平成24年度学位申請論文

複数の感覚モダリティー刺激による逸脱検出反応の修飾： 脳磁計による研究

（Modification of mismatch response by multimodal stimulation: A magneto-encephalographic study）

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1 Introduction

An event-related brain response, mismatch negativity (MMN), elicited by deviant stimuli during a sequential acoustic stimulation (Garrido et al., 2009; Hari et al., 1984; Näätänen et al., 1978, 1997, 2011). MMN is usually peaking at 150-250 ms from deviant stimuli onset. The MMN reflects the brain's ability to perform pre-attentive automatic comparisons between consecutive stimuli, and provides an electrophysiological index of sensory learning and perceptual accuracy (Garrido et al., 2009). MMN was obtained in the visual and somatosensory modality, as well as auditory modality, in the previous studies (Kekoni et al., 1997; Kimura et al., 2011; Pazo-Alvarez et al., 2003; Shinozaki et al., 1998). The mechanism of MMN production might involve a similar mechanism in each modality of stimulation.

Recent studies showed that cross-modal stimulation, which comprised simultaneously administrated auditory and visual stimuli, opens up certain possibilities to obtain information or understand the meaning of stimulation, e.g., facial movement and speech (Barkhuysen et al., 2010; Joassin et al., 2011). A series of studies allowed authors to conclude that such MMNs involve sensory integration of multimodal stimuli (Colin et al., 2002a, 2002b; Kislyuk et al., 2008). These studies employed audio-visual integration using a McGurk effect or ventriloquist illusions. It was reported that MMNs were produced by mismatch between auditory and visual stimuli, i.e., the McGurk effect, using deviant stimuli involved audio-visual incongruent stimuli (acoustic /pa/ with visual /ka/). Not only was an interaction caused by incongruence between audio and visual stimuli, but congruent audio-visual interaction also occurred in the superior temporal sulcus; the peak latency of MMN was 150-200 ms with respect to the stimulus (Möttönen et al., 2004). Similarly, audio and somatosensory integration regarding MMN was investigated (Pantev et al., 2009); there was enhancement of MMN in the right hemisphere through multimodal training. These previous results suggested the possibility that multimodal stimulation affected the mismatch response, as Besle et al. (2009) reviewed, but the mechanisms of generating mismatch responses following multimodal stimulation are not clear.

Mismatch magnetic fields records using a magnetoencephalography (MEG) technique and indicates below as MMNm are the magnetic equivalents of MMN. MEG can record brain activities with high temporal resolution, and is available to analyze the generator localization with high reliability, since the skull having less of an effect on the magnetic fields than when electrical potentials are recorded by electroencephalography (EEG).

My study was aimed at clarifying the fundamental effect of cross-modal stimulation on MMNm using MEG technique. This study was consisted of two experiments; 1) Auditory mismatch responses modified by visual stimulation accompanying auditory stimulation, and 2) Effects of simultaneous stimulation of a different modality on auditory mismatch magnetic fields.

In experiment 1, I focused on simultaneousness to clarify the effect of bimodal stimulation on MMN, while in experiment 2, I investigated the difference of the effect on MMN among the combinations of modalities.

2 Methods

2.1 Subjects

Ten healthy right-handed volunteers (6 men and 4 women, mean age 29.5 ±7.2 years, range 24-48 years) participated in the study. None of them had a history of neurological or psychiatric problems, and no subjects had hearing and vision problems in their daily life. Corrected eyesight was more than 1.0. The subjects could discriminate standard and deviant auditory stimuli given using earphones. Written informed consent prior to the Experiment was obtained from all subjects. The study was approved by the Ethical Committee of the Nagoya University (No. 10-601, School of Health Sciences, Nagoya University, Japan).

2.2 Experiment 1

2.2.1 Object

Experiment 1 was aimed at clarifying the fundamental effect of visual stimulation accompanying auditory stimulation on the production of a mismatch response using the MEG technique. The objective of this study was to clarify whether or not the auditory mismatch response is affected by constant visual stimulation accompanying auditory stimulation. I used auditory stimulation with dissimilar frequencies of standard and deviant stimuli to evoke MMNm and added different modes of visual stimulation to both standard and deviant auditory stimuli. My hypothesis was that an additional modality of stimulation with sequential auditory stimulation might change the feature of deviant stimulation, resulting in modulation of the mismatch response. In experiment 1, I compared MMNms evoked by auditory stimulation with static visual stimulation and those evoked by auditory stimulation accompanied by synchronous or asynchronous visual stimulation.

