

Review

The mismatch negativity in cognitive and clinical neuroscience: Theoretical and methodological considerations

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Abstract

Mismatch negativity (MMN) component of the event-related brain potentials has become popular in cognitive and clinical brain research during the recent years. It is an early response to a violation of an auditory rule such as an infrequent change in the physical feature of a repetitive sound. There is a lot of evidence on the association of the MMN parameters and behavioral discrimination ability, although this relationship is not always straight-forward. Since the MMN reflects sound discrimination accuracy, it can be used for probing how well different groups of individuals perceive sound differences, and how training or remediation affects this ability. In the present review, we first introduce some of the essential MMN findings in probing sound discrimination, memory, and their deficits. Thereafter, issues which need to be taken into account in MMN investigations as well as new improved recording paradigms are discussed.

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1. Introduction

With event-related brain potentials (ERPs), the neural basis of perception and cognition can be investigated with high temporal resolution. While ERPs do not reveal accurate information on the loci of activated brain areas, they do provide temporally high information on the various stages of information processing and the neural components associated with perception and behavior. With them, for example, the sequence of the brain's perceptual, memory, and attention systems can be probed.

One component belonging to the family of cognitive ERPs is the mismatch negativity (MMN; Näätänen et al., 1978; Näätänen, 1992, 1990; Picton, 2000). The research using MMN has shed light to auditory sensory memory processes, resolution of the auditory system in discriminating sound features, as well as to impairments in these processes. While the MMN has originally been observed and thereafter intensively studied in the auditory modality, some reports suggest that it can be elicited also in the visual (Tales et al., 1999; Czigler et al., 2004; for a review, see Pazo-Alvarez et al., 2003) and tactile (Kekoni et al., 1997; Shinozaki et al., 1998; Akatsuka et al., 2005) systems. Yet, the theory on the MMN is primarily based on the empirical evidence obtained in the auditory modality. Besides electrophysiological means, MMN has been recorded also with other methods, like magnetoencephalography (MEG; Hari et al., 1984), positron emission tomography (PET; Tervaniemi et al., 2000b; Müller et al., 2002), optical imaging (OI; Rinne et al., 1999b), and functional magnetic resonance imaging (fMRI; Opitz et al., 2002, 2005; Mathiak et al., 2002; Doeller et al., 2003; Molholm et al., 2005).

Traditionally, the MMN has been recorded in the so-called oddball paradigm, in which a repetitive sound ("standard") and rare occasional deviant sounds are presented. The repetitive sound forms a memory trace in the auditory system, and if a new sound does not match this memory trace, the MMN is elicited after about 100–250 ms (Näätänen, 1992; Näätänen and Winkler, 1999). This indicates that the auditory system was able to distinguish between these two sounds.

It has become evident that the MMN reflects even more complex auditory processes than only those related to the discrimination of physical features of sounds. In fact, the MMN reflects a deviation from the preceding stimulus events or regularities rather than merely the deviation from static stimulus properties (Näätänen and Winkler, 1999). This is evidenced by the MMN elicitation even when an abstract rule of auditory input is violated (Saarinen et al., 1992; Tervaniemi et al., 1994a; Paavilainen et al., 1998, 2001; for a review, see Näätänen et al., 2001). In this case, the rule represents the "standard" in the auditory system and a violation of the rule is the "deviant" eliciting the MMN. This was demonstrated, for

instance, by Paavilainen et al. (2001) whose standard stimulus varied over a wide range in intensity and frequency so that there was no physically constant, repetitive standard stimulus. However, the exemplars of the "standard" stimulus obeyed a rule "the higher the frequency, the louder the intensity". Sounds violating this rule, for instance, a low-frequency loud stimulus, elicited an MMN. Another example is provided by the MMN elicitation to an ascending pitch and to a pitch repetition in a sequence of regularly descending sounds (Tervaniemi et al., 1994a). In such a case, pitch repetition violated the rule and prediction about the descending direction of the pitch change between subsequent sounds.

Quite surprisingly, the auditory system can detect irregularities even when the subject is not aware when they occur. van Zuijen et al. (in press) recorded MMN for descending tone pairs (high–low) among ascending pairs (low–high) when the pairs were randomly varying between the frequencies of 262 and 523 Hz in semitone steps. After the MMN recording, it was determined whether subjects could identify deviant stimuli within the sequence. Although deviant pairs elicited a significant MMN, 19 out of the 23 subjects could not consciously identify deviant pairs. After a training session there were still two subjects who had not learned to discriminate the standard and deviant pairs, but these subjects nevertheless displayed an MMN.

These results clearly demonstrate that the MMN reflects not only simple representations of the physical stimulus features of recent sounds but also more "intelligent" abstract representations of complex auditory rules. These findings on the MMN's nature in auditory cognition have important implications in understanding, for example, to what extent complex information can be processed without attention. Furthermore, these results imply that when designing MMN experiments it is important to keep in mind that both recent stimulus events (feature processing) as well as the relationships (regularities in complex auditory information) of the stimuli have an effect on MMN.

Several cerebral sources have been reported for the MMN, each of which presumably having a specific role in early cognition. The major generators are located in the right and left auditory cortices (Alho, 1995). Also other MMN generators have been reported. One MMN source is in the frontal areas, proposed to be involved in the attention switch after the sound change has been analyzed in the temporal lobes (Rinne et al., 2000; see, however, Giard et al., 1990, suggesting that the frontal MMN may precede the temporal one). In addition, MMN generators have been reported in the parietal lobe (Lavikainen et al., 1994; Levänen et al., 1996) and subcortically (Csepe, 1995).

Neurochemical mechanisms underlying the MMN have been under intensive investigation during the recent years. The

most systematic results have been found on the NMDA receptors, whereas the data on the role of serotonergic (Ahveninen et al., 2002; Kähkönen et al., 2005; Umbricht et al., 2003), dopaminergic (Kähkönen et al., 2002), cholinergic (Pekkonen et al., 2001), and GABAergic (Nakagome et al., 1998; Smolnik et al., 1998; Kasai et al., 2002) receptors in MMN generation are less conclusive. NMDA receptors have an important role in long-term memory initiation and in learning (for a review, see Cotman and Monaghan, 1988). Both animal models and human studies have shown that NMDA antagonists block the MMN generation, while they do not affect the N1 generation (Javitt et al., 1996; Umbricht et al., 2000; Kreitschmann-Andermahr et al., 2001).

Although attention can under particular circumstances modulate MMN amplitude, MMN is elicited even when the subject is not attending to the stimuli (Woldorff et al., 1991, 1998; Näätänen, 1991). In fact, the MMN elicitation may lead to an attention switch towards a sound change in an unattended environment if the deviant sound is intrusive. The sign of such attention switch is the P3a component (Donchin and Coles, 1988; Escera et al., 2000a) following the MMN. Often attention switch is also reflected by the elicitation of the N2b, which follows and partly overlaps the MMN and precedes the P3a (Näätänen et al., 1982; Näätänen, 1992; Novak et al., 1992). This feature of the MMN that it is elicited even when stimuli are not attended has made it widespread in investigating patients with communication or attention problems (for example, Aaltonen et al., 1993; Deouell et al., 2000; Fischer et al., 2000; Morlet et al., 2000; Ilvonen et al., 2001, 2003, 2004; Kane et al., 1993; Luaute et al., 2005), as well as children and infants (Alho et al., 1990; Cheour et al., 1998; Winkler et al., 2003), even fetuses (Huotilainen et al., 2005).

The MMN has recently been used for investigating speech sound representations of the auditory system, too. It was suggested that sound changes crossing the native-language phonetic boundaries elicit larger MMNs than physically comparable within-category changes (Winkler et al., 1999b; Dehaene-Lambertz, 1997). Furthermore, the MMN to non-linguistic sound changes is usually elicited more strongly in the right than left-hemisphere (Giard et al., 1995; Paavilainen et al., 1991; Tervaniemi et al., 1999a), whereas the language-specific MMN source has a predominance in the left temporal lobe, as indicated by neuroimaging studies using methods with high spatial resolution (Näätänen et al., 1997; Shtyrov et al., 2000; Tervaniemi et al., 2000b; Koyama et al., 2000; Pulvermüller et al., 2001). This has been demonstrated with studies using phonemes, syllables, as well as words. Moreover, it was found that the physical constancy of the standard sounds is not a necessity for MMN elicitation (Shestakova et al., 2002; Jacobsen et al., 2004). For instance, when 150 exemplars of vowel /a/, spoken by different speakers, were presented, a vowel belonging to a different category (/e/) elicited an MMN (Shestakova et al., 2002). This implies that the MMN generation mechanism indeed works at the level of advanced abstract sound representations rather than simple acoustic features.

In the current review, we will discuss how the MMN can be used for probing auditory perception and cognition. Some

examples are also given on the clinical applications of the MMN, but we will not systematically review these applications since it has already been carried out in several articles (for example, Csepe and Molnar, 1997; Näätänen and Escera, 2000; Näätänen, 2003).

