Towards Optimal Testing of Auditory Memory

- Methodological development of recording of the mismatch negativity (MMN) of the auditory event-related potential (ERP)

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Academic Dissertation

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Abstract

The overlapping sound pressure waves that enter our brain via the ears and auditory nerves must be organized into a coherent percept. Modelling the regularities of the auditory environment and detecting unexpected changes in these regularities, even in the absence of attention, is a necessary prerequisite for orientating towards significant information as well as speech perception and communication, for instance. The processing of auditory information, in particular the detection of changes in the regularities of the auditory input, gives rise to neural activity in the brain that is seen as a mismatch negativity (MMN) response of the event-related potential (ERP) recorded by electroencephalography (EEG).

As the recording of MMN requires neither a subject's behavioural response nor attention towards the sounds, it can be done even with subjects with problems in communicating or difficulties in performing a discrimination task, for example, from aphasic and comatose patients, newborns, and even fetuses. Thus with MMN one can follow the evolution of central auditory processing from the very early, often critical stages of development, and also in subjects who cannot be examined with the more traditional behavioural measures of auditory discrimination. Indeed, recent studies show that central auditory processing, as indicated by MMN, is affected in different clinical populations, such as schizophrenics, as well as during normal aging and abnormal childhood development. Moreover, the processing of auditory information can be selectively impaired for certain auditory attributes (e.g., sound duration, frequency) and can also depend on the context of the sound changes (e.g., speech or non-speech).

Although its advantages over behavioral measures are undeniable, a major obstacle to the larger-scale routine use of the MMN method, especially in clinical settings, is the relatively long duration of its measurement. Typically, approximately 15 minutes of recording time is needed for measuring the MMN for a single auditory attribute. Recording a complete central auditory processing profile consisting of several auditory attributes would thus require from one hour to several hours. In this research, I have contributed to the development of new fast multi-attribute MMN recording paradigms in which several types and magnitudes of sound changes are presented in both speech and non-speech contexts in order to obtain a comprehensive profile of auditory sensory memory and discrimination accuracy in a short measurement time (altogether approximately 15 min for 5 auditory attributes). The speed of the paradigms makes them highly attractive for clinical research, their reliability brings fidelity to longitudinal studies, and the language context is especially suitable for studies on language impairments such as dyslexia and aphasia. In addition I have presented an even more ecological paradigm, and more importantly, an interesting result in view of the theory of MMN where the MMN responses are recorded entirely without a repetitive standard tone. All in all, these paradigms contribute to the development of the theory of auditory perception, and increase the feasibility of MMN recordings in both basic and clinical research. Moreover, they have already proven useful in studying for instance dyslexia, Asperger syndrome and schizophrenia.

Tiivistelmä

Tarkoituksenmukainen ääniympäristössä toimiminen, kuten ääniympäristön merkityksellisiin tapahtumiin suuntautuminen ja kielellinen kommunikointi edellyttävät ääniympäristön säännömukaisuuksien, ja näistä poikkeavien tapahtumien tarkkaavuudesta riippumatonta mallintamista ja jäsentämistä yhtenäiseksi havaintokokonaisuudeksi. Tällaisen esitietoisen kuuloinformaation käsittelyn, erityisesti ääniympäristöstä poikkeavien äänien havaitsemisesta syntyvä hermosolujen aktivoituminen näkyy aivosähkökäyrässä tapahtumasidonnaisena MMN-jännitevasteena.

Koska MMN:n rekisteröiminen ei edellytä tutkittavalta tehtävän tekemistä tai ärsykkeiden aktiivista kuuntelemista, sen avulla voidaan tutkia sensorisen kuulomuistin toimintaa jo vauvaiästä vanhuuteen saakka. Perustutkimuksen lisäksi MMN:ää voidaan hyödyntää erilaisten aivoperäisten ja aivoihin vaikuttavien sairauksien ja tilojen, kuten lukihäiriön, ikääntymisen ja skitsofrenian tutkimuksessa. Viimeaikaiset tutkimukset osoittavatkin, että kuuloinformaation prosessointi MMN:llä tutkittuna on poikkeavaa erilaisissa aivosairauksissa kuten skitsofreniassa, mutta muuttuu myös kehityksen ja normaalin ikääntymisen myötä. Edelleen on osoitettu, että nämä kuuloinformaation prosessoinnin muutokset voivat ilmetä valikoivasti joillekin äänen piirteille (esim. äänen kesto tai taajuus) sekä vain joissakin yhteyksissä (esim. vain puheäänissä).

Vaikka MMN-tutkimuksella onkin huomattavia etuja verrattuna behavioraalisiin menetelmiin, sen yleistymistä laajempaan käyttöön, erityisesti kliiniseen tutkimukseen ja diagnostiikkaan, jarruttaa MMN-rekisteröinnin suhteellinen hitaus. Tavallisesti MMN-rekisteröinti yhdelle äänen piirteelle vaatii n. 15 minuuttia, joten useamman äänen piirteen erottelun profiilin rekisteröiminen vie helposti tunnista useaankin tuntiin. Tässä väitöskirjatutkimuksessa tavoitteena oli kehittää MMN-rekisteröinnissä käytettävää koeasetelmaa siten, että rekisteröinti voitaisiin tehdä aiempaa nopeammin, mutta yhtä luotettavasti. Väitöskirjatutkimuksessa kehitettiin koeasetelmia, joilla voidaan rekisteröidä lyhyessä ajassa (noin 15 minuuttia viidelle eri äänen piirteelle) useiden äänten piirteiden ja erikokoisten äänimuutosten prosessoinnin profiilit sekä puheäänille että ei-puheäänille. Koska näillä koeasetelmilla saadaan tietoa kuuloinformaation prosessoinnista huomattavasti aikaisempaa lyhyemmässä ajassa, ne parantavat MMN:n käytettävyyttä erityisesti kliinisissä tutkimuksissa. Edelleen, lyhyt rekisteröintiaika mahdollistaa entistä kattavamman ja monipuolisemm an kuvan muodostamisen tutkittavien erottelukyystä eri äänen piirteiden välillä. Korkea reliabiliteetti puolestaan tuo luotettavuutta erityisesti pitkittäistutkimuksiin ja puhekonteksti soveltuu erityisesti kielen ja sen häiriöiden kuten dysfasian ja afasian tutkimukseen. Kehitimme myös vielä näitäkin taloudellisemman koeasetelman, jossa MMN vaste rekisteröitiin uudella tavalla, ilman toistuvaa ääntä ja tämän osatutkimuksen tulos on merkittävä myös MMN:n ja kuuloinformaation prosessoinnin teorian kannalta. Kaiken kaikkiaan nämä väitöskirjatyössä kehitetyt koeasetelmat tuovat uutta tietoa kuuloinformaation käsittelystä, ja parantavat huomattavasti MMN-menetelmän käytettävyyttä sekä perus- että kliinisessä tutkimuksessa. On myös huomionarvoista, että näiden koeasetelmien on jo osoitettu olevan hyödyllisiä mm. lukihäiriön, Aspergerin syndrooman ja skitsofrenian tutkimuksessa.

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Helsinki, February 2011 Satu Pakarinen

List of original publications

Study I	Näätänen, R., Pakarinen, S., Rinne, T. & Takegata, R. (2004) The mismatch negativity (MMN): towards the optimal paradigm. *Clinical Neurophysiology*, 115, 140-144.
Study II	Pakarinen, S., Takegata, R., Rinne, T., Huotilainen, M. & Näätänen, R. (2007) Measurement of extensive auditory discrimination profiles using the mismatch negativity (MMN) of the auditory event-related potential (ERP). *Clinical Neurophysiology,* 118, 177-185.
Study III	Pakarinen, S., Lovio, R., Huotilainen, M., Alku, P., Näätänen, R. & Kujala, T. (2009) Fast multi-feature paradigm for recording several mismatch negativities (MMNs) to phonetic and acoustic changes in speech sounds. *Biological Psychology,* 82, 219-226.
Study IV	Pakarinen, S., Teinonen, T., Shestakova, A., Kwon, M. S., Kujala, T., Hämäläinen, H., Näätänen, R. & Huotilainen, M. Fast parametric evaluation of central speech-sound processing with mismatch negativity (MMN). *Submitted to Clinical Neurophysiology*.
Study V	Pakarinen, S., Huotilainen, M. & Näätänen, R. (2010) The mismatch negativity (MMN) with no standard stimulus. *Clinical Neurophysiology*, 121, 1043-1450.

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Abbreviations

ANOVA	analysis of variance
Dev	deviant tone
EEG	electroencephalograph, electroencephalograpy
EOG	electro-oculogram
ERP	event-related potential
FA	false alarm
fMRI	functional magnetic resonance imaging
HEOG	horizontal electro-oculogram
HR	hit rate
LM	left mastoid
LSD	least-significant difference
MEG	magnetoencephalograph, magnetoencephalography
MMN	mismatch negativity
MMNm	mismatch negativity, magnetically recorded
RM	right mastoid
RT	reaction time
SOA	stimulus-onset-asynchrony
SSG	Semisynthetic Speech Generation method
Std	standard tone
VEOG	vertical electro-oculogram

1 Introduction

A wealth of information enters the auditory system continuously. The auditory information, i.e. the sound waves (Klinke, 1989) are represented in the brain as neural activity throughout the ascending auditory pathway, from the inner ear via subcortical nuclei to the auditory cortex . At the subcortical level, the auditory information is mainly represented as physical sound features, such as sound intensity and frequency (Klinke, 1989; Shamma, 2001). At the cortical level the auditory information is represented as physical sound features (e.g. sound frequency; Elberling *et al.* 1982; Yamamoto *et al.* 1992; Tiitinen *et al.* 1993; Pantev *et al.*, 1995), but also as higher-order representations that consist of several features bound together to form a coherent entity i.e. an auditory object (e.g., pitch; He and Trainor, 2009). As the auditory information is non-static, the sound-pressure waves oscillating and decaying in time, the concept of auditory memory is especially important for this sensory modality. The auditory information is temporarily stored in sensory memory (Sperling, 1960) consisting of two subsystems: the shorter 100–200 ms form of sensory memory which is perceived as "an afterimage" of a sound (Cowan 1984; 1988) and the longer sensory storage that operates on the scale of approximately 10–20 s and is perceived as a vivid memory of the stimulus (Cowan 1984; 1988).

The cortical processing of auditory information can be examined with electroencephalography (EEG), a brain research technique in which the electrical activity of synchronous cortical neurons is recorded with electrodes attached to the scalp (Regan, 1989; Picton *et al.*, 1995). From the EEG one can further extract event-related potentials (ERPs) by averaging the EEG signal to a repeatedly presented stimulus, revealing the neural activity related to the processing of the stimulus (Picton *et al.*, 1995). The mismatch negativity (MMN) response (Näätänen *et al.*, 1978) of the ERPs has been proposed as an index of the longer form of auditory sensory memory (Näätänen *et al.*, 1992) and during the last decade, it has become an increasingly popular method in the studies of cortical auditory processing and sound discrimination.

One of the major advantages in recording the MMN comes from the fact that it can be recorded in a passive listening situation without the subject's attention to the stimulation (Näätänen *et al.*, 1978, 1993, 1999; Alho, 1992; Paavilainen *et al.*, 1993a). Thus, it can be easily recorded even from subjects who cannot be examined with the more traditional behavioral methods of sound discrimination. The MMN has indeed been successfully applied in a multitude of clinical studies, for instance in patients with schizophrenia (Michie *et al.*, 2000; Michie, 2001) or an attention deficit (Oades *et al.*, 1996; Kemner *et al.*, 1996; Sawada *et al.*, 2010), and even with patients in coma or persistent vegetative state (Kane *et al.*, 1993; 1996; Fischer *et al.*, 1999; 2010; Wijnen *et al.*, 2007). The MMN is also commonly used in studies of normal development and ageing, as well as their disorders, such as developmental language disorders (e.g., specific language impairment and dyslexia; for reviews, see Kujala *et al.*, 2007; Bishop, 2007) and neurodegenerative diseases (e.g., Parkinson's and Alzheimer's diseases; Pekkonen *et al.*, 2000; Brønnick *et al.*, 2010). Moreover as the MMN can be obtained also from fetuses in uterus (MMNm, recorded with the magnetoencephalography, MEG; Huotilainen *et al.*, 2005; Draganova *et* *al.*, 2005; 2007), newborns during sleep (Morr, 2002; Huotilainen *et al.*, 2003; Novitski *et al.*, 2007; Draganova *et al.*, 2007; Vestergaard *et al.*, 2009), as well as preterm babies (Fellman *et al.*, 2004; Mikkola *et al.*, 2007), it provides a means to evaluate the development, both the maturational as well as learning-related changes in central auditory processing already at very early, often critical stages in development.

The so-called oddball paradigm has traditionally been used for recording the MMN. With this approach the recording sessions tend to be long and provide usually information on cortical discrimination of 1–2 sound features. Especially in clinical studies and in studies with children and infants, short recording times are of major importance. Children have a limited patience to sit still and in long recording sessions, the signal-to-noise ratio tends to become poor. The aim of this Doctoral Thesis was to develop fast and reliable MMN recording paradigms in order to obtain a comprehensive profile of auditory sensory memory and discrimination accuracy in a short, also clinically feasible 15–30-minute recording time. These profiles can be useful in evaluating specific impairments of central auditory processing, as well as the development and plasticity of the system (for reviews, see Näätänen and Escera, 2000; Näätänen, 2003; Näätänen *et al.*, 2007). In addition, these studies have provided novel insights into how the brain extracts the regularities and detects changes in the environment, a necessary prerequisite of coherent perception and appropriate functioning in the environment.

1.1 Electroencephalography (EEG) and event-related potentials (ERPs)

Electroencephalograpy (EEG) provides a non-invasive low-cost method for studying the neural activity in the human brain. An array of electrodes is attached to the surface of the skin and small potential differences, in the range of millivolts, between the electrodes are recorded. These differences in electric potential arise from synchronous firing of large neuronal populations. The neural activity of single cells is too weak to be detected with EEG, but populations of hundreds or thousands of synchronously active neurons will contribute to the EEG signal. The neuronal populations giving rise to the EEG signal lie mainly at the cortex with the majority of the signal presumably coming from the post-synaptic potentials of cortical pyramidal cells. The pyramidal cells are systematically aligned perpendicular to the cortical surface thus allowing synchronous firing and voltage summation that is large enough to be detected (Regan *et al.*, 1989; Hämäläinen *et al.*, 1993; Picton *et al.*, 1995). As the temporal resolution of the EEG is in the scale of milliseconds, it is especially suitable for studying fast brain processes, such as cortical auditory processing. The spatial resolution of EEG however is limited by volume conduction and the anisotropic conductivity of the head structures (brain tissue, cerebro-spinal fluid, skull, and scalp; Regan *et al.*, 1989; Picton *et al.*, 1995), and therefore the most accurate source-localization studies are often conducted with other brain research methods, such as magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI).

The EEG signal includes the overlapping contribution of a great many simultaneous brain processes. In order to extract the microvolt-scale processes that are related to the brain functions time-locked to events of interest, such as auditory attention or processing of a sound, the EEG signals are commonly averaged across tens of presentations of experimental stimuli. This averaging attenuates the activity that is not time-locked to the stimulation such as rhythmic background activity and noise, and reveals the event-related potentials (ERPs), i.e., the activity that is time-locked to the stimulation (Hämäläinen *et al.*, 1993; Luck, 2005; Picton *et al.*, 1995). Further, ERP components are peaks in ERPs that are recognized according to their latency, scalp distribution, location of the brain generators and/or the function they are assumed responsible for (Picton *et al.*, 1995; Luck, 2005). There are several benefits in using ERPs in the assessment of auditory functions. First, the method is completely non-invasive and thus the recordings can be repeated several times for the same subjects and patients. Second, the method is inexpensive. Third, the recordings that are made in passive listening situation are not affected by motivation, decision making and other task-related variables. Fourth, the assessment is possible also with subjects unable to perform the behavioural discrimination tasks. Fifth, with the development of technology, the recordings can easily be done wherever the subjects or patients are, for instance at schools and hospitals. And sixth, there is a long tradition in interpreting the results and a wealth of information already gathered on the basis of auditory processing: the development of the auditory system as well as impairments of processing in different conditions.

1.2 The mismatch negativity (MMN)

The mismatch negativity (MMN) is a component of the event-related potential (ERP; Näätänen *et al.*, 1978). Typically, the MMN is recorded in an oddball paradigm, where the constant repetitive "standard" sound (P ≈ .90), which represents the auditory regularity is occasionally replaced with a rare regularity violating "deviant" sound ((P ≈ .90; see for details the oddball paradigm under the chapter "MMN recording paradigms"). The MMN is extracted by subtracting the averaged ERP response to the standard sounds from the averaged response to the deviant sounds. In this difference signal, the MMN is most often seen between 100 and 250 ms from the onset of deviation. When the nose is used as a reference site, the polarity of the MMN is negative at the frontal electrodes and inverts to positive at the mastoids (Alho *et al.*, 1993).

