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COGNITIVE AUDITORY EVOKED POTENTIALS IN INVESTIGATION OF HEARING DISCRIMINATION

by

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To my family

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Cognitive Auditory Evoked Potentials in Investigation of Hearing Discrimination.
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ABSTRACT

Preattentive perception of occasional deviating stimuli in the stream of standard stimuli can be recorded with cognitive event-related potential (ERP) mismatch negativity (MMN). The earlier detection of stimuli at the auditory cortex can be examined with N1 and P2 ERPs. The MMN recording does not require co-operation, it correlates with perceptual threshold, and even complex sounds can be used as stimuli.

The aim of this study was to examine different aspects that should be considered when measuring discrimination of hearing with ERPs. The MMN was found to be stimulus-intensity-dependent. As the intensity of sine wave stimuli was increased from 40 to 80 dB HL, MMN mean amplitudes increased. The effect of stimulus frequency on the MMN was studied so that the pitch difference would be equal in each stimulus block according to the psychophysiological mel scale or the difference limen of frequency (DLF). However, the blocks differed from each other.

The contralateral white noise masking (50 dB EML) was found to attenuate the MMN amplitude when the right ear was stimulated. The N1 amplitude was attenuated and, in contrast, P2 amplitude was not affected by contralateral white noise masking.

The perception and production of vowels by four postlingually deafened patients with a cochlear implant were studied. The MMN response could be elicited in the patient with the best vowel perception abilities.

The results of the studies show that concerning the MMN recordings, the stimulus parameters and recording procedure design have a great influence on the results.

Key words: preattentive discrimination, MMN, N1, P2, cochlear implant

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Kognitiiviset kuuloherätevasteet kuulon erotuskyvyn tutkimuksessa.
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TIIVISTELMÄ

Standardiärsykkeiden sekaan sirotellujen satunnaisten poikkeavien ärsykkeiden havaitsemista ennen tietoisuutta voidaan mitata kognitiivisella herätevastepotentiaalilla, jota kutsutaan poikkeavuusnegatiivisuudeksi (mismatch negativity, MMN). Aiemmin tapahtuvaa ärsykkeiden havaitsemista kuuloaivokuorella tutkitaan N1 ja P2 herätevasteilla. MMN-rekisteröinti ei vaadi ko-operaatiota, se korreloi behavioraalisen havaitsemisen kanssa ja monenlaisia ääniä voidaan käyttää ärsykkeinä.

Tämän tutkimuksen tarkoituksena oli selvittää kuulontutkimuksessa käytettävien herätevasteiden rekisteröinnissä huomioon otettavia asioita. MMN-vasteen havaittiin olevan riippuvainen ärsykkeen voimakkuudesta. Kun siniääniärsykkeen voimakkuutta nostettiin 40:stä 80:een dB HL, vasteen keskiamplitudi kasvoi. Ärsykkeen taajuuden vaikutusta MMN-vasteeseen tutkittiin siten, että eri ärsykeblokeissa äänenkorkeuden ero pyrittiin pitämään samana. Ärsykkeiden valinnassa käytettiin psykofyysistä mel-asteikkoa sekä aiemmin tehtyjä tutkimuksia äänenkorkeuden erojen havaitsemisessa. Vasteet kuitenkin erosivat toisistaan.

Vastakkaiseen korvaan annettu valkoinen kohina (50 dB EML) vaimensi MMN-vastetta, kun ärsyke annettiin oikeaan korvaan. Toisessa tutkimuksessa vastakkaiseen korvaan annettu valkoinen kohina vaimensi N1-vastetta, mutta ei vaikuttanut P2-vasteeseen.

Kielellisen kehityksen jälkeen kuuroutuneiden sisäkorvaistutepotilaiden vokaalien havaitsemista ja tuottamista koskevassa tutkimuksessa havaittiin, että potilaalta, joka havaitsi vokaaleja parhaiten, saatiin myös rekisteröityä MMN-vaste vokaaliärsykkeillä.

Tutkimusten tulokset osoittavat, että MMN-rekisteröinneissä ärsykkeiden valinta ja rekisteröintitapahtuma vaikuttavat tuloksiin.

Avainsanat: preattentiivinen erotuskyky, MMN, N1, P2, sisäkorvaistute

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ABBREVIATIONS

ABR	Auditory brainstem response
AEP	Auditory evoked potential
BAEP	Brainstem auditory evoked potential
BEHL	Better ear hearing level
CATCH	Syndrome (cardiac, abnormal facies, thymus, cleft, hypoparathyreosis)
CI	Cochlear implant
DLF	Difference limen of frequency
EML	Effective masking level
EOG	Electrooculography
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
HL	Hearing level
IPL	Interpeak latency
ISI	Interstimulus interval
ISO	International Organization for Standardization
mel	Subjective pitch unit
MEG	Magnetoencephalography
MLAEP	Middle latency auditory evoked potential
MMF	Mismatch field
MMN	Mismatch negativity
MMR	Mismatch response
MOA	Method of adjustment
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
Nc	Negative component
N1m	Magnetic counterpart of N1
NMDA	*N*-methyl-D-aspartate
OAE	Otoacoustic emission
OVE 1b	Vowel synthesizer for research use
Pc	Positive component
PET	Positron emission tomography
SPL	Sound pressure level
SRT	Speech reception threshold
SD	Standard deviation

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, later referred to in the text by the Roman numerals I, II, III, IV, and V.

I **Salo S, Lang AH, Aaltonen O, Lertola K, Kärki T.** Automatic detection of frequency changes depends on auditory stimulus intensity. Ear and Hearing 1999; 20: 265-270.

II **Saura S, Lang AH, Johansson R, Sivula M, Jääskeläinen S.** Automatic preattentive pitch discrimination of different fequencies – MMN study. Submitted.

III **Salo SK, Lang AH, Salmivalli AJ.** Effect of contralateral white noise masking on the mismatch negativity. Scandinavian Audiology 1995; 24: 165-173.

IV **Salo SK, Lang AH, Salmivalli AJ, Johansson RK, Peltola MS.** Contralateral white noise masking affects auditory N1 and P2 waves differently. Journal of Psychophysiology 2003; 17(4): 189-194.

V **Salo S, Peltola MS, Aaltonen O, Johansson R, Lang AH, Laurikainen E.** Stability of memory traces for speech sounds in cochlear implant patients. Logopedics Phoniatrics Vocology 2002; 27: 132-138.

1 INTRODUCTION

The cognitive research on the perception and processing of auditory information in the brain has both theoretical and clinical importance. Auditory evoked responses are useful in examining the objective perception of sounds and discrimination accuracy of hearing (Purves et al. 2008, Katz 2009). The exogenous long latency auditory evoked potentials may be used to measure preattentive detection of tone. Although the clinical significance of late latency AEPs has remained marginal in audiology, they are useful in cognitive neuroscience research for studying memory. So-called working memory can be examined by recording the preattentive comparison of random auditory stimuli to the traces that are left in sensory memory by the previously received stimuli. This automatic comparison of stimuli that differ in some physical quality evokes mismatch negativity (MMN) response (for review, see Näätänen 1992, 2008 and Kujala et al. 2007). The discrimination process is then followed by the necessary behavioural action. Recordings with stimuli deviating in different aspects provide information on auditory and cortical function and deficits. The fact that MMN correlates with behavioural discrimination (Lang et al. 1990) makes it useful in many theoretical and clinical questions concerning auditory and speech dysfunctions. Development of the paradigm designs and recording equipment has made it possible to obtain more precise information about these cerebral responses.

There is already a wide range of possible clinical applications of MMN. For correct conclusions concerning the neurophysiological recording results, it is necessary to know how different aspects of stimulation parameters and paradigms affect the responses in normal conditions and healthy subjects.

Subjective pitch discrimination at different frequencies and intensities has been widely studied with psychophysical tests. It is known to be better with louder stimuli and within the speech frequency range (500-2000 Hz). At different frequencies, the magnitude of the perceived difference can be equated with the psychophysical scale (unit mel) (Stevens & Volkmann, 1940). Because MMN amplitude and behavioural performance correlate, it could be assumed that stimulus intensity affects MMN but the previous studies on this effect have been contradictory and have not shown this effect clearly. There are no reference values of MMN at different frequency levels. Often, stimulus differences are chosen as percentage values which lead to incomparable MMN responses. It may be that the size of MMN evoked with frequency deviations at different frequency levels could be predicted utilizing the results from behavioural experiments.

In the recordings where unilateral stimuli of 50 dB SL or over are used, contralateral masking is needed, because stimuli are conducted to the opposite ear via the skull bone which may affect the results (Katz 2009). It is not known whether masking in turn would affect MMN, and there are few previous studies of its effect on other AEPs.

Clinical applications of MMN include, for example, the examination of cognitive, speech and linguistic functions of newborns and non-cooperative patients. In addition, cognitive ERPs have been applied to study psychiatric, neurological and comatose patients as well as to evaluate musical abilities.

This study aimed to investigate several factors related to the physical properties of the auditory stimuli used for recording long latency AEPs, the MMN, N1, and P2 responses in order to develop the ERP techniques for use in clinical audiology.

2 REVIEW OF THE LITERATURE

2.1 Physiology of hearing

Auditory pathways and perception

The external ear collects sound waves and focuses the acoustic energy on the tympanic membrane (Purves et al. 2008, Katz 2009). In the middle ear, the sound pressure is conducted from the tympanic membrane onto the smaller-diameter oval window by the middle ear bones (malleus, incus and stapes). In the inner ear, the sound makes the cochlear basilar membrane vibrate, maximally at different positions as a function of stimulus frequency (Figure 1). This travelling wave moves from the base toward the apex to the point of maximal displacement. In addition to these passive resonance properties, an active biomechanical process, most likely at outer hair cell level, improves the sensitivity of the ear. The travelling wave displaces the hair cells and the motion between the basilar and tectorial membranes bends stereociliae at the apical ends of the hair cells leading to receptor potentials.

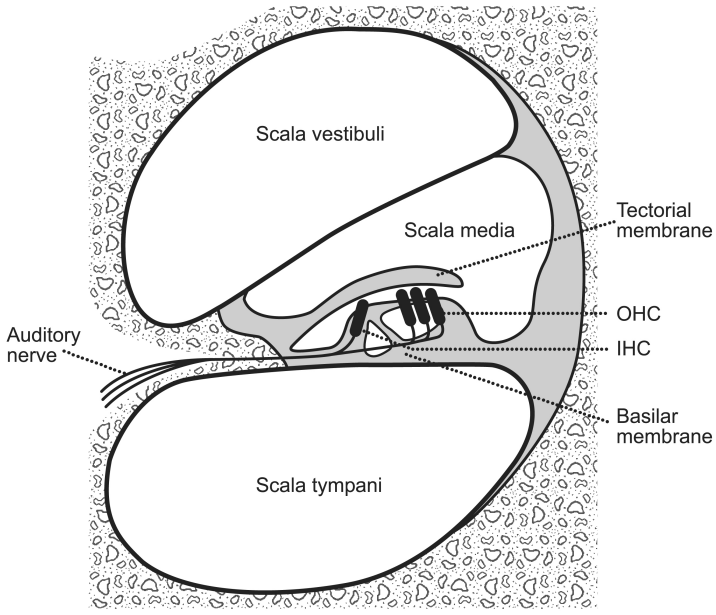

Figure 1. Anatomical cross-section of human cochlea. OHC = outer hair cells, IHC = inner hair cell.

Auditory nerve fibres originating at the apical end of the cochlea transmit information on low frequencies, while the ones at the basal end respond to high frequencies. Each bipolar spiral ganglion cell contacts one inner hair cell and sends the central process to the cochlear nucleus in the brainstem. These central processes form the auditory nerve, which together with the vestibular nerve constitutes cranial nerve VIII. In the cochlear nucleus, each auditory nerve fibre branches and sends an ascending branch to the anteroventral cochlear

nucleus, and descending branches to the posteroventral and dorsal cochlear nuclei (Figure 2). The medial and lateral superior olives and the medial nucleus participate in localizing the sound source. The other pathways from the cochlear nucleus bypass the superior olive and terminate in the lateral lemniscus on the contralateral side. Here the onset of sound and other temporal aspects, such as duration, are processed. In the midbrain auditory centre, the inferior colliculus, a topographical representation of auditory space is produced and sounds with complex temporal patterns are preprocessed.

All ascending auditory information to the cortex passes through the medial geniculate complex in the thalamus. This is an important stage for processing the different features of speech. The primary auditory cortex is located on the superior temporal gyrus. Also secondary regions of the auditory cortex seem to be involved with pitch perception so that two speech sounds can be heard as distinct even when they have overlapping spectral content. The major speech comprehension areas are located adjacent to the auditory cortex.

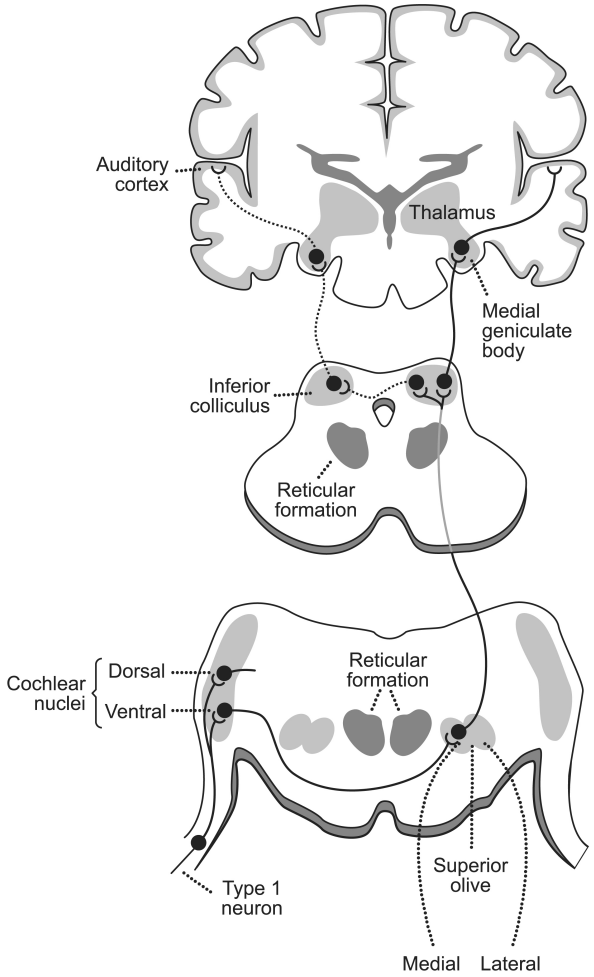

Figure 2. Auditory pathways. Auditory nerve fibers terminate in the cochlear nuclei. The superior olive is where input from both ears first converges. From there, the major output is via the lateral lemniscus, which terminates in the inferior colliculus.