2. What can be studied with the MMN?

The basic research on the MMN, carried out since the late 1970s (Näätänen et al., 1978) is extensive. Therefore, there is now ample knowledge on the processes it reflects. Below we discuss which aspects of cognition can be investigated with the MMN and how it has been applied to, for example, clinical studies.

2.1. Sensory memory

Although the MMN is affected by long-term sound representations, it operates at the sensory memory level (Näätänen, 1992; Näätänen and Winkler, 1999; Näätänen et al., 1997; Schröger et al., 2004). Näätänen (1985) proposed that each sound forms a memory trace in the auditory system, and if an incoming sound violates the neural memory representation of the recently heard sounds, it elicits an MMN. It has been suggested that if the stimulus interval is sufficiently prolonged, the memory trace of each stimulus fades away by the presentation of the next stimulus, in which case the deviant no more elicits an MMN. For example, Mäntysalo and Näätänen (1987) found that when the constant inter-stimulus offset-to-onset interval (ISI) was 1 or 2 s, the MMN was elicited, whereas with ISIs of 4 and 8 s it was no more elicited (see, however, e.g., Böttcher-Gandor and Ullsberger, 1992; Sams et al., 1993; Winkler et al., 2002, suggesting longer sensory memory lifetimes).

Cowan et al. (1993) addressed with MMN how longer lasting memory traces are built up during an experimental session. They used stimulus trains including nine stimuli, the ISI being 610 ms between the tones within the trains and the inter-train interval being 11–15 s. In one condition, the standard-stimulus frequency was constant (constant-standard condition) and in the other condition, it varied between the stimulus trains (roving-standard condition). A higher frequency deviant stimulus randomly occurred at stimulus positions 1, 2, 4, 6, or 8 in the stimulus trains. It was found that in the constant-standard condition, deviants in all positions except in the first one elicited an MMN, whereas in the roving-standard condition, the deviant in the fourth position was the first one to elicit an MMN. Thus, a strong memory trace was formed when the standard stimulus was the same over the different stimulus trains, strengthening the neural representation for this particular stimulus frequency. In the roving-standard condition, long-term memory trace was not built up since the frequency varied between the stimulus trains.

Also with backward-masking paradigms one can investigate the functioning of the sensory memory. In such paradigms, masking stimuli are presented after sounds that subjects try to discriminate from one another. It has been found that if the

interval between the sounds and maskers is short, subjects cannot discriminate the sounds, whereas with longer intervals they are able to discriminate the sounds (Hawkins and Presson, 1986). These results have been interpreted to reflect an interference of the sound memory trace by the masker (Hawkins and Presson, 1986). If a masking sound is presented soon, 20–50 ms, after the offset of a brief tone, tones with deviant frequencies can neither be behaviorally discriminated from standard tones nor do elicit an MMN (Winkler and Näätänen, 1992). However, when this interval is prolonged to 150 ms, deviant sounds elicit an MMN and they can also be discriminated. The similarity of the masking effects on the MMN and behavioral discrimination performance suggests that the MMN in masking paradigms can be used for probing sensory memory functions.

The memory-erasing effect of masking stimuli soon following the test sounds has been suggested to reflect the auditory system's ability to integrate successive events to meaningful entities (Bregman, 1990). The cortical mechanism of this temporal window of integration (TWI) within which this integration process occurs has been probed with the MMN. Originally, TWI was observed with the MMN by using a paired-sound paradigm, with sound omission as the deviant event (Tervaniemi et al., 1994b). It was found that if the sounds within a pair were separated by 40 or 140 ms, an MMN was elicited whereas with longer within-pair intervals than that, the MMN was no longer present. With isosynchronous stimulation, also sound omission as the deviant, the TWI has consistently been shown to be about 170 ms in duration (e.g., Yabe et al., 1997, 2001).

Based on the observations described above, the MMN has been used both in basic research addressing how the human sensory memory operates as well as in clinical research. MMN paradigms addressing memory lifetime by ISI manipulations have been applied to investigate memory dysfunctions in various subject groups and conditions, like Alzheimer patients (e.g., Pekkonen et al., 1994; Engeland et al., 2002), aging (e.g., Pekkonen et al., 1996; Cooper et al., 2006), and in alcoholism (Polo et al., 1999; Grau et al., 2001; Zhang et al., 2001). For example, when the effect of ISI, 1 s versus 3 s, on the MMN was compared between patients with Alzheimer's disease and age-matched control subjects, a group \times ISI effect was found resulting from a diminished MMN in Alzheimer patients for the longer ISI (Pekkonen et al., 1994). In normal aging, a diminished MMN was reported in a long-ISI condition in older than younger adults, whereas no group differences were found for MMN in a short-ISI condition (Pekkonen et al., 1996).

In alcoholism, a memory impairment has been demonstrated with an ISI manipulation (Grau et al., 2001) and with a masking experiment (Ahveninen et al., 1999). In the masking experiment, both abstinent alcoholics and social drinkers had an MMN in the baseline condition involving no masking stimuli. However, in the condition in which each stimulus was followed by a masking sound after 100 ms, the MMN of alcoholics was abolished. Furthermore, this effect both correlated with the self-reported alcohol consumption of the subjects and predicted their working-memory impairment.

When using MMN for determining the lifetime of sensory memory in basic and clinical research the following ambiguities have to be considered (cf. Winkler et al., 2001). First, when an increase in ISI leads to a reduction in MMN amplitude in the grand-average waveform, this reduction may result from each subject having a small loss in MMN or because some subjects have a complete loss of MMN but others have a full-amplitude MMN. Thus, it is unknown whether the reduction is due to a gradual decay of memory or to an all-or-none phenomenon of MMN. Second, a decrease in MMN amplitude (in either the grand-average waveform or in the individual averages) with increasing ISI might not necessarily be attributed to sensory memory, as it may also be the case that the memory is fully intact but the MMN system does not compare the current stimulus with the trace for the standard. For example, it has been shown that a deviant following a long silent interval (>10 s) may not elicit MMN, presumably suggesting that the memory record for the standard has been decayed (Cowan et al., 1993). However, when a deviant following such a long silent interval is preceded by a single standard stimulus then it may again elicit MMN. This suggests that after 10 s or more there is still a memory representation for the standard stimulus which, however, is not used by the pre-attentive deviant detection system. A single presentation of the standard stimulus after the long silent interval can then reactivate this memory as a valid standard against which deviations can be detected (Cowan et al., 1993; Ritter et al., 2002).

The finding that subjects who do not have MMN in long-ISI condition can still behaviorally detect deviants (Gaeta et al., 2001) also suggests that the absence of MMN with long ISIs does not necessarily support the conclusion that the respective memory for the standard is completely lost. In this situation, the behavioral test probably taps a memory process different from that associated with the MMN. It was suggested that while the representation of the standard stimulus is still active, it is not regarded relevant for the MMN system after the silent period (Gaeta et al., 2001). It could also be speculated that during a long silent interval the sensory memory trace fades away, whereas a rehearsal of the stimulus features during the active sound discrimination condition keeps its representation in the working-memory system, allowing the detection of a deviant after the silent period.

2.2. Early phases of attention switching

Studies addressing involuntary attention switching have shown that MMN is associated with triggering the orienting response which is characterized by various physiological responses such as an increase in skin-conductance and a decrease in heart rate (Lyytinen et al., 1992; Öhman, 1979; Sokolov, 1975). Moreover, MMN is often followed by the P3a, a fronto-centrally distributed positivity occurring at around 300 ms after stimulus onset. P3a is associated with the actual switching of attention towards the deviant event (Ford et al., 1976; Knight and Scabini, 1998; Squires et al., 1975; Woods, 1990; Escera et al., 2000a). As a consequence, less attention is

devoted to the stimulus information related to the primary task (subject's task unrelated to the auditory stimuli) and the behavioral performance may be impaired (e.g., increase in reaction times and/or decrease in hit rate) (Jääskeläinen et al., 1996; Berti et al., 2004).

The hypothesis that MMN is a possible cause for involuntary attention switching is supported by studies showing that increasing the difference between the deviant and standard stimulus increases MMN and P3a amplitudes, as well as behavioral impairment in the primary task (Berti et al., 2004; Escera et al., 1998; Schröger, 1996). However, MMN itself should not be taken as an indicator for attention switching as it is not necessarily followed by a P3a or associated with an impairment of performance in the primary task or responses of the autonomic nervous system. It merely indicates that the pre-attentive deviancy-detection system has registered a difference between a current stimulus and the prediction derived from the extracted regularities. The dissociation between MMN and involuntary attention switching can be explained by a variable threshold that has to be exceeded before the MMN signal may finally result in distraction (Näätänen, 1992). The threshold depends on a variety of factors such as psychological distance between task-relevant information and task-irrelevant (distracting) information, working-memory load, or intentional top-down control (Berti and Schröger, 2003; Schröger and Wolff, 1998; Sussman et al., 2003).

