Do tone duration changes that elicit the mismatch negativity also affect the preceding middle latency responses?

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学 位 論 文

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（ミスマッチ陰性電位を誘発する持続長変化音は、
先行する中間潜時反応に影響を与えるか？）

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論　文　内　容　要　旨（和文）

学位論文題名	Do tone duration changes that elicit the mismatch negativity also affect the preceding middle latency responses? （ミスマッチ陰性電位を誘発する持続長変化音は、先行する中間潜時反応に影響を与えるか？）

　人間の脳は、本人が特に意識せずとも、周囲の音の変化を自動的に識別する能力を持っています。反復する音の中に、まれに別の音が混ざる一連の音を聞かせると、被験者が音に注意を払っていない状況であっても、珍しい音を聞かされてから 100~250 ミリ秒後にミスマッチ陰性電位(mismatch negativity, MMN)という事象関連電位が引き起こされることが報告されています。

　一方で近年、音を聞いてから 10~50 ミリ秒後、つまり MMN よりも早くに発生する中間潜時反応(middle latency response, MLR)もまた、音の変化に対する無意識的認知を反映する可能性が指摘されています。いくつかの研究において、音の定位変化や周波数の変化を含むオドボール課題に応じて、MLR の頂点振幅が変化することが報告されています。しかし MMN が音の定位・周波数・長さなど様々な種類の音の変化で引き起こされることが知られている一方、MLR に反映される音の変化の種類については十分に調べられておらず、特に音の長さの変化（持続長変化）については十分な研究がありませんでした。本研究では、MMN と精神疾患との関係で特に注目されている、持続長変化を含むオドボール課題が、MLR の頂点振幅を変化させるかどうかを調べることを目的としました。

　20 名の健常な日本人男性ボランティア（年齢：23.9±2.9）を対象として、長さ 10 ミリ秒の刺激音が繰り返される中に、まれに長さ 5 ミリ秒の短い音が混ざる一連の音（持続長変化オドボール課題）を聞かせました。それによって MMN が誘発されるかどうか、および MLR の頂点振幅が変化するかどうかを調べました。

　その結果、持続長変化オドボール課題によって明瞭な MMN が誘発されましたが、MLR の頂点振幅に統計的に有意な変化はみられませんでした。定位変化・周波数変化・持続長変化はいずれも MMN を誘発しますが、定位変化と周波数変化が MLR の頂点振幅を変化させるのと対照的に、持続長変化は MLR の頂点振幅を変化させませんでした。

Do tone duration changes that elicit the mismatch negativity also affect the preceding middle latency responses?

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Abstract

The human brain can automatically detect sound changes. Previous studies have reported that rare sounds presented within a sequence of repetitive sounds elicit the mismatch negativity (MMN) in the absence of attention in the latency range of 100–250 ms. On the other hand, a previous study discovered that occasional changes in sound location enhance the middle latency response (MLR) elicited in the latency range of 10–50 ms. Several studies have reported an increase in the amplitude of the MLR within the frame of oddball paradigms such as frequency and location changes. However, few studies have been conducted on paradigms employing a duration change. The purpose of the present study was to examine whether the peak amplitudes of the MLR components are enhanced by a change in duration. Twenty healthy Japanese men (age: 23.9 ± 2.9 y) participated in the present study. We used an oddball paradigm that contained standard stimuli with a duration of 10 ms and deviant stimuli with a duration of 5 ms. The peak amplitudes of the MLR for the deviant stimuli were then compared with those for the standard stimuli. No changes were observed in the peak amplitude of the MLR resulting from a duration change, whereas a definite MMN was elicited. The amplitude of the MLR was increased within the frame of oddball paradigms such as frequency and location changes. By contrast, the amplitude of the MLR was not changed within the duration-change oddball paradigm that elicited the MMN.

Abbreviations

MMN, mismatch negativity

ERP, event-related potential

MLR, middle latency response

EEG, electroencephalography

EOG, electrooculography

ANOVA, analysis of variance

1 | Introduction

The neural discriminative response, which is reflected by the mismatch negativity (MMN), has been used as a tool to study a variety of cognitive disorders in audition (Näätänen *et al.*, 2014). The MMN is elicited at a latency of about 100–250 ms (Näätänen, 1992) by various types of sound changes, such as frequency, intensity, spatial location, and especially, duration change.