Audiological examinations

In cooperating subjects, psychophysically determined pure tone auditory thresholds (audiogram) provide information about the type of hearing loss and quantify frequency-specific threshold elevations (Katz 2009). Bone-conduction thresholds are essential in evaluating the sensitivity of the sensory-neural system and in differentiating outer and middle ear from cochlear pathology. The results are often compared with speech audiometric test results which provide information on a patient's discrimination ability and the reliability of pure tone audiometry. Retrocohlear hearing loss may cause poorer word recognition scores than expected from pure tone measurement. Reliable data require calibration of audiometers, which includes, in addition to accuracy of pure tone frequency and level, the assessment of attenuator linearity, harmonic distortion, as well as stimulus rise and fall times.

The most important limitation of all psychophysical audiological tests is that reliable results can not be achieved in poorly cooperating patients: infants, small children, demented subjects etc. Yet, the development of linguistic abilities is crucially dependent on early recognition of hearing deficits in newborn infants. Furthermore, simulation of poor hearing for possible economic benefits may be problematic.

Middle ear function can be objectively measured with tympanometry and acoustic stapedius reflex. Elevated acoustic reflex thresholds are associated with retrocochlear disorders, as is abnormally rapid reflex decay (Johnson 1977, Bergenius et al. 1983).
Otoacoustic emissions (OAEs) are sounds which auditory stimulation causes by the motion of the cochlea's sensory hair cells (for review, see Kemp 2002). The recording is made by a microphone fitted into the ear canal. This non-invasive method is widely used in newborn hearing screening and in theoretical studies of cochlear mechanisms and function, but it only provides information on the function of the peripheral auditory pathway.

Behavioural examinations on pitch discrimination

Subjective pitch discrimination is usually studied so that two stimuli with different frequencies are delivered and the subject has to determine which one is higher. The pitch difference (in Hz) at which 75% of answers are right, is called the frequency difference limen (DLF). It grows at higher frequency levels and is smallest at speech frequency range. There is a linear positive correlation between the DLF and the frequency on a logarithmic scale (Wier et al. 1977).

Stevens and Volkmann have created a pitch scale, which equates the magnitude of perceived difference at different frequency levels. This scale has been constructed by two methods and the unit is called mel. In the first method, the subjects search for the stimulus, the pitch of which is perceived as half of the standard stimulus (method of fractionation). In the second method, the subjects are given stimuli with high and low pitches and they are asked to set three other tones at equal pitch intervals between the two extremes (method of equisection). Using this scale, the Hz values can be transformed to mels. (Stevens & Volkmann 1940).

2.2 Auditory evoked potentials (AEPs)

The auditory evoked potentials (AEPs) are changes in brain electrical activity caused by auditory stimulation (Figure 3). They can be recorded with scalp electrodes used for measuring the electroencephalogram (EEG). Because voltage changes of AEPs are very small, in the order of 0.1-1.0 μV, and they are embedded in the background EEG activity, a large number of potentials must be collected, filtered and averaged to enhance the signal-to-noise ratio and to obtain a clear evoked potential. Exogenous AEP components are determined by the physical and temporal aspects of stimulation. They are named according to their polarity (P for positive and N for negative).

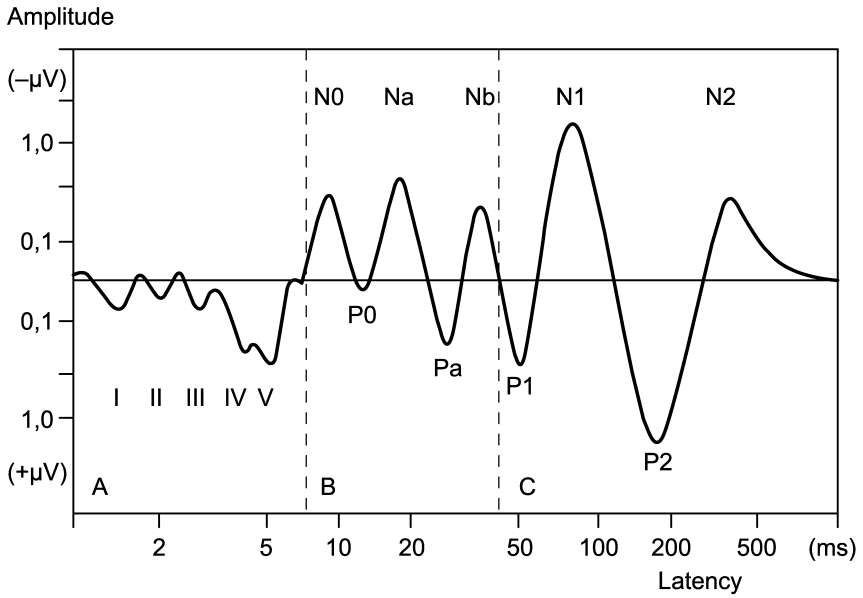

Figure 3. Acoustically stimulated auditory evoked potentials. Brain stem potentials I-V, middle latency potentials N0-Nb and late latency potentials P1-N2.

2.2.1 Short and middle latency auditory evoked potentials (BAEPs, MLAEPs)

The brainstem auditory evoked potentials (BAEPs) (for review, see Markand 1994, Stone et al. 2009, Katz 2009) are the most frequently used AEPs in the clinic, because they are unaffected by subject variables, clearly definable, and good predictors of cochlear sensitivity and the retrocochlear status of the auditory pathway within the brainstem (Cummings et al. 1986). These responses occur at 2 to 7 ms after brief simple auditory stimuli such as clicks or pure tone beeps. BAEPs have been used in clinical medicine from the 1970s for the diagnosis of brainstem pathology and audiological dysfunction**.**

Middle latency auditory evoked potentials (MLAEPs) are recorded 10-70 ms after stimulus onset and reflect the activation of the thalamocortical pathway and the primary auditory areas (Hansen & Woldorff 1991).

BAEP components and recording

In normal BAEP, seven waves (I-VII) (Jewett & Williston 1971) are identified within 10 ms following the stimulus. Widely accepted generator sites are: auditory nerve (wave I), intracranial part of VIII nerve (wave II), superior olivary complex (wave III), lateral lemniscus (wave IV), and inferior colliculus (wave V). However, the BAEP waveforms are considered to result from the superimposition of potential components from several generators (Caird et al. 1985, Katz 2009). Waves IV and V are often fused into a single broad complex. Waves VI and VII are inconsistent and are not used in clinical diagnostics.

Monaural click stimuli and contralateral white noise are generally used in clinical BAEP recordings. The BAEP technique can be used to perform brainstem audiometry for hearing detection threshold estimates and neurological topographical diagnostics of structural pathology within the peripheral and brainstem pathways (Katz 2009).

Recording scalp electrodes are placed at Cz and inside the left (A1) and right (A2) ear canal (tubal insert phones) or at the ear lobule/promontorium: 1000-4000 individual trials are averaged. At least two averaged waveforms are obtained for each ear.
Usually analyzed parameters are peak latencies of waves I, III and V, interpeak latencies (IPL) I-III, III-V and I-V, and V/I amplitude ratio (Katz 2009).

MLAEP components and recording

At the midline electrodes Cz and Fz, Na is seen at about 20 ms and a robust Pa wave at about 30 ms. Pb is evoked at 53 ms at the vertex, but is seen consistently only with binaural and right ear stimulation. At laterally placed T3 and T4 electrodes, there is a smaller positivity at 35 to 42 ms called TP41 (Cacace et al. 1990). Pa may serve as an indicator of memory formation of an acoustic stimulus (Smith & Zapala 1998). Short Nb latency has been associated with awareness (Thornton et al. 1989). Retest reliability of MLAEPs is good (Rentzsch et al. 2008).

In animal models, the generation of MLAEP reflects the interplay of primary and nonprimary areas in the auditory thalamo-cortical pathway (Kraus & McGee 1993). Intracerebral recording in man has shown that the generators for MLAEP components are distributed medio-laterally along Heschl's gyrus. The 30 and 50 ms components are generated within the primary auditory area, and later components in the secondary areas (Liégeois-Chauvel et al. 1994).

Subject factors

Both sex (Rosenhall et al. 1985, Sato et al. 1991) and age influence the BAEP waveforms. Thus, it may be necessary to have separate reference values of latencies and IPLs for both sexes. Already in the fetal and neonatal BAEPs, waves I, III and V have been consistently identified (Staley et al. 1990, Markand 1994). In children from one year to 10 years of age, amplitudes of waves II-V increase (Psatta & Matei 1988). In the elderly, the latencies increase (Rosenhall et al. 1985) and amplitudes decrease with increasing age, while the I-V IPL remains unchanged.

The BAEP waveform is not altered by sleep, which is useful in neonatal and pediatric recordings (Deacon-Elliott et al. 1987). Centrally active drugs produce only little or no alterations in BAEPs (Markand 1994), while hypothermia slightly increases latencies (Markand et al. 1987) and IPLs (Stockard et al. 1978).

Most studies have failed to reveal any attention effects on BAEPs, although efferent pathways paralleling the afferent auditory pathways in the brain stem would give an anatomical basis to expect them (Hansen & Woldorff 1991).

In fetal studies, middle latency potentials with waveforms that correspond to those of neonates, have been recorded (Staley et al. 1990). Pa latency and amplitude increase with age throughout the life span (Woods & Clayworth 1986). Gender effects were not found in this study.

Clinical applications

BAEP recording is noninvasive, easily performed and cheap compared to MRI. Patients with acoustic tumour have delayed wave III-V latencies (Stephens & Thornton 1976). Interaural wave I-V IPL is diagnostic for all tumours larger than 2 cm (n=105) but only in 69% for tumours less than 1 cm in diameter (Gordon & Cohen 1995). Peripheral hearing defects, both sensorineural and conductive, prolong the BAEP latencies but do not affect IPLs.

BAEP enables hearing threshold estimation in infants and children who are not able to cooperate e.g. due to young age (Ferber-Viart et al. 1996). Hearing screening in high-risk neonates with BAEP-based audiometry is more reliable than with OAEs or automated auditory brainstem response (single stimulus intensity, automated detection of response), and the threshold estimation is more optimal. In diagnosing hearing loss in neonates, the sensitivity of BAEP is 100% and specificity 90.8% (Suppiej et al. 2007).

Intraoperative BAEP recording in acoustic neuroma surgery is sensitive in detecting auditory nerve damage (Schmerber et al. 2004). BAEP recordings can also be used to grade coma and predict its outcome (Soustiel et al. 1993, Garcia-Larrea et al. 1992). Absent or grossly abnormal BAEP associates with poor outcome.

Clinical use of MLAEPs includes determination of low-frequency hearing thresholds, the assessment of cochlear implant and auditory pathway function, and the localization of auditory pathway lesions (Kraus & McGee 1993). Postlingually deafened cochlear implant patients have shorter latencies and higher amplitudes than prelingually deafened patients (Kurnaz et al. 2009). MLAEPs have been used to measure and monitor the depth of anesthesia (Drummond 2000), and they may also have prognostic value in aphasic stroke patients (Rojas Sosa et al. 2009). Measures of sensory processing at the mid-latency range are attenuated in schizophrenia patients (Boutros et al. 2004). In young children, middle latency response generators are active only during certain stages of sleep, which limits the clinical use of MLAEPs in pediatrics (Kraus & McGee 1993).

2.2.2 Long latency auditory evoked responses

The long latency auditory evoked response potentials occurring at and after 100ms reflect higher cortical functions, like working memory, attention and preattentive auditory processing. Endogenous ERP components which are affected by the attention and cognitive processing of stimuli may be used to investigate the neural basis of perception and cognition. These ERPs include N1, P2, P300 and MMN, which can be elicited in the discrimination task by detected irrelevant rare tones and novel sounds in a sequence of standard tones. In this oddball paradigm (Näätänen et al. 1978), deviant stimuli are randomly presented among standard stimuli. Attention effects N1, P2 and P300 but its effect on MMN is controversial.

2.2.2.1 N1 and P2 potentials

Components and generation sources

The first long latency AEP, the N1 does not reflect a single underlying cerebral process, but it appears to contain both stimulus-specific and stimulus-nonspecific components (Figure 3). Auditory N1 consists of at least three components (for review, see Näätänen & Picton 1987). The first component is a frontocentral negativity generated bilaterally in the auditory cortices having a peak latency around 100 ms (Vaughan & Ritter 1970). It reflects, at least in part, activation of feature detectors extracting information from the stimulus (Näätänen et al. 1988). The second component is the biphasic T-complex which is supposed to be generated in the auditory association cortex in the superior temporal gyrus (Wolpaw & Penry 1975). The positive Ta peaks at about 100 ms and the negative Tb at 150 ms. The third component is a negative wave at the vertex at 100 ms (Hari et al. 1982). It is probably generated in the frontal motor and premotor cortices and has a maximum somewhat posterior to that of the first component.

The generation source location of N1 depends on stimulus frequency. Magnetic encephalographic (MEG) recordings show that when stimulus frequency is increased, the N1m, the magnetic counterpart of N1, location is shifted to deeper structures along the surface of the auditory cortex which is likely to result from activation of secondary auditory areas (Pantev et al. 1995). Woods et al. (1993) have found that N1 is more frontally distributed following 4000 Hz than 250 Hz tone burst stimuli.

P2 arises with a latency of 150-250 ms (for review, see Crowley & Colrain 2004). It is maximal over the vertex and is generated mainly in the vicinity of the auditory cortex within the temporal lobe. P2 appears to represent activity from at least two sources, the planum temporale and the auditory association cortex.

Aspects of the stimuli

A change in the energy level of the stimulus and stimulus per se elicits N1. The possible reasons are the cerebral systems that respond specifically to the stimulus onset, or that

the neuronal responses are sufficiently synchronized to generate a field potential only at stimulus onset (Näätänen & Picton 1987). N1 can also be elicited by the offset of a stimulus (Hillyard & Picton 1978) and by a change in the frequency or intensity of a continuous stimulus (Spoor et al. 1969). The advantage over brainstem audiometry is that long-duration tonebursts with spectra similar to those of pure tones may be used as stimuli (Cone-Wesson & Wunderlich 2003). Any developmental studies should use both lateral and midline recording electrodes.