2.2.2 Experimental and stimulus condition

Auditory evoked MMNms were recorded under conditions with and without visual stimuli. Three Experimental blocks were employed (Fig. 1):

1) Auditory stimulation consisting of standard and deviant stimuli with a static visual background, i.e., a static checkerboard pattern (A-0 condition).

2) Auditory stimulation consisting of standard and deviant stimuli with synchronously changing checkerboard patterns (AV-S condition).

3) Auditory stimulation consisting of standard and deviant stimuli with changing checkerboard patterns at a timing irrelevant to auditory stimuli (AV-R condition).

The auditory stimuli included two tones (standard and deviant ones). Deviant stimulation comprised 2,000 Hz pure tones (probability: 20%), and standard stimulation comprised 1,000 Hz pure tones (probability: 80%). The duration of each tone was 500 msec, and interstimulus intervals (ISIs) were 500 msec long. The stimuli were produced by Sound Forge 7.0 software (Sony, Japan) and presented to subjects by ear tips via plastic tubes. The stimulus intensity was 80 dB SPL for both types of stimuli.

Subjects were placed in a supine position in a magnetically shielded room. On a 30 × 25-cm square screen placed 45 cm in front of the subject, sentences to read and checkerboard stimulation were presented in the central and peripheral fields, respectively. In the central area, sentences of a story were presented on a 12 × 12-cm square area, and the subjects were instructed to read them, while avoiding head movements. Pattern-reversal black and white checkerboard patterns were presented in the peripheral field, outside the central area. The size of one checker was 0.5 cm^2 (0.74 deg). The timing of reversal of the checkerboard pattern was 1 sec^{-1} for the AV-S condition, in which the pattern was inversed at the onset of auditory stimulation. Under the AV-R condition, the timing of inversion of the checkerboard patterns was irrelevant to the auditory stimulation occurring at a randomized mode between 0.67 and 1.33 sec^{-1} (ISI: 0.75-1.5 sec). The checkerboard pattern was not changed under A-0 conditions. Visual stimuli were projected using crystal digital light projector, which was placed outside the magnetically shielded room.

2.3 Experiment 2

2.3.1 Object

In Experiment 2, I investigated a characteristic of MMNm using auditory stimulation accompanied with another modality of stimulation to clarify whether MMNm was differently affected by adding stimulation of another modality without a change in the physical amount of stimulation using MEG. The hypothesis was that adding a modality of stimulation to standard and deviant stimuli would change their feature of stimulation, and that MMNm could be affected by the modality of additional stimulation. In experiment 2, visual or somatosensory stimuli were added to each standard and deviant auditory stimulus simultaneously in the temporal course during MMNm recording. Thus, I investigate whether the generator localizations for MMNm could be modified by visual or somatosensory stimulation.

2.3.2 Experimental and stimulus condition

In experiment 2, auditory evoked MMNm were recorded with simultaneous visual or somatosensory stimuli. Three Experimental conditions were employed as follows:

1) Auditory stimulation with standard and deviant stimuli (A-0 condition)

with no additional synchronous stimulation, but a static visual stimulation.

2) Auditory standard and deviant stimuli with a synchronous pattern-reversal visual stimulus (A-V condition).

3) Auditory standard and deviant stimuli with a synchronous somatosensory stimulus (A-S condition).

The auditory stimuli included two tones (standard and deviant tones). The standard tone was a 1,000 Hz pure tone (probability: 80%), and the deviant tone was a 2,000 Hz pure tone (probability: 20%). The duration of each tone was 500 msec, and the inter-stimulus intervals (ISIs) were 500 msec. The tones were produced by software (Sound Forge 7.0, Sony Inc.), and presented to subjects by ear tips via plastic tubes. The stimulus intensity was 80 dB for both stimuli at the ear tips (SPL).