Cognition is often affected by a variety of neuropsychiatric, neurological, and neurodevelopmental disorders. The neural discriminative response as reflected by the MMN has been used as a tool to study various neuropsychiatric disorders such as schizophrenia, bipolar disorder, and autism spectrum disorder (Näätänen *et al.*, 2014). In particular, the duration of the MMN may help in the diagnosis of schizophrenia. Bodatsch *et al.* showed that the duration of the MMN was significantly decreased in at-risk subjects converting to first-episode psychosis compared with nonconverters (Bodatsch *et al.*, 2011). Shaikh *et al.* showed that among those with an at-risk mental state, a reduction in MMN amplitude was associated with an increased likelihood of developing frank psychosis (Shaikh *et al.*, 2012).

The latency of the MMN is earlier than that of the attention-related event-related potential (ERP) components N2b and P3b; however, it is not the earliest stage of the neural discriminative response. The auditory middle-latency responses (MLRs) are auditory ERPs in the latency range of 10–50 ms. Several studies have reported that deviant sounds increase the peak amplitude of different MLR components within the frame of oddball paradigms (Escera *et al.*, 2014). In addition, the Na component of the MLR has been shown to be enhanced by a location change (Sonnadara *et al.*, 2006; Cornella *et al.*, 2012; Grimm *et al.*, 2012), and the Nb component by a frequency change (Grimm *et al.*, 2011; Alho *et al.*, 2012; Leung *et al.*, 2012).

However, to our knowledge, few attempts have been made to examine whether changes in tone duration affect MLRs. Leung *et al.* (Leung *et al.*, 2012) employed a multi-feature paradigm with four types of deviants: duration, frequency, intensity, and interaural time difference. Unexpectedly, they reported finding no differences resulting from a duration change between the responses to standards and deviants in any MLR components; however their method regarding the duration stimuli seemed to be inadequate. They employed 75 ms (including a 5-ms rise and a 10-ms fall time) as the standard stimulus and 25 ms (including a 5-ms rise and a 10-ms fall time) as the deviant stimulus. Individual peak latencies of the MLR were obtained from the largest peak in the time windows of 5–15 ms (P0), 20–30 ms (Na), 30–40 ms (Pa), and 38–48 ms (Nb). No differences in their stimuli should occur until 15 ms in latency from the sound onset. Thus, it is difficult to evaluate the P0 and Na components. Therefore, the purpose of the present study was to clarify whether the peak amplitude of the MLR is enhanced by duration change by employing a shorter duration change compared with that of Leung *et al.*

2 | Materials and methods

2.1 | Participants

Twenty healthy Japanese males (age: 23.9 ± 2.9 y) who provided written informed consent participated in the present study. None of the participants had any mental disorders or hearing impairments. Only male partici-

pants were selected so that a more homogenous population could be investigated.

2.2 | Stimuli and procedure

Auditory stimuli were presented with a constant stimulus onset asynchrony of 500 ms to both ears of the participants through earphones (YE-103J; Nihon Kohden, Tokyo, Japan). All the stimuli consisted of a sinusoidal tone of 1000 Hz and a sound pressure level (SPL) of 80 dB. The standard stimuli (10 ms in duration) were presented at a probability of 80%, while the deviant stimuli (5 ms in duration) were presented at a probability of 20% (Figure 1). Standard and deviant stimuli were presented in the same block and randomized using computer software (Stim2; Compumedics/Neuroscan; El Paso, TX, USA). In total, 4000 standard and 1000 deviant stimuli were presented. On the other hand, the reversed-standard stimuli (5 ms in duration) and reversed-deviant stimuli (10 ms in duration) were presented at probabilities of 80% and 20%, respectively (Figure 1). In total, 1000 reversed-standard and 250 reversed-deviant stimuli were presented in the same way.