P2 is affected similarly to N1 by many factors, for example, when the stimulus intensity decreases the amplitude decreases and latency increases (Picton et al. 1978), and when the stimulus frequency increases the amplitude decreases (Hari et al. 1982). N1 diminishes particularly at frequencies higher than 2000 Hz (Antinoro & Skinner 1968, Wunderlich & Cone-Wesson 2001). However, there is evidence that N1 and P2 are results of independent processes, though little has been done to investigate the neurological correlates or clinical significance of P2 (Crowley & Colrain 2004). It has been usual to measure N1 and P2 peak-to-peak amplitude as a single component which makes it impossible to separate the differential effects of variables on the response components. N1P2 amplitude increases with increasing intensity of auditory stimulation up to 70 dB ISO (International Organization for Standardization) where a decline in this relationship can be seen (Picton et al. 1970). N1P2 amplitude decreases as the rise-time or fall-time of the stimulus becomes longer than 30-50 ms (Kodera et al. 1979). The N1 wave is sensitive to the stimulus repetition rate. When regular ISI is increased (0.5-6 s), the N1P2 amplitude increases (Davis et al. 1966).

In the beginning of the recording, the second stimulus elicits N1P2, which is clearly smaller than the response to the first stimulus. For example, when stimuli are presented in pairs with 0.5 s ISI and with inter-pair interval of 3.0 s, the second response within the pairs is only one third to half of the first (Davis et al. 1966). This is caused by habituation of the nonspecific attention related components of the N1 which are evoked by stimulus novelty aspects. Usually the first few trials of the recording are omitted to avoid the first larger potentials in the averages. There is also long-term decrement of N1 during repetitive stimulation, which may represent genuine habituation (Näätänen & Picton 1987).

Näätänen and Picton (1987) noticed that the first component of N1 is probably about 10% larger contralaterally to the ear of stimulation. This can be explained by the fact that crossing auditory pathway connections are stronger than non-crossing ones (Rosenzweig 1951). There is no consistent asymmetry between responses elicited with stimulation of the left and right sides (Näätänen & Picton 1987).

Subject factors

N1 and P2 potentials are physiologically similar to each other. Their scalp distribution and the effect of aging on N1 and P2 in adults are almost identical (Anderer et al. 1996).

With advancing age, N1 latency increases parietally and P2 latency frontally, while amplitudes of both are enhanced frontally. There are also differences between these two responses. P2 matures early reaching adult values by 2-3 years of age, while evolution of N1 extends into adolescence (Crowley & Colrain 2004). This indicates different pathways and neural generators for these two responses. There is evidence that also sleep has distinct effects on N1 and P2, attenuating N1 and increasing P2 (Näätänen & Picton 1987). Temporal-parietal lesions reduce N1 amplitude but have no significant effect on P2 (Knight et al. 1980).

Auditory selective attention is suggested to increase N1. However, in most conditions, this increase is caused by the superimposition of a processing negativity on the N1, but under certain conditions attention may also truly enhance N1 (Davis 1964, Hillyard et al. 1973, Bertoli et al. 2005). The magnitude of enhancement varies with the amount of attention allocated to the stimuli (Schwent & Hillyard 1975). The N1 amplitude is larger when the subject is performing a cognitive task during the recording, and the response is even larger with a more demanding task. This may be due to an increase in the excitability of some neuronal populations contributing to N1 (Näätänen & Picton 1987).

Possibly because of the decrease in the level of attention, during the process of falling asleep, N1 gradually declines in amplitude (Crowley & Colrain 2004). In non-REM sleep, the N1 is usually further attenuated or even absent. During REM sleep, it is approximately 25-50% of its waking amplitude. In contrast, most studies show that the P2 amplitude increases at sleep onset and continues to increase into Stage 2 of non-REM sleep and slow-wave sleep; thus the N1P2 peak-to-peak amplitude does not change across sleep-wake states. In addition, this has been suggested to happen because a slow negative wave overlapping the waking waveform is abolished at sleep onset. Ethanol has been found to attenuate the amplitude of the N1 (Jääskeläinen et al. 1998).

Clinical Applications

The clinical use of N1 and P2 responses has remained minimal. They may be used to estimate hearing thresholds in awake, alert subjects who are quiet enough, but reference data during early childhood are lacking (Cone-Wesson & Wunderlich 2003). P1 has been used to study children with cochlear implants (Sharma et al. 2009), but it has not been much used in the clinic. Maturation of central auditory pathways, reflected by P1, is earlier in children implanted at early childhood (for review, see Sharma et al. 2007)

Children with auditory neuropathy show an association between the presence of N1 and P2, speech perception scores, and hearing aid benefit. The presence of ERPs might reflect some preservation of neural synchrony encoding temporal information (Rance et al. 2002).

2.2.2.2 P3a and P3b

P300, also known as P3, is easy to record with the auditory oddball paradigm when the subject pays attention to stimuli. It is composed of subcomponents P3a and P3b; P3a is

evoked by novelty stimulus from stimulus-driven frontal attention mechanisms, whereas P3b is evoked by small stimulus deviance from temporal-parietal activity associated with attention (for review, see Duncan et al. 2009, Polich 2007, Picton 1992). The centrally dominant P3a source peaks at 230 ms, and a later P3a source at 315 ms with a right-frontal scalp maximum (Escera et al. 1998). P3b is recorded maximally over centroparietal regions, such as electrode Pz (Martin et al. 2008). Generators of auditory P300 are at the auditory cortex, centroparietal cortex, hippocampus, and frontal cortex (Martin et al. 2008).

P300 amplitude is a measure of central nervous system activity as incoming information is processed and incorporated into memory representations, whereas latency is a measure of stimulus classification speed and is associated with cognitive capacity (Polich 1998). P3a amplitude is attenuated with the repetition of the eliciting novel effect. When the novel stimuli are repeated, P3 scalp distribution shifts a more frontal to a more posterior location in younger adults, while this is not evident in older adults (Friedman & Simpson 1994).

Normal aging and patients with a variety of neurologic and psychiatric disorders can be studied with P3 (for review, see Polich 1998). The latency of P3 is prolonged and amplitude decreases gradually with advancing age (Knight 1987, Anderer 1996). P3 latency has been reported to be abnormally long in patients with dementing illness (Goodin et al. 1978). Temporoparietal P300 amplitude reduction and frontal P300 amplitude increase seem to associate with increased risk of schizophrenia (Winterer et al. 2003). Haloperidol reduces P3a amplitude which is mainly observed in the parietal areas (Kähkönen et al. 2002).

Clinical Applications

The clinical use of P300 in audiology remains rare because recording requires special equipment and a large number of electrodes, normative data are lacking and responses vary widely between subjects (Martin et al. 2008). Furthermore, if a patient can perform a behavioural discrimination task, a standard speech perception test can be used.

2.2.2.3 Mismatch negativity (MMN)

A brief automatic attention switch to environmental novel stimuli even outside the focus of attention is an important vital function for reorienting attention. Frequently-occurring standard stimuli cause a working memory trace in the brain, and when occasional deviant stimuli are randomly presented among standard stimuli (oddball paradigm), they are automatically compared with the recent memory trace and the possible difference is registered preattentively at the cortical circuits. This cortical event-related response can be recorded as a negative long latency evoked potential around 200 ms, the mismatch negativity (MMN) (Näätänen et al. 1978, for review, see Näätänen 1992, 2008 and Kujala et al. 2007) (Figure 4). Convincing evidence for the automaticity of the MMN generator is that it can be recorded even in comatose patients (Fischer et al. 2000).

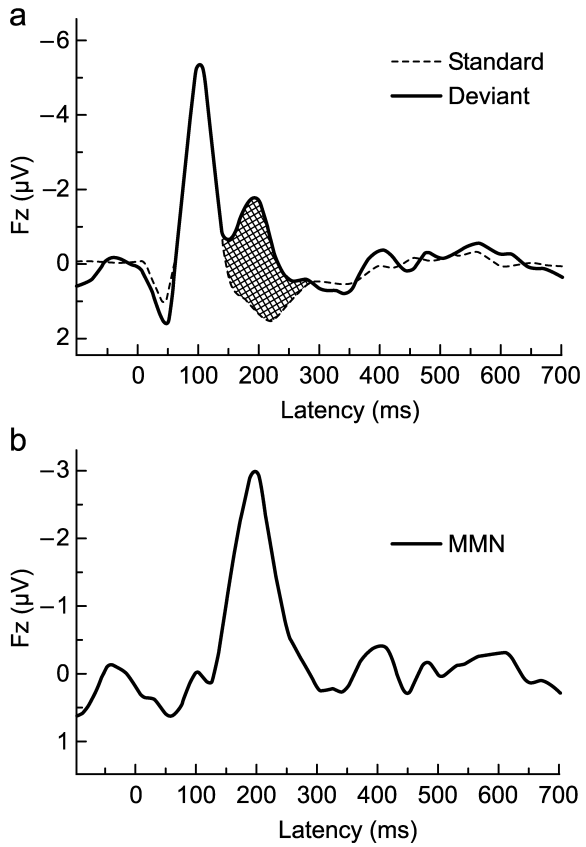

Figure 4. Responses evoked by standard and deviant stimuli (a) and difference curve (b) (MMN). Notice different amplitude scaling in the figures.

The MMN has mainly been used to study auditory memory processes, but it can be evoked also by changes in other sensory modalities (visual, somatosensory). The auditory MMN can be elicited to differences in frequency (Sams et al. 1985), intensity (Näätänen et al. 1989a), duration (Näätänen et al. 1989b), direction of sound (Paavilainen et al. 1989), phonetic characterics (Aaltonen et al. 1987), complex sounds (Alho et al. 1996), rise time (Lyytinen et al. 1992) and interstimulus interval (ISI) (Näätänen et al. 1993a). Variable sound features can also be used in stimulation. For example, a rich harmonic sound structure facilitates frequency discrimination (Tervaniemi et al. 1993). There is evidence that also visual stimuli can be used to evoke mismatch negativity (Heslenfeld 2003, for review, see Pazo-Alvarez et al. 2003). When vibratory stimuli have been presented at different skin sites using the oddball paradigm, negativity between 100-200 ms latency is evoked, probably analogous to the auditory MMN (Kekoni et al. 1997).

An alternative hypothesis to the working-memory-based change detection mechanism suggests that MMN is in fact a N1 response (Jääskeläinen et al. 2004), which is suppressed and delayed by stimulus-specific adaptation (May et al. 1999). However, in their review, Näätänen et al. (2005) conclude that the presence of a memory representation of the

standard stimulus is required for the elicitation of MMN. Their statement is based on several findings. First, the time course of MMN extends well beyond that of N1, thus supporting the theory that separate mechanisms account for N1 and MMN (Lang et al. 1990, Haenschel et al. 2005). MMN can also be elicited in recordings that do not elicit N1. For example, stimulus omission in a sequence of brief tone pips elicits MMN (Yabe et al. 1997), but N1 neurons cannot be activated without an existing stimulus. MMN can be recorded in newborns (Alho et al. 1990) and in REM sleep when no well-defined N1 can be recorded (Atienza & Cantero 2001). Even without standard stimulus repetition that could cause selective adaptation, an MMN can be elicited (Tervaniemi et al. 1994). Also lateralization of responses supports different phenomena; N1 is larger contra- rather than ipsilateral to the stimulated ear (Näätänen & Picton, 1987) while MMN (evoked by alterations in frequency, duration or intensity) is larger in the right hemisphere irrespective of the stimulated ear (Paavilainen et al. 1991). Furthermore, pharmacological manipulations (Umbricht et al. 2000) and cortical lesions (dorsolateral prefrontal cortex lesions, Alho et al. 1994) can affect N1 and MMN differently. Discrimination training increases the size of MMN with no effect on N1 (Näätänen et al. 1993c). Thus, several studies show that the MMN is generated by pre-attentive memory-related mechanisms; it cannot be explained simply by activation of the afferent system and elicited by a single stimulus per se. The discussion continues, and in a recent review, May and Tiitinen (2010) suggest that MMN is generated by fresh-afferent activity of cortical neurons and is a latency- and amplitude-modulated expression of N1 response. They also challenge the status of MMN, which is obtained through subtraction of responses, as a representation of genuine brain activity.

In their review, Garrido et al. (2009) propose predictive coding as a common framework for these two hypotheses, which they call the model adjustment and adaptation hypotheses. In predictive coding, sensory information from the environment and predictions based on a model of what caused that sensory information, are integrated for perception.

Concept of automatic processing

Because MMN recording does not need attention, it is possible to investigate subjects who cannot cooperate in behavioural tests, for example, newborns, children, disabled, and unconscious patients.

Näätänen et al. (1978) have first proposed that MMN is an attention-independent response, based on the similar MMN amplitude evoked both by the attended and unattended stimuli in the dichotic listening experiment. In the dichotic listening task, identification of two different stimuli simultaneously presented one to each ear, is compared. It provides a method for assessing cerebral dominance of language function.

Woldorff et al. (1991) have also conducted an experiment with the dichotic listening paradigm and hypothesize that MMN could be influenced by focused selective auditory attention. Näätänen (1991, Näätänen et al. 1993b) has agreed, that MMN evoked with

intensity but not frequency change is attenuated when attention is strongly focused on other stimuli. Also some other studies suggest that the MMN generating system would be sensitive to attentional modulation (Arnott & Alain 2002, Müller et al. 2002).

Sussman et al. (2003) claim that attention affects MMN only when a competition is set for MMN generation by presenting similar deviants in two concurrent channels, and this competition is biased by the subject's goals. However, in most experiments the designs have not been so complicated.

The automatic MMN process can lead to attention switch, initiate orienting basal ganglia reactions and begin further central processing of a potentially important stimulus, which eventually leads to a possible behavioural reaction. This attention switch can be proved with simultaneous elicitation of P3a (Escera et al. 2000) and N2b (Näätänen et al. 1982). Correlation between the MMN parameters and behavioural responses imply that pre-attentive neural functions determine the accuracy of the subsequent attentive processes (Novak et al. 1990).

Cerebral sources

MMN is generated by auditory cortical structures located bilaterally in the supratemporal plane which are related to the working memory mechanisms (Hari et al. 1984, for review, see Alho 1995, Näätänen & Alho 1995). In the right frontal hemisphere there is a third MMN generator which is related to the automatic attention-switching process (Giard et al. 1990). This generator might explain the right hemisphere dominance of the MMN scalp distribution (Paavilainen et al. 1991). Anyhow, in both attentive listening (Auzou et al. 1995) and ignore situation (Tervaniemi et al. 2000) the processing of phonetic information lateralizes to the left hemisphere, while musical information is processed in the right hemisphere. MMNm responses (magnetic counterpart of MMN) elicited by frequency, intensity or duration deviant stimuli are associated with neuronal activity in the supratemporal auditory cortex (Sams et al. 1991).

