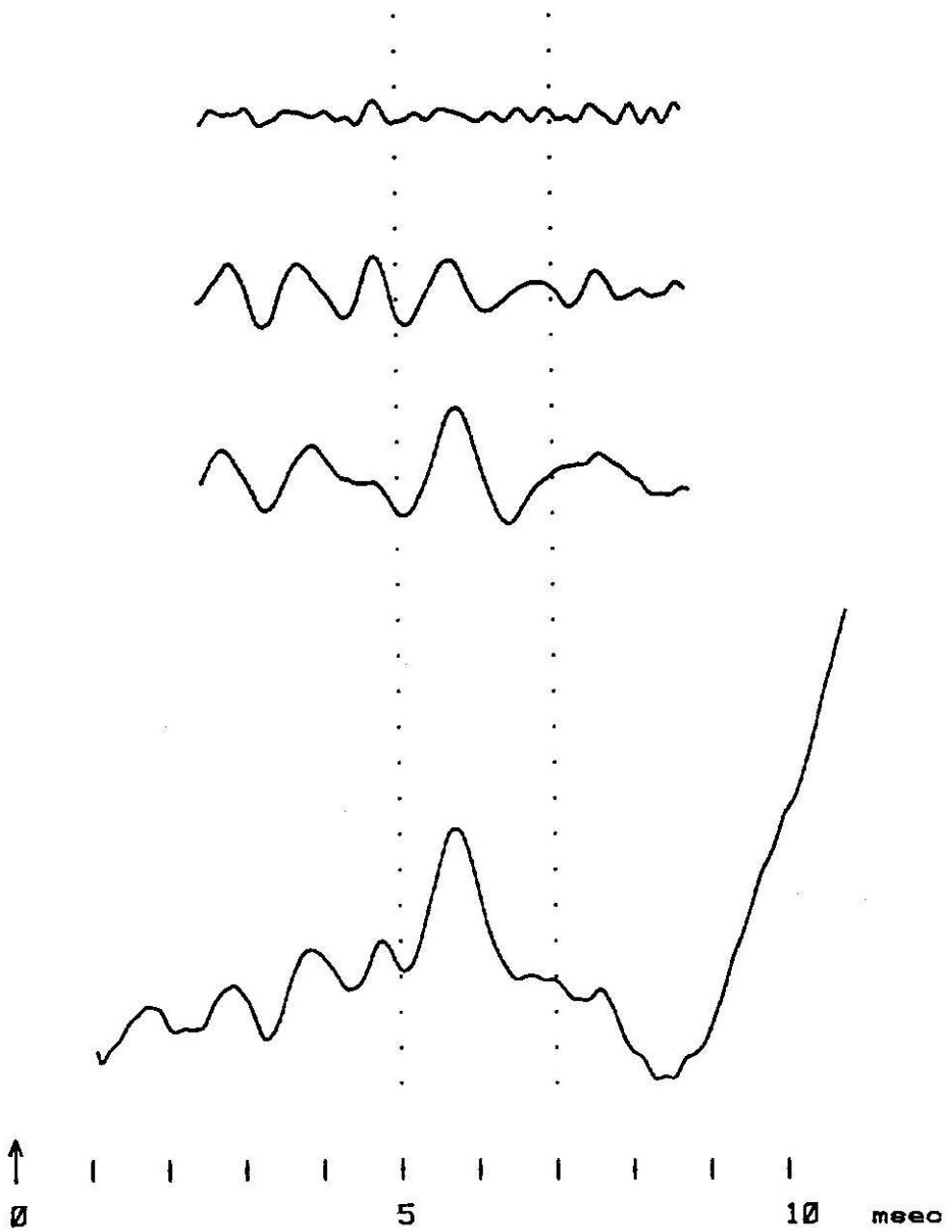


Fig. 41 Resonator filter

Same man in previous figure. Right-sided condensation record.

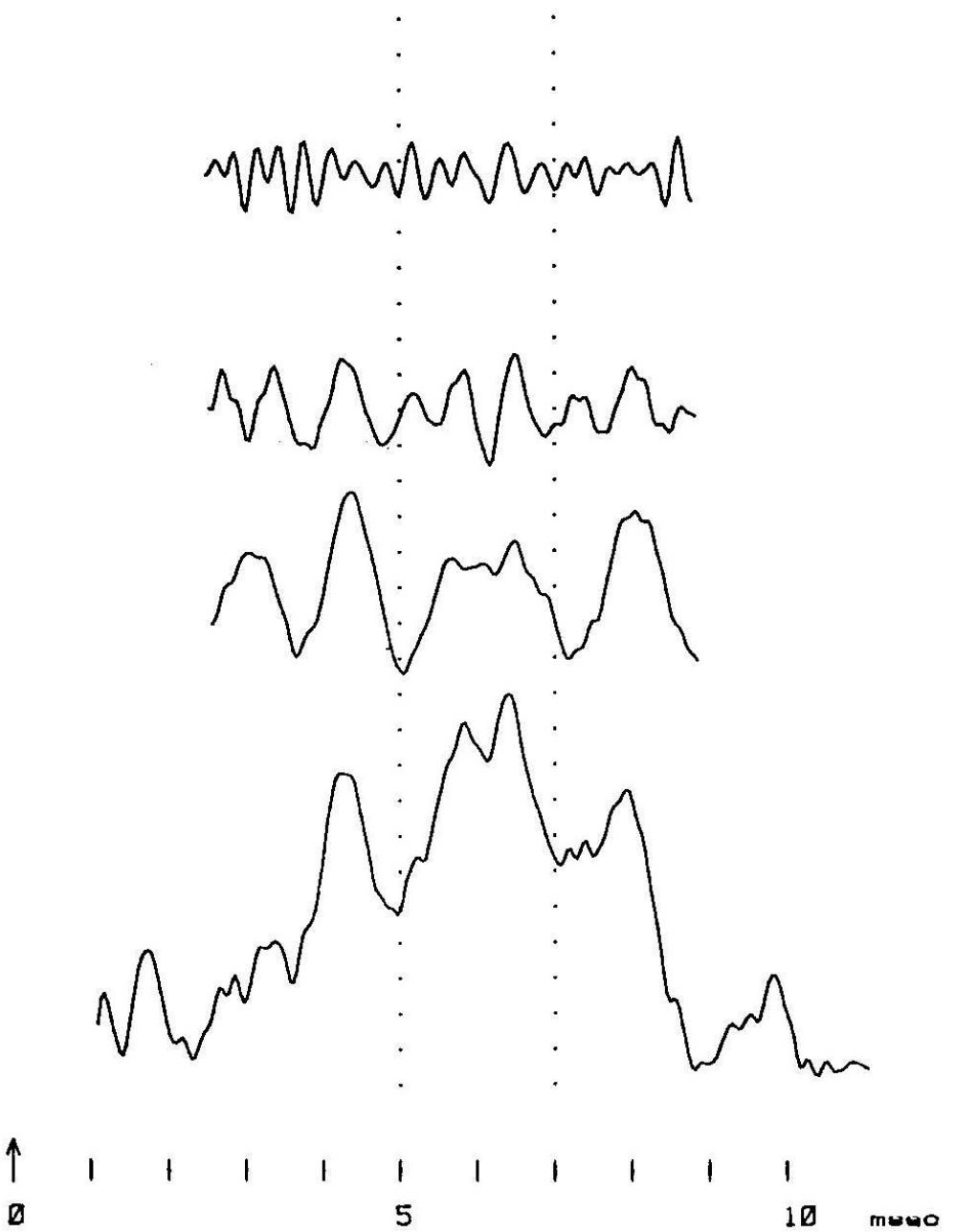


Fig. 42 Resonator filter

Woman (AT), 36, with obscure white matter degeneration.
Right-sided rarefaction record.

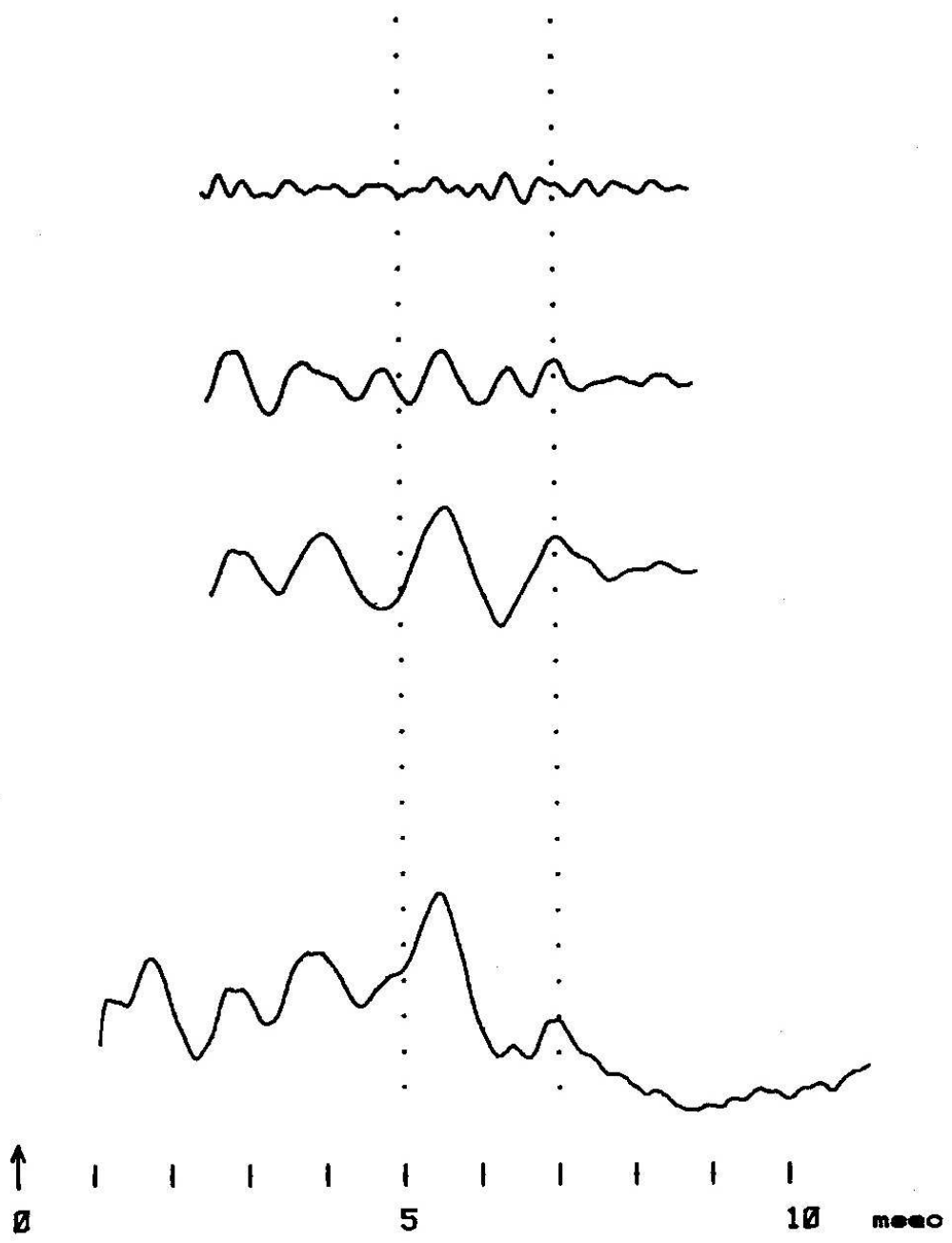


Fig. 43 Resonator filter

Woman (CO), 35, with early MS. Left-sided rarefaction record.

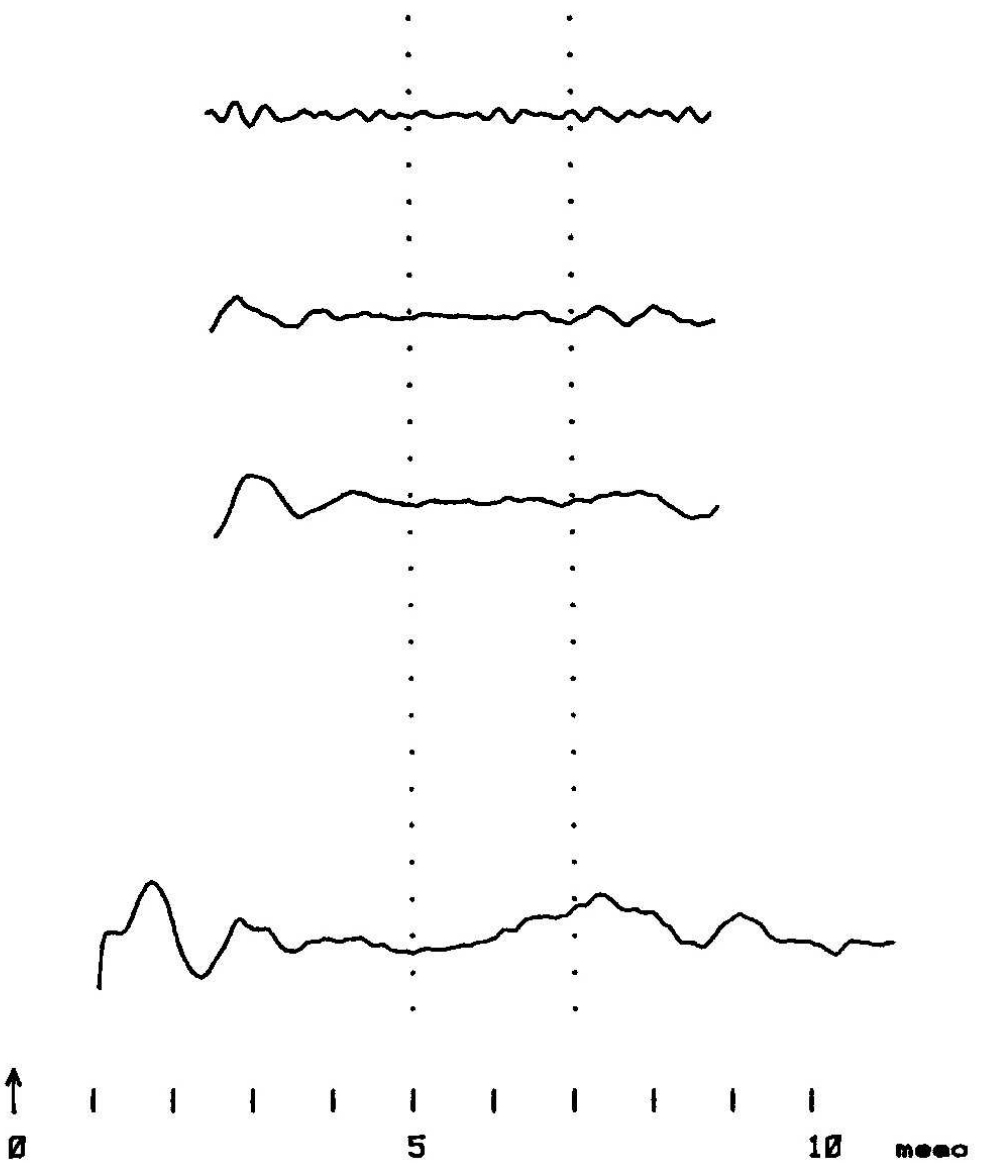


Fig. 44 Resonator filter

Same record as in previous figure, but two years later.

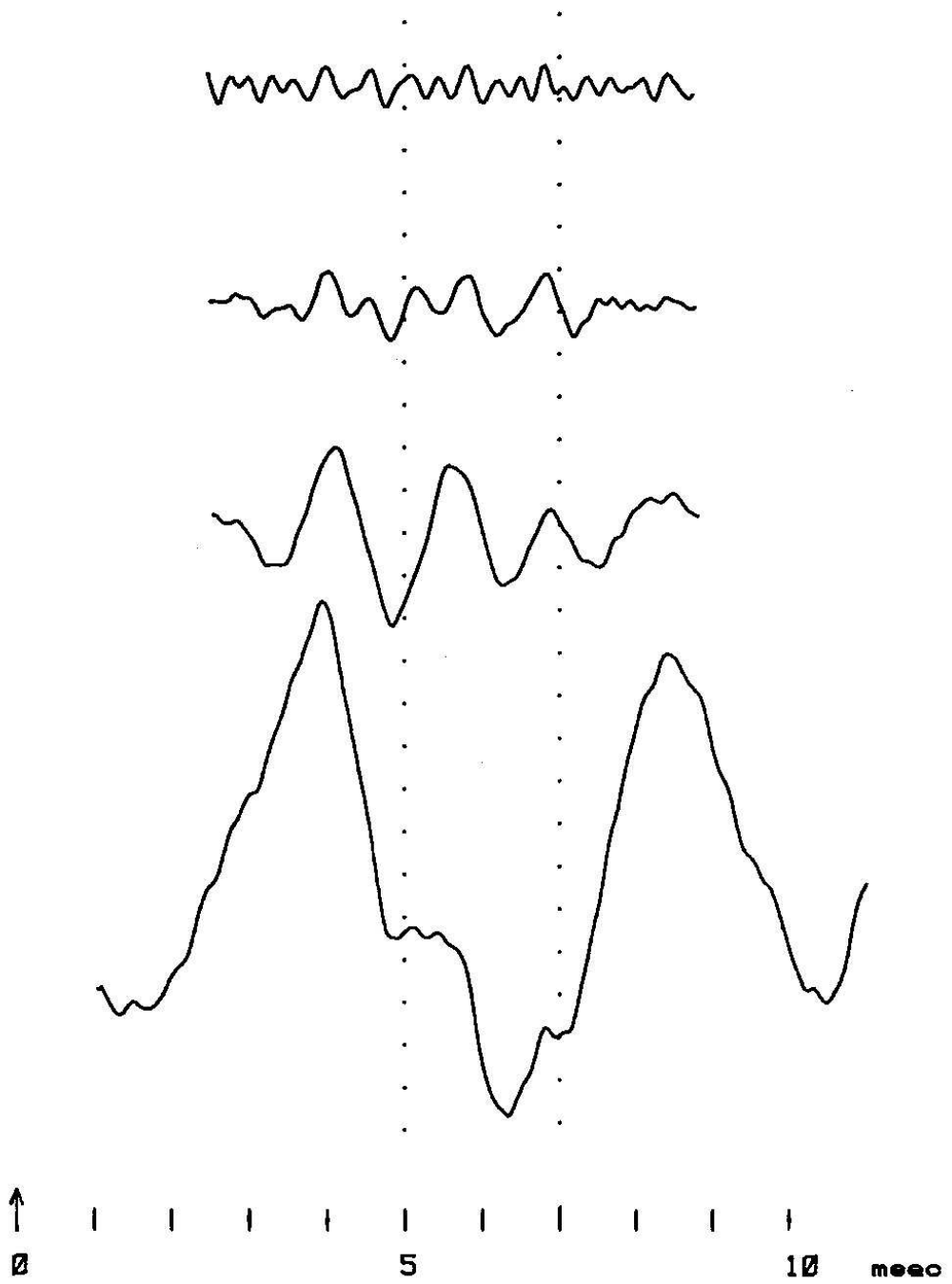


Fig. 45 Resonator filter

Woman (JR), 53, with MS. Right-sided rarefaction record.

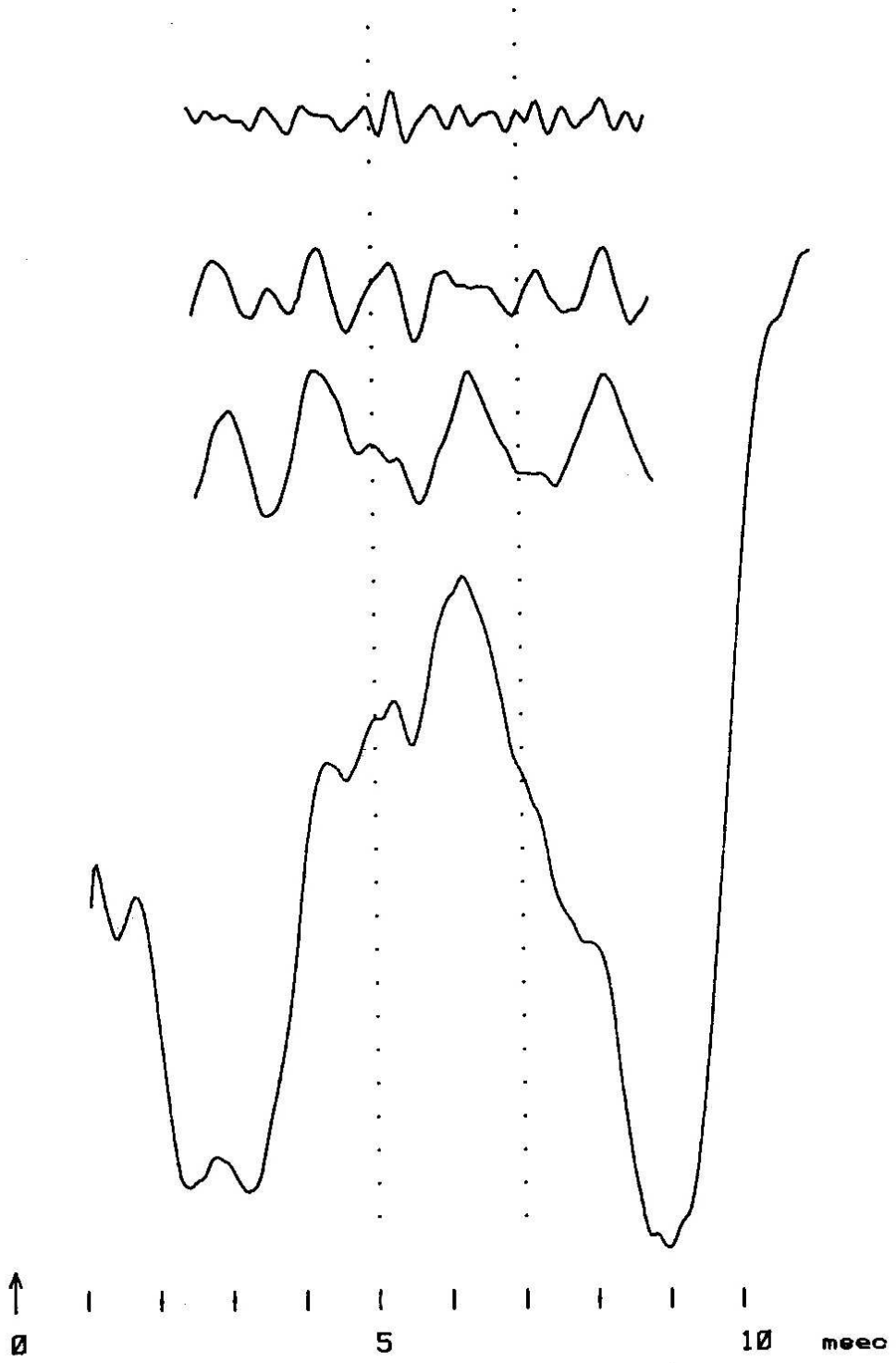


Fig. 46 Resonator filter

Woman (JS), 66, with signs of brainstem infarction.

Right-sided condensation record.

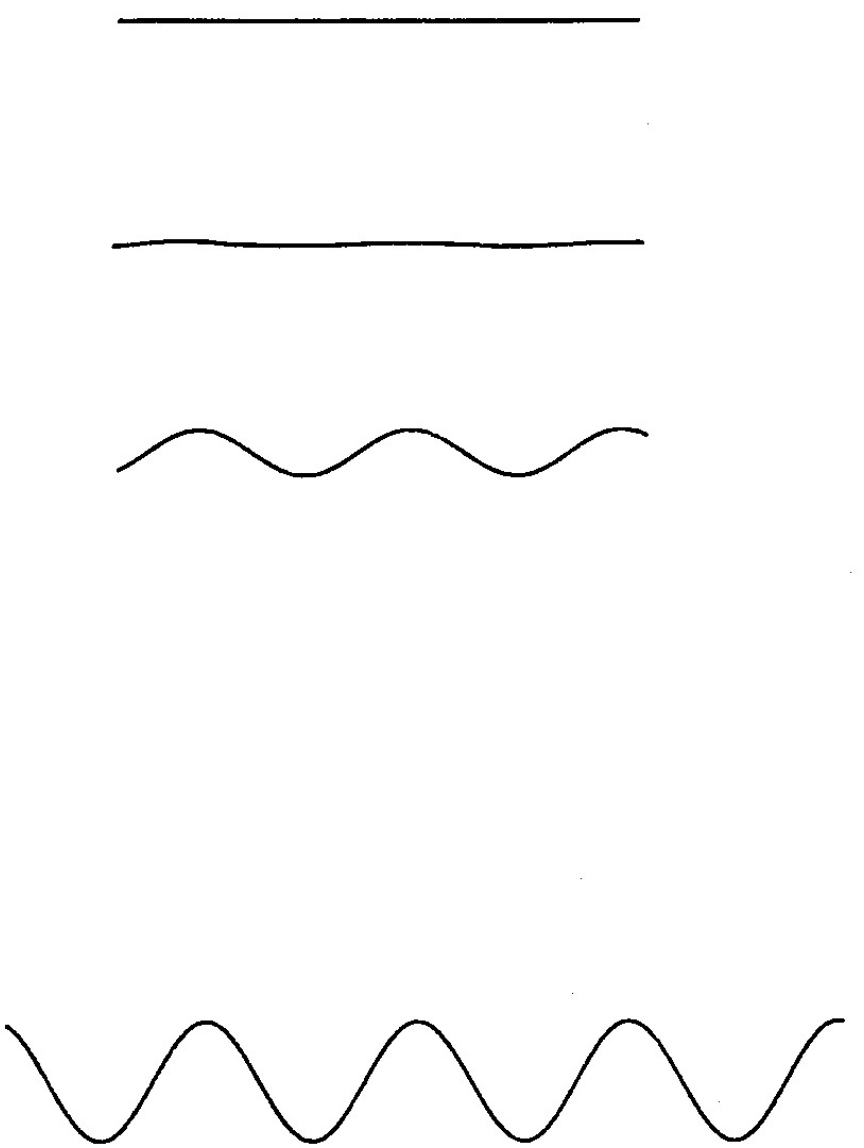


Fig. 47 Resonator filter

400 Hz sine wave (corresponding to BAEP scale)

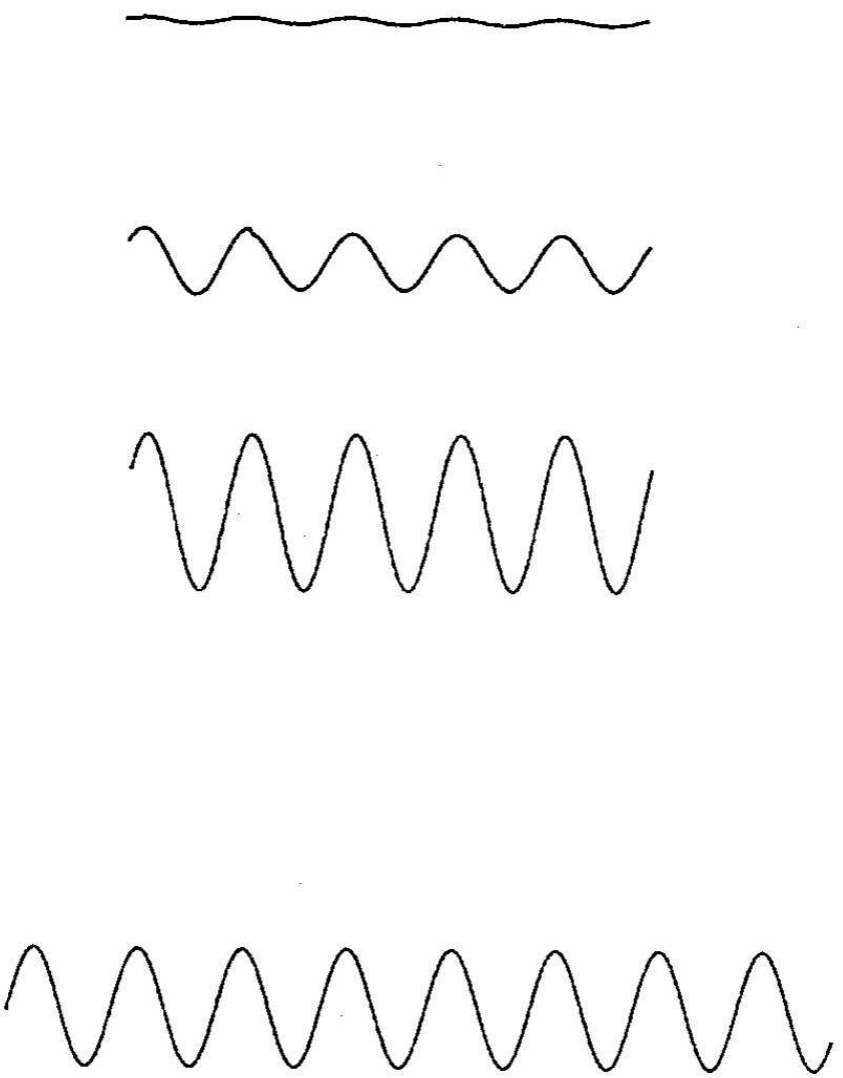


Fig. 48 Resonator filter

800 Hz sine wave (corresponding to BAEP scale)

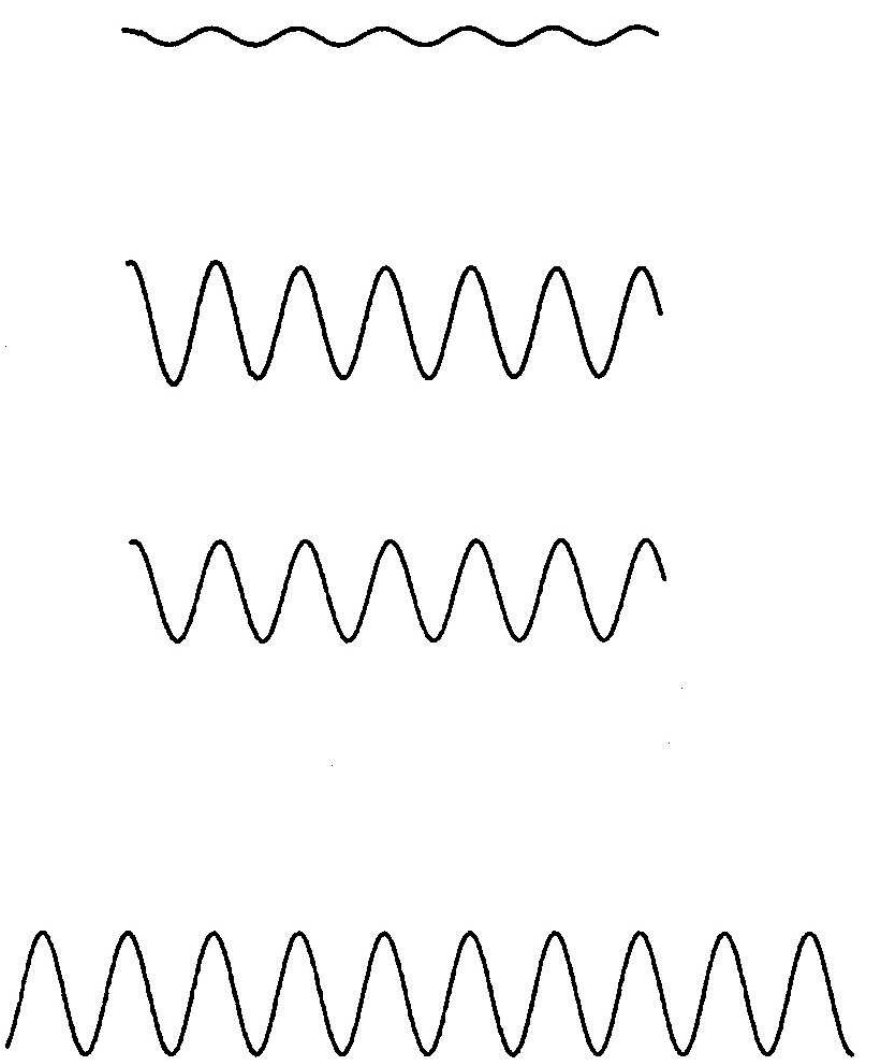


Fig. 49 Resonator filter

1000 Hz sine wave (corresponding to BAEP scale)

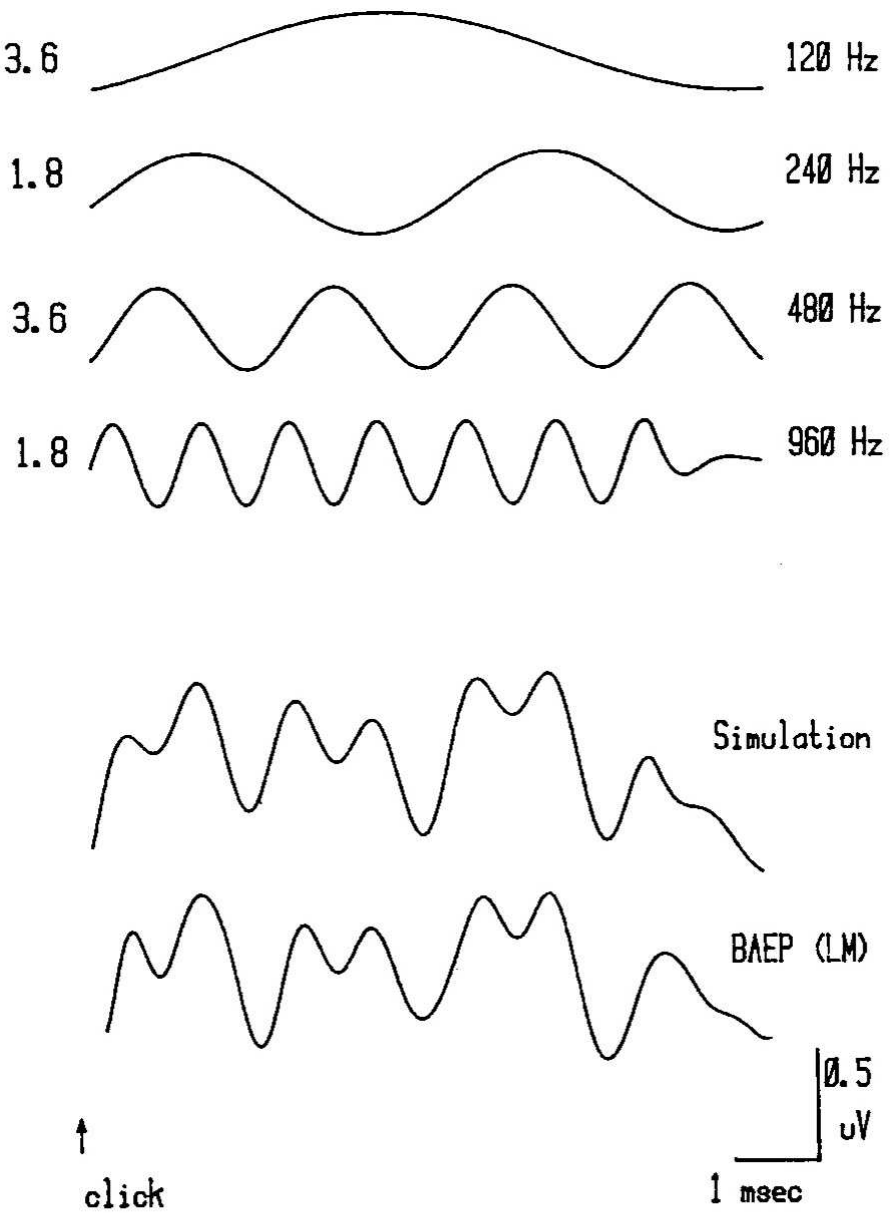


Fig. 50 Simulation model

Algebraic addition of four sine waves (top) produces simulates normal BAEP. These sinusoids begin simulateneously, but 960 Hz is damped at 6 msec. They are also of equal amplitude but of doubling frequencies (right end) and with a peculiar pattern of phases (ratio of 2:1:2:1, left end).

altering the phases of these sinusoids, the combination which simulated the BAEP was found.