2.3 | Electroencephalography recording and data analyses

The participants were asked to sit on a chair in a shielded room and to concentrate on watching a self-selected silent video with subtitles during the measurements. Electroencephalography (EEG) data were recorded on 64 channels using sintered Ag/AgCl electrodes placed according to the 10/10 system. The tip of the nose was used as a system reference. The sampling rate was 2000 Hz. Electrode impedance was maintained below 10 kΩ. Vertical and horizontal electrooculography (EOG) data were recorded from an electrode placed 1.5 cm above the outer canthus of the right eye. EEG and EOG data were recorded using a 64-channel recorder (Vision Recorder; Brain Products GmbH; Gilching, Germany) for offline analyses using the Brain Vision Analyzer (Brain Products GmbH). Unstable segments in which the difference between the maximum and minimum value of each of the 64 channels was larger than 100 μV were excluded from the analysis.

2.4 | Analyses of the MLR

All data were band-pass filtered (15–200 Hz), re-referenced to linked mastoids, segmented from 50 to 250 ms post-stimulus, and baseline-corrected to the 50 ms pre-stimulus epoch. The linked mastoid was used as a reference. The peak amplitude of the MLR on Fz and Cz were calculated for each participant and condition. Individual peak latencies of the MLR were obtained from the largest peak in the time windows of 5–15 ms (P0), 20–30 ms (Na), 30–40 ms (Pa), 38–48 ms (Nb), and 48–68 ms (Pb) from the tone onset. A two-way repeated measures analysis of variance (ANOVA) was conducted to examine the effects of the channel (Fz, Cz) and condition (reversed-standard, deviant) for each component of the MLR. Greenhouse–Geisser corrections were made when appropriate. The statistical significance level was set at $p<0.05$. All statistical analyses were performed using SPSS Statistics 22 (IBM, Armonk, NY, USA).

2.5 | Analyses of the MMN

All data were band-pass filtered (0.5–30 Hz), referenced to the tip of the nose, segmented from 100 ms to 400 ms post-stimulus, and baseline-corrected to the

3

100 ms pre-stimulus epoch. To delineate the MMN at Fz, Cz, T5, and T6, ERPs elicited by the reversed-standard stimuli were subtracted from ERPs elicited by corresponding deviant stimuli. The MMN peak latency was defined as the latency measured from the end of the shorter stimuli, that is, from 5 ms after onset of the stimuli. The MMN shows the largest negative peak at Fz and Cz in the latency range of 90–250 ms. The MMN amplitudes were calculated as the mean voltage at the 40-ms period centered at the peak latency in the grand average waveform. One-tailed *t*-tests were conducted to determine whether the MMN mean amplitudes significantly differed from zero. Statistical analyses were performed using Microsoft Excel (Microsoft Co., Redmond, WA, USA).