MMN may also have subcomponents generated in other cortical and subcortical structures. MMNm responses to changes in stimulus frequency, duration, and ISI are generated in different areas of the supratemporal auditory cortex (Levänen et al. 1996). The equivalent current dipole of the duration deviant MMNm in the auditory cortex has been recorded slightly posterior to that for the frequency deviant MMNm, suggesting separate working memory representations for sound duration and frequency content (Sysoeva et al. 2006). Also in fMRI recordings, frequency and duration deviants activate anatomically distinct networks of the auditory cortices (Molholm et al. 2005), supporting the hypothesis that MMN generators in the auditory cortex are feature-dependent. There is evidence that when MMN for changes in two features (frequency and intensity) is recorded simultaneously, the temporal subcomponent of MMN is additive whereas the frontal is non-additive (Paavilainen et al. 2003). fMRI recordings suggest that also the right fronto-opercular cortex may be a part of the MMN source (Opitz et al. 2002). However, the problem with

fMRI studies is poor time resolution (in seconds) compared to EEG / MEG with real time resolution in milliseconds. MEG recordings have also provided evidence for an additional MMN generator in the parietal cortex (Lavikainen et al. 1994). In intracranial recordings, MMN has been recorded by electrodes located in or close to the superior temporal lobe (Kropotov et al. 1995), and additional evidence for participation of the frontal lobe in MMN generation has been found (Rosburg et al. 2005).

Neurotransmitters

Intracortical recordings and pharmacological micromanipulations in monkeys suggest that MMN represents selective current flow through open, unblocked *N*-methyl-D-aspartate (NMDA) channels (Javitt et al. 1996). Ketamine, a noncompetitive NMDA receptor antagonist, selectively impairs MMN generation in humans without reducing sensory EPs (Umbricht et al. 2000). MMN even seems to provide an index for the functional state of NMDA receptor mediated transmission, because a small MMN has been found to be vulnerable to ketamine administration (Umbricht et al. 2002).

The roles of dopamine, serotonin, muscarin and GABA receptors in MMN generation are still controversial, while the evidence for the importance of nicotinic receptors is stronger (Garrido et al. 2009). Dopamine D2 receptor antagonist haloperidol has been found to increase MMN amplitude evoked by frequency deviance in healthy volunteers (Kähkönen et al. 2001). However, in another study, Kähkönen et al. (2002) did not find a significant haloperidol effect on MMN or MMNm, maybe because of different stimulation and task parameter designs. Leung et al. (2007) found no effects on MMN when D2 receptor was stimulated by bromocriptine, or D1 and D2 receptors were stimulated by pergolide. Nicotine administration has been reported to augment the MMN amplitude (Baldeweg et al. 2006, Dunbar et al. 2007), while Knott et al. (2006) did not find any effect. Low brain serotonin (5-hydroxytryptamine; 5-HT) level reduces MMN amplitude, suggesting serotonergic modulation of auditory involuntary attention (Ahveninen et al. 2002, Kähkönen et al. 2005). Benzodiazepines also attenuate MMN (Nakagome et al. 1998, Rosburg et al. 2004) with possible GABAergic activation per se or the lowered vigilance level. On the other hand, benzodiazepine antagonist flumazenil has no significant effect on MMN (Smolnik et al. 1998).

Antihistamine *d*-chlorpheniramine attenuates frequency deviant MMN, suggesting an involvement of the histamine H1-receptor in the genesis of the response (Serra et al. 1996).

Overall, pharmacological studies have revealed controversial results regarding the role of different neurotransmitter systems on MMN.

Recording and analysis

MMN recordings should be done in a sound proof room because background noise diminishes the MMN. The ignore condition is preferred in recordings to avoid N2 and

P3 responses typical of active conditions (Näätänen 1995). Usually subjects watch a silent video movie or read a book to distract attention from the auditory stimulation. The diagnostic sensitivity of the MMN appears to increase if the electrode yielding the largest amplitude is used (Lang et al. 1995). Therefore, it is beneficial to use at least seven active recording scalp electrodes (Fpz, F4, Fz, F3, C4, Cz, and C3), in addition to the reference and electrooculography (EOG) electrodes for control of eye movement artefacts. For 10-20 electrode system, see Figure 5. Theoretically, the use of the nose as reference instead of the ear or mastoid could be recommended, because the place shift in parasagittal and temporal derivations makes it easier to identify the MMN topographically and to distinguish it from the N2b (Näätänen 1992). In clinical practice, however, use of the nose as a reference has been shown to be difficult because of numerous artifacts, particularly in children (Lang et al. 1995), so combined mastoids / ears are most often used. For reviews of recording standards of event-related potentials, see Picton et al. 2000 and Duncan et al. 2009.

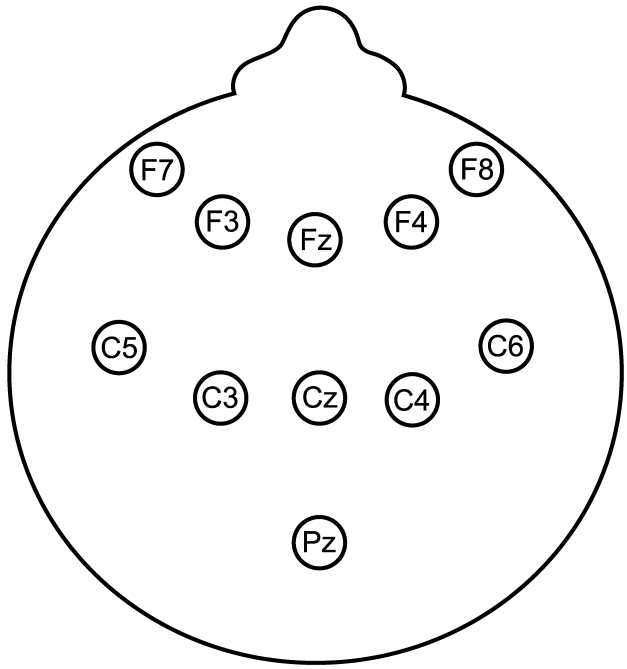

Figure 5. Position of different electrodes on the scalp.

MMN response increases with increasing number of standards (Sams et al. 1983, Näätänen 1992). This memory trace effect is reported to be caused mainly by a slow positive wave, "repetition positivity", from 50 to 250 ms post-stimulus in the standard ERP (Haenschel et al. 2005). This may represent rapid stimulus-specific adaptation. Even more than 10 000 responses to deviant stimuli should be averaged to resolve the hypothetical 0.3 μV MMN response from the backgorund EEG (Lang et al. 1995). In practice, however, it is usually possible to record MMN by collecting 200 to 300 responses to deviant and 1200 to 2700 to standard stimuli to keep the total recording time reasonable. The responses are collected, the data epoched and averaged. Averaging is done separately for both stimuli responses,

to the standard and the deviant stimuli, and is begun after the first 10-20 stimuli to avoid unwanted first high N1 responses. MMN is obtained by subtracting the response elicited by the standard stimuli from the one elicited by the deviant stimuli. If the standard stimuli evoke flat responses, the responses to the deviant stimuli can be used in analysis without subtraction (Sinkkonen & Tervaniemi 2000).

Since the peak latency of the MMN varies even in normal adult subjects within the range of 80 to 250 ms, the recording time window has to be at least 300 ms (Lang et al. 1995). However, in children and with long duration stimuli, such as syllables, the MMN peak latencies can even exceed the limit of 300 ms. Moreover, the window should begin about 50 ms before the stimulus time to allow measurement of the pre-stimulus baseline and noise level. Sinkkonen and Tervaniemi (2000) state that the frequency range of the MMN responses is between 1 and 20 Hz and, consequently, a sampling rate of 40 Hz should be sufficient.

Because the duration and amplitude of a typical MMN are known, specific filters or templates can help to reduce the impact of unwanted signals on the ERP. Sinkkonen and Tervaniemi (2000) suggest that slow baseline shifts should be removed from the raw EEG by a low (0.01-0.2 Hz) high-pass filter.

MMN is analysed by measuring the size and latency of the response. The amplitude, onset latency, peak latency, and duration of the MMN seem to represent different central mechanisms, and therefore both the amplitude and latencies of the MMN should be measured (Lang et al. 1995). Different measurement systems have been developed. In addition to amplitude minimum and maximum, averages over various time intervals, such as interval around peak latency and fixed time windows, and area analysis have been used (Sinkkonen & Tervaniemi 2000). If a fixed latency window is used for amplitude measurements, there is the risk that information is lost due to the large variation in responses. In the attended discrimination condition, in addition to MMN, N2b is elicited by the detected deviants (Sams et al. 1985). These waveforms can be automatically distinguished, because N2b has somewhat longer latency, its midline distribution is posterior to MMN and, as mentioned above, it is elicited only in attended conditions.

When EEG is used to record MMN (Näätänen et al. 1978), the localization of the generator sources is not precise, and better source localization can be gained with MEG recordings (Hari et al. 1984). To increase accuracy of localization, haemodynamic measures by PET may be used to examine the sources of automatic neural functions associated with the MMN paradigm despite its remarkably lower temporal resolution than that of EEG and MEG (Tervaniemi et al. 2000). fMRI has also been used (Opitz et al. 2002), with the same problem of poor time resolution. In addition, in auditory fMRI research, the loud acoustic noise produced by the magnetic resonance scanner interferes with recordings and reduces MMN and P3a responses (Novitski et al. 2006). If fMRI is used, it is recommended that the sound stimuli should be spectrally separated from the fMRI scanner noise spectrum.

Stimulus parameters and paradigms

Deoull and Bentin (1998) have compared the MMN responses in different stimulus paradigms, first determining the subjects' behavioural discrimination thresholds for deviations in frequency, intensity, stimulation rate, and location of stimuli. The MMN responses have then been scaled according to the individual thresholds and it has been found that the MMN amplitude evoked by the frequency deviant is larger than the MMN to deviances in other modalities. Duration deviance was not used in this study, but Pekkonen et al. (1995b) have found that MMN is larger for duration deviances than for intensity or frequency deviances. However, in duration MMN paradigms, an offset-N1 may be elicited affecting the MMN waveform. This problem can be avoided if the stimulus block includes several stimuli varying along the dimension characterizing the deviant (Kujala et al. 2007).

Concerning pitch, it has been found that the amplitude of MMN is directly proportional to the logarithm of frequency difference when either 1000 Hz (Tiitinen et al. 1994) or 600 Hz (Yago et al. 2001) standard stimuli are used. The area of MMN decreases as a function of frequency when the stimulus deviance is held constantly at 10% (Wunderlich & Cone-Wesson 2001). On the other hand, across the frequency range of 250-4000 Hz, the MMN latency is shortest at the standard stimulus levels from 1000 to 2000 Hz when an equal percentage of frequency deviance is used (Novitski et al. 2004).

The optimal magnitude of stimulus deviance is usually limited by the growth of N1, N2b and P3a at larger differences between deviant and standard stimuli (Sinkkonen & Tervaniemi 2000). If the deviance exceeds a certain limit, a passive switch of attention occurs (Näätänen 1995), and a P3a response is evoked instead of MMN. Consequently, large stimulus differences between the standard and deviant stimuli must be avoided. For example, if a pure tone of 1 kHz is used as a standard stimulus, a deviance of more than 100 Hz is usually obtrusive (Lang et al. 1990).

Schröger (1994) has claimed that MMN elicited by a frequency change is not greatly influenced by stimulus intensity as long as a certain minimum intensity is exceeded. Thus, the MMN would be sensitive mainly to the information contents of the stimuli, irrespective of the total amount of energy. In another study, Schröger (1996) has obtained somewhat larger frequency MMNs evoked at higher stimulus intensity (70 dB SPL versus 55 dB SPL). In these experiments, the duration of the stimuli was only 50 ms, which may have affected the loudness level sensation, because the frequency and loudness of a tone are related via equiloudness contours (Robinson & Dadson 1956). In brief-tone audiometry, the psychophysically measured detection threshold diminishes, when the stimulus duration is increased from 50 ms to 100 ms (Pedersen 1974).

MMN amplitude increases with increasing stimulation rate (Näätänen et al. 1987). A possible explanation for this phenomenon is that as the repetition rate of the standard stimuli increases, the memory trace evoked by it becomes more intense. In practice, an ISI of about 300 ms has been shown to be appropriate for MMN applications when

simple tone pips or vowel stimuli are used (Lang et al. 1995). The duration of the memory trace is about 10 s and if the deviant follows the standard after a longer silent interval, no MMN is elicited (Cowan et al. 1993).

The size of the MMN is directly proportional to the logarithm of the deviant stimulus probability (Sinkkonen & Tervaniemi 2000). The amount of deviant stimuli used is usually 10-20%. Long recording time is a problem when several stimulus blocks are needed. In the multifeature "Optimum 1 paradigm" (Näätänen et al. 2004), every other stimulus tone is a standard and every other a deviant stimulus of various types. With this paradigm, five different modality MMNs (frequency, duration, intensity, location and gap deviants) can be recorded simultaneously, thus reducing the time needed for recording multiple MMN responses. Deviant stimuli strengthen the memory trace of the standard for those stimulus attributes they have in common. Central auditory detection of changes in speech sounds is more demanding than in harmonic sounds. However, the fast multi-feature paradigm with speech stimuli (changes in syllable intensity, frequency, vowel length, consonant and vowel change) provides MMN responses similar to those in the oddball paradigm (Pakarinen et al. 2009). The results have been reproducible in two recordings made 1-7 days apart with only minor differences. In a recent study (Pakarinen et al. 2010), the multifeature MMN paradigm has been used without standard stimulus and all sound changes have elicited MMN response. This has been explained to be possible because a memory trace is constructed for the invariant features. Almost 50% shorter recording time is possible when standard stimuli are omitted. This also improves the cost-efficiency.