Now it might be argued that that single BAEP happened to have this waveform by chance and indeed, this may be the case. But it would be implausible that the summation of activity in discrete nuclei or fibre tracts (as Jewett's hypothesis, or its variants, has it) should, by chance, produce a BAEP that can be simulated by only four sinusoids, of exactly equal amplitudes and exactly doubling frequencies. If chance did have any role, it would have been in the way that this particular BAEP was recorded: on tape, to 0.75 Hz click rate, for 100 msec after the click and with no post stimulus delay. I recorded with these different parameters (cf. Method p.2) because I was looking for oscillations during the first second after the click. I thought that, if the BAEP is sinusoidal, then, as in the EEG, some of its oscillations might repeat some time after they had died down during the first 10 msec. In fact, this recording shows the 450 c/s oscillation continuing to form waves "VIII" and "IX" (Fig. 35).

It might be argued that this simulation model is a form of Fourier's analysis. It is, but with the following important differences:

1. It includes only four sinusoids; Fourier's theory, for discrete time series with a frequency range of 50-3000 Hz (allowed by the amplifier's bandpass), requires about thirty sinusoids to obtain the approximation

2. The four sinusoids are of equal amplitude; with Fourier's, amplitudes are variable

3. The four sinusoids are harmonics; according to Fourier's theory, frequency steps (for the BAEP sampled at 256 points) are of 100 Hz

4. The phases of onset of the four sinusoids (in both simulations in Figs. 50 and 51) have a peculiar pattern. In Fourier's analysis, phases are variable and determined by whatever value is required to simulate a waveform; obtaining such a distinctive pattern (as in the BAEP simulations) would be remarkable

5. In the four sinusoids model, the 960 Hz sinusoid is damped, after about 6 msec (on the BAEP scale); Fourier's theory allows no damping. To reproduce its effect, a yet larger number of sinusoids, of varying frequencies and amplitudes must be added

The similarity, therefore, between the simulation model and Fourier's analysis is superficial. But, for the sake of argument, even if the simulation did require larger number of sinusoids, of variable amplitudes and frequencies, this by itself does not mean that the BAEP does not originate in that way. In fact, because Fourier's theory states that every signal can be decomposed into sinusoids, it does not mean that no signal whatever originates from the superimposition of oscillations. A musical tone, otherwise, would cease to be generated by vibrations.

The next step was to see if this model can explain other BAEP waveforms. This was done by changing the phases of the sinusoids and their durations. The bases for this are: (1) the marked changes in the BAEP, produced by reversing click polarity, are caused by change in phase of oscillations; (2) oscillations must die down at some point. And because they are of different frequencies, these damping points are also likely to be different.

Thus, in another BAEP, different forms and amplitude ratios of waves I through V, produced by the two click phases, are simulated (Fig. 51). In these simulations, it is noted that the phase differences between corresponding sinusoids show an interesting pattern. The shift (in pi radians) for the 120 Hz sinusoid is 1/4, for the 240 Hz, 1/2; and for the 480 and 960 Hz, roughly 1 pi radian (180°) each. This is significant since, on reversing polarity, the sound waves in the click also invert by 180°. It is also noted that, on subtraction between BAEP to the two click polarities, the difference is composed largely of these oscillations. Thus, from the simulation it is seen that the phase shift is least for the lowest frequency, increases by steps of multiples of 2 for the succeeding two oscillations (whose frequencies also double), until it reaches the maximum of 180° with the third sinusoid. The mechanism behind this pattern is probably related to cochlear function and may also explain the controversy in the literature concerning the degree of latency shifts caused by reversing click polarity.

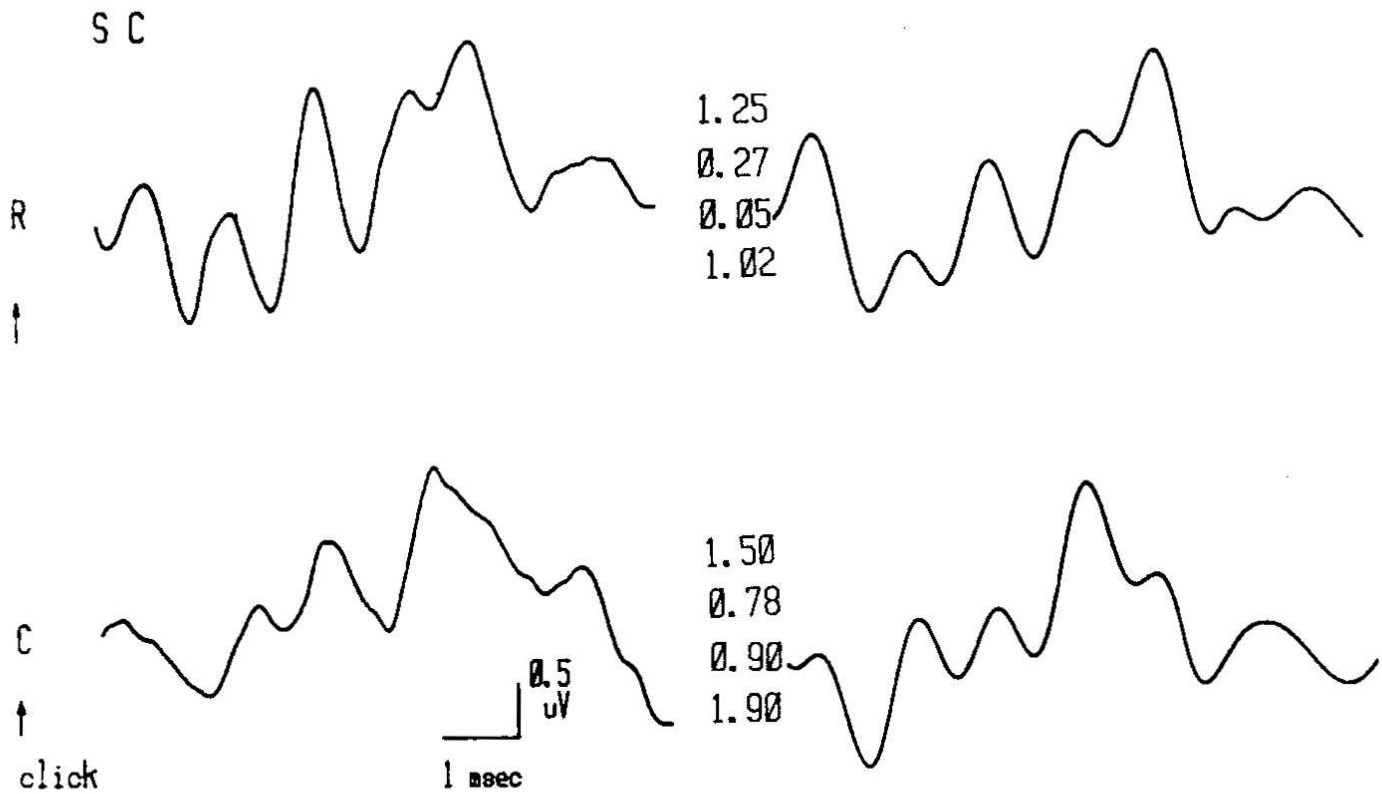


Fig. 51 Simulations of effect of click polarity

Normal BAEP (left) to two click polarities, and their simulations. Approximations are not exact but configurations and relative amplitudes of waves III, IV and V are reproduced.
Relative phases of sinusoids in simulations marked at begining. Differences in these phases show peculiar pattern: smallest difference for lowest frequency, doubles progressively with doubling of frequency, and reaches maximum with 480 and 960 Hz; largest phase shift in 960 Hz.

Interwave latencies I-III and III-V, are also mimicked by the simulations. For example, two mean normal values for waves I-III and III-V intervals (msec) are 2.1 and 1.9 and 2.13 and 1.94 (Chiappa, 1983a and Stockard and Stockard, 1983); the I-III/III-V ratio is 1.1. In the simulations, this ratio is also 1.1. Permutations (Fig. 52) based on what may happen in disease i.e. loss of an oscillation or slowing of its frequency, produce ratios actually observed in abnormal BAEP.

Admittedly, however, the four sinusoids model does not reproduce all BAEP variations. It is made up, after all, of perfect, computer-generated sine waves, and, apart from damping, their amplitudes and frequencies are rigidly fixed. The situation is unlikely to be the same in the nervous system. Furthermore, imperfections in recording, such as amplifier noise and distortion and electrical interference, in addition to EEG and EMG artefacts, complicate the BAEP waveform. If all these variables could ever be simulated, more variations of the BAEP may be accounted for. But by reproducing changes in the waveform (to click phases, for example), the model suggests the mechanism of its generation. As illustrated in the simulation, the first six waves at least, including wave V, are formed from the four oscillations.

Finally, the sinusoid hypothesis does not exclude the occurence of activity in brainstem nuclei and pathways as a result of the click. It does imply, however, that if these do occur, they are not recorded in the BAEP.

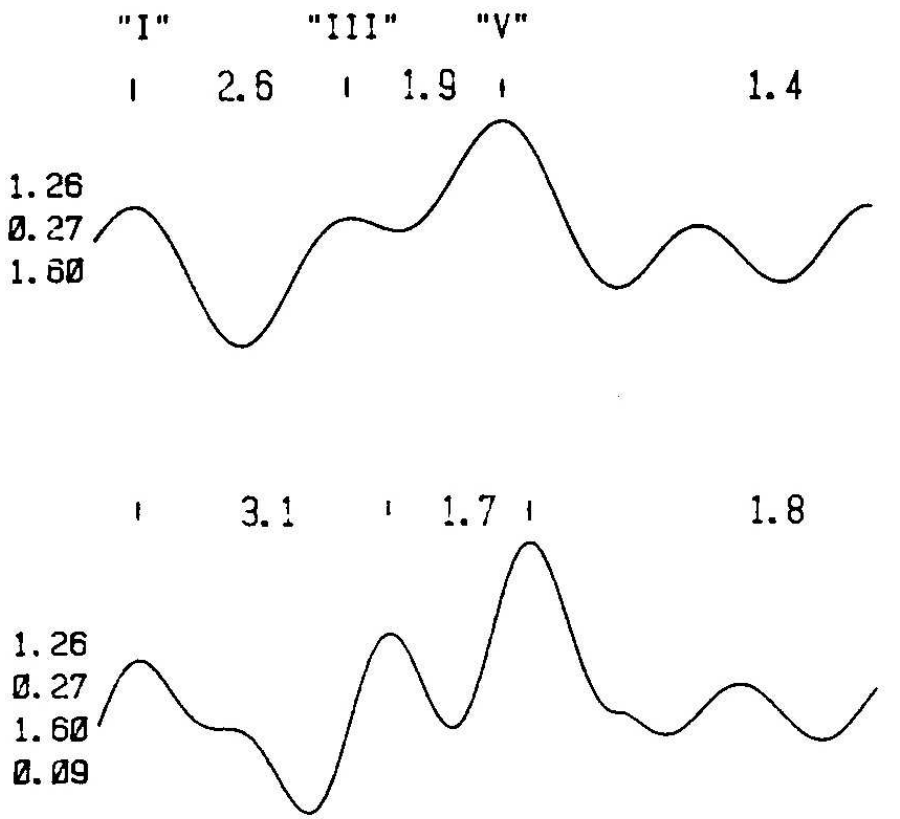


Fig.52- Simulations showing different ratios (far right) of I-III/III-V intervals. The upper is produced by omittig the fourth (960 Hz) sinusoid, and in the lower this sinusoid is replaced by one at 665 Hz, of the same amplitude. Relative phases (pi radians) are marked near the begining of the traces.

Analogies

Function in different parts of the CNS shows analogies that support the sinusoidal composition of the BAEP:

1. Møller and Jannetta (1982), recording several peaks separated by intervals of about 1 msec, from the inferior colliculus in man, inferred that this structure consists of more than one order of neurones. But the same observation may also be interpreted as cyclical discharges in the same group of neurones. In the turtle, for example, Nicoll and Jahr (1982) found that the olfactory bulb neurones show long-lasting depolarizations, giving rise to repetitive firing.

2. Frequency following potentials (FFP). When the click is replaced by a low frequency (<1000 Hz) tone burst, a sinusoidal potential is evoked which is strongly related to tone frequency. It begins about 6 msec from tone onset and is thought to be generated by the inferior colliculus (Sohmer et al., 1976). Merzenich et al. (1983) observed that, in the cat, the FFP originates from several sources, but principally from the cochlear nucleus. Similarly, the cochlear microphonics are sinusoidal potentials closely following the sound stimulus characteristics and thought to be generated by the outer hair cells of the cochlea (Ottoson, 1983).

3. In the flash evoked potential, the late component frequently shows a nearly perfect sine oscillation, and in the somatosensory evoked potential to a train of shocks, nearly perfect sine oscillations persist longer than the stimulus

train duration (Bezzera, 1984). Eisen et al. (1984), filtered out a sinusoidal component from the SEP. They thought it is related to recurrent intrathalamic oscillatory discharges. In fact, that sinusoidal component (Fig. 4 of their paper) is seen to be composed of two harmonic oscillations, and indeed, the SEP in the same figure resembles a BAEP.

4. In treatment with phenytoin (Green et al., 1982), barbiturate overdose, alcohol intoxication, hypothyroidism, (Sohmer, 1983), and MS, the BAEP shows increased peak and interpeak latencies, indirectly suggesting decreased oscillation frequency. In all these conditions, the EEG alpha rhythm is slow.

5. In infants, BAEP wave latencies are longer than in adults, and they are longer still in neonates (Starr et al., 1977). This is ascribed to slower axonal conduction. But why should there be a concomitant increase in the rise and fall time of waves? This broadening of waves, in fact, reflects slower frequencies of BAEP oscillations; in infants, EEG rhythms are slower (Niedermeyer, 1982). Similarly, in women the BAEP shows shorter absolute and interpeak latencies; their EEG has a higher frequency of the occipital alpha rhythm (Kellaway, 1979).

Given these analogies, it would be logical to assume that if function in one part of the nervous system takes the form of sinusoidal oscillations, other parts--including that generating the BAEP, for example--may also have the same property.

Frequency analysis

Having proposed that the BAEP is generated from superimposed oscillations, frequency analysis becomes the method of choice for its study.

For frequency analysis, however, several methods exist (Childers, 1978): Fast Fourier transform (FFT), maximum entropy, autoregression, maximum likelihood. These methods, in turn, can be performed by different procedures. The FFT, for example, can be applied using autocorrelation methods (four different ones) and direct methods (four also), and maximum entropy can be performed using Burgs or Barrodale & Erickson algorithms. The purpose of this listing is only to show that none of these methods gives perfect results.

Of these methods also, the FFT is the oldest and perhaps the best known. As for the newer methods, which are thought (Childers, 1978) to have superior resolution for signals with narrow separation between frequency components (as in the BAEP),* appropriate computing programmes do not yet exist, at Oxford's University Computing Service at least. The FFT, therefore, was used to study the normal BAEP I have collected.

* Maximum entropy (the most recently developed), is currently being tried on the BAEP and its simulation, but results have so far proved inferior to those of the FFT.

Discussion 27

At first, FFT was applied using standard values for autocovariance lag. Rules determining this "standard" value merit some detail and are perhaps best described in the following quotation from Chatfield (1980):

> The choice of the [autocovariance lag], M, is rather difficult and little clear-cut advice is available in the literature. It has to be chosen subjectively so as to balance 'resolution' against 'variance'. The smaller the value of M, the smaller will be the variance of f (w) but the larger will be the bias... If M is too small, important features of f (w) may be smoothed out, while if M is too large the behaviour of f (w) becomes more like that of the periodogram with erratic variation. Thus a compromise value must be chosen. A useful rough guide is to choose M to be about 2 $\sqrt{N}$...
> [And for making the compromise] ...experience is the real teacher and that cannot be got from a book'.

According to the guide above, the value of the autocovariance lag would be 32. Yet, the FFT with this value would only resolve a continuous spectrum, extending from a peak magnitude at the frequency band of zero to a minimum at about 2000 Hz (Fig. 53). But when later a BAEP was simulated, with only four sine waves of known amplitudes and frequencies, that BAEP and its simulation provided good waveforms for testing the application of the FFT. Again, using the "standard" lag value of 32, results were a continuous spectrum, with peak at zero and minimum at 2000 Hz.

Trials, therefore, with different lag values were made for arriving at one which resolved distinct frequency bands (Fig. 53). This was found to be 200. It is noted that with this large value, precision of the FFT decreases, but compromise had to be made for the sake of resolution. Application of the FFT, with this new parameter, to normal BAEPs now showed three frequency peaks, roughly at 240, 480 and 960 Hz (Figs. 55-59). These are

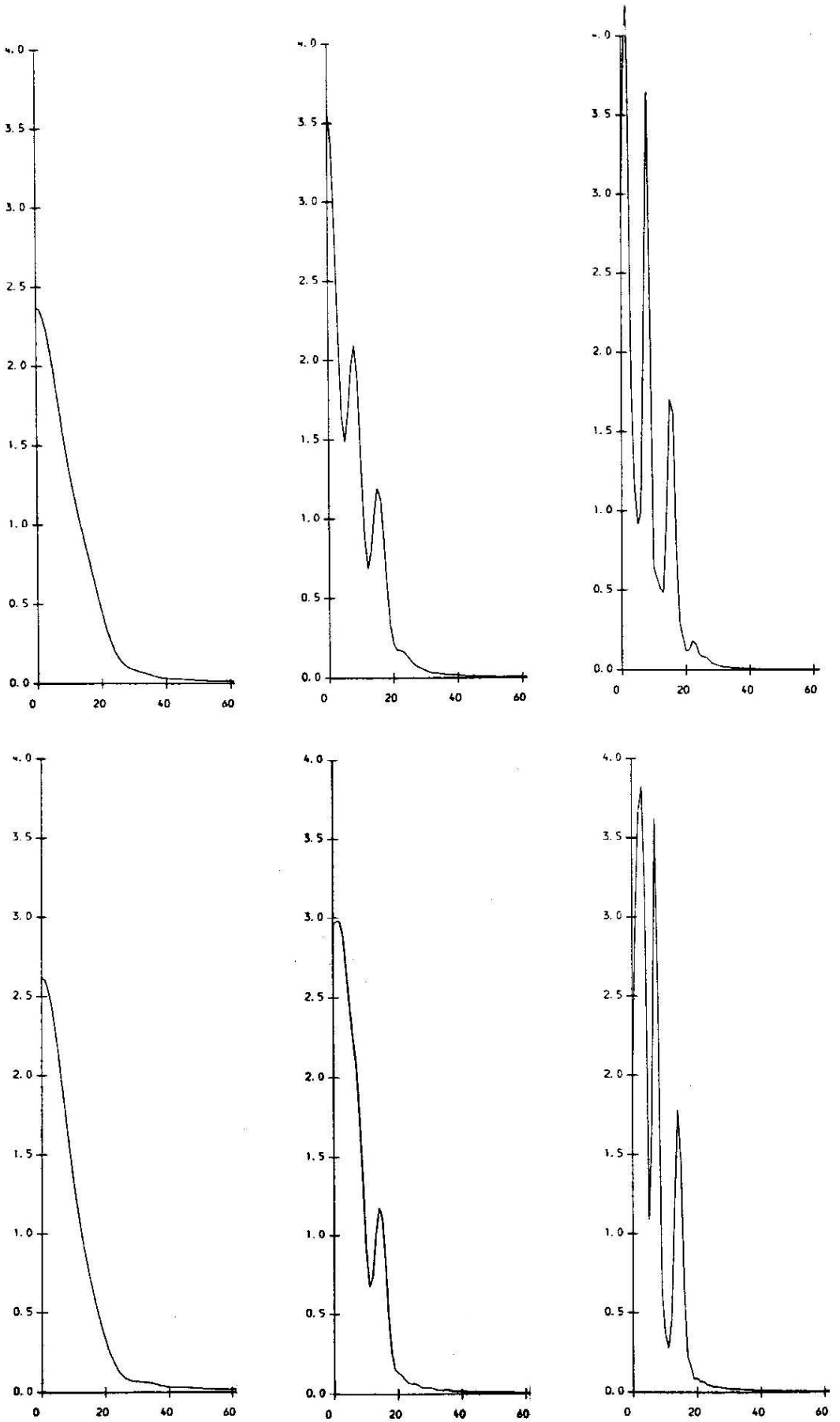


Fig. **53** Spectral density estimates with different FFT autocorrelation lags

Lag values are 32 (left), 80 (middle) and 200 (right).
Top: FFT applied on simulation; bottom: on normal BAEP.
On ordinate, 20 corresponds to 1.28KHz.

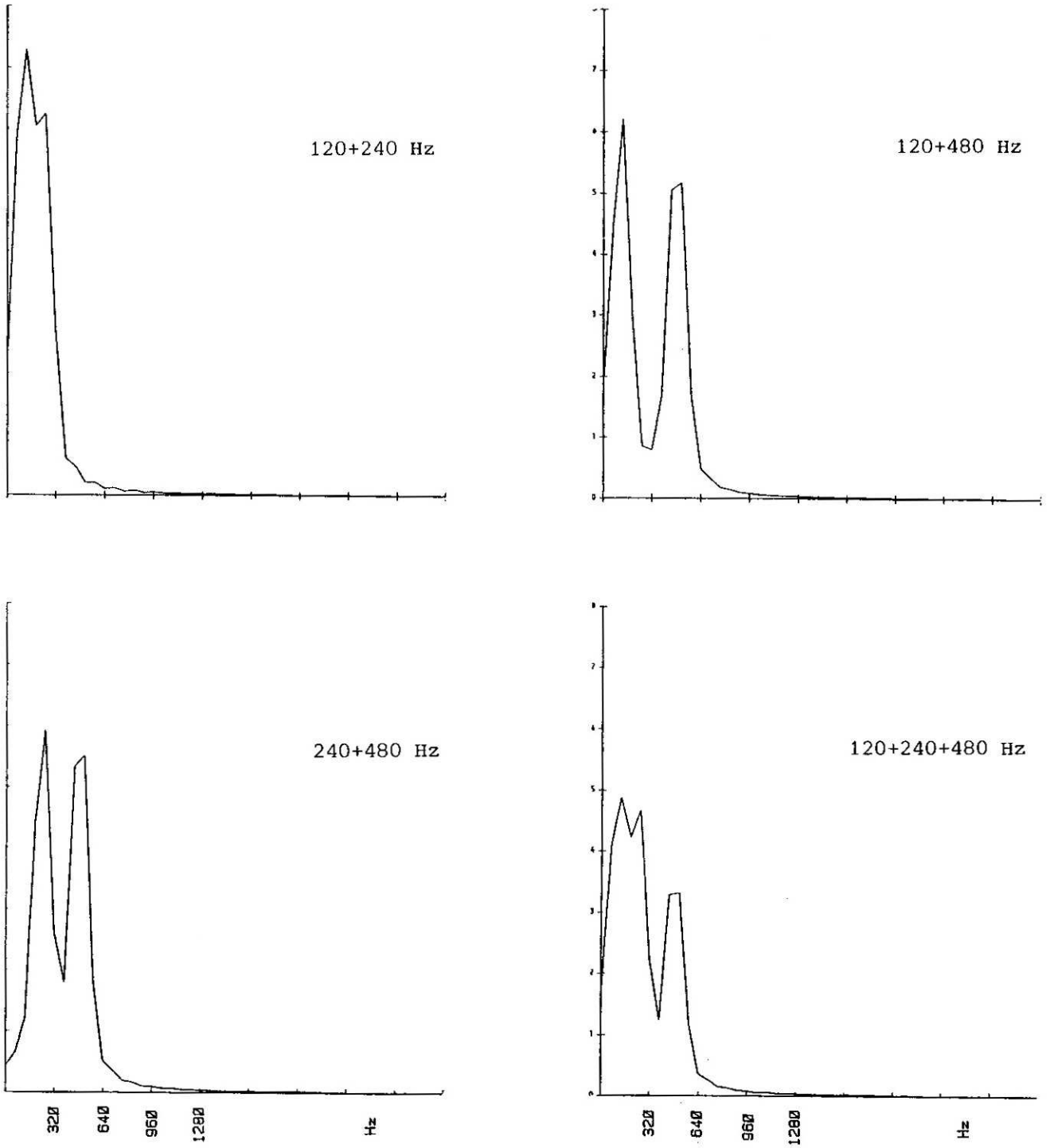


Fig. 54 Spectral density estimate on sine waves

Because of leakage and frequency scale steps, resolution of 120+240 Hz is low.

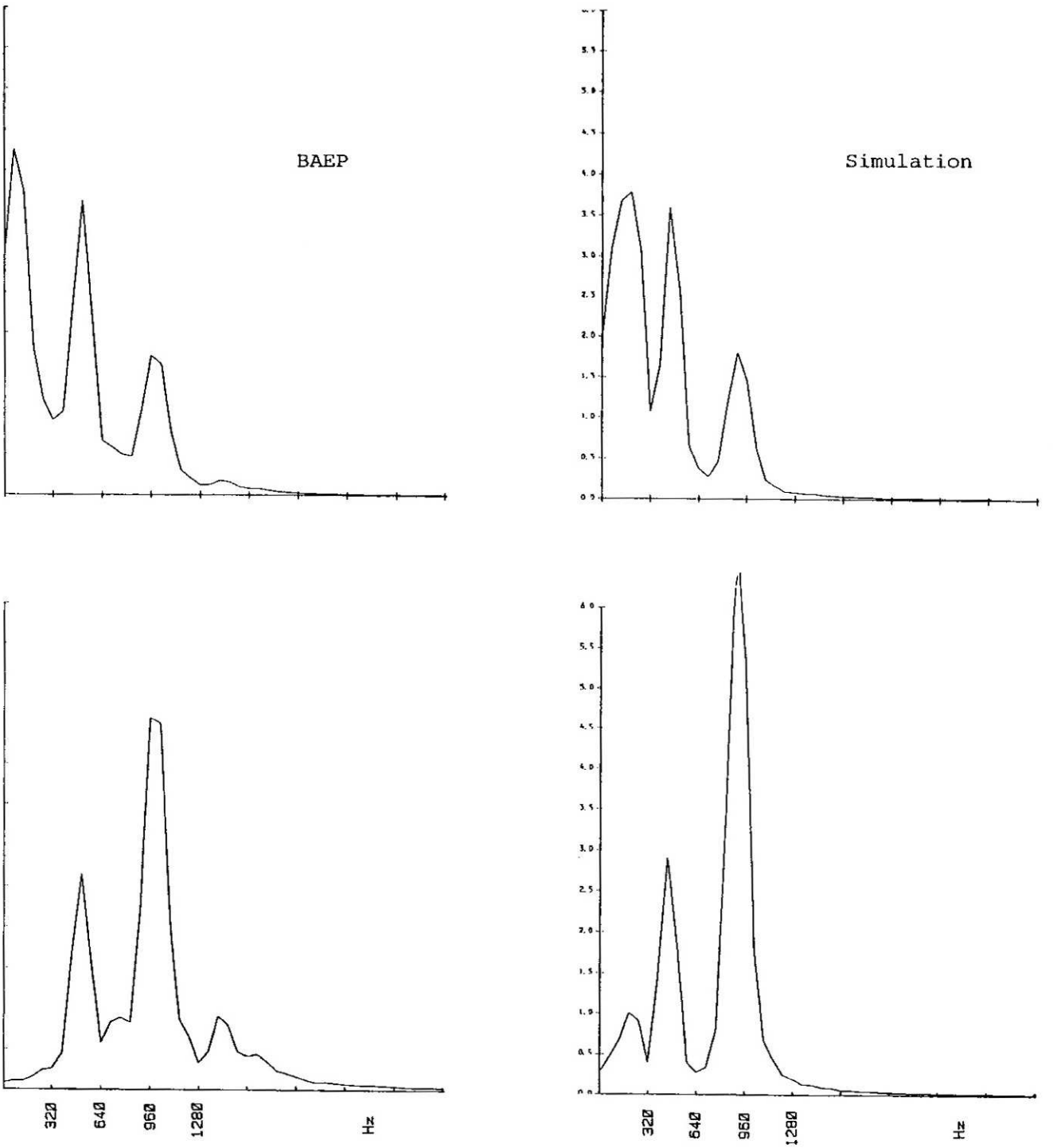


Fig. 55 Spectral density estimate on normal BAEP (left) and its simulation.