3 | Results

3.1 | MLR data

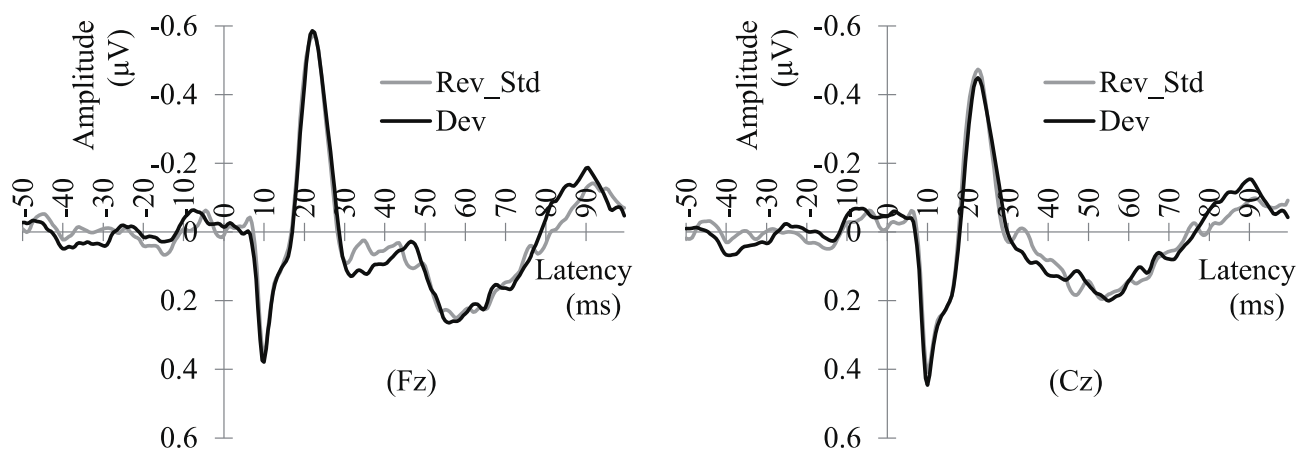The number of segments included in the analysis was 982.5 ± 48.0 for the reversed-standard and $986.6 \pm$ 24.9 for the deviant condition per each 1000 segments. Table 1 shows the peak amplitudes of the MLR. The results of two-way ANOVA were as follows. For P0, channel: $F_{(1,19)}=15.752$, $p=0.001$; condition: $F_{(1,19)}=0.375$, $p=0.548$; channel* condition: $F_{(1,19)}=0.398$, $p=0.536$. For Na, channel: $F_{(1,19)}=39.712$, $p<0.001$; condition: $F_{(1,19)}=0.480$, $p=0.497$; channel* condition: $F_{(1,19)}=3.946$, $p=0.062$. For Pa, channel: $F_{(1,19)}=2.601$, $p=0.123$; condition: $F_{(1,19)}=0.060$, $p=0.809$; channel* condition: $F_{(1,19)}=0.109$, $p=0.745$. For Nb, channel: $F_{(1,19)}=15.982$, $p=0.001$; condition: $F_{(1,19)}=0.189$, $p=0.669$; channel* condition: $F_{(1,19)}=0.417$, $p=0.526$. For Pb, channel: $F_{(1,19)}=15.982$, $p=0.001$; condition: $F_{(1,19)}=0.189$, $p=0.669$; channel* condition: $F_{(1,19)}=0.417$, $p=0.526$. No significant interaction was observed between the channel and the condition, nor any significant main effect of the condition. Figure 2 shows the grand average waveforms of the MLR elicited by reversed-standard and deviant stimuli at Fz and Cz, respectively.
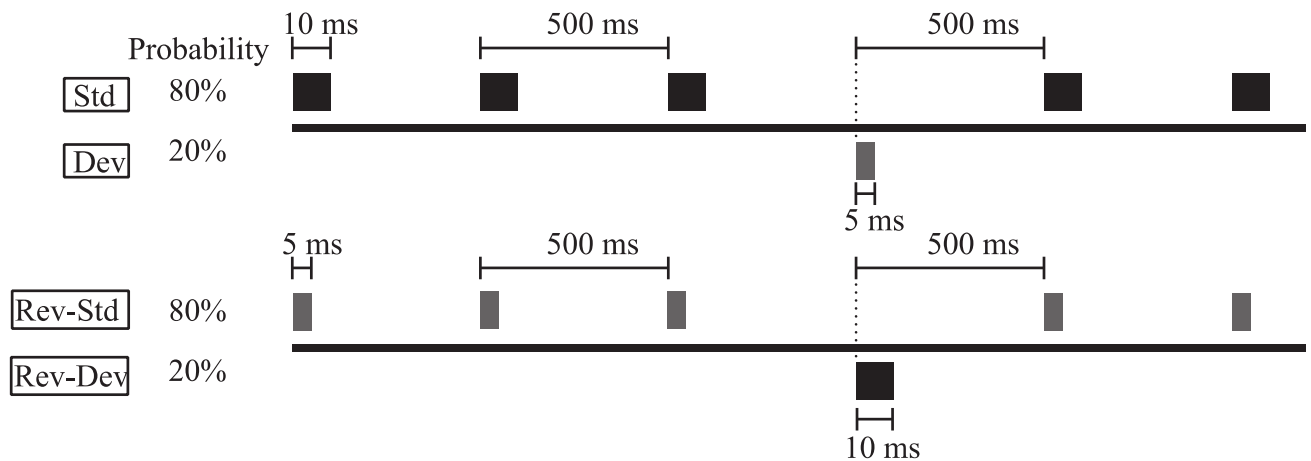
Figure 1. In total, 4000 standard stimuli (10 ms in duration at the probability of 80%) and 1000 deviant stimuli (5 ms in duration at the probability of 20%) were randomly presented. On the other hand, 1000 reversed-standard stimuli (5 ms in duration at the probability of 80%) and 250 reversed-deviant stimuli (10 ms in duration at the probability of 20%) were presented in the same way.