One interesting clinical condition with a special attention impairment is unilateral neglect, which usually results from a right-hemisphere lesion in the parietal areas and is characterized by inattention to the left space (Heilman et al., 1993). Deouell et al. (2000) addressed whether the early attention-switching mechanisms are impaired in neglect patients by recording MMN to location, pitch, and duration changes in stimuli presented to the left and right hemifields. They found unimpaired MMNs to the right hemifield stimulation whereas the MMNs were diminished for the left hemifield stimulation, the finding being most robust for the location changes and insignificant for the duration changes. These results support an early stage, bottom-up attention-switching dysfunction in neglect patients. The location MMN impairment is in agreement with visual ERP studies showing that stimuli tapping the dorsal pathway ("where" system) are abnormally processed in neglect whereas stimuli activating the ventral pathway ("what" system) are normally processed (Spinelli et al., 1996).

2.3. Discrimination accuracy

A large body of evidence suggests that the MMN reflects sound discrimination accuracy, promoting its usefulness in determining auditory abilities in groups of individuals with special abilities, like musicians, or in patient groups with auditory impairments. Large stimulus differences elicit large-amplitude and short-latency MMNs, whereas when the differences are made smaller, the MMN amplitude decreases and latency increases (Sams et al., 1985; Tiitinen et al., 1994; Novitski et al., 2004; Fig. 1). Furthermore, the MMN

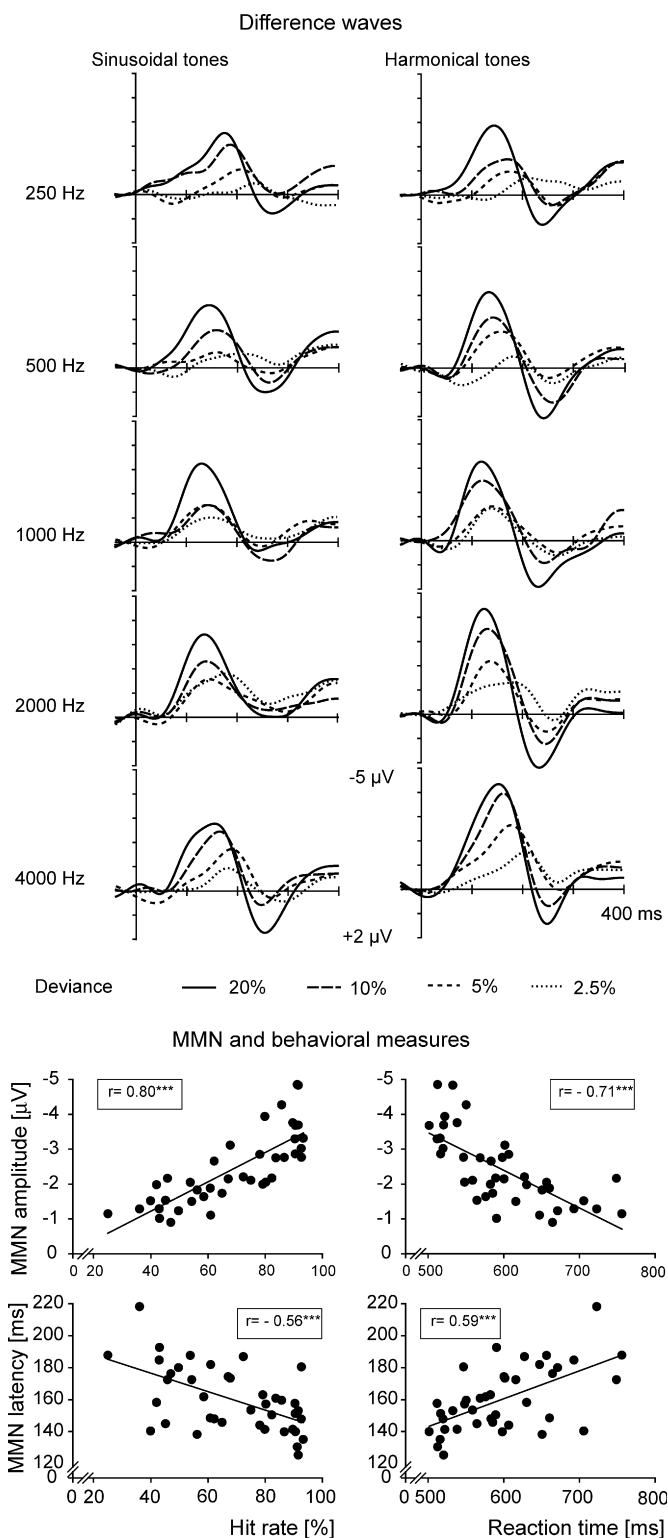


Fig. 1. MMN and behavioral responses to pitch changes of various magnitudes. Top: MMN responses (ERP elicited by the standard stimulus subtracted from that elicited by the deviant stimulus) to four different deviant magnitudes when the standard stimulus was 250–4000 Hz (five steps) in frequency. The left column shows the responses for sinusoidal tones and the right column for harmonical tones. Bottom: The correspondence of the MMN amplitude and latency with the hit rate and reaction time. Each dot represents the average of all subjects. Figure adapted from Novitski et al. (2004).

parameters and behavioral discrimination ability have a strong relationship (see, for example, Winkler et al., 1999a; Amenedo and Escera, 2000; Atienza and Cantero, 2001; Kujala et al., 2001a; Novitski et al., 2004). For example, the relationship of the MMN amplitude and behavioral discrimination of sound pairs with different silent inter-pair intervals was investigated (Kujala et al., 2001a). MMN was elicited by such interval differences that were also behaviorally discriminated by the subjects, whereas no MMN was elicited by an interval that subjects did not behaviorally discriminate. Furthermore, there was a significant correlation between the MMN amplitude and the reaction time so that the larger the MMN the shorter the RT.

Numerous studies have applied the MMN to determine discrimination abilities in a variety of patient groups (for reviews, see Csepe and Molnar, 1997; Näätänen and Escera, 2000; Näätänen, 2003). For example, diminished MMNs have been reported in the following disorders: in specific language impairment for speech–sound differences (Kraus et al., 1996), in dyslexia for consonant (Schulte-Körne et al., 1998; Leppänen et al., 2002), frequency (Baldeweg et al., 1999; Renvall and Hari, 2003; Kujala et al., 2003), and rhythm differences (Kujala et al., 2000), and in aphasia for tone-duration (Ilvonen et al., 2001), tone-frequency (Alain et al., 1998), and speech–sound differences (Aaltonen et al., 1993; Wertz et al., 1998; Ilvonen et al., 2004; Pettigrew et al., 2005). Abnormally large MMNs have been reported, for instance, in abstinent alcoholics (Ahveninen et al., 1999). Augmentation of other ERP amplitudes has also been observed in abstinent alcoholics, which has been interpreted to reflect the withdrawal-related hyperexcitability of the central nervous system (for a review, see Ahveninen et al., 2000). One possible mechanism underlying the enhanced ERPs was suggested to be the dysfunction of inhibitory GABAergic neurons, which are hypothesized to gate cortical input in the thalamus (Ahveninen et al., 2000).

Several clinical studies suggested a strong relationship between the group differences in the MMN and behavioral measures. For example, Baldeweg et al. (1999) showed that the MMN elicited by frequency changes is diminished in dyslexic individuals who were also impaired in pitch discrimination as compared with control subjects. Furthermore, the MMN latency and frequency detection performance significantly correlated with reading errors for regular words and non-words.

Todd et al. (2003) showed that a sound discrimination impairment may be selectively associated with a particular MMN subprocess. They addressed tone-duration discrimination in schizophrenia. The patients were divided into two groups, one performing normally in duration discrimination and the other one being impaired in duration discrimination as compared with healthy control subjects. It was found that the MMN at frontal scalp areas (Fz) was smaller than normal in both patient groups, the groups not differing from one another. However, at the mastoid leads, which are thought to primarily record MMN originating from the temporal lobes (Näätänen, 1992), the MMN was diminished only in the patient group which had an impaired duration discrimination performance.

Although there is a plenty of evidence on the correlation of MMN and behavioral measures both from basic and clinical studies, the relationship between these measures is not a simple one. Some studies have shown no correlation between these measures. For example, some studies have found significant differences between the MMN amplitudes elicited in different experimental conditions or groups, whereas there were no differences in the behavioral target discrimination performance (Bradlow et al., 1999; Jaramillo et al., 2001; Kozou et al., 2005). Bradlow et al. (1999) compared the discrimination of formant-transition durations in 6–16-year-old children with or without learning problems by measuring behavioral discrimination thresholds and MMN. They found that the learning-impaired children were generally worse than control children in discriminating the speech sounds, whether or not the formant transition was short or long. In contrast, the MMN was diminished in the learning-impaired children only for the stimuli with short formant transitions. In some studies, in turn, the behavioral measures differentiated the different conditions or groups, whereas statistically significant MMN amplitude effects were not found, although the grand-mean MMN plots showed results with a similar pattern as the behavioral measures (Savela et al., 2003; Tervaniemi et al., 2005a).