Top: original BAEP and unfiltered simulation
Bottom: after application of first-order differencing filter.

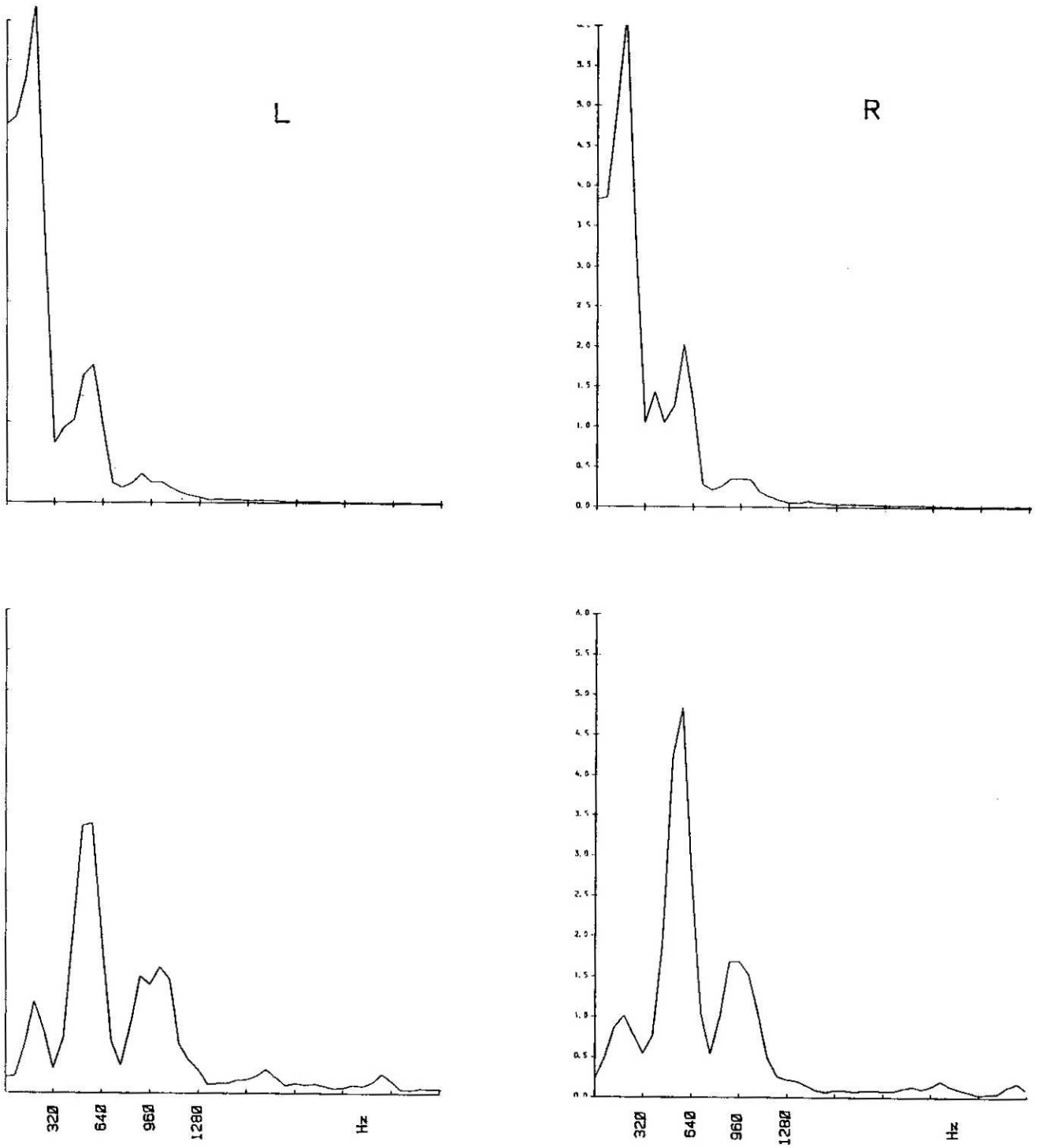


Fig. 56 Spectral density estimate on normal BAEP

Man (MA),37.
Top: original BAEP from two ears
Bottom: after application of first-order differencing filter.

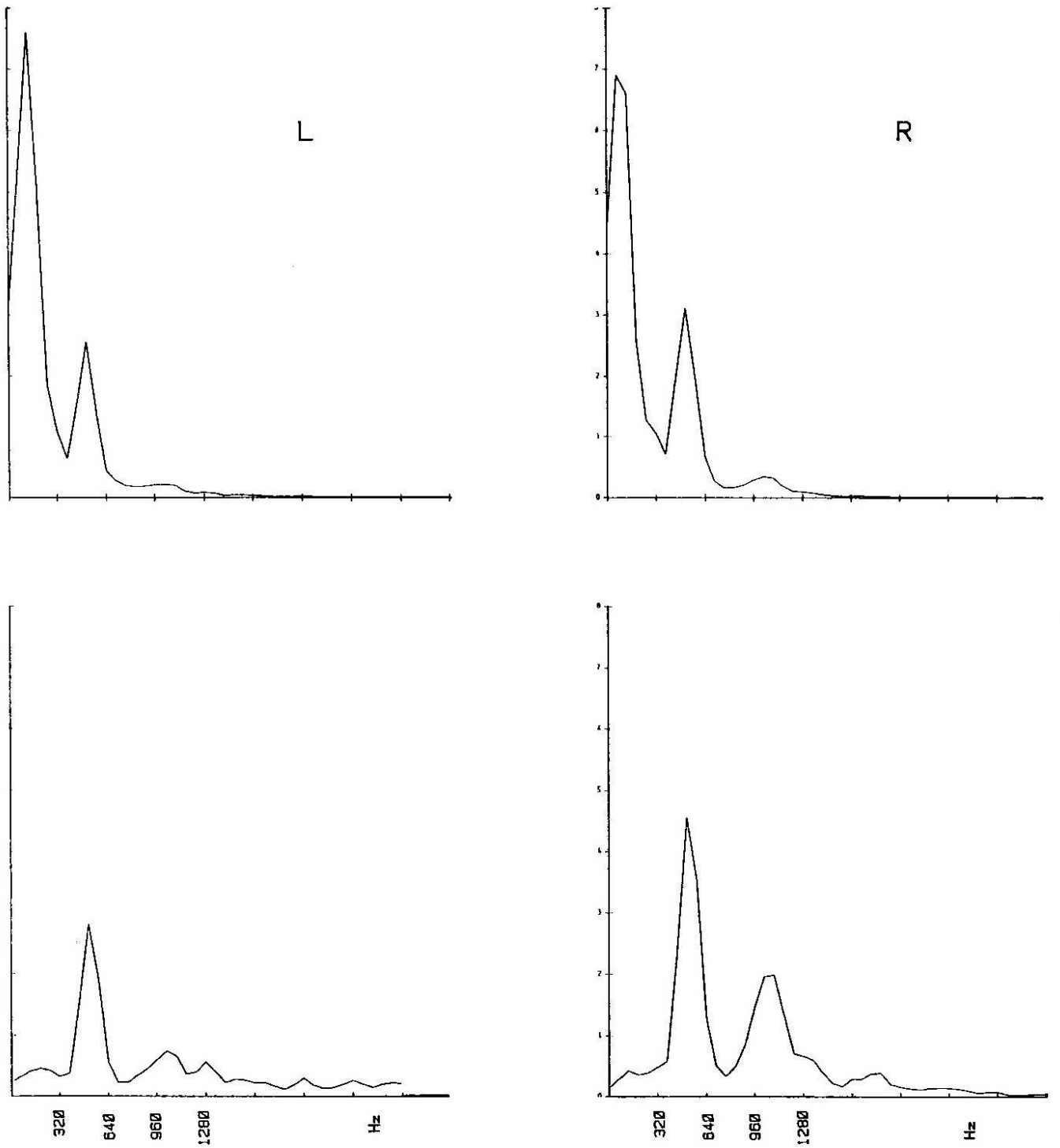


Fig. 57 Spectral density estimate on normal BAEP

Woman (LC),24.
Top: original BAEP from two ears
Bottom: after application of first-oreder differencing filter.

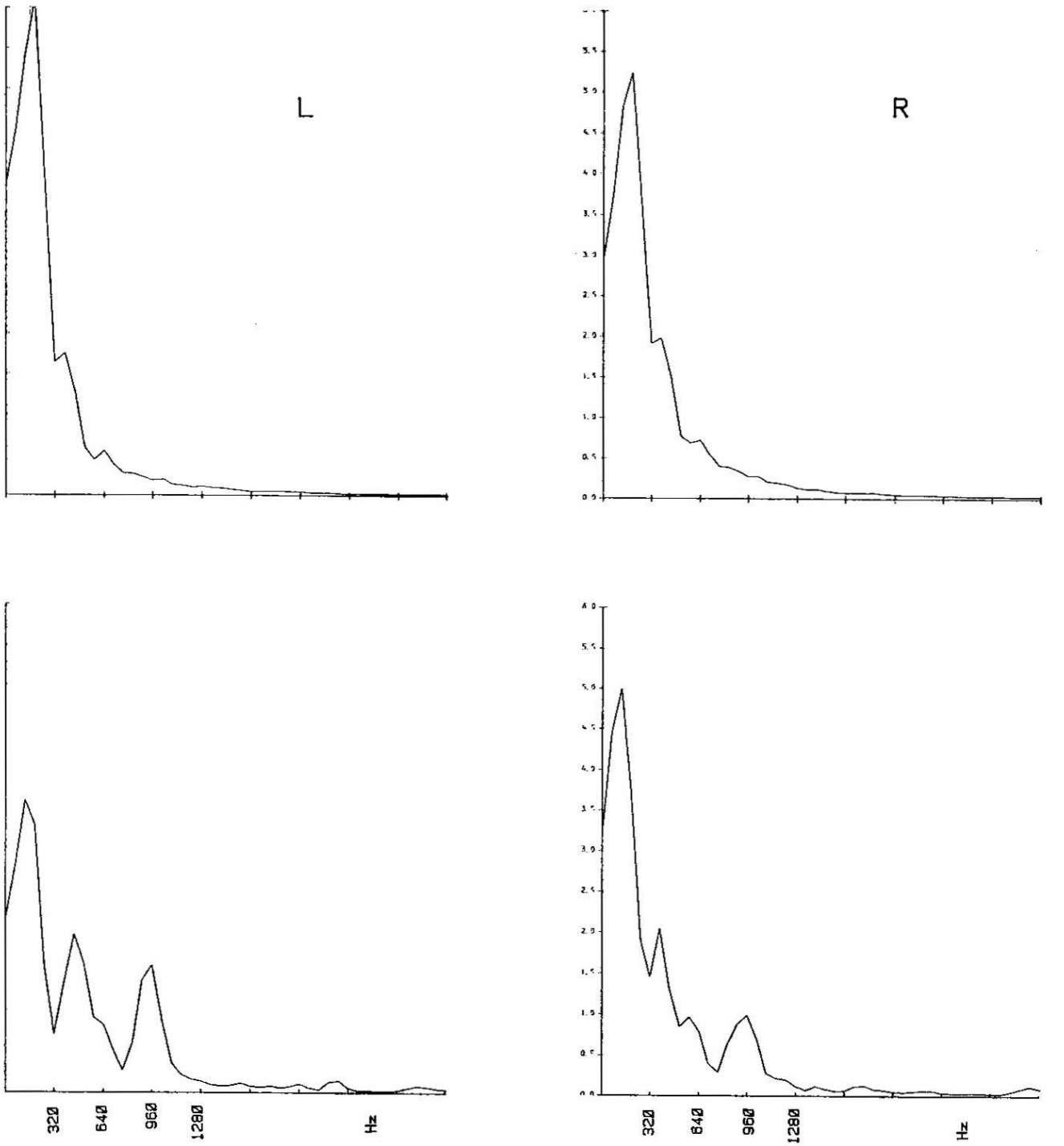


Fig. 58 Spectral density estimate on normal BAEP

Man (JA),26.
Top: original BAEP from two ears
Bottom: after application of first-order differencing filter.

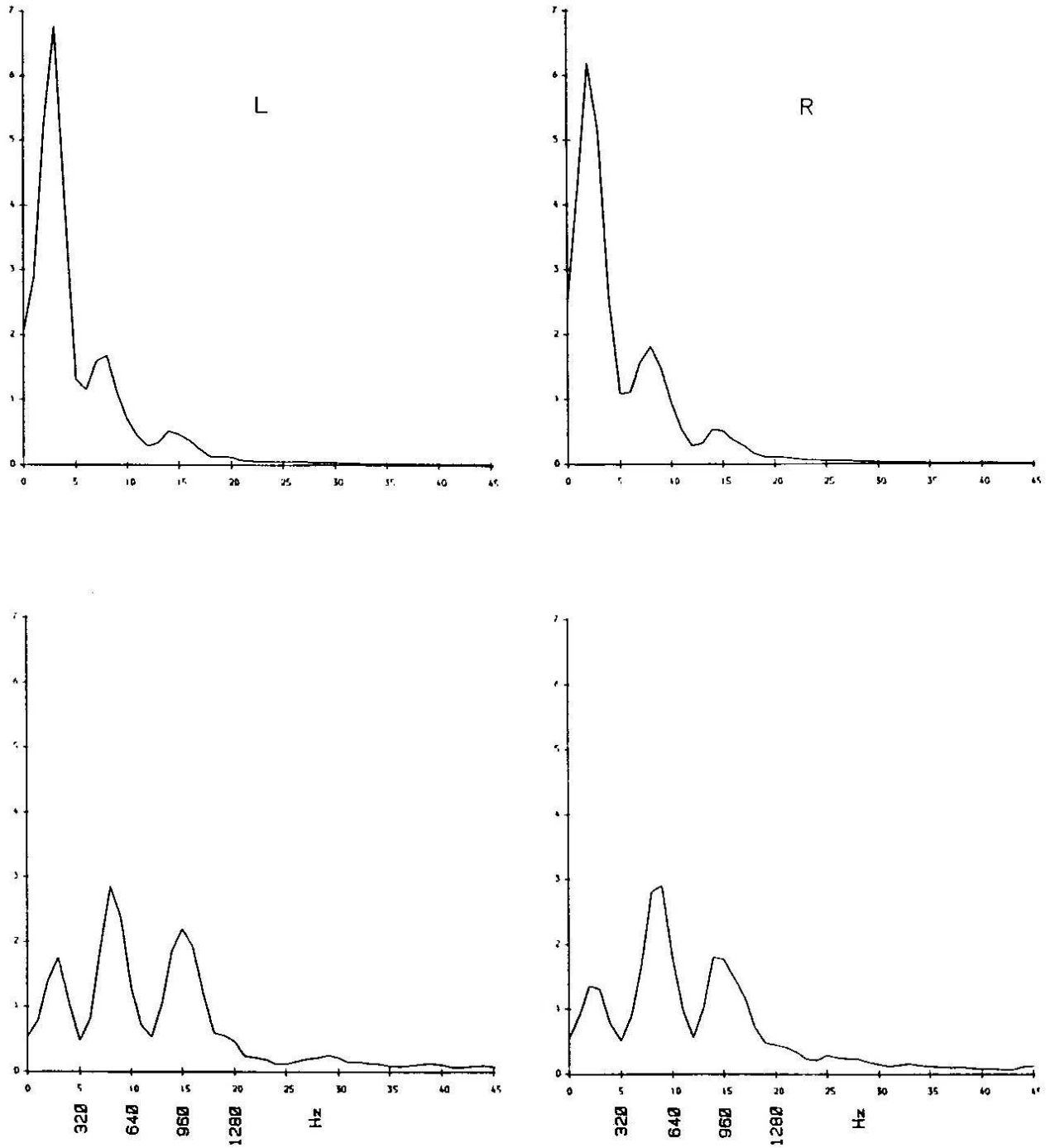


Fig. 59 Spectral density estimate on normal BAEP

Average of ipsilateral monaural records from six healthy persons.

Top: on original BAEP

Bottom: after application of first-order differencing filter.

the exact frequencies of the 2nd, 3rd and 4th sinusoids in the simulation. But what about the first simusoid?

To answer this question, it is necessary to discuss the limitations of the FFT (Ramirez, 1975), as far as the BAEP is concerned:

1. "Leakage" error: This error "...takes power from components existing in the continuous waveform and gives power to frequency components that don't exist in the continuous waveform." It occurs when the waveform contains non-integer number of cycles of some frequency components. In the BAEP, this may occur with all the component oscillations (because of "window" effect), but it is also bound to occur with that of 120 c/s, because this oscillation could only be present in the BAEP (10msec) in non-integer number of cycles. Thus, power would be taken from that 120 c/s and added either to a lower or higher bands.

2. Mean value of the signal. For amplitude resolution, the FFT works better if the signal has zero mean. But because the BAEP has low frequency oscillations (present in less than one complete cycle), its mean would not be zero and amplitude resolution of BAEP oscillations, therefore, decreases.

3. Resolution of the FFT. This partially depends on the number of points used in sampling the BAEP; the higher the number relative to that needed for resolve the highest frequency in a signal, the lower the resolution. The opposite is true for

resolution in the time domain, that is for latency measurement. But as I thought that latency was the mainstay in BAEP analysis, I sampled it with 256 points. (Attempts to apply the FFT on alternate points of the BAEP, in the University's computer, failed.)

4. Frequency scale of the FFT. Frequency bands, from zero to Nyquist frequency, are spread on the FFT scale in linear steps. Thus, from 100 to 200 Hz there is one step; from 200 to 400 Hz, three steps. Combined with the effects of leakage and mean, these scale steps impair resolution of the 120 Hz component. To test for this effect, the FFT was applied to only the first two sinusoids (added) of the simulation model. The result shows that, even with these computer-generated sine waves of exactly equal amplitudes and exactly doubling frequency, FFT resolves only a single peak, at 240Hz. But when applied to the 120 and 480Hz, and the 240 and 480 Hz sinusoids, two distinct peaks are resolved (Fig. 54).

Fridman et al. (1982) applied FFT to the BAEP, but on an empirical basis. They were looking for the labile spectral components (which they considered artefacts) so that a digital filter could be devised to remove them, and thereby improve automatic latency measurement. They found the main spectral component of the BAEP at 900 Hz. Similarly, Boston (1981) applied the FFT for defining the effect of filters on latencies and amplitudes. His results, however, are closely similar to those presented here: three components: around 100, 500 and 1000 Hz.

Discussion 30

Figs. 55-64 are representative of applying the FFT (with autocorrelation lag value of 200) to the ipsilateral monaural BAEP. For each person, two sets of results are shown: one on the original BAEP, and the other on the BAEP after applying a "first-order differencing" filter (Method p.4), which removes very low frequencies. In both sets (in the normal BAEP), three oscillations are resolved: roughly 200, 500, and 900 Hz. This gives further support to the simulation model and the oscillatory origin of the BAEP.

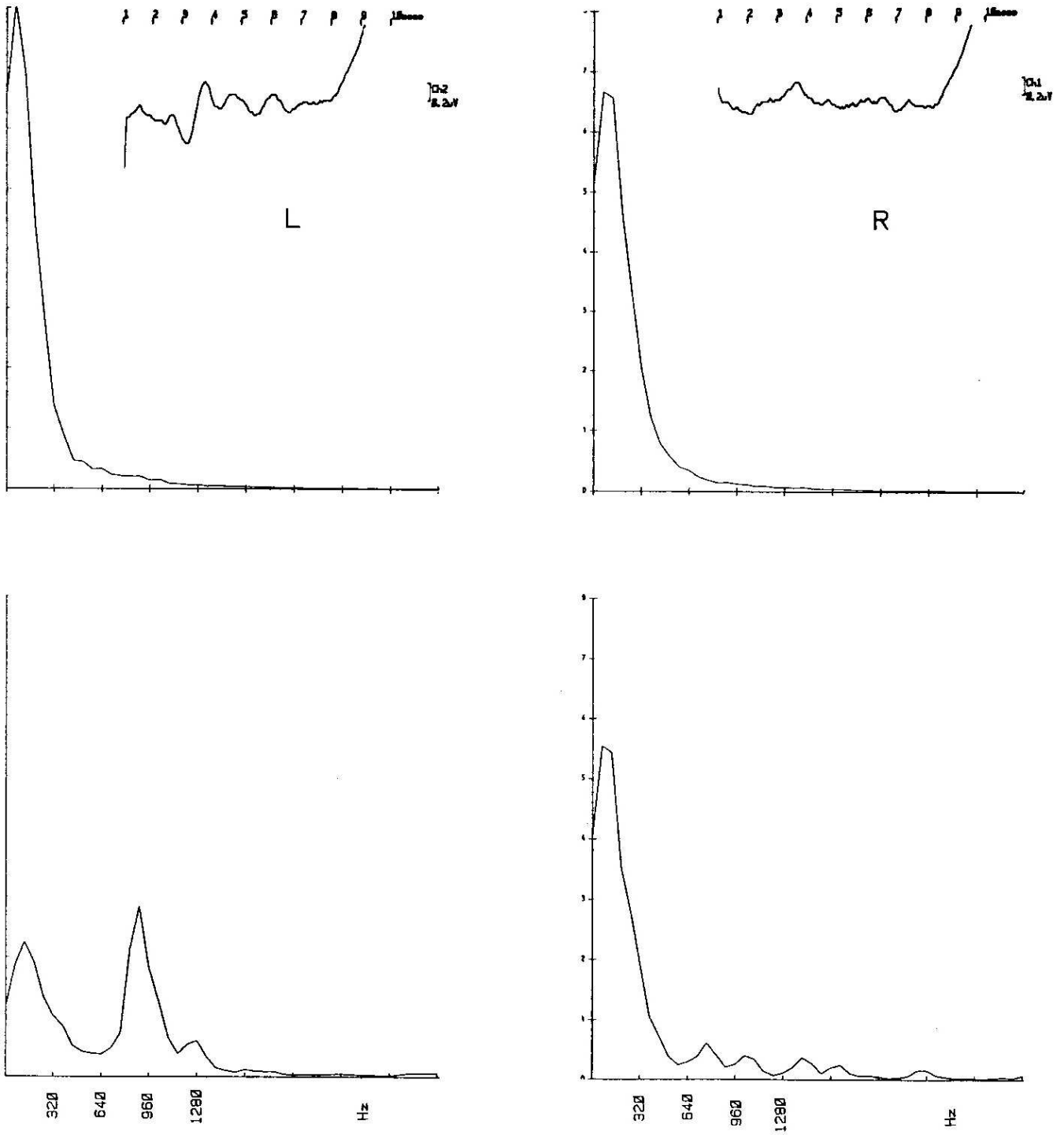


Fig. 60 Spectral density estimate on abnormal BAEP

Woman (NJ),63, investigated for ?demyelinating disease.
Top: on original BAEP from two ears
Bottom: after application of first-order differencing filter.

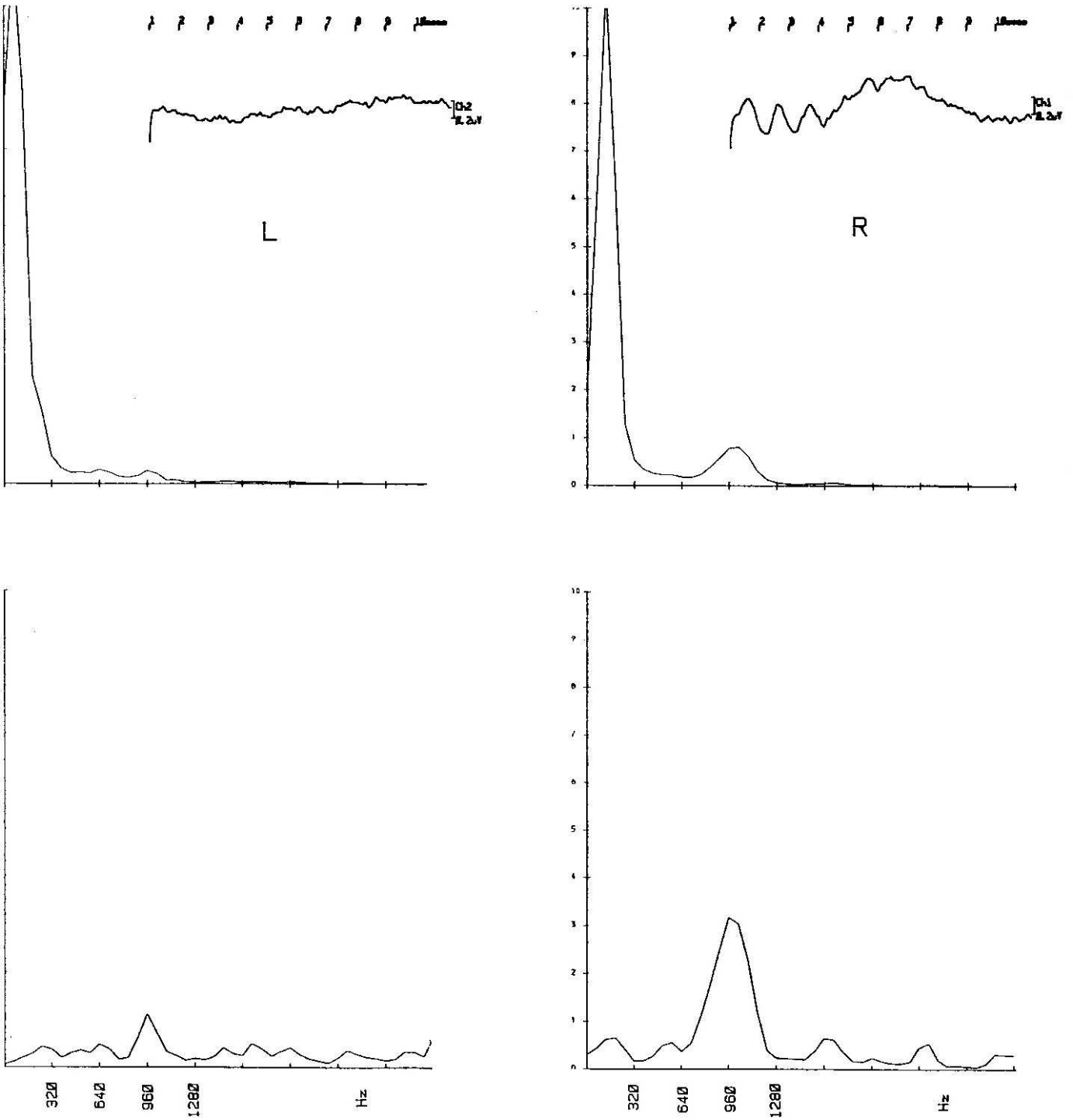


Fig. 61 Spectral density estimate on abnormal BAEP.

Man (SP),33, with MS confined to spinal cord.
Top: on original BAEP from two ears
Bottom: after application of first-order differencing filter.

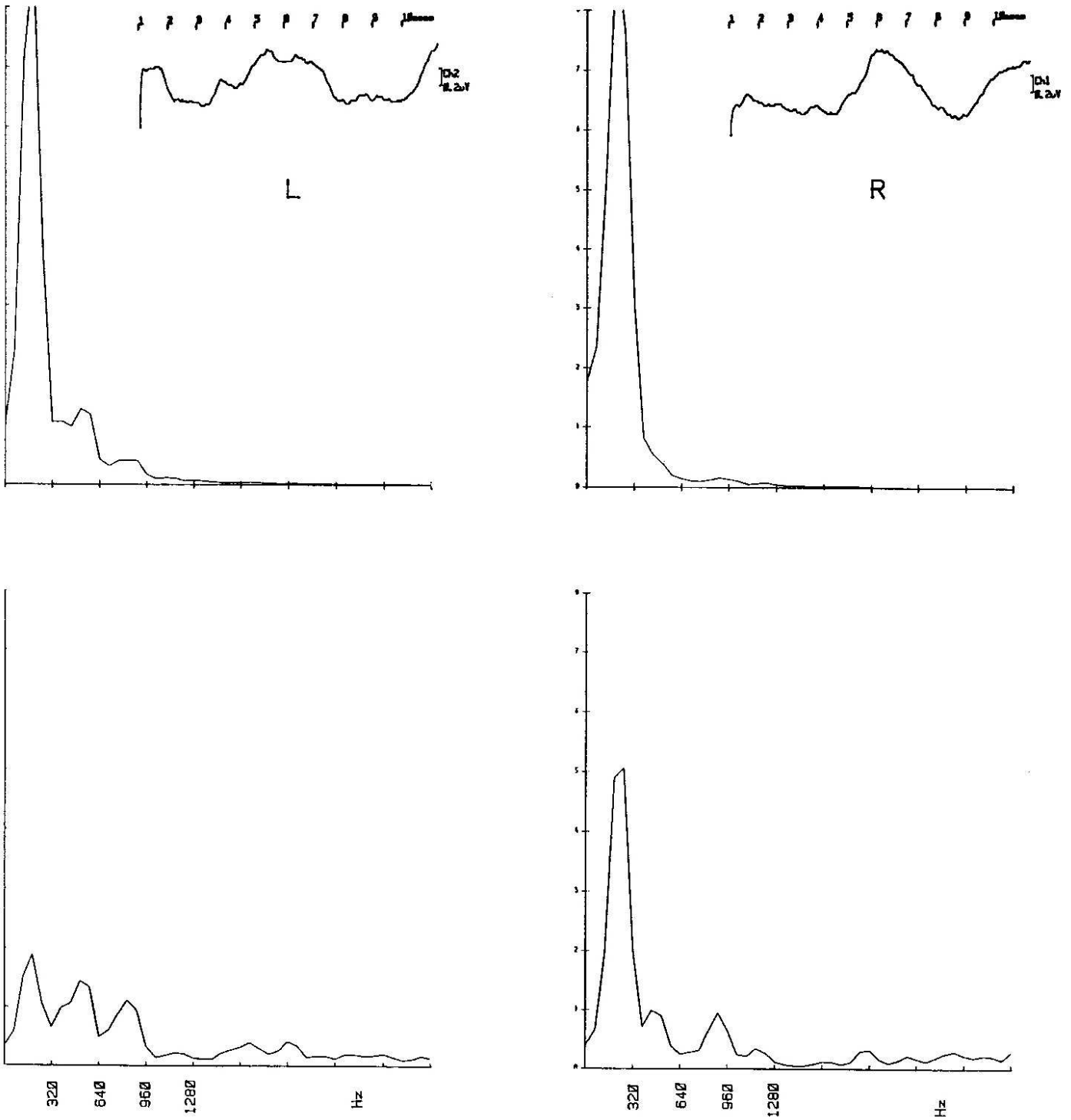


Fig. 62 Spectral density estimate on abnormal BAEP

Woman (AK),38, with MS.
Top: on original BAEP
Bottom: after application of first order differencing filter.

