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# THE MISMATCH NEGATIVITY EVOKED BY CHANGES IN THE FREQUENCY OF AN AUDITORY STIMULUS

by

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# Vitae

Jiri Vajsar was born in Prague, Czechoslovakia, on April 16, 1952. He graduated from Charles University in Prague with M.D. degree in 1976. From 1985 to 1987 he studied for a Master of Science in Physiology at the University of Ottawa. His research supervisor was Dr. Terence Picton. Currently, Dr. J. Vajsar is completing his training in Child Neurology at the Hospital for Sick Children in Toronto, Ontario.

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Abstract

The current knowledge of human auditory evoked potentials (AEPs) is far from complete and extensive research is necessary for full understanding of these potentials. This thesis deals with some of the unknown issues in slow AEPs.

Slow AEPs were recorded in 10 healthy reading subjects in response to a 400 ms tonebursts presented every 0.9 s. The N1, P2 and sustained potential were recorded from 14 scalp-attached electrodes. A change in the frequency of the tonebursts elicited an additional negativity - the mismatch negativity (MMN). The amplitude and latency of MMN changed with the magnitude of frequency deviance between stimuli which was varied between 50 and 2000 Hz. The latency of MMN increased as the amount of deviance decreased. The amplitude remained stable until large deviances at which time it increased significantly.

The voltage distributions of the MMN and N1 were significantly different from that of the SP. The MMN and N1 had their maximal amplitudes in the fronto-central areas, whereas the maximal amplitude of the SP was recorded frontally. The topographic mapping and statistical analysis of voltage distribution of individual waves enabled us to recognize and differentiate between the possible generators of the MMN, N1 and SP. Both the MMN and N1 are generated in the auditory cortices. The SP is more complexed and may consist of more than one component.

Introduction

The investigation of the neural basis of human hearing has advanced with the development of evoked potential (EP) techniques. Evoked potentials can provide measurements of brain activity either during elementary auditory

functions like hearing pure tones or during more complex functions like perceiving speech. The scalp-recorded EPs represent the spatial and temporal summation of volume-conducted electrical activity generated in different areas of the brain during the processing of incoming sensory information.

Auditory evoked potentials (AEP) can be divided on the basis of stimulus characteristics into transient, steady-state and sustained responses. Transient responses are the potentials evoked by a change in the stimulus such as an onset or offset during a relatively slow stimulus rate which enables the response to be finished before the beginning of the next stimulus.

The transient responses are usually divided on a temporal basis into several overlapping groups (Davis, 1976; Picton et al., 1985):

| | | |
|---|---|---|
| First | (0 - 5 ms) | - Cochlear Nerve Action Potential (N1, N2). |
| Fast | (2 - 20 ms) | - Auditory Brainstem Response (I - VII). |
| Middle | (10 - 100 ms) | - Middle Latency Response (No, Po, Na, Pa, Nb, Pb). |
| Slow | (50 - 300 ms) | - Vertex Potential (P1, N1, P2, N2). |
| | | - Processing Negativities (Nd, N2a, N2b). |
| Late | (250 - 1000 ms) | - Late Positive Waves (P3a, P3b). |
| | | - Slow Negative Wave (SNW). |

Unfortunately some parts of this classification are not generally accepted and we can find in the literature that the first and fast AEPs are called "short", the slow AEPs are called "late" and the late AEPs are called "long" (Polich and Starr, 1983). For the purpose of this review we will use the afore-mentioned classification.

Steady-state potentials, such as the 40 Hz potential in the auditory modality, are elicited in response to relatively fast stimulus rates. This causes an overlapping of the responses to succesive stimuli and the result is

periodic response at the frequency of stimulation or some harmonic thereof (Regan 1982).

The sustained potential (SP) is evoked by the continuation of stimulation (Picton et al., 1978a). To elicit a distinct SP during auditory stimulation, the duration of the stimulus has to continue beyond the latencies of the N1-P2 complex.

The slow components of AEPs are quite variable. They depend on both the physical nature of the stimulus and the perceptual meaning of the stimulus. For example, the N1 amplitude increases with higher intensity and also increases with attention paid to the stimuli (Picton et al., 1974; Naatanen and Picton, 1987).

AEPs can be evoked by different types of stimuli. Thus we can consider AEPs to acoustic (clicks, tone bursts), phonetic (phonemes, e.g. consonant-vowel syllable) and semantic (words) stimuli. Evoked potentials to these different types of stimuli may allow the differentiation of brain activities related to acoustic versus phonetic or semantic analysis.

The present study deals with slow transient AEPs and the cortical sustained potential (SP). These potentials originate principally in the auditory cortices (Elberling et al., 1982; Hari et al., 1982; Scherg and von Cramon, 1986) and therefore a basic knowledge of the cortical organization of the auditory system is essential.

## Anatomical and physiological remarks on the auditory cortex

In spite of more than 100 years of gradually accelerating study, the auditory cortex still presents something of a functional puzzle. We are still a long way from being able to define what it does, let alone how it does - though we can say a little about what it does not. At present we are still

lacking functional definition of the auditory cortex and therefore any delimitation of that cortex must itself be anatomical.

A. Organization of the auditory cortex

In 1878 Heschl traced the auditory radiations in the human brain from the medial geniculate body to the superior temporal convolution. The classical cytoarchitectonic maps, dividing brain into several regions of specific structures (Campbell, 1905), designated the temporal transverse convolutions of Heschl as audiosensory. In Brodmann's classification the region comprised areas 41 and 42 (Brodal, 1981). This area of auditory koniocortex, located in primates on the supratemporal plane, became known as a "primary auditory cortex" (Fulton, 1943). It was believed to have an elementary sensory function like hearing of buzzing, clicking, booming, etc. (Pfeifer, 1936). However, more advanced studies using axonal transport techniques, such as the horseradish peroxidase technique, allow a definition of the cortical areas on the basis of their anatomical connections and, together with cytoarchitectonic and microelectrode mapping techniques, these procedures have revealed that the organization of auditory cortex is far more complicated. Furthermore, there are significant anatomical differences in auditory koniocortex between primates and other animals.

B. Animal studies

Woolsey and Walzl (1942) recognized in electrophysiological studies on cats that in addition to primary auditory cortex there was a secondary auditory cortex which was an adjacent cortical band with well-defined connections in the medial geniculate body (pars magnocellularis). It was believed to respond to more intense stimuli and to play a role in integration

of acoustic reflexes. Rose (1949) described three cytoarchitectonically distinct areas in cats: primary auditory cortex - AI; secondary cortex - AII; and a further auditory area on the posterior ectosylvian gyrus (Ep).

Merzenich and Brugge (1973) studied auditory cortex in macaque monkeys and redefined "primary auditory cortex" - AI area occupies only a part of its former region in superior temporal gyrus. Adjacent to AI area are several additional auditory fields described on the basis of their architectonic and electrophysiologic characteristics. The topographically (tonotopically or cochleotypically) organized fields are: LAF - lateral auditory field; RAF - rostrolateral auditory field; a,b and c - other topographically organized fields. There is also a NT-CMAF (nontopographically organized caudiomedial auditory field).

The topographically organized auditory fields are connected via multiple parallel sensory pathways with auditory thalamus. These auditory thalamocortical connections are even more complicated. Each subdivision of auditory cortex receives input from one or more of the component nuclei or subnuclei of the ventral, dorsal and medial divisions of the medial geniculate complex (Merzenich and Kaas, 1980). This allows each cortical representation to be simultaneously activated by direct thalamic projections as well as by cortical connections.

Auditory information is relayed from the auditory cortex to auditory association areas for higher order analysis and synthesis requiring integration of sensory information. Pandya and Seltzer (1982) described two auditory association areas AAI and AAII in monkeys. The AAI area is located in the posterior portion and AAII in the more anterior part of the superior temporal gyrus. Primary auditory cortex, i.e. AI, located in the middle part of the supratemporal plane (in upper part of the superior temporal gyrus),

projects to the AAI area which connects back to the AII primary sensory cortex located in the innermost portion of the supratemporal plane. The AI area projects also to the AAII association area and to the premotor cortices of the frontal lobe. The AAII region projects to the paralimbic area of the temporal lobe, to the polymodal association areas in the parietal and temporal lobes, and to the prefrontal cortex. There are also complex connections between the subcortical structures (thalamus and reticular formation as well), primary auditory areas and the polysensory areas in the other cortices.

B.(i) Tonotopic organization

Electrophysiological studies on monkeys showed tonotopic organization in some of the primary auditory cortices. Thus the AI area has the higher frequencies located caudally and medially and the lower frequencies rostrally and laterally. Between these two there is a complete frequency spectrum representing different stimulus frequencies, with strips of the same frequency located perpendicularly to the line of frequency progression (Tunturi, 1950; Merzenich et al., 1975). Also as mentioned previously, some of the newly described areas have tonotopic organization.

The cortical fields with topographic organization receive thalamic input from a different group of thalamic nuclei than the other cortical fields without obvious topographic organization (Merzenich and Kaas, 1980).

B.(ii) Ablation studies

Ablation of the auditory cortices in cats does not lead to a complete loss of hearing (Pickles, 1982; Durrant and Lovrinic, 1984). Trained cats after bilateral removal of the auditory cortical areas may perform some of the

following tasks:

1. Respond to the onset of a sound.
2. Respond to changes in the intensity of a tone.
3. Respond to changes in the frequency of a tone.
4. Respond to changes in the location of a sound.

For example, a cat trained to go to one place when it hears a tone of slightly changing frequency will perform the same task after bilateral ablation of auditory cortices. On the other hand the same cat may show a deficit in the performance of the following tasks:

1. Discrimination of tonal pattern.
2. Discrimination of sound duration.
3. Localization of sounds in space.

Again the example is the cat trained to respond only to the one type of sequence of tones of different frequency (e.g. ABA) which postsurgically is not able to distinguish this sequence from AAB or BAA.

The available evidence from animal studies indicates that considerable auditory perception must occur subcortically. Also the difficulty of the discrimination task may be an important factor whether the discrimination occurs at the cortical or subcortical levels. Cranford et al. (1976) suggested that in difficult discrimination tasks for cats, cortical lesions produce deficit, but when the tasks are easy the deficit is not present. It is also possible that the more difficult auditory discrimination tasks (based on the temporal dimension) utilize auditory short-term memory whereas the easy ones do not. This further suggests that the auditory cortex is necessary for auditory short-term memory.

C. Human studies

The organization and limits of the auditory cortex in man were defined mainly from cytoarchitectonic studies and clinico-pathological correlations in patients. Recently, also other methodologies like positron-emission tomography, blood flow studies with radioactive material and magnetoencephalograms have showed their importance in the physiology of the auditory cortex.

C.(i) Cytoarchitectonic studies

Galaburda and Sanides (1980) showed similarities in architectonics between human and monkey auditory cortices. The authors confirmed that the human auditory cortex is located primarily on the supratemporal plane, where the middle part is the transverse temporal gyri of Heschl, and in the surrounding parts of the superior temporal gyrus. The auditory cortices are divided into core and belt portions that relate to different evolutional stages. At the center of the transverse gyrus of Heschl the newer core is divided into the lateral (lateral koniocortex) and medial zones (medial koniocortex). This division probably reflects different connectivity. The medial part in the macaque (medial koniocortex) is rich in callosal connections (Pandya and Sanides, 1973). The core is highly granular, especially in layers II-IV. Layer V is relatively hypocellular and parvocellular and layer VI appears as a relatively more dense parvocellular narrow strip. Concentrically surrounding the core there are several belt areas of parakoniocortex which are phylogenetically older and have different cytoarchitectonic organization.

Auditory cortex is not solely restricted to the temporal lobe. Galaburda and Sanides (1980) reported that parts of the inferior parietal lobule which are receiving inputs from the magnocellular and supragenicular nuclei of thalamus belong to the auditory cortex.

C.(ii) Tonotopic organization

The tonotopic organization of core has been studied with positron-emission tomography (PET). The results revealed that the changes in regional cerebral blood flow in auditory cortex induced by the tones of higher frequencies were located deeper, posteriorly and medially to the changes induced by the tones of lower frequencies (Lauter et al., 1985). However, the PET had a resolution about 2 cm and did not allow precise localization of activated regions of the cortex. Transient auditory evoked magnetic fields were also used to investigate the tonotopic organization of the human auditory cortex. The location of the current dipole elicited by 500 Hz tones was anterior to that of 4000 Hz tones in the tangential plane of the transverse temporal gyri (Eberling et al., 1982; Pantev et al., 1988).

C.(iii) Clinical studies

With intact peripheral auditory and eighth nerve function, pure tone audiometry reveals no abnormalities in patients with unilateral cortical lesions involving auditory areas (Hodgson, 1967). However, Jerger et al. (1969) in a patient with unilateral damage to the temporal lobe found deficits in sound localization and also abnormal threshold for brief stimuli.