One would expect that in case different deviant stimuli are equally well discriminated, they should elicit MMNs with similar amplitudes. This hypothesis was tested by Deouell and Bentin (1998) who with careful behavioral testing adjusted the magnitudes of deviant stimuli for each subject individually and thereafter recorded MMN. Four deviant attributes, frequency, intensity, stimulus-onset asynchrony (SOA), and location, were included in their study. It was found that whereas the MMNs for other types of deviants were of equal amplitude at Fz scalp location, the MMN for the frequency deviant was larger than for the rest of them. The authors suggested that the enhanced frequency MMN at Fz might be caused by its source orientation. Namely, it has been shown that MMNs for different deviant attributes have dissimilar dipole orientations, which may result in differences in amplitudes at fronto-central scalp areas (Giard et al., 1995).

The MMN may even be similarly elicited in two groups which, however, differ in terms of behavioral discrimination accuracy. For example, ERPs and discrimination accuracy were compared between dyslexic and control adults by using sound duration differences embedded within pseudo-words or complex sound patterns (Kujala et al., submitted for publication). The duration difference between the standard and deviant stimuli was large (100 ms versus 200 ms). Large duration differences were previously shown to be discriminated normally by dyslexic subjects when presented as single sound events in oddball sequences (not embedded within other stimuli; Baldeweg et al., 1999). When presented within the pseudo-words and tone patterns, it was also found that the duration MMN was similar in the dyslexic and control subjects (Kujala et al., submitted for publication). However, in the active sound discrimination session, the dyslexic subjects discriminated significantly worse the deviant sounds, and, furthermore, had smaller N2b responses to these deviants than control

subjects in ERPs recorded simultaneously with the behavioral task. In the behavioral task, subjects had to identify the deviant stimulus and to press one of the three response keys corresponding to the position (first, second, or third) of the detected deviant segment. Interestingly, neither group had false button presses to standard pseudo-words or complex sound patterns. The lower accuracy rate in dyslexic subjects resulted from their misidentification of the deviant-stimulus position. These results show that sometimes the MMN process may be intact, while there is an impairment at some later stage of information processing. While the large sound duration differences could be cortically discriminated, as reflected in the MMN, the later process of identifying in which part of the speech/complex stimulus the deviant sound occurred was impaired in dyslexia as reflected in the N2b and behavioral measures.

In summary, while it is evident that the MMN is associated with behavioral discrimination accuracy, it is not a direct index of that process. It reflects the early cortical stages of sound discrimination and may be dissociated from the behavioral response for a number of reasons. For instance, the behavioral task can be affected by the subject's motivation or attention, which may often be the case in children (e.g., Bradlow et al., 1999) or patients (Ilvonen et al., 2001, 2003). Furthermore, some stage of stimulus processing following the MMN may be impaired, which impairs the behavioral response while the MMN is intact (e.g., Kujala et al., submitted for publication). Of course, also changes in the processes preceding the MMN (for instance, at brain stem level) may also result in an abnormal MMN.

2.4. Brain plasticity

Since the MMN is associated with cortical discrimination accuracy, changes in this accuracy resulting from, for example, learning-induced plasticity, should have an effect on the MMN. Following this reasoning, Näätänen et al. (1993) carried out a study in which MMN was recorded during passive blocks in a session which also included active training conditions hypothesizing that the MMN should emerge if the subjects learn to discriminate the stimuli. They used complex sound patterns which were originally too difficult to discriminate for most of the subjects, in whom no MMN was observed either. As predicted, in those individuals who learned to discriminate the sound patterns during discrimination training, MMN also emerged, whereas in those who failed to learn the discrimination, no MMN was found.

The increment of MMN as a result of discrimination learning has been demonstrated in subsequent studies for, for example, speech sounds (Kraus et al., 1995; Tremblay et al., 1998; Menning et al., 2002) and sinusoidal tones (Menning et al., 2000). Therefore, the MMN can be applied to determine the effects of language learning or musical expertise (Winkler et al., 1999a; Shestakova et al., 2003; Koelsch et al., 1999; Rüsseler et al., 2001; Tervaniemi et al., 2001). For example, the discrimination of a Finnish phonetic contrast /e/ versus /ae/ was compared between adult Finns, Hungarians who did not know

Finnish, and Hungarians who had a good command of Finnish (Winkler et al., 1999a). It was found that this contrast, not present in the dialect of the Hungarian subjects, was not discriminated by Hungarians not knowing Finnish, whereas it was discriminated by Finns and Hungarians who had a good command of Finnish. Consistent with this, in these latter two groups, this contrast elicited very similar MMNs, which was absent in Hungarians not knowing Finnish (Fig. 2).

Effects of musical expertise on frequency discrimination were studied by Koelsch et al. (1999) who compared MMN elicited by a frequency change between violin players and non-musicians. The stimulation included frequent major chords and infrequent deviant chords in which the middle tone was mistuned by 1%. It was found that only musicians had an MMN evoked by mistuned chords. Thus, when compared with non-musicians, violin players have more accurate automatically activated pitch representations.

The MMN has also been used in determining brain's plastic changes during the recovery from brain damage (Ilvonen et al., 2003) and as a result of intervention (Kujala et al., 2001b). Left-hemisphere stroke patients were followed up for 6 months post-stroke onset with the MMN and speech-comprehension tests (Ilvonen et al., 2003). Progressive improvement was observed in speech-comprehension skills in these patients. In parallel, the MMN increased in amplitude, being at normal level 3 months after stroke onset. Effects of intervention on the MMN and reading skills were demonstrated in dyslexic first-grade children (Kujala et al., 2001b). In this study, the improved reading skills caused by audiovisual training were accompanied with an MMN amplitude increment. Furthermore, the MMN amplitude change from the first to the second recording session significantly correlated with the change in the reading-skill scores.

3. Recent paradigm improvements

3.1. Controlling the exogenous effects on MMN

The traditional approach in recording the MMN has several problems. First, without appropriate control conditions, exogenous/obligatory responses differently contributing to the repetitive standard stimulus and the rare deviant stimulus affect the results. For example, when the MMN for deviations in sound duration has to be determined, the offset-N1 will be elicited at different latencies depending on the durations of the sounds. When the deviant is of shorter duration than the standard it will have the offset-N1 at a shorter latency than the standard which may erroneously be interpreted as MMN in the deviant–standard difference wave. Vice versa, when the deviant is longer than the standard, the MMN to the longer deviant may fall in the time range where the offset-N1 to the shorter standard is to be expected. Thus, when subtracting the ERP to the standard (containing the offset-N1) from the ERP to the deviant (containing the MMN), no MMN might be visible in the difference wave (although there is one). This problem arises with any sound including variation over time such as speech stimuli or environmental sounds.

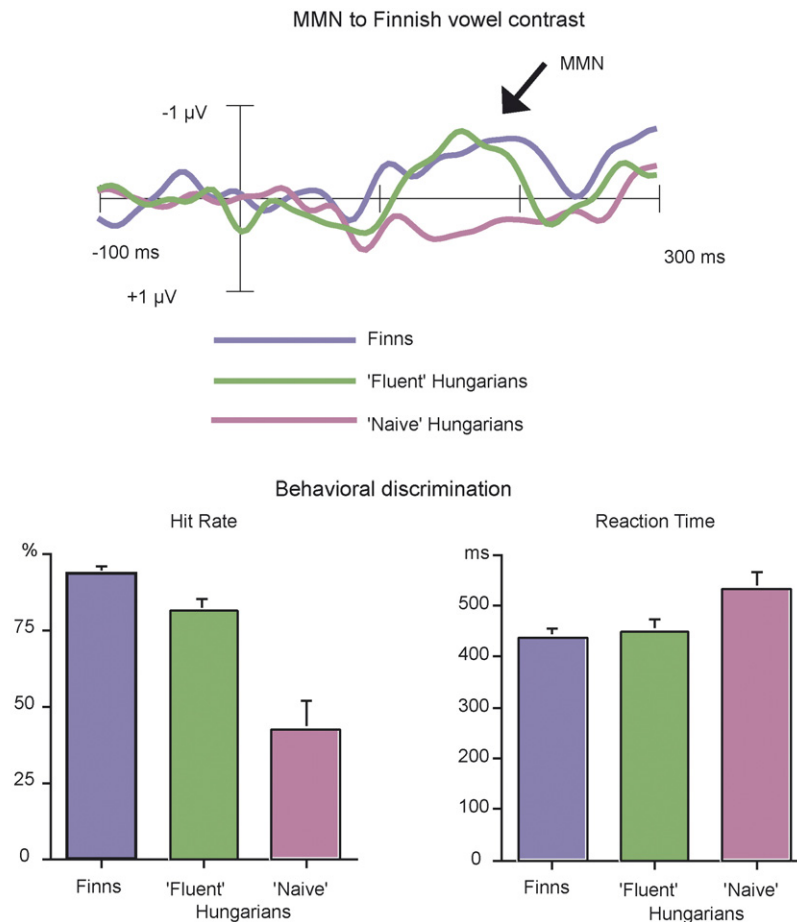


Fig. 2. The effect of native-language and foreign-language learning on MMN and behavioral responses. Top: MMN elicited by a Finnish vowel contrast (/e/–/ae/) in native Finnish speakers, in Hungarians not knowing Finnish, and in Hungarians having a good command of Finnish. There is no MMN in Hungarians not knowing Finnish for this contrast, which does not exist in the dialect of these subjects. However, both in Finns and Hungarians fluent in Finnish, there is a clear MMN response. Bottom: Hit rate and reaction time in discriminating these two sounds. The performance of the Hungarians not knowing Finnish is much poorer than in the other two groups. Figure adapted from Winkler et al. (1999a).