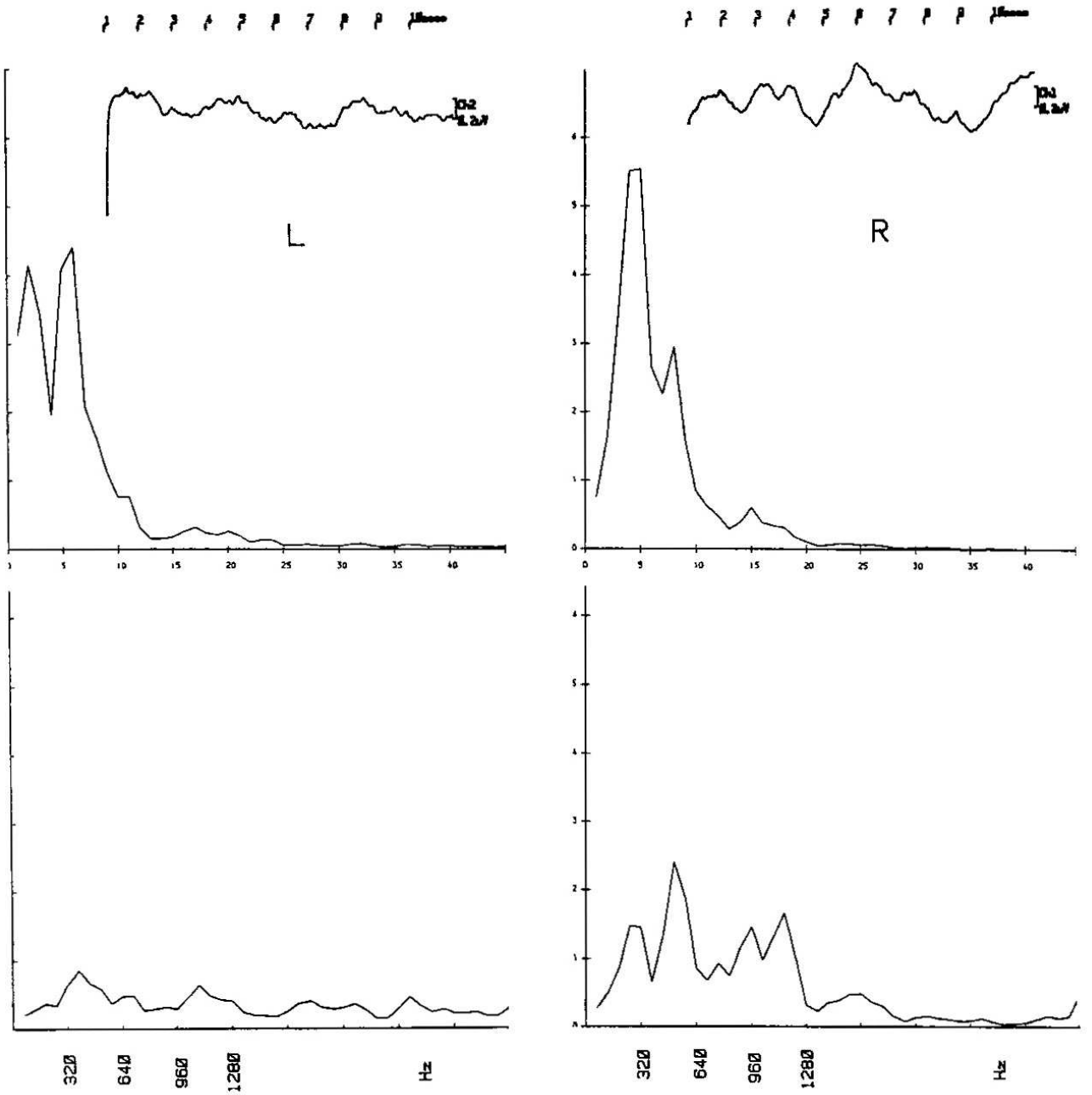


Fig. 63 Spectral density estimate on abnormal BAEP

Man (CF), 49, with possible MS.
Top: on original BAEP
Bottom: after application of first order differencing filter.

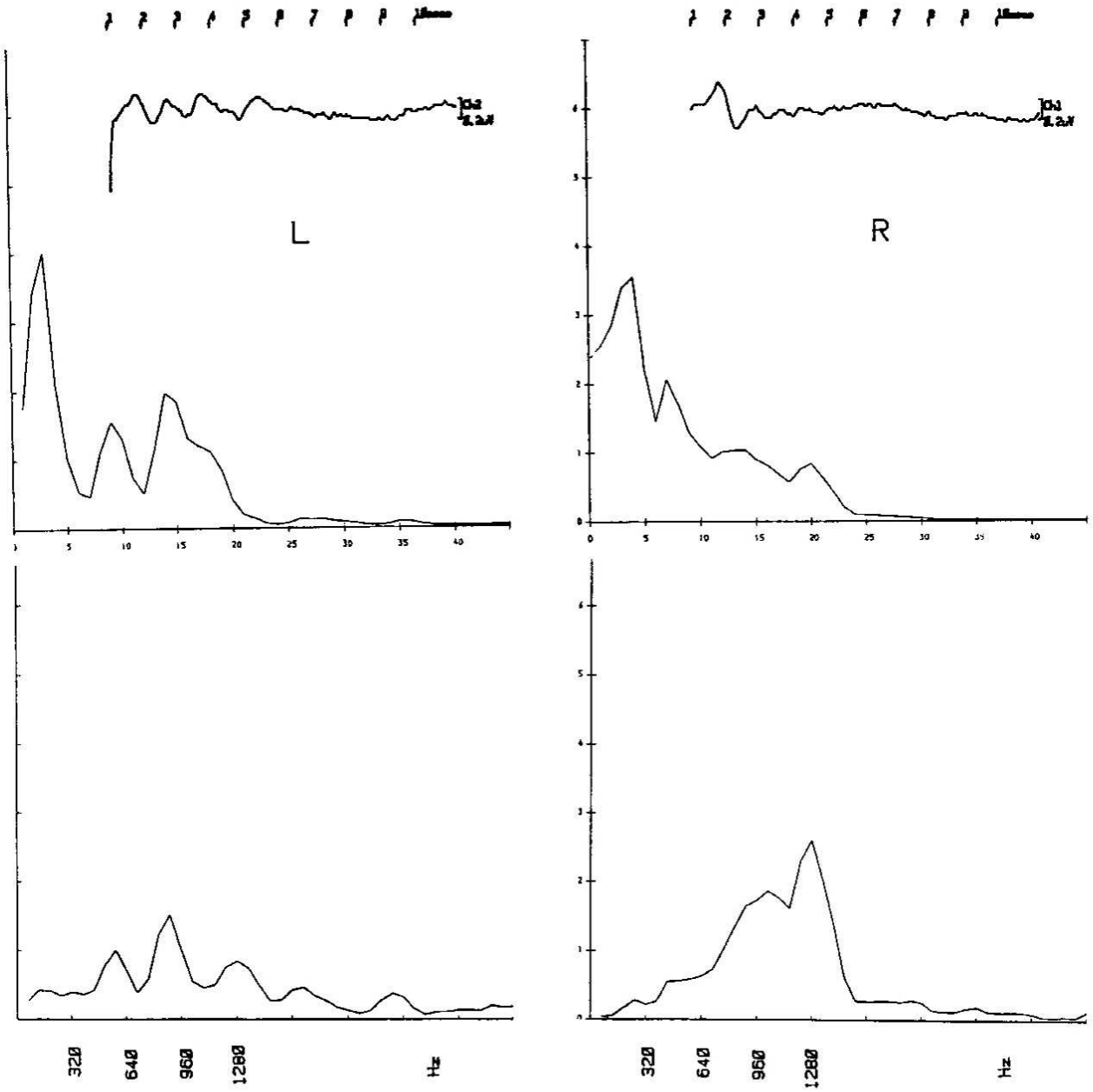


Fig. 64 Spectral density estimate on abnormal BAEP

Woman (BB), 37, with brainstem tumour.
Top: on original BAEP
Bottom: after application of first order differencing filter.

IMPLICATIONS

The hypothesis that the BAEP consists of superimposed oscillations has the following implications for origin, normal variation, recording and interpretation of the BAEP in disease:

Implications for origin

1. BAEP oscillations begin simultaneously. They are, therefore, likely to originate from a single structure. And because they have different frequencies and independently variable phases, that structure is likely to consist of several groups of neurones.

2. Since these oscillations begin in less than 0.4 msec after the click--the figure is probably shorter, but it is difficult to determine because of the stimulus artefact--their origin is likely to be peripheral. This is based on the following calculation:
   a) Conduction velocity in the cochlear nerve, according to two estimates, ranges from 10 to 20 m/s and 12 to 25 m/s, and length of the nerve in adult man is 16 to 19 mm and 20 to 24 mm (Garg et al., 1982 and Spire et al., 1982)
   b) From these ranges, taking the upper limit of velocity and the lower of length, in 0.4 msec a nerve volley would not have enough time to traverse the full length of the cochlear nerve

Given this assumption, and granted that nerve fibers (in the cochlear nerve) are unknown to produce oscillations, the cochlea becomes the structure that best fits the criteria for the BAEP generator.

The following phenomena support this speculation:

1. Jewett et al. (1971) found that "The ear canal was the only location (compared to other scalp locations) in which small changes in electrode position significantly affected the [BAEP] waves." This observation suggests that the generator of these waves is close to the ipsilateral ear canal

2. The cochlear hair cells are known to respond to different sound frequencies by producing neuronal oscillations

3. Clicks with different acoustic waveform produce different BAEP

4. Although in MS--where the BAEP may certainly be abnormal--the cochlea is not known to be affected, there is growing evidence that this disease does affect the peripheral nervous system (Hopf and Eysholdt, 1978 and Weir et al., 1980)

5. In Meniere's disease, which affects the peripheral vestibular system, the BAEP may be abnormal (Fig. 65). In that BAEP, although I-V latency is normal, the waveform appears abnormal; the abnormality can be explained on the basis of oscillations. Two examples from the literature, which describe normal BAEP in this disease, rely (for detecting

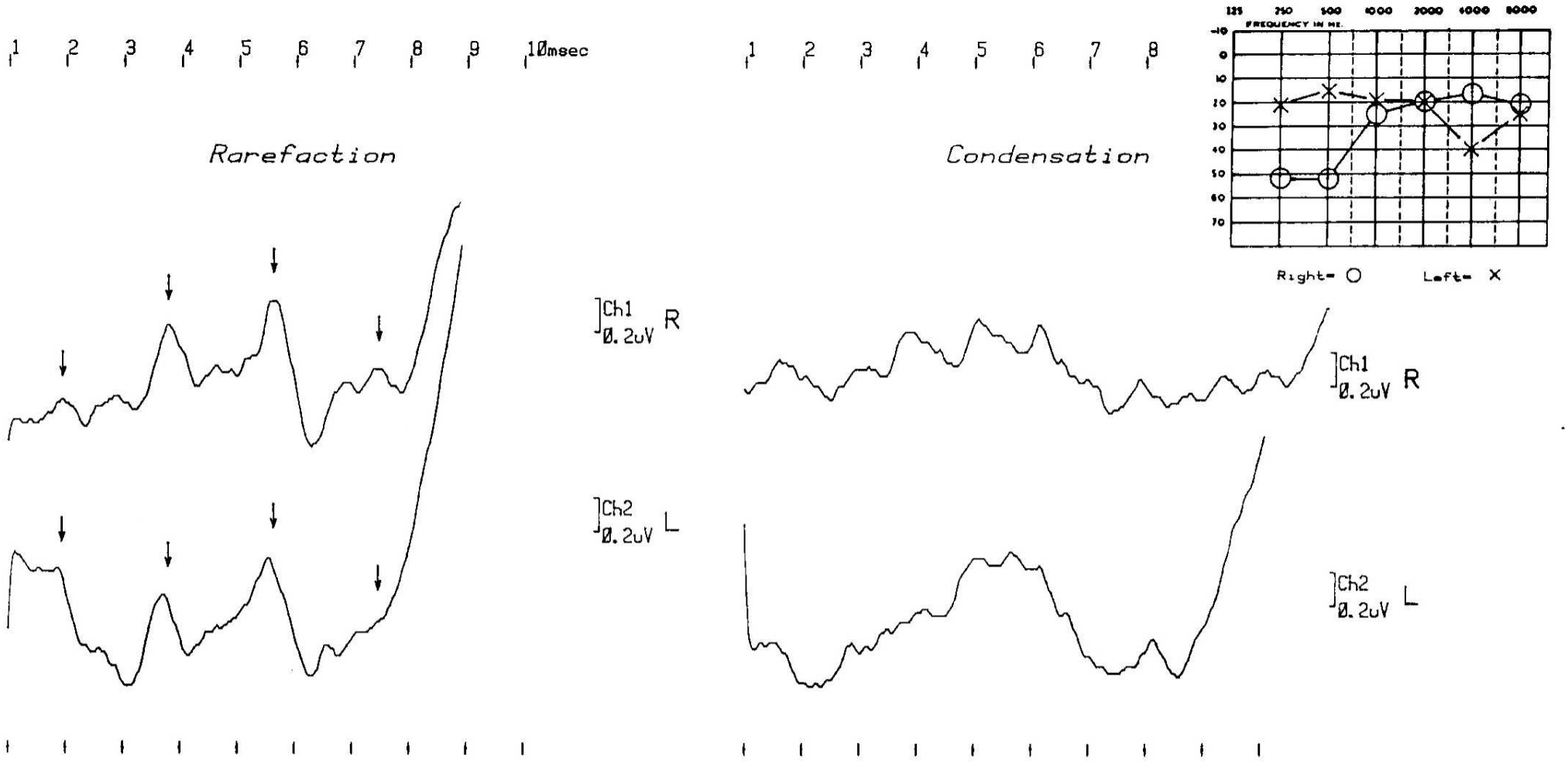


Fig. 65 Relation between cochlea and BAEP

Woman (ME), 29, with Meniere's disease.
On rarefaction, waves I, III and V (540 c/s oscillation, arrows) are well formed, with normal peak and interpeak latencies. BAEP waveforms, however, are abnormal; waves II and IV (>1000 c/s) are reduced and differences between click polarity are marked. The 120 c/s oscillation is also more pronounced on the left side. Audiogram (inset) shows that hearing acuity for low frequencies is also better on the left.

abnormality) only on interpeak latency I-V (Chiappa, 1983b and Robinson and Rudge, 1982).

Nevertheless, it is noted that:

1. The BAEP is known to be abnormal in patients with normal hearing. But this observation must be qualified. For example, Hausler and Levine (1980) found that such patients, on psychophysical testing, are likely to have impaired sound localization. Furthermore, audiometric tests are not failproof. Their results (in MS patients with abnormal BAEP) are sometimes "not clearly understood"; the patients in Figs. 34 and 66 are examples.

2. Cerebellopontine angle tumours: In tumours arising from or close to the VIII nerve, the BAEP is often abnormal, especially from the ear on the side of the growth. A variety of abnormal patterns are noted, such as absence of all the waves or only some of them, where only wave I may be visible. The criterion most often looked for, however, especially in early presentation, is an increase in the interpeak latencies I-III, III-V or I-V (Chiappa, 1983). When the tumour is large, the BAEP may also be abnormal from the opposite ear. This may seem to contradcit the speculation of the cochlear origin of the BAEP, since, when the traditional hypothsis is held, these abnormalities are easily explained by the tumour pressing on the VIII nerve, or the adjacent brainstem, thereby impairing the passage of information through the auditory pathways (Robinson and Rudge, 1982).

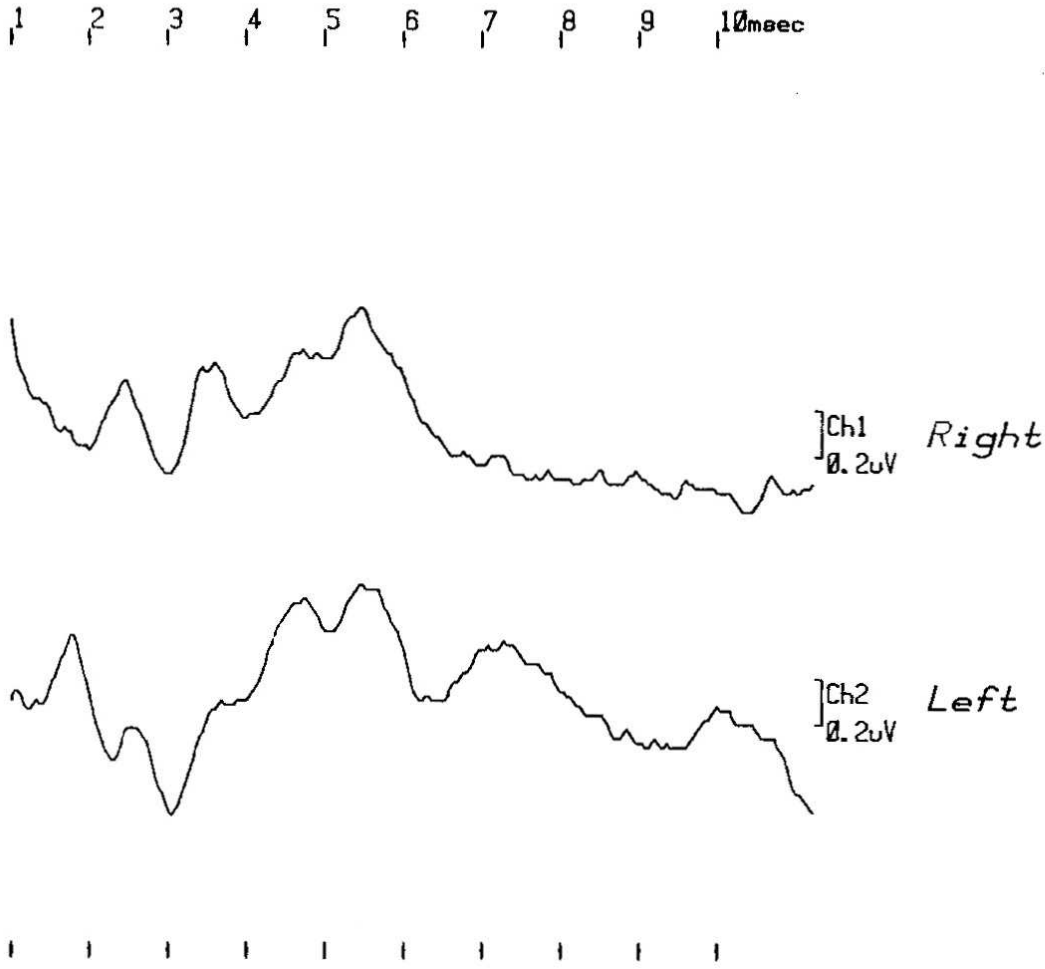


Fig. 66 Deafness and wave I

Woman (MP), 45, with MS. Records to binaural rarefaction clicks show wave I on left side, which had 10 dB higher click-hearing threshold than right. Audiogram showed "moderate sensori-neural deafness affecting the left ear with an average 40% loss of hearing. On the right side, there is a quite different graph, which shows a moderate conductive deafness and a high tone sensori-neural deafness, which ...[is not understood]..." Wave I is absent on the right side.

Nevertheless, it is noted that these tumours, even when small, may disrupt the blood supply of the cochlea, and most of these patients have progressive hearing loss; in 37 patients with acoustic neuromas studied by Robinson and Rudge (1983), all had auditory symptoms and signs and in 69% of them the hearing loss exceeded 70 dB. In addition, although it is claimed that the BAEP abnormality in cerebellopontine angle tumours is different from that een in cochlear hearing loss (Chiappa, 1983), Robinson and Rudge (1983) cite examples, from three sources, of BAEP abnormality in the hearing loss of Meniere's disease, which was difficult to differentiate from the abnormality seen in retrocochlear deafness.

3. This speculation on the cochlea as the generator also depends on the accuracy of the anatomical and physiological data above.

In conclusion, BAEP oscillations are likely to originate in a structure outside the brainstem, probably the cochlea, yet they are not directly related to neural transmission of sound. The observation that best supports both these statements simultaneously is that marked changes in the BAEP are produced by the two click polarities, the difference between which is subjectively imperceptible.

Explaining normal BAEP phenomena

The following points might have more appropriately been discussed earlier, with those pointing to the alternative hypothesis of origin. This discussion has been deferred, however, because the explanations suggested require reference to the simulation model.

1. Oscillations account for the ambiguity in the literature in setting limits for the normal amplitude ratios between waves, e.g. V/I. This is because small phase shifts between the four oscillations result in large amplitude variations. Thus it is seen that such variations are often reversed: when the amplitude of wave I, for example, decreases on reversing click polarity, that of wave V increases.

2. Differences between ipsilateral and contralateral records. This may be explained in the following way. As they travel from generator to different electrodes, BAEP oscillations undergo differential filtering, influenced by differences in:
   a) frequencies of oscillations
   b) volume conducting properties of tissues
   c) tissue between generator and different electrodes

   Explanations based on orientation and configuration of dipoles (Barajas, 1982) do not account for the sinusoidal pattern of differences between these montages. Figs.67-70 show examples of these differences. They also illustrate that, in some persons, the phase shifts and amplitude

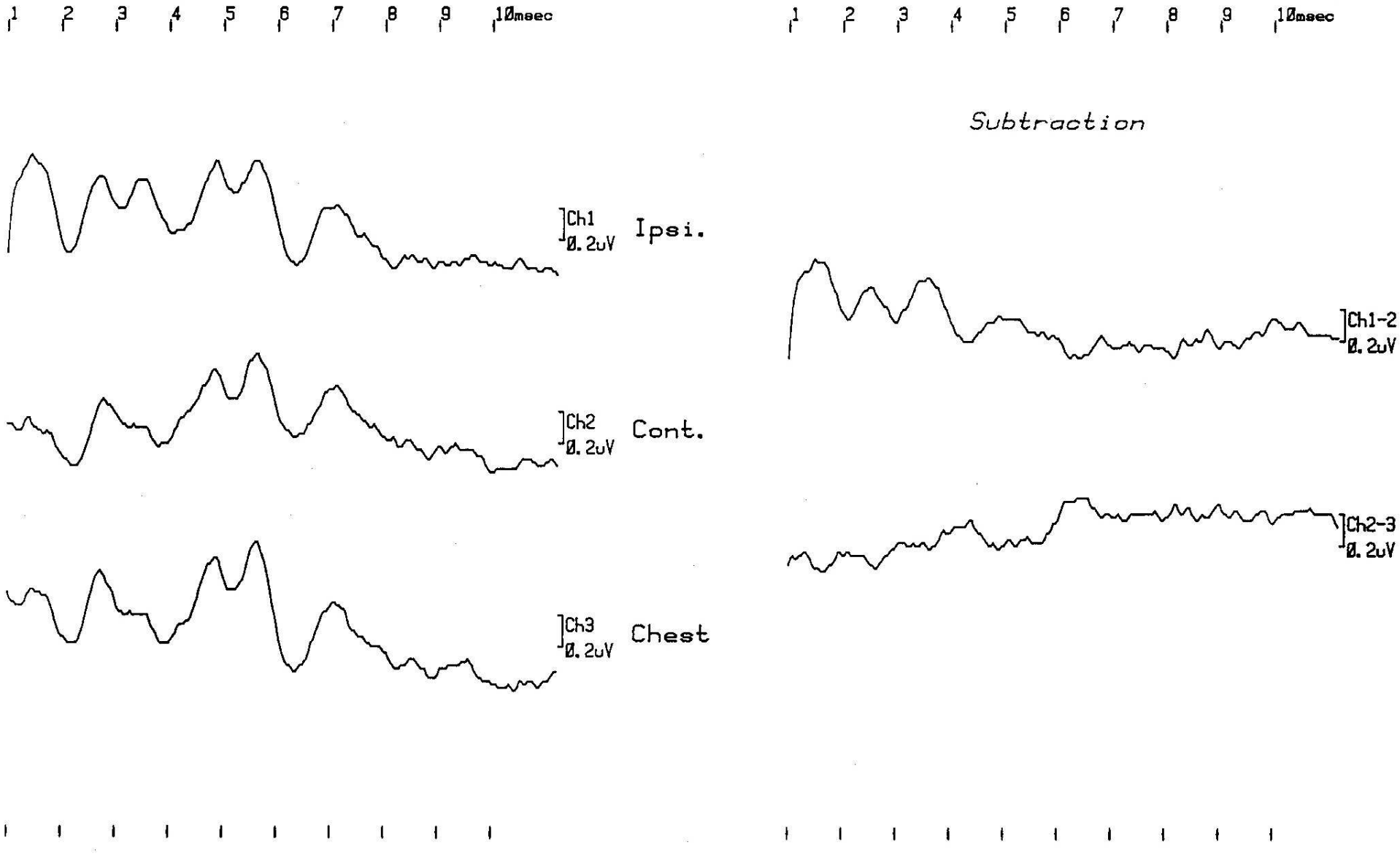


Fig. 67 Differences between montages

Healthy woman (LR),31. Left-sided rarefaction records. Contralateral and chest channels closely similar. Differences from ipsilateral channel mainly due to change in 960c/s oscillation (subtractions).

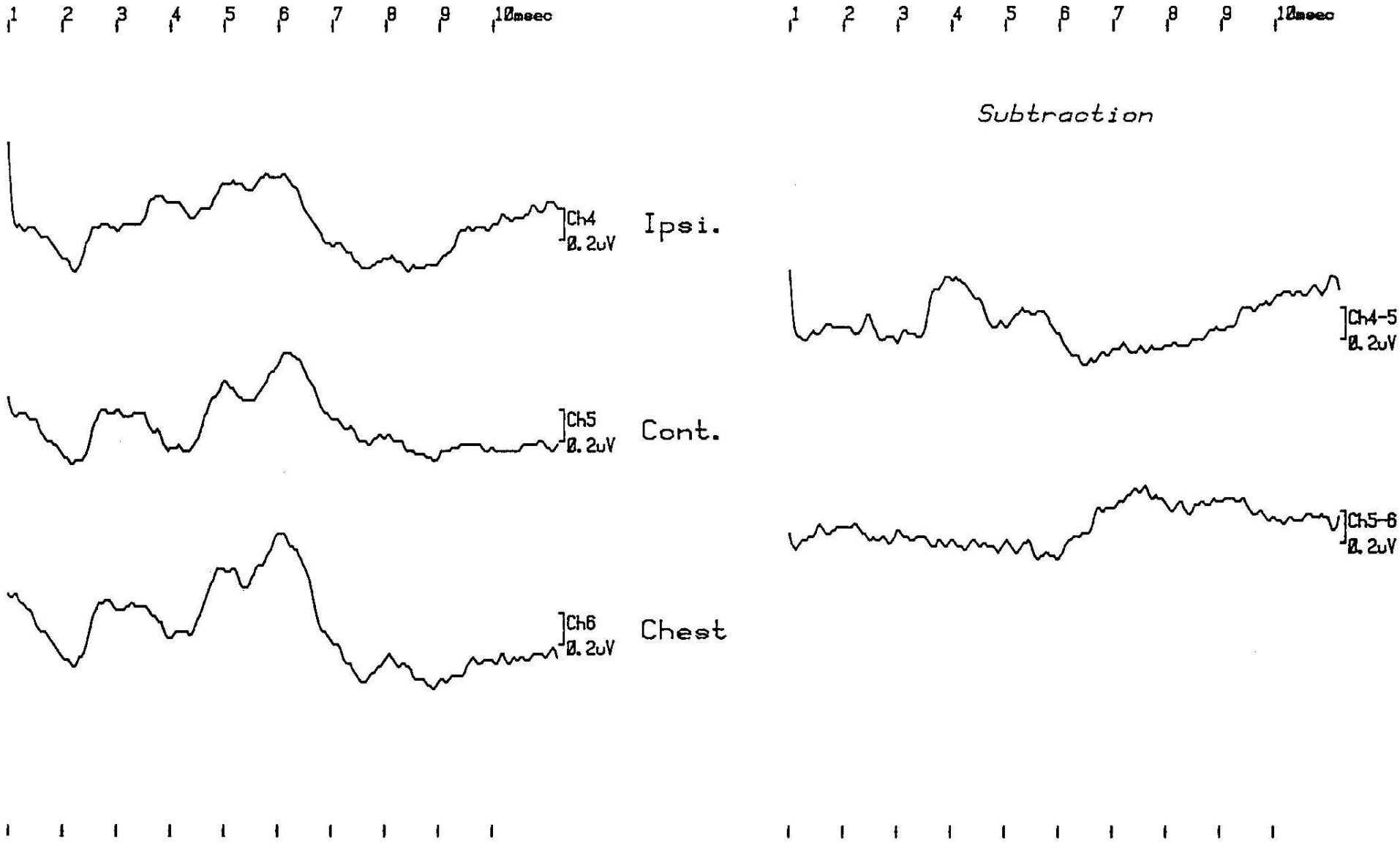


Fig. 68 Differences between montages

Healthy man (JA),26. Left-sided condensation records. Contralateral and chest channels closely similar (subtractions).

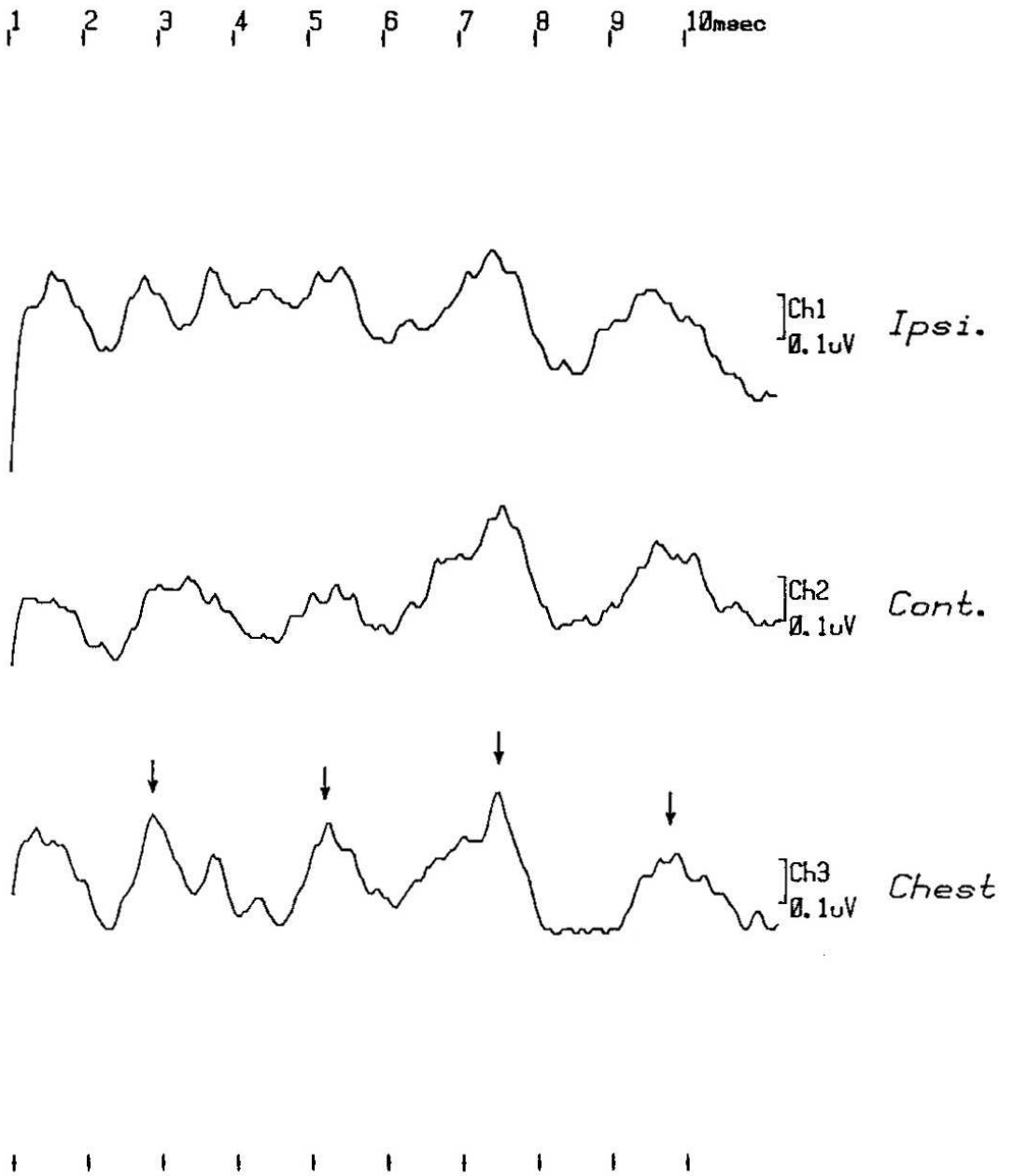


Fig. 69 Differences between montages

Man (AK), 44, with MS. Left-sided rarefaction records. Propagation of BAEP oscillations through tissues results in filtering out of the 960 c/s component, especially from contralateral record, and lower frequency oscillations become more apparent. Arrows on chest channel at 435 c/s.