Patients with bilateral damage of auditory cortices are rare and hearing abnormalities are usually associated with such damage and tests complicated by accompanying aphasia of various degrees and types. Henschen (1922) reviewed 1337 cases of aphasia and found nine patients in which bilateral restricted vascular lesions of the transverse gyri of Heschl resulted in deafness. However, Jerger (1964) and Kanshepolsky (1973) reported patients with bilateral lesions of auditory cortices who suffered little or

no impairment in recognizing the frequency or intensity of pure-tones. Earnest et al. (1977) reported a patient with bitemporal infarction on CT scan who suffered total deafness and aphasia with recovery to 65 - 80 dB loss. Graham et al. (1980) also reported a patient with bitemporal embolism who became deaf and aphasic with no responses on pure audiometry.

Variable results in clinical studies of hearing deficits of cortical origin derives from the fact that damage is rarely restricted to only Heschl's gyri. The lesions of vascular origin are usually more extensive because branches of middle cerebral artery, which supply the auditory cortices, also supply portions of the frontal, parietal and inferior temporal lobes which are the regions of auditory association areas. Therefore a "simple" hearing deficit of central origin, i.e., strict pure tone deafness, is very rare.

Another important factor in clinical assessment of deafness is the time of clinical assesment. Jerger et al. (1969) and Miceli (1982) reported cases of cortical deafness in which hearing of pure tones improved from total deafness to a slight threshold elevation, but the discrimination of sounds remained impaired.

From these few examples it is evident why we can only hypothesize the general functions of the auditory cortex and how difficult it is to localize auditory functions on the basis of clinico-pathological studies. It is therefore necessary to study and to interrelate results obtained with other techniques, such as evoked potentials.

## Slow transient auditory evoked potentials

The waveform recorded from the scalp in response to slow presentation rates of an auditory stimulus consists of several recognizable waves in the

range 50 - 300 ms (Picton et al., 1974; Polich and Starr, 1983). The P1, N1, P2 and N2 waves are parts of the vertex potential and the Nd, N2a (also called the mismatch negativity) and N2b waves are processing negativities (Picton et al., 1985). All these waves are affected by both physiological parameters of the stimuli and the psychological state of subjects.

The present study deals with the vertex potential and the mismatch negativity (MMN). Both potentials can be recorded from subjects not paying any attention to stimuli. The MMN is obtained by subtracting the response to an ignored stimulus from the response to another ignored stimulus with different physical characteristics (deviant stimulus). On the other hand both the Nd and the N2b are recorded only when the subject is detecting some of the eliciting stimuli. The Nd can be obtained by subtracting the averaged response to an ignored stimulus from the response to the same stimulus when it is being attended (Naatanen et al., 1978; Hansen and Hillyard, 1980; Hillyard and Kutas, 1983). The N2b is obtained in addition to the N2a when attention is directed to the deviant stimulus (Naatanen et al., 1982).

The following chapters will review the literature findings on the individual slow transient AEPs relevant to the present experiment.

## A. The N1-P2 complex

During studies devoted to sleep research Pauline Davis (1939) found a clear potential change in the electroencephalogram evoked by a peripheral stimulation (pure tones, electrical shocks and flash light) in the waking brain. The pure tone stimulation elicited a negative wave with peak latency between 100 - 150 ms which was followed by a positive wave. The response had the largest amplitude at the vertex. Similar waves had been obtained in many other studies and the response became known as the vertex or the V potential

(Davis and Zerlin, 1966; Butler, 1968; Kooi et al., 1971; Picton et al., 1974). The vertex potential consists of four peaks: P1, N1, P2, and N2. The peaks N1 and P2 have the largest amplitude. These two peaks have been usually referred together as the N1-P2 complex (Wood et al., 1984).

A.(i) Scalp distribution and origin

The N1-P2 complex is broadly distributed over the scalp with amplitude maximum in the midline slightly anterior to the vertex (Vaughan and Ritter, 1970; Kooi et al., 1971; Picton et al., 1974; Wood and Wolpaw, 1982). Initially in the 1960s it was believed that the vertex potential reflected activity of "diffuse nonspecific thalamocortical pathways" (Wood et al., 1984). Vaughan and Ritter (1970) found inverted polarity of the N1 and P2 over the approximate location of the Sylvian fissure. They concluded that the distribution of the N1 and P2 "was most consistent with dipole layer sources within the primary auditory projection cortex of the supratemporal plane". The summation of the potentials from two auditory cortices was thought to be the cause of the maximal amplitude in the midline electrodes. Kooi et al. (1971), using the sternovertebral noncephalic reference of Stephenson and Gibbs (1951), did not find the polarity inversion of the N1 and P2 waves over the Sylvian fissure. Picton et al. (1974), using a chest reference, confirmed that the N1 and P2 have their maximum over the fronto-central scalp region. Therefore,the authors suggested that the N1 and P2 originate largely from the frontal association cortex.

Wood and Wolpaw (1982) analyzed the potential field over the duration of the N1-P2 complex and constructed isovoltage topographic maps. It was clear from the maps that there is an existence of voltage of opposite polarities at posterotemporal and frontocentral scalp locations. The authors suggested that

AEPs in the latency of the N1 and P2 waves are generated by multiple sources which partially overlap in time and that one of the sources is in the auditory cortex.

Scherg and von Cramon (1986) developed the concept of "dipole source potentials", which defines slow AEP activity as tangential and radial "dipole source components". The tangential component, negative at 100 ms and positive at 180 ms, was more prominent than the radial component which was positive at 100 ms and negative at 150 ms. The dipole sources were located in the temporal lobes.

Naatanen and Picton (1987) reviewed the literature on component structure and possible sources of the N1 wave was hypothesized that the following six components contribute to the N1 wave:

1. Negative wave with a peak latency at 100 ms, maximally recorded from frontocentral scalp and slightly greater over the hemisphere contralateral to the stimulation. The amplitude of this component increases with increases in stimulus intensity. The refractory period is about 4 s. It is possible that this component may enhance with attention.

   The equivalent current dipole source is located predominantly on the cortex of the supratemporal plane.

2. A component with a positive wave at 100 ms and a negative wave at 150 ms. The component has a maximum amplitude at the midtemporal electrodes and is greater over the hemisphere contralateral to the ear of stimulation. This component is enhanced with attention.

   The generator is probably in the superior temporal gyrus. The authors concluded that "This component would be generated in the auditory association areas, activated by connections from the primary auditory

cortex and also possibly from the thalamus". The component has a radially oriented generator and is not detected by magnetoencephalogram.

3. A negative wave, maximal at the vertex, with a peak latency at about 100 ms. It is most easily recorded with auditory stimuli greater than 60 dB SPL and when ISIs are greater than 3 s. This component is not modality specific.

   The component is probably generated in the frontal motor cortex under the influence of the reticular formation and the VL nucleus of the thalamus.

4. The processing negativity-Nd is sensory-specific and attention related. It starts at about 50-100 ms and lasts during the processing of an attended auditory stimulus.

   The authors suggest that this "...component is probably generated in the auditory sensory and association areas on the supratemporal plane and on the lateral aspects of the temporal lobe".

5. A second component of the processing negativity called the "attentional supervisor". It has a somewhat different scalp distribution and it lasts longer than the sensory-specific processing negativity. The "attentional supervisor" is more frontal in the later part. It is probably generated in the premotor frontal cortex.

6. The last component, the mismatch negativity, is very complex and will be dealt with in a later chapter.

The following section deals with latency and amplitude changes of the N1 and P2 in relation to the changes in stimulus parameters.

A.(ii) Latency changes

The peak latency of the N1 wave increases with decrease in stimulus intensity. This effect is more prominent for tones than for click stimuli (Rapin et al., 1966; Picton et al., 1977). The N1 near threshold is a broad wave with peak at about 150 - 200 ms. The mean threshold for the N1 in one study was 27 dB SL with a range of 10 to 45 dB SL and in another 16 dB SL with a standard deviation of 17.2 dB (Mendel et al., 1975; Stapells, 1984). The N1 and P2 latencies also increased when the rise time of the stimulus tone exceeded 30 ms (Onishi and Davis, 1968).

A.(iii) Amplitude changes

The amplitude of the N1-P2 complex generally increases with increasing stimulus intensity (Davis and Zerlin, 1966; Picton et al., 1977). However, some individuals demonstrate a saturation or flattening of amplitude at high intensities (Buchsbaum, 1976). The amplitude of the N1 also relates to the tonal frequency (Antinoro et al., 1970; Picton et al., 1978a). It remains largest and approximately the same for the tones up to 2000 Hz, for tones above this level amplitude decreases. The P2 is smallest for 500 Hz tones with an increase in amplitude for tones below and above this frequency (Picton et al., 1978a). Both the N1 and the P2 increase in amplitude with longer interstimulus intervals (ISI). However, the longest ISIs used to obtain the maximal amplitudes are different for different intensities (Davis et al., 1966; Nelson and Lassman, 1968; Milner, 1969; Picton et al., 1977; Picton et al., 1978a; Hari et al., 1982). Binaural stimulation produces about 20% larger N1-P2 complex than monoaural presentation (Davis and Zerlin, 1966). However, only the P2 and not the N1 showed the same effect in another study (Picton et al., 1978a). There is also asymmetry in the N1 amplitudes

related to the ear of stimulation (Vaughan and Ritter, 1970; Picton et al., 1978a). The contralateral response to the ear of stimulation is larger and the response tends to be greater over the right hemisphere.

A.(iv) Amplitude changes in relation to pitch changes

Ritter et al. (1968) studied habituation of the N1-P2 complex. The amplitude of the N1-P2 response to 1000 Hz stimuli dropped to 50% by the fourth stimulus when the stimuli were presented at the rate of 0.5 Hz. To prove that this decrement is due to habituation the authors tried to demonstrate that the amplitude change can be reversed by dishabituation. The frequency of the 21st stimulus was changed to 2000 Hz. However, the amplitude of the N1-P2 complex to this different stimulus did not show significant change. Since the authors failed to demonstrate dishabituation they suggested that "...an alternative explanation for the short term decrement with a 2 sec inter-stimulus interval would invoke relative refractoriness within the generators of the AEP".

Contrary to this are the findings of Butler (1968) who showed that the amplitude of the N1-P2 complex to test stimuli of certain frequencies presented every 5 sec was significantly reduced when tones of the same or nearly the same frequency (intervening tones) were presented between the test tones. When the frequency of intervening tones was further removed from that of the test tones the amplitude of the response to the test tones was significantly greater. The author proposed that the changes in the amplitude of the N1-P2 complex is to some extent frequency-specific. The amplitude change of the N1 and P2 waves in relation to the change in the stimulus frequency has been confirmed by other investigators (Picton et al., 1978b; Woods and Elmesian, 1986).

A.(V) Age related changes

Latency and amplitude changes of the N1 and P2 peaks have been studied in subjects ranging in age from childhood to old age (Weitzman and Graziani, 1968; Schenkenberg, 1970). The studies have revealed that the latencies were longest in infancy, decreased through adolescence and remained stable thereafter. The N1-P2 complex was already present in 25 weeks old babies. The latencies of the N1 and P2 peaks at that age were about 250 ms and 650 ms, respectively.

The amplitude of the N1-P2 complex increases steadily from childhood through adolescence and remaines at that level through old age (Callaway and Halliday, 1973). In infancy influence of the phase of sleep upon the amplitude of the N1-P2 complex and the N2 peak has been demonstrated (Rapin and Graziani, 1967; Ellingson et al., 1974). The P2 wave was detected most consistently regardless of the state of arousal and the latency and amplitude of this response remains reasonably stable both within and between recording sessions. The N1-P2 complex was significantly larger and the latencies of the N1 and P2 waves longer during quiet sleep than during wakefulness or active sleep.

B. The auditory sustained potential

Kohler et al. (1952) first recorded a negative baseline shift from the fronto-central regions of the scalp in response to a sustained acoustic stimulus. This negative shift, called sustained potential, has been studied by several authors mainly in relation to changes in the eliciting stimulus (Keidel, 1971; David et al., 1969; Picton et al., 1978a; 1978b). The onset latency of the SP is about 150 ms (Picton et al., 1978a). The amplitude

of the SP is maximal at the fronto-central region, which is also the region of the largest N1 wave (Picton et al., 1978c; Polich and Starr, 1983) and MMN (Naatanen et al., 1982). Despite the fact that all these potentials have their maximal amplitudes in the same region they may have different scalp distribution. For example, the SP has a different scalp distribution from the N1 (Picton et al., 1978c). Principal component analysis of amplitudes of the SP and N1 waves measured at 17 scalp electrodes showed significantly different scalp distribution of the SP from the N1 wave. The analysis revealed that the SP is more frontal and much less posterior and temporal than the N1 wave.

Because of the proximity of the SP to the transient slow AEP, the following section will review important findings on the sustained potential in relation to physical changes in the auditory stimulus.

B.(i) Stimulus duration

David et al. (1969) and Keidel (1971) reported that the duration of the SP is determined by the stimulus duration. Picton et al. (1978b) recorded a SP to tones lasting up to 9 s but he found that the SP decreased in amplitude for the tonebursts longer than 3 s.