An easy but time-consuming way to overcome this problem is to measure the deviant ERP and the standard ERP for physically identical stimuli. This can, for example, be achieved by reversing the role of standards and deviants between blocks, that is, the deviant becomes the standard and the standard the deviant in separate blocks. As a consequence, the physical differences will contribute equally to standard and deviant ERPs. Another, less time-consuming, approach is to include one block in which only the stimulus that serves as deviant in the oddball blocks is presented. The respective ERP can then be used as the standard ERP.

However, the usage of physically identical stimuli serving in some blocks as deviants and in the other blocks as standards will not altogether abolish contributions of various refractoriness effects on the MMN. This is an issue for all sound dimensions that are processed by feature-specific neurons. A good example is frequency processing, which is based on tonotopic organization. The auditory system is organized in a tonotopic way from the cochlea to the cortex, so that different frequencies are mapped to (partly) different neurons (Pantev et al., 1988; Romani et al., 1982). When, for example, the deviant stimulus has a low frequency and the standard a high

frequency, the more frequent presentation of the standard stimulus will cause a larger degree of refractoriness in neurons specialized in the frequency of the standard. These neurons will show reduced activity and, as a consequence, the standard will yield smaller obligatory components such as P1 or N1. When a deviant stimulus is presented, neurons that are sensitive to the features of the deviant come into play. Since they are less refractory than neurons processing the standard stimulus, the neurons specialized to the features of the deviant generate larger obligatory ERPs than neurons activated by the standard stimulus. Especially the increase in N1 (and sometimes in N2) may be mistakenly interpreted to be a genuine MMN even though it actually is a joint N1 and MMN effect.

By designing appropriate control conditions, one may avoid contributions from various refractoriness effects. In one such control condition (Fig. 3), the stimulus set includes several sound exemplars varying along the dimension characterizing the deviant. For example, when a 500 Hz tone serves as a deviant among 550 Hz standard tones in the oddball block (deviant probability being 10%), it will be presented in a control block using altogether 10 different stimuli with frequencies of

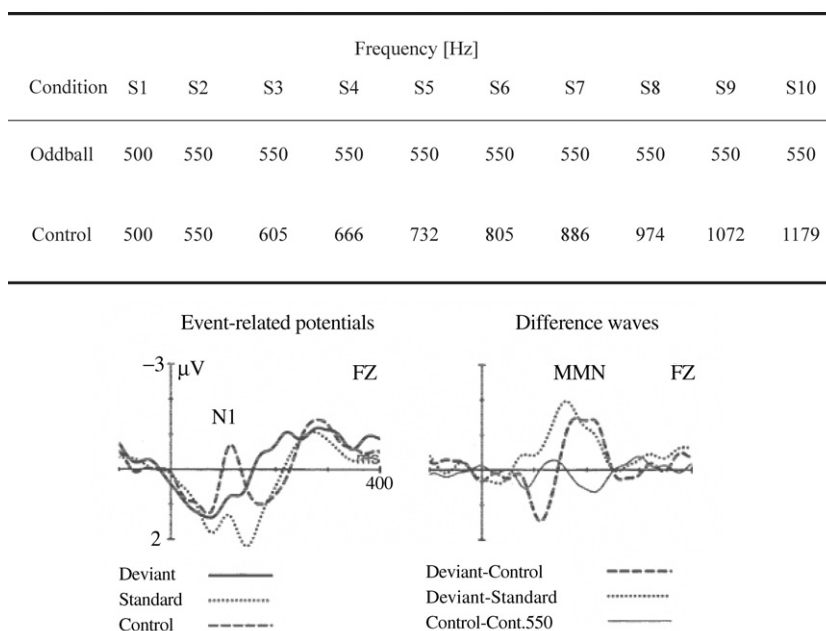


Fig. 3. Experimental protocol for controlling the refractory effects when recording MMN elicited by frequency changes. Top: The frequencies used in the oddball and control conditions are shown. In the oddball condition the frequency of the deviant is 500 Hz (S1) and that of the standard 550 Hz (S2–S10). In the control condition, the 500 Hz deviant stimulus is equiprobably presented with the other nine stimuli of different frequencies (S2–S10). The “classical” MMN is measured in the oddball condition by subtracting the ERP elicited by the standard 550 Hz stimulus from the ERP elicited by the deviant 500 Hz stimulus. The MMN with no refractoriness effects can be obtained by subtracting the ERP to the 500 Hz stimulus (S1) obtained in the control condition from the ERP (S1) to the 500 Hz deviant stimulus obtained in the oddball condition. Bottom (left): The ERPs to the deviant (500 Hz) and standard (550 Hz) stimulus of the oddball condition and to the control (500 Hz) stimulus are shown; (right) the difference waves obtained in the oddball condition (dotted line) and those obtained by subtracting the ERP to the 500 Hz stimulus of the control condition from the 500 Hz deviant stimulus (oddball condition; dashed line) are shown. In addition, the difference wave resulting from a subtraction of the ERP to the 550 Hz stimulus from that to the 500 Hz stimulus in the control condition (continuous line) is shown. Figure adapted from Jacobsen and Schröger (2001).

500, 550, 605, 666, 732, 805, 886, 974, 1072, and 1179 Hz. Therefore, neurons tuned to frequencies of about 500 Hz will not have a higher degree of refractoriness in the control condition than in the oddball condition since they are presented with the same probability as the physically identical tones serving as deviants in the oddball condition. This manipulation prevents the contribution of the relative increase of N1 elicited by deviant stimuli to the MMN; in fact, the “true” MMN measured with this controlled paradigm may even be underestimated (cf., e.g., Jacobsen and Schröger, 2001; Näätänen and Alho, 1997; Schröger and Wolff, 1996).

Variations of this paradigm controlling for refractoriness effects have been applied to frequency MMN (Jacobsen and Schröger, 2001), location MMN (Schröger and Wolff, 1996), intensity MMN (Jacobsen et al., 2003), and duration MMN (Jacobsen and Schröger, 2003). These studies showed that when using this paradigm for controlling the exogenous effects, a genuine MMN is present for each deviant type. However, it also turned out that this controlled paradigm yields a comparable, but not identical, MMN as the MMN obtained in the classical oddball condition. Thus, it is not always necessary to use this controlled protocol. Yet, whenever there is a large physical difference between the deviant and standard stimulus or when changes in temporal aspects of a stimulus are involved (e.g., duration), at least a simple control condition with a repetitive stimulus physically identical to the stimulus serving as the deviant in the oddball condition is recommended.

3.2. Signal-to-noise ratio and data recording time

Another major problem with an oddball paradigm is that it involves a small percentage of deviant stimuli and thereby the data recording time becomes long if one wishes to collect an appropriate amount of ERP trials for the deviant stimuli. This difficulty is amplified when the lifetime of the sensory memory is studied, since conditions with long ISIs have to be included. Furthermore, one often would like to study the processing of more than one or two types of deviant stimuli, but having several oddball conditions would make the recording several times longer.

Recent experimental work has suggested new ways to improve the signal-to-noise ratio and to shorten the data recording time. Based on the observation that a frequency change in piano tones evokes a larger MMN than an identical frequency change of sinusoidal sounds (Tervaniemi et al., 1993), Tervaniemi et al. (2000a) determined the effects of spectral sound structure on MMN elicitation by varying the number of harmonical partials of the sounds. They used sounds with 1, 3, and 5 partials. In parallel, they determined whether sound duration has an effect on frequency MMN elicitation. To this end, there were sounds of 100 and 250 ms. The data indicated that, first of all, the frequency MMN was enhanced by the presence of three harmonic partials over 1-partial sounds, however, without further enhancement caused by additional partials. In parallel, the sound duration did not affect the elicitation of the frequency MMN.