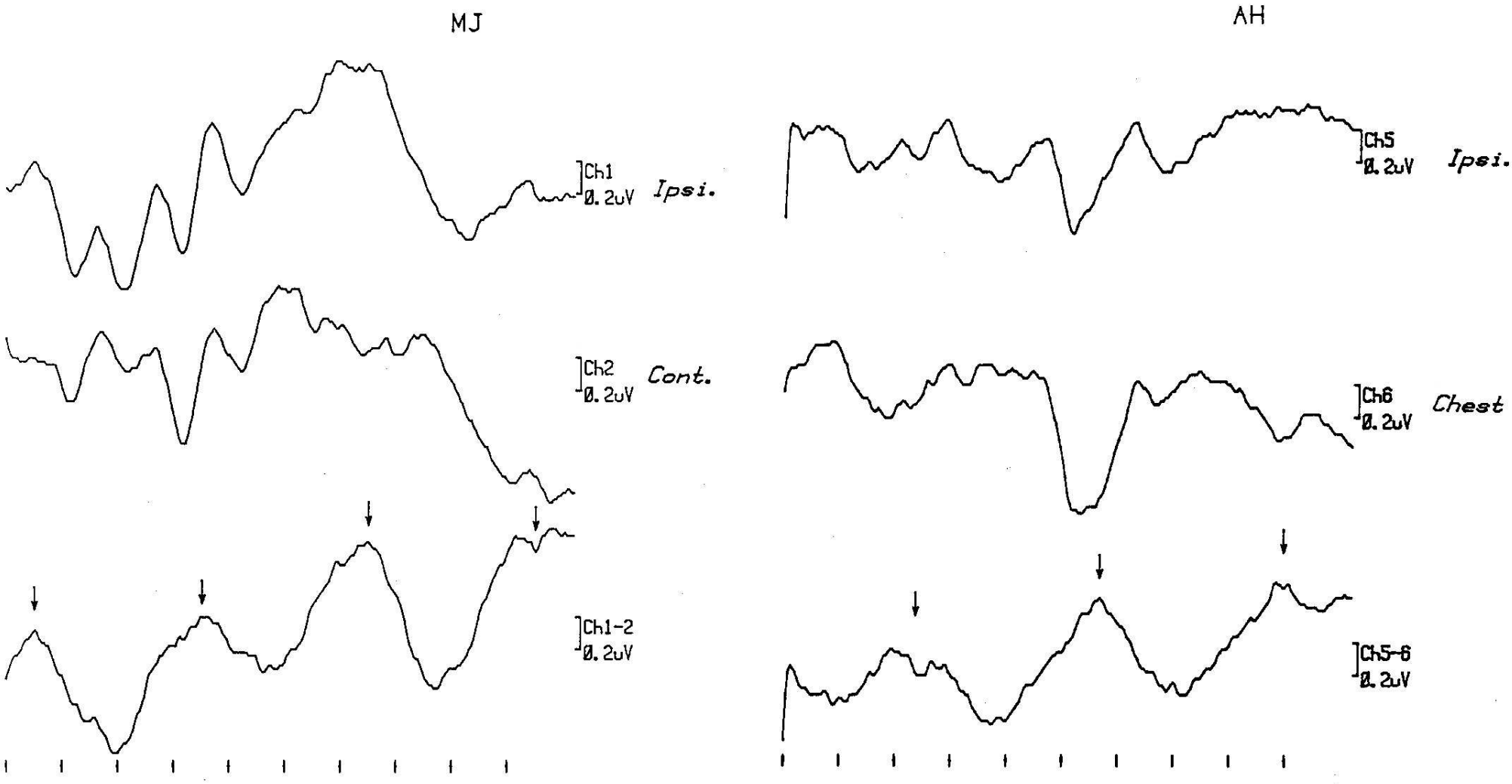


Fig. 70 Differences between montages

Left: Left-sided records to 75dBSL, from woman (MJ),24, with MS.
Right: Left-sided records from man (AH),18, with temporal lobe epilepsy.
Despite dissimilar records, subtractions show similar pattern of 330 (MJ) and 300c/s (AH) oscillations. Change in these oscillations, probably produced by filtering effect of tissues of neck, explains differences. The slightly higher frequency in woman is remarkable.

reduction these oscillations undergo as they propagate are closely similar for the contralateral and chest channels.

Thus, in patients with neurological disease and abnormal BAEP (studied in this work), in no case did the contralateral or chest record show abnormality not seen in the ipsilateral channel. Barajas (1982) made similar observations in MS.

3. Click polarity differences. Oscillations explain how the 180° reversal in click waveform produces the commonly observed less than half a cycle shift in BAEP waves. Because usually the half cycle phase shift occurs only in the 480 and 960 c/s oscillations (the 120 and 240 c/s shifting only by 45° and 90°), the overall effect on wave phase becomes less than half a cycle. But this is not invariable; Fig. 71 shows a complete (180°) phase shift in the first three waves. In this healthy person, the shift (seen in the subtraction) has occured in all the oscillations. Added to that, duration of the oscillations also plays a role: the 960 c/s, which shows the maximum shift, normally dies down at about 6 msec. Late waves, therefore, would be affected to a lesser extent.

4. Shorter click duration produces sharper waves. The explanation here is that decrease in duration accentuates high frequencies in the click's waveform, thereby enhancing amplitude of the high frequency BAEP discharges.

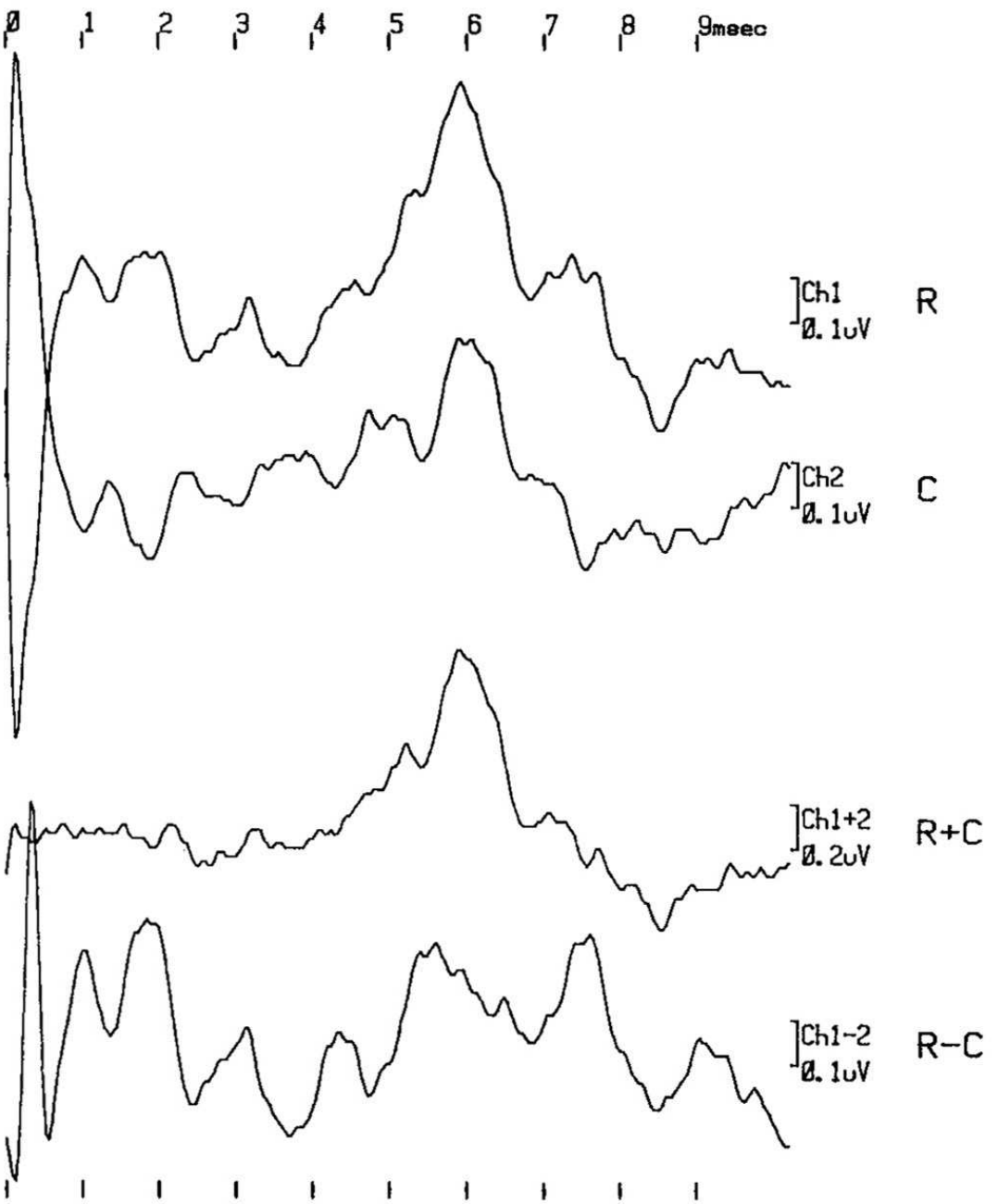


Fig. 71 Click polarity effect

Healthy man,34. Right-sided records (upper two) showing almost complete reversal of waves I to IV. Adding these two traces (R+C) to simulate alternating click polarity results in BAEP in which only waves IV and V are clear. By itself, this waveform would be regarded abnormal. Changes in 240, 480 and 960c/s oscillations (subtraction) explain effect.

Interpretation of the BAEP in disease

Oscillations allow better explanation of different BAEP abnormalities:

1. Absence of waves, after 4 msec, for example. This may be explained as early damping of all the oscillations; that is, impairment of the ability of neurones to sustain long-lasting depolarizations. On the other hand, an abnormal waveform, in MS for example, with a paradoxically large wave I (Elidan et al., 1982) and presence of distorted succeeding waves, may be caused by slowing, phase shift or absence of an oscillation which, in normally having negative phase between 1-2 msec, reduces the amplitude of wave I.

2. Disease may cause decrease in the frequency, early damping or absence of an oscillation (Figs. 72-80). Prasher and Gibson (1982), for example, observed a link between progression of demyelination and increase in interpeak latencies. In MS, the EEG also shows slowing.

   Absence of an oscillation, on the other hand, may be explained in two ways; first, neurones fail to oscillate; and second, they do oscillate but at rapidly varying frequency or phase which results in cancellation on averaging. The authors above also found little superimposition of the BAEP on consecutive repetitions in MS.

3. Distortion of the BAEP is not due to abnormal synchronization. Relative phases (and probably amplitudes) of

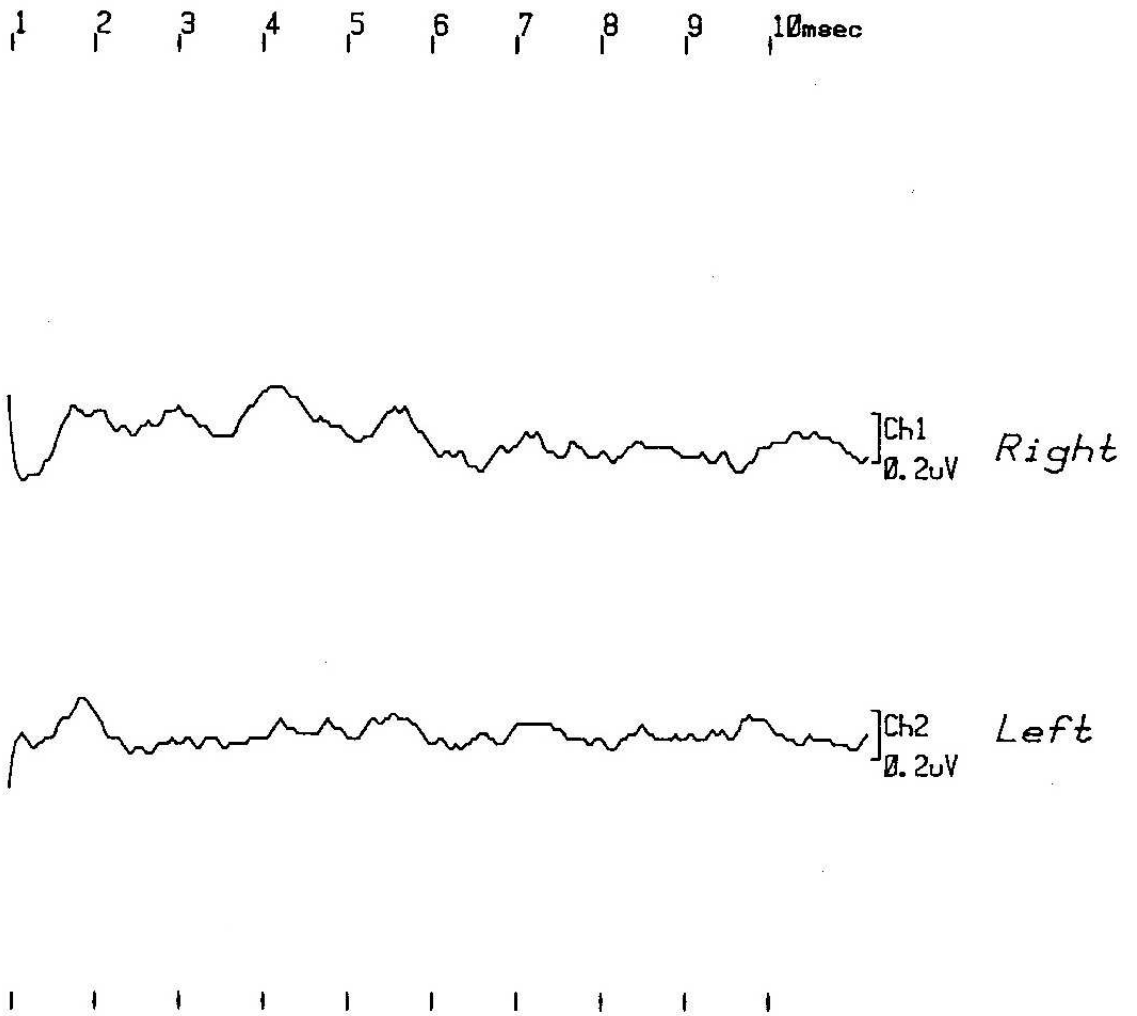


Fig. 72 Unsustained oscillations

Man (DC),67, with atypical presentation of MS. Ipsilateral rarefaction records.
Low frequency oscillations absent and high frequency ones low in amplitude and prematurely damped.

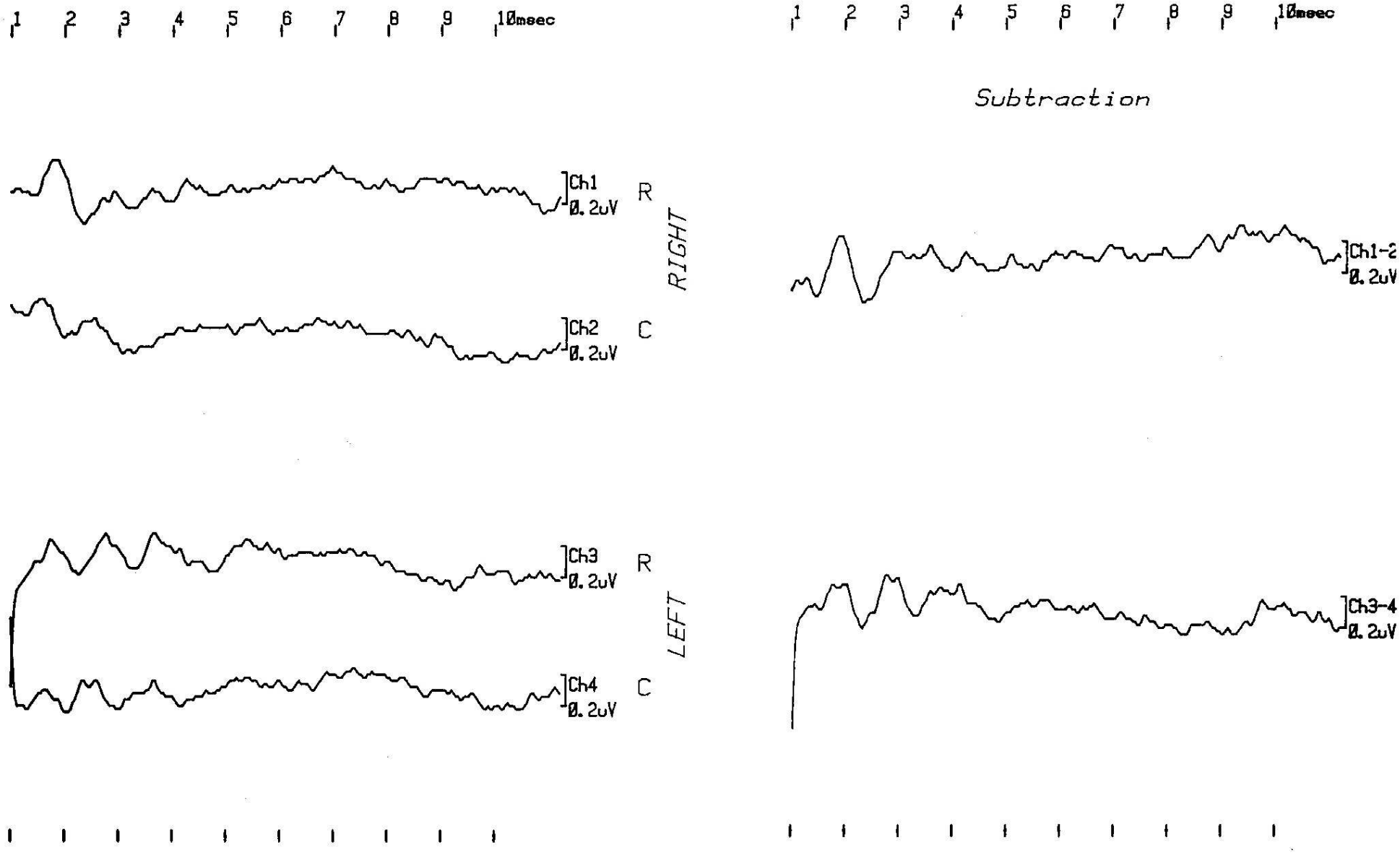


Fig. 73 Unsustained oscillations

Woman (BB),37, with brainstem tumour. Low frequency oscillations indistinct, and higher frequency ones unsustained.

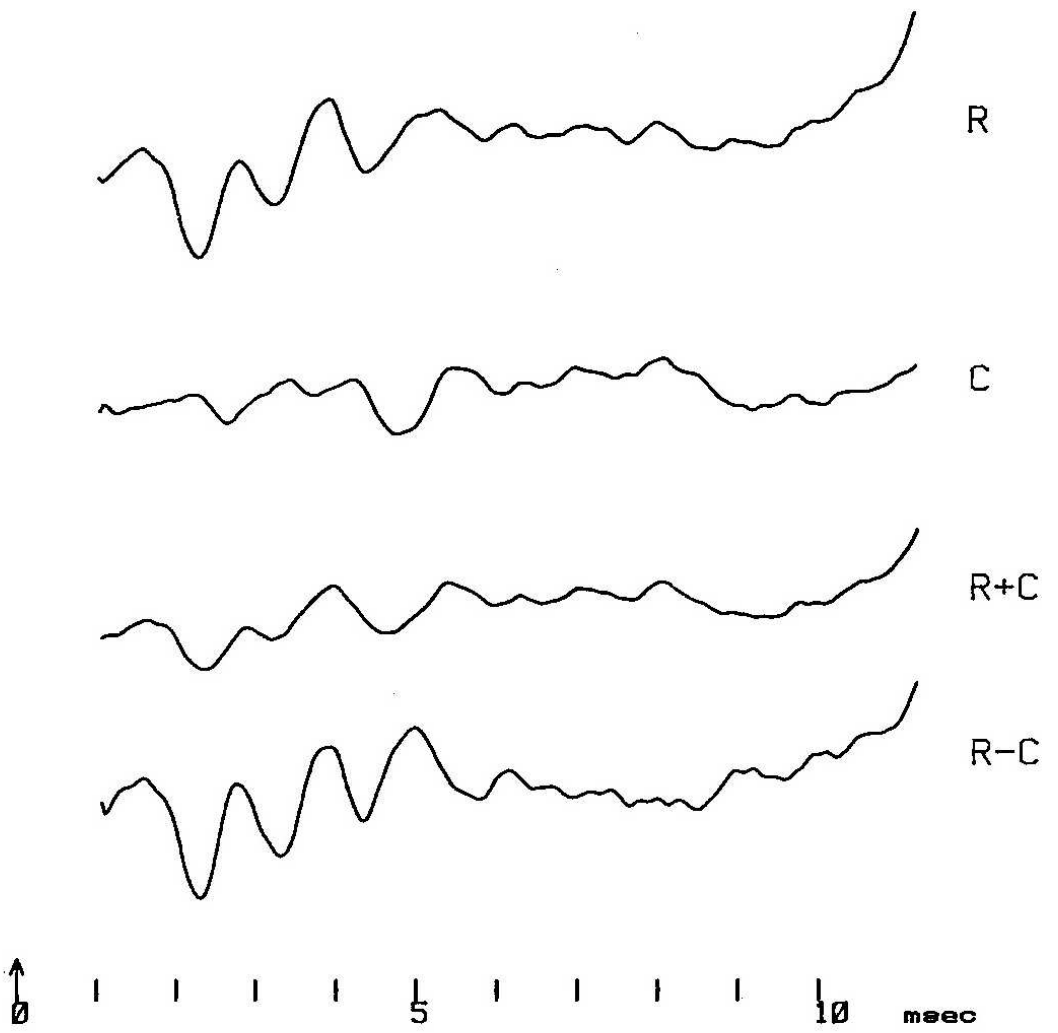


Fig. 74 Poorly sustained oscillations

Man (JA),22, with MS. Right-sided records showing poorly sustained oscillations, especially low frequency ones. Polarity difference is sinusoidal (subtraction).

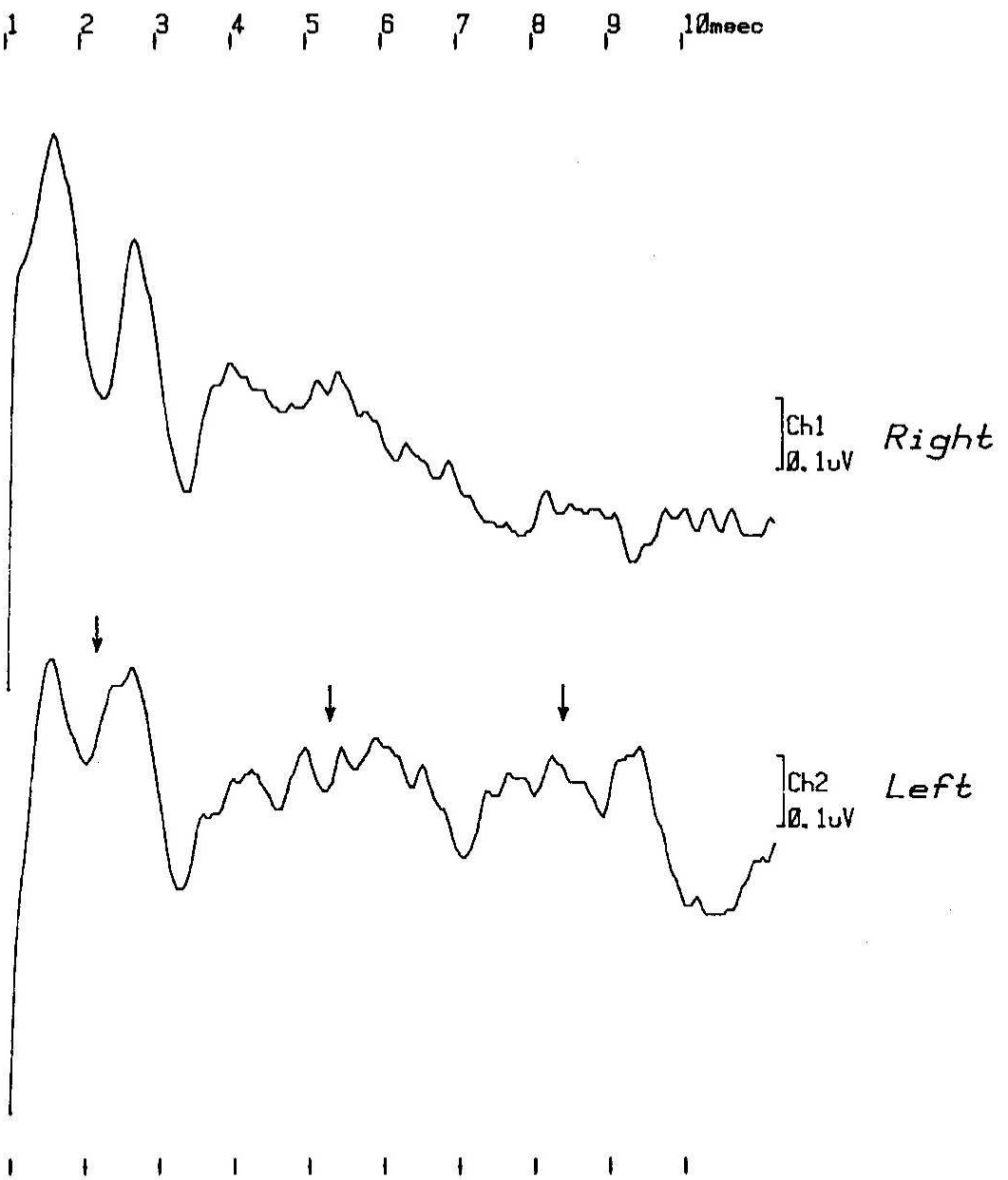


Fig. 75 Unsustained oscillations

Woman (SH),44, with MS. Right-sided record shows predominantly 960 c/s oscillation, prematurely damped. On the left, a 320c/s oscillation (arrows) is also present. Traces are of low amplitude.

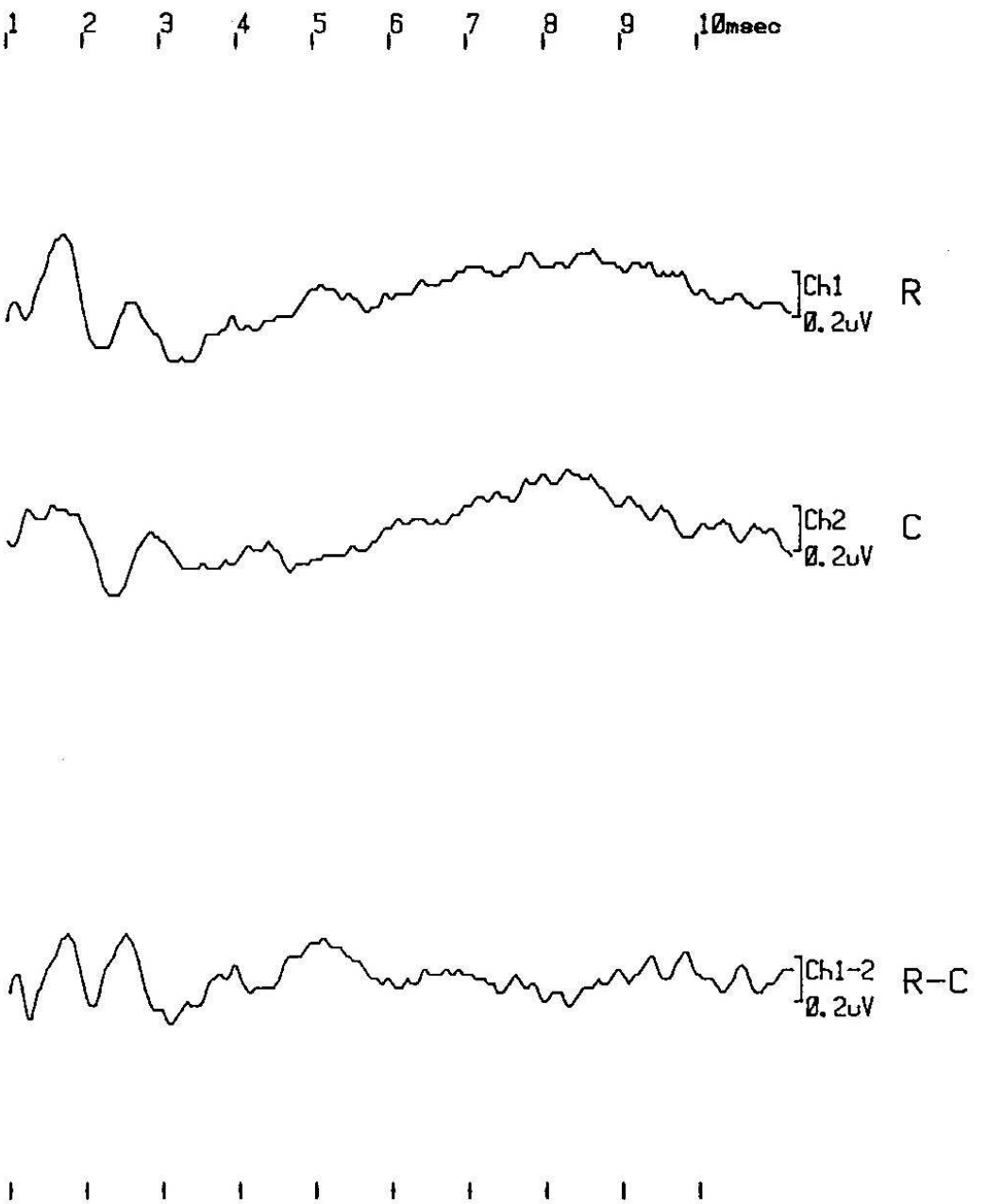


Fig. 76 Unsustained oscillations

Woman (SF),36, with MS. Right-sided records. 480 and 960c/s oscillations prematurely damped; 240c/s indistinct.