Variation within and between subjects

Large inter and intraindividual variations of the MMN and dependence on the general state of vigilance introduce problems in the diagnostic application of MMN in clinical practice. Interindividual variation can be caused e.g. by variations in discriminative ability, which correlates with MMN (Lang et al. 1990). There are healthy people who for some reason do not show MMN to tone stimuli and, apparently, this cannot be considered a pathological finding (Lang et al. 1995). However, when the speech stimuli are used, MMN seems to be elicited in all normal school-aged children and adults (Kraus et al. 1992b). Also dipole orientation of the MMN may result in individual variation in the scalp distribution of the responses (Lang et al. 1995).

Variation in MMN variables from one recording to another in the same subjects even with the same stimuli, raises the question of the reliability of MMN measurements. When three subjects have been examined on five days using four different frequency deviances, coefficients of variation have been considerably higher for the MMN amplitude than for the latency (Lang et al. 1995). However, when duration and frequency deviance evoked MMNs have been recorded in two sessions separated by one month, it has been found that the amplitude evoked by duration but not by frequency deviance shows significant intraindividual test-retest stability (Pekkonen et al. 1995b). In multi-feature paradigm

to phonetic and acoustic changes in speech sounds the results have been reproducible (Pakarinen et al. 2009). Also 7-11- year-old children show stability in duration deviance MMN when tests are done twice during a two week period (Uwer et al. 2000). However, the stability seems to be somewhat lower in children than in adults. In a study where a tone pair with 120 ms ISI has served as standard stimulus and tone pairs with varying ISI as deviant stimuli, two sessions separated by 4-21 days have been held (Kujala et al. 2001a). When the difference in stimuli is large enough, MMN is elicited with high reliability and repeatability. Alertness of the subject also affects MMN (Lang et al. 1995) that is attenuated by a decrease in alertness even before an actual sleep state is reached (Sallinen & Lyytinen 1997). In conclusion, MMN might be used in follow-up studies also at the individual level (Pekkonen et al. 1995b). Clinical use of MMN is still significantly limited because of the lack of large reference value data bases. However, Cone-Wesson and Wunderlich (2003) suggest that it should be possible to develop latency and amplitude reference limits for MMN obtained with several speech sound contrasts.

Subject factors

In fetal MEG recordings when complex tones are delivered over the maternal abdomen (oddball paradigm) MMN response can be elicited in 48% of recordings (Draganova et al. 2005). Alho et al. (1990) have used a frequency deviant oddball paradigm and have found in newborns a large slow negative ERP component which resembles the MMN. Already in healthy premature infants born 30-35 weeks after conception MMN has been elicited by speech sounds (Cheour-Luhtanen et al. 1996). In 2- and 3-month-old subjects, frequency change in piano notes (oddball paradigm) evokes a left-lateralized positive slow wave, and a faster, adultlike MMN, lateralized to the right hemisphere, from two months on (He et al. 2007).

In their review, Cheour et al. (2000) state that MMN amplitude is only smaller in infants than in school-aged children but in other aspects, MMN does not seem to differ much from responses in adults. MMN latency seems to be slightly longer in infants but adult values are reached already by early school-age. A clear difference is that a prominent MMN can be obtained in all waking- and sleep states in infants, contrary to adults who show attenuated MMN during sleep. Also MMN scalp distribution seems to differ, being broader and more central in children compared to frontal predominance in adults.

School-aged children from 7 to 13 years show negative correlation between the MMN peak latency and age in frequency and duration oddball paradigms (Korpilahti & Lang 1994). Shafer et al. (2000) have also found MMN latency decrease from 4 to 10 years of age, while no developmental change in amplitude has been found. In 7-9-year-old children, MMNs evoked by frequency deviance are larger with 1400 ms than 700 ms ISI, which is interpreted as an age-specific phenomenon (Ĉeponienė et al. 1998). On the other hand, Kraus et al. (1992b) have not found any maturational MMN changes (speech stimuli) in children aged 7-11 years.

Children aged from 5 to 10 years evoke greater temporal components of MMN amplitudes than adults, while frontal components do not differ (Gomot et al. 2000). From childhood (11 years) to adulthood, maturational changes in the topography of MMN (frequency deviants) occur (Martin et al. 2003).

The MMN evoked by frequency deviance (stimuli delivered at a rate of 1 per s) has been reported to attenuate in elderly people (Gaeta et al. 1998). Age-related reduction has also been found in the MMN amplitude evoked by ISI deviance, which supports the hypothesis that aging decreases automatic processing of time-dependent stimulus features (Kisley et al. 2005). In the frequency deviance paradigm, prolonging ISI from 1 s to 3 s diminishes the MMN area in the elderly, suggesting that sensory auditory memory is impaired with increasing age (Pekkonen et al. 1993). When ISI has been prolonged to 4.5 s, the MMN/N2b-complex attenuates more in older than younger subjects (Pekkonen et al. 1996). This suggests that aging does not impair the automatic stimulus discrimination per se, but the stimulus trace decays faster. However, in another study (Fabiani et al. 2006), MMN has also been larger for 1 than for 5 s delay between trains of five stimuli, but no difference between younger and older adult groups has been found. This discrepancy between the results may be due to the differential overlap with the N2b. Cooper et al. (2006) have recorded MMN evoked with duration and frequency deviants at short (450 ms) and long (3 s) stimulus onset asynchrony (SOA) and have found smaller and later MMN in the elderly (mean age 69 years) compared to young (mean age 21 years) subjects.

Neither gender nor educational level affects MMN when pure tone stimuli with frequency deviance are used (Schiff et al. 2008, Ikezawa et al. 2008). With phonetic stimuli (syllables) deviance, MMN is larger in females than males especially in the right hemisphere (Ikezawa et al. 2008). Gender has an influence also on the MMN evoked by complex stimuli; MMN latency is longer in females than in males when vowel stimuli are used (Aaltonen et al. 1994). Gender differences are also found in music processing, so that music-synthetic MMN is generated bilaterally in females but with right hemispheric predominance in males (Koelsch et al. 2003).

Clinical applications

MMN deficiency appears to index cognitive decline (for review, see Näätänen et al. 2012). It provides the objective measure of the central auditory function, which makes it suitable for clinical use (Näätänen 2000). The attention-independence makes it useful also in infants, children and non-cooperative patients. The development of new multi-feature MMN paradigms (Näätänen et al. 2004) shorten the over-all recording time, thus being more feasible for the patients, as well as more economical. Various patient groups have already been studied with MMN techniques (for reviews, see Csepe & Molnar 1997, Näätänen & Escera 2000, Näätänen 2003, Cone-Wesson & Wunderlich 2003) (Table1). However, the current use of the MMN for studying individual patients is at best doubtful (Katz et al. 2009). In some normal individuals the MMN is frequently not recordable even to easily perceptible contrasts.

Table 1. Different clinical applications studied by MMN.

AUDIOLOGY	*SPEECH RESEARCH*	*PSYCHIATRY*	*NEUROLOGY*
non-cooperative patients	***reading disabilities***	***schizophrenia***	***Parkinson's disease***
hearing deficits	***discrimination training following***	***medication response***	***Alzheimer's disease***
benefits of hearing aids	***language learning***	***depression***	***MS***
auditory neuropathy	***CI patients***	***posttraumatic stress disorder***	***prediction of coma outcome***
CATCH syndrome			***pain effects***

Audiology

MMN reflects sound discrimination accuracy and behavioural discrimination ability; the better the pitch discrimination, the larger the MMN amplitude (Lang et al. 1990, Kraus et al. 1993a). Attention independence makes it a feasible tool for examination of patients who cannot cooperate in behavioural tests, for example, newborns and children. Newborn brains monitor changes in the acoustic environment already at the early ontogenetic stage (Alho et al. 1990), and even fetal MMN recordings in-utero can be made (Draganova et al. 2005). Thus, recordings can help to find deficits of central auditory processes at very early stages.

MMN may be suitable for examining the central auditory discrimination processes in hearing deficits, for example, presbyacusis, because psychoacoustic measures do not provide information about the level of the deficit, nor about the unattended sound processing. In a study on two hearing deficit patients with a hearing aid and similar audiograms and ABRs but different behavioural and central electrophysiologic profiles, Kraus et al. (1995) found that the MMN responses to speech stimuli reflected the functional differences; the patient with poor behavioural discrimination did not evoke MMN, while the patient with good discrimination did. However, when sensorineural hearing impairment has been studied with speech stimuli, it has been concluded that the feasibility of MMN is limited due to its high variability and lower detection rate compared with N1, N2 and P3 (Oates et al. 2002).

Benefits of hearing aids for speech discrimination can be objectively measured with MMN recording in hearing-impaired patients (Korczak et al. 2005). In this experiment, 14 adults with sensorineural moderate (50 to 74 dB HL) or severe-profound (75 to 120 dB HL) hearing loss and 20 normal-hearing adults have been compared using /ba/ and /da/ speech stimuli. The majority of the patients have demonstrated increased MMN amplitude and shorter latency in the aided versus unaided condition at 65 dB SPL, but

not at 80 dB SPL stimuli. The result suggests that the hearing aid helps to process speech stimuli with greater accuracy, especially at lower stimulus intensity.

Based on MMN findings, Cheour et al. (1998) concluded that auditory sensory memory is deficient in cleft palate patients. However, they did not carry out audiological examinations in the patients though most children with cleft palate will probably develop persistent middle ear fluid with conductive hearing loss (Szabo et al. 2010). MMN is attenuated in children with CATCH syndrome and in children and newborns with cleft palate but without the CATCH syndrome (Cheour et al. 1999).

Auditory neuropathy is a hearing disorder with abnormal auditory nerve function but normal cochlear cell activity. In an experiment with 14 patients with auditory neuropathy, MMN was evoked with syllables in nine patients, even though five of them could not behaviourally discriminate stimulus pairs (Kumar & Jayaram 2005).

Speech research

Speech-evoked auditory ERPs provide information about the biological processes underlying speech processing. The brain mechanisms of speech perception and understanding can be studied with MMN because it reflects the auditory sensory memory function. In dysphasic children, the frequency MMN is attenuated and the responses are more widespread, symmetric and central than those of healthy subjects (Korpilahti & Lang 1994). Aphasic patients with posterior lesions who do not elicit MMN response to synthetic vowels, may, however, produce MMN to sine wave stimuli (Aaltonen et al. 1993). Children with reading disabilities process rise time changes differently from control children. MMN is smaller in disabled children (Hämäläinen et al. 2008).

In a longitudinal study, children with familial risk for dyslexia have been followed from birth to school age (Lyytinen et al. 2004). The ERP recordings taken already immediately after birth have shown that newborns at familial dyslexia risk respond with a different discriminative response to various speech sounds compared with controls. After nonlinguistic audiovisual training with a computer game, reading-impaired children (7 years) have shown considerably increased MMN to tone-pair stimuli deviances (Kujala et al. 2001b). MMN can also measure parallel behavioural detection of stimulus duration (Jaramillo et al. 2000) and synthetic vowels (Aaltonen et al. 1994). Thus, MMN has clinical benefits both in identifying the risk of dyslexia and in following plastic changes induced by discrimination training.

It has been shown with MMN to frequency deviant stimuli, that learning can take place even without focused attention or awareness (Cowan et al. 1993). Newborns have been trained to discriminate speech sounds /y/ vs. /i/ and /y/i/ while they are sleeping and the effect of learning has been verified with improvements in MMN (Cheour et al. 2002). There is evidence that neurophysiological changes reflected in MMN responses even precede the behavioural change (Tremblay et al. 1998).

Especially elderly people often complain of difficulty in understanding speech. When the ISI deviance paradigm with ISIs from 6 to 24 ms is used, elderly subjects evoke reduced MMN peak amplitudes and increased MMN latencies compared to young subjects (Bertoli et al. 2002). This reduction in the automatic orienting system correlates with problems in the performance of complex behavioural tasks and could underlie the speech understanding problems.

In an MMN study with Finnish and Estonian subjects, it has been found that phonemic traces are language-specific (Näätänen et al. 1997). MMN is enhanced when the deviant stimulus is a prototype of the subject's native language compared to a non-prototype deviant. MEG recordings locate the source of this enhancement in the auditory cortex of the left hemisphere.

Studies on MMN recordings with speech stimuli concerning patients with cochlear implant are explained elsewhere.

Psychiatry

As a preconscious cognitive response, MMN can be used to investigate the pathophysiology of neuropsychiatric states. Garrido et al. (2009) claim that the most promising clinical application of MMN is in schizophrenia research. Most studies on the relationship between MMN and schizophrenia have found that both untreated and treated patients have lower MMN amplitudes than healthy controls, with the deficit being poorest frontocentrally (for review, see Urban et al. 2007). There is also an association between the deficit in MMN generation and poorer social functioning. This might be used as a predictor of functional deterioration in patients. In a meta-analysis of 32 studies (Umbricht & Krljes 2005), MMN to deviant stimuli differing in duration has appeared to be more impaired in schizophrenia than MMN evoked by frequency deviants. These MMN changes correlate with duration of illness. The MMN deficits in chronic patients have been associated with poor functional status and they are repeatable even when recorded twice over a 1-2-year period (Light & Braff 2005).

Patients with depression have been studied with the frequency difference oddball paradigm (Ogura et al. 1993). MMN amplitude has been reduced, but N2b may have been evoked to frequent stimuli more often in the patients than in the control group.

Patients with posttraumatic stress disorder show reduced amplitude of the MMN (deviances in frequency, intensity, duration, direction and a gap in the sound) (Menning et al. 2008).

In conclusion, MMN attenuation is not specific to any psychiatric disorder, but it may be useful for assessing medication response, prognosis and other factors in longitudinal studies.

Neurology

Parkinson's disease patients show smaller MMN than control subjects, which may be caused by dopamine deficiency (Pekkonen et al. 1995a, review Pekkonen 2000) or early dementia.

In Alzheimer patients, MMN amplitude decreases as the ISI is prolonged from 1 s to 3 s while N1 response does not attenuate, suggesting that dementia causes problems with sensory memory rather than discrimination (Pekkonen et al. 1994, review Pekkonen 2000).

Multiple sclerosis (MS) patients show reduced MMN areas when duration deviance is used (Jung et al. 2006). Alterations are more pronounced in cognitively impaired patients and, thus, MMN recordings may represent an objective index of cognitive disturbances in MS.

MMN recordings may also be useful in predicting whether or not a comatose patient will regain consciousness (Kane et al. 1996, Fischer et al. 2000, Wijnen et al. 2007, Daltrozzo et al. 2007). When MMN is present in comatose patient, the consciousness will recover in nearly 100% of the cases (Kane et al. 1996, Fischer et al. 2010). Few patients in a permanent vegetative state are likely to evoke MMN to duration deviances, mainly when the state is not due to anoxia (Fischer et al. 2010). Thus, diagnostic criteria and predictive evaluation of comatose patients should be based not only on behaviour or clinical indices, but should also include functional brain investigations.