Based on these findings, Tervaniemi et al. (1999b, 2005b) then compared the test–retest replicability of the MMN and its magnetic counterpart MMNm evoked by changes in sound frequency, duration, and intensity by using relatively short 75 ms sounds which contained three lowest harmonic partials of a 500 Hz sound. The SOA was minimized to 300 ms to reduce the N1 amplitude evoked by each sound onset and to enable fast data collection. The magnitudes of the deviance were chosen after careful pilot recordings so that they would be perceptually discriminable but as small as possible to minimize N2b–P3a contamination. In the resulting paradigm there were frequency deviances of 5 and 10%, intensity decrement of 15 dB, and duration decrements of 25 and 50 ms. The ERP data indicated that the smallest deviances (5% frequency change, duration decrement of 25 ms) were too slight to evoke a reliable MMN signal. When the remaining three MMNs were compared, the duration MMN amplitude offered the most reliable MMN estimator in test–retest evaluations. Consistent results were obtained with the simultaneous MMNm recording (Tervaniemi et al., 2005b). Furthermore, the MMNm data showed that the right-hemispheric responses were more stable than the left-hemispheric ones in test–retest evaluations both in terms of latency and amplitude.

The next step in the paradigm development was taken by Näätänen et al. (2004) who rejected the use of a single repetitive standard tone during the recordings in order to

shorten the data-collection time. Five different deviant stimuli – frequency, duration, intensity, location, and gap – are used, alternating with the standard (50%) stimuli, all sounds being in the same blocks (each block starting, however, with 15 repetitions of the standard tone) (Fig. 4). This paradigm (called “Optimum 1 paradigm” by Näätänen et al., 2004; “Multi-feature paradigm” herein) is intended to probe the accuracy of discriminating physical stimulus features (see paragraphs 3–6 in Section 1). The rationale of this Multi-feature paradigm is that the deviant stimuli would strengthen the memory trace of the standard with respect to those stimulus attributes they had in common. Thus, in this paradigm, one sound feature remained constant for three to six sound presentations while some other sound features were changing. The data collection in this paradigm lasted only for 15 min (the total number of stimuli being 1845) and all deviant sounds elicited statistically significant MMNs. The MMN amplitudes varied between -2.80 and $-6.75 \mu\text{V}$ in this condition, whereas the corresponding values were between -1.60 and $-5.69 \mu\text{V}$ in the oddball conditions, in each of which there was one deviant stimulus type, the rest of the deviant stimuli being replaced with the standard stimulus.

Recently, the applicability of this paradigm to study auditory impairments in dyslexia was determined (Kujala et al., 2006). In this study, the MMN elicited by the five different deviant types (with slightly adjusted stimulus parameters) was

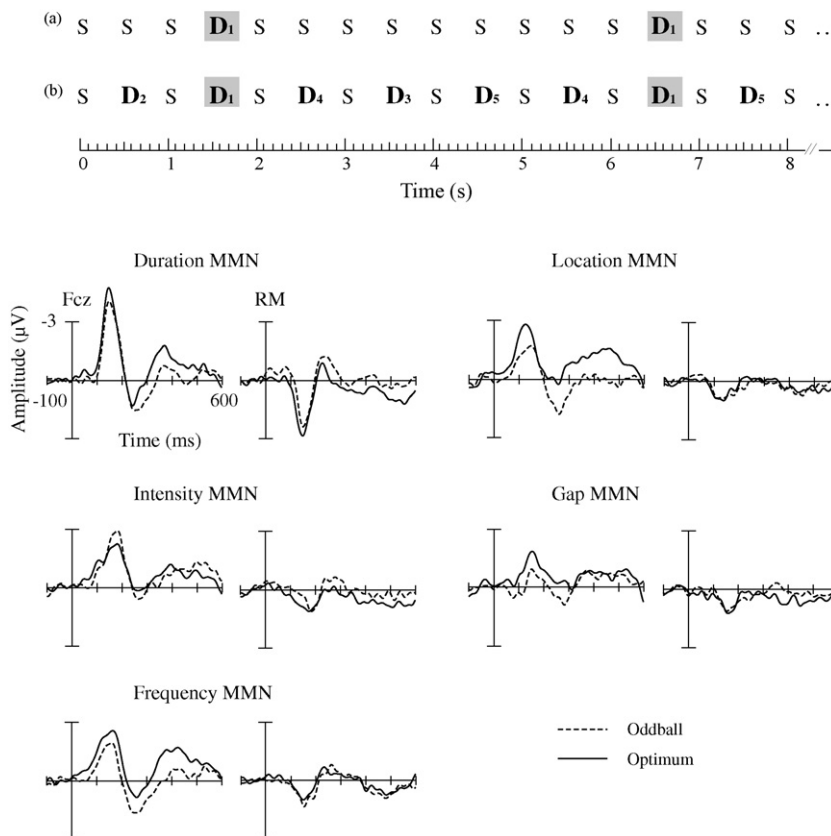


Fig. 4. A paradigm with which MMN can be recorded for five different deviant attributes. Top: A schematic illustration of the stimulus sequence in (a) an oddball condition and (b) in the multi-feature condition. S: standard stimulus; D1–D5: deviant stimuli with different attributes (duration, location, intensity, gap, and frequency). Bottom: MMN (difference waves obtained by subtracting the ERP elicited by each deviant stimulus from the ERP elicited by the standard stimulus) recorded for the different deviant stimuli in these two conditions. Figure adapted from Näätänen et al. (2004).

compared between dyslexic and control adult subjects. In addition, the MMN elicited by pitch and duration changes in the Multi-feature paradigm as compared with an oddball paradigm was evaluated. First of all, it was found that Multi-feature paradigm indeed suggested an abnormal pattern of cortical sound discrimination in dyslexic subjects so that their pitch MMN was diminished and location MMN enhanced. Furthermore, pitch and duration MMNs of the dyslexic subjects were more diminished in this than in the oddball paradigm, suggesting that the Multi-feature paradigm is more sensitive than the oddball paradigm in indicating auditory impairments in dyslexia. Perhaps the high degree in stimulus-feature variation affects the formation of the standard-stimulus representation in dyslexic subjects. It should be noted that since natural auditory signals like speech have constant variation, the Multi-feature paradigm, in fact, gives a better estimate on sound discrimination associated with normal listening conditions than the traditional oddball paradigm.

As reviewed above, in some clinical conditions sensory memory functions are impaired (e.g., dementia, alcoholism), and the MMN often diminishes in these conditions only if the interval between the stimuli is long enough. Thus, the paradigm improvements described above with ISIs well below one second are not helpful in tapping these impairments or in follow up. To solve the problems caused by long ISI (e.g., low signal-to-noise ratio; see Escera et al., 2000b), Grau et al. (1998) developed a paradigm combining the benefits of short and long ISIs (Fig. 5). Within one sequence, the sounds were first presented with a short SOA of 300 ms. During this phase, the memory trace was formed for the standard tone parameters. This short-paced sequence was followed by either a standard or a deviant sound, separated from the previous sounds by a longer ISI of 0.4 or 4.0 s (in separate blocks; memory-probe interval). The results showed that, without significant differences in the resulting

MMN parameters when compared with those obtained with conditions using constant ISIs, the experimental session is shortened to one-third.

The applicability of this paradigm in evaluating memory impairments was tested by addressing sensory memory functioning in abstinent chronic alcoholics (Grau et al., 2001). It was found that when the memory-probe interval was 0.4 s, no differences in the MMN amplitudes were found between the alcoholic and control subjects. However, with a memory-probe interval of 5 s, the MMN in the alcoholic group was no more significant, whereas in the control group it was, having, however, a diminished amplitude and a prolonged latency. There was also a significant group difference in the MMN amplitude.

In the interpretation of the results obtained with this paradigm one has to take into account the possibility that also other phenomena than those directly related to the lifetime of the sensory memory may underlie them. If standard stimuli occur closely in time and the deviant is presented after a long silent interval, the auditory system may group together the standard stimuli and the deviant is regarded as not belonging to that group. Therefore, the deviant might not be compared with the standard stimuli. For example, it was shown that MMN was elicited in all subjects if a constant 7-s stimulus interval was used, whereas it was elicited in only 9 out of 16 subjects if standard stimuli were presented with 0.5-s intervals followed by a deviant after 7 s (Winkler et al., 2001). This phenomenon has also been shown to occur perceptually (Bregman, 1990; Cowan et al., 1997). For example, the discrimination of sound pairs is better when the inter-pair interval is long than short (Cowan et al., 1997). Thus, both the lifetime of the memory trace and perceptual grouping effects may affect the results when the paradigm of Grau et al. (2001) is used.