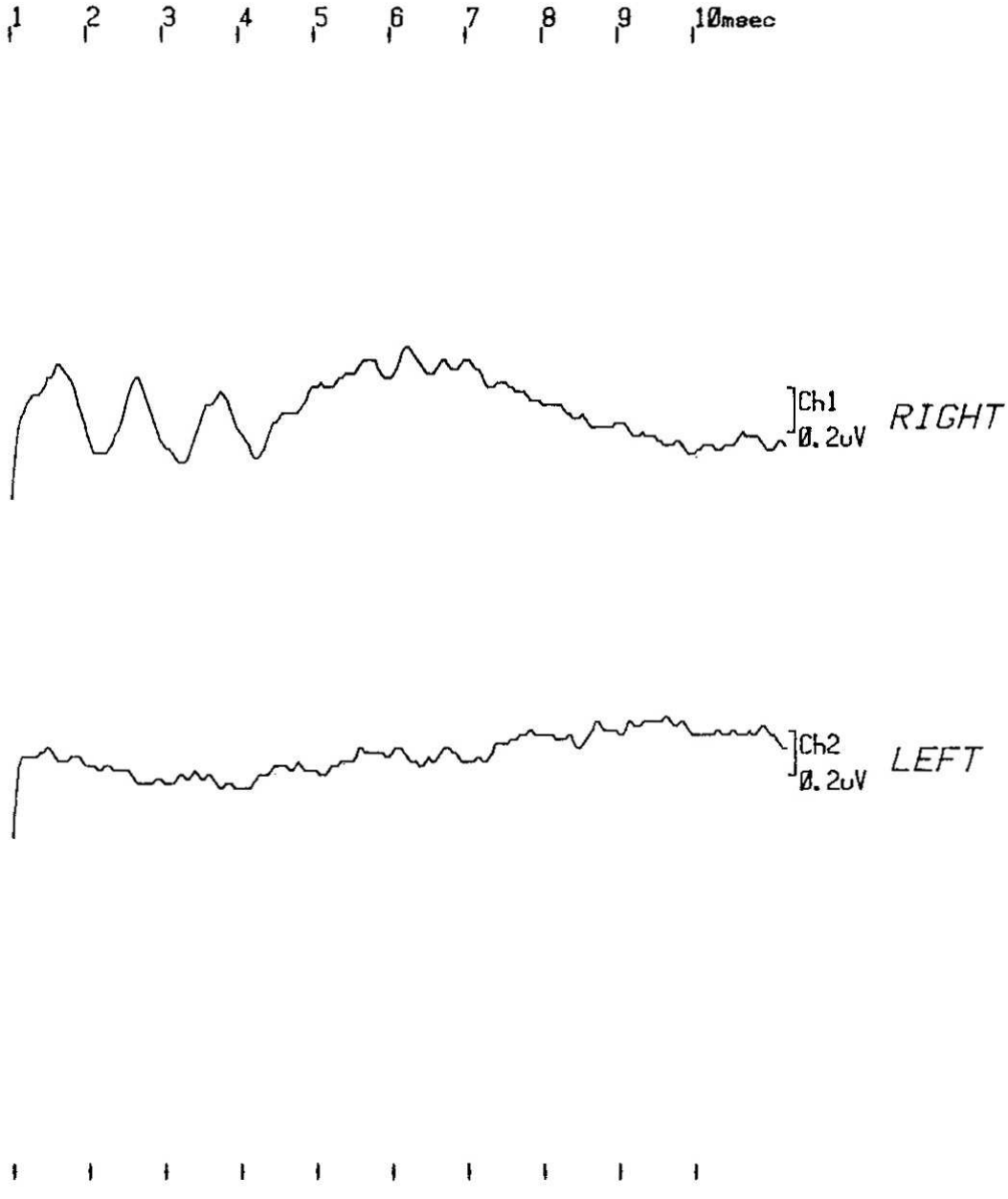


Fig. 77 Unsustained oscillations

Man (SP), 33, with MS. Rarefaction records.
Absence of distinct peaks after III on right can be explained by prematurely damped 960 c/s oscillation. The 120 c/s can still be made out. Complete failure of oscillation explains the waveform on the left.

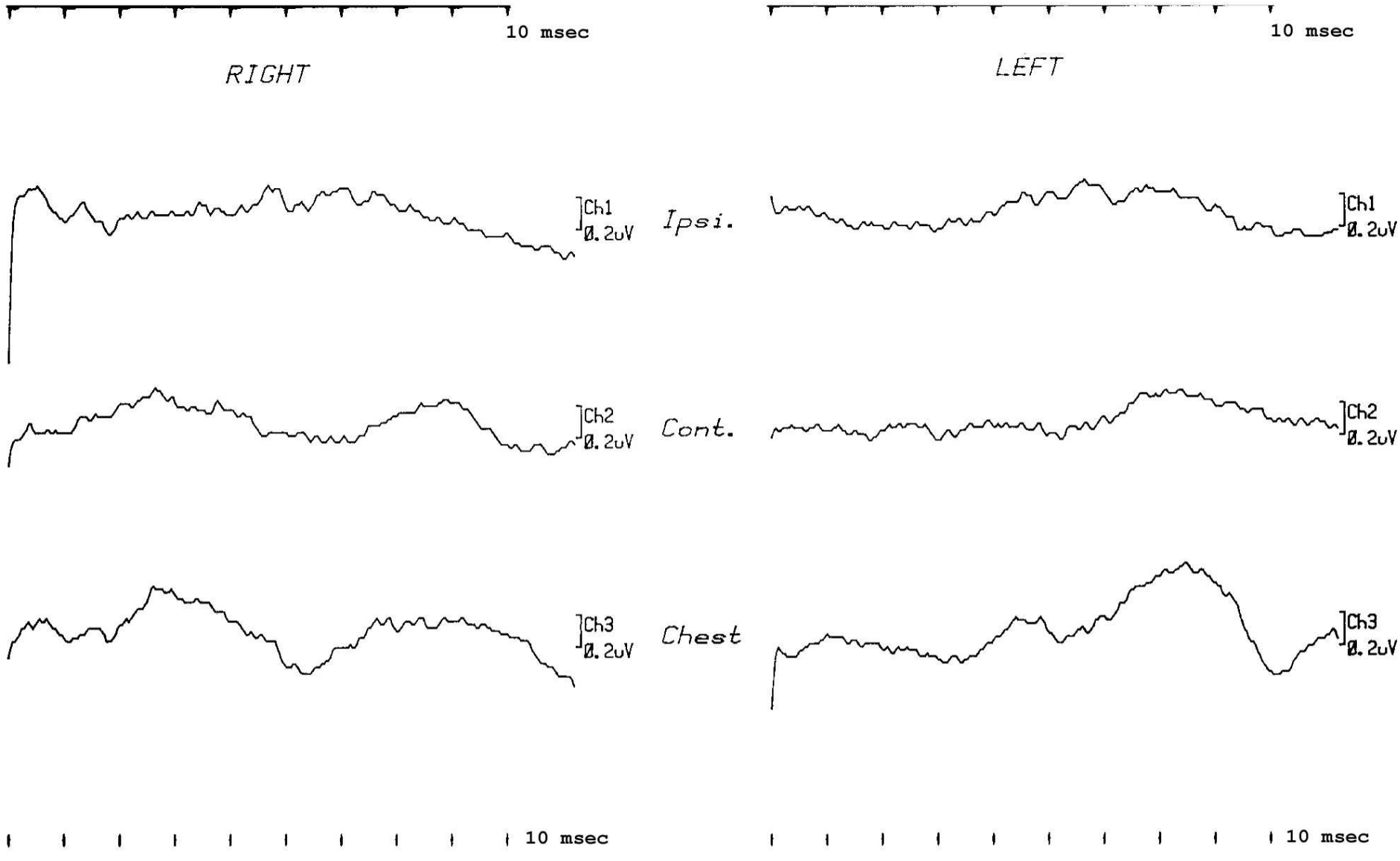


Fig. 78 Unsustained oscillations

Man (EA),45, with MS. Rarefaction records.
In the right ipsilateral record, the 960 c/s oscillation is seen, at low amplitude and for only 2 msec. Rest of channels contain mainly low frequency oscillations, which are probably artefacts.

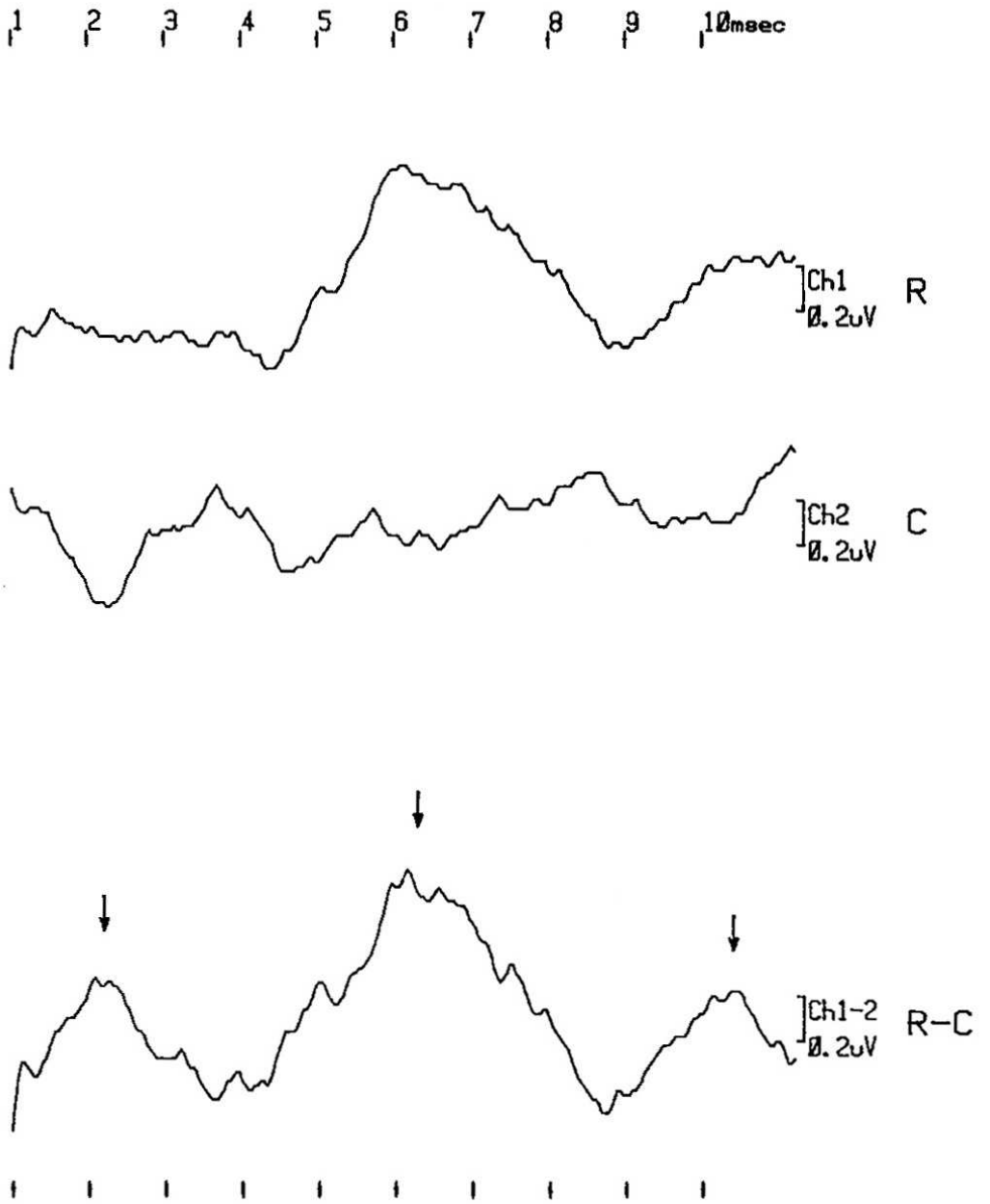


Fig. 79 Low frequency BAEP

Woman (AK),38, with MS. Right-sided records.
Change in 240 c/s oscillation (arrows) explains click polarity effect.

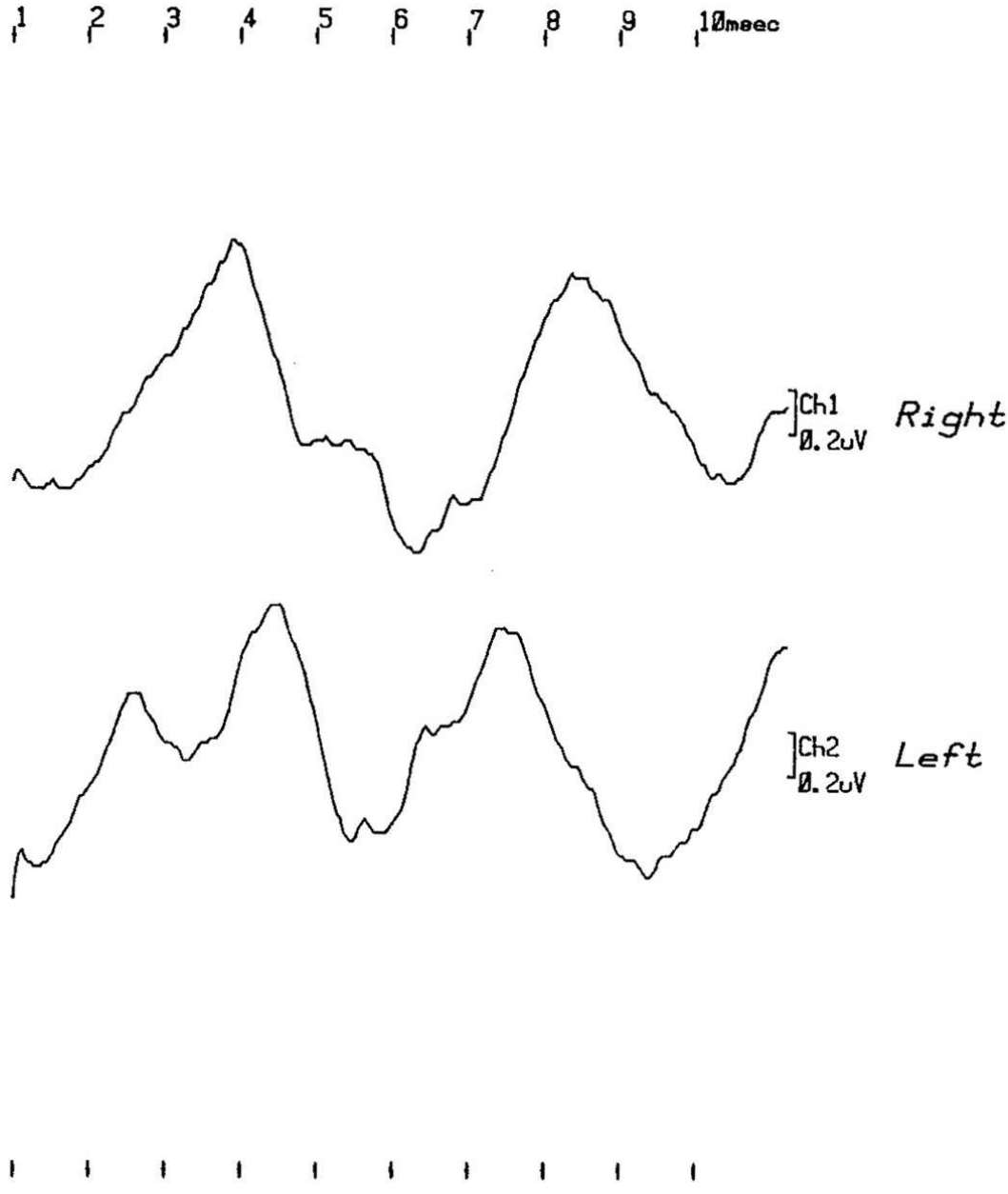


Fig. 80 Low frequency BAEP

Woman (JR),53, with MS. Right-sided trace shows mainly 220 c/s oscillation. On the left, the 480 c/s oscillation is also present, extending halfway through the BAEP, and the relative phases of the two discharges produces double shoulder-wave pattern.

the component oscillations may occur in a combination that results in small waves with multiple peaks. But such combinations are not invariably abnormal. The best example is the occasional "distortion" of the normal BAEP on one of the click polarities (Figs.2 and 14).

4. The pattern of "progressive" brainstem death. At first, interpeak latencies ("BTT") are prolonged, followed by disappearance of latter waves. While this is thought to indicate brainstem death begining rostrally and progressing caudally, it might alternatively be explained by decrease in the duration of oscillations.

Implications for recording

1. The importance currently given to latency, the relatively few montages needed in recording, and the speed and memory capabilities of modern averagers, all permit using large number of sampling points i.e. 256 and higher. As the highest BAEP oscillation is less that 1.5 KHz, high sampling rates are unnecessary. It is better, therefore, to use 128 points (80 usec interval) for sampling. This allows direct application of the FFT, with higher resolution.

2. For the same reason, and particularly for improving resolution of the 120 and 240 c/s oscillations, it is also better to use as long a sweep as permitted by the averager. This allows inclusion of more points for the FFT autocorrelation as well as optimal "windowing". (As seen in Fig. 35, BAEP oscillations may extend beyond 10 msec.)

3. Blockage of the external auditory meati by wax may produce an abnormal waveform. The effect of placing cotton in the ear canal (Fig. 24) illustrates the point. Wax may act like the cotton wool and alter the acoustic waveform of the click, without necessarily damping its intensity. Even if it does lower click intensity, the complex effect on the acoustic waveform is not neutralized by increasing click volume.

Implications for analysis

Wave peaks and polarity of peaks are not related to time required for nerve volley to travel between nuclei or in fibre tracts. Rather, they reflect interaction between cyclical polarizations and depolarizations in a neuronal mass fixed in space. A positive peak, for example, is not generated by the propagation of a potential towards or away from an electrode, as Jewett (1970) proposed and, indeed, on which he partly based his hypothesis of wave generation. Nor does positivity reflect post-

synaptic potentials (Buchwald, 1983). Rather, a positive, or negative, peak anywhere in the BAEP is determined by the summation of oscillations with different frequencies, phase of onset, and duration. Measuring both the positive as well as the negative peak of a wave (suggested by Wada and Starr [1983b]) would be irrelevant.

In addition, the mechanism proposed earlier for the polarity differences between montages has a direct implication for the vectogram. Plotting the intersection of corresponding points from two (Robinson and Rudge, 1981 and in this thesis) or three channels (Pratt et al., 1983) on planar or three dimensional axes gives information mainly on volume conducting properties of tissues intervening between the BAEP genarator and electrode. Such a plot, therefore, is unlikely to summarize "all [BAEP] activity recorded at the surface" (Pratt et al., 1983). Figs. 81-88 are vectograms of normal BAEP. A common general pattern, if any, is not easily seen. Thus, in the last vectogram (Fig. 89) for the right-sided BAEP of the patient with MS (in Fig. 34), the pattern does not obviously justify labelling it as abnormal. But when compared with that recorded two years earlier, the condensation record begins to show differences: absence of the 960 c/s oscillation. The left-sided BAEP of this patient is clearly abnormal without any further analysis.

Given that measurement of latency and amplitude--and analyses based on them e.g. the vectogram--are misleading, and given that as yet no ideal mathematical method for frequency analysis exists, let alone the availability of suitable computer

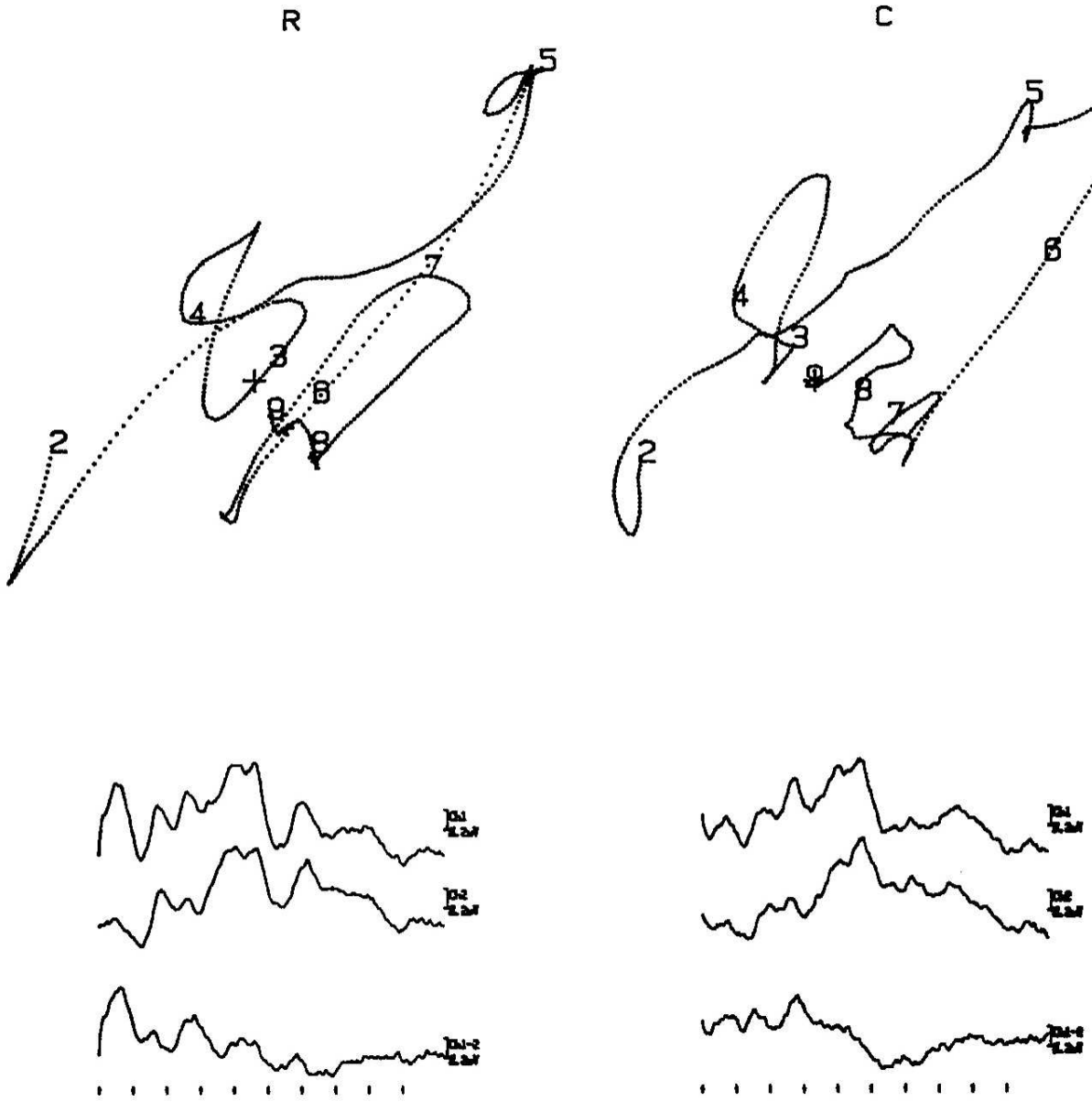


Fig. 81 Planar vectogram

Healthy woman (LR), 31.

R: rarefaction
C: condensation

Right-sided records.

Cross near centre of vectogram is centre of x and y axes.

Numbers in vectogram represent time in msec (2 - 9).

Speed of inscription is represented by spacing between dots: the wider the spacing the faster the speed.

Below each vectogram are corresponding ipsilateral (top) and contralateral BAEP, with their subtraction (bottom).

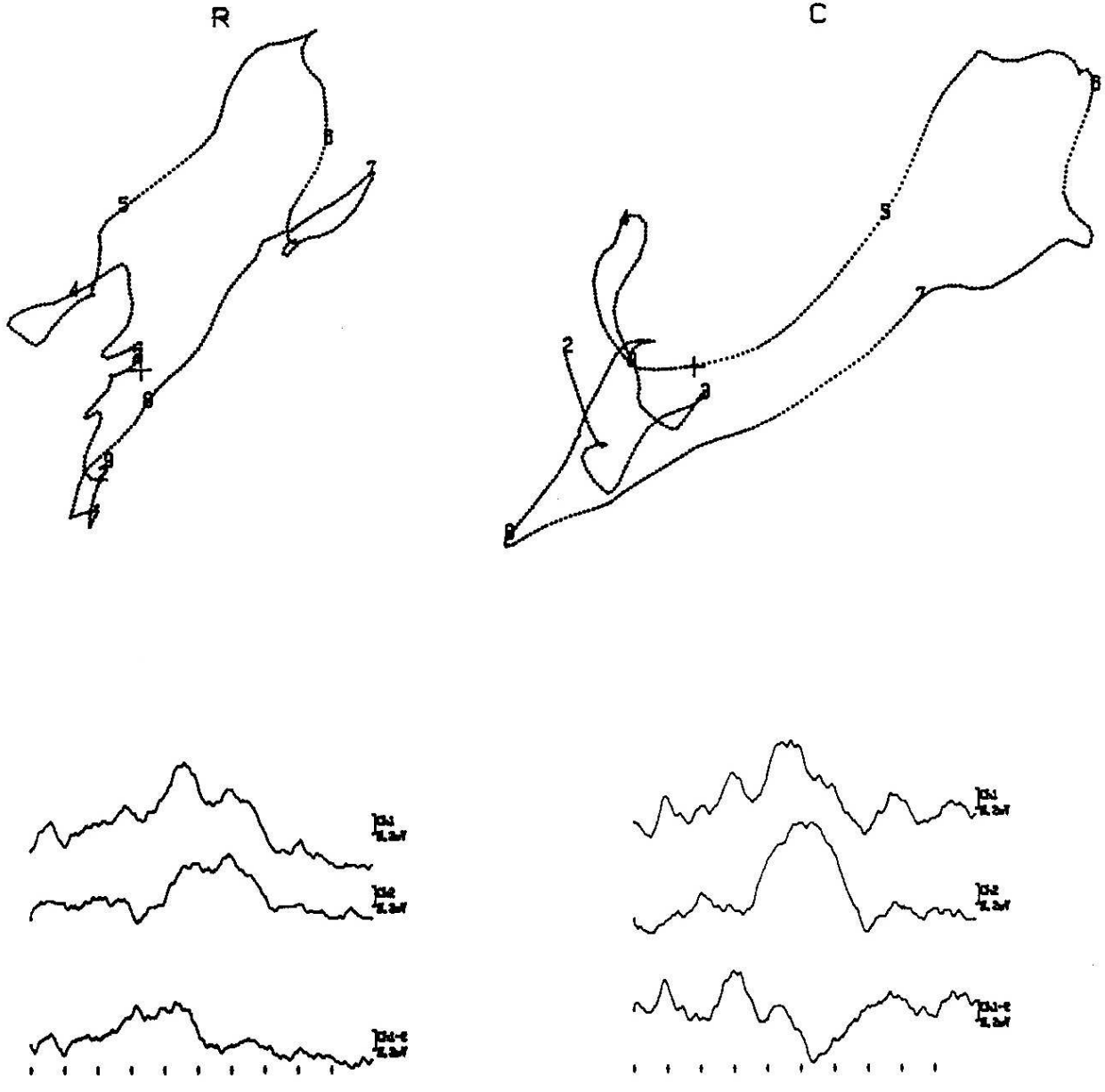


Fig. 82 Planar vectogram

Healthy woman (AE), 27.

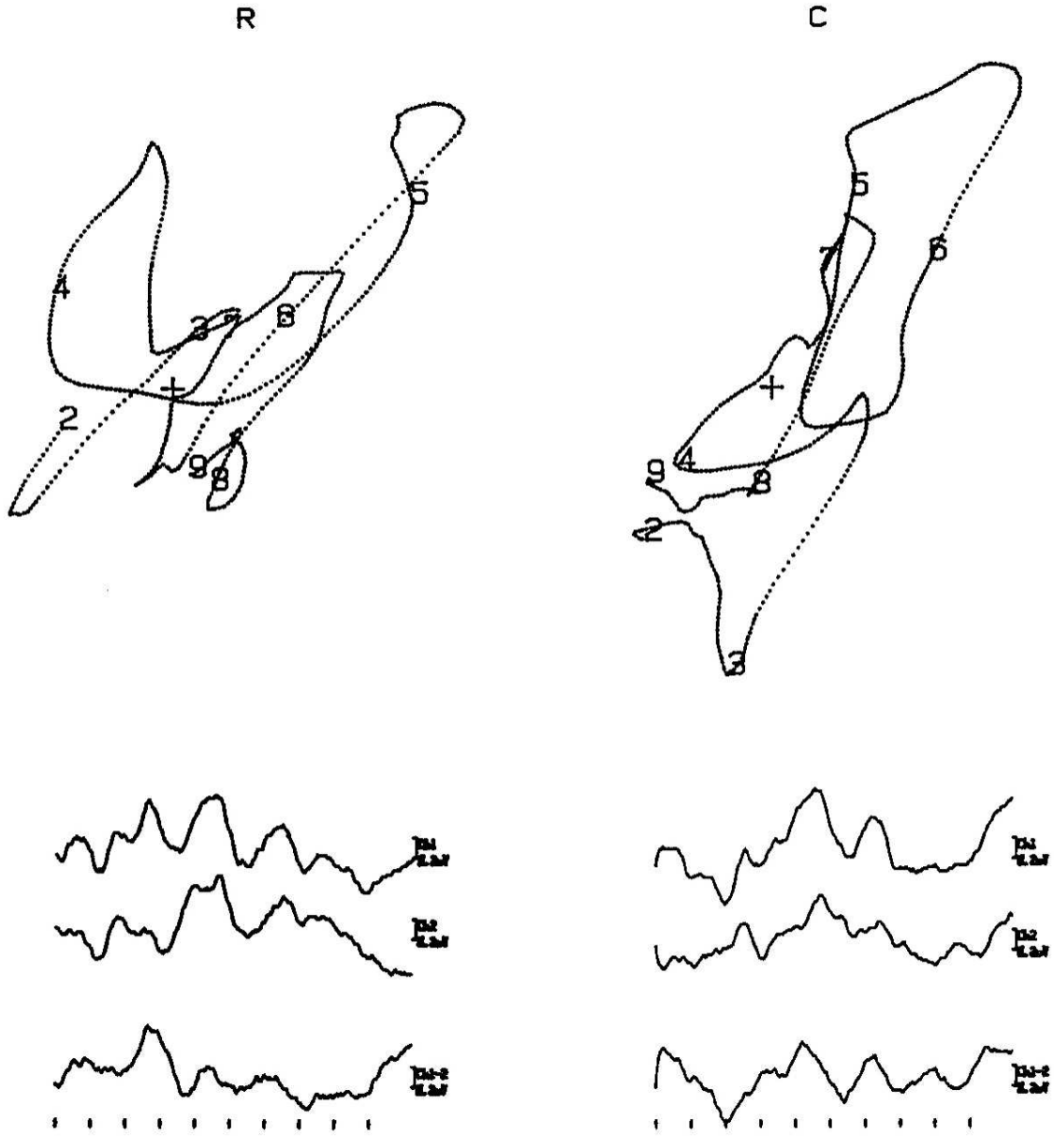


Fig. 83 Planar vectogram

Healthy woman (RG), 24.

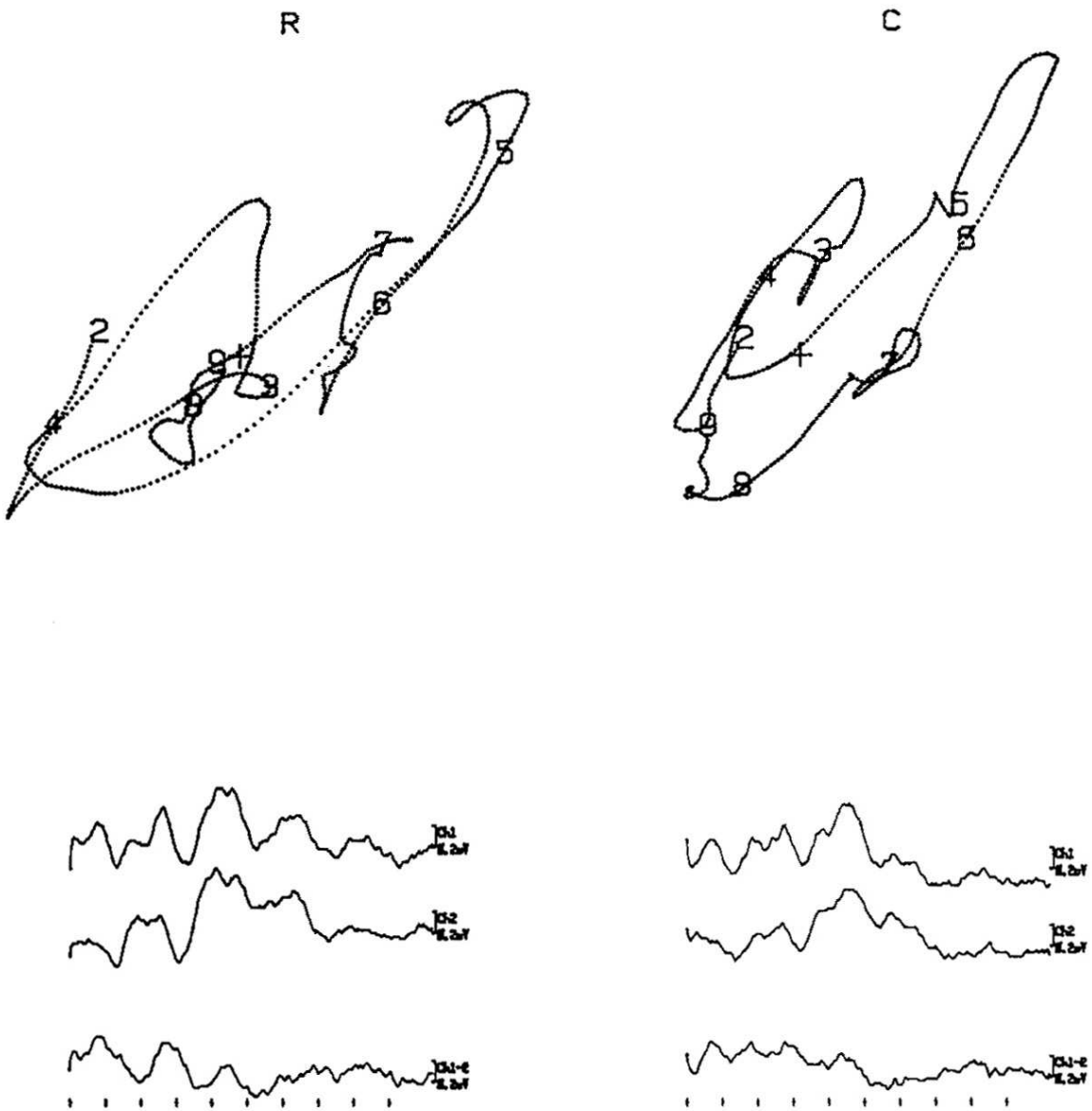


Fig. 84 Planar vectogram

Healthy woman (LC), 24.