The MMN is elicited in a situation where an auditory regularity is violated in a perceptible manner. At its simplest, this violation can be a change in one sound feature, such as frequency (Sams *et al.*, 1985; Paavilainen *et al.*, 1993a; Tiitinen *et al.*, 1994) or intensity (Näätänen *et al.*, 1989; Woldorff *et al.*, 1991), within an otherwise homogenous stream of sounds. It can also be a more complex one, such as a repetition of a sound in a descending pitch trend (Tervaniemi *et al.*, 1994), an omission of sound in an otherwise steady sound sequence (Nordby *et al.*, 1994; Yabe *et al.*, 1997), or even a change in a complex spectro-temporal rule (Paavilainen *et al.*, 2007; Bendixen *et al.*, 2008). Initially, the MMN was interpreted to represent a comparison process where the current auditory input is compared to and found deviating from, i.e., mismatching with, the memory trace representing the preceding auditory input (Näätänen, 1978). Later on, the theory was revised so that the memory trace includes not only the information of the previous auditory input but also predictions of future auditory events in the form of rules or trends (Näätänen and Winkler, 1999; Näätänen *et al.*, 2010). According to some views, however, the MMN is not related to memory processes but rather refractoriness-like fatigue of the neural networks receiving the auditory input (N1 neurons are less refractory for rarely occurring deviants than for the frequently occurring standards; May and Tiitinen, 2010). These theories, however, might have problems in explaining the MMN responses obtained to omission of a stimulus from a continuous stream of sounds (Nordby *et al.*, 1994; Yabe *et al.*, 1997) or the ones elicited by complex spectro-temporal rules (Paavilainen *et al.*, 2007; Bendixen *et al.*, 2008). According to some other theories, the MMN is generated when the predictive models of the auditory environment fail, with the main function of the MMN-generating process being in adjusting the neural model to better describe the regularities of the auditory environment (Winkler *et al.*, 1996; Winkler, 2009).

1.3 Neural generators of the MMN

The MMN is thought to consist of at least two subcomponents that differ both in their loci of origin as well as their sound-processing functions (for a review, see Alho, 1995). The principal neural generator of the MMN, and its magnetic equivalent MMNm (recorded with the MEG) have been localized to the supratemporal planes of both left and right temporal lobes, to the vicinity of the primary auditory cortices (e.g., Hari *et al.*, 1984; 1992; 1989; Kaukoranta *et al.*, 1989; Sams et al, 1991; Tiitinen *et al.*, 1993; Alho *et al.*, 1993; 1995; Frodl-Bauch *et al.*, 1997). This temporal component is proposed to be responsible for the actual modeling of the auditory events, namely change detection in the comparison process between the perceived and predicted input (Näätänen, 1992). Further, it has been proposed as the first level of auditory object formation, i.e., the first level of processing where the features of the sound are bound together as an unitary auditory object (Ritter *et al.*, 2000; Winkler *et al.*, 2009). In addition to the temporal component, several studies suggest also the existence of a frontal subcomponent, possibly functionally related to the modulation of attention towards the auditory events (Giard *et al.*, 1990; Deouell *et al.*, 1998; Rinne *et al.*, 2000; for a review, see Deouell, 2007).

In addition, when presenting speech stimuli, also other subcomponents, overlapping with the two aforementioned ones, have been proposed. One of them is elicited for changes in phonemes of ones own native (Näätänen *et al.*, 1997) or second language (Winkler *et al.*, 1999), and it is usually lateralized to the language-dominant hemisphere (typically left; Näätänen *et al.*, 1997; Shestakova *et al.*, 2002; 2003). This MMN component has been interpreted to represent the activation of long-term memory traces for familiar speech sounds (Näätänen *et al.*, 1997; Winkler *et al.*, 1999; Shestakova *et al.*, 2002, 2003). Similarly, enhanced MMN-amplitudes have been found also for words, with distributed sources of activity depending on which characteristics of the words are being processed, e.g., lexical contrast (words vs. pseudowords: Pulvermüller *et al.*, 2001;2004; Shtyrov *et al.*, 2008) or semantic contrast (different word meanings; Pulvermüller *et al.*, 2004; 2005; Shtyrov *et al.*, 2004). As with the speech sounds, this enhancement of MMN amplitude has been interpreted to represent the automatic activations of long-term memory traces for meaningful words (Pulvermüller and Shtyrov, 2006 and Shtyrov and Pulvermüller, 2007).

1.4 The MMN and auditory perception

The relationship between the MMN parameters, namely the amplitude and latency, and the behavioral sound discrimination is well-known. The MMN amplitude directly correlates with the relative magnitude of the regularity violation, and usually, to the actual perception of the difference between the expected and the occurred auditory event (for a review, see Kujala and Näätänen, 2010). Larger violations elicit higher MMN amplitudes in relation to smaller violations of similar type (e.g., a small pitch change elicits a smaller MMN amplitude as compared with an MMN elicited by a larger pitch change; Sams *et al.*, 1985; Tiitinen *et al.*, 1994; Pakarinen *et al.*, 2007). The MMN amplitude correlates with the behavioral detection accuracy of the violations (Amenedo and Escera, 2000; Pakarinen *et al.*, 2007), and an increase in MMN amplitude coincides with increased behavioral detection accuracy as a result of discrimination training (Näätänen *et al.*, 1993; Tervaniemi *et al.*, 2001; Kujala *et al.*, 2001; for a review, see Kujala and Näätänen, 2010). Correspondingly, the MMN is typically not elicited when the sound change is not perceived (Winkler *et al.*, 1999).

There is also evidence that in some rare cases the information encoded in the sensory memory, as indicated by the MMN, is not available for conscious perception, but nevertheless can be used for intuitive decision making (van Zuijen *et al.*, 2006; Paavilainen *et al.*, 2007). In these cases, the MMN is elicited, and the subjects' task performance is above chance level even though they do not have any explicit knowledge of the rules embedded in the stimulation, suggesting that they not only possess but also can utilize this hidden information intuitively (van Zuijen *et al.*, 2006; Paavilainen *et al.*, 2007). This interpretation is also supported by the finding that when subjects are learning a discrimination task, the learning follows the appearance of the MMN (Tremblay *et al.*, 1997).

As with amplitude, the average latency of the MMN varies for different types of violations, the MMN usually peaking earlier, for instance, for duration, than for location changes (Tiitinen *et al.*, 1994; Pakarinen *et al.*, 2007). When the violation magnitude is varied within the deviation type, as in presenting different sizes of pitch changes, the latency is typically shorter for large as compared with smaller sound changes, though this variation may differ according to what type of sound changes are used (Pakarinen *et al.*, 2007). For instance, the MMNs peak earlier for larger and later for smaller pitch changes, and the latencies directly correlate to the behavioral detection speed of these changes, whereas, in contrast the MMN latencies for different magnitudes of duration changes may not significantly differ from each other or predict the behavioral performance (Pakarinen *et al.*, 2007).

1.5 The MMN as an index of auditory sensory memory in the brain

Sensory memory (Sperling, 1960) is part of the human memory system including the short-term/working memory and long-term memory. Initially, sensory memory was seen as a passive storage of information (James, 1890; Hebb, 1949; Sperling 1960), but in modern theories, sensory memory is given a more active information processing role (Cowan, 1984; 1995). The sensory memory consists of two subsystems. The shorter sensory storage is 100–200 ms in duration and it is perceived as "an afterimage" of a sound (Cowan 1984; 1988). The longer sensory storage operates on the scale of approximately 10–20 s and is perceived as a vivid memory of the stimulus (Cowan 1984; 1988). As many of the properties of the MMN correspond to those of the longer sensory storage, it has been proposed as an index of the longer form of auditory sensory memory (Näätänen *et al.*, 1992), in this Thesis referred to as sensory memory, for simplicity.

By examining what type of sound-changes elicit an MMN one can determine which properties of the sound are encoded in the sensory memory. The MMN is elicited for a multitude of changes, for instance in sound frequency (Näätänen *et al.*, 1978; Sams *et al.*, 1985; Paavilainen *et al.*, 1993a; Tervaniemi ym., 1999; Rosburg, 2003; Novitski *et al.*, 2004), duration (Paavilainen *et al.*, 1993b; Jacobsen and Schröger., 2003b; Rosburg, 2003; Grimm *et al.*, 2004), intensity (Näätänen *et al.*, 1989; Tervaniemi *et al.*, 1999; Jacobsen *et al.*, 2003a; Rosburg, 2003), perceived sound-source location (Paavilainen *et al.*, 1989; Schröger and Wolff, 1997), t as well as for changes in more abstract properties of sound, such as the order of presentation (Kujala *et al.*, 2001) or violation of a complex spectro-temporal rule (Paavilainen *et al.*, 2007; Bendixen *et al.*, 2008) indicating that all these aspects of auditory stimulation are automatically encoded in the sensory memory without attention specifically paid towards these features or even towards the sounds themselves.

The MMN also provides the means to examine the resolution of these sound representations, i.e., memory traces in the sensory memory. For instance, the temporal resolution of the auditory sensory memory can be examined by presenting deviant tones with a brief silent gap in the middle of the tone. The smallest deviation that elicits the MMN corresponds to the temporal resolution of the sound representation in the sensory memory (Desjardins *et al.*, 1999; Uther *et al.*, 2003).

Further, the duration and the decay of the sensory memory trace, in turn, can be examined by comparing different presentation rates of the stimuli (Sams *et al.*, 1993; Grau *et al.*, 1998; Pekkonen *et al.*, 1993; 1996). With this method it has been shown that the memory trace weakens exponentially over time since the last standard stimulus presentation and that the duration of the memory trace in young healthy subjects is approximately 10 seconds (as the MMN is no longer elicited at an inter-stimulus-interval of ~10 seconds; Sams *et al.*, 1993).

1.6 MMN as an index of long-term memory traces in the brain

Long-term memory is the storage of information (James, 1890) with virtually unlimited and infinite capacity. The information stored in the long-term memory can be available for days, years or even a lifetime. Already Hebb (1949) saw that long-term memory is based on relatively permanent changes in the inter-neuronal connections that result from synchronous firing of the neighboring cells. Subsequent research has shown that both cortical and hippocampal neurons show long-term changes in the firing patterns as a result of earlier neural activity (Bliss and Gardner-Medwin, 1973; Bliss and Collingridge, 1993). This phenomenon, called the long-term-potentiation (LTP) is currently regarded as one of the most plausible mechanisms of the long-term memory (see, for reviews Brown *et al.*, 1988; Muller *et al.*, 2002) and even receptors functioning as "coincidence detectors" have been identified (Harris *et al.*, 1984).

One can examine the sound representations encoded in the long-term memory with the MMN. The activation of a long-term memory trace is seen as an enhanced MMN response as compared to the responses elicited by a mere sensory violation without the long-term memory trace activation. For instance, with the MMN the long-term memory traces for the phonemes of our native language have been shown to reside in the left auditory cortex (Näätänen *et al.*, 1997; Shestakova *et al.*, 2002). In their study Näätänen and colleagues (1997) compared the MMN responses for vowel changes of the subjects' own and foreign language and found enhanced responses for the native-language phonemes. Similarly, when acoustically the same change is introduced in native-language phonemes compared to phonemes with no existing long-term traces, the MMN shows enhanced amplitudes suggesting faster memory trace formation (Huotilainen *et al.*, 2001). Furthermore, long-term memory traces for known words have been similarly inferred from the MMN recordings using words and pseudowords (Pulvermüller and Shtyrov, 2006; Shtyrov and Pulvermüller, 2007; Shtyrov *et al.*, 2010).

By following the evolution of these (both long- and also short-term) memory traces one can study the development and plasticity of the auditory system with both active and passive sound exposure. For instance, newborn babies learn to discriminate speech sounds during their sleep in only few ours exposure to these sounds (Cheour *et al.*, 2002a). Further, the MMN recordings also suggest that the long-term memory traces of native language are formed after birth, before the end of first year of life and importantly that the sound-discrimination has correspondingly improved during this period (Cheour *et al.*, 1998). Similarly, the memory traces have been shown to emerge and strengthen and the discrimination improve with second-language learning in children (Cheour *et al.*, 2002b; Shestakova *et al.*, 2003) and adults (Winkler *et al.*, 1999).

1.7 MMN recording paradigms

Oddball-paradigm. Typically, the MMN has been recorded using the oddball paradigm, in which infrequent (P = 10–20 %) 'deviant' sounds are interspersed within a stream of continually repeated 'standard (P = 80–90 %) sounds (Figure 1a). The advantages of the oddball paradigm lie in its simplicity and in its applicability to many types of stimuli and experimental manipulations. Oddball sequences can be easily constructed for different types of stimuli at different levels of abstraction: the stimuli can be individual sounds, sound pairs (Saarinen *et al.*, 1992) or more complex sound-structures, such as a brief melodies or excerpts of speech. Further, in the oddball paradigm, the sounds may follow abstract rules determining the features of the sounds (e.g., the higher the frequency, the longer the duration; Paavilainen *et al.*, 2007; Bendixen *et al.*, 2008).

One of the greatest downsides of the paradigm, however, is the relatively long duration of the recording. For every deviant sound, there are nine standard sounds in the sequence, and the recording time is increased by 100 % when a new auditory attribute is brought to the study. For instance, recording the MMN for frequency change requires approximately 15 minutes, and investigating also the MMN to an intensity change brings another 15 minutes to the experiment. It is thus quite common for the oddball recordings to take an hour or two, as usually the recording of only one or two MMNs is not sufficient to answer the researcher's or clinician's question.

In order to save time, some faster variations of the oddball paradigm have been developed. Most often, the recording time has been shortened by presenting more than one deviant in the stimulus sequence. For instance Tervaniemi *et al.* (1999) recorded the MMN responses to five deviants (intermediate and large duration change, an intensity change, and small and slightly larger frequency change) from a 75 ms 500 Hz standard tone. Each of the deviants was presented with a probability of 4 % and the probability of the standard tones was 80 %. This arrangement reduced the number of standard tone representations without increasing the probability of the deviant in time and the recording was made in 55 minutes as compared to the 75 minutes with the conventional oddball paradigm (Tervaniemi *et al.*, 1999). The second downside of the oddball paradigm is that the responses of neurons with different state of refractoriness as well as possibly different neuronal populations are compared with each other. As the neuronal populations responding repeatedly to the standard tone are more refractory as compared to the neurons responding to the rarely presented deviants, the MMN amplitude may be slightly overestimated (Schröger and Wolff, 1996; Jacobsen and Schröger, 2001; Jacobsen *et al.*, 2003a,b). To solve this problem, a separate control condition has been devised, in which the deviant tone is presented among several other tones, each having the same probability as the deviant in the oddball condition (Jacobsen *et al.*, 2003a,b). The refractoriness difference can then be partially eliminated by comparing the deviant in the oddball condition to the deviant in the control condition (Jacobsen *et al.*, 2003a,b). The need for this kind of control condition, again, unfortunately increases the recording time.

Roving paradigm. The time-course of the formation of the memory trace can not be estimated when the same standard is repeated throughout the experiment. With the roving paradigm (sometimes called roving-standard paradigm; Ritter *et al.*, 2002) one can, however, elegantly explore also the evolution of the memory trace over repeated presentations of the standard tone. In this paradigm, the stimuli are presented as changing stimulus trains, with the first

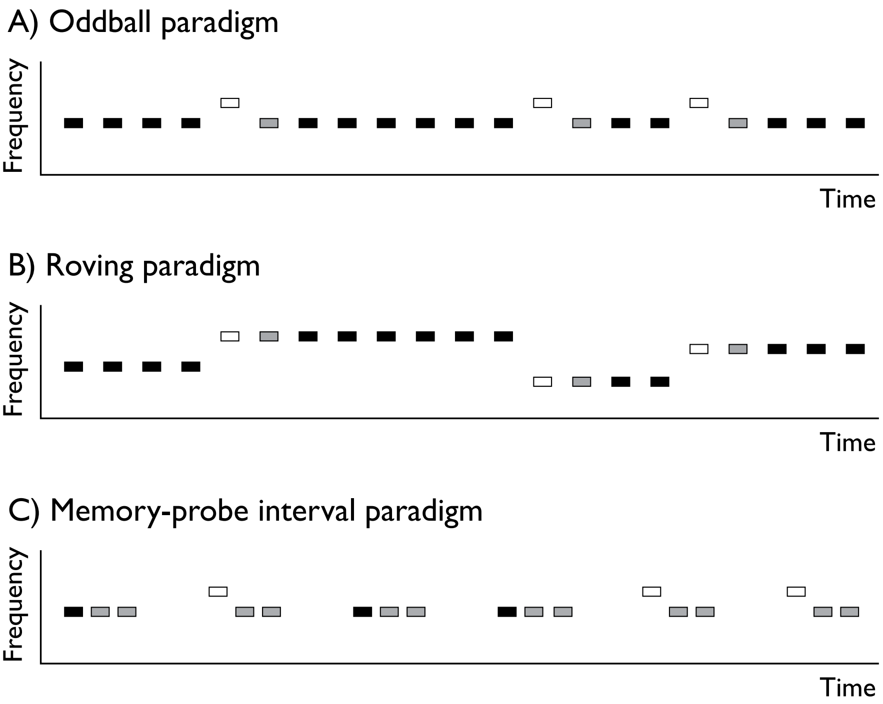

Figure 1. A schematic illustration of the following paradigms used to record MMNs: oddball paradigm (a), roving paradigm (b), memory-probe interval paradigm (c). The black tetragons represent the standards, the white ones the deviants and the grey tetragons the standard tones that are usually discarded from the averaging.

stimulus of each train serving as a deviant (Figure 1b). By using this paradigm, it has been shown that the MMN amplitude increases, indicating strengthening of memory trace, with the number of standard stimulus repetitions (Huotilainen *et al.*, 2001; Baldeweg *et al.*, 2004; Haenschel *et al.*, 2005).