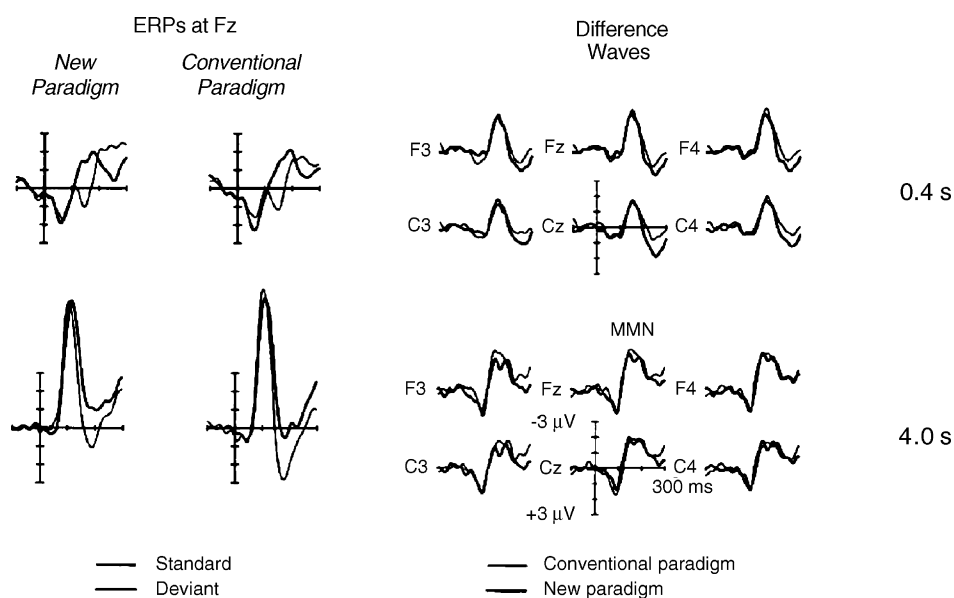


Fig. 5. A time-effective MMN paradigm for investigating sensory memory duration. Grand-mean ERPs on the left and difference waves on the right, with the responses from the two paradigms superimposed. In the upper part of the figure, the data were collected with a 0.4 s ISI and in the lower part of the figure, the data were collected with a 4 s ISI. Figure adapted from Grau et al. (1998).

During the recent years, MMN has become popular in probing speech perception and phonetic representations as well as their dysfunctions. Therefore, improved paradigms for investigating speech processing with the MMN are urgently needed. Huotilainen et al. (2001) showed that many repetitions of standard stimuli are actually not needed for eliciting a robust MMN for vowels. Huotilainen et al. (2001) used a roving MMN paradigm for comparing the discrimination of changes in prototype versus non-prototype vowels and sinusoidal tones. In this paradigm, a stimulus is repeated, and when a deviant sound is presented, it will thereafter serve as the standard so that it is being repeated for some time, until a new deviant is introduced, and so on. It was found that the MMN was larger for changes of prototype vowels than for those of non-prototype vowels and sinusoidal tones when only few repetitions preceded a stimulus change. However, no differences were found in the MMN amplitudes for the different stimulus types when there were four to five repetitions.

Thus, first of all, for recording robust MMNs for prototypical vowels (or perhaps for any other highly familiar sounds with strong long-term memory traces), standard-stimulus repetitions are needed much less than for unfamiliar sounds, which shortens the data-collection time. Second, this paradigm as such shortens the data-collection time since each deviant stimulus also serves as the first standard for developing the memory trace against which the next deviant stimulus is compared. Another advantage of this paradigm for speech studies is that it involves less stimulus repetition than the traditional oddball paradigm, in which the perception of the repetitive vowel may finally become distorted (McGee et al., 2001).

4. Practical issues in MMN recording and analysis

4.1. Data collection

The MMN is a small neural response, and therefore easily masked by the large background EEG activity. Therefore, it is important that a sufficient number of trials are collected for the deviant stimuli. The reliability of the MMN elicitation has been addressed already by a large number of studies (Pekkonen et al., 1995; Escera and Grau, 1996; Joutsiniemi et al., 1998; Tervaniemi et al., 1999b, 2005b; Frodl-Bauch et al., 1997; Kathmann et al., 1999; Kujala et al., 2001a; Cacace and McFarland, 2003; Schröger et al., 2000; for a review, see Sinkkonen and Tervaniemi, 2000). Since small physical sound differences elicit small MMNs, the large number of trials is particularly important when recording MMN to small sound contrasts, which also often are more sensitive indicators of group differences than large ones. When the study aims at showing significant differences between the groups in MMNs, less trials are needed than when the aim is to inspect data at the individual level (for individual MMN analysis, please, see Ponton et al., 1997).

During data collection, background conditions such as environmental noise or sound of the movie (if movie watching is the primary task) may affect the MMN results, since acoustic

background noise has been shown to diminish the MMN (Martin et al., 1999; Levänen and Sams, 1997; McArthur et al., 2003; Kozou et al., 2005). Different kinds of background noises affect differently the MMN amplitude, and noise affects differently speech versus non-speech processing (Kozou et al., 2005). Furthermore, noise alters the hemispheric lateralization of speech processing so that the predominance of the MMN is shifted from the left to the right-hemisphere (Shtyrov et al., 1998). Thus, background noise is an important factor that should be taken into account when designing the experiment and in interpreting the results. Importantly, other types of primary tasks (than book reading or watching movies) should be considered if it is critical to obtain a more careful control for the direction of attention during the stimulation or to obtain information about the behavioral distraction caused by deviant tones (Müller-Gass et al., 2005).

The MMN is maximal over the fronto-central areas of the scalp, particularly at Fz, F3, and F4. However, when possible, it is advisable to have a larger set of electrodes in MMN recording. Having Fz, Cz, and Pz as well as the left and right mastoids as a minimum is helpful in separating the MMN from some other ERP components like the N1 and N2b (Näätänen, 1992; Schröger, 1998). The N1 has usually a central (Cz) maximum, whereas the MMN typically is larger at Fz than Cz. The N2b, often following the MMN if the deviant stimuli are intrusive (Näätänen et al., 1982), is usually largest at Cz, being also often more pronounced than the MMN at Pz. Furthermore, N2b does not invert its polarity at mastoids, whereas the MMN does (Näätänen, 1992). Therefore, in order to be able to identify the MMN and to separate it from the other ERP components, one should initially place the reference on the nose, not at mastoids. Before the statistical analysis it is sometimes recommendable to re-reference the data to mastoids or to average reference (discussed below).

4.2. Data quantification

As with any other ERP component, there is no general recipe how to optimally quantify and analyze MMN. In general, we recommend the common guidelines for ERP analysis suggested by Picton et al. (2000). A few MMN-specific notions are as follows. Very often MMN is graphically shown in the deviant minus standard difference waves and quantification operates on these difference waves. In most of the MMN studies, nose reference is used. In this case, MMN is of negative polarity at fronto-central leads, gets smaller in the posterior direction, and may even invert polarity at leads below the Sylvian fissure. With nose reference MMN can be distinguished from N2b, which does not invert polarity at mastoids. When the MMN signal is small, it is reasonable to re-reference the data against the mastoids. This adds the “negative” and the “positive” parts of the MMN resulting in a larger response with a higher signal-to-noise ratio. Average reference (which shows the activity of each channel measured relative to the mean of the activity of all channels measured) has been proposed to be useful for dipole modelling, for comparison of topographic maps, and for correlation-based analyses (Cuffin, 2001; Dien, 1998). However,

when MMN results should be compared with data published previously, use of nose reference or presenting some figures with nose-referenced data allowing visual inspection is recommended, as most of the published studies have used this as the “standard” procedure.

The MMN may overlap with other ERP components and also with various kinds of artifacts (e.g., related to eye-movements, muscle activity, heart beat). As a consequence, it may be difficult to identify and quantify MMN. When the morphology and the topography of the MMN is known, the usage of filters or templates can help to reduce the impact of (unwanted) signals on the ERP that do not meet the characteristics of the MMN response. It is beyond the scope of this article to describe these highly sophisticated approaches (cf., e.g., Sinkkonen and Tervaniemi, 2000). Nevertheless, some more simple means may already be advantageous in many situations. Considering that the MMN usually has duration of about 80–200 ms one can disregard signals with frequencies clearly below or above the lower and upper frequency limits of a typical MMN, that is, below 1 Hz or over 5–10 Hz. In order to avoid filtering out other ERP components of interest with a spectrum differing from that of the MMN (especially in the upper frequencies), a band-pass filter of 1–25 Hz could be

applied to the EEG/ERP signal. This reduces in a quite optimal manner the contribution of slow drifts and high-frequency noise in the ERP.