The morphology of the SP is correlated with the envelope of the stimulus intensity (Keidel, 1971; Picton et al., 1978a). The onset latency of the SP was calculated at about 150 ms at the vertex recordings (Picton et al., 1978a) which is well before the P2 peak latency. Accordingly the P2 is modified by the SP. The authors concluded that "This probably explains why the P2 did not pass baseline in a significant proportion of our recordings, and generally tended to be lower in amplitude than in the response to a simple transient stimulus" (pp 195).

B.(ii) Presentation rate

The SP decreases in amplitude with a decrease in ISI. Picton et al. (1978b) reported almost 25% drop in amplitude of the SP when the ISI decreased from 3 s to 1.5 s. When the ISI decreased from 6 s to 3 s the decrease in amplitude was about 10% and was evident only for 90 dB stimuli but not for 70 dB nor for 50 dB stimuli.

B.(iii) Intensity

For 90 dB tonebursts the amplitude of the sustained potential was about -5 uV (Picton et al. 1978b). The amplitude progressively decreased with lower intensities of stimuli. The logarithmic regression line showed $r = 0.87$. The amplitude decreased 0.05 uV with each intensity drop of 0.05 dB. Exponent of the power function was $r = 0.80$.

B.(iv) Tone frequency and frequency specificity of the refractory period

Picton et al. (1978b) recorded the SP for different frequencies in the range 0.25 kHz to 8 kHz. The amplitude of -5 uV for 250 Hz tones decreased with increasing tone frequency.

The amplitude of the SP was also investigated in response to 1000 Hz, 600 ms, 80 db HL test tones in between which intervening tones of the same duration and intensity were presented (Picton et al., 1978b). The test tone occurred every 4 s and there were 3 intervening tones between each pair of test tones. The frequencies of the intervening tones were 250, 750, 1000, 1500, 2000, and 4000 Hz. The smallest amplitude was recorded for the intervening tone of 1000 Hz and the only significant increase in amplitude was when the measurements were compared between intervening stimuli of 1000

Hz and either 500 or 1500 Hz.

Because of the significant decrease in amplitude of the SP to the test tone when the intervening tone was 1000 Hz, and insignificant changes for the other frequencies, the authors concluded that there might be two distinct generator processes for the auditory SP, one quite nonspecific in its frequency receptive field, and one quite specific.

B.(v) Ear of stimulation

The SP recorded separately to left ear and to right ear stimulation did not show any asymmetry in scalp distribution which would be related to the ear of stimulus delivery (Peronnet and Michel, 1977; Picton et al., 1978b). There was a significant increase in amplitude with binaural stimulus presentation. Picton et al. (1978b) concluded that "...right ear stimuli and left ear stimuli activate underlying generators that are to some extent separate and additive, but which have similar electrical field distributions at the scalp".

C. The mismatch negativity in acoustic stimulation

In the last decade several authors have studied paradigms in which changes in the physical characteristics of sensory stimuli in the train of standard stimuli evoke a neuronal mismatch process in the brain. The neuronal activity underlying this mismatch process generates a potential field that can be recorded from the scalp as a negative wave with peak latency between 100 and 400 ms in the acoustic modality. Naatanen, Gaillard and Mantysalo (1978; 1980) recorded AEPs in a group of healthy subjects who performed a dichotic-listening task. The subjects were instructed to discriminate and count occasional slight pitch changes (deviant stimuli) in the stimulus

sequence of standard stimuli presented to a designated ear and to ignore the input to the other ear. The stimuli were delivered to either left or right ear with an interstimulus interval of 800 ms. The sequence of the deviant stimuli was randomized. In the left ear the standard and deviant stimuli were 1000 Hz and 1150 Hz, respectively; in the right ear they were 500 Hz and 575 Hz. The number of deviant stimuli varied from 2 to 9% in different stimulus series. The AEPs were recorded from Cz, T3 and T4 electrode positions (10/20 system) referenced to the right mastoid. Both standard and deviant stimuli elicited the usual N1 deflection at about 100 ms. In addition the deviant stimuli elicited a second, later negative wave. The difference between AEPs to standard and deviant stimuli obtained by subtracting the standard stimulus AEP from the deviant stimulus AEP disclosed a negative shift with an onset latency at about 100 ms and duration of 200 ms. This negative shift was very similar for the attended and unattended inputs. This negative shift has been labelled by Naatanen et al. (1978; 1980) as the mismatch negativity.

... insert Figure 1 about here...

The mismatch negativity (MMN or N2a) is a component of AEPs that is superimposed on the potentials evoked by a repeating sensory stimulus when the stimulus differs from those preceding it. The MMN appears to reflect an automatic process of auditory discrimination that occurs independent of attention in awake and healthy individuals.

C.(i) Relation to other components

Naatanen (1986) classified MMN as a component of the N2 deflection. The term component refers to a contribution from a cerebral generator source to

AEP waveform. A deflection is a wave which usually has one or several peaks which are recognized as points of maximal amplitude. Such deflection may be composed of several overlapping components of the same or different polarity. In the existing literature it is often difficult to delineate the individual components of the N2 wave because in many cases the data have been analyzed and interpreted in terms of a unitary N2 wave. Naatanen proposed the following components of the N2 deflection: "1. MMN whose source in case of an auditory pitch deviation can be located to the primary auditory cortex; 2. N2b, a modality-nonspecific later and shorter negative component whose cerebral source is unknown; 3. a positive component "P2" which may in fact be two components; and, perhaps, 4. a "P165" positivity which precedes, and appears to be intimately linked with N2b and overlaps the early portion of MMN. When the stimulus sequence is not attended, P165 and N2b are not elicited".

The MMN is quite dependent on experimental conditions. The following paragraphs will review the findings on the MMN in the literature.

C.(ii) Interstimulus interval

The amplitude of MMN is a function of the duration of ISI. Naatanen et al. (1986) reported the largest amplitude of the MMN (over 2 uV) with an ISI of .3 s. When the ISI was increased to .5 s there was a slight decrease in the amplitude and the amplitude remained at the same level for an ISI of 1 sec. Further increases in the ISI above 1 s substantially attenuated the amplitude of MMN. When the ISI was about 10 s MMN disapeared.

C.(iii) Probability of the deviant stimulus

Naatanen and Gaillard (1983) showed that the MMN amplitude is dependent

upon the level of overall probability of the deviant stimulus. They compared 2% and 10% levels of probability for the deviant stimulus and found larger MMN amplitudes for the low probability stimuli. They hypothesized that when the probability of a deviant stimulus is low, the standard stimulus which is present much more often strengthens the neuronal activity associated with the standard stimuli. Therefore the mismatch in the brain generated by the rare deviant stimulus is more significant and the MMN amplitude is greater.

Sams et al. (1983; 1984) investigated the effect of the "microsequence" of stimuli. They averaged AEPs into different categories according to the preceding sequence of a few stimuli (microsequence). The different sequences for stimuli A and B were: AAAAB, AAAB, AAB, AB, etc. The authors found that the stimulus elicited larger MMN when it was preceeded by a longer sequence of the other stimulus. Based on this observation it appears that the formerly postulated probability effect (Naatanen and Gaillard, 1983) is mediated by the "microsequence" of stimuli, and the global (overall) probability does not have an independent influence (Naatanen and Picton, 1986). Sams, Alho and Naatanen (1984) also recorded the MMN to the deviant stimuli presented immediately after the same deviant stimuli in the train of standard stimuli. The first deviant occurred at probability 10%, the deviant following the deviant was only every 100th stimulus. The amplitude of the MMN to the repeated deviant was significantly smaller. The authors concluded that "This demonstrates strong short-term habituation of the MMN generator process".

C.(iv) Persistence of mismatch negativity

An identical MMN was recorded to first 8 and last 8 widely deviant tones of 2999 Hz presented in a long sequence of standard tones of 2030 Hz (Naatanen and Gaillard, 1983). This is an important observation since it

shows that the MMN can be recorded in long blocks without any distortion.

C.(v) Stimulus frequency

The latency and amplitude of MMN varies with the magnitude of the stimulus deviance. The latency is longer and the amplitude smaller for smaller stimulus deviance. MMN with a peak latency of 225 ms was recorded to deviant tones of 1020 Hz in the train of 1000 Hz tones. When the frequency of deviant tones was changed to 3020 Hz, the peak of MMN was at 140 ms (Naatanen and Gaillard, 1983).

The duration of the MMN is also dependent on the magnitude of deviance. For small deviance the MMN lasts several hundred ms and for large deviance its duration is about 100 ms (Naatanen et al., 1982).

The amplitude of the MMN is bigger when there is a greater change in deviance (Naatanen et al., 1984; Sams et al., 1985b). The authors used different frequencies of deviant tones to elicit MMN. The amplitude of MMN increased considerably with only a small increase in the frequency of the deviant tone and with further increase it reacheded plateau very quickly. Naatanen (1984) suggested that "...the neuronal population of the MMN generator mechanism is assumed to be organized in a sharp tonotopic manner".

A MMN with very small amplitude was recorded even when the deviance was at the behavioral discrimination threshold of subjects for different frequencies (Sams et al., 1985b). The standards used were 1000 Hz and the deviants at threshold level were 1008 Hz. The author did not record any MMN for deviants of 1002 and 1004 Hz which were below the discrimination threshold.

C.(vi) Stimulus intensity

The MMN can be elicited by either an increase or a decrease in the

intensity of an auditory stimulus. Naatanen (1986) recorded MMN to deviant stimuli of 70 dB and 57 dB in a train of standard stimuli of 80 dB. The frequency of both standard and deviant tones was 1000 Hz. The MMN elicited in both conditions was larger for the deviant tones of 57 dB. If the deviant tones were entirely omitted or the intensity change was below the behavioral discrimination threshold, the MMN was absent.

C.(vii) Scalp distribution and generator source

Naatanen et al. (1982) and Sams et al. (1985b) recorded components of N2 deflection from electrodes in different scalp locations (Fz, Cz, Pz) referenced to linked mastoids. The largest amplitude of the MMN occurred at Fz, but the difference between amplitudes at Fz and Cz did not reach statistical significance. The MMN recorded from T3 and T4 was slightly larger than that recorded from Cz when the subjects performed a dichotic listening task (Naatanen et al., 1980).

Hari et al. (1984) and Sams et al. (1985a) recorded magnetoencephalographic responses to standard and deviant stimuli in reading subjects. Detailed mappings and calculations of the magnetic response localized the generator source of the magnetic MMN to primary auditory cortex. Naatanen (1986) suggested that the primary auditory cortex is also the principal site of generation of the electric MMN.

C.(viii) Ear of stimulation

Different investigators have been using either one or both ears for stimulation (Sams et al., 1983; Naatanen et al., 1982). However, there has not been a study comparing the side effect of stimulation and mono versus binaural stimulation. In one study subjects performed a dichotic listening

task (Naatanen et al., 1978) in which they had to detect deviant stimuli in one ear and ignore the input to the other ear where different standard and deviant stimuli were also presented. The MMN was similar whether the stimulation was in the right or left ear. However, the frequency of stimuli differed between the ears.

Maiste and Picton (1987) recorded significantly greater MMN over the scalp (C3 or C4) contralateral to the ear of stimulation.

C.(ix) Level of arousal and attention

Paavilainen et al. (1987) recorded MMN to frequency changes in awake and sleeping subjects. The MMN was present during drowsiness but disappeared as the subjects entered sleep stage I. An insufficient number of reliable periods of REM sleep prevented recording the MMN in REM sleep.

Attention to deviant tones does not change the MMN (Naatanen et al., 1978; 1982).

D. The mismatch negativity in phonetic stimulation

Lawson and Gaillard (1981) investigated the relationship between EPs and phonetic stimuli in a two-choice selective discrimination task. The phonetic stimuli were consonant-vowel (CV) syllables. Subjects were instructed to respond to target stimuli. The difficulty of the discrimination was manipulated by varying the number and the type of phonetic cues which distinguished target from nontarget stimuli. The targets stimuli differed from the nontarget stimuli in:

1. place of production of the consonant (ke x te);
2. place of production of the vowel (ke x ka);
3. place of production as well as the voicing of the consonant (ke x be);

4. place of production of both consonant and vowel and the voicing of the consonant (ke x ba);
5. target and nontarget stimuli were the same CV(ke) but they differed by 10 dB; and,
6. target and nontarget stimuli were the same tones (1000 Hz) but they differed by 10 dB.

The intensity of stimuli was 60 dB SPL, the ISI was 1 s, and the probability of target stimuli .15. The results were analysed for several peaks including a negative wave in averaged responses after target stimuli which in this study was labelled as a MMN or N2 and whose peak latency in this study was between 194 and 220 ms. From the literature review it appears that calling this negative wave in a conscious discrimination task a MMN is incorrect. The N2 wave combines both the MMN and N2b and therefore the interpretation of the results in terms of MMN is not fully appropriate. The shortest latency of the negative peak at around 200 ms in EPs after targets was in condition 4, where three phonetic features distinguished target from nontarget stimuli. Also the amplitude of the same wave was largest for condition 4. On the other hand the smallest amplitude and longest latency was obtained in condition 1, where only one phonetic cue distinguished target from nontarget stimuli.

