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# Middle latency response correlates of single and double deviant stimuli in a multi-feature paradigm

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HIGHLIGHTS

- Double deviance-related middle latency response (MLR) modulations recorded with the time-saving optimum-2 multi-feature paradigm.
- MLR enhancements elicited by frequency–intensity double deviants equal the sum of the amplitude differences elicited by frequency and intensity single deviants.
- Double deviant mismatch negativity (MMN) is unaffected by multiple deviant types, but P3a gets smaller.

ABSTRACT

*Objective:* This study aimed to test single and double deviance-related modulations of the middle latency response (MLR) and the applicability of the optimum-2 multi-feature paradigm.
*Methods:* The MLR and the MMN to frequency, intensity and double-feature deviants of an optimum-2 multi-feature paradigm and the MMN to double-feature deviants of an oddball paradigm were recorded in young adults.
*Results:* Double deviants elicited significant enhancements of the Nb and Pb MLR waves compared with the waves elicited by standard stimuli. These enhancements equalled approximately the sum of the numerical amplitude differences elicited by the single deviants. In contrast, the MMN to double deviants did not show such additivity. MMNs elicited by double deviants of the multi-feature and the oddball paradigm showed no significant difference in amplitude or latency.
*Conclusions:* The optimum-2 multi-feature paradigm is suitable for recording double deviance-related modulations of the MLR. Interspersed intensity and frequency deviants in the standard trace of the optimum-2 condition multi-feature paradigm did not weaken the double MMN.
*Significance:* The optimum-2 multi-feature paradigm could be especially beneficial for clinical studies on early deviance-related modulations in the MLR, due to its optimized utilization of the recording time.


## 1. Introduction

The detection of changes from the recent auditory past operates on an automatic basis and is an ubiquitous property of the auditory system (Grimm and Escera, 2012; Escera and Malmierca, 2014; Malmierca et al., 2014; Nelken, 2014). It can trigger an involuntary attention switch (Escera et al., 1998; Escera and Corral, 2007), which is essential for an adequate reaction to novel sounds in everyday life and particularly in dangerous situations. The most prominent human auditory evoked potential (AEP) reflecting the detection of an auditory deviation is the mismatch negativity (MMN) – a negative deflection of the AEP with its maximum over fronto-central scalp areas between 100 and 250 ms after stimulus onset (Näätänen et al., 1978; for reviews see Näätänen et al., 2007, 2014; Garrido et al., 2009). The MMN has held promises as an

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objective tool for the evaluation of automatic central sound discrimination in a range of neurologic, psychiatric and neurodevelopmental conditions (Näätänen and Escera, 2000; Näätänen et al., 2011, 2012), and in recent developments the protocols to obtain the MMN to multiple auditory contrasts simultaneously were optimized (i.e., the so-called multi-feature paradigm; Näätänen et al., 2004; Pakarinen et al., 2007, 2009). Yet, the MMN is no longer considered to be the single and earliest correlate of auditory deviance detection in humans, since a range of recent studies have shown that, in addition to and preceding MMN, auditory deviations from a regular sound pattern can be reflected by modulations of the middle latency response (MLR) of the AEP at latencies from 20–50 ms after stimulus onset (Althen et al., 2011; Grimm et al., 2011, 2012; Grimm and Escera, 2012; Escera and Malmierca, 2014).

The latencies of these deviance-related modulations are similar to the response latencies of the "novelty neurons" found in animal auditory midbrain and cortex (e.g. Ulanovsky et al., 2003; Pérez-González et al., 2005; Antunes et al., 2010), which show stimulus-specific adaptation to standard sounds and restored or enhanced responses to deviant sounds (for reviews see Nelken and Ulanovsky, 2007; Escera and Malmierca, 2014). Therefore the MLR of the human AEP is an interesting tool for exploring the mechanisms underlying auditory deviance detection and in particular to clarify further the linkage between the early traces at cellular level and the MMN, which reflects later processes. Moreover, in order to understand fetal and neonatal MMN, the role of lower auditory tract structures should be considered, due to the cortical immaturity at fetal and neonatal periods. Moreover, peripheral structures and functions mature earlier than more central structures and functions (Moore and Linthicum, 2007). Yet, obtaining deviant-related correlates in the MLR latency range is a very demanding and challenging approach, as the number of trials necessary to obtain a good signal-to-noise ratio in the average responses is at least five times as large as for recording the MMN, due to the very small amplitude of the MLR (<1 μV). Especially in clinical and infant studies long recording times pose a problem because they can lead to excessive movement artefacts. Therefore, improvement in the protocol to obtain MLR correlates of deviance detection is a necessity.