4.3. Determining MMN generators

It is difficult to disentangle the different MMN generators in an EEG-based recording because of the spreading of the electric fields over the scalp. This may explain, for example, why electrophysiological studies have not consistently reported laterality effects of speech-elicited MMN (Sharma et al., 1993; Jaramillo et al., 2001; for a review, see Kraus and Cheour, 2000). In separating the left and right temporal lobe MMN sources, MEG and haemodynamic methods are of great help (Fig. 6). The MMN sources in the temporal lobes are tangentially oriented and, therefore, well detected by planar gradiometers of MEG (for a review, see Hämäläinen et al., 1993). Furthermore, since with planar gradiometers one can record the highest signal right above the activity source, the magnitudes of the left and right-hemisphere MMNs can be separately evaluated and compared with each other. Another feasible approach for evaluating the left–right asymmetry of the MMN is to use high-resolution EEG together with realistically

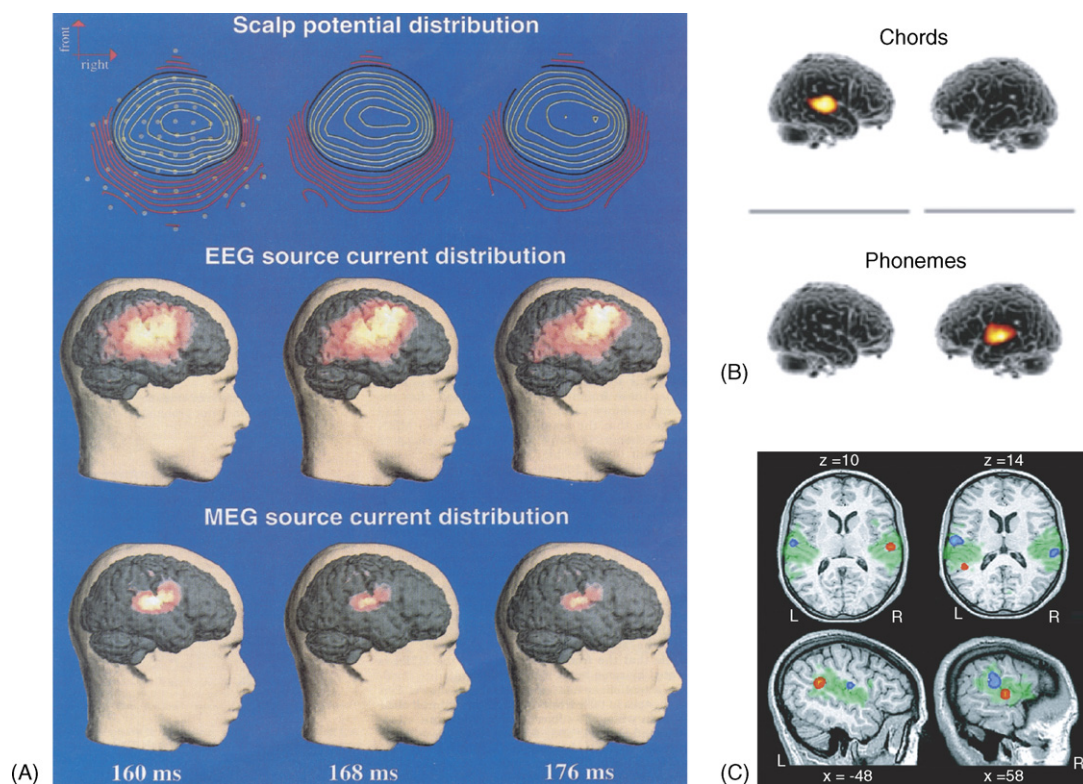


Fig. 6. MMN generators detected with EEG and MEG (A), PET (B), and fMRI (C). (A) Sources for MMN elicited by duration changes were determined for data recorded with high-resolution EEG and whole-head MEG. The data were analyzed with minimum-norm estimates (Hämäläinen and Ilmoniemi, 1994). It was found that the center of gravity of the activity changes towards frontal areas over time in the EEG data but not in the MEG data demonstrating that MEG detects the temporal but not the frontal MMN source (figure adapted from Rinne et al., 2000). (B) The MMN sources activated by chords and phonemes were determined with PET. The MMN process was tapped so that in some conditions there were both standard and deviant stimuli (separate scans for chords and phonemes), and in some of them only standard stimuli. Then, the activation caused by the stimulation including only standard sounds was subtracted from the activation caused by both standard and deviant sounds (figure adapted from Tervaniemi et al., 2000b). (C) MMN generators for duration and pitch changes were located with fMRI. In “MMN blocks”, the stimuli were presented in an oddball paradigm and in “control blocks” the two stimuli were presented in an alternating manner (separate scans for obtaining the duration and pitch MMN). Duration-related activations are shown in blue and frequency-related activations in orange (figure adapted from Molholm et al., 2005).

shaped head models (Rinne et al., 1999a; Ha et al., 2003). With this approach, differences in the hemispheric ratios of the MMN for linguistic versus non-linguistic stimuli have been demonstrated (Rinne et al., 1999a).

While the MEG is well suited for separating the MMN of the two hemispheres, it has the drawback of not detecting generator sources with radial orientations when a planar gradiometer is used (Hämäläinen et al., 1993). Perhaps because of this, frontal MMN generators have not been detected with MEG. This was demonstrated in a combined MEG and high-resolution EEG (64 channels and realistically shaped head models) study on the temporal and frontal MMN generators (Rinne et al., 2000). It was found that with the EEG data it was possible to identify a temporal-lobe MMN 160 ms from stimulus-change onset, whose center of gravity moved towards frontal brain areas as a function of time. However, with MEG activity associated with MMN could be seen in the temporal cortex only.

5. Summary and conclusions

MMN, which belongs to the family of stimulus deviance-elicited responses, is the first change detection response of the long-latency ERPs, reflecting the early stages of sound discrimination. Because of the extensive basic research on the MMN, its nature is already very well known. It operates at the sensory memory level, reflecting the early stages of stimulus discrimination (Näätänen, 1992; Schröger, 1997, 1998; Näätänen and Winkler, 1999). However, its link to the long-term memory is evident by studies showing that strong long-term memory representations of sound features elicit larger MMNs than weak ones (Näätänen et al., 1997; Winkler et al., 1999a,b; Koyama et al., 2000). Consistent with this, sound differences that do not originally elicit MMN, will elicit it if the subject learns to discriminate the differences (Näätänen et al., 1993; Kraus et al., 1995; Tremblay et al., 1998; Menning et al., 2000; Atienza and Cantero, 2001; Shestakova et al., 2003).

During the recent years, the MMN has become particularly popular in addressing auditory perception in a variety of patient groups (for reviews, see Csepe and Molnar, 1997; Näätänen and Escera, 2000; Näätänen, 2003) as well as in investigating the development of the auditory and speech systems (Alho et al., 1990; Winkler et al., 2003; Huotilainen et al., 2005). The reason for this is, first of all, that MMN can be recorded even from relatively uncooperative and inattentive individuals. Second, its functional role in perception is quite well known, and it more selectively reflects particular processes than several other cognitive ERP components.

While it is evident that the MMN is a valuable tool for addressing certain questions in cognitive neuroscience, there are some limitations in using MMN that have to be kept in mind. Some of the limitations inherently relate to the MMN phenomenon itself and are thereby associated with its functional specificity, some are purely methodological, and can be tackled with improvements of paradigms and analysis techniques. Although several studies have shown a strong association between the MMN parameters and behavioral measures in healthy subjects (Winkler et al., 1999a; Amenedo

and Escera, 2000; Kujala et al., 2001a; Novitski et al., 2004), some studies show a dissociation (Bradlow et al., 1999; Jaramillo et al., 2001; Kozou et al., 2005), which may be caused by a number of reasons. For example, some subject groups like children or patients with attention or communication problems may be unable or not motivated in carrying out behavioral tasks, whereas the MMN may be normally elicited. The perceptual impairment, reflected in behavioral performance, may also be associated with a deficit in a further processing stage following an intact MMN (Kujala et al., submitted for publication). Sometimes the reason for discrepant MMN and behavioral results may be methodological, for example, the number of trials or subjects might simply be too small for obtaining reliable results. Therefore, one should be cautious in interpreting on the basis of MMN data only what the subject or patient actually perceives. Whenever possible, a more complete picture of perception should be acquired by recording behavioral responses and other ERPs in addition to the MMN.

The methodological limitations in recording MMN are mostly associated with its poor signal-to-noise ratio, since it is a small ERP response, easily masked by the background EEG activity. The traditional approach of recording MMN in an oddball paradigm, in which there are repetitive standard stimuli and rare deviant stimuli, makes the MMN recording times very long in case one wants to acquire a clear and reliable MMN signal. This naturally reduces its attractiveness especially in clinical studies. Obligatory responses elicited by stimulus repetition can be acquired in much shorter recording time. However, the clear advantage of the MMN over the obligatory responses is that it reflects discrimination and memory unlike, for instance, the P1, N1, or P2. The recent development of paradigms shortening the recording time and analysis methods improving the MMN signal help overcome these obstacles (Tervaniemi et al., 1999b, 2005b; Grau et al., 1998; Sinkkonen and Tervaniemi, 2000; Näätänen et al., 2004). One of the greatest challenges in future work concerning the MMN is to find means for reliably recording and analyzing it at the individual level. MMN recording is an attractive approach for clinical use since stimulus discrimination accuracy and memory functions can be evaluated with the MMN even from inattentive subjects. However, in order to make it a feasible clinical tool, there should be reliable means for identifying it in individual subjects.

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