Rodriguez el al. (personal communication) recorded AEPs in from eight subjects who were instructed to read and ignore phonemic stimuli. These stimuli were CV syllables (da) of two different frequencies at 85 dB SPL. Low frequency (da) were standard stimuli that occurred with 85% probability, and high frequency (da) were deviant stimuli. The grand mean latency of the obtained MMN at Cz was 209 $\pm$ 17.4 ms and the amplitude was -4.7 $\pm$ 1.6 uV. The MMN was also recorded at T3 and T4 electrodes but the amplitudes were

smaller.

Clinical implications of slow auditory evoked potentials

A. Brain lesions

The temporal lobe lesions involving the superior temporal plane should produce changes in the N1-P2 complex which is believed to be generated predominantly in this area. However, the AEP findings in patients with temporal lobe lesions are variable and quite often even normal.

In patients with unilateral damage of temporal-parietal area as determined by CT scan, Knight et al.(1980) reported a marked decrease in N1 wave amplitude across different scalp locations. Patients with frontal lesions had a significantly larger N1 wave on both sides of the scalp if the stimuli were presented to the ear contralateral to the side of the lesion. Both frontal and temporal-parietal lesions did not influence P2. On the other hand markedly reduced amplitude of the N1-P2 complex was recorded on the side of a unilateral temporal lobe lesion documented by CT scan (Wood et al., 1984).

In cases with lesions in both temporal lobes where the patients were reported to have cortical deafness, the N1-P2 complex was small or absent (Michel et al., 1980; Miceli, 1982; Bahls et al., 1988). In all these cases the CT scan revealed lesions in the distribution of both middle cerebral arteries involving the superior temporal plane and extending into areas posterior and superior to primary auditory cortex. Autopsy, if performed, revealed cystic infarctions involving both superior temporal gyri and adjacent white and grey matter.

Woods et al. (1984) reported dissociation between AEPs and perception in a patient with succesive bilateral infarcts of the middle cerebral arteries. CT scan showed extensive damage to most of the superior temporal plane

bilaterally. The patient had markedly elevated pure tone audiometry, was unable to discriminate sounds and could not understand speech. The auditory brainstem responses were normal. Tones, complex sounds and speech stimuli presented below and above the patient's perceptual threshold elicited a normal N1-P2 complex. The AEP to deviant tones of 1000 Hz in a train of standard tones of 500 Hz showed an increase in amplitude of the N1-P2 complex "...although the patient was unable to detect the change in the frequency of the stimulus, the degree of specificity of refractoriness of the N1-P2 complex was comparable to that seen in normal population in a similar paradigm". In a recent paper, Woods et al. (1987) showed that patients with bitemporal lesions did not have an N1 wave if the lesion on CT scan extended to the inferior parietal lobule which is a multimodal area with inputs from auditory, visual and somatosensory pathways (Geschwind, 1965). On the other hand, patients with restricted lesions to frontal or temporal lobes did not show any abnormality in N1 wave recordings. Therefore, the multimodal areas of the inferior parietal lobule appear to have a modulatory influence over the N1 wave generator circuits outside of the superior temporal plane.

Scherg and Von Cramon (1986) reported 2 types of AEP abnormality in patients with lesions in the auditory cortical pathway. The dipole source for both the middle and late (in our terminology slow) potentials were abolished over the damaged hemisphere in patients whose CT scan showed unilateral lesions involving the auditory cortex (AI/AII, AAI) and the distal portion of acoustic radiation. A second type of abnormality was unilateral reduction of dipole sources for middle latency AEPs and in most cases a delayed (20 - 30 ms) dipole source for late AEP ipsilateral to the side of lesion, probably reflecting cortical activation via commissural fibres. The lesion in this type of abnormal pattern spared the auditory cortex but involved the acoustic

radiation only. The amplitudes for both middle and late AEPs were slightly larger in response to ipsilateral (to the side of lesion) ear stimulation.

Infants with brain damage of different etiology may have abnormal slow AEPs (Rapin and Graziani, 1967). In two infants with isoelectric EEGs (one infant with hydranencephaly and one with traumatic subdural hematoma and respiratory arrest) slow AEP's were absent. Another infant with holoprosencephaly and an abnormally large amount of CSF between brain and skull showed low voltage of both the EEG and the AEP. An 18 month old child with hydrocephalus, right hemiparesis and right homonymous hemianopsia with relatively normal language development, had asymmetric slow AEP responses. The P2 and N2 waves recorded from the parietotemporal regions were smaller on the left side when compared to those recorded on the right.

B. Dementia, psychopathology and other applications

Peak latency of the N1 wave was significantly prolonged in patients with dementia which is predominantly of subcortical origin (Hungtington's disease and Parkinson's disease), whereas patients with predominantly cortical disease (Alzheimer's disease) had normal N1 peak latencies (Goodin and Aminoff, 1987). The later N2 and P3 peak latencies were delayed in all groups of demented patients and were not helpful in distinguishing among them.

The latencies of peaks P1, N1, P2 and P3 have been reported significantly shorter in autistic children than in normal controls (Small et al., 1971, Martineau et al., 1984).

Peak latencies of the N1 and P2 waves in a group of patients with Friedreich's ataxia were significantly longer than in normal controls (Taylor et al., 1982). Only three of twelve patients had N1 and P2 peak latencies beyond the normal limits (2.5 s.d. above the mean in normal subjects).

However, the majority of patients also had abnormal brainstem auditory evoked potentials (BAEPs) and two had a moderate bilateral hearing loss on audiological testing. It is known that stimulation with lower intensities will delay the peak latencies of the N1 and P2 waves, but it is not clear whether and how the BAEP abnormalities may affect slow AEP's (Satya-Murti et al., 1983). Therefore, the slow AEP abnormality, which was suggested to represent cortical involvement in the auditory system of patients with Friedreich's ataxia, should be interpreted cautiously with regard to associated hearing loss and/ or abnormal conduction in the brainstem.

Amplitudes of the N1 and P2 waves were smaller and latencies shorter in a group of schizophrenic patients than in normal subjects (Shagass et al.,1977; Saletu et al., 1971). Peak latencies of the N1 and P2 waves were shorter in autistic children than in normal controls, although amplitudes were the same in both groups (Small et al., 1971; Martineau et al., 1984).

Satterfield and Braley (1977) reported abnormal changes in amplitude of slow AEPs with maturation in hyperactive children. The obtained data were compared with age-matched controls. The results showed that younger hyperactive children (6 - 7 years) had abnormally low amplitudes measured between the peaks P1-N1 and P2-N2, whereas older hyperactive children (10 -12 years) had abnormally large amplitudes measured between the P1-N1 peaks. However, the difference reached statistical significance only in older groups for amplitudes measured between the peaks P1-N1 and N1-P2. There were no statistically significant amplitude differences when the total groups (younger and older) were compared with age-matched controls.

In another study Satterfield et al. (1988) recorded slow and late AEPs in twenty 6 years old boys with attention deficit disorder with hyperactivity and in healthy age-matched controls. The AEPs were recorded from 19 electrode

sites in a complex information processing task. The only effects between the two groups were that the N2 response in healthy boys was significantly larger in response to the target stimulus in an attend auditory condition and that the Nd was absent in abnormal boys.

The authors included MMN in the discussion by explaining that "...the N2 component in children is analogous to the N2 component in adults, which is thought to be a component (mismatch negativity) of the orienting reflex to a novel stimulus...". However, it should be emphasized that the only significant effect the authors found was in an attend condition and not in an ignore condition, which is important for the recording of MMN.

Slow AEPs were also studied in children with minimal brain dysfunction, dyslexia and reading disabilities (Satterfield et al., 1972; Satterfield, 1973; Sharrad, 1971; Beagley, 1971). However the results have not been clearly conclusive and sometimes were difficult to fully evaluate and interpret. The children were studied at different ages, with different stimulus modalities (clicks, tones) and within modality parameters, and under different experimental conditions. This incongruity in the design made any attempt to correlate the results impossible and more precisely designed studies have been suggested (Shagass et al., 1978).

Hypotheses

This thesis was designed to confirm the existence of the MMN and to evaluate the effects of different stimulus parameters on the MMN. The first four hypotheses expand on effects already reported in the literature. The subsequent hypotheses deal with some of the unknown issues in slow AEP.

1. Existence of MMN

The first goal of this thesis was to replicate the basic paradigm necessary for eliciting MMN. Since the MMN has the largest amplitude in the frontocentral recording sites, the initial analysis aimed to confirm the existence of MMN evaluated data only from these sites.

2. MMN and changes in the frequency of an auditory stimulus

The MMN should increase in amplitude and decrease in latency as the amount of deviance between the standard and deviant stimuli increases.

3. Lateralization

The MMN should be larger over the scalp contralateral to the ear of stimulation as shown in a recent study (Maiste and Picton, 1987).

4. Hemispheric predominance

The MMN should be larger over the right hemisphere (Naatanen, in press).

5. Direction of deviance

The MMN should remain the same despite the change in the direction of stimuli: i.e., a 1100 Hz deviant stimulus in a train of 1000 Hz standard stimuli will elicit the same MMN as a 1000 Hz deviant stimulus in a train of

1100 Hz standard stimuli.

6. Regularity of the stimulus presentation

The MMN should be unaffected if the deviant stimulus occurs regularly or irregularly in the stimulus sequence, giving the same degree of probability of the deviant stimulus.

7. Scalp distribution

The MMN has a characteristic scalp distribution that differs from the scalp distributions of the N1 and SP waves.

Methods

(i) Subjects

Ten healthy volunteers (22 - 44 years old; 8 males and 2 females) participated in this study. They were free of any neurological or audiological disease and they had normal thresholds (<20 dB ISO) for tones of 1000 and 2000 Hz. All subjects were strongly right-handed with average laterality quotient of 80.1 (range from 53 to 100) on the Edinburgh Inventory (Oldfield, 1971). The subjects sat in a comfortable chair and read material of their own choice during the recording.

(ii) Stimuli

The stimuli were 400 ms tonebursts with rise and fall times of 10 ms each and an intensity of 75 dB SPL. The frequencies used were 1000, 1050, 1100, 1500, 2000, 3000 Hz. The tones, arranged in blocks of 250, were presented monaurally through TDH-49P earphones at an ISI of 0.9 s. There were two modes of presentation - "regular" and "irregular". In the regular mode the deviant

stimulus (0) occurred every fifth stimulus (XXXX0XXXX0XXXX0X...). In the irregular mode the deviant stimulus occurred randomly at a probability of 0.2 (XXX0XXXXX0XX00XXXX0...).

(iii) Experimental Design

The experiment consisted of two parts. Five subjects participated in one part and another five in both parts. Each part presented recordings in 16 different conditions. The conditions consisted of randomly presented blocks of stimuli which differed by the ear of stimulus delivery (right or left), by the mode of presentation (regular, irregular) and by the frequency. The frequencies used in the first part were: 1000, 1050, 1100 and 2000 Hz. In the second part they were: 1000, 1100, 1500 and 3000 Hz. The frequencies of the standard and deviant stimuli were arranged in the following manner: for example in one condition there were 1000 Hz standard with 1100 Hz deviant stimuli and in the next there were 1100 Hz standard and 1000 Hz deviant stimuli. The same arrangement applied for all other frequencies with the rule that in each condition there was a tone of 1000 Hz presented either as the standard or the deviant stimulus.

(iv) Recordings

The responses were recorded from F5, Fz, F6, M1, T3, C3, Cz, C4, T4, M2, P5, Pz, P6, Oz scalp locations. M1 and M2 were the left and right mastoid processes. F5 was located midway between F7 and F3, F6 midway between F4 and F8, P5 midway between P3 and P5, and P6 midway between P4 and P6. Grass gold-plated cup electrodes were referred to a non-cephalic reference between the right sternoclavicular joint and the C7 vertebra that was balanced to eliminate interfering EKG artifacts (Stephenson and Gibbs, 1951; Wolpaw and

Wood, 1982). The ground electrode was placed on the neck. Vertical eye movements were recorded from electrodes placed on the upper and lower ridges of the right eye and horizontal eye movements were recorded between electrodes placed at the external canthi. The electrodes were filled with conductive jelly and attached by collodion-soaked gauze pads. Inter-electrode impedances were below 3 kOhms.

The EEG and EOG signals were amplified by Grass model 8A5 EEG preamplifiers with a filter bandpass from 0.1 - 70 Hz. The amplified EEG and EOG signals were digitized by a PDP-11/44 computer at a rate point per 3 ms over a 768 msec sweep duration beginning 18 ms prior to stimulus onset. Digitized and coded individual sweeps were stored on tape for off-line analysis. The ongoing EOG activity was monitored visually through each block of stimuli to ensure that subjects were awake and reading.