Memory-probe interval paradigm. On the other hand the memory trace also weakens over time since the last standard stimulus presentation (Sams *et al.*, 1993). Thus, a common procedure to study the duration of the sensory memory trace is to compare the MMNs recorded with different inter-stimulus-intervals, e.g. the MMN recorded with the oddball paradigm with an ISI of a 0.5 – 1 second is compared to an MMN recorded with an oddball paradigm with an ISI of 5-10 seconds. As the longer inter-stimulus-intervals in these studies need to be in the order of seconds, the recording time also increases easily up to several hours. Grau *et al.*, (1998) however, managed to shorten the recording time by manipulating the presentation rate of the standard stimuli. In their recording paradigm (Grau *et al.*, 1998; Figure 1c), here referred to as memory-probe interval paradigm, the standard tones are presented at a fast rate (3 Hz), and after a variable memory probe interval (1 or 4 s) either a standard or a deviant tone is presented. The MMN is delineated by subtracting the response to the standard after memory-probe interval from the response to the deviant after memory-probe interval. This way the recording time was reduced by 66 % as compared with a conventional oddball paradigm. Importantly, the responses with this memory- probe interval paradigm were comparable to those obtained with the oddball paradigm with constant inter-stimulus-interval that was comparable to the duration of the memory-probe interval. The memory-probe interval paradigm is suitable for studies that require long presentation intervals, but it does not bring relief for the most common studies with the stimulus presentation rate of ~2Hz.

1.8 Theoretical bases of the multi-feature paradigm

Three earlier studies served as a starting point for the development of the multi-feature paradigms: From the study of Tervaniemi *et al.* (1999) it was known that several different deviant tones can be presented within one stimulus sequence, at least when a sufficient number of standard tones is presented in between them (Tervaniemi *et al.*, 1999). Secondly, Huotilainen and colleagues (1993) had shown that the MMN can be elicited in spite of considerably large variation in features irrelevant for the deviant detection. In their study, (Huotilainen *et al.*, 1993) MMN responses to a frequency change were recorded within a stimulus stream, in which both the deviant and standard sounds had varying durations, intensities, rise- and fall times, as well as timbres. The sound frequency, however was constant: 1000 Hz for the standards and 1050 Hz for the deviants. (The MMN amplitude recorded in this paradigm was on the average 33 % smaller than the one recorded with the conventional oddball paradigm; Huotilainen *et al.*, 1993). Finally, Nousak and colleagues (1996) showed that the different sound features (intensity, frequency) are independently stored in the auditory system. Therefore, it is assumed that the MMNs could be independently elicited and recorded for different auditory attributes, and this information was used in order to develop an optimal recording paradigm for the MMN with respect to the measurement time.

2 Hypotheses and aims of the present Thesis

The general aim of this Doctoral Thesis was to develop faster, reliable paradigms for mismatch negativity (MMN) recordings.

2.1 The main assumptions

The multi-feature paradigms developed in this Doctoral Thesis are based on three main assumptions:
#1 The MMNs can be independently elicited for different auditory attributes.
#2 Variation in the irrelevant features does not disrupt the encoding of the feature of interest.
#3 The deviant tones can strengthen the memory trace of the standard with respect to those stimulus attributes they have in common.

2.2 Specific aims and hypotheses of the studies

Study I aimed at exploring the optimal arrangement of stimuli in the sound sequence for the shortest recording time, yet not compromising the data quality. The MMN-responses recorded with three different stimulus sequences were compared to each other: 1) the conventional oddball paradigm (90 % standards, 10 % deviants), 2) the new multi-feature paradigm with the standard alternating with several deviants (optimum-1: 50 % standards, 50 % deviants), and 3) a compromise between these two, with 3 standards in succession and every 4th tone as one of the several deviants (optimum-2: 75 % standards, 25 % deviants).

The specific hypotheses of Study I were:
#1 The deviant tones can strengthen the memory trace of the standard with respect to the stimulus attributes they have in common. Thus, the responses recorded with the multi-feature paradigm (optimum-1) would correspond to those recorded with the oddball paradigm.
#2 The three standard tones presented in succession in the compromise condition (optimum-2) could form a sufficiently strong memory trace for the standard, or the deviants could serve as standards for each other. Thus, the responses recorded with this condition would correspond to those recorded with the oddball.

#3 The deviants may equally strengthen the memory trace for the standard in the multi-feature paradigm (optimum-1) and in the compromise condition (optimum-2), but because the probability of the deviants in time is lower and/or because the number of standard presentations is higher in the compromise paradigm than in the multi-feature paradigm the MMN responses in the multi-feature paradigm would be smaller than in the compromise condition.

Study II extended the idea of the multi-feature paradigm to include also different deviance magnitudes and examined the relationship between the MMN responses and behavioral sound-change detection. The specific hypotheses of Study II were:
#1 The MMNs can be separately examined for different magnitudes of auditory attributes.

#2 The MMN amplitude is directly related to the sound-change magnitude, i.e., the MMN amplitude is higher for larger sound changes and smaller to the smaller sound changes of similar type (e.g., larger vs. smaller frequency changes).

#3 The MMN latency is inversely related to the magnitude of sound change (i.e., earlier responses for large and later responses for small sound changes of similar type).

#4 The MMN amplitude is directly related to the accuracy of behavioral sound-change detection (i.e., the larger the amplitude, the higher the hit rate).

#5 The MMN latency is directly related to the speed of behavioral sound-change detection (i.e., the shorter the latency, the faster the reaction time).

Study III aimed at developing a multi-feature paradigm for speech sounds. Also reliability of the responses obtained with this new paradigm as compared to those obtained in the oddball paradigm was explored.

The specific main hypotheses were:
#1 Multi-feature paradigm can be used also with more complex sounds than tones, such as speech.

#2 The MMN responses are replicable, i.e., the responses do not differ between repeated recording sessions.

#3 The MMN responses do not differ between the oddball and the multi-feature paradigms.

Study IV aimed at developing a paradigm for obtaining a multi-feature profile for central auditory processing of different magnitudes of prosodic and phonetic changes in speech sounds.

The specific hypotheses of Study IV were:
#1 The MMN can be separately examined for different sizes of prosodic and phonetic changes in speech sounds.

#2 MMN reflects both acoustic and phonetic differences between standard and the deviant sounds, i.e., the acoustical difference between the sounds and the activation of the long-term memory traces for the speech sounds.

Study V explored whether the MMN could be recorded entirely without the standard tone and compared the responses in the no-standard paradigm to those recorded in the conventional multi-feature and oddball paradigms.

The specific hypotheses of Study V were:
#1 The memory trace is constructed for the invariant (standard) features of the auditory input. Thus, the MMNs can be independently elicited for different auditory attributes even without the presentation of a standard tone, i.e., the memory trace is constructed on the basis of classifying auditory attributes, not entire sounds, as common and rare.

#2 As the MMN amplitude increases with an increased number of standard feature repetitions, the MMN amplitude is the largest in the multi-feature paradigm, intermediate in the oddball paradigm, and the smallest in the no-standard paradigm.

3 Methods

3.1 Subjects

Participants were healthy adults, aged 20 to 40 years, with no reported neurological or hearing deficits. Details of the participants in each study are given in Table 1. All participants gave written informed consent prior to recordings after the nature of the study was explained to them. The studies were approved by the Ethical Committees of the Department of Psychology, University of Helsinki.

3.2 Stimuli

The stimuli in Studies I, II and V were harmonic tones. This tone structure was chosen because it is very common in MMN studies, it is easy to report and produce, and it has been shown to result in higher MMN amplitudes than when using simple sinusoidal tones (Tervaniemi *et al.* 1999; Tervaniemi *et al.* 2000). In Studies III and IV the stimuli were semi-synthetic Finnish-language speech sounds, created using the Semisynthetic Speech Generation method (SSG; Alku *et al.*, 1999).

The tones used in Studies I-II were composed of 3 harmonic sinusoidal partials, with a fundamental frequency of 330 Hz (Study I) and 523 Hz (Study II). The intensities of the second and third partials were lower than that of the first partial by 3 and 6 dB, respectively. The duration of the standard tone (std) was 75 ms, including 5 ms rise and fall times. The deviant (dev) tones differed from the standards either in frequency, intensity, duration, or perceived sound-source location. In addition, in Study I there was a gap deviant, with a 7 ms silence (1 ms fall and rise times included) in the middle of the stimulus. Furthermore, in Study II also the magnitude of the deviation from the standard tone varied across six levels (from the smallest to the largest magnitudes of change, L1 to L6, respectively, for each of the four attributes), resulting in a total of 24 deviants. The details of the stimuli in Studies I and II are given in Table 2.

In Study V the standard tone was composed of eight equally loud sinusoidal harmonics with a fundamental frequency of 330 Hz. The duration of the standard tone was 100 ms, including 10-ms rise and fall times. There were eight deviation categories: duration, frequency, intensity, perceived sound-source location, gap,

Table 1. Subjects in Studies I-V. (N/A indicates that the information is not available.)

Study	N	Males	Age/yrs (Mean)	Left-handed
I	11	4	20-39 (25)	N/A
II	9	6	23-27 (24)	N/A
III	15	10	20-40 (25)	N/A
IV	16	4	N/A (23)	2
V	11	7	21-26 (24)	1

density, brightness, and noise level. The details of the stimuli are given in Table 2 The stimuli in Study III were consonant-vowel (CV) syllables. The syllables were created with a semi-synthetic method developed by Prof. Paavo Alku (Alku *et al.*, 1999). In this method, the consonant is taken from a recording of a steady male voice pronouncing the syllable. Thereafter, the natural glottal pulse is extracted from the utterance, and this natural glottal signal is fed into a vocal tract model which allows one to set the formant frequencies of the stimulus. Thus, from one naturally varying glottal pulse it is possible to produce phonemes that have perfectly controlled formant frequencies but naturally varying glottal pulse. In this procedure, natural variation is introduced in the sounds, but the differences between the stimuli lie only in the formant frequencies.

The standard tones were /te:/ and /pi:/. The pitch was 101 Hz, which is typical for a male voice, and the syllable duration 170 ms. The deviant stimuli differed from the standard stimuli either in features that are related to prosody: syllable pitch, syllable intensity, or to semantics: consonant or vowel identity, or vowel duration, which is a semantic feature in quantity languages such as Finnish. In the duration control condition, the durations of the stimuli were reversed so that all other stimuli were 100 ms in duration, except for the vowel-duration deviant which was 170 ms. Thus, in this duration control condition, the standard stimuli were 100 ms long syllables /te/ and /pi/, and the corresponding frequency, intensity, consonant and vowel deviants were also 100 ms whereas the vowel duration deviant was 170 ms in duration. In Finnish language, syllable durations of 100 ms is quite consistently interpreted as "short", whereas syllable durations of 170 ms is interpreted as "long". The details of the tones in Study III are given in Table 3.

The sounds were delivered via headphones in all studies except for Study IV in which plastic tubes and earpieces were used. The stimuli were delivered binaurally and the intensity was 50 dB (Study III) or 60 dB (Studies I, II, IV & V) above the subject's hearing threshold which was measured using the multi-feature condition stimulus sequence in the beginning of the ERP recording. This method enables the comparison of responses also in individuals who have slightly elevated hearing thresholds.

3.3 Experimental paradigms and conditions

Procedure. During all ERP recordings, the subjects sat in an electrically shielded room, watching a self-selected subtitled video film (silenced) and were instructed to not pay attention to stimuli. In addition, Studies II and III included also a behavioral auditory discrimination task. Studies I, IV and V were carried out in one single recording session, and Studies II and III were carried out in two separate sessions with an interval of 1-7 days (median = 1 day) in between them. A summary of all ERP and behavioral conditions in each study is given in Table 4. In Studies I and III the MMN responses recorded with the new multi-feature paradigm were compared with those recorded with the traditional oddball paradigm. In addition, In Study I, these two paradigms were also compared with a compromise paradigm (optimum-2 in the original publication).

In studies II and III, the MMN peak amplitude and peak latency for the sound changes were compared with the behavioral

Table 2. Stimulus parameters and probabilities for harmonical tones in Studies I, II and V. Half of the frequency deviants were higher and half lower than the standard tone. Similarly, half of the location deviants were perceived as coming from the left and half from the right. The gap deviants consisted of a fall time, silence period and rise time. In a half of the density deviants, the partials were linearly modified so that the amplitude of the fundamental frequency was attenuated 0% (no attenuation) and the partials by steps of 14.3% until the highest harmonic partial was 100% attenuated (full attenuation). In the other half, of the density deviants, the attenuation pattern was the opposite. In a half of the brightness deviants, the even partials and in the other half, the odd partials were attenuated. The noise-level deviant was created by adding pink noise to the standard tone. Std denotes standard and Dev deviant tone. The rightmost column represents the magnitude of deviation ranging from the smallest (L1) to the largest (L6) one, when applicable.

	Duration	Intensity	Frequency	Location		Gap	Density	Brightness	Noise	Probability
	Ms	dB	Hz	Time	Degrees	Ms, Rise, Fall	low/high %	even/odd dB	dB	
Study I										
Std	75	60	500	0	0		0			$P_{standard} = 0.5$
Dev										$P_{deviants} = 0.5$
	25	50/70	550/490	800	90°	5, 1, 1				$P_{devtype} = 0.1$
Study II										
Std	75 ms	60 dB	523 Hz	0 µs	0° (centre)					$P_{standard} = 0.5$
Dev										$P_{deviants} = 0.5$
L1	67	57.5	519/ 527	50	5					$P_{type} = 0.125$
L2	59	55	512/ 535	100	10					$P_{level} = 0.083$
L3	51	52.5	501/ 546	250	25					
L4	43	50	487/ 562	400	40					
L5	35	47.5	470/ 583	550	60					
L6	27	45	450/ 609	700	90					$P_{level\ x\ type} = 0.125/6$
Study V										
Std	100	60	330	0 µs	0° (centre)					$P_{standard} = 0.5$
Dev										$P_{deviants} = 0.5$
	60	56/64	354/307	450	45°	2, 5, 1	14.3	7	14	$P_{devtype} = 0.1$

Table 3. Stimulus parameters and probabilities for speech sounds in Studies III and IV. In Study III, half of the stimulus sequences had syllable /te:/ and half had a syllable /pi:/ as standards. Half of the intensity deviants were softer and half louder than the standards. In Study III, half of the frequency deviants were higher and half lower than the standard tone. Std denotes standard and Dev deviant tone. The rightmost column represents the magnitude of deviation ranging from the smallest (L1) to the largest (L3) one, when applicable.

	Intensity dB	Pitch Hz	Vowel duration Ms	Vowel change	Consonant change	Probability
Study III						
Std						$P_{standard} = 0.5$
/te:/	50	101	170			
/pi:/	50	101	170			
Dev						$P_{deviants} = 0.5$
/te:/	Std	93/109	100	/ti:/	/pe:/	$P_{devtiant\ type} = 0.1$
/pi:/	50/70	93/109	100	/pe:/	/ti:/	
Duration control						
Std						$P_{standard} = 0.5$
/te/	50	101	170			
/pi/	50	101	170			
Dev						$P_{deviants} = 0.5$
/te/	50/70	93/109	100	/ti/	/pe/	$P_{deviant\ type} = 0.1$
/pi/	50/70	93/109	100	/pe/	/ti/	
Study IV						
Std						$P_{standard} = 0.5$
/i:/	60	101	170			
Dev						$P_{deviants} = 0.5$
L1	55/64	110	135	/y:/		$P_{deviant\ type} = 0.125$
L2	53/66		100	/e:/		$P_{level} = 0.166$
L3	51/68	136	70	/a:/		$P_{level\ x\ type} = 0.125/3$

discrimination accuracy and speed in detecting the same sound changes. In the study III there was also a duration control condition, in which the sound durations of the standards and deviants were reversed. In Study III the multi-feature condition and the oddball condition for vowel change were repeated on the second recording day in order to evaluate the reliability of the MMN responses.

ERP paradigms. In the multi-feature paradigms (Figure 2c) every other tone was always a standard and every other tone one of the several deviant tones. Thus, half of the sounds were standards ($P_{std} = 0.5$) and the other half consisted of equiprobable different deviants. In Study I there were five deviant categories, each deviant being presented with a probability of 0.1. In Study III there were four deviant categories, each deviant being presented with a probability of 0.125 and in Study V there were eight deviant categories, each deviant being presented with a probability of 0.125. In Studies II and IV there were also different magnitudes of sound changes (Figure 2d) from the smallest to the largest changes in 6 steps in Study II, and in 2 –3 steps in Study IV, thus each deviant being presented at a probability of 0.02 and 0.04, respectively.

In the oddball paradigms the stimuli were presented so that a large majority of the sounds were standards ($P_{std} = 0.8$-0.9; Figure 2a). In Studies I and III only one type on deviant was presented in each oddball-sequence, with a probability of 0.1, whereas in Study V there were two different deviants within the oddball sequence, each of them presented at a probability of 0.1. To ensure maximal similarity and thus highest possible comparability, the oddball sequences were always constructed from the multi-feature sequences by replacing all deviants except for those of one category with standards. In this way, the occurrence of a certain type of deviant stimulus in the sequence was identical to those of multi-feature condition.

In addition, there was another version of the multi-feature paradigm (named as optimum-2 in the original publication) in Study I (Figure 2b). This was a compromise between the multi-feature and the oddball paradigm, with three standards ($P_{std} = 0.75$) in succession and every fourth sound as one of the five different deviants ($P_{dev} = 0.05$). In the Study V the idea of the multi-feature paradigm was further cultivated by omitting the standard tones from the sequence entirely. Thus, in this no-standard paradigm (Figure 2e) only deviant tones ($P_{dev} = 0.125$) were presented in the sequence.