In the present study, we had two main research goals. First, we aimed at testing the applicability of the optimum-2 condition of the multi-feature paradigm in studies on deviance-related modulations of the MLR. To overcome the problem of excessive recording time in MMN studies, Näätänen and colleagues developed the multi-feature paradigm (Näätänen et al., 2004). It allows testing at the same time up to five types of deviant stimuli, differing from the standard stimuli in different auditory features, or to different degrees in the same auditory feature. In the optimum-1 condition of the multi-feature paradigm, standard and deviant stimuli are presented alternately. The comparatively small number of standard stimuli is compensated by the fact that the standard trace is also strengthened by the non-deviating features of the deviant stimuli. Comparisons of MMNs measured in a multi-feature paradigm and in a classical oddball paradigm, where only one type of deviant is presented, suggest that the MMNs elicited in the two different paradigms are similar (Näätänen et al., 2004; Grimm et al., 2008; Lovio et al., 2009; Pakarinen et al., 2009). The multi-feature paradigm is frequently applied in non-clinical studies (e.g. Pakarinen et al., 2007, 2013; Mittag et al., 2011) as well as in clinical studies (e.g. Korostenskaja et al., 2010; Fisher et al., 2012; Torppa et al., 2012) and there is evidence that the multi-feature paradigm is even more sensitive to impaired deviance-detection than the oddball paradigm, for example, in individuals with dyslexia (Kujala et al., 2006). Leung and colleagues, 2012 applied the optimum-1 condition of the multi-feature paradigm with four deviant types (frequency, duration, intensity, and interaural time difference) for measuring deviance-related MLR modulations. Positive results were obtained only for the frequency domain. Possibly the standard trace was not formed firmly enough to allow detection of the other deviant types. To overcome this limitation, in the present study we tested the applicability of the optimum-2 condition of the multi-feature paradigm, where only every fourth stimulus is a deviant (see Näätänen et al., 2004; Jankowiak and Berti, 2007).

The second objective of this study was to compare deviance-related modulations of the MLR elicited by double and single deviants. While MMN to double deviants has been explored (e.g. Levänen et al., 1993), to the author's knowledge, it has not been investigated yet how the MLR reacts to sound stimuli, which deviate in two auditory features from the standard trace. Intensity and frequency were chosen as deviant features in this study, since it had already been shown that intensity deviants elicit an enhancement of the MLR at the transition from the Na to the Pa component (Althen et al., 2011) and that pure tone frequency deviants elicit a negativity at the Nb component (Grimm et al., 2011; Alho et al., 2012; Leung et al., 2012). Since, to our knowledge, there is no study exploring whether MMN elicited by double deviants presented in a multi-feature paradigm and MMN elicited by double deviants presented in an oddball paradigm are similar, we included a short oddball paradigm into the present study, to shed light on this question.

## 2. Materials and methods

### 2.1. Participants

Twenty-two young adults took part in the experiment for compensation with movie tickets or culture vouchers. None of them reported any neurological or psychiatric disorder or any treatment with psychotropic drugs. By means of an audiometry the hearing of the participants was assessed in the frequency range 125 Hz to 8 kHz (11 test frequencies). All participants included into the final data analysis had normal hearing, i.e. equal to or below 20 dB SPL, in the frequency range of the stimuli used in the experiment (880 Hz and 1240 Hz). Moreover, they showed a normal threshold in the whole frequency range tested, except for one participant, who had a hearing threshold of 10 dB above normal for 6 kHz and of 15 dB above normal for 8 kHz. Participants gave written informed consent before the experiment. Ethical permission for the present study was granted by the Ethical Board of the Institute of Behavioural Sciences at University of Helsinki, and the experimental protocol was in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

### 2.2. Experimental design

Participants were sitting comfortably in an electrically shielded and sound-attenuated room. They were asked to relax, to concentrate on a silent movie with subtitles and to ignore the sounds. Pure tones of 50 ms duration with a rise/fall time of 5 ms were presented binaurally through headphones with an onset-to-onset interval of 400 ms. Sound presentation was controlled using the software Presentation® (Neurobehavioral Systems, Albany, CA, USA). Stimuli were presented in six different auditory sequences – a variation of the optimum-2 condition of the multi-feature paradigm with three deviant types (frequency, intensity and frequency–intensity double deviants), three reversed multi-feature paradigms (one for each deviant type), an oddball paradigm with frequency–intensity double deviants and a reversed oddball paradigm.