(v) Response Analysis

The AEPs to standard and deviant stimuli were averaged separately in each block. The first two stimuli, always the standard stimuli, were omitted in each block from the averaging. Off-line artifact rejection was applied when amplitudes were greater than $\pm$ 150 uV at any of the scalp electrodes. This process rejected trials contaminated by movement artifacts, such as those arising from the chest reference. Eye movement compensation procedures followed the artifact rejection. The effects of blinks and eye movements were separately determined from the non-time-locked components of the raw EEG and EOG data using regression techniques and were subtracted from the raw ERP data (Gratton et al., 1983; Picton, 1987).

In all figures the average waveforms are plotted such that positive polarity at the scalp is represented as an upward deflection.

(vi) Measurements

The difference waveforms were obtained by subtracting the averaged evoked potential to the standard stimuli from the averaged evoked potentials to the deviant stimuli. Amplitudes were measured relative to the average amplitude during the 18 ms prestimulus waveform. Latencies were measured relative to stimulus onset. The following measurements were taken:

A. on waveforms to standard stimuli:

N1 at Fz between 80 - 130 ms;

P2 at Cz between 130 - 200 ms;

SP as an averaged mean amplitude at Fz between 300 - 390 ms;

B. on difference waveforms (AEPs to deviant - AEPs to standard stimuli):

amplitude identified at the latency of N1 measured as in A; and

MMN peak negativity between N1 latency and 350 ms at Fz.

If there were 2 peaks, one at N1 and one later, the second peak was taken, provided that the amplitude was at least 75% of N1 peak. Otherwise the N1 peak was taken.

If there was no definite single peak, the waveforms were smoothed until the main peak was clear. The unsmoothed waveform was then measured at the main peak latency. Amplitudes at other electrodes were measured at the latency of each particular component or wave.

(vii) Data Analysis

The latencies and amplitudes were measured and analyzed using repeated measures analyses of variance (ANOVA) at the electrode where the wave was identified (Fz or Cz); or at homologous electrodes over the two hemispheres (C3 abd C4) when assessing asymmetries. Conservative Greenhouse-Geisser

corrections were used to compensate for violations of the repeated-measures assumptions. Post hoc analyses were done using Newman-Keuls test. Results were considered significant at $p<0.05$.

(viii) Scalp Distributions

The amplitudes for the waves averaged across the experimental conditions were mapped on an outline of the head viewed from above. On these maps, the front of the head is at the top, the left is on the left and the right is on the right. The electrode locations were positioned on this outline according to an azimuthal equidistant projection (Maling, 1973) that extended down to the level of the mastoids. In this projection the scale is linear along all lines radiating from the centre (Cz). Map contours were interpolated using surface splines (Harder and Desmarais, 1972; Perrin et al., 1987; Picton, 1988).

The scalp distributions were studied by two procedures. In the first, the amplitudes of individual waves in all scalp locations were converted to percentages, with limits of $\pm$200%. One hundred percent was the amplitude of each component measured at the location where the component was identified.

In the second procedure, to compare the scalp distributions overall differences in amplitude between conditions or between waves had to be removed, since these differences could cause spurious interactions (McCarthy and Wood, 1985). Data were therefore transformed using the technique recommended by these authors. For each subject, wave and condition, the amplitude at a particular electrode (Xi) was converted to a percentage of the range between the minimum amplitude (Xmin) and maximum amplitude (Xmax) for that particular subject, wave and condition:

$$Xi = (Xi-Xmin)/(Xmax-Xmin)$$

The transformed data were then analyzed using repeated measures ANOVAs with Greenhouse-Geisser corrections for the significance levels. A change in the scalp distribution shows up on such an analysis as an interaction with the electrode factor.

## Results

### (i) Direction of Deviance

An initial analysis using data measured at Cz evaluated whether there were any significant differences related to the direction of the deviance. Figure 2 shows the AEPs recorded at Cz in response to stimuli presented to the right ear in the irregular mode. The responses to 1000 Hz standard stimuli contained: N1 (average latency 101 ms, amplitude -3.7 $\pm$ 2.5 uV), P2 (latency 161 ms, amplitude 0.8 $\pm$ 0.9 uV) and SP (amplitude -2.6 $\pm$ 1.7 uV) waves. The responses to 1100 Hz deviant stimuli showed the same waves. The deviant-standard difference waveform demonstrated a clear MMN.

...insert Figure 2 about here...

The MMN in the condition with 1100 Hz deviant stimuli and 1000 Hz standard stimuli, irregular mode, right ear stimulation, had a mean peak latency of 186 ms and a mean amplitude of -2.6 $\pm$ 2.3 uV. The $p<0.01$ confidence limits of the mean of the amplitude are at -0.2 to -4.9 uV. The MMN to 1000 Hz deviant in the train of 1100 Hz standard stimuli had an amplitude of -2.6 $\pm$ 2.1 uV and the mean peak latency was also 186 ms. The measurements were not significantly different when the frequency of the standard stimulus was 1100

Hz and when it was 1000 Hz. The measurements for the 1000 Hz and 2000 Hz responses were also virtually identical when one or the other was the deviant stimulus.

Because of the slightly different peak latencies of MMN in individual subjects the average mean amplitude measured between 170 and 210 msec in the difference waveform was also calculated. In the condition with the 1000 Hz standard and 1100 Hz deviant stimuli the average mean amplitude was -2.2 $\pm$ 2.8 uV, and in the condition with the 1100 Hz standard and 1000 Hz deviant it was -2.5 $\pm$ 2.1 uV. In the condition with the deviant stimuli 2000 Hz and standard stimuli 1000 Hz, the averaged mean amplitude measured at Cz between 100 and 140 ms was -2.7 $\pm$ 1.5 uV. In the condition where these frequencies were reversed (1000 Hz deviant and 2000 Hz standard stimuli) the same measurement was -2.7 $\pm$ 2.4 uV.

Since the amplitude data of both N1 and MMN were not significantly affected by the direction of the frequency difference between standard and deviant stimuli, the data were collapsed across the direction of deviance prior to further analysis. For example, the difference waveform from condition 1100 Hz standard and 1000 Hz deviant stimuli was collapsed with the difference waveform from condition 1000 Hz standard and 1100 Hz deviant stimuli. Similar collapsing was applied to all other frequencies.

(ii) Effect of Frequency Change and Mode of Stimulation

The effect of different frequencies and modes of stimulation on the latencies and amplitudes of MMN, N1, P2 and SP was evaluated in this analysis using data from recordings in 5 subjects. Because of the time involved only the right ear was stimulated.

The N1, P2 and SP latencies and amplitudes were measured at Cz on

waveforms recorded in response to standard stimuli of different frequencies. The latency and amplitude changes of individual potentials analyzed by a 5x2 (frequency: 1050, 1100, 1500, 2000 and 3000 Hz X mode of stimulus presentation: regular, irregular) repeated measures ANOVA did not show any significant effect. This result proved that the N1, P2 and SP recorded in response to standard stimuli do not significantly change if the frequencies of an auditory stimulus presented in either regular or irregular mode are varied between 1050 Hz and 3000 Hz.

The MMN, measured at Fz and analyzed with the same 5x2 repeated measures ANOVA, increased in amplitude ($F(4,16) = 5.04$, $p<0.01$) with increasing frequency difference between standard and deviant stimuli (Figure 3). Post hoc testing revealed significant differences between the MMN amplitude when the difference was 2000 Hz (1000-3000) and the amplitudes when the difference was 500 Hz or less.

In comparison with the amplitude the peak latency of MMN appeared to be more sensitive to frequency difference between standard and deviant stimuli. The latency decreased with increased frequency difference ($F(4,16) = 25.12$, $p<0.001$). The latencies evaluated by the Newman-Keuls test showed that the MMN to 50 Hz (1000-1050) and 100 Hz (1000-1100) deviations had significantly longer latencies (233.1 and 186.6 ms respectively) than MMNs elicited by greater frequency differences (Figure 3).

...insert Figure 3 about here...

The different mode of presentation, regular versus irregular, influenced neither the amplitude nor the latency of MMN.

Close examination of the waveforms in Figure 3 suggests that there may be

two components to the negative wave found in the deviant-target difference waveform. There appears to be a negative wave at the latency of the N1 peak in the standard waveform that increases regularly with increasing frequency-deviance. As well there seems to be a later negative wave that decreases in latency with increasing frequency-deviance. At deviances of 50 or 100 Hz only the late wave is clearly recognizable; at 500 Hz and 1000 Hz there are two recognizable peaks; at 2000 Hz the peaks are difficult to separate.

On the basis of these results, deviances of 100 Hz and 1000 Hz were used for the final experiment - using 10 subjects and stimulating both the left and the right ears.

(iii) Ear of Delivery

In order to evaluate whether the change in the ear of stimulus delivery had any effect on MMN, amplitudes in response to the left and to the right ear stimulation were measured. The amplitudes were measured at C3 and C4 electrode locations. The data were analyzed using a 2x2x2x2 (ear of stimulus delivery X frequency difference: MMN to deviance 1000 and 100 Hz X mode of presentation X location) repeated measures ANOVA. The only significant effect was for the frequency condition ($F(1,9) = 23.41$, $p<0.001$). The mean amplitude of MMN was -3.7 uV for the 1000 Hz deviance and -1.9 for the 100 Hz deviance.

There were no significant ear by electrode interactions, the contralateral/ipsilateral ratios being 1.03 and 1.02 for MMN (100 Hz) and MMN (1000 Hz). There were also no significant hemispheric asymmetries, the left/right ratios being 0.83 and 1.01 respectively. The MMN at a difference of 100 Hz was somewhat larger at C4 compared to C3 regardless of which ear was stimulated but, because of the low signal-to-noise ratio of these

measurements, this difference failed to reach significance ($p>0.20$) on an arbitrary post hoc evaluation limited to the data at 100 Hz.

The peak MMN latency measured at Fz and analyzed in a 2x2x2 (ear of stimulus delivery X frequency difference: MMN to deviance 1000 and 100 Hz X mode of stimulus presentation) repeated measures ANOVA showed again the only effect for frequency difference ($F(1,9) = 92.06$, $p<0.001$). The MMN peak latency was 133 ms for 1000 Hz deviance and 175 ms for 100 Hz deviance.

(iv) N1 Refractory Effects

To evaluate whether the amplitude change of N1 peak in response to deviant stimuli (Butler, 1968; Picton et al., 1978b) is solely due to an effect of frequency specificity of the refractory period of the N1-P2 complex, or whether the amplitude change is also related to some other processes, i.e. mismatch negativity process occurring at the same time, we measured the amplitude changes on the difference waveforms at the latency of N1 peak recorded in response to standard stimuli. The different parameters, evaluated in a 2x2x2x2 (ear of delivery X frequency: difference waveform to 1000 and 100 Hz deviance X mode of presentation X location: C3 and C4) repeated measures ANOVA showed only a frequency effect. The amplitude increases on difference waveforms at the N1 latency ($F(1,9) = 30.35$, $p<0.001$) were -2.6 uV for the deviance of 1000 Hz and -0.2 uV for 100 Hz.

Scalp Distribution

(i) Maps

The grand mean evoked potentials to the standard stimuli at the different scalp-locations are shown in Figure 4. For this figure data were averaged across all the experimental parameters in the final experiment: mode (regular

or irregular), ear (left or right), direction of deviance (up or down), and frequency: deviance 100 Hz (1000-1100 Hz) and 1000 Hz (1000-2000 Hz). The left-ear responses were left-right reversed prior to averaging so that the left side of the figure shows the responses from the scalp contralateral to stimulation. The next two figures show the grand mean difference-waveforms for a deviance of 100 Hz (Figure 5) and 1000 Hz (Figure 6).

...insert Figures 4, 5 and 6 about here...

Scalp-distribution maps were constructed from the average peak measurements across the 10 subjects using surface-spline interpolations. Figure 7 shows the maps for N1, SP and the two MMNs. For this figure separate maps were constructed for right-ear and left-ear stimuli. For ease of reference the MMN obtained for the 100 Hz deviance is referred to as MMN1 and the MMN obtained with the 1000 Hz difference as MMN2. The maps are not reliable in the frontal-prefrontal areas where there were no electrodes.

...insert Figure 7 about here...

(ii) Analysis

Since the P2 measurement was small and very variable scalp-distribution analyses were restricted to N1, SP and MMN. The measurements for each subject and each condition were initially converted to percentages of the amplitude measured at the location where the wave was identified. This technique worked well for the N1 and MMN. However, the SP showed an inversion of polarity in the temporal and occipital electrodes, and the overall mean value was therefore less than that of the other waves which showed no such inversion.

Consequently, the changes in scalp-distribution across conditions could be evaluated, but comparisons could not be made of scalp distributions across components. Therefore the scalp-distribution of these waves was analyzed after compensating for differences in overall amplitude across the experimental conditions using the techniques of McCarthy and Wood (1985). The initial analyses compared the scalp-distributions of each of the N1, SP and MMN waves across the different experimental manipulations using 2x2x2x13 (mode X ear X frequency X electrode) ANOVAs. A change in the scalp distribution of a wave would show up on such an analysis as an electrode-interaction. This would provide evidence for a change in the underlying generators of the wave in different experimental conditions. For each of the three waves there was a highly significant main effect of electrode - each had a clearly defined scalp-distribution and was not homogeneously recorded over the scalp. No significant electrode-interactions were obtained. The waves showed consistent scalp-distributions across the different experimental manipulations.