A rectangular screen with a width and height of 30 × 25 cm was placed 45 cm in front of the subject. Sentences to read and checkerboard stimulation were presented in the central and peripheral fields, respectively, on the screen. In the central area, within a 12 × 12-cm rectangular area, sentences of a story were presented, and the subjects were instructed to read them while avoiding head movement. Pattern-reversal black and white checkerboard patterns were presented in the peripheral field, outside the central area. The size of one rectangular was 0.5 cm^2 (0.74 deg). The timing of the reversal of the checkerboard pattern was 1 Hz for the A-V condition, in which the pattern was inversed at the onset of auditory stimulation. The checkerboard pattern was not changed under the A-0 condition. Visual stimuli were projected using a crystal digital light projector, which was placed outside the magnetically shielded room.

Somatosensory stimuli were presented to right median nerves via felt-tip surface electrodes. These stimuli were square-wave pulses (duration: 0.2 ms) generated by the somatosensory stimulator (SEM-4201, Nihon Kohden, Japan). The intensity of the stimulus was just above the motor threshold, which caused a slight twitch of the abductor pollicis brevis muscle. The onset of the electrical stimulation was the timing of the onset of auditory was stimulation. The somatosensory stimulation similarly was given with standard and deviant tone stimulation for the A-S condition.

2.4 MEG recording

Subjects were placed in a supine position in a magnetically shielded room. All subjects were instructed to avoid head movement and look at and read the sentences presented in the central area of the screen.

Magnetic fields were recorded with an MEG system (PQ1160C, Yokogawa, Japan), which consisted of 160 axial gradiometers. The spectral density of the intrinsic noise in each magnetic channel was less than 10 fT/0.5 Hz for frequencies below 100 Hz. Recordings were filtered with a bandpass filter of 0.1-100 Hz and digitized at a sampling rate of 2,000 sec^{-1}. The MEG signals were collected from 50 msec prior to the onset of the auditory stimulus to 500 msec afterward. The baseline was offset using signals from 50 msec before to the onset of the stimulus. Epochs with MEG signals over 3,000 fT were automatically rejected. In one block, 80 artifact-free epochs were collected and averaged for each standard and deviant stimulus. Therefore, approximately 400 standard and 80 deviant auditory stimuli were delivered during one block. Two blocks for three stimulus conditions were repeated in a random order for one subject in both experiments.

2.5 Data and statistical analyses

2.5.1 Experiment 1

To investigate the modification of MMNm by stimulus conditions, auditory-evoked magnetic fields produced 100 msec after stimulation (N1m, an equivalent of an N1 ERP component) and MMNms were analyzed

(Jacobson, 1994). Thirty gradiometer channels were selected in each hemisphere, as shown in Fig. 2, to calculate N1m and MMNm responses. For the N1m amplitude, the root mean square (R.M.S.) of signals obtained from 30 channels at each sampling point was calculated. The N1m component was determined as a deflection at approximately 100 msec after the stimulus onset, and the peak latency and R.M.S. value at the peak were obtained for this component. MMNms have been determined as deflections obtained by subtracting the standard evoked waveform from the deviant one within a time range 100 to 200 msec after the stimulus onset, as in previous reports (Rinne et al., 2000; Näätänen et al., 2004). Then, a deflection of the subtracted waveforms at a latency between 100 and 200 msec after the onset was determined as MMNm. The mean R.M.S. values within a 50-msec-long time window centered at the peak latency were compared among the conditions (De Sanctis et al., 2009). Although a major generator for MMNm was suggested to be in the supratemporal gyrus (Alho, 1995), such generator localization has not been confirmed in three conditions. Thus, I used the R.M.S. to analyze the magnitude of MMNm in experiment 1 (Hoshiyama et al., 2007). For the MMNm and N1m, the R.M.S. values were compared among conditions using one-way (stimulus conditions) repeated-measures analysis of variance (ANOVA) followed by the Fisher's protected least significant difference (Fisher's PLSD) test for multiple comparisons. The difference between the N1m peak latencies for standard and deviant stimuli was also compared among conditions using ANOVA with the Fisher's PLSD test. The significance was set at $P < 0.05$.