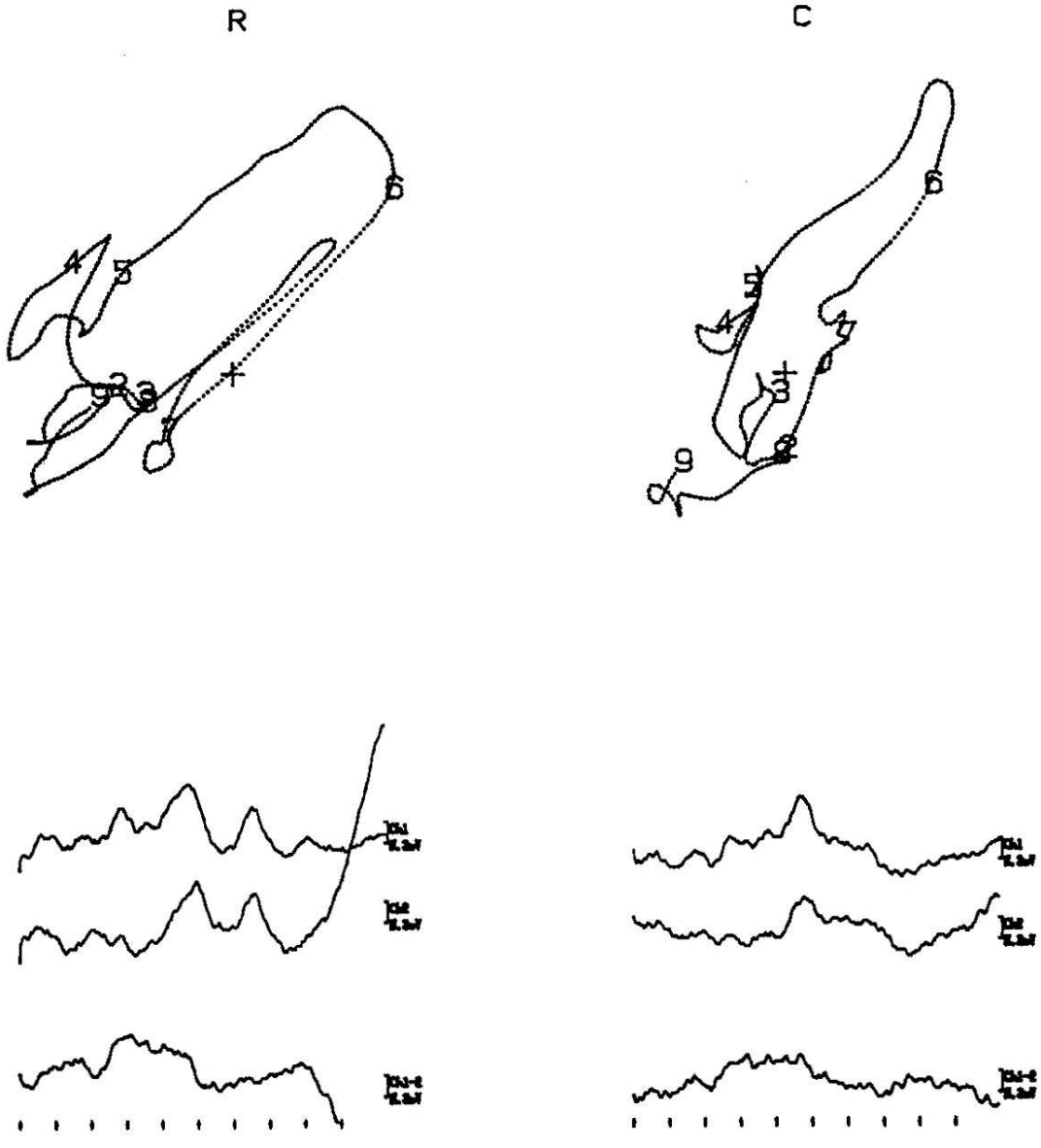


Fig. 85 Planar vectogram

Healthy man (MD), 33.

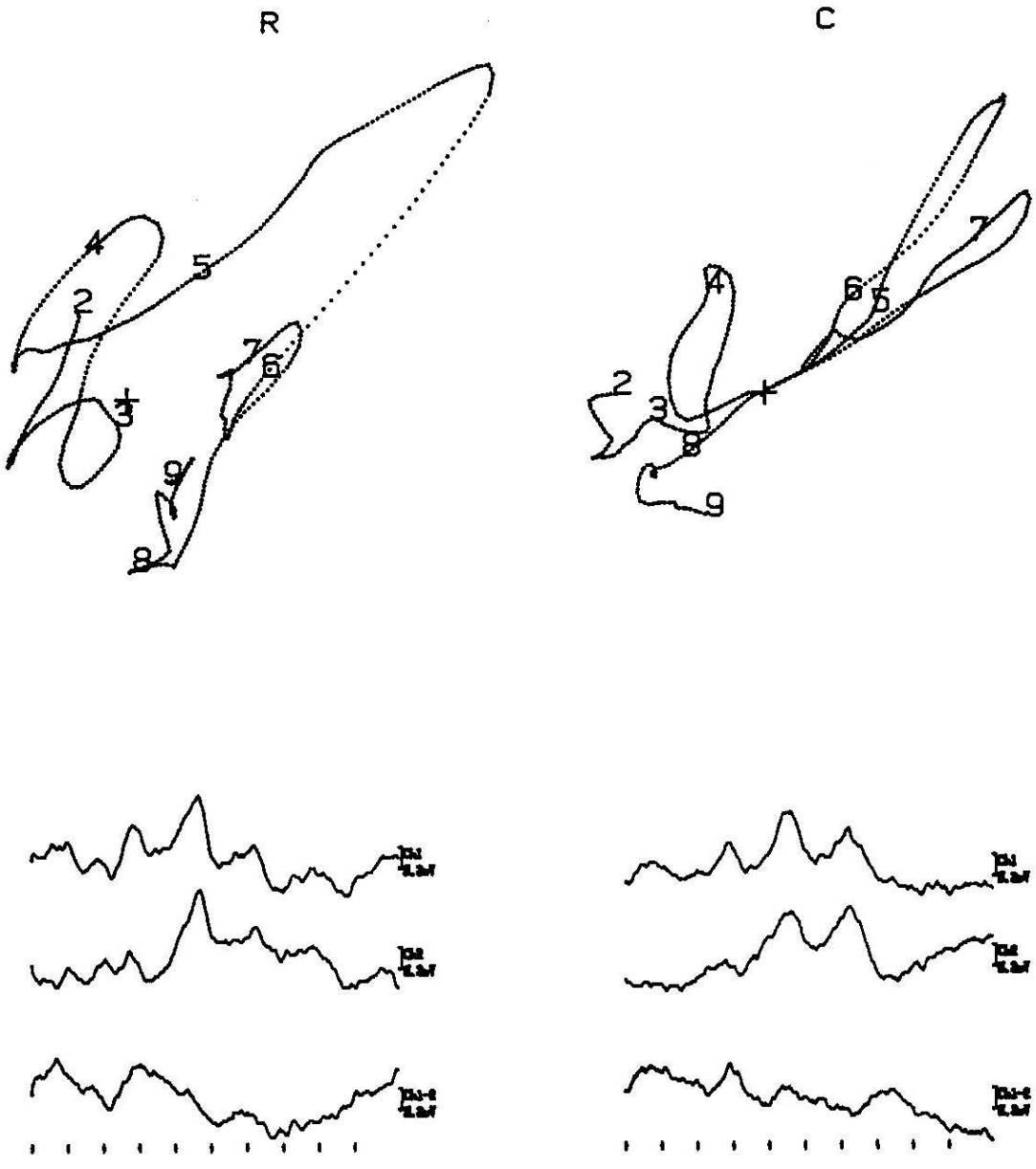


Fig. 86 Planar vectogram

Healthy man (RHJ), 31.

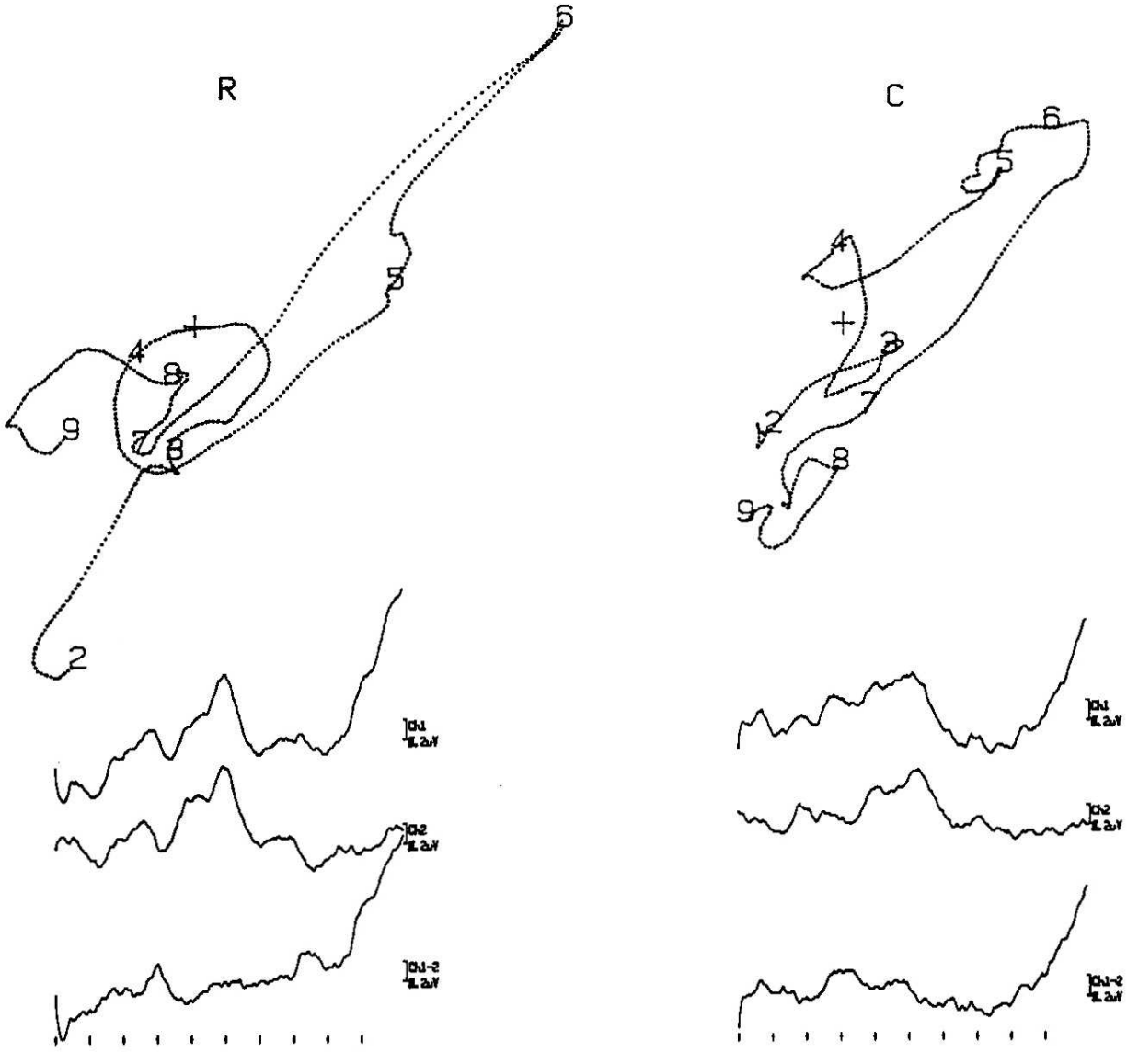


Fig. 87 Planar vectogram

Healthy man (JA), 26.

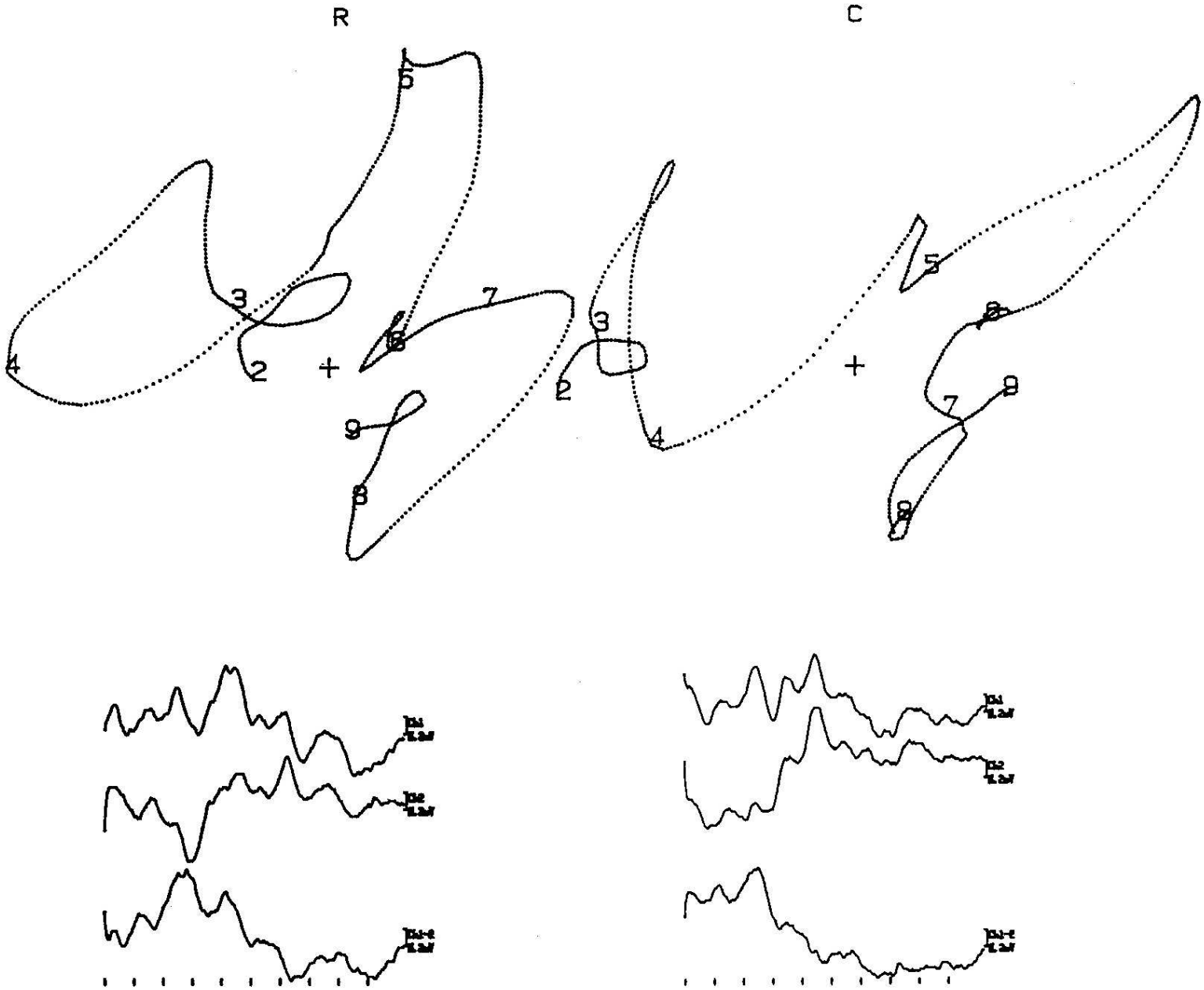


Fig. 88 Planar vectogram

Healthy man (PC), 25.

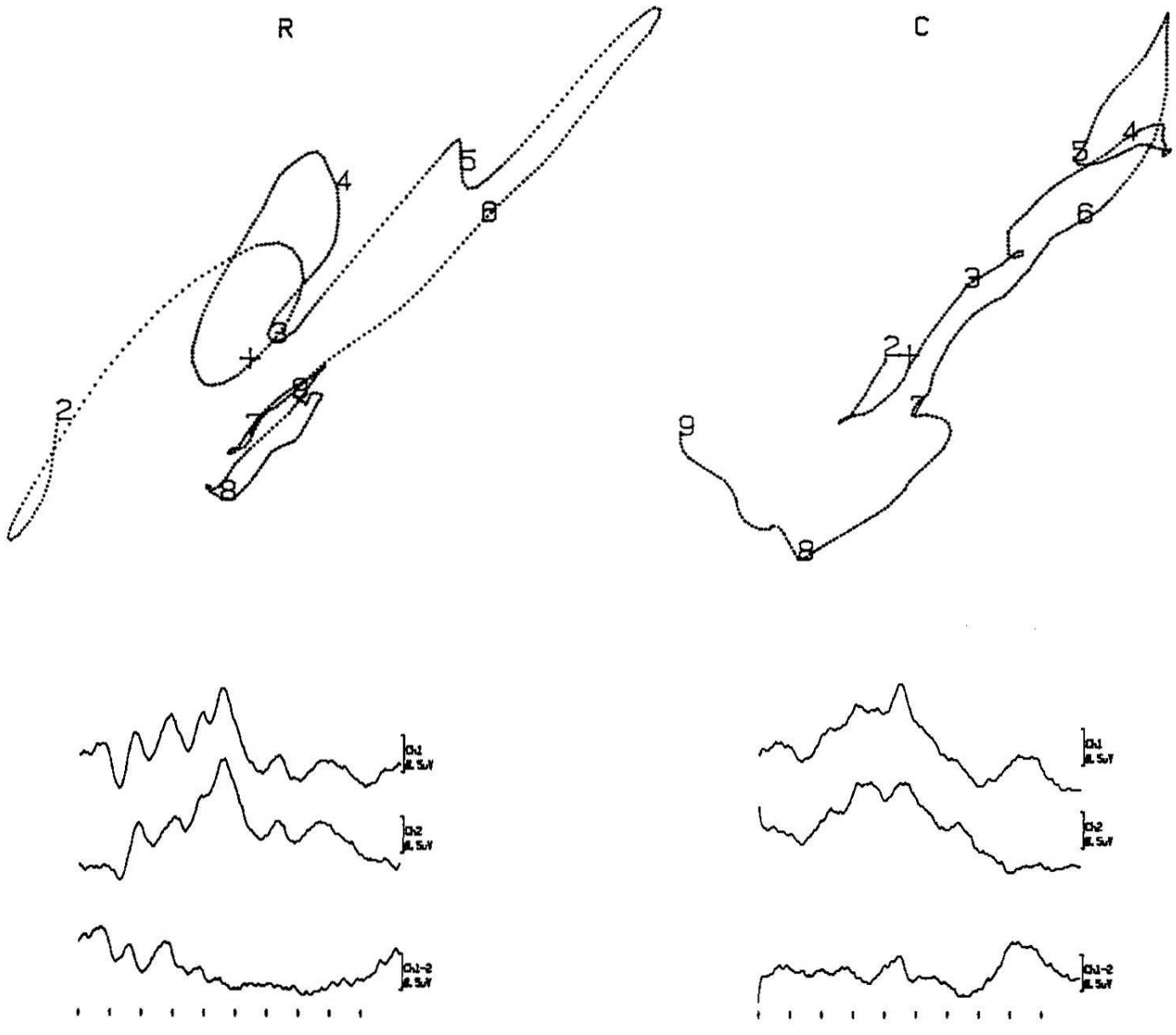


Fig. 89 Planar vectogram

Woman (CO), 37, with two years history of MS.
Same patient in Fig. 34.

programmes for implementing them, the most practical examination of the BAEP would be visual analysis. From the literature, support for this view is provided by the following observations: Ohrlich et al. (1978) describe EP as "signatures" and Robinson and Rudge (1981), describe BAEP in MS normal in latencies and amplitudes but "appeared distorted on subjective appraisal".

At this point, it might be argued that, pending improvment of mathematical frequency analysis, and to retain some measure of objectivity, one would be justified in continuing to use latencies and amplitudes (without attaching to them any physiological significance) for classifying the BAEP. Against this contention, however, is the fact that, even in normal BAEP, in Fig. 90, for example, wave peaks (for latency and amplitude measurements) may not be easy to determine.

In pattern visual evoked potentials, to bring an analogy, this problem with latency may not be as significant, given the larger and fewer waves. Neverthelss, Blumhardt (1983), describes situations where VEP latencies do pose similar "dilemmas".

It is true that description based on visual analysis may hinder objective communication. It is also true that something described in numbers, blended with statistical terms, is more convincing. But the examples of deductions (Introduction p.8) made from statistics on BAEP latencies, show that numbers do not guarantee relevance. These examples, as well, of course, as the

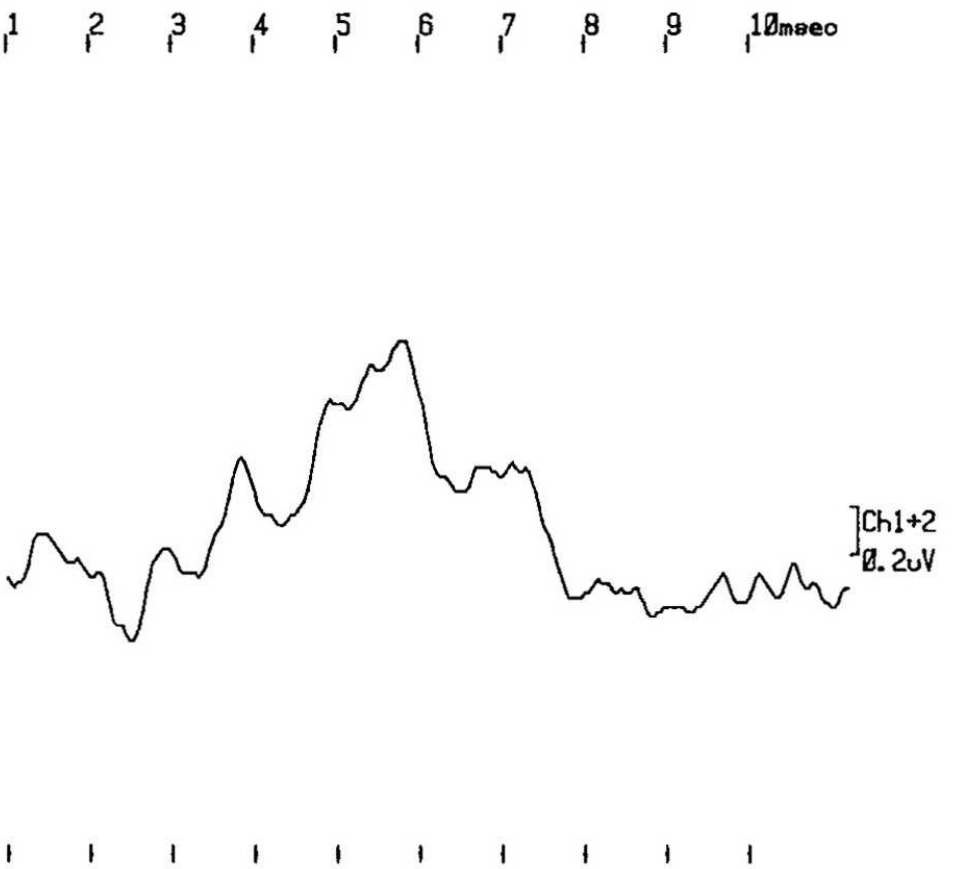


Fig. 90 Multiple peaks

Healthy man (AI),21. Average of two consecutive runs of left-sided condensation BAEP.
Waves I,IV,V,VI and VII have multiple peaks, making it difficult to determine their latencies.

use of mathematical frequency analysis in this thesis, justify a historian's observation (Plumb, 1973):

> We are becoming a numerate society: almost instinctively there seems now to be a greater degree of truth in evidence expressed numerically than in any literary evidence, no matter how shaky the statistical evidence, or how acute the observing eye. It is often not the numbers, the statistics that speak the truth, rather there is a quicker acceptance of them in ourselves--almost an excitment.

Finally, speaking of objectivity, for an important parameter of the mainstay of mathematical frequency analyses, the Fast Fourier Transform, the choice is subjective (Discussion p. 23).

Visual analysis, however, would be enhanced when the composition of the BAEP from oscillations is held in mind. It would be assisted even further by using digital subtraction (directly on the averager's screen). Thus, when no difference exists, between records from the two ears or two periods, for example, subtraction shows a slanting line or an irregular pattern, with a frequency content (if discernable) less than that of the lowest BAEP oscillation (Figs. 91-93). Such a low frequency may be due to instrument noise or to EMG or EEG artefacts (EEG slow components when dozing, for example). But when differences are due to changes in BAEP oscillations, subtraction shows which of these oscillations altered. As an example, Fig. 24 shows that the "delay" of wave I, caused by cotton wool in the ear canal, is due to phase shifts in the 500 and 1000 c/s oscillations. Figs. 94-99 show further examples.

Thus, recognition of the oscillatory origin of the BAEP, and using subtraction, allow the investigator to go beyond stating

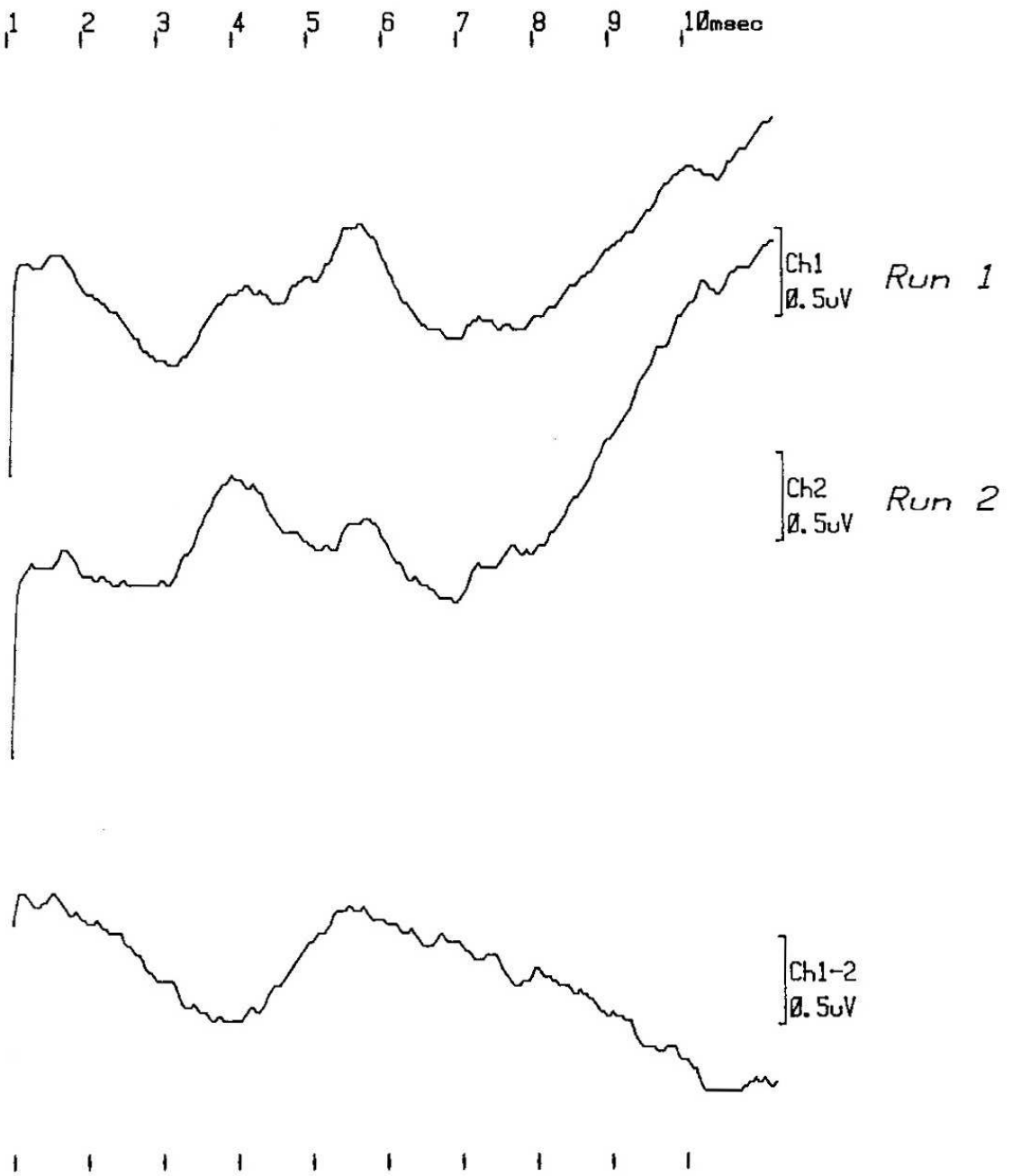


Fig. 91 Variability between runs

Healthy woman,20. Left-sided rarefaction records, 10 minutes apart.
Subtraction shows irregular low frequency pattern, likely to be artefact.