A second analysis compared the scalp-distibutions of the three different waves. For this analysis the data were collapsed across mode and frequency since these parameters had not shown any effects on the previous analysis. The ear was kept as a parameter because of the reports in the literature of ear-related asymmetries (Picton et al., 1978b; Woods and Clayworth, 1987). A 3x2x13 (wave X ear X electrode) ANOVA was then conducted on these data. As expected this showed a highly significant effect of electrode. The wave by electrode interaction was also highly significant ($F(26,234)=5.17$, $p<0.005$). The N1, SP and MMN are thus different in their scalp distributions. Post hoc analyses showed that the SP differed significantly from both N1 and MMN, and that the N1 and MMN did not differ significantly from each other. As can be

seen from the maps in Figure 7, the SP is more anteriorly (or less posteriorly) distributed than the other waves. The analysis also showed an ear by electrode interaction that just reached significance ($F(13,117)=3.07$, $p<0.05$). This appeared due to some slight predominance of the waves (particularly SP) over the scalp ipsilateral to stimulation, although none of the post hoc tests reached significance.

## Discussion

A widely distributed MMN with frontal maximum was recorded in response to deviant stimuli which differed in frequency from ongoing trains of standard sti. li. The MMN will be discussed in relation to N1, P2 and SP waves and in view f possible generators in the brain.

Firstly, the same MMN was recorded despite the change in the direction of stimuli (up or down): i.e., MMN to 2000 Hz deviant in the train of 1000 Hz standard stimuli was the same as MMN to 1000 Hz deviant in the train of 2000 Hz standard stimuli. This applied also to other frequencies. From this observation we may assume that if the standard stimulus activates a certain neural population and the deviant stimulus activates new units in excess of those already activated, then either the same population of new neural units or even a population of different neural units generating a similar electrical field are activated in the brain regardless of the direction of frequency difference between standard and deviant stimuli.

The MMN varies with the magnitude of deviance. The amplitude change of MMN can be interpreted similarly to the theory of overlapping receptive fields for the generator processes of the "vertex" potential for different frequencies (Butler, 1968). The standard stimulus of a certain frequency activates a receptive field which is recorded as the N1-P2 complex. When the

interspersed deviant stimulus is presented, the extent of activation exceeds the already activated population of neural units and spreads to new ones. With the increase in the frequency difference between standard and deviant stimulus the activated receptive field extends and a greater N1 and similarly also greater MMN are recorded. On the other hand, when the frequency of the deviant stimulus closely approximates that of the standard stimulus there will be only few new neural units activated, and none when the frequencies are the same. Under these conditions the MMN and the N1 waves will be smaller or absent (Sams et al., 1985b; Naatanen et al., 1988).

Although the changes in amplitude of both the N1 and MMN are similar to a certain degree, the changes in latencies are not. Application of the theory of overlapping receptive fields to the MMN process does not explain the MMN latency changes, i.e., shorter latency with greater deviance between standard and deviant stimuli and vice versa. It can be hypothesized, however, that the greater deviance leads to an "easy" and "early" mismatch process in the brain resulting in a shorter latency MMN, which is close to the latency of N1 wave. On the other hand, smaller deviance leads to a more difficult "delayed" mismatch process resulting in a longer latency of MMN. The peak latencies of N1 and P2 recorded in response to standard stimuli 1000-3000 Hz did not show any significant change.

From the present study, it can be concluded that the amplitude and latency of MMN are functions of the magnitude of deviance between the two stimuli. The present results strongly support findings of Naatanen et al. (1986). The only difference is that unlike the latter, in the present study, further significant increases in amplitude of MMN beyond the 10% change in the frequency difference between standard and deviant stimuli were noted. This observation may be partly based on different methods. In the present study

stimuli were considerably longer in duration, thus eliciting a SP. The SP has an onset latency at approximately 150 ms and the response continues beyond the end of the eliciting stimulus. The amplitude of SP is frequency specific (Picton et al., 1978b). This wave showed a statistically significant increase when the frequency of intervening tones differed by 500 Hz from the 1000 Hz test tones. Therefore the amplitude increase of MMN for certain frequencies may be related to the amplitude increase during the duration of frequency specific changes in the SP.

When the frequency of deviant stimuli was considerably removed from the frequency of standard stimuli, i.e., 2000 Hz difference in the condition 1000 Hz standard and 3000 Hz deviant stimuli, the peak latency of MMN (107 ms) shifted towards the N1 latency (101 ms). From this observation it may be hypothesized that the neural process leading to the frequency specific refractory period of the N1-P2 complex proposed by Butler (1968) might be very closely related, although not identical, in time and space to the neural process generating MMN during greater deviance between standard and deviant stimuli. The analysis of amplitude increase of the MMN waveform measured at the latency of N1 peak recorded in response to standard stimuli contributed to this hypothesis. The amplitude and latency of the N1 peak remains almost identical for the tones up to 2000 Hz. On the other hand, the MMN waveform showed a significant amplitude increase at the latency of the N1 peak when the waveforms recorded to 100 Hz deviance (1100-1000) were compared with the waveforms recorded to 1000 Hz deviance (2000-1000). Yet, the MMN waveform always continued to increase in amplitude and reached its maximum beyond the N1 peak. Therefore the neural process leading to MMN must be longer in duration than the neural process leading to the N1 wave. However, because of the time overlap it may be concluded that the amplitude increase of N1-P2

complex in response to test or deviant stimuli might be partly due to the neural process eliciting mismatch negativity. In this view the existence of frequency specificity refractory period of N1-P2 complex during greater degree of deviance may be questioned as the only source of its amplitude increase. On the other hand the amplitude differencies between MMN and the N1 wave, i.e. due to effect of frequency change, suggest existence of two different neural processes, one responsible for the frequency specificity of the N1 wave or N1-P2 complex, and the other for MMN. This view is in agreement with the previous report of Naatanen and Picton (1986) who showed a clear difference between the MMN and N1. The MMN had a different amplitude as a function of the magnitude deviance up to 10%, compared with the same function for the amplitude of frequency specificity of the N1 wave (Naatanen et al., 1988).

Other methodological differences between Butler's and Naatanen's experiments, which might have led to the proposal of frequency-specificity refractory period of N1-P2 complex and existence of a separate process generating MMN, were different modes of stimuli presentation and different probabilities of deviant stimuli. In Butler's experiment the test tones were presented in a regular mode, every fourth stimulus. In Naatanen's experiment the deviant stimuli were presented irregularly with probability 2 to 9%. In relevant conditions in the present study, keeping the same probability of the deviant stimuli, it was found that the different mode of presentation did not affect any wave. The MMN and the other waves recorded in response to standard stimuli did not show any significant change in either amplitude or latency.

MMN shows voltage asymmetry recorded between homologous scalp locations. The MMN is larger over the right hemisphere (Naatanen, in press). This

right-hemisphere predominance only for MMN1 is evident from Figure 7. However, statistical analysis for this side-predominance did not attain significance, perhaps because the signal-to-noise ratio of this difference-waveform was very low. If the asymmetry of the MMN is correct, it can be interpreted in one of two ways. On one hand, there may be greater activity in right hemisphere generators. On the other hand, the two hemispheres may be equally active but the orientation of the generator(s) in the two hemispheres may not be symmetrical (both hemispheres may have MMN generators that are oriented toward the right).

Scalp Distribution

An evoked potential recorded from scalp electrodes in response to some physical or psychological event may be composed of several waves, the components of which may derive from several, spatially separate, generators. Each generator creates its own electrical field. Topographic analysis of the voltage distribution of individual waves of evoked potentials may help to separate these waves from each other. An evoked potential or its wave with significantly different voltage distribution across various scalp locations must derive from different generators. Either the activated population of neurons is different, or it is differently responsive due to modulation from other brain areas, or there are different contributions from various primary or association cortices. In the statistical analysis a significant wave main effect indicates differencies between waves averaged over all other conditions. A significant wave x location interaction is necessary to claim differences in distribution between individual waves of an evoked potential (McCarthy and Wood, 1985).

The present study demonstrated clear differences between the scalp

distribution of the SP and MMN and N1 waves. When averaged across all scalp locations the voltage distribution of the SP was significantly different from those of the N1 and MMN. N1 and MMN had their maximal amplitudes in the frontocentral areas and there was no significant difference between voltage distribution of these two waves. In keeping with previous results (Picton et al., 1978c), the scalp distribution of the SP was more anterior than that of the N1 wave. In comparison to N1 and MMN, the SP showed a greater decrease in amplitude across almost all but frontal scalp locations. The SP was especially smaller in posterior locations. In the temporal locations the amplitude of the MMN was greater then the amplitudes of the N1 and SP waves.

The scalp distribution of the slow auditory evoked potentials was not influenced by the ear of delivery, different mode of presentation or by different frequency of the eliciting tones used in the scalp distribution part of the study. Responses were collapsed across frequency prior to voltage distribution analysis, and therefore the scalp distributions of waves recorded to standard stimuli at different frequencies were not compared. Magnetic studies have revealed that the human auditory cortex shows a tonotopic organization with higher frequencies activating more lateral regions of the temporal plane (Pantev et al., 1988). Theoretically the combination of 1000 and 1100 Hz might therefore show a different scalp distribution than the combination of 1000 and 2000 Hz tones.

The interpretation of the possible source of the MMN is difficult. It has been postulated that the MMN is generated within the primary auditory cortex (Hari et al., 1984; Naatanen, 1986). The primary auditory cortex probably also generates the N1 wave and the auditory SP (Picton et al., 1978c; Naatanen and Picton, 1987). As shown in this study, the scalp distribution of MMN was similar to that of N1 and different from that of SP. Although all

three waves are probably generated in the auditory cortices, the neural processes leading to various dipole sources of each wave may be different. The dipole source analysis of MMN and SP is currently under way. Scherg and von Cramon (1986) postulated that bitemporal tangential dipoles generated in the human auditory cortices are the sources of the same N1 wave evaluated in this study. Since the MMN has a scalp distribution of the voltages similar to that of the N1 wave, it is postulated that the MMN has a similar tangential dipole, generated also bitemporally in the auditory cortices.

Kohler and Wegener (1955) postulated that the SP is generated in the primary auditory cortex. However, Peronnet and Michel (1977) suggested that the SP derives from the frontal association areas. The scalp distribution study did not resolve this problem and it was postulated that the SP has probably two components with different contributions from both the primary auditory cortex and frontal association cortex (Picton et al., 1978c). A similar scalp distribution of the SP was also noted in the present study. However, the scalp distribution of the SP was significantly different from the scalp distributions of both the MMN and N1. Therefore the dipole sources of the SP must be different from those of the N1 and MMN. This finding supports the proposal that the SP might consist of more than one component.

The present study showed differences in spatiotemporal sequence of brain processes that accompany acoustic perception and discrimination. The tasks associated with auditory perception and discrimination generate several waves of an auditory evoked potential which can be recorded from the scalp-located electrodes. This study, which compared the topography of only a few waves, showed that some of the spatiotemporal effects can be resolved with the topographic methods employed. The statistical evaluation of scalp distribution differences between individual waves thus enables the

recognation of and differentiation between the possible generators of evoked potentials. These results show the utility of topographic mapping of the voltage distribution of individual waves in obtaining more precise information on cortical processing.

## Conclusions

This study proved that a clear MMN can be recorded in normal subjects.

The amplitude and the latency of the MMN are functions of the frequency deviance between standard and deviant stimuli. The amplitude remains stable until a large deviance is attained and then it increases with the increasing amount of deviance.

This study did not replicate previously reported asymmetries of the MMN.

The MMN was not affected by the regularity of stimulus presentation or by the direction of deviance between the standard and deviant stimuli.

The MMN has a characteristic scalp distribution which is different from the scalp distribution of SP but similar to the scalp distribution of N1.

The largest amplitude of both the N1 and MMN waves were recorded in the frontocentral area. The SP wave was largest in the frontal region.

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# Figure Captions

Figure 1. Deviant-standard difference waveforms. This figure illustrates how difference-waveforms were obtained. At the top of the figure are the standard and deviant responses at each of the two frequency-deviations (100 Hz and 1000 Hz). The deviant waveforms are shown in continuous lines and the standard waveforms in dotted lines. The N1, P2 and sustained potential (SP) are indicated. The bottom tracings represent the differences between the deviant and standard waveforms. A mismatch negativity (MMN) is clearly identifiable. For the 100 Hz deviation this peaks at about the same latency as the P2 wave. For the 1000 Hz deviation, it peaks just after the N1 wave. These waveforms were recorded between the vertex (Cz) and a sternovertebral (SV) reference. They represent the average waveforms of 10 subjects collapsed over the mode of stimulation (regular vs. irregular) and the ear of stimulation.

Figure 2. Direction of deviance. This figure illustrates the waveforms obtained when the deviant stimulus was higher in frequency than the standard stimulus and when the deviant stimulus was lower in frequency. The left column shows the responses to the standard stimuli, the middle column the responses to the deviant stimuli and the right column the difference-waveforms obtained by subtracting the standard response from the deviant response. The waveforms plotted with the continuous lines were obtained when the deviant stimulus had a higher frequency than the standard.