In all studies the stimuli were divided in short 5–6 minute stimulus sequences. Each stimulus sequence began with a small number (5–8) of standard repetitions. The stimulus-onset-asynchrony (SOA) was 500 ms in Studies I, II and V, except for the optimum-2 condition in Study I in which the SOA was 300 ms. In Study III the SOA was 650 ms, and in the Study IV it was 430 ms. A summary of the stimulus-onset-asynchronies, stimulus probabilities and recording times is given in Table 4.

Behavioral tasks. In Study II the same stimulus sequences as those used in the ERP measurement were presented to the subjects who were instructed to press a button when hearing a change of any magnitude in the auditory attribute designated (e.g., frequency) and to ignore changes in the other attributes. In this behavioral measurement, 50 trials per each of the 24 deviants were obtained in a total of 80-min time.

In Study III the behavioral test was always

Table 4. Experimental paradigms and conditions in each study.

	P(std)	P(dev)	SOA (ms)	Trials/ dev	Total recording time (min)
Study I					
Oddball for duration deviants	0.9	0.1	500	180	15
Oddball for frequency	0.9	0.1	500	180	15
Oddball for intensity	0.9	0.1	500	180	15
Oddball for locations	0.9	0.1	500	180	15
Oddball for gap	0.9	0.1	500	180	15
Optimum-1 for all 5 deviants	0.5	0.1	500	180	15
v	0.75	0.1	300	180	18
Study II					
Multi-feature paradigm for 4 deviants and 6 magnitudes of deviation	0.5	0.125/6	500	225	90
Behavioural detection test					80
Study III					
Oddball for intensity deviants	0.9	0.1	650	180	20
Oddball for pitch	0.9	0.1	650	180	20
Oddball for vowel duration	0.9	0.1	650	180	20
Oddball for consonant change	0.9	0.1	650	180	20
Oddball for vowel change	0.9	0.1	650	180	20
Oddball for vowel change, 2nd recording	0.9	0.1	650	180	20
Multi-feature for all 5 deviants	0.5	0.1	650	180	20
Multi-feature for all 5 deviants, 2nd recording	0.5	0.1	650	180	20
Duration control condition	0.5	0.1	650	180	20
Behavioural discrimination test					18
Study IV					
Multi-feature paradigm for 4 deviants and 3 magnitudes of deviation	0.5	0.125/3	430	200	34
Study V					
Multi-feature paradigm for 8 deviants	0.5	0.06	500	180	12
Multi-feature no-standard for 8 deviants	0	0.12	500	180	6
Oddball for frequency and density devs	0.8	0.1	500	180	15

performed after the second ERP recording in order to avoid carry-over effects of attention or learning to the ERP recordings. The stimuli were presented in pairs with a within-pair SOA of 650 ms and an inter-pair SOA of 2650 ms. The first syllable of the pair was always the standard syllable, and it was followed by a probe syllable. In 50 % of the trials the probe syllable was a standard and in remaining 50 % of the trials it was one of the 5 deviants ($P_{\text{deviant type}} = 0.10$). The order of the deviants was randomly assigned, so that each of the five deviants was presented 20 times within the sequence of the 200 syllable pairs. The subjects' task was to judge whether the probe syllable was the same as or different from the standard syllable.

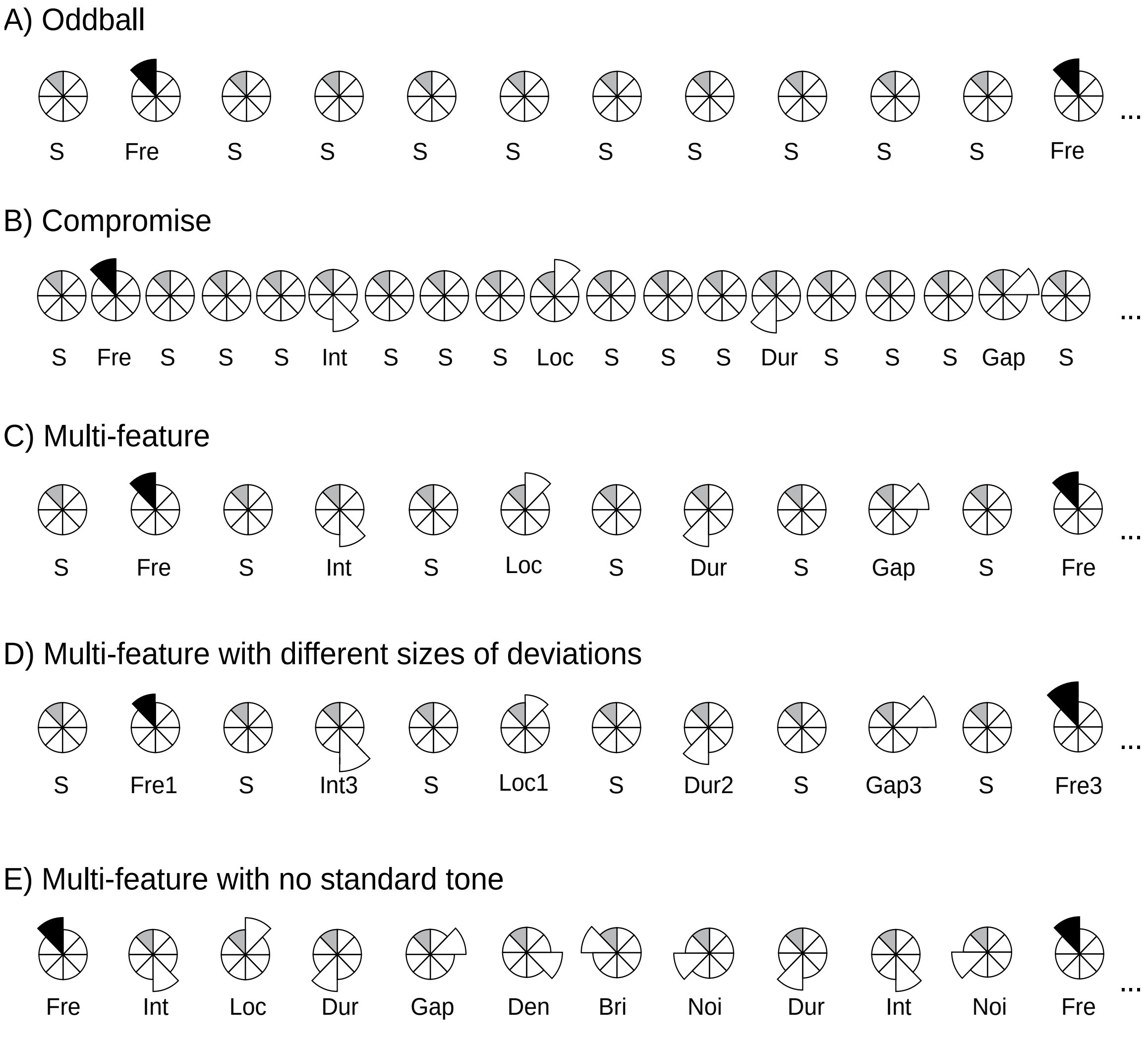

Figure 2. A Schematic illustration of the different recording paradigms used in this Doctoral Thesis: oddball paradigm (a), compromise paradigm (b), multi-feature paradigm (c), multi-feature paradigm with different sizes of deviations (d), and the multi-feature paradigm with no standard tone (e). Circles represent the sounds and the slices within the circle represent the eight different sound features of the sound with the size of the enlarged slice representing the magnitude of deviation within that sound feature. The slices representing the frequency deviations have been darkened as an example. S denotes the standard tone and the Dur, Fre, Int, Loc, Gap, Noi, Den, and Bri refer to the different deviant tones: duration, frequency, intensity, perceived sound-source location, gap, noise level, density, and brightness, respectively. The illustration depicts the basic principles and the timing of sound in the paradigms with harmonical tones used in Studies I, II and V. The same principles apply to the speech-sound paradigms used in Studies III and IV.

ERP recordings. The EEG was recorded (DC or 0–40/100 Hz, sampling rate 500 Hz) using Ag/AgCl electrodes with an electrode placed at the nose as a common reference. An electrode cap with 30-64 electrodes was used in all studies, except for Study V, in which 9 electrodes were placed according to the international 10-20 System of Electrode Placement (F3, F4, C3, Cz, C4, P3, P4, LM, RM). Moreover, in order to exclude artifacts from eye-movements the horizontal electro-oculogram (HEOG) as well as the vertical electro-oculogram (VEOG) were recorded in all studies.

The EEG was filtered (bandpass 1–20 or 1–30 Hz) offline. Epochs of 100 ms pre-stimulus and 600 ms post-stimulus periods were separately averaged for the standard and for the different deviant stimuli in each condition. The mean voltage of the 100 ms pre-stimulus period served as a baseline for amplitude measurement. Epochs including a large (+/- 75–150 μV, depending on the study) EEG or EOG change and the first standard repetitions in the beginning of each sequence were omitted from the analysis.

To delineate the MMN, the standard stimulus ERPs were subtracted from the corresponding deviant-stimulus ERPs (of the same condition). In addition, in Study V, also the response to the standard tone recorded in the multi-feature paradigm was subtracted from the responses to the deviants in the no-standard multi-feature paradigm. In Study II also the response to the standard (100 ms in duration) syllable in the duration control condition was subtracted from that to the physically identical duration deviant of the multi-feature condition (100 ms) and similarly, the response to the standard syllable in the multi-feature condition (170 ms) was subtracted from that to the deviant in the duration control condition (170 ms).

In order to pool the strength and timing of MMN activity to frontal-electrode sites the responses were re-referenced to the mean of the two mastoid electrodes in Studies I, II and III. This kind of analysis of mastoid-referenced frontal-electrode (Fz) MMN data is fast and simple, and thus more applicable to clinical settings as compared with more complex multi-electrode analysis methods, and it is shown to provide a good estimate of both mastoid and frontal MMN activity (Näätänen, 1990; Schröger, 1997), resulting in a single signal from which the MMN amplitude and latency can easily be estimated.

The fronto-central electrode with the largest amplitude was chosen for further analysis in Studies I-IV (Fcz in Study I, Fz in Studies II and III, and Cz in Study V). In Study IV also the amplitudes at LM and RM were determined whereas in Study V, the fronto-central average of Fz and Cz, and the mastoid average of LM and RM were used.

The MMN peak latency in Studies I-IV, as well as the MMN peak amplitude in Studies II-IV were measured from the largest peak within the time interval (90–250ms) of MMN response. The MMN mean amplitudes in Studies I-IV were calculated as a mean voltage at the 40–60 ms period centered at the peak latency in the grand-average signal.

In Study V, the MMN amplitude and latency were determined in a slightly different manner as compared with the other studies. The MMN mean amplitudes were calculated as a mean voltage at the 40-ms period centered at the peak latency at Fz in the grand-average difference signal. The MMN peak latencies were measured from the largest peak (negative at fronto-central electrodes and positive at mastoidal electrodes) occurring at the 40 ms period centred at the peak latency at Fz in the grand-average response. The average of the MMN mean amplitude at the mastoid electrodes RM and LM, and the average of the MMN mean amplitude at Fz and Cz, as well as the corresponding averages for the MMN peak latencies were calculated.

The peak latencies of the gap (only in study V) and duration MMNs were corrected in relation to the deviation onset (while latencies of other MMNs were measured from the stimulus-onset). In order to statistically compare the size of the MMN responses at mastoid electrodes to those at the frontal ones in Studies IV and V, the mastoid amplitudes were multiplied by -1.

Statistical testing was carried out to determine the existence of MMN responses and to examine differences between MMN responses for different stimuli in different paradigms. One-tailed t tests were conducted to determine whether the MMN peak (Study II) or mean (Studies I and III-V) amplitudes significantly differed from zero. Analyses of variance (ANOVA) with repeated measures were conducted to test the effects of different paradigms, deviant types, deviation magnitudes, electrode locations, and recording sessions (1st vs 2nd recording), when applicable. Details of the analyses of variance with repeated measures are given in Table 5. For all analysis of variance in Studies I, III and V, Greenhouse-Geisser corrections were applied where appropriate, and Newman–Keuls tests were carried out as post hoc analyses. In Study II, Huynh–Feldt corrections were applied and Newman–Keuls tests were carried out as post hoc analyses, whereas in Study IV, Greenhouse-Geisser corrections were applied and least-significant difference (LSD) tests were carried out as post-hoc analyses. For all studies, the original degrees of freedom and P-values after the correction are reported. In addition, in Study III, paired samples t-tests were carried out to compare the peak amplitude of the vowel-duration MMN in the multi-feature condition (1st recording) with that of the vowel-duration MMN obtained by subtracting the 100 ms standard of the duration control condition from the 100 ms deviant of the multi-feature condition, as well as with the peak amplitude of the vowel-duration MMN obtained by subtracting the 170 ms standard of the multi-feature condition from the 170 ms deviant of the duration control condition. In Study V, Pearson product moment correlations for MMN amplitude and latency (pooled over all eight deviation types, three paradigms and two electrode locations) were calculated for each subject and one-tailed t-tests were conducted to determine whether the correlations differed significantly from 0.

Behavioral data. In Study II, button presses occurring 200–1200 ms from target onset were identified as correct responses. The mean hit rates (HR, number of correct responses divided by number of targets) and reaction times (RT, mean time from target onset to button press) for correct responses were separately calculated for the 24 deviants and the RTs for the duration deviants were corrected in relation to the onset of deviation. The false alarm (FA) rate (number of button presses to non-targets divided by number of non-targets) was calculated for each attribute across the six levels of deviation magnitude. Two-way analyses of variance for repeated measures were conducted for both the HR and RT. To evaluate the relationship between the ERPs and the behavioral measures, general linear mixed-model analyses with repeated measures were separately performed for the deviant types (duration, intensity, frequency and location). The HR and the RT were assigned as dependent variables and the magnitude of deviance as within-subject factor.

In Study III button presses occurring 200 – 1200 ms after the probe onset were identified as responses. The correct responses were separately calculated for the stimuli that served as standards and deviants in the ERP session. As the deviants appeared randomly in the same sequence, an average false alarm rate was calculated separately for the standard and across the five deviants. Two-way ANOVA for repeated measures was conducted to test the effects of stimulus sequence (2 levels: /te:/, /pi:/) and stimulus type (6 levels: standard, frequency, intensity, duration, consonant and vowel change) on percent of correct responses. The relationship between the behavioral and brain responses was evaluated by calculating the Pearson product moment correlation coefficients between the measures for the five deviant types, i.e., the percent of correct responses and false alarms were correlated with the MMN peak amplitudes and latencies recorded with the multi-feature condition (1st recording).

4 Results

4.1 The new multi-feature paradigm allows fast recording of the MMN responses (Study I)

In all three conditions: oddball, multi-feature and compromise condition, the deviants elicited significant ($t_{10} = 3.7–14.6$, $P < 0.005$) MMNs, except for the MMN to the gap deviant in optimum-2 condition (Figure 3). The MMN amplitude was largest in multi-feature condition and smallest in compromise condition (main effect of condition: $F_{2,20} = 12.78$, $P < 0.05$ for all combinations). The MMN amplitude also varied between the deviant types (main effect of deviant type; $F_{4,40} = 27.04$, $P < 0.001$): the MMNs for the gap change ($P < 0.01$) being smaller and the MMN to the duration ($P < 0.001$) change being larger than those for all other deviants.

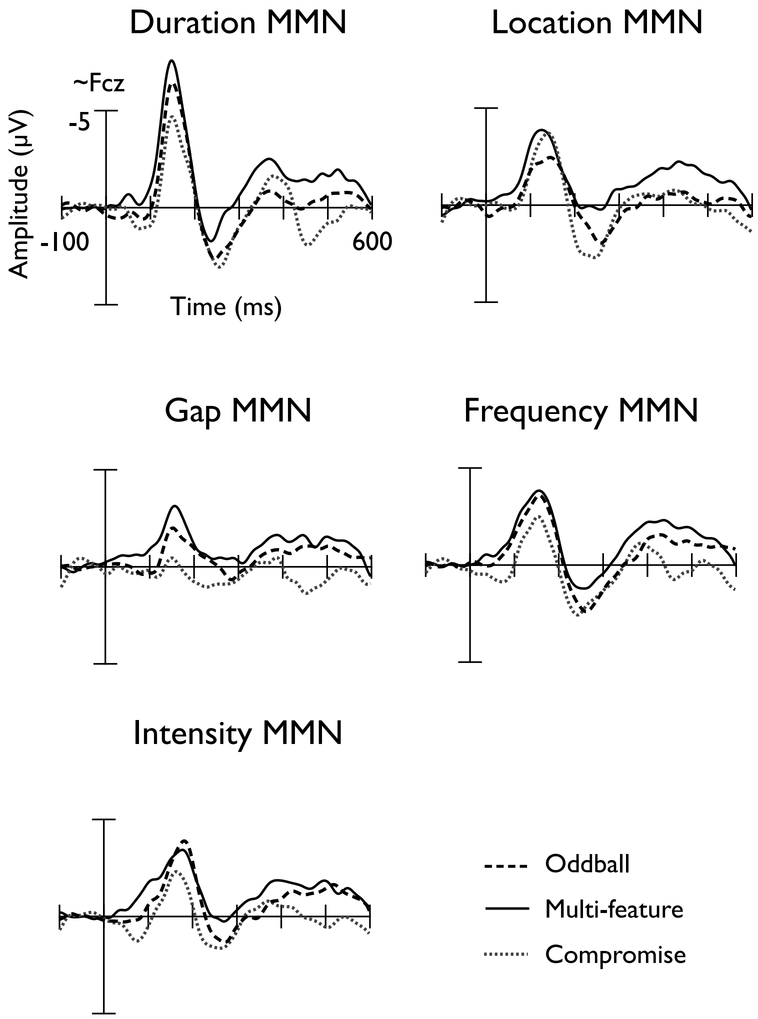

Figure 3. Grand average difference signals of 11 subjects for duration, location, intensity, gap and frequency changes at a frontocentral (approximately FCz) and right-mastoid electrode.
Overlaid are the MMNs for the same type of deviation in the different conditions. The dashed line indicates the MMN in the traditional oddball condition, the solid line that in the multi-feature condition and the dotted line that in the compromise condition. The data were referenced to the nose electrode.