ERP recordings can demonstrate how pain affects cognitive brain processes. In their experiment, Dick et al. (2003) found that in subjects experiencing chronic neuropathic pain, the MMN amplitude (frequency change oddball paradigm) increases following a successful nerve block procedure.

Lesions of the frontal cortex diminish the MMN evoked by frequency deviance (Alho et al. 1994).

MMN might provide information about the progress of the neurological disorders and possible associated deficits in cognitive function.

Alcohol and drug effects

MMN can be used to study alcohol and drug effects on cortical functions (Table 2).
Even a small alcohol amount influences the detection of especially small deviations in the information flow (Jääskeläinen et al. 1995). Drug-effect experiments may offer important information on how cognitive processes are affected and whether the ability to carry out high-risk tasks is impaired during medication. For example, MMN is attenuated in the morning following night sleep with benzodiazepine triazolam administration (Nakagome et al. 1998). Sedation with propofol results in reduced MMN, indicating that

the auditory sensory memory is still active, although strongly reduced, during anesthesia or sedation (Heinke et al. 2004, Koelsch et al. 2006).

Table 2. Alcohol and drug effects on MMN.

alcohol attenuates MMN (frequency and duration deviance) (Jääskeläinen et al. 1995, 1996)
benzodiatsepines triazolam attenuates MMN, lorazepam attenuates MMNm (Nakagome et al. 1998, Rosburg et al. 2004)
haloperidol seems to increase MMN (Kähkönen et al. 2001)
antihistamine *d*-chlorpheniramine attenuates MMN (frequency deviance) (Serra et al. 1996)
naltrexone with ethanol increases MMN peak latency (Jääskeläinen et al. 1998)
propofol attenuates MMN (Heinke et al. 2004, Koelsch et al. 2006)
nicotine shortens MMN latency (Inami et al. 2005)

Musicality

MMN can be used as an objective measure of tone discrimination ability and learning effects (Lang et al. 1990). Recent views emphasize cognitive factors in musicality. Musical subjects evoke larger MMNs (pitch deviance) than non-musical ones suggesting that the cognitive component of musicality is present already at the pre-attentive level (Tervaniemi et al. 1997). In another study (Tervaniemi et al. 2005), musicians have detected not only 0.8% but also 2% frequency changes better than non-musicians. However, the MMN and P3a of these groups did not differ. This may indicate that musical expertise may anyhow have an affect merely at attentive levels of discrimination processing.

2.3 Effects of masking and surrounding noise in audiological examination and evoked response recordings

When the stimuli are presented via air conduction to one ear but their intensity is over 50 dB HL, they are conducted via the skull bones to the opposite ear. Contralateral masking, usually white noise, is used in audiological examinations to avoid the effect of contralateral conduction on the results (Katz 2009). In pure tone audiometry, masking is used in the clinic. Masking does not affect the latencies and amplitudes of brainstem responses significantly, so it can be used in clinical work also in the BAEP recordings (Humes & Ochs 1982, Boezeman et al. 1983, Smyth 1985)

There are not many previous studies on the contralateral masking effects on N1 and P2 responses. Furthermore, masking intensities have usually been quite high and the results so far are rather controversial. The effect of contralateral masking on N1P2 peak to peak amplitude has been studied by Chueden (1972). Contralateral white noise did not significantly influence the amplitude. Chueden claimed that masking has central effects, but that it does not affect the summation of cortical responses. The brain would, thus, more or less ignore the "steady-state" masking even if it were stronger than the pure-tone stimulus. In cats, contralateral masking has diminished the baseline to peak negativity amplitude (at 25-50 ms), but the effect on the latency is inconsistent (Phillips & Kelly 1992). Connolly (1993) used 1 kHz tone burst stimuli with 70 and 90 dB SL intensities and conralateral white noise, which was presented at the same intensity level as the stimuli. He has found that P2 amplitudes are generally larger during masking. However, in that study, the masking noise was always strong enough to be conducted through the skull to the opposite ear. Contralateral pure tone (continuous 4 kHz tone, 45 dB SL) reduces the N1 amplitude evoked by the same frequency range clicks at 30 and 40 dB SL (Folsom & Owsley 1987). Bertoli et al. (2005) have found that contralateral cafeteria noise (long-term average of 70 dB SPL) increases N1 amplitude and reduces P2 amplitude. In this study, the right ear was stimulated with 1000 Hz pure tones in normal-hearing young adults. In the same study, N1 amplitude decreased in elderly hearing-impaired subjects indicating that the audibility of the stimuli presented to the contralateral ear is reduced by masking noise when there is a hearing deficit.

Contralateral continuous noise (0.25-3 kHz, 84 dB SPL) has no significant effect on the neuromagnetic N100m responses evoked with stimuli given to the right ear (Hari & Mäkelä 1988). On the other hand, both ipsi- and contralateral speech, music, intermittent noise, and continuous sine tone attenuate N100m. Thus, masking stimuli that are modulated in intensity and frequency would have a more central effect than noise. However, all the maskers that were used in this experiment were so strong that they were probably conducted to the ear not being examined. The real-life noise (babble, industrial, traffic and wide band noise) and silent condition have been used to study noise effect on MMNs evoked by speech and non-speech sounds (Kozou et al. 2005). In this study, stimuli have been presented by loudspeakers with real-stimulus intensity of 65 dB SPL and surround noise intensity of 55 dB SPL. It was found that processing of the speech stimuli is affected more by noise than processing of the non-speech stimuli. Furthermore, babble and industrial noises dramatically reduced the MMN amplitudes for both stimuli, but traffic noise affected only the speech-stimuli evoked responses. Wide band noise had the smallest effect on the MMN. The attentive behavioural discrimination tasks (same stimuli as in MMN recordings) showed no differences between processing speech and non-speech stimuli, and there was no significant effect of noise. In another study with speech stimuli, continuous background speech masking noise at either 65, 70 and 75 dB SPLs or quiet condition has been used (Muller-Gass et al. 2001). As masking decreases the audibility, the MMN peak amplitude also decreases and the MMN peak latency increases. Contrary to the finding of Kozou et al. (2005), the behavioural data in

this study are in accordance with the MMN results. An intermittent structured stimulus delivered ipsilaterally before or after the stimulus (forward or backward masking) clearly attenuates the MMN amplitude, and the behavioural discriminatory performance is reduced in the same proportion (Winkler et al. 1993).

In a neuromagnetic mismatch field (MMF) experiment, both contra- and ipsilateral masking by music abolished the MMF, while only ipsilateral white noise affected the MMF (Levänen & Sams 1997). Also in this experiment, the masking was loud, 82 dB SPL for the noise masking and, on average, 80 dB SPL for the music masking. MMNm recordings with speech stimuli have shown that in silence the response is stronger in the left than in the right hemisphere, while during a white noise background, MMNm in the left hemisphere diminishes and in the right hemisphere increases (Shtyrov et al. 1998).

2.4 Perception and production of speech in cochlear implant patients

The MMN elicited by the stimulus pair /da/ and /ta/ has been found to be remarkably similar in cochlear implant patients and normal-hearing subjects (Kraus et al. 1993b). This result shows that MMN may be useful as an objective measure of speech perception in patients with a cochlear implant. MMN can be used to assess the functional status of the auditory cortex in children with cochlear implants and it might be an objective measure to predict future performance (Singh et al. 2004, 2006). In children with cochlear implants, speech sounds elicit MMNs of longer latencies, reflecting higher acoustic complexity of speech sounds compared to simple tones varying either in intensity or frequency (Kileny et al. 1997). The information delivered through the implant seems to activate neural phonetic traces required for the generation of MMN.

There are differences in the scalp distribution of MMN between implanted patients and normal-hearing subjects; the locus of MMN activity being lower in the patients (Ponton et al. 2000). Frequency deviance evoked MMN latency and the thresholds for pure-tone detection and word discrimination correlate so that MMN peak latency increases as the word discrimination threshold increases (Roman et al. 2005). In adult cochlear implant patients, MMN (frequency deviant) is absent or diminished in subjects with poor speech scores (Kelly et al. 2005, Groenen et al. 1996). Even physically deviant chords elicit a MMN in cochlear implant patients, although of smaller amplitude than that of controls (Koelsch et al. 2004). Also Sandmann et al. (2010) have found that, according to the MMN responses the perception of musical sound is impaired in the cochlear implant patients.

Pure-tone detection as reflected in N1P2 has been found to be similar regarding latency and amplitude in cochlear implant patients and control subjects. Pediatric cochlear implant patients with poor speech perception skills have prolonged P3 latencies compared with those who have good speech perception (Benyon et al. 2002).

Perkell et al. (1992) have studied vowel production in postlingually deafened cochlear implant patients. They speculated that speech production ability is influenced at least as much by prior linguistic experience as by perceptual gains. Pelizzone et al. (1991) have examined a patient who was first implanted in the congenitally-deaf right ear. This led to clear sound perception but no speech recognition. Two years later, the same patient got an implant also in the acquired-deaf left ear, which enabled the patient to understand speech without lip-reading. Brainstem and middle latency evoked potentials were similar in both ears but the congenitally-deaf ear did not evoke P1 and N1; instead, an abnormal peak at 65 ms was seen, suggesting that the congenitally-deaf ear elicited an abnormal activation of the auditory cortex.

MMN has been suggested to be valuable in evaluating the efficacy of speech-processing strategies and auditory training approaches. Lonka et al. (2004) have measured MMN for vowel changes and speech-discrimination performance in five adult cochlear implant patients. Speech discrimination was shown to be improved at follow-up, and, after 2.5 years, MMN could be recorded in all patients, first for the larger and later for the smaller vowel difference. However, when MMN has been recorded by stimulating three pairs of different electrodes, no relationship between MMN and speech performance has been found (Wable et al. 2000). MMN studies in cochlear implant patients reflect discrimination ability at the group level, but the methods have more limitated value in individual patients (Cone-Wesson & Wunderlich 2003). Cone-Wesson and Wunderlich (2003) recommend speech stimuli, such as vowel and consonant-vowel segments, for testing cochlear implant patients.

MMN can be valuable in studying speech perception, training effects and predicting future performance in patients with cochlear implant.

3 AIMS OF THE STUDY

The aims of the present study were to investigate long latency auditory evoked potentials and their clinical uselfulness for objective measurement of hearing discrimination.

The specific aims were to:

1. Examine how the stimulus intensity level influences on the MMN responses (I).
2. Examine how the stimulus frequency influences on the MMN responses (II).
3. Investigate how contralateral white noise masking alters the MMN responses (III).
4. Evaluate whether contralateral masking has an effect on the N1 and P2 waveforms (IV).
5. Study postoperative vowel identification and production and clinical application of MMN on postlingually deafened cochlear implant patients (V).

4 MATERIALS AND METHODS

4.1 Subjects and patients

In total, 57 right-handed healthy volunteers and four cochlear implant patients participated in the studies (Table 3).

Table 3. Demographic data on the subjects.

	Subjects (n)	*Mean age (years)*	*Range (years)*	*Males*
Study I	*10*	*26*	*19-45*	*4*
Study II	*9*	*26*	*19-33*	*4*
Study III/1	*11*	*26*	*20-35*	*4*
Study III/2	*11*	*22*	*17-27*	*2*
Study IV	*15*	*27*	*18-40*	*5*
Study V	*4 CI patients*	*40*	*29-55*	*2*
	+ 1 healthy subject		*22*	*1*

Four postlingually deafened patients (aged 29-55 years, mean 40 years, two males) participated in study V. The cochlear implant used was a Nucleus Mini 22 with Spectra speech processor (Cochlear Ltd., Australia). The peak energy of the F1 pulse is placed on one of the apical seven electrodes (21 to 14) and the F2 pulse on one of the basal 14 electrodes. A detailed information of the patients and subject can be found from the Study V.

Table 4. Cochlear implant patients' hearing during the study.

	SRT (dB HL)	*Recognation score*	*Age at implantation (years)*	*Implant ear*
Patient 1	*23*	*90*	*42*	*left*
Patient 2	*29*	*80*	*27*	*right*
Patient 3	*34*	*87*	*30*	*left*
Patient 4	*32*	*66*	*55*	*left*

SRT = speech reception threshold

4.2 Experimental design

4.2.1 Stimuli in ERP recordings

ERP recordings were carried out in an electrically isolated and sound proof room. The subjects were sitting in a chair and watching a silent video, being told to ignore the stimuli. They were monitored by TV-camera.

Tones: In studies I, II and III, the MMN stimuli consisted of various sine tones (Table 5). In studies I and III the stimulus frequencies were the same as in other studies in our

laboratory in order to get comparable results. Mel scale and previous DLF studies were used to choose the stimuli in study II. Standard stimulus frequencies were also used for N1P2 measurements. Stimulus duration was 100 ms, ISI 1 s, and intensity 65 dB HL. In study IV, tone pips (intensity 65 dB HL, duration 100 ms, ISI 1 s) with a frequency of 500 Hz presented to the right ear were used as stimuli.

Masking: In studies III and IV, white noise was used as contralateral masking. In study III, masking noise intensity was 50 dB effective masking level (EML). In the first experiment, it was delivered to the left ear and in the second experiment, either to the left or right ear, contralateral to the stimuli. In both experiments a no-mask condition was also used. In study IV, masking was delivered at the intensities of 35, 50, 65, or 75 dB EML, and a no-mask condition was also applied.

Vowels: In the MMN recordings of study V, the prototypical Finnish /i/ (F2 2230 Hz) was used as the standard stimulus and vowels deviating from it by 30, 60, 90, or 120 mel in F2 (F2 2313, 2400, 2488 and 2578 Hz, respectively) were deviant stimuli. Another four stimulus blocks were produced so that the former deviant stimuli were used as standards and the standard stimulus as the deviant.

The tone stimuli in studies I, II and IV were generated by Neurostim equipment (NeuroSoft Inc., USA). In Study III, the tone stimuli were generated by a computer-controlled waveform generator (Wavetek 175). The white noise in studies III and IV was produced by an audiometer (Interacoustics AC4). The stimuli were delivered by insert earphones in study I, and by air conduction earphones (Telephonics TDH-39) in studies II, III, IV and V. In study V, the microphone of the cochlear implant was fixed between the earphones.

Table 5. Sine tone stimuli in MMN recordings.