Table 1. Means of the peak amplitudes and standard deviations (in parentheses) of the MLR were calculated. No significant difference between the reversed-standard and deviant conditions was observed using the paired *t*-test.

Peak amplitude (µV)	P0	Na	Pa	Nb	Pb
[Fz]					
Reversed-standard	0.454	−0.671	0.248	−0.173	0.439
	(0.238)	(0.241)	(0.212)	(0.222)	(0.223)
Deviant	0.423	−0.636	0.237	−0.177	0.427
	(0.186)	(0.176)	(0.250)	(0.179)	(0.222)
[Cz]					
Reversed-standard	0.503	−0.569	0.204	−0.0890	0.395
	(0.247)	(0.194)	(0.151)	(0.191)	(0.193)
Deviant	0.492	−0.488	0.203	−0.0878	0.356
	(0.240)	(0.199)	(0.228)	(0.171)	(0.197)

Figure 2. Grand average MLRs in response to reversed-standards and deviants on Fz and Cz. No significant interaction was observed between the channel and the condition, nor any significant main effect of the condition.

Figure 3. The grand average MMN waveform was obtained by subtracting the reversed-standard from the deviant at Fz, Cz, T5, and T6. The MMN was elicited at a latency of 180 ms at Fz.
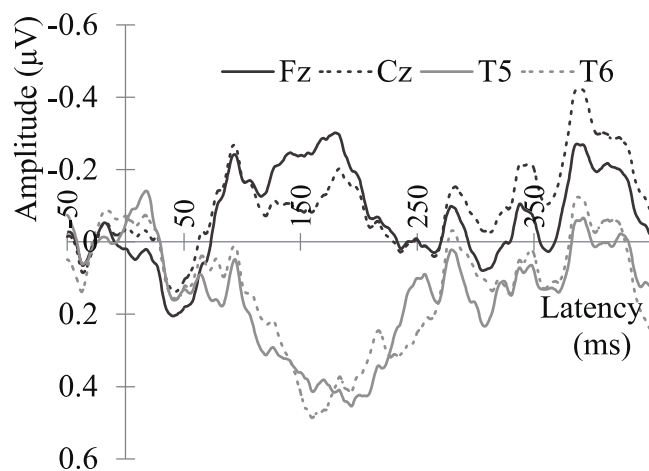
3.2 | MMN data

The number of segments included in the analysis was 784.0 ± 244.7 for the reversed-standard and 743.9 ± 276.9 for the deviant condition per each 1000 segments. The grand average ERPs are presented in Figure 3. A distinct negativity (identified as the MMN) peaking at about 180 ms was elicited. The peak latency at Fz was 180 ms. The mean amplitude at Fz was –0.258±0.0397 μV, which significantly differed from zero ($t(19)$=4.24, $p<0.001$). The mean amplitude at Cz was –0.154±0.0290 μV, which was lower than that at Fz.

4 | Discussion

Most researchers agree that the auditory MLR is generated from anatomical sites between the inferior colliculus and the auditory cortex, although some disagreement exists in regard to the specific sites (Musiek & Nagle, 2018). Kuriki et al. and Yvert et al. narrowed the location of the MLR down to Heschl's gyrus (Kuriki et al., 1995; Yvert et al., 2001; Musiek & Nagle, 2018). As with the MLR, a major MMN source is located in the auditory cortex (Alho, 1995; Giard et al., 1995).

Sonnadara et al. and Grimm et al. reported that the discrimination process of location change was reflected in the Na composition of the MLR in the latency range of 20–30 ms (Sonnadara et al., 2006; Cornella et al., 2012; Grimm et al., 2012). Grimm et al., Alho et al., and Leung et al. also reported that the process of frequency change is reflected in the Nb composition in the latency range of about 38–48 ms (Grimm et al., 2011; Alho et al., 2012; Leung et al., 2012). Thus, they found that the neural system in which the MLR was generated could discriminate the change in sound

stimuli for the first time, at least the location and frequency changes.

On the other hand, Leung et al. conducted experiments regarding the duration change (Leung et al., 2012). They used a stimulus sound longer than the beginning of the latency range of the P0 and Na components of the MLR. Thus, their study did not clarify whether the neural system of the MLR was able to discriminate the duration change for the P0 and Na components.