4.2 Parametrical multi-attribute central auditory discrimination profiles recorded with the multi-feature paradigm (Study II)

ERPs. All 24 sound changes elicited significant MMN responses ($t_8 = 5.01$–11.90, $P < 0.01$). Fig. 2 (upper panel) presents the mean MMN peak amplitudes and latencies for the four deviant types as a function of stimulus deviance. The MMN amplitude increased with increasing deviance for all four types of changes (main effect of deviation magnitude: $F_{5,40} = 11.96 - 30.48$, $P < 0.001$; contrast for linear increase: $F_{1,8} = 18.91 - 56.40$, $P < 0.01$)

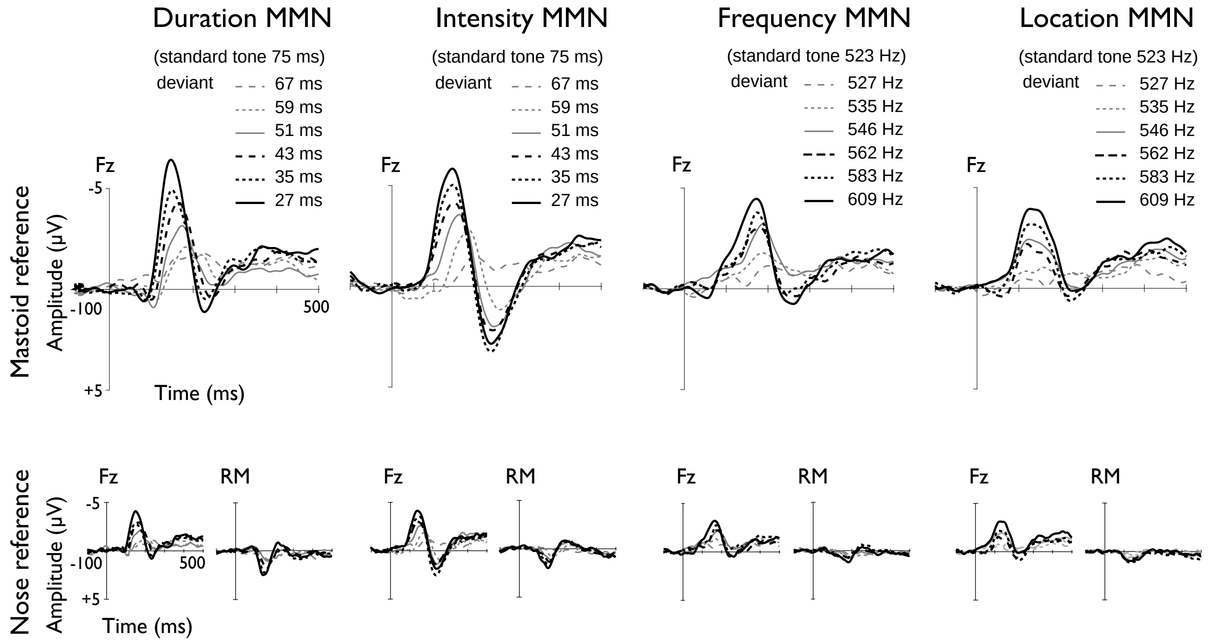

Figure 4. Grand-average difference signals of nine subjects for changes in sound duration, intensity, frequency, and perceived sound-source location for six different magnitudes of deviance at electrode Fz and referenced to the mean of the two mastoid electrodes (upper panel). The same signals referenced to the nose electrode and shown from the Fz and the right mastoid (RM; lower panel). Sound onset is always at 0 ms.

Whereas the peak latencies of frequency and location MMNs decreased with increasing magnitude of deviation (effect of deviation magnitude: frequency $F_{5,40} = 12.77$, location $F_{4,40} = 4.30$, $P < 0.01$; contrast for linear change: frequency $F_{1,8} = 34.42$, $P < 0.001$; location $F_{1,8} = 9.93$, $P < 0.05$) the magnitude of intensity and duration deviations had no effect on MMN peak latency.

The duration and frequency deviants elicited larger-amplitude MMNs than the intensity and location deviants (main effect of deviant type: $F_{3,24} = 6.39$, P < 0.01; Newman–Keuls: $P < 0.05$ for duration vs. intensity, duration vs. location, frequency vs. intensity, frequency vs. location, other comparisons ns.). Moreover, the duration MMNs peaked earlier and the intensity MMNs later than the other ones, whereas the peak latencies of the frequency and location MMNs did not differ from each other (main effect of deviant type: $F_{3,24} = 19.51$, $P < 0.001$; Newman–Keuls: $P < 0.05$ for all comparisons except for frequency vs. location).

Behavioral detection. For the four types of deviations, the mean HR was above the chance level (12.5 %) for all but the smallest magnitude of deviation and the mean FA rate was low (1.0–3.3 %). The larger sound changes were more often detected as compared with the smaller ones (main effect of deviation magnitude: $F_{5,40}$ = 44.50 - 75.37, $P < 0.001$; contrast for linear change: $F_{1,8}$ = 82.55 - 600.29, $P < 0.001$; Newman–Keuls: $P < 0.05$ for all comparisons, except for L5 that did not differ from L6). Moreover, the detection for the frequency deviants approached ceiling level faster than the detection for the other deviant types (interaction of deviant type and magnitude: $F_{15,120} = 6.78$, $P < 0.001$). The larger sound changes were detected faster as compared with the smaller sound changes (main effect of deviation magnitude:

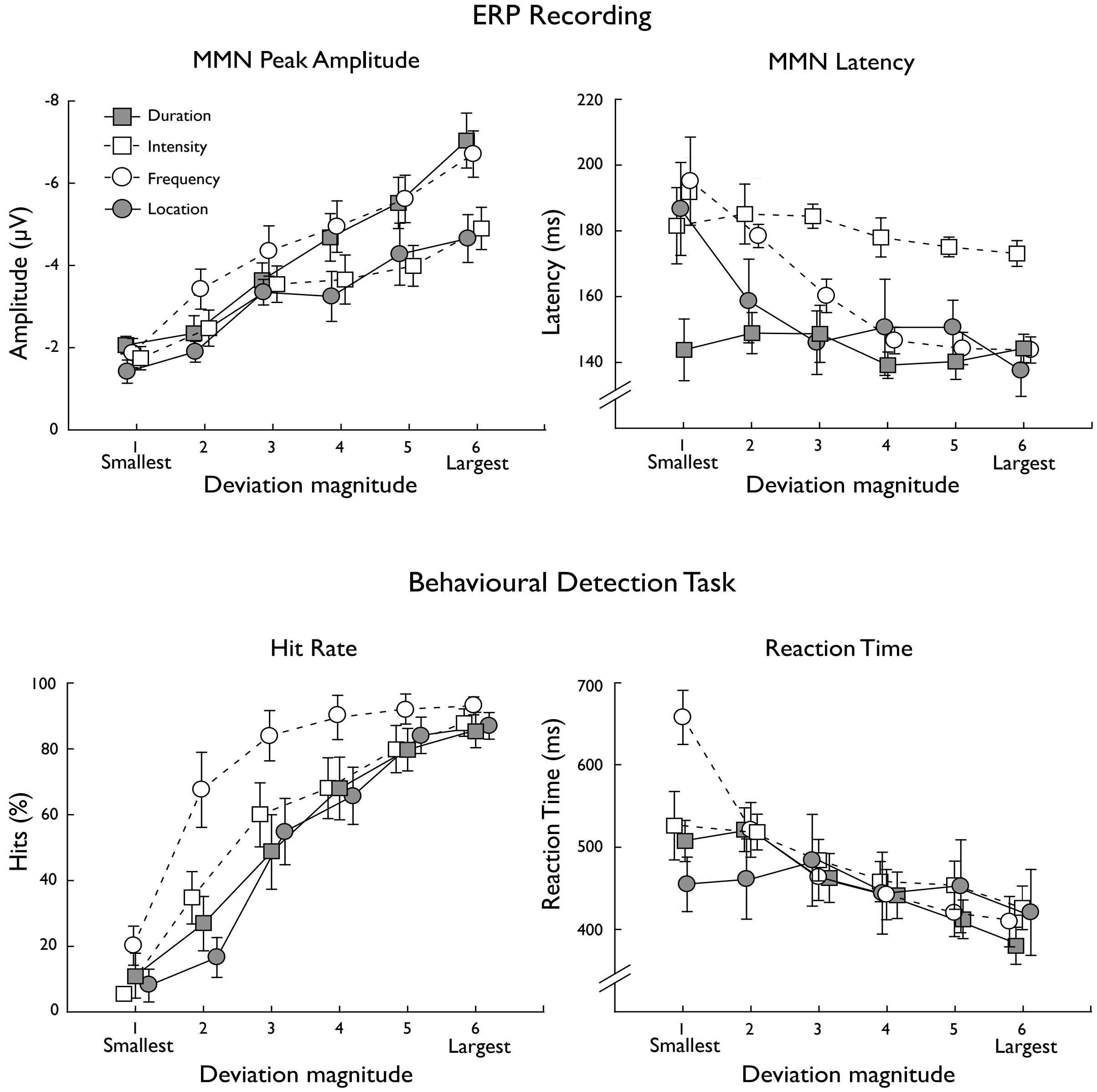

Figure 5. The mean (±SEM) MMN amplitude (upper left panel) and latency (upper right) at electrode Fz and behavioural measures hit rate (HR; lower left) and reaction time (RT; lower right) as a function of stimulus deviance. The MMN latencies and RTs are presented in relation to sound onset, except for the duration deviations, which are presented in relation to deviation onset. The reaction time was calculated for correct responses only. The ERP data were referenced to the mean of the two mastoid electrodes.

$F_{5,20-30} = 16.48 - 41.88$, $P < 0.001$; contrast for linear change: $F_{1.4-6} = 57.06 - 123.75$, $P < 0.001$) except for location changes, for which the RT remained unaffected.

MMN and behavioral detection. MMN amplitude predicted HR for all types of sound changes (Duration $F_{1,45.97} = 43.83 - 84.40$, $P < 0.001$) and RT for duration, frequency, and intensity (Duration $F_{1,43.34} = 42.47$, $P < 0.001$; frequency $F_{1,45.50} = 57.19$, $P < 0.001$; intensity $F_{1,42.48} = 93.76$, $P < 0.001$), but not for location changes. MMN latency predicted HR for frequency and location changes (frequency $F_{1,49.19} = 35.56$, $P < 0.001$; $F_{1,29.31} = 10.39$, $P < 0.001$) and RT for frequency changes (frequency $F_{1,42.33} = 132.43$, $P < 0.001$) only.

4.3 The multi-feature paradigm allows reliable and fast (30 min.) measurement of the detection of prosodic and phonetic changes in speech sounds (Study III)

ERPs. The syllable frequency, intensity, vowel-duration, and vowel-identity changes elicited statistically significant MMN mean amplitudes in all conditions (Figure 6; $t_{14} = 12.9 - 2.7$, $P < 0.001$;), whereas the MMN mean amplitude for the consonant change was significant only in the 1st recording with the multi-feature paradigm ($t_{14} = 3.2$, $P < 0.001$).

The MMN amplitude was smaller in the duration-control multi-feature paradigm than in the multi-feature (1st recording) or oddball paradigms (main effect of paradigm: $F_{2,28} = 23.25$, $P < 0.001$; Newman–Keuls: $P < 0.001$ for duration control paradigm vs. multi-feature and oddball, other comparisons ns.). In addition, the MMN peaked earlier in the duration control multi-feature paradigm than in the multi-feature or oddball paradigms (main effect of paradigm: $F_{2,28} = 4.83$, $P < 0.05$; Newman–Keuls: $P < 0.05$ for duration control paradigm vs. multi-feature and oddball, other comparisons ns.).
The MMN for the consonant change was smaller, and that to the vowel change larger

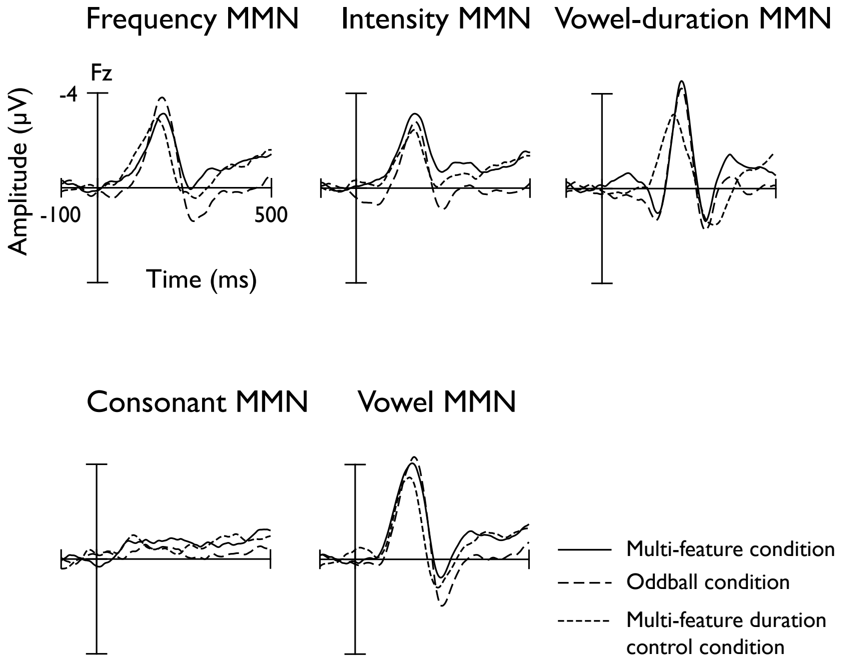

Figure 6. Grand-average difference signals of 15 subjects for changes in syllable frequency, syllable intensity, vowel-duration, consonant change, and vowel change at electrode Fz in the multi-feature condition (1st recording session; solid line), oddball condition (thick dashed line) and multi-feature duration-control condition (thin dashed line). The data were referenced to the mean of the two mastoid electrodes (LM and RM). Sound onset is always at 0 ms.

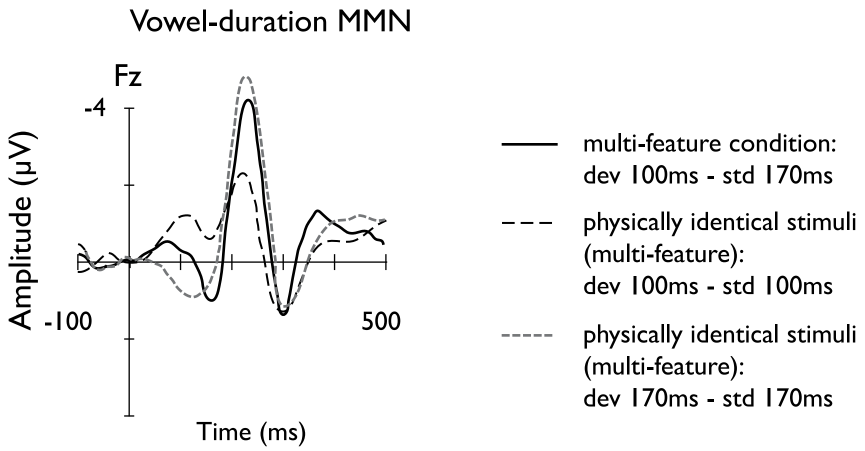

Figure 7. Grand-average difference signals of 15 subjects referenced to the mean of the two mastoid electrodes for changes in vowel duration at Fz electrode. The solid line denotes MMN response recorded with the multi-feature condition (1st recording session; deviant 100 ms minus standard 170 ms), the thick dashed line denotes the difference signal constructed from the responses to the 100 ms long stimuli (deviant in the multi-feature condition minus standard in the duration multi-feature condition) and the thin dashed line denotes those to the 170 ms long stimuli (deviant in the duration control multi-feature condition minus standard in the multi-feature condition). The data were referenced to the mean of the two mastoid electrodes. Sound onset is always at 0 ms.

as compared with the other sound changes (main effect of deviant type: $F_{4,56} = 34.15$, $P < 0.001$; Newman–Keuls: $P < 0.05$ for consonant vs. other changes and for vowel vs. other changes, other comparisons ns.). In line with this, the MMN peaked later for the consonant change and earlier for vowel-duration change as compared with the other changes and the latency for the frequency change was later than that for the vowel change (main effect of deviant type: $F_{4,56} = 48.27$, $P < 0.001$; Newman–Keuls: $P < 0.05$ for all comparisons except for intensity vs. vow and intensity vs. frequency).