	Frequency (Hz) standard/deviant	***Duration (ms)***	***ISI (ms)***	***Intensity (dB HL)***	***Deviant stimulus probability (%)***	***Stimulated ear***
Study I	*1000/1141*	*100*	*350*	*40, 50, 60, 70, 80*	*10*	*both*
Study II	*125 /174* *125/157* *500/571* *500/560* *1000/1100* *2000/2159* *2000/2260* *4000 /4277* *4000/4631*	*100*	*350*	*65*	*20*	*both*
Study III/1	*500/600* *2000 /1900* *2000/1600*	*40*	*300*	*70*	*20*	*right*
Study III/2	*500/600*	*40*	*300*	*70*	*20*	*right or left*

4.2.2 ERP recordings

The EEG in studies I, II, IV and V was recorded, averaged and edited using the NeuroScan equipment (NeuroSoft Inc., USA). In study III, EEG was recorded by two dual-channel amplifiers (Disa 15 C 01) and averaged by DataPrecision 6000. The recordings were made using silver-silverchloride electrodes (Ag/AgCl) fixed to the scalp according to the international 10-20 system.

We used the electrodes F3, Fz, F4, C3, Cz, C4 and Pz in studies I, II and IV. In study III, only the midline electrodes Fz, Cz and Pz were used. In study V, the complete 10-20 system electrode set-up was used. Linked ears served as references. The electrodes for eye movement recording (electrooculography, EOG) were attached to the lateral upper canthus of the right eye and the lateral lower canthus of the left eye. The signals were filtered with a low frequency cut-off of 0.3 Hz and a high frequency cut-off of 70 Hz, except in study III where the filter settings were 0.5 Hz and 60 Hz. The EEG epochs with eye movement artifacts were automatically rejected, the average rejection level being ± 50 μV, except ± 100 μV in study III. The EEG signal was monitored visually during the recording. Recordings were made by a nurse, trained in EEG and evoked potential recordings. The time window of recordings was between –50 ms and 350 ms in studies I, II and IV. In study III, it was between 0 ms and 300 ms, and in study V between –50 ms and 700 ms.

In studies I and II, we used the evoked potential analysis software developed in our laboratory based on the Origin software (Microcal Software Inc., Northampton, MA) to analyse the MMN responses (Figure 6).

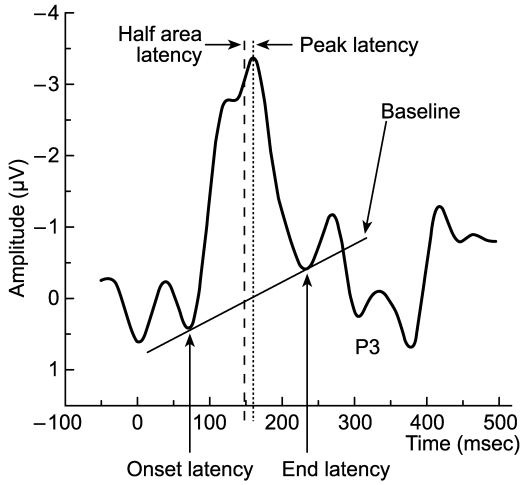

Figure 6. Measurement principles of latency and amplitude values of the mismatch negativity waveform.

The MMN onset and offset points were marked manually. As baseline, we used the line between these two points to reduce undesired variation caused by slow trends and other

artifacts. The MMN area was calculated by intergrating the area between the MMN-waveform and baseline. Mean amplitude was calculated by dividing the area by the difference between the peak latency and onset latency. The half area rise time is the difference between the half area latency (the latency at which the numerical integration of the area from onset latency reaches half of the total area) and onset latency. In study III, only the onset latency, peak latency and MMN amplitude were measured. In study V, the significance of difference between standard and deviant ERP waveforms was evaluated by a nonparametric computer program (Lakkisto, 1991). It compares whether the average distance of curve pairs elicited by standard and deviant stimuli differs statistically significantly. In the MMN recording of one patient, there was a significant MMN, and its onset latency, peak latency and amplitude were measured.

In study I, P3, when elicited, was measured from the Cz electrode. In study II, N1 latency and N1P2 amplitude and in study IV, N1 and P2 amplitudes, N1P2 peak to peak amplitude and the peak latencies were additionally measured.

4.2.3 Statistical analysis

For statistical analyses, analysis of variance for repeated measurements (rmANOVA) was used in studies I, II, III and IV. The General Linear Models Procedure of the SAS software (SAS Institute Inc., Cary, Nc, USA) was applied for the analyses. In studies I, III and IV, Greenhouse-Geisser adjusted *p* values were used, when appropriate. In study I, the within-subject factors were stimulus intensity and electrode location. In addition, the stimulus intensity level of 80 dB HL was compared with other levels using contrast (1)-statement inside the repeated sentence in the General Linear Models Procedure. In study II, repeated measures analysis of variance was made separately for mel blocks with basic block (1000 / 1100 Hz), DLF blocks with basic block, and N1-P2 recordings. Within-subject factors were stimulus frequency and electrode location. Paired T-test was applied to test the difference between the basic block and the other blocks and Huynh-Feldt adjusted p-values were used. In study III, the repeated factors were the stimulus block, masking sound and electrode location in the first experiment. In the second experiment, the stimulated ear replaced the stimulus block. In the analysis of the combined material from these two experiments, the masking sound and electrode location served as repeated factors. In study IV, masking sound level and electrode location were used as within factors. If an interaction effect was present, the repeated measures analysis was made at each electrode separately, and contrasts were used to compare the no mask situation with other levels of masking. In addition, tests monitoring F3 versus F4 and C3 versus C4 electrodes were done to determine the possible lateralization. In study V, no statistical analysis was done because of the small number of patients.

4.2.4 Behavioural methods

In study V, method of adjustment (MOA) was used to examine the vowel system of cochlear implant patients and one normally hearing subject. The subjects were asked to

adjust F1 and F2 parameters of the OVE 1b, vowel synthesizer, a manually controllable synthesizer of vocalic sounds according to Fant (1998), to produce each of the Finnish vowel phonemes (/a/, /e/, /i/, /o/, /u/, /y/, /æ/ and /ø/) in alphabetical order. The frequencies of the formants F3 and F4 were fixed at 3400 and 4700 Hz, respectively. The F0 was set at 120 Hz. The vowel chosen by the subject was analyzed by the sound spectrograph (DSP Sona-Graph, Model 5500), and F1 and F2 were defined. In the second part of the behavioural session of study V, the patients and healthy subject were asked to produce their own isolated long variant of Finnish vowels, and F1 and F2 of these were measured. Each subject was given a few opportunities to produce the best possible vowel. The results of MOA and the production session were plotted in a conventional F1/F2 vowel chart.

4.2.5 Ethical aspects

Oral, informed consent was obtained from all the volunteers and patients. Studies were approved by the Ethical Committee of the University of Turku.

5 RESULTS

5.1 Effect of stimulus intensity on the MMN (Study I)

The stimulus intensity had a significant effect on the MMN waveform (Figure 7). With increasing stimulus intensity, the MMN mean amplitude clearly increased ($p = 0.0117$). Electrode location affected the MMN mean amplitude ($p = 0.0046$) so that the maximal amplitudes were elicited at the midfrontal electrode on the right (F4). Both the intensity ($p = 0.0287$) and electrode location ($p = 0.0085$) had an effect also on the half area rise time of the MMN. The longest mean rise time values were recorded with the 60 and 70 dB HL stimuli at the electrode F4. The shortest MMN onset latencies (mean values) were recorded with the 60 and 70 dB HL stimuli at the frontal electrodes. P3 amplitude increased with stronger stimulus intensities ($p = 0.0128$). The largest amplitudes were elicited with 70 dB HL stimuli.

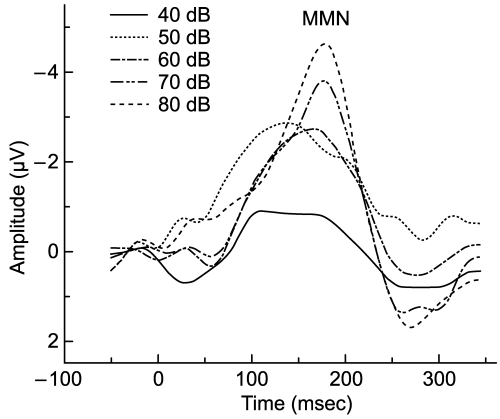

Figure 7. MMN grand average waveforms at electrode F4 with different stimulus intensities.

5.2 Effect of stimulus frequency on the MMN (Study II)

In the statistical analysis between the mel blocks and the basic block the MMN mean amplitudes differed from each other (p=0.0059) and also the recording site affected amplitudes (Figure 8). The largest MMN responses were evoked at the highest stimulus frequencies at the electrodes Fz and F4. The mel block with the highest frequency differed significantly from the basic block, while the mel block with the lowest frequency did not differ from the basic block significantly, although some differences can be seen in the mean values. The MMN onset latencies were not influenced by the block, but the recording site did affect them. The shortest latencies were recorded at the frontal and central electrodes. The block or electrode site did not have effects on MMN peak latency.

When the DLF blocks and the basic block were compared, the MMN mean amplitudes differed significantly (p=0.0152). However, the paired t-tests did not show any differences between the DLF blocks and the basic block. The MMN onset latency was affected by the block, but not by the electrode. The basic block differed significantly from the DLF block with the lowest frequencies, and from the two blocks with the highest frequencies. MMN peak latency of the DLF blocks was not affected by the block or the electrode location.

Thus, the MMN mean amplitudes evoked by the mel blocks differed from each other as did the MMN mean amplitudes and onset latencies evoked by the DLF blocks. The largest responses were evoked by the highest stimulus frequencies. The mean amplitude of the 4000 Hz standard stimulus seemed to be saturated already with a smaller deviant, but differences in onset latencies remained.

The N1P2 amplitude was affected by the stimulus frequency so that the amplitude evoked by the 1000 Hz stimulus was larger than the amplitudes evoked by the 2000 and 4000 Hz stimuli. The latency evoked by the 1000 Hz stimulus differed from those evoked by the 125 and 2000 Hz stimuli. The shortest mean latencies were evoked by the 2000 Hz stimuli and the longest by the 125 Hz stimuli.

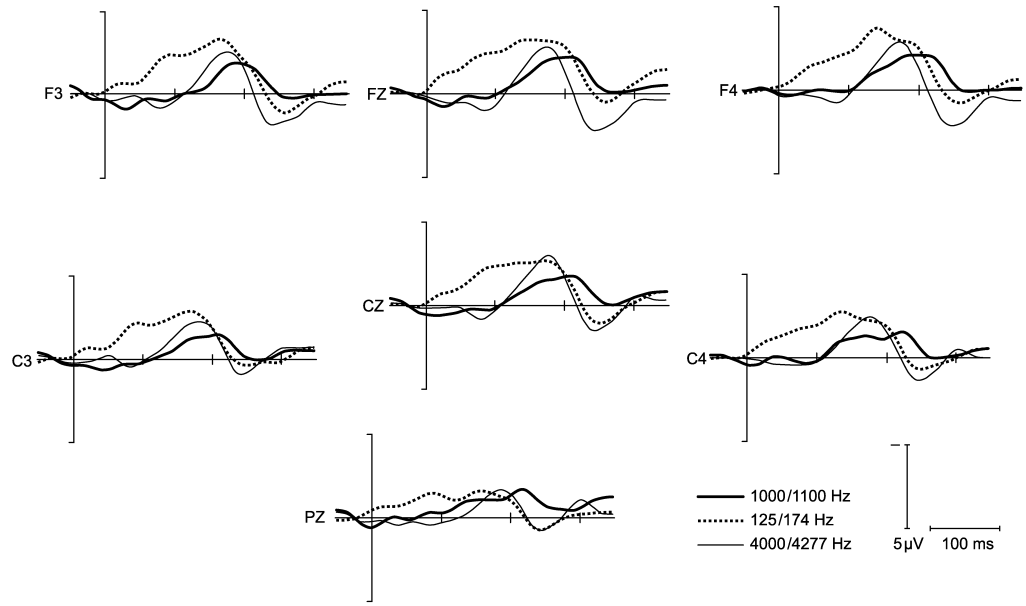

Figure 8. MMN potentials evoked at different frequency levels and electrodes.

5.3 Effect of contralateral white noise masking on the MMN, N1 and P2 (Studies III and IV)

In the first experiment of study III, the mean MMN amplitudes were regularly smaller when contralateral white noise masking was used, but the effect was not statistically significant (p=0.0590). The greatest MMN potentials seemed to be evoked by the

500/600 Hz stimulus block, but this was not statistically confirmed since there was an interaction between the stimulus block and the electrode site. For the 500/600 Hz and 2000/1600 Hz blocks, the maximum mean amplitudes of the MMN were recorded at electrode Fz, while for the 2000/1900 Hz block they were recorded at electrode Cz. Neither noise masking nor the electrode site affected the MMN onset or peak latencies. The stimulus block had a significant effect on the onset latency but not on the peak latency. The longest mean onset and peak latencies were most often recorded when using the 2000/1900 Hz block.

In the second experiment of study III, white noise masking had no effect on the MMN amplitude, onset or peak latencies. The electrode location affected both the MMN amplitude and the peak latency. An interaction between masking noise and stimulated ear was found at the electrode Fz. According to the paired t-test, the MMN amplitude was attenuated by the contralateral masking when the stimulus was delivered to the right ear. When the stimulus was delivered to the left ear, masking of the contralateral ear did not influence the MMN amplitude.

When the results of the two experiments concerning the 500/600 Hz block were combined, it was found that white noise masking attenuated the mean MMN amplitude ($p=0.0499$). The onset and peak latencies were not influenced by masking, but the recording site affected both the latencies and the amplitude.

In study IV, the N1 amplitude was attenuated with contralateral 75 dB EML masking (Figure 9). The largest responses were recorded at the electrodes Fz and Cz. The amplitudes were of the same size on homologous electrodes on the left and right sides. The post hoc t-tests showed that at the electrode Fz, already 50 dB EML masking increased P2 amplitude. There were no differences in masking effect at the electrode pairs F3 versus F4 and C3 versus C4. The largest mean N1P2 amplitudes were recorded at the electrode Cz. The amplitudes (mean values) were larger at electrode F4 than at F3. The longest mean N1 latencies were recorded at the electrodes Fz and F4. The latencies recorded at the electrodes F3 versus F4 and C3 versus C4 differed significantly. Longer mean latencies were recorded at the electrodes F4 and C4. The shortest P2 latencies were found in responses recorded at the electrode Fz. Masking did not affect P2 amplitude, N1P2 amplitude, N1, or P2 latencies.