Many previous studies using a duration oddball task conducted experiments with stimulus sounds whose lengths were longer than the beginning of the latency range of the P0 or Na component, such as 25 or 50 ms (Paavilainen et al., 1991; Yabe et al., 1997; Joutsiniemi et al., 1998; Todd et al., 2008; Leung et al., 2012; Shaikh et al., 2012). To examine the earlier components of the MLR properly, we employed a shorter stimulus length of <5 ms, which is the beginning of the latency range of the P0 component.

The peak amplitude of the Na component tends to be enhanced by duration-deviation sounds (p=0.062). In this study, numerous MLR components and electrodes on the scalp were analyzed, which made the family-wise error rate difficult to control. In other words, we may have missed the MLR because we used very conservative multiple comparison correction. Improved statistical analysis methods (Guthrie & Buchwald, 1991; Oostenveld et al., 2011; Aghamolaei et al., 2016) could help control these errors more effectively.

We reanalyzed these data using the "statistical-graphical method" proposed by Guthrie and Buchwald (Guthrie & Buchwald, 1991). Figure 4 shows a series of p-values calculated using a paired t-test (y-axis on the left side) and differences in ampli-

tudes (y-axis on the right side): length of simulated time interval T = 150, autocorrelation $\phi = 0.9$ ($\phi = 0.88$ for Fz, $\phi = 0.90$ for Cz) and number of subjects N = 20. There were some consecutive values below the cutoff p-value of 0.05. If the number of consecutive points below the cutoff is greater than the number determined by the data length, number of subjects, and autocorrelation coefficient, it is determined that there is a statistically significant difference. The longest run of significant values was only 3 points for $\theta = 0.05$ and only 5 points for $\theta = 0.10$ (θ = graphical threshold). These were too short to show statistical significance.

Consequently, the neural mechanism of recognition as reflected by the MLR might not discriminate the duration change of the sound. However, regardless of simultaneous recording, the neural mechanism as reflected by the MMN clearly detected the duration change.

Giard *et al.* suggested that generators of the MMNs elicited by deviating sounds with either frequency, intensity, or duration change differ from each other (Giard *et al.*, 1995). Liegeois-Chauvel *et al.* reported that the distribution of the generators of each component of the MLR was different (Liegeois-Chauvel *et al.*, 1994; Musiek & Nagle, 2018). These differences may have caused the difference in the response of each component, that is, location-deviation sounds enhance the Na component, while frequency-deviation sounds enhance the Nb component, and duration-deviation sounds do not enhance any components.