The peak amplitude of the vowel-duration MMN recorded with the multi-feature paradigm (1st recording session; std 170 ms, dev 100 ms) significantly differed from the peak amplitude of the control MMN constructed from the responses to the physically identical 100 ms (deviant from the multi-feature condition minus standard from the control condition; $t_{14} = 3.3$, $P < 0.01$; Figure 7.) stimuli, but not from that to the corresponding 170 ms stimuli.

Replicability of the MMN. The responses were larger in amplitude on the first than the second recording session (Figure 8; main effect of recording session: $F_{1,14} = 6.17$, $P < 0.05$). When the MMN peak amplitude and latency for the vowel change in the two multi-feature and oddball recording sessions were examined, neither effects of paradigm (multi-feature vs. oddball) nor recording session (1st vs. 2nd session) were found.

The standards were correctly identified as same as the probe in 96 % of the trials (range 91–98 %). Moreover, the intensity, frequency, vowel-duration, and vowel deviants were correctly identified as being different from the probes in more than 90 % of trials (average 92–95 %, range 53–100 %), whereas the consonant deviant was identified as different from the probe in only 75 % of the trials (range 5–100 %).

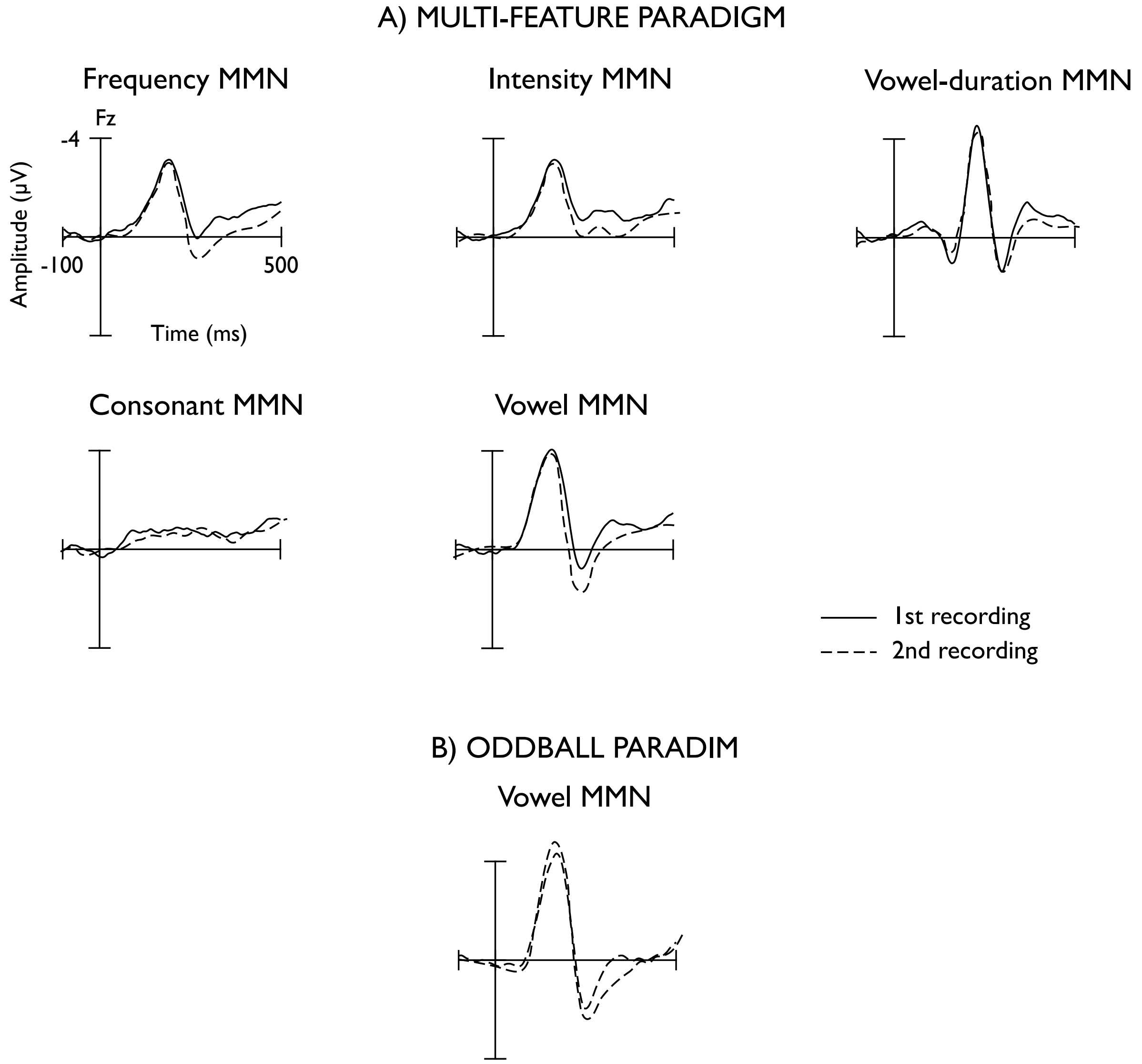

Figure 8. Grand-average difference signals of 15 subjects at Fz electrode over the two repeated recording sessions for changes in syllable frequency, syllable intensity, vowel duration, consonant change, and vowel change in the multi-feature condition (panel A) and for vowel change in the oddball condition (panel B). The solid line denotes the first recording session and the dashed line the second recording session. The data were referenced to the mean of the two mastoid electrodes. Sound onset is always at 0 ms.

The false alarm (FA) rate for the standards was 7.5 % and for deviants 10 % on the average. There were less correct responses for the consonant probe than for the other stimuli (main effect of deviant type: $F_{5,70} = 4.95$, $P < 0.05$; Newman–Keuls: $P < 0.001$ for consonant vs. all other probes).

Relationship between the MMN and behavioral discrimination. Only the MMN latency for the intensity deviations correlated with the percent of correct responses ($R = 0.523$, $P < 0.01$) and misses ($R = 0.662$, $P < 0.001$) for the same deviations. All other correlations were not significant. This was probably due to lack of statistical power, which resulted from the low variation (low task difficulty) and the relatively small sample size.

4.4 Parametrical central auditory discrimination profiles for speech-sound changes recorded in 30 minutes (Study IV)

For all 12 sound changes, statistically significant MMN responses (Figure 9) were elicited at Cz (t_{15} = 1.8 - 11.2, $P < 0.05$).

The magnitude of the deviation modulated the MMN amplitudes (Figure 10, upper panel) of all deviant types (main effect of deviance magnitude: $F_{2, 30}$ = 3.93 - 7.39, $P < 0.05$; contrast for linear change $F_{1,15}$ = 5.96 – 11.21, $P > 0.05$). For the intensity changes the MMNs were larger for the large sound-change as compared with the other two sound-changes (LSD: $P < 0.05$ for large vs. small and medium) and for the vowel-duration and vowel changes the MMNs were smaller in amplitude for the small than for the other two sound changes (LSD: Dur, Vow $P < 0.05$ for small vs. medium and large). The MMN was larger for the large pitch change as compared with the two small pitch changes (LSD: $P < 0.05$ for large vs. small1 and small2). Magnitude

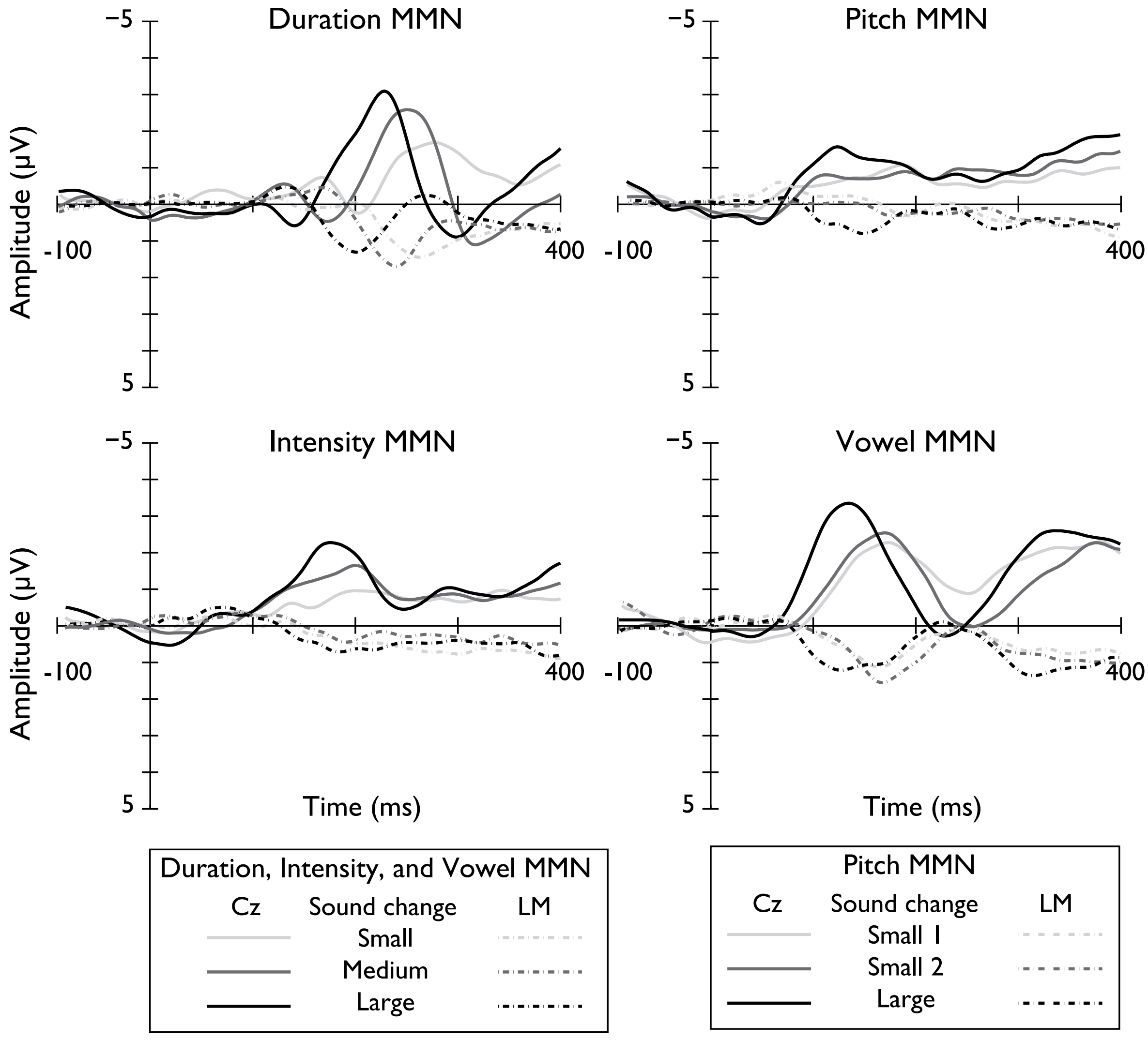

Figure 9. Grand-average difference signals of 16 subjects for the small, intermediate and large sound changes in the vowel duration, intensity, and vowel identity changes, as well as for the two small and one large pitch changes. The solid lines denote the signals at Cz, and the dashed lines those at the LM. Sound onset is always at 0 ms.

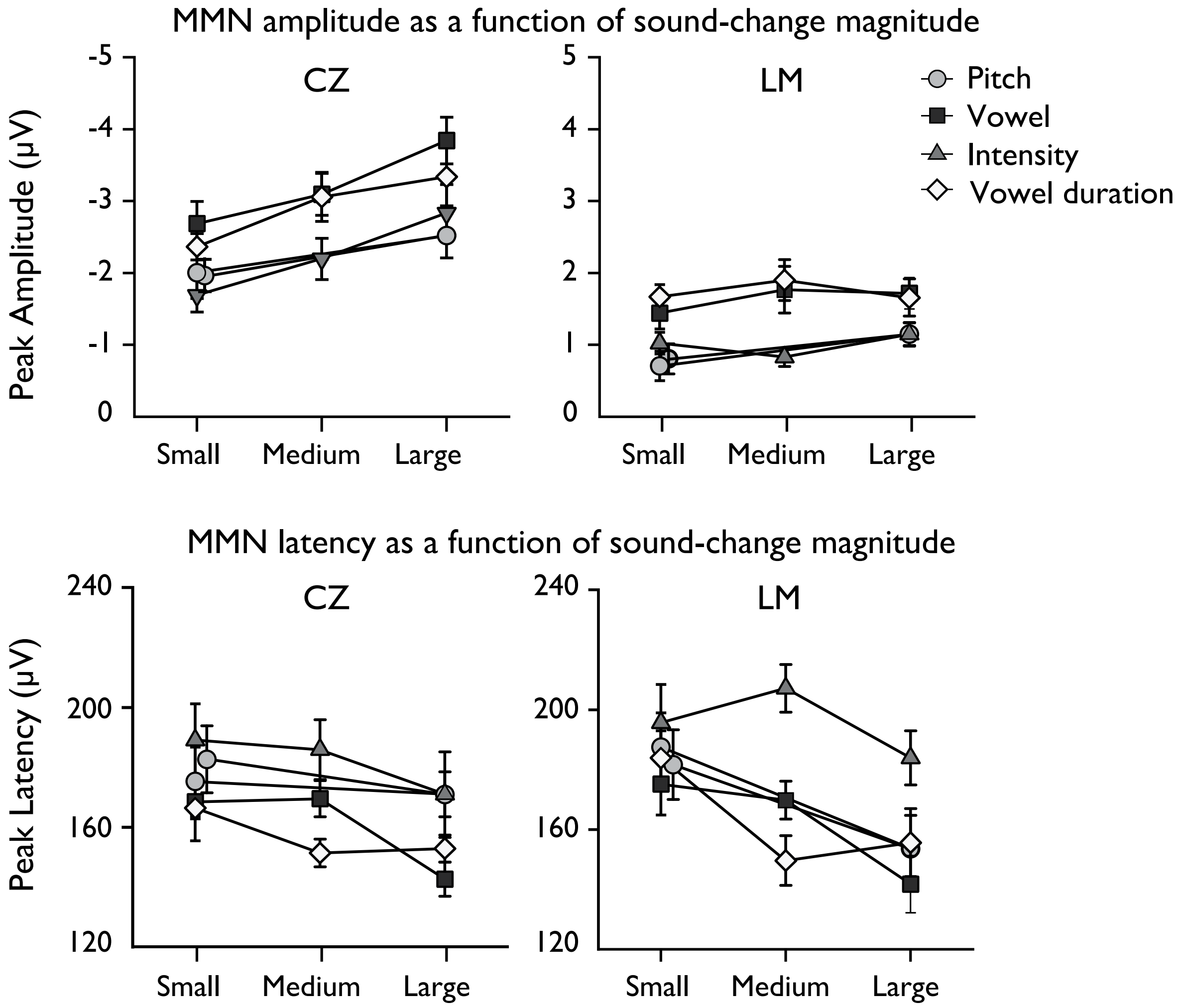

Figure 10. The MMN peak amplitude at Cz (upper left panel) and LM (upper right), and the MMN peak latency at Cz (lower left) and LM (lower right) as a function of stimulus deviance. Error bars denote the standard error of mean. The MMN latencies are presented in relation to sound onset, except for the vowel-duration changes, which are presented in relation to deviation onset.

of deviation also modulated the MMN latencies (Figure 10, lower panel) for pitch and vowel changes (main effect of deviation magnitude: pitch $F_{2, 30}$ = 14.86, $P < 0.001$, contrast for linear change as a function of deviation magnitude $F_{1,15}$ = 19.59, $P >$ 0.001; vow $F_{2, 30}$ = 9.46, $P < 0.01$, contrast for linear change $F_{1,15}$ = 10.15, $P > 0.01$). For the vowel changes the MMNs were earlier for the large than for the small and medium sound changes (LSD: $P < 0.01$, for large vs. small and medium). For the pitch changes, the MMNs peaked earlier for the large than for the two small sound changes (LSD: P < 0.001, for large vs. small1 and small2).

The MMNs for the pitch and intensity changes were smaller than those for the vowel duration and vowel changes (main effect of deviant type: $F_{3,45}$ =36.44, $P < 0.001$; LSD: $P < 0.001$ for pitch and intensity vs. duration and vowel). The MMNs were smaller at the mastoid electrodes than at Cz (main effect of electrode: pitch $F_{2, 30}$ = 8.14 – 9.33, $P <$ 0.01; LSD: $P < 0.05$ for Cz vs. RM and LM).

4.5 The MMN recorded with no standard tone (Study V)

All sound changes elicited significant MMN responses both at fronto-central and mastoid electrode locations in all three recording paradigms (Figure 11). The mastoidal MMN mean amplitude (the average of the mean amplitude at RM and LM) significantly differed from zero for all deviant types in all paradigms ($t_{10} = 2.2 – 12.0$, $P < 0.05$; Table 2). Similarly, the fronto-central MMN mean amplitude (average of the mean amplitude at Fz and Cz) significantly differed from zero for all deviant types in all paradigms ($t_{10} = 1.9 – 11.0$, $P < 0.05$). The MMN mean amplitude and the MMN peak latency did not correlate to each other ($t_{10} = 1.1$, ns.).

When the MMN amplitude was compared between the multi-feature paradigms the MMN amplitude was smaller in the no-standard than in the conventional multi-feature paradigm (main effect of paradigm: $F_{1,10} = 8.7$, $P < 0.05$). The MMN peaked earlier in the no-standard than in the conventional multi-feature paradigm (main effect of paradigm: $F_{1,10} = 88.5$, $P < 0.001$).