The waveforms plotted with the dotted lines show the responses when the deviant stimulus had a lower frequency than the standard.

Figure 3. Amount of frequency-deviation. On the left of this figure are plotted the average difference-waveforms from five subjects at five different frequency-deviations: 2000, 1000, 500, 100 and 50 Hz. The continuous lines represent the waveforms when the stimulus-sequence was regular and the dotted lines represent the waveforms when it was irregular. The responses were recorded from the Fz electrode using a sternovertebral reference. The vertical line shows the latency of the N1 component of the standard waveform. The arrows indicate the mismatch negativity (MMN). On the right are plotted the amplitudes and the latencies of the MMN at different amounts of frequency-deviation.

Figure 4. Evoked potentials to the standard stimulus. These tracings represent the average responses of 10 subjects to the standard stimulus. The responses were recorded from 14 scalp electrodes using a sternovertebral reference. The waveforms were collapsed across the frequency of the stimuli and the mode of stimulation (regular or irregular). The stimuli were also collapsed across ear of delivery such that the recordings from the scalp contralateral to stimulation are on the left and the recordings from the scalp ipsilateral to stimulation are on the right.

Figure 5. Mismatch negativity when the frequency-deviation was 100 Hz. The

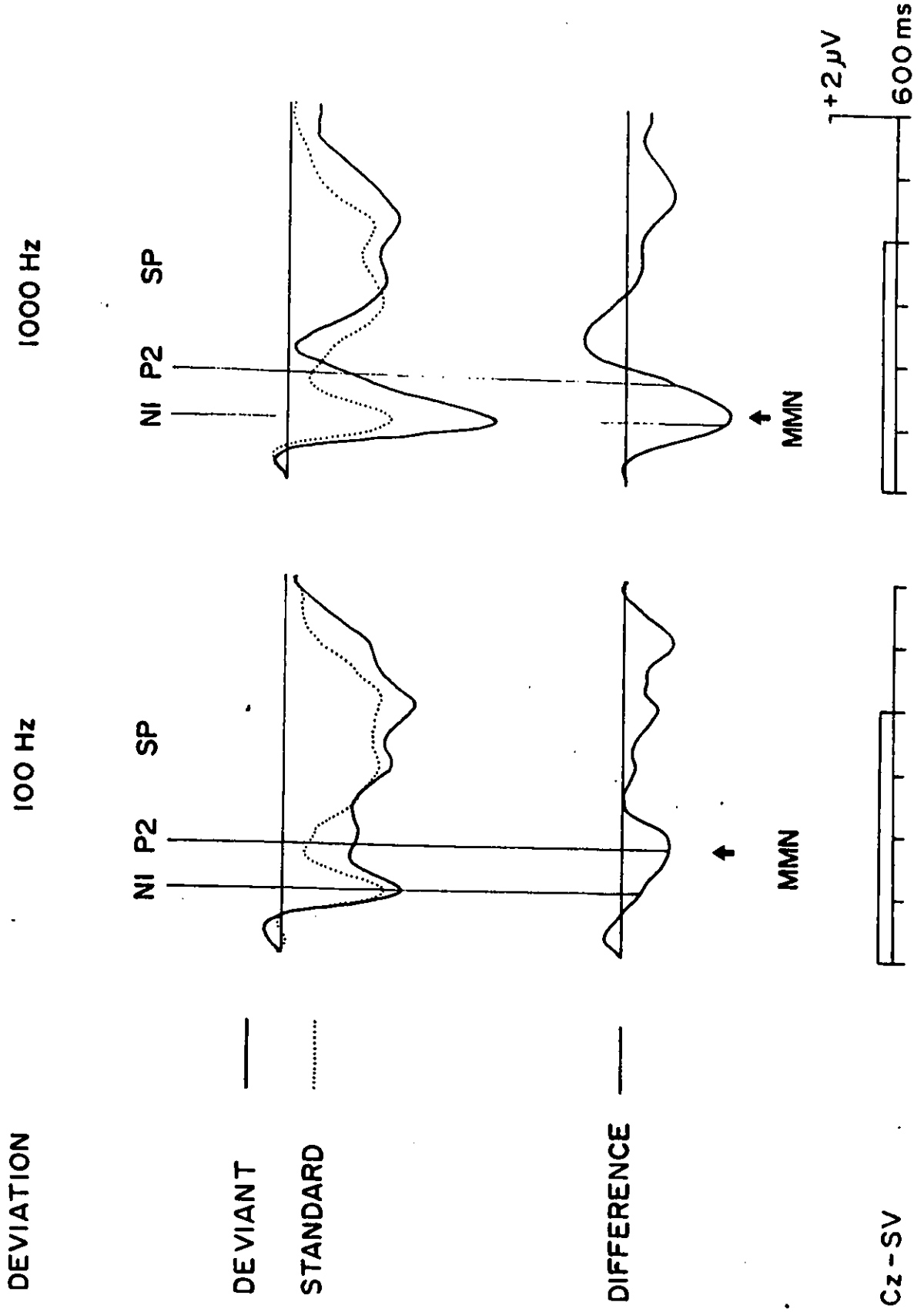
data represent the average waveforms from 10 subjects collapsed across the mode of stimulation (regular vs. irregular). The data were also collapsed across the ear of stimulation such that the recordings from the scalp contralateral to the ear stimulated are plotted on the left and the recordings from the scalp ipsilateral to the ear stimulated are recorded on the right.

Figure 6. Mismatch negativity when the frequency-deviation was 1000 Hz. The data in this figure were averaged similarly to the data in Figure 5.

Figure 7. Scalp distributions. In this figure are plotted the scalp distributions for the N1 component, the sustained potential (SP), the mismatch negativity obtained for a 100 Hz deviation (MMN1) and the mismatch negativity obtained for a 1000 Hz deviation (MMN2). The upper maps represent the response to left ear stimulation and the lower maps, the response to right ear stimulation. The maps were obtained using voltage data averaged across the 10 subjects at each of the 14 electrodes. The data were collapsed across the mode of stimulation (regular vs irregular). The maps were interpolated (and extrapolated) from measurements at the 14 electrodes shown in Figure 17 using a surface spline algorithm. The left scalp is on the left and the right scalp is on the right. The contours are plotted at 0.4 uV intervals. For the N1 component, the contours begin at -0.4 uV and have their maximum negativity at the vertex and midfrontal region. For the sustained potential, the contours begin at 0 uV and reach their maximum negativity at the midfrontal region. For the MMN scalp-distributions, the

contours begin at -0.8 uV and have their maximum negativity frontally.

Figure 1


DEVIATION
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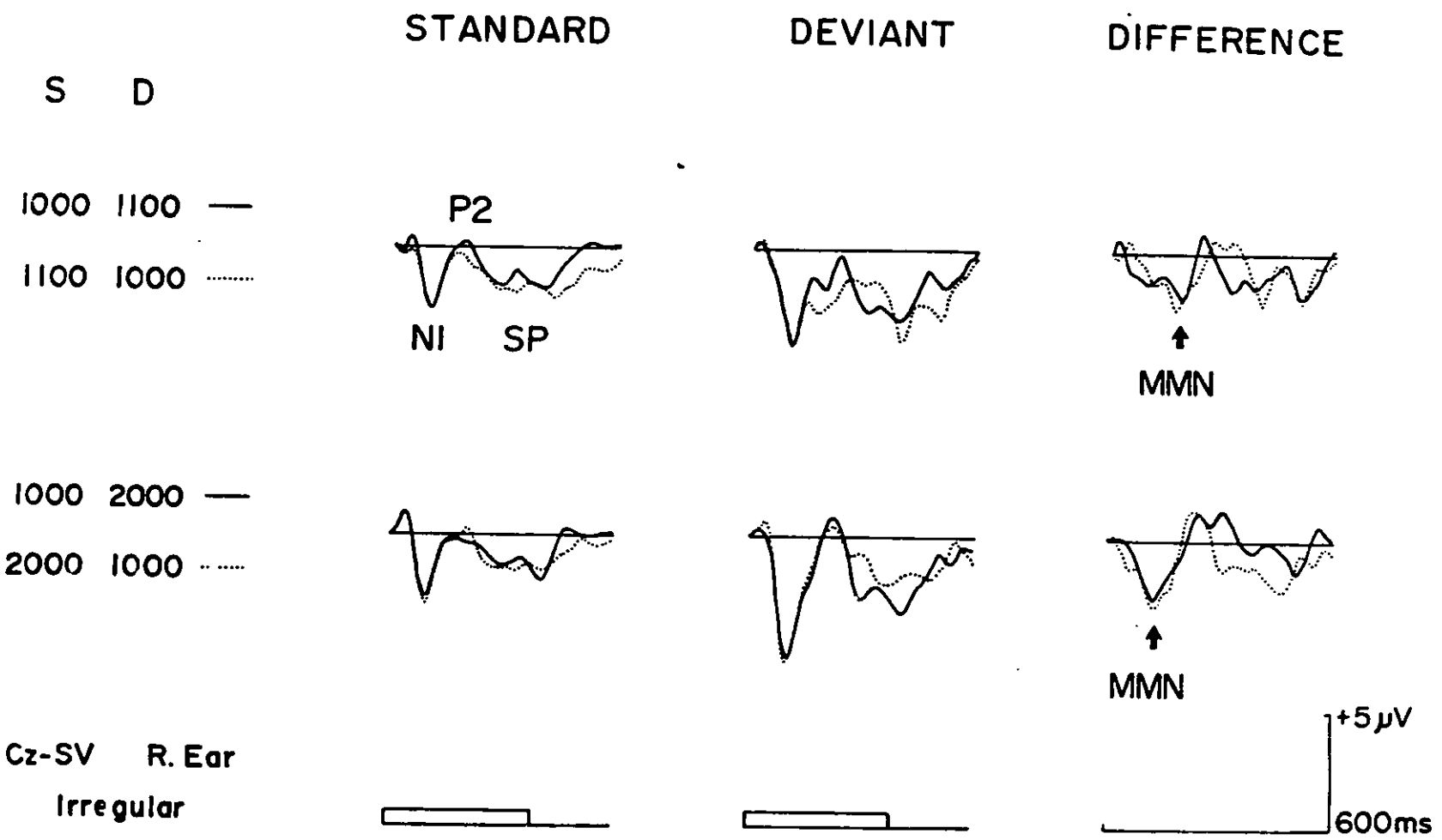
N1 P2 SP
DEVIANT
STANDARD
DIFFERENCE
MMN
MMN
+2 μV
600 ms
Cz - SV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2000 1000
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Cz-SV R. Ear
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+5 μV
600ms

Figure 2

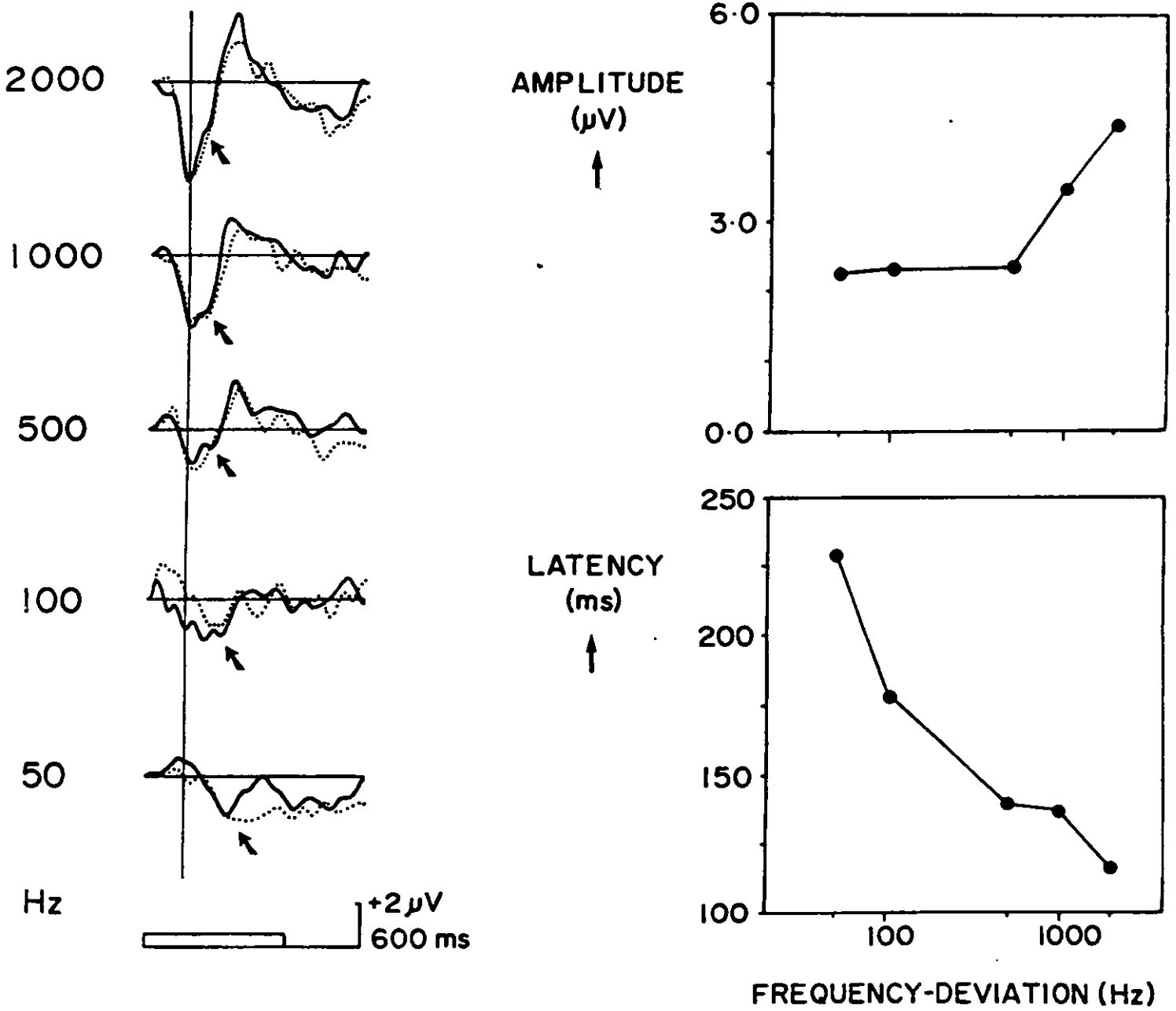
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Figure 3