We also carefully confirmed that the waveform we believe to be the MMN was indeed the MMN. The negativity in the latency range of 100–250 ms elicited by the stimuli was identified as the MMN, not N1 or
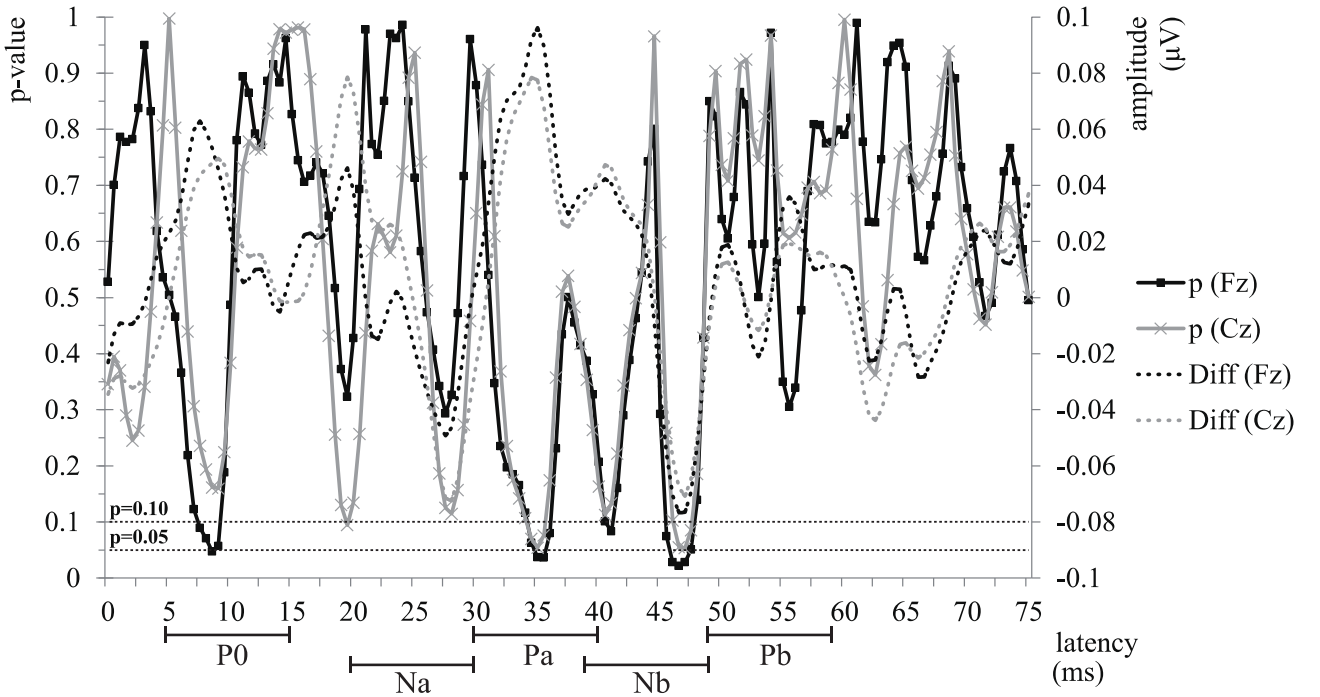
Figure 4. Series of p-values calculated using a paired *t*-test (y-axis on the left side) and differences in amplitudes (y-axis on the right side). There were some consecutive values below the cutoff p-value of 0.05. The longest run of significant values was only 3 points in the Nb range. These were too short to show a statistically significant difference between the standards and deviants.

N2b, because the scalp distribution of the negativity showed a frontal midline maximum and polarity reversal in the mastoid (Yabe *et al.*, 1997).

The peak latency of the MMN was 180 ms measured from the onset of sounds in the grand average waveform at Fz, in other words, 175 ms measured from the offset of the shorter sounds; this seems too late for a duration MMN. Regarding the latency of the MMN, Joutsiniemi *et al.* suggested that the length of the difference between standard and deviant stimuli did not change the latency of the duration MMN (Joutsiniemi *et al.*, 1998). Conversely, Näätänen showed that the latency of the MMN is early if the intensity of the deviant stimuli is far from that of the standard stimuli, and late if it is extremely close (Näätänen, 1992). Thus, a small deviation causes a delayed latency. Joutsiniemi *et al.* used standard stimuli with 75 ms and deviant stimuli with 50 ms or 25 ms, in other words, they used a larger deviation than did we in the present study. Therefore, we speculate that the latency in this study might have been delayed because of the extremely small difference between the standard and deviant stimuli we used.

N2b, one of the attentional ERP components, had a latency range similar to that of the MMN. Therefore, it is necessary to distinguish the MMN from N2b. Each obtained waveform was identified as the MMN because its scalp distributions showed a front-central maximum and polarity inversion at the opposite side across the Sylvian fissure, such as T5 or T6 (Paavilainen *et al.*, 1991; Näätänen, 1992; Yabe *et al.*, 1997). In other words, this finding suggested that all participants automatically detected slight changes in the series of sounds.

We used deviant tones 5 ms in duration and standard tones 10 ms in duration, both of which were delivered at 80 dB SPL. The deviant stimulus tones sounded softer than the standard ones, which is known as loudness summation (Yabe *et al.*, 1997; Oceak *et al.*, 2006). It is considered that loudness summation should be caused by the temporal window of integration, as reflected by the study of the MMN. In other words, this study involves the physiological examination of the response due to loudness summation.

In contrast to the frequency and location changes, the duration change was not detected by the neural process related to the MLR. On the other hand, it was detected by the mechanism related to the MMN. These findings suggest that MMN-related processes can detect changes in location, frequency, and duration, whereas MLR-related processes can detect changes in only location and frequency.

Conflict of Interest

The author has no conflict of interests to declare.

Ethical approval

All procedures in the present study were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. The study

was approved by the Ethics Committee of Fukushima Medical University (Authorization No.: 2026).

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