Then, a mean dipole localization was estimated according to 20 sampling points, for 10 msec, around the peak of MMNm. For each 30 channels selected in both temporal/parietal areas, a single current dipole model was used to estimate the locations of the cortical activities that produced the magnetic fields (Sarvas, 1987). I accepted equivalent current dipoles (ECDs) with a goodness-of-fit (GOF) value of 90%, and the location in three-dimensional planes was compared among stimulus conditions using one-way (stimulus conditions) repeated-measures analysis of variance (ANOVA).

2.5.2 Experiment 2

The analyses were similar to Experiment 1. 26 gradiometer channels were selected in each hemisphere, as shown in Fig. 7, to calculate MMNm responses. The single current dipole model was used to estimate the locations of the cortical activities that produced the magnetic fields (Sarvas, 1987). The equivalent current dipoles (ECDs) with a goodness of fit (GOF) over 90% were included in the analysis. The equivalent current dipoles at each sampling point in a 50-msec time window centered at the peak of R.M.S. were estimated, and the mean localization and current intensity of the dipole ($|Q|$) were obtained for MMNm.

The peak latency of R.M.S. for MMNm and mean intensity and location of ECD for MMNm were compared among the conditions. Statistical analysis was carried out using three-way (stimulus, condition, and hemisphere) analysis of variance (ANOVA) with Bonferroni-Dunn's test for multiple comparisons. Anatomical landmarks, the nasion and bilateral pre-auricular points, were used to create the MEG head-based 3-D coordinate system. The origin (zero point) was the point exactly halfway (x-axis) between the pre-auricular points, and the y-axis points toward the nasion from the midpoint of the x-axis, and z-axis points vertically from the y-axis. Three coordinates (x, y, and z values) in each hemisphere were compared using two-way (condition, and coordinate) repeated measures ANOVA. Significance was set as $P < 0.05$.

3 Result

Deflections corresponding to MMNm were successfully obtained under all conditions in 8 of the 10 subjects in each experiment. Thus, the following analyses were performed involving these 8 subjects.

3.1 Experiment 1

The peak latencies of N1m and the R.M.S. values at the peak of the N1m are shown in Tables 1 and 2. There was a main effect of condition on the difference of the N1m peak latency between standard and deviant stimuli in the right hemisphere (F[2, 7] = 5.60, $P = 0.016$, ANOVA), but not in the left hemisphere (F[2, 7] = 2.6, $P = 0.12$). Multiple comparisons showed that the difference of the peak latency in the right hemisphere was lower under AV-S than those under A-0 ($P = 0.007$) and AV-R ($P = 0.027$) conditions (Fig. 3B). There was no significant effect of condition on the N1m amplitude and R.M.S. evoked by standard or deviant stimuli in both hemispheres.

Figure 4 shows the grand average waveforms of MMNm and the respective R.M.S. under each condition. The MMNm deflections were recognized within the period between 150-200 msec after stimulus onset. There was a main effect of condition on the R.M.S. value for MMNm that showed a significant difference in the right hemisphere (F[2, 7] = 6.78, $P = 0.0087$, ANOVA), but not in the left hemisphere (Fig. 5). Multiple comparisons showed that there was a significant difference in the R.M.S. value between A-0 and AV-S ($P = 0.046$) and between AV-S and AV-R conditions ($P = 0.026$), but no significant difference was found between A-0 and AV-R conditions.

The dipole analysis showed that the dipole was located in the temporal area, but there were no differences in location among stimulus conditions in both hemispheres (Fig. 6).

3.2 Experiment 2

Table 3 shows the peak latency and mean GOF for ECD estimation each condition and for each hemisphere. Fig. 7 shows the waveforms and R.M.S. under each condition. There was no significant difference in the peak latency (Table 3). For the estimated intensity, there was no interaction of hemispheres (F [1, 14] = 1.76, $P = 0.206$), but the main effect of stimulus condition was significant (F [2, 14] = 3.64, $P = 0.039$, ANOVA). Multiple comparisons with Bonferroni-Dunn's test showed significant difference between A-V and A-S conditions ($P = 0.016$, Fig. 8). No significant difference was found between A-0 and A-V conditions, or between A-0 and A-S conditions. Figure 9 shows the ECD coordinates of