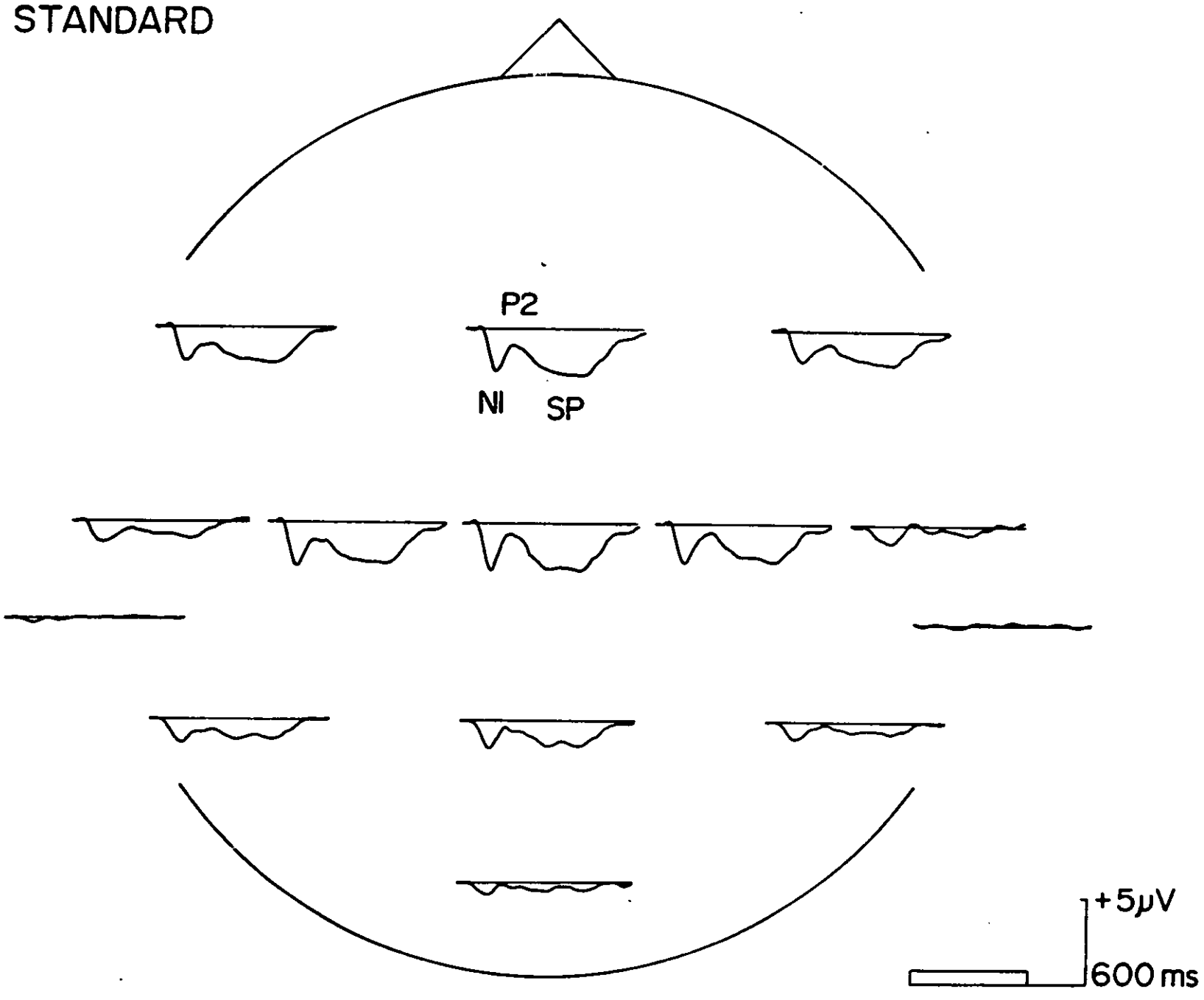


Figure 4

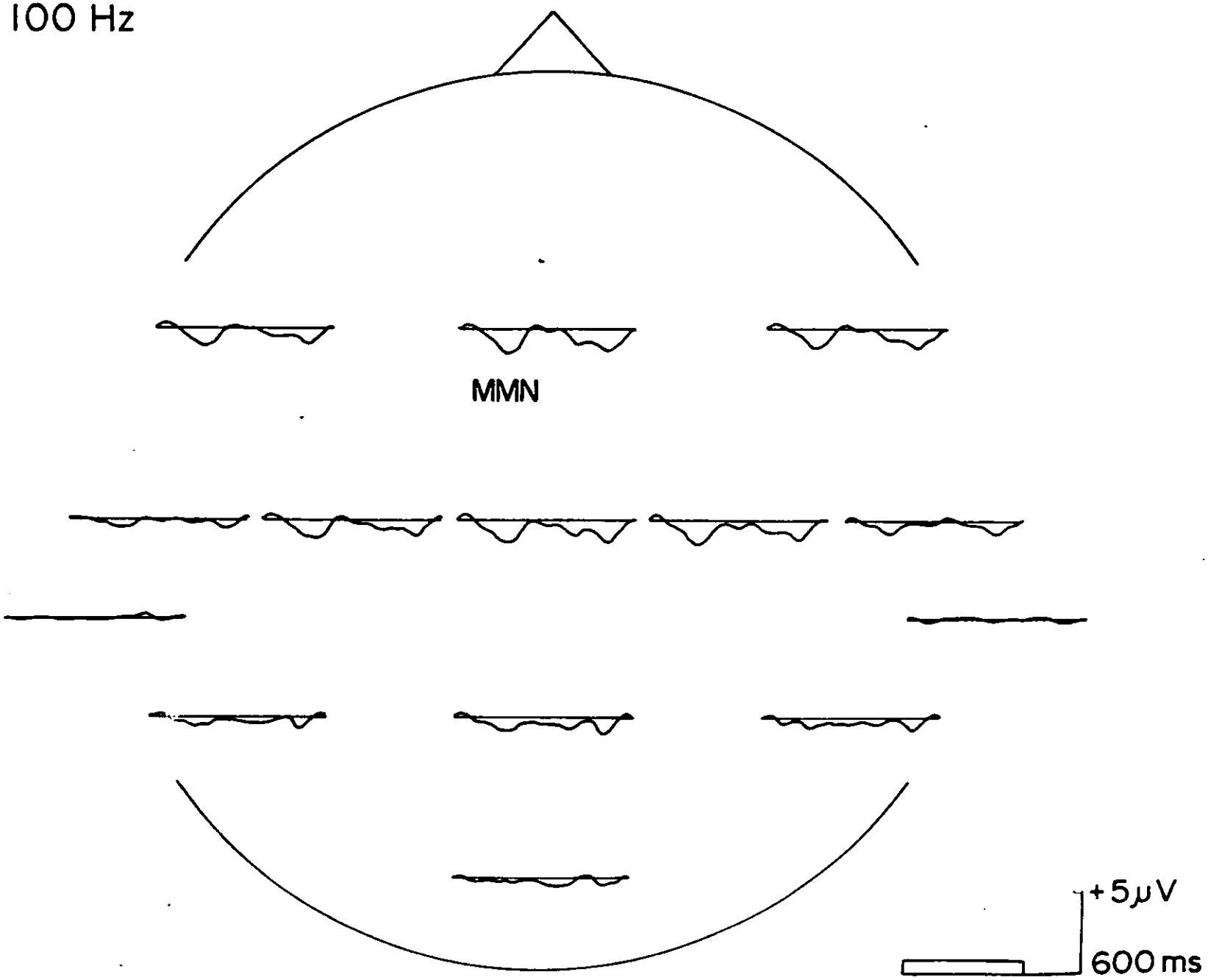


Figure 5

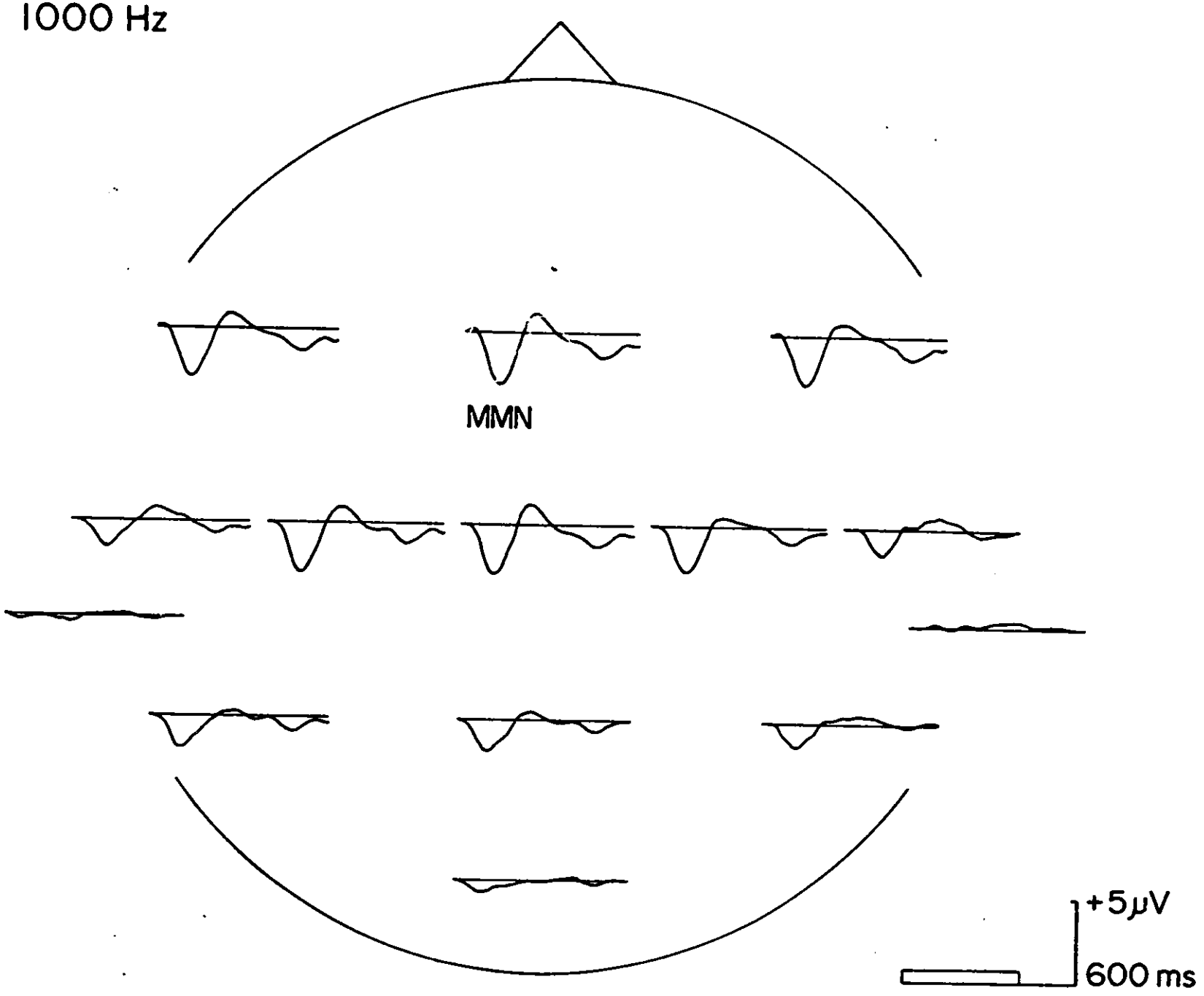


Figure 6

Figure 7