When comparing the MMN mean amplitude for deviations in frequency and density in all three paradigms: conventional multi-feature, no-standard, and oddball paradigm it was found that the MMNs in the no-standard paradigm were smaller than those in the conventional multi-feature paradigm (main effect of paradigm: $F_{2,20} = 3.6$, $P < 0.05$; Newman-Keuls: $P < 0.05$ for no-std vs. multi-feature). Moreover, the MMNs in the no-standard paradigm peaked the earliest, the ones in the oddball paradigm came the second and the MMNs in the multi-feature paradigm with standard tone peaked the latest (main effect of paradigm: $F_{2,20} = 25.7$, $P < 0.001$; Newman-Keuls: $P < 0.01$ for all comparisons). Moreover, an interaction of electrode location and paradigm was found (interaction electrode location x paradigm: $F_{2,20} = 5.8$, $P < 0.05$) as the latency differed between the paradigms at fronto-central location only (Newman-Keuls: $P < 0.05$ for no-standard vs. oddball vs. conventional multi-feature at fronto-central location), so that it was the shortest in the no-standard paradigm, the longest in the conventional multi-feature paradigm, with the latency of the MMNs obtained in the oddball paradigm being in between.

In the comparison between the multi-feature paradigms it was found that the duration change elicited larger responses than the noise level, sound-source location, intensity, and frequency changes, and further, the density change elicited larger responses than did the noise level, sound source location, intensity and frequency changes, whereas the intensity change elicited smaller responses than did the sound-source location, density, gap and duration changes (main effect of deviant type: $F_{7,70} = 7.3$, $P < 0.001$; Newman-Keuls: $P < 0.05$ for duration vs. noise, location, intensity, frequency; for density vs. noise, location, intensity, frequency and for intensity vs. location, gap, other comparisons ns.). Moreover, an interaction of the electrode location and deviant type (interaction electrode location x deviant type: $F_{7,70} = 3.1$, $P < 0.01$) was observed. The MMN amplitudes were larger for sound-source location, density, and duration changes at the fronto-central than mastoid location, whereas for the other deviants, there was no difference between the electrode locations (Newman-Keuls: $P < 0.05$ for location, density, and duration at fronto-central location vs. frequency, intensity, noise, brightness at fronto-central location). Also the MMN latency differed between the

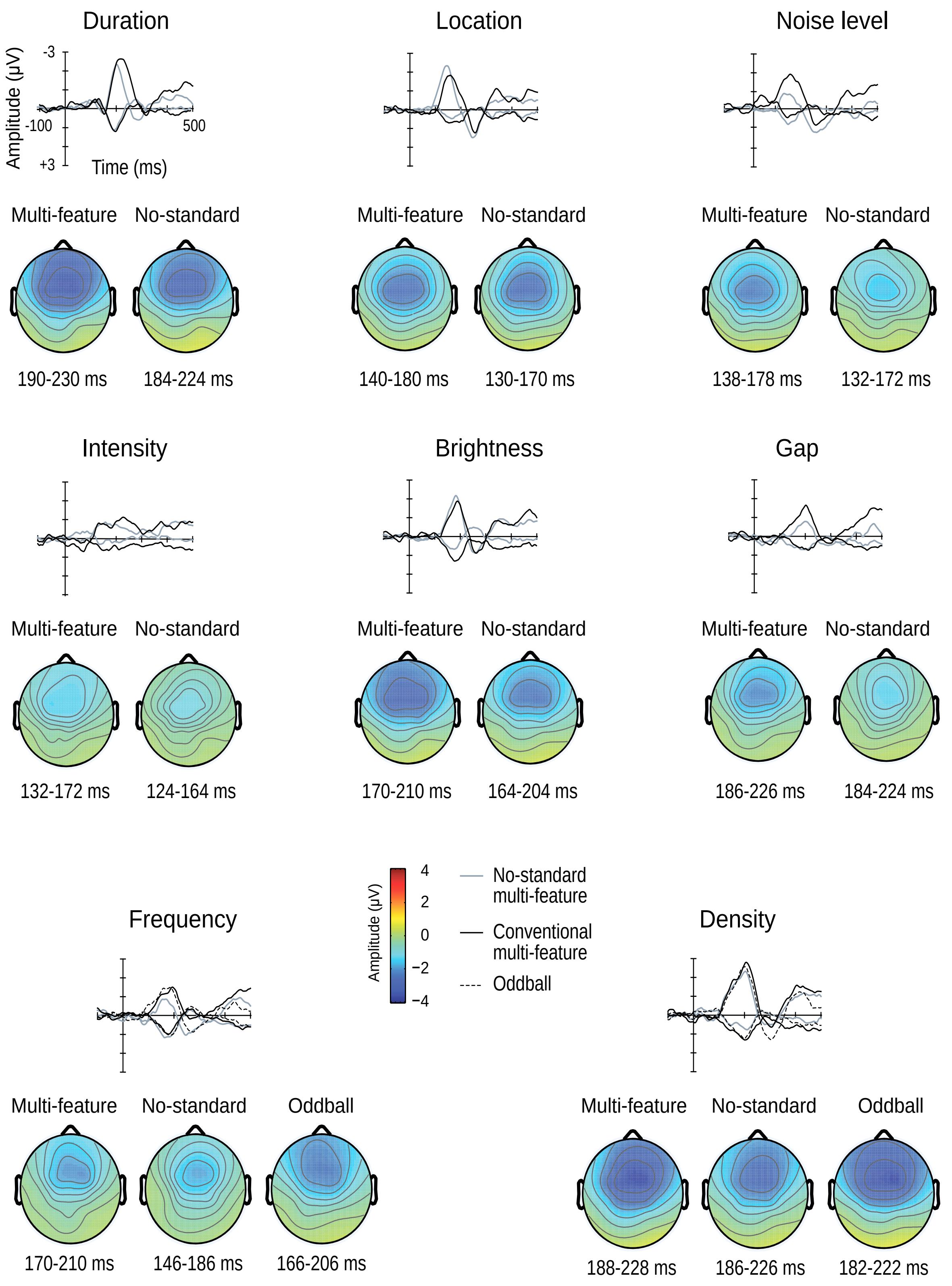

Figure 11. Grand average deviant-minus-standard difference signals of 11 subjects at Fz and RM as well as the corresponding voltage maps for all 8 sound changes: duration, frequency, intensity, sound-source location, gap, density, brightness and noise level recorded in the conventional multi-feature paradigm, in the no-standard paradigm, and in the oddball paradigm. Sound onset is always at 0 ms.

different deviant types. The MMNs for the density and brightness changes peaked later than those for the all other sound changes, and the MMN for the frequency change peaked later than those for the duration, intensity, sound source location and noise-level changes, whereas the MMN for the gap deviation was earlier than those for the other changes (main effect of deviant type: $F_{7,70} = 171.2$, $P < 0.001$; Newman-Keuls: $P < 0.05$ for density and brightness vs. duration, frequency, intensity, location, gap, and noise; frequency vs. duration, intensity, location, and noise; gap vs. all others). Moreover, the MMNs for the duration and frequency changes peaked later in the conventional multi-feature than in the no-standard paradigm, whereas the MMN latencies for the other sound changes did not differ between the paradigms (interaction paradigm x deviant type: $F_{7,70} = 2.6$, $P < 0.05$; Newman-Keuls: $P < 0.05$ for duration and frequency in multi-feature vs. duration and frequency in no-standard).

When the comparison was made between the MMNs to the frequency and density changes in all three paradigms including the oddball, the MMN mean amplitude for the change in density was larger than that for change in frequency (main effect of deviant type: $F_{1,10} = 29.9$, $P < 0.001$). This relationship was further defined so that the MMN mean amplitude was larger at the fronto-central location for density change as compared with that in the mastoid location, whereas the amplitude for the frequency change did not differ between the locations (interaction electrode location x deviant type: $F_{1,10} = 13.4$, $P < 0.05$; Newman-Keuls: $P < 0.001$ for density at mastoid location vs. density at fronto-central, frequency at fronto-central and frequency at mastoid locations, other comparisons ns.).

The MMN peaked earlier for the change in sound frequency as compared with that to the density (main effect of deviant type: $F_{1,10} = 192.3$, $P < 0.001$). Moreover, the latency differed between paradigms at fronto-central location only (interaction electrode location x paradigm: $F_{2,20} = 5.8$, $P < 0.05$; Newman-Keuls: $P < 0.05$ for no-standard vs. oddball vs. conventional multi-feature at fronto-central location), so that it was the shortest in the no-standard paradigm, the longest in the conventional multi-feature paradigm, with the latency of the MMNs obtained in the oddball paradigm being in between. In addition, an interaction of paradigm and deviant type was found (interaction paradigm x deviant type: $F_{2,20} = 11.7$, $P < 0.001$) as the MMN for the frequency change peaked earlier in the no-standard paradigm as compared with those in the other two paradigms, and the latency for the density change did not differ between the paradigms (Newman-Keuls: $P < 0.001$ for frequency change at no-standard vs. oddball and conventional multi-feature).

Both in the comparison between the multi-feature paradigms, and also in the comparison for deviations in frequency and density in all three paradigms: conventional multi-feature, no-standard, and oddball paradigm, the MMN amplitude was larger at the fronto-central than mastoid site (main effect of electrode location: $F_{1,10} = 16.5$, $P < 0.01$; main effect of electrode location: $F_{1,10} = 9.1$, $P < 0.05$, respectively).

5 Discussion

The main aim of the present Doctoral Thesis was to develop fast reliable MMN paradigms for measuring the central auditory processing of several types of sound changes (e.g., pitch, duration, vowel change) at different deviation magnitudes (from barely detectable to easily discernible) in both speech and non-speech contexts. It was also determined whether the MMN can be recorded even without the standard stimulus, with the invariant properties of the deviant stimuli serving as a standard against which to detect the sound changes.

5.1 Multi-feature paradigms allow fast and reliable MMN recordings

MMN responses with the multi-feature paradigm correspond to those recorded with the oddball paradigm. Studies I, III, and V showed that the MMNs recorded with the multi-feature paradigms, every other tone as a standard and every other tone as a deviant closely correspond to the responses recorded with the conventional oddball paradigm. Importantly, with the multi-feature paradigm, the same data quality was obtained with a considerably shorter recording time (typically 5 times faster, directly depending on how many deviant types are examined) than in the oddball paradigm.

The compromise paradigm of Study II, with three standards in succession and every fourth as a deviant, produced decreased MMN amplitudes compared with the other two paradigms. This was probably because of its relatively short stimulus-onset-asynchrony (SOA; Schröger, 1996), as the SOA was shortened from 500 to 300 ms to compensate for the prolonged recording time caused by the two additional standards. It is likely that with a longer SOA, substantial MMN amplitudes could have been measured, but with the cost of an increased measurement time.

Since the multi-feature paradigm produced similar responses as the oddball in the shortest recording time, the multi-feature paradigm was recommended to be used in MMN recordings instead of oddball paradigm. In comparison to using separate oddball paradigms in a sequence for each deviant type, the benefit of the multi-feature paradigm is the shortening of the recording time. In contrast, no recording time is saved when the multi-feature paradigm is compared to the oddball paradigm recorded for only one deviant type. In that case, the benefit of the multi-feature paradigm is that it brings information on five different deviant types in the same time that would be spent for recording only one deviant type in the oddball paradigm.

Since the multi-feature paradigm was so successful, it was also selected for further developmental work in the subsequent studies of the thesis, with one of the goals being to design multi-feature paradigms for speech sounds and also to include different sizes of deviations.

The MMN amplitude and latency reflect the magnitude of sound change. In Studies II and IV the MMNs were recorded with the multi-feature paradigm for different types but also different sizes of sound changes. Both studies showed, in line with majority of the previous the literature (Näätänen, 1992; Näätänen and Winkler, 1999), that the MMN peak amplitude increases with increasing stimulus deviance. It should be also noted, that the need for the control procedures suggested by Schröger and Wolff (1996) in order to avoid the refractoriness differences between the neuronal populations responding to the standard and the deviant may be smaller in the multi-feature paradigms where the amount of standard repetitions is considerably reduced as compared to the oddball paradigm. Moreover, the results are difficult to explain by refractoriness differences as the responses recorded with the multi-feature and the oddball paradigms were of similar magnitude (see also the more detailed discussion on refractoriness hypothesis under the heading "Theoretical implications"). For these two reasons, our results do not support the suggestion of Horvath *et al.*, (2008) that the MMN amplitude would not be affected by the deviation magnitude and that the increase in the amplitude at the MMN latency range would result from the differences in the neural refractoriness as reflected by the N1 component of the ERP. In contrary, the results of the present Thesis support the prevailing theories that the MMN amplitude indexes not only sound change per se, but also its degree in a fine-grained manner.

The MMN latency changes as a function of deviation magnitude were not as straightforward as they were with the MMN amplitude. In Study II with harmonical tones, the MMN peak latency for frequency and location deviations decreased with the magnitude of deviation, whereas the latencies of intensity and duration MMNs were not affected. Similarly, in Study IV, which used speech sounds, the MMN peaked earlier for the large vowel and pitch changes as compared with the smaller ones, whereas the latencies of intensity and vowel-duration MMNs were not affected. This lack of latency effect for intensity and vowel-duration MMNs is in contrast with the prevailing theory that the MMN peaks earlier the larger the deviation is (Näätänen, 1992; Näätänen and Winkler, 1999). In Study II, only intensity decrements (deviants with lower intensity than in the standard) were used, and it was thought that the lower power of these stimuli may have delayed the N1 and thus affected the accuracy of the MMN latency estimation. However, Study IV also used intensity increments, and yet the latencies for the different sizes of deviations remained unaffected by the magnitude of deviance. It appears that the MMN latency is not as dependant on the deviation magnitude as the MMN amplitude. An alternative explanation is that the MMN latency is more difficult to measure reliably, as compared with the MMN amplitude, often expressed as the mean voltage around the peak of the signal.

Obtaining the MMN responses with different deviation magnitudes requires a longer time than recording with only one magnitude for each deviant type. It may, however, be extremely important in some clinical populations, especially in situations where it is not yet known what deviation magnitudes would be most informative, or if one wishes to show that the discrimination is selectively affected for some deviation magnitudes. For example, individuals with severe problems in speech comprehension or a high degree of auditory processing deficiencies, such as individuals using cochlear implants, may not be able to discriminate small sound-changes. In theses cases the larger deviation magnitudes would bring most information about the change-detection and memory-related processes. In contrast, when studying expertise related to sounds, for example in musicians or in Morse-code experts, the differences between the experts and novices are more likely to be found with the small deviations as compared with the intermediate and large deviations. Indeed, it has already been shown that, for instance, in dyslexia the auditory discrimination may be selectively impaired for minor frequency changes, with the processing of larger frequency as well as all magnitudes of duration changes being intact (Baldeweg *et al.*, 1999). In these specific occasions, several magnitudes of sound changes are likely to be beneficial for the study. In general, however, only one range of deviation magnitudes (small, intermediate or large, depending on the focus of the study) is typically sufficient.

The MMN reflects also phonological characteristics of the sound changes. In Study IV the MMNs were recorded for different types and magnitudes of changes in Finnish-language vowels. Importantly, the MMN amplitude for the vowel-duration changes reflected both the physical, i.e., acoustic difference between the sound deviations and the categorization of the phoneme durations to short and long categories of /i:/. This is a highly relevant contrast in Finnish, a quantity language in which variations in the duration of, e.g., phoneme /i/ are interpreted as two categories, short /i/ and long /i:/, giving rise to semantic differentiation in words (e.g. the written word 'tuli', pronounced as [tuli] stands for 'fire', whereas the written word 'tuuli', pronounced as [tu:li] stands for 'wind') . That the MMN was elicited at all for all these changes, also to that within the phoneme category (the change from the standard tone categorized as long /i:/ to the deviant categorized as long /i:/) reflected the processing of acoustical differences within these vowels. The phonological processing of these vowels was seen in that the MMN amplitude for the two largest vowel-duration changes, i.e., to the 70-ms and 100-ms deviants which are interpreted to belong to the same phoneme category and are perceived by a Finnish listener as short /i/ did not differ from each other, even though they vary in their acoustical deviance from the standard /i:/. Moreover, these MMNs differed from those to the small 135-ms vowel-duration deviant, which is perceived as long /i:/ in Finnish language. Thus, the MMN responses were more similar for the within-category, than for the between-category changes, indicating the pre-attentive categorization of speech sounds according to their duration (Näätänen ym., 1997; Shestakova ym., 2002; Nenonen *et al.*, 2003).

Further, the MMN amplitude for the vowel changes from standard /i:/ to a rather close vowel /e:/, slightly further /y:/, and the clearly furthest /a:/ on the phoneme map were expected to directly reflect the distance between these different phoneme categories on the phoneme map. Indeed, there was a significant trend towards increasing MMN amplitude with increasing phonemic deviance, although in the pairwise comparisons only the MMN to the smallest deviant /e:/ differed from the MMN amplitude to the vowels /y:/ and /a:/. The effect of the distances on the phoneme map on the MMN amplitude may have been weakened by the fact that all phoneme changes were changes from one phoneme category to another phoneme category - none of the phonemes used in this experiment were on the borders or outside of phoneme categories. Thus, long-term memory traces for the standard and deviant phonemes were activated by each presentation.