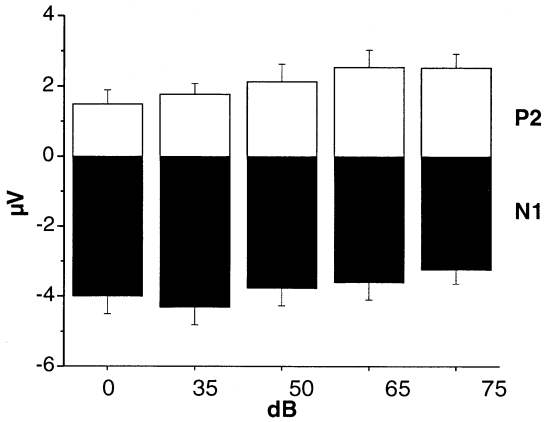

Figure 9. Mean N1 and P2 amplitudes at the Cz electrode with different contralateral masking intensities.

5.4 Perception and production of vowels by cochlear implant patients (Study V)

5.4.1 Behavioural test results

MOA showed that all patients could synthesize Finnish vowels following the general lines of the Finnish language. However, the patients also had some difficulties both in synthesizing and producing vowels.

Patient 1 synthesized the vowel phonemes clearly distinctively, but he tried to exaggerrate the closeness of /i/, /u/ and /y/ to maximize the difference in comparison with the other vowel categories. He had difficulties producing /e/ and /ø/, whereas the other vowels were clearly distinct but farther back and more open (Figure 10).

Patient 2 had difficulties with the behavioural task. She synthesized the close vowels /i/, /y/ and /u/ so that they had high positioning in the F1-F2 diagram. Also the front vowels /i/, /e/ and /æ/ were difficult. She did not make a distinction between /e/ uttered during normal speech and /æ/ produced with the synthesizer. Her own vowel /u/ had low positioning and a noticeably low F2.

Patient 3 had problems with some vowels, but the F1-F2 diagram was shaped in the rather conventional form of a quadrangle. The open vowels /a/ and /æ/ had excessively high F1 values both in the subject's own productions and in the synthesized variants. The synthesized /i/ and /e/ had high F2 values, whereas his own variants were more centrally positioned. This subject seemed to exaggerate the distinctions between the categories when he synthesized the vowels.

Patient 4 was able to distinguish between all the relevant categories. However, the close vowels /i/ and /u/ were synthesized with very low F1 values. They were situated far from the centre of the diagram. His own productions of /i/ and /y/ were distinct from each other and /y/ was located in the immediate vicinity of both the vowel /ø/ (own production) and the synthesized /e/. Also /u/ had an excessively low value for both F1 and F2.

Subject 5, who was a normally hearing person, produced a conventional Finnish quadrangular vowel system both with the synthesizer and during his own production. He also exaggerated the distinctiveness of the four corner vowels /i/, /æ/, /a/ and /u/.

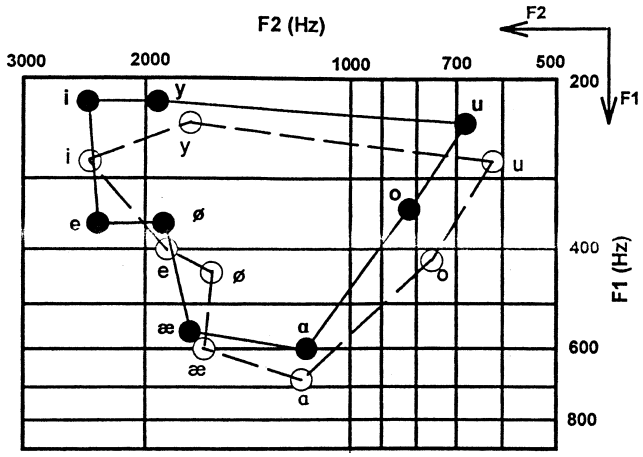

Figure 10. Vowel perception and production chart of patient 1.
●, vowels produced by OVE 1b; o, vowels pronounced by patient 1.

5.4.2 Results of the ERP recordings

In the MMN recordings of patient 1, a significant ($p<0.05$) MMN response was evoked when the difference between the standard /i/ stimulus and the deviant stimulus was largest (120 mel). The onset latency measured at the electrode Fz was 53 ms, the peak latency 214 ms and the amplitude –3.2 μV (the onset amplitude subtracted from the peak amplitude). When the prototype /i/ served as a deviant simulus, the MMN was obtained already when the standard stimulus differed from it by 90 mel. At the electrode Fz the MMN onset latency was 76 ms, the peak latency 325 ms, and the amplitude –5.8 μV.

In the MMN registration of subject 3 there seemed to be a negative potential (-2.85 μV at 212 ms) when the deviant stimulus differed 120 mel from the standard /i/. However, according to the computer program (Lakkisto 1991) the signal did not differ significantly from noise.

Patients 2 and 4 did not show any MMN responses.

6 DISCUSSION

In the ERP recordings, the quality and parameters of the stimulation are essential to achieve reliable results. In our study (I) we assumed that the stimuli with higher intensities would cause stronger sensory inflow and thus larger MMNs, while the other stimulus parameters were unchanged. This assumption seems to be correct, because the results showed that the stimulus loudness had an effect on the MMN waveform in a constant pitch-difference condition. The mean amplitude of MMN increased as the intensity of the stimulus was increased; the stronger the stimuli, the larger the potentials. The shortest onset latencies were measured with 60 and 70 dB HL stimuli, perhaps indicating that automatic frequency discrimination is fastest with stimulation at these intensities. Previously, Schröger (1994) has claimed that MMN would be influenced mainly by the information contents of the stimuli, not the total energy amount. The explanation for the differing results is probably methodological. Firstly, in Schröger's studies, the duration of the stimuli was half of that applied in our study (50 ms versus 100 ms) and the duration of the tone affects the loudness level sensation. The frequency and loudness of a tone are related via equiloudness contours (Robinson & Dadson 1956). If a duration of less than 50 ms is increased, the intensity experienced also increases. According to the brief-tone audiometry results (Pedersen 1974), the measured threshold diminishes when the stimulus duration is increased from 50 ms to 100 ms. Thus, the 50 ms stimulus used in Schröger's studies may have been too short to clearly show the effect of intensity on the MMN waveform. In addition, Schröger determined the MMN amplitude as the mean amplitude within the fixed 110 ms to 210 ms time window. According to our experience (Lang et al. 1995), the MMN latencies vary significantly among individuals and the use of a fixed time window is not recommended. In a later study by Schröger et al. (1996), the results were not significant perhaps also because of the small number of subjects.

In many previous MMN studies, stimulus calibration has not been performed and the exact sound pressure levels applied have thus been unknown. This is a significant problem particularly when stimuli of wide frequency range are used. When air conduction earphones (Telephonics TDH-39) are used, the calibration can be done by means of the artificial ear and the sound level meter according to the ISO standard scale. However, in longer recording sessions it is not possible to use the air conduction earphones because of their inconvenience. In that case, insert headphones must be used and the calibration is not so accurate. Measurement of sound stimuli with an oscilloscope before MMN recordings ensures that all frequencies are presented properly. It is important to use stimuli that are loud enough to evoke proper MMN responses. On the other hand, P3 amplitude increases with stronger stimulus intensities indicating attention which can affect responses. In our studies, the quality of stimuli was carefully considered because we wanted to examine the usefulness of recordings in clinical audiological testing.

In MMN studies, often the same difference in percentage between standard and deviant stimuli frequencies is used over the stimulus blocks. However, in this way comparable responses cannot be recorded because the frequency deviant evoked MMNs are not similar over a wide frequency range, when a constant 10% deviance is used (Wunderlich & Cone-Wesson 2001). This is logical, because pitch discrimination varies at different frequencies, being at its best within the speech frequency range. In our study (II), we tried to choose deviant stimuli so that difference between standard and deviant stimuli would be psychophysically equal at all frequency levels. It would be useful in clinical practice to be able to design stimulus paradigms so that the responses over wide frequency range would be equal in normal subjects. However, both the mel scale and the DLF-based standard vs. deviant stimulus pairs evoked MMNs of different sizes at different frequency levels. The MMNs with 4000 Hz standard stimuli appeared to be larger than expected. This may be due to the better pre-attentive discrimination at high frequencies than was assumed according to the previous behavioural measures. Also the activation of new afferent elements that could be used in processing high frequency stimuli might explain the finding. In that case, it could have been assumed that also the N1P2 waveform would have increased at high frequencies but this did not happen. However, the number of subjects (nine) in our study was quite small. Thus, it seems to be difficult to create any scale or reference values of MMN evoked by pitch change at different frequency levels.

Contralateral masking in audiological examinations is needed to avoid the effect of bone conduction when stimuli over 50 dB HL are delivered unilaterally, for example, when examining unilateral hearing defects (Katz 2009). It could be assumed that masking would affect MMN results by central masking, which causes an increase in the auditory threshold in the examined ear even if the masking noise is not strong enough to be conducted via the skull to the examined ear. In previous studies, the intensity of masking has been so loud that it has been conducted to the opposite ear. We wanted to examine, if contralateral white noise at intensity of 50 dB EML could be used in MMN recordings without effects on the results. However, according to our studies, contralateral white noise masking (50 dB EML) has an effect on MMN (Study III). The latency of MMN was not affected by contralateral masking noise, but MMN amplitude was attenuated when the right ear was stimulated.

If masking affects the sense organ or the cells of the primary cortex peripherically, it should also attenuate the exogenous N1 component of the primary auditory cortex. The previous few studies have given controversial results. Often only N1P2 peak to peak amplitude has been measured and, thus, the effect on the responses has not been studied separately. However, there is evidence that N1 and P2 are results of independent processes and should be considered separately in the responses. In previous studies intensity of masking has been so high that it is conducted via bone to the opposite ear. In our study (IV), we measured both N1 and P2 amplitudes separately, and N1P2 peak to peak amplitude. We used white noise masking with also low intensities (35, 50, 65 and 75 dB EML, as well as a no-mask condition). Masking with 75 dB EML white noise

attenuated N1 amplitude and increased P2 amplitude, which seemed to increase already at the 50 dB EML. N1P2 amplitude was not affected. This differential behaviour of the N1 and P2 responses is in line with studies claiming that these two waveforms have different sources (Näätänen & Picton, 1987).

The masking effect on MMN, N1 and P2 amplitude may be due to that of central masking, which is mediated via the efferent pathway.

We conducted a clinical study (V) to examine the benefit of a cochlear implant in the speech perception and production of postlingually deafened patients. MOA was used to examine the vowel system and MMN recording to find neural phonetic traces. Thus, both behavioural studies and objective MMN recordings were used. An association between these was found in our experiment where the patient with the best behavioural vowel perception showed a MMN response evoked by vowel stimuli. This suggests that the phonetic memory traces for vowels may remain stable in spite of deprivation for years. The result agrees with a study (Pelizzone et al. 1991) according to which behavioural speech recognition is better when acquired-deaf than when the congenitally-deaf ear is implanted. In our study, only four cochlear implant patients and one healthy subject were included.

The large within- and between-subject variation in the MMN waveform is a problem for its clinical use. There are also healthy subjects who do not show any MMN response for unknown reason (Lang et al. 1990, 1995). Intraindividual test-retest stability also depends on stimulus features (Pekkonen et al. 1995). Thus, and because of the fact that behavioural performance correlates with MMN values, reference values, for example, according to age, have not been published. According to our study, it is also difficult to compare behavioural discrimination ability with MMN results at different frequency levels. However, Cone-Wesson and Wunderlich (2003) state that reference values for MMN obtained with several speech sound contrasts could be developed. In spite of these problems, MMN is already in clinical use. The results of our study show that the effect of stimulus loudness on the automatic detection of frequency changes must be taken into consideration when MMN recordings are designed. The use of contralateral masking in MMN studies must be carefully considered. However, it may be less harmful to the results than the effect of a loud unilateral stimulus without masking. The result that contralateral masking effects N1 and P2 differently confirms the idea that they reflect different events in brain. This could provide aspects for the usefulness of these responses. The most promising clinical applications of MMN at the moment seem to be in recordings of children with language learning and speech problems, intensive care, psychiatric and neurological patients, patients with hearing disorders and effects of drugs and alcohol. In the prognosis of comatose patients, the existence of MMN is a reliable prognosis for recovery. At individual level, MMN might be useful in follow-up (Pekkonen et al. 1995) and prognostic studies, e.g. in speech perception of cochlear implant patients. Audiologists are interested in studying changes occurring with use of hearing aid at group level. More research is needed to evaluate optimal stimulation and recording parameters before reliable paradigm recommendations for clinical use can be made.

7 CONCLUSIONS

In the present studies, the effects of stimulus intensity and frequency on MMN were investigated. We also examined whether contralateral white noise masking affects MMN and N1P2. Clinical application of MMN was studied and compared with vowel perception and production in postlingually deafened cochlear implant patients.

The following conclusions can be drawn:

1. Automatic auditory discrimination, measured with MMN, seems to be dependent on the sound pressure level of the stimuli: a higher intensity level evokes a larger MMN. Thus, in MMN recordings, calibration of stimuli is very important and intensities high enough are preferable (I).

2. Objective pre-attentive pitch difference discrimination at high frequencies seems to be better than would have been expected on the basis of previous behavioural studies: the largest MMN responses were evoked at 4000 Hz with a stimulus deviance based on both mel and DLF behavioural scales (II).

3. Contralateral white noise masking attenuates MMN when the right ear is stimulated. This seems to happen already with 50 dB EML. Consequently, its use in the examination of patients with unilateral auditory defect must be carefully considered. However, the conduction of a loud stimulus to the opposite ear may affect MMN more than the use of a contralateral mask (III).

4. N1 and P2 waves are affected differently by contralateral masking; N1 amplitude is attenuated and P2 amplitude is increased. The result indicates that these responses are evoked by independent processes that cannot be separated if only peak to peak amplitude is measured (IV).

5. Phonetic memory traces once developed in early childhood seem to remain irrespective of long-lasting postlingual deafness. The MMN responses with phonetic stimuli could be measured in a CI patient with good behavioural ability (V).

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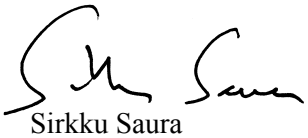

Sirkku Saura

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