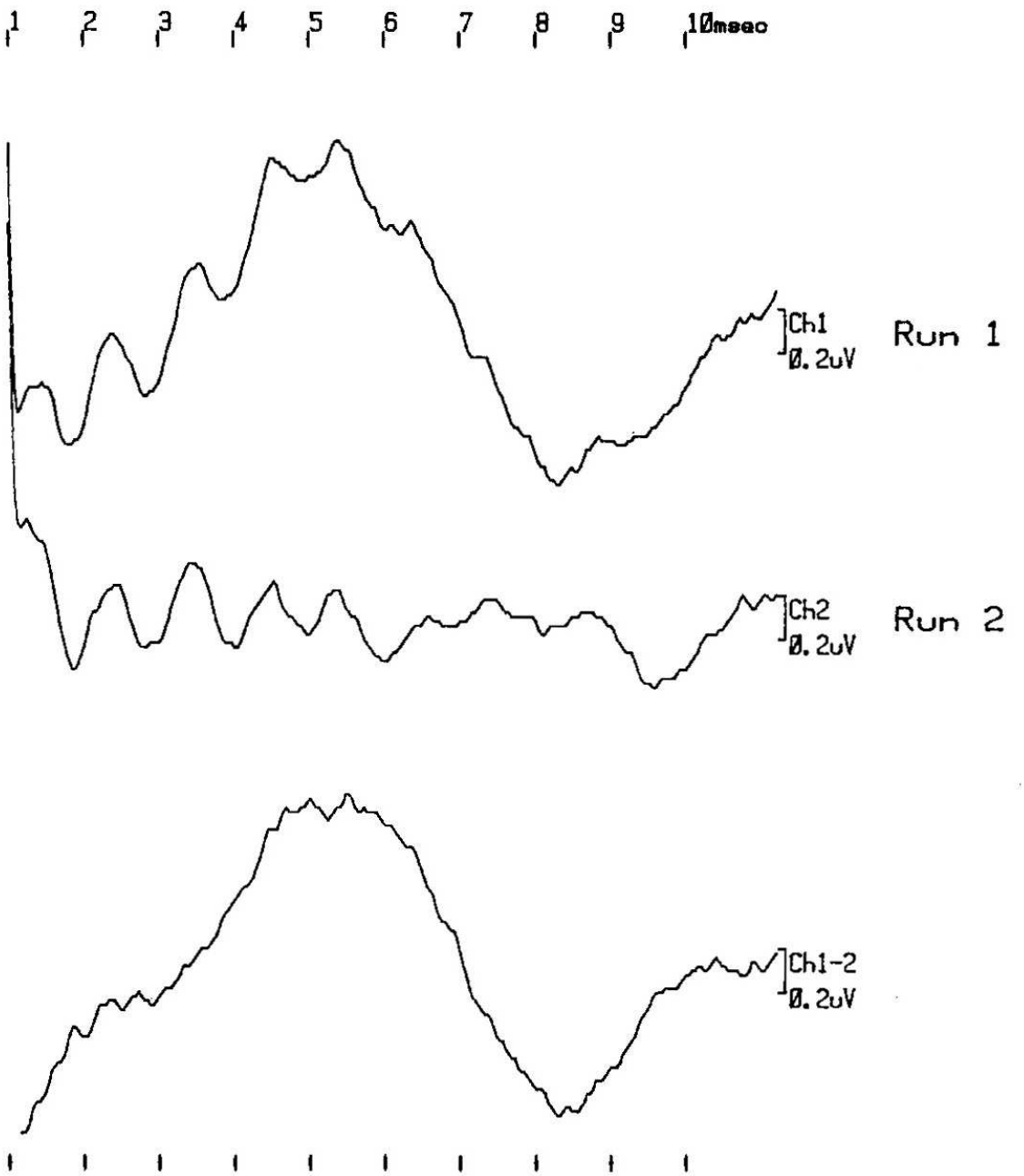


Fig. 92 Variability between runs

Healthy woman,30. Left-sided condensation records, 15 minutes apart. Second record, by itself, would be regarded abnormal.
Subtraction shows irregular low frequency pattern, likely to be artefact.

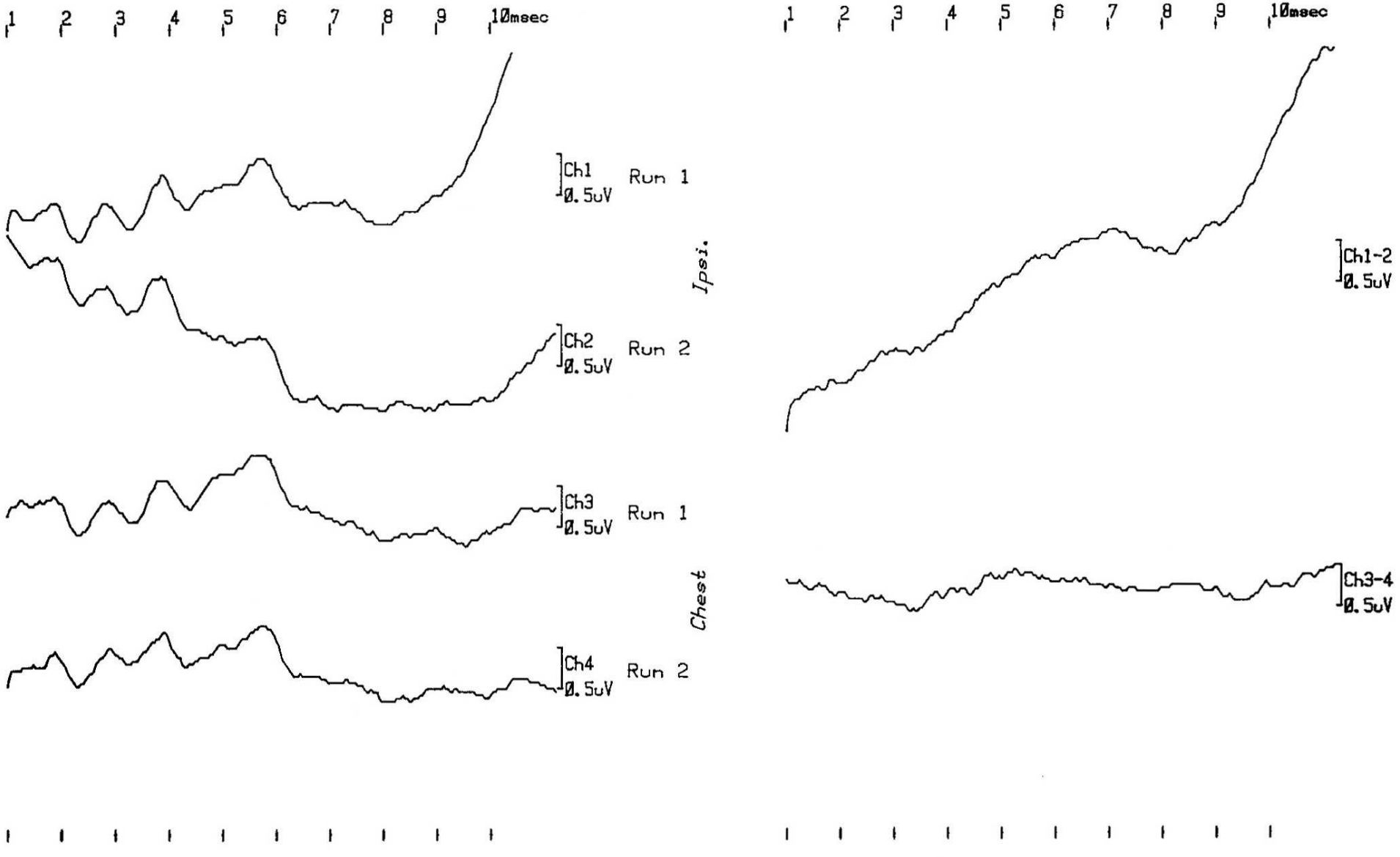


Fig. 93 Variability between runs

Healthy man (SC),18. Two runs, about 15 minutes apart, of left-sided rarefaction records. Artefact affecting ipsilateral channels (upper two traces) shows in subtraction as irregular low frequency pattern.

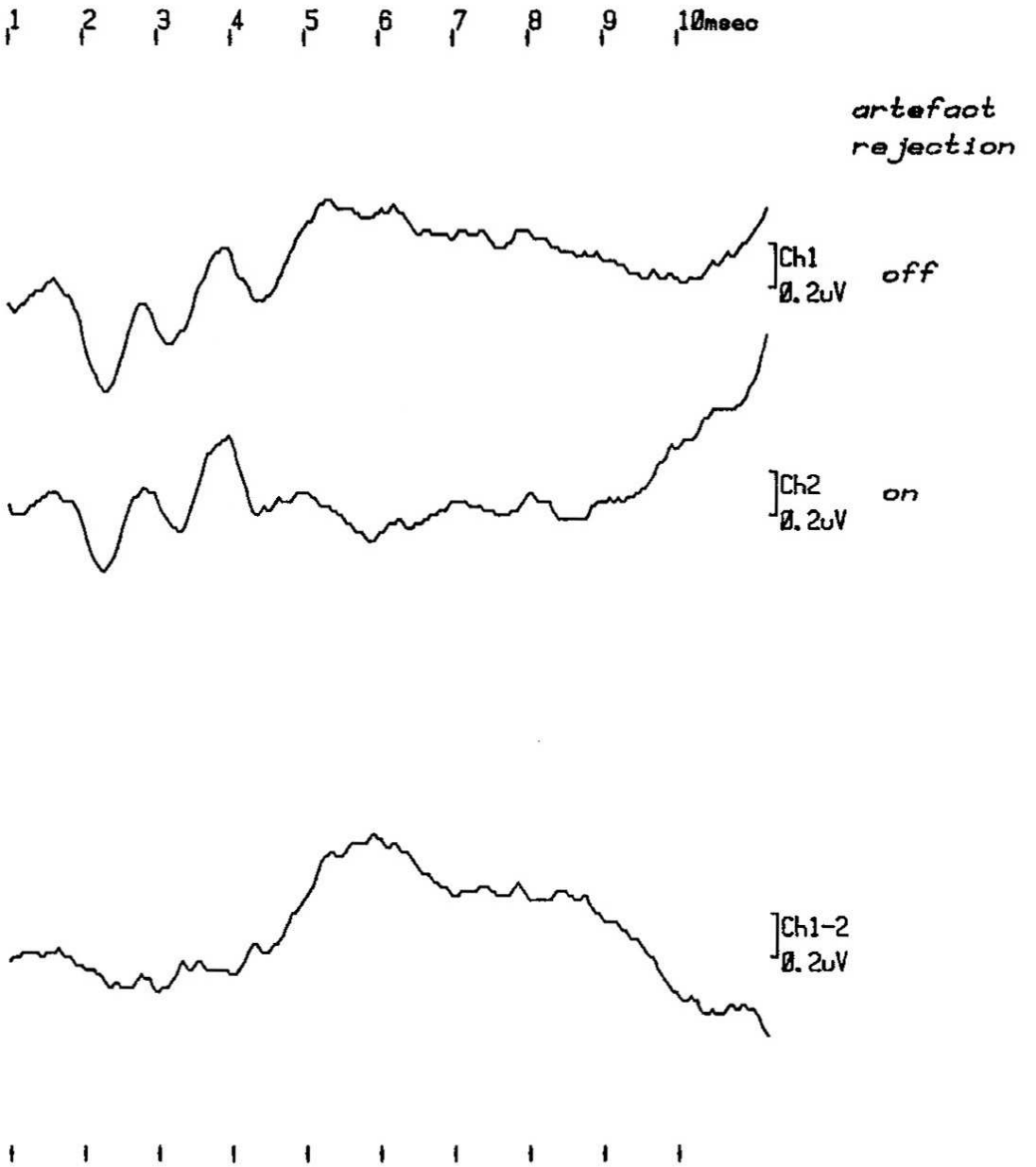


Fig. 94 Variability between runs

Man (JA),22, with MS. Two runs, 15 min. apart, of right-sided records with and without automatic artefact rejection.
Irregular low frequency pattern in subtraction suggests artefact as cause of variability.

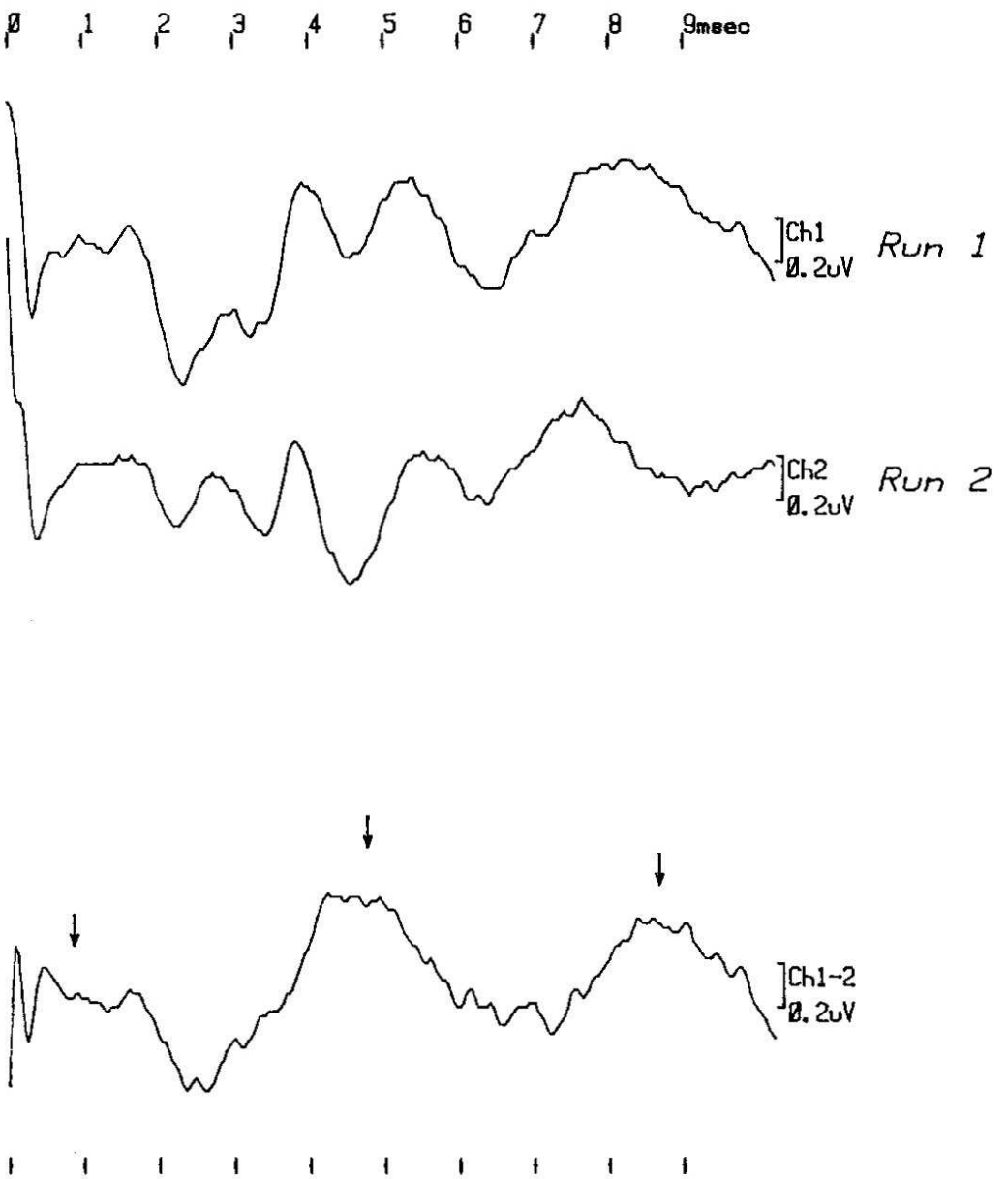


Fig. 95 Variability between runs

Man (DT),48, with MS. Two runs, 10 minutes apart, of right-sided record.
Subtraction shows variability due mainly to change in 250c/s (arrows) oscillation.

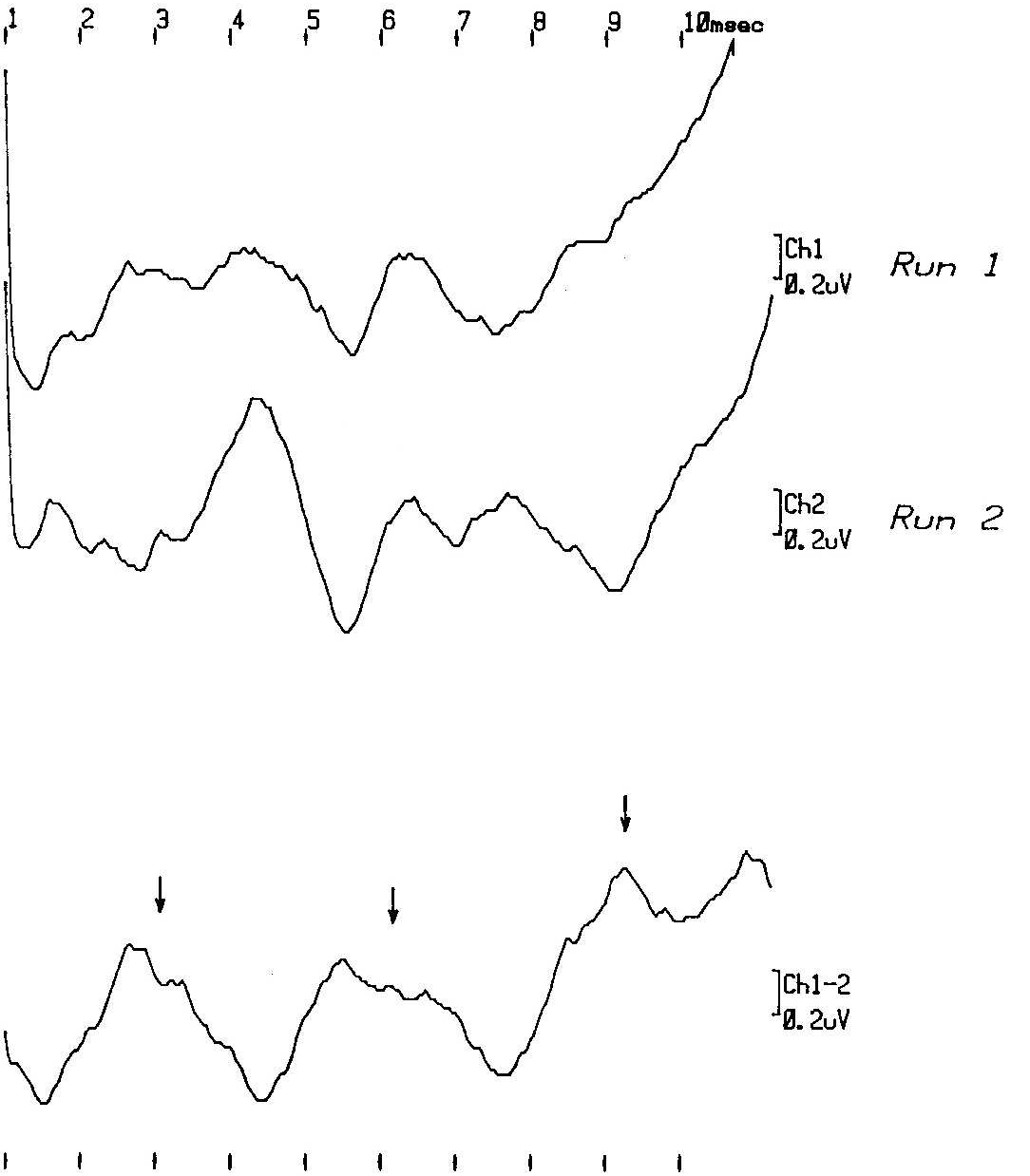


Fig. 96 Variability between runs

Woman,(JS),66, with signs of brainstem infarction. Two runs, 20 min. apart, of left-sided records. Subtraction shows lability due to change mainly in 320c/s oscillation (arrows). Intermediate slow activity dominated her EEG background activity.

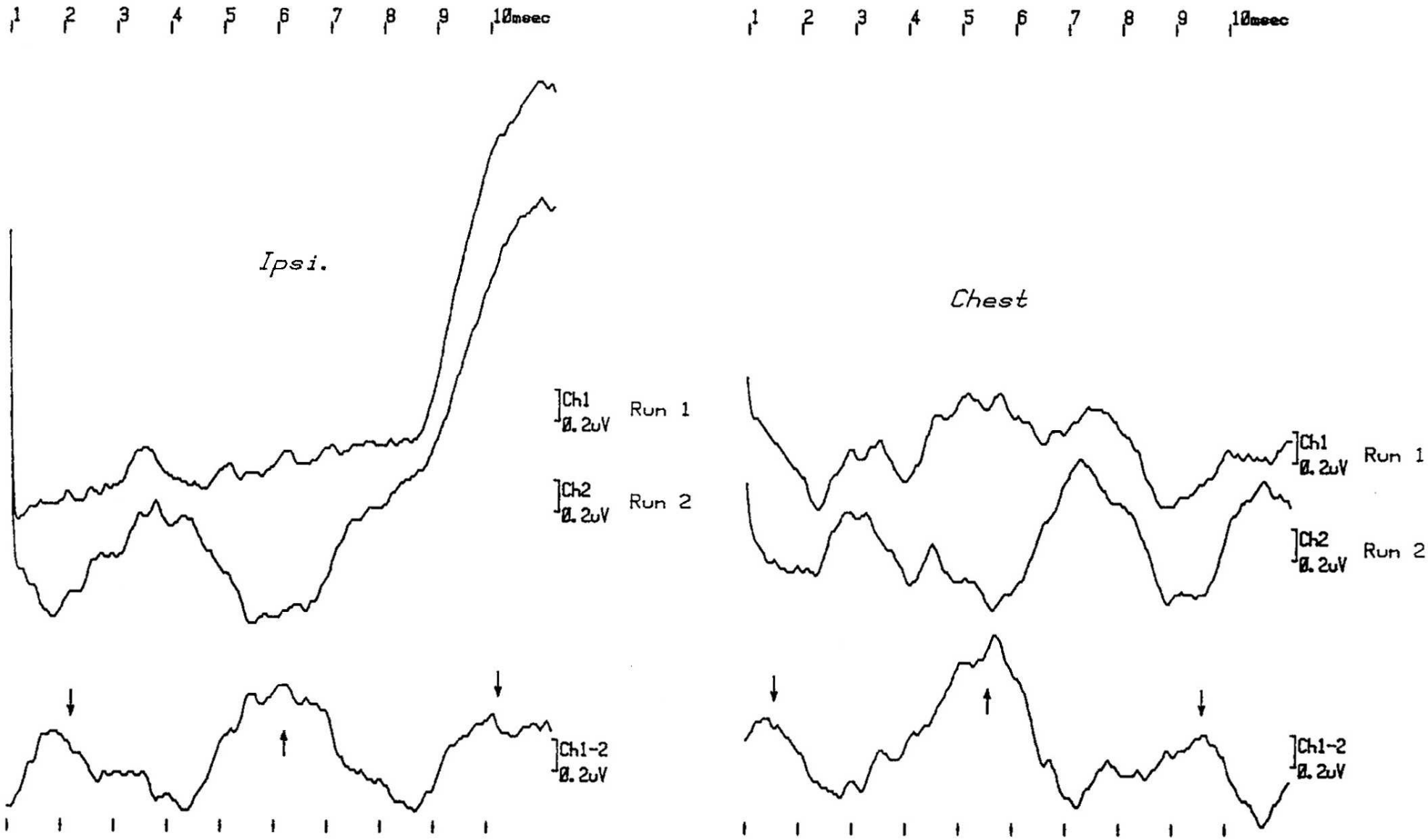


Fig. 97 Variability between runs

Woman (NJ),63, investigated for demyelinating disease. Two runs, approx. 20 minutes apart, of left-sided condensation records. Waveforms are distorted, waves indistinct. Change in 250 c/s oscillation (arrows) explains variability.

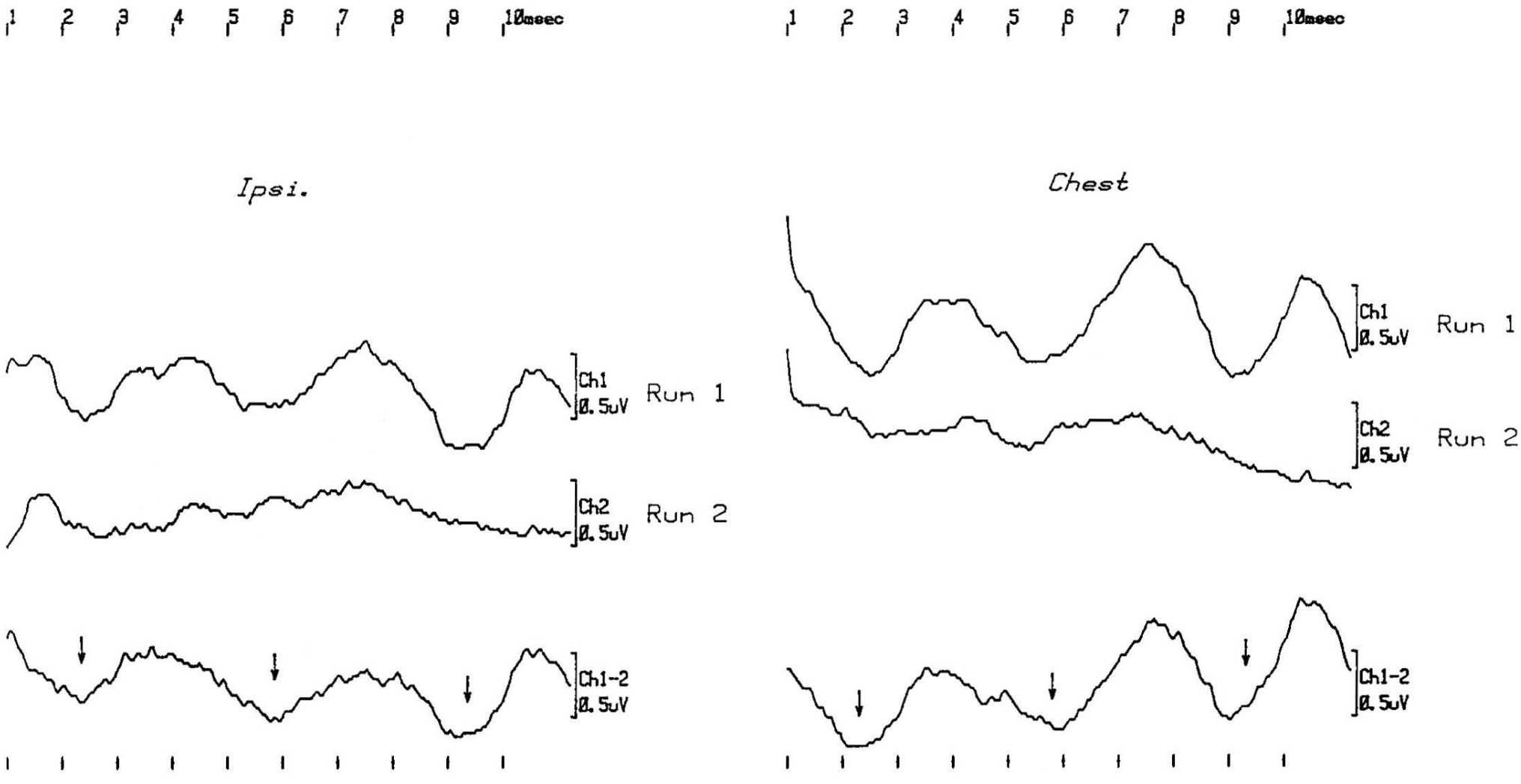


Fig. 98 Varaibility between runs

Man (JW),46, with MS. Two runs, about 20 minutes apart, of right-sided records. High frequency oscillations are negligible.
Subtractions show lability due mainly to change in 290 c/s oscillation (arrowed, equidistantly for both channels).

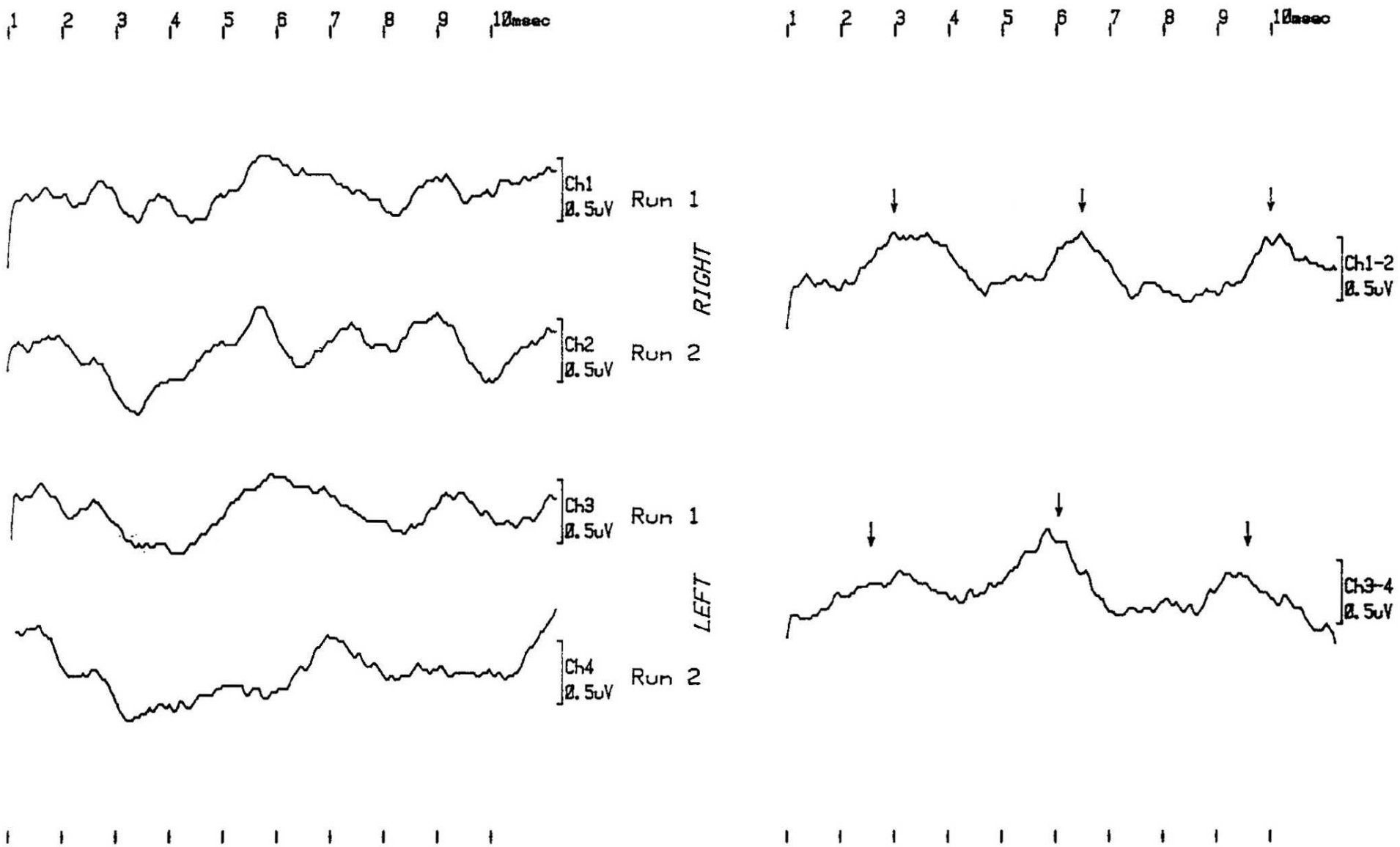


Fig. 99 Variability between runs

Man (NS),31, with MS. Two runs from the two sides: second run on right is two week from first; on left 15 min.
Variability due mainly to change in 290c/s oscillations (arrowed in subtractions).

that a BAEP looks abnormal. He can express abnormality in specific terms e.g. failure to sustain or absence of a specific oscillation. And, unlike latencies, these descriptions may prove to have physiological significance.

Finally, given that the BAEP is composed of oscillations, the following questions are raised:

1. What is the chemical basis, at the cellular level, for these oscillations?

2. From which structure do they come?

3. What do they have in common with oscillations in other parts of the nervous system?

4. What function do they serve, and what significance does their varying characteristics (e.g. phase, duration) have?

5. In what way is pathology (demyelination for example) related to the changes in these oscillations, and does this relation explain other manifestations of MS?

6. Can generation of other evoked potentials be explained in a similar way?

To conclude, a model of BAEP generation has been produced. This model fits the various BAEP phenomena observed in this work, both in normal persons and in patients. Based on this model, it is

proposed that the origin of the BAEP must be peripheral, and likely to be the cochlea.

This hypothesis may be tested by studying the BAEP in patients on treatment with drugs, such as the aminoglycoside antibiotics, that are ototoxic, and known to exert their effect on the cochlear hair cells and not on the auditory nerve. In fact, Chiappa (1983) has reported on six patients receiving these antibiotics; their BAEP did show latency changes, even absence of waves. But given the controversy this thesis raises with the widely accepted BAEP origin from the brainstem, not the cochlea, and the implication this has on the use of the BAEP, it is important to study more such patients.

For the same reason, it would also be useful if blocking (as by applying a local anaesthetic) of conduction in the VIII nerve in animals, can be shown to have no effect on the BAEP. Results of such test, however, would be meaningful only if one can be certain that the technique of making the conduction block has no effect whatsoever (impairment of blood supply, for example) on the cochlea.

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