The processing of different auditory attributes as indicated by the MMN. In all studies, the MMN responses for different deviation types were compared with each other. In studies I-IV the interpretation of these comparisons was limited by the fact that the magnitudes of sound changes were not matched between the deviation types. Thus, the MMN for some sound feature may have differed from that to another sound feature merely because the changes were of different perceptual magnitude. However, for Study V, pilot experiments were conducted in order to perceptually match the magnitudes of the different types of sound changes. Despite this matching, the MMN mean amplitudes as well as peak latencies considerably varied between the different deviants: the MMNs were largest for the duration and density changes, and smallest for the intensity changes. This result was not unexpected, as corresponding results have been previously obtained despite carefully matching the dimensions even for individual subjects (e.g., Deouell and Bentin, 1998).

The differences in the MMN amplitudes for the different deviation types can be mainly attributed to the actual strengths of the MMN generator processes that depend on the deviation magnitudes, and to the differences in their loci and orientations. The orientations of the MMN sources differ depending on the deviation type (Giard *et al.*, 1990), leading to different amplitudes and distributions over the scalp and explaining why the MMN amplitude may differ between the different deviation types even if the magnitudes of these sound changes were perceptually similar.

It was also thought that the amplitude variation may result from differences in the independency between the deviant types. For instance, the perception of sound intensity is strongly connected with the perception of sound duration: short sounds (< 200 ms) appear to have lower intensity than they actually have. These types of co-dependencies of the deviation types may play a role in the response strengths. Following this logic, the small MMN amplitude for the intensity changes in Study V was suggested as resulting from the residual intensity variation in the stimulus sequence (despite normalizing the intensities of the sounds and adjusting them by ear). However, this hypothesis should be appropriately tested by comparing the intensity MMNs recorded in the multi-feature paradigm to those recorded with the oddball paradigm lacking the residual variation.

The MMN predicts behavioral discrimination accuracy. In Studies II and III also the participant's perception of the sound-changes was examined and compared with the MMN responses to the same sounds. In Study II the MMN amplitude predicted both the detection speed and accuracy for the sound changes. The participant's task was to detect one type of sound changes at a time within the multi-feature stimulus sequence. The MMN amplitude (recorded in passive condition) increased with increasing stimulus deviance as did the participants' detection accuracy and speed. This is in line with previous studies showing that the MMN amplitude is directly related to the behavioural discrimination accuracy (Näätänen *et al.*, 1993; Amenedo and Escera, 2000; Tervaniemi *et al.*, 2001; Kujala *et al.*, 2001). Only the location changes made an exception: the detection accuracy for location changes improved with the deviation magnitude, but the speed of detection did not. This may have resulted from the fact that the two smallest location changes were only rarely (<20 %) detected, and therefore the average reaction time to those was based on only a few observations, thus being less accurate. Though the MMN amplitude predicted the behavioral performance very well, the predictive power of the MMN latency was poorer. The MMN latency predicted detection accuracy only for frequency and location changes and the detection speed only for frequency changes.

In Study III, the subjects' task was to decide whether the probe syllable (either a standard or a deviant) was the same as or different than the standard syllable. The MMN amplitude was the smallest, or even non-significant for the consonant change and in line with this the behavioral discrimination test showed that the consonant change was more difficult to discriminate as compared with the other sound changes. The consonant change from /t/ to /p/ and vice versa is perhaps the most challenging one in Finnish since the Finnish clusile consonants are very weak and the acoustic difference is very small. Moreover, the MMN amplitude was largest for the vowel-change MMN as compared with the MMNs for the other sound changes, and the vowel change was also most accurately discriminated in the discrimination task. These results are consistent with previous findings (cf. Tiitinen *et al.*, 1994; Jaramillo *et al.*, 2000; Pakarinen *et al.*, 2007) showing that the MMN response (especially the MMN amplitude) reflects the degree of perceived sound change magnitude. However, only the MMN latency for the intensity deviations correlated with the percent of correct responses and misses for the same deviations, with the other correlations being non-significant. This was probably due to lack of statistical power, which resulted from the low variation (low task difficulty) and the relatively small sample size (considerably larger samples are generally used for correlation studies).

5.2 Theoretical implications: How are the regularities of the auditory environment represented in sensory memory?

While the main focus of the Doctoral Thesis was in developing the recording paradigms, important insights on the extraction of auditory regularities and how they are represented in the sensory memory were also obtained in the studies.

Auditory regularities are represented at the feature level. The fact that the MMNs are reliably recorded with the multi-feature paradigm further strengthen the view that the auditory attributes are independently stored and processed (Nousak *et al.*, 1996). The fact that the MMNs in the multi-feature paradigm were comparable to those of the oddball suggest that the variation in the other sound attributes (such as intensity) does not affect the processing of another attribute (e.g., pitch) in situations in which these properties are unrelated to each other. Even stronger evidence for this view came from Study V in which the MMN responses were successfully recorded without the standard tone actually ever being presented in the stimulus sequence. In this paradigm, the tones themselves could not be classified as standards or deviants in the traditional sense, as they all differed from each other, and were equiprobable. The different sound features, however, could be classified as common and rare, as their probabilities varied in the sequence. For instance, the frequency of the tones was identical in 87.5 % of the trials, and either higher or lower in the remaining 12.5 %. The elicitation of the MMN to frequency change under such conditions indicates that an accurate memory trace was constructed for the invariant (standard) features of the auditory input.

This was further supported by the comparison between the MMN amplitudes in the oddball, conventional multi-feature and multi-feature without standard tone paradigms. The MMN mean amplitudes were slightly smaller in the no-standard paradigm as compared with those recorded with the conventional multi-feature paradigm. Those (frequency and density) MMNs that were recorded with the oddball paradigm were intermediate in amplitude and did not differ significantly from those recorded with either one of the other paradigms. These amplitude differences, though subtle, may reflect differences in the strengths of the standard-stimulus memory traces between the three paradigms, as the memory-trace strength is assumed to increase with the number of repetitions of the standard or the standard features (Cowan *et al.*, 1993; Sams *et al.*, 1983, 1984). There were on average seven standard-feature repetitions before each deviation in the no-standard paradigm, nine in the oddball paradigm, and 15 in the conventional multi-feature paradigm as opposed to 0, 8 and 1 standard tone repetitions in these paradigms, respectively. Thus, the MMN amplitudes may increase with an increased number of standard feature repetitions, rather than that of standard tone repetitions.

Indeed, it is unclear whether in this case, the separate features of the standard sound (imaginary in the paradigm without standard, actual in the other paradigms) were ever integrated into a coherent percept. It should be noted, however, that with a converse design to this one, where the deviants and standards were not classifiable on the basis of any one sound feature but instead always required a combination of three features (Ruusuvirta and Huotilainen, 2004) the integration of the sound features occurs during (or before) the memory-trace-formation process (Ruusuvirta and Huotilainen, 2004), as suggested by Näätänen and colleagues (Näätänen and Winkler,1999; Näätänen *et al.*, 2011). Further, this integration has been shown to occur even in sleeping newborns (Ruusuvirta *et al.*, 2004), suggesting that it is a fundamental, stimulus-driven property of central auditory processing. On the other hand, the fact that the MMN can be recorded with the multi-feature paradigm already from birth (Sambeth *et al.*, 2009) suggests also that the feature-level analysis would be stimulus-driven and fundamental property of auditory processing. It appears, that the sensory information is intelligently organized already at the very early cortical levels of auditory (and likely also the sensory information at other modalities) information processing (for a review, see Näätänen *et al.*, 2010).

The extraction of auditory regularities may be probabilistic instead of sequential. Omitting the standard tones from the multi-feature sequence in study V resulted also in another fundamental difference between the no-standard multi-feature paradigm and the conventional multi-feature and oddball paradigms. In the no-standard paradigm, the successive deviants differ from each other in two sound features at a time, e.g., a duration deviant differs from the preceding frequency deviant not only in duration, but also in frequency, whereas in the conventional multi-feature and oddball paradigms, the successive sounds always differ from each other in one respect only. However, the difference signals of the MMNs recorded with the two multi-feature paradigms are strikingly similar in form; for instance, the MMNs to duration changes show a much sharper peak than those for the noise level, for which the signal is more widely distributed in time. Thus, it appears that, at least in the multi-feature type of stimulation, the sequential information (which stimulus precedes which) is not of major importance, but it is the overall distribution of sound features in time that matters.

The MMN does not result merely from differences in neuronal refractoriness. The effects of neural refractoriness, and specifically the differences in the refractoriness between the neurons responding to the standards and the deviants, have been offered as an explanation for the neural basis of the MMN responses (e.g., May and Tiitinen, 2010). However, Study V showed that this hypothesis is not tenable as differences in neuronal refractoriness cannot alone account for the amplitude differences between the oddball, the conventional multi-feature, and the no-standard multi-feature paradigms. It is important to note that the differences between the two multi-feature paradigms are solely attributable to the deviant stimulus responses, as exactly the same standard response was subtracted from those to the deviants. The neurons responsive to the deviants in the conventional multi-feature paradigm may have been slightly less refractory, as these deviants occur twice as rarely as compared with those in the no-standard paradigm. However, the neurons responsive to the standard in the oddball paradigm should exhibit the most refractoriness, as they were repeated the most frequently. Notably, the neurons responsive to the deviants in the oddball paradigm should be the least refractory, and thus subtracting the response to the standard in the oddball paradigm from the deviant in the very same paradigm should have lead to the largest (or most exaggerated) MMN response. The result, however, was that the MMN amplitude was smallest in the no-standard paradigm, the largest in the conventional multi-feature paradigm, and intermediate in the oddball paradigm.

5.3 The reliability of MMN recordings

In this Thesis, the reliability of the MMN recordings was also assessed. Study III showed that at the group level the MMN amplitude and latency are well replicated over successive repeated recording sessions. The MMN multi-feature recording with five different deviants and the oddball recording for the vowel change were recorded twice on the same subjects, on separate days. MMN peak amplitude recorded in the multi-feature paradigm was slightly smaller in the second than in the first recording. This was mainly due to the consonant change eliciting a significant MMN response in the first recording session only. In the peak latencies, there were no differences between the two multi-feature recording sessions. Moreover, when the MMN for the vowel change, which was recorded twice both with the multi-feature and with the oddball paradigm, was examined, no differences were found between the paradigms or the recording sessions. The reliability of the recordings is very important as it is one of the key factors determining the value of the MMN measures in clinical settings.

5.4 Evaluation of multi-feature paradigms

Multi-feature MMN recordings are fast. The most obvious advantage of the multi-feature paradigm over the oddball and other paradigms is its efficiency. With the multi-feature paradigm one can record MMNs in considerably shorter time than with other recording paradigms. For instance, obtaining MMNs for five deviant types requires only 15 minutes with the multi-feature paradigm and 75 minutes with the oddball. The characteristic of the paradigm makes it highly practical in clinical settings, where time efficiency is of major importance. Short recording time is also practical when investigating subjects, such as small children, who can sit still for a limited time only. Shorter-duration recordings are also less prone to long-term habituation and amplitude fluctuation effects as compared with long continuous recordings. For instance, MMN for the speech sounds begins to fluctuate and increasingly attenuate as soon as after 15 min of continuous recording (McGee *et al.*, 2001).

Auditory discrimination profiles – a comprehensive view of discrimination ability. The efficiency of the paradigm also allows one to collect more information and examine the auditory discrimination parametrically for several deviant types and deviation magnitudes. For instance, by recording the MMN responses to five types and three magnitudes of deviations in speech and non-speech contexts one could in just slightly over an hour's recording time obtain a very extensive profile of central auditory processing. This is important in many clinical studies, as it is known that the processing of auditory information may be selectively affected for only some auditory attributes or even at some difficulty levels. For instance, in children with dysphasia, the MMN amplitude for frequency change can be more attenuated than that to duration (Korpilahti and Lang, 1994). Moreover, in adult dyslexics the MMN amplitude has been found attenuated only for smaller frequency changes, with the duration processing being intact (Baldeweg *et al.*, 1999). Further, it has been suggested (Kujala and Näätänen, 2001) that dyslexic individuals have difficulties in processing small acoustic differences, and that this could be the cause of their problems in phonological processing.

Multi-feature sequence improves the ecological validity of the recordings. The constant repetition of the standard in an oddball paradigm is far from real life listening situations. The multi-feature sequences include substantial amount of acoustic variation and thus come closer to the natural variation in our auditory environment. Especially in speech, there are rare occasions when a phoneme or a syllable would be repeated more than twice in succession as is done in the oddball paradigm. Subjects often report a loss of "speechness" of the standard vowel or syllable in oddball paradigms, i.e., even though a speech stimulus were perceived as natural in a prior listening session, the repetition of it for dozens of times makes the stimulus sound unnatural. In the multi-feature paradigm, such effects are less obvious.

Multi-feature paradigms may be particularly efficient in the detection of abnormal processing. There is also some evidence that the responses recorded with more challenging paradigms, as compared with the traditional oddball paradigm, may more appropriately characterize the processes underlying subtle cognitive impairments (see, for instance, Baldeweg *et al.*, 2004; Kujala *et al.*, 2006; Thönnessen *et al.*, 2008). More static ERP measures, in turn, may be more appropriate for the most severe impairments. For instance, Thönnessen *et al.* (2008) compared the MMN responses recorded with the multi-feature paradigm and the oddball paradigm both with the EEG and MEG. They showed that the multi-feature paradigm was faster than the oddball in detecting the MMN, and that the MMN was the most reduced in schizophrenia when measured with the MEG in the multi-feature paradigm, concluding that multi-feature paradigms improve sensitivity and speed for the detection of MMN as a schizophrenia endophenotype.

Multi-feature paradigms are successfully applied in basic as well as clinical research. Until recently, the studies comparing the processing of different auditory attributes at different difficulty levels have been quite rare because of their long recording time. However, the development of multi-feature paradigms has now changed the situation. In fact, the multi-feature paradigms with tones have already been successfully applied in healthy children (Lovio *et al.*, 2009) and newborns (Sambeth *et al.*, 2009) as well as in several other studies including schizophrenia (Fisher *et al.*, 2008; Thönnessen *et al.*, 2008), epilepsy (Korostenskaja *et al.*, 2010), post-traumatic stress disorder (Menning *et al.*, 2008), adults with dyslexia (Kujala *et al.*, 2006) and Asperger syndrome (Kujala *et al.*, 2007), and effects of mobile phone electromagnetic fields on the adult and child central auditory processes (Kwon *et al.*, 2009; 2010).

Also the multi-feature paradigm with consonant-vowel syllables (Study III; Pakarinen *et al.*, 2009) has been applied to clinical studies with children at risk for dyslexia (Lovio et el., 2010) and those with Asperger syndrome (Kujala *et al.*, 2010). In addition, a multi-feature MMN paradigm with pseudowords has been developed for studying auditory perception of emotions, prosody (Thönnesen *et al.*, 2010) and a multi-feature paradigm with words (Shtyrov *et al.*, 2010) has been developed to study word encoding and perception, for instance word-frequency effect. Furthermore, a multi-feature paradigm with clarinet (Sandmann *et al.*, 2010) and piano (Torppa *et al.*, in preparation) sounds has been used to study music perception of cochlear implant users.

Future development of the multi-feature paradigms. The recording efficiency could be further developed by combining the multi-feature and the no-standard multi-feature paradigm. Study V showed that the MMNs can be recorded even without the standard stimulus as long as there is a sufficient number of independent deviations. However, in order to obtain a difference signal (response to deviant minus response to standard), one also needs to record the standard response. In Study V, the same standard response from the conventional multi-feature paradigm with standard stimulus was employed for both multi-feature paradigms (conventional and no-standard). However, the standard could also be easily presented within the stimulus stream, equiprobably with each of the deviants. For instance, there could be eight different deviations and the standard, each appearing with a probability of approximately 11 %. This arrangement would decrease the recording time as compared with presenting the standard as every other tone, with a probability of 50 %.

An additional advantage in this arrangement with equiprobable standards and deviants would be in that the possible differences in refractoriness or in signal-to-noise ratios between the standard and the deviants would be entirely avoided.

6. Conclusions

The new multi-feature mismatch negativity (MMN) paradigms introduced in this Doctoral Thesis allow one to reliably record several MMN responses in a short recording time. For instance, recording of five MMNs with the multi-feature paradigm requires only 15 minutes, while the same recordings require as much as 75 minutes with the oddball paradigm. Notably, the MMN responses recorded with the multi-feature paradigm are comparable with those recorded with the conventional oddball paradigm. It was further shown that the reliability of the MMN responses is high, the responses replicating in repeated recording sessions as well with the multi-feature as with the oddball paradigm.

In addition, the MMN can be recorded even without the standard stimulus, indicating that an accurate memory trace for the auditory regularities can be constructed even for the invariant features of the auditory input and not on the stimulus level only. It was further shown that at least in the multi-feature type of stimulation, the auditory regularities are represented as overall probabilities instead of as sequential rules. For instance, obtaining a profile for small, intermediate and large vowel, pitch, intensity, and vowel-duration changes requires a recording time of only 34 minutes (Study V). Together with a 30-minute non-speech multi-feature paradigm with three magnitudes of deviations for pitch, intensity, duration, and location changes (Study II) one could in just slightly over an hour's recording time obtain a very extensive profile of central auditory processing of both speech and non-speech sounds. These paradigms introduced here could provide new insights in evaluating whether the underlying problems, for instance in language disorders, are specific to language content or more general in nature. One could also use these paradigms to follow the development of phoneme categories during the native or second language learning and simultaneously determine whether these changes in speech processing are also generalized to the processing of non-speech sounds. Moreover, the 15-minute recording time is also feasible in clinical settings, and offers a good starting point for the development of MMN-applications for clinical use.

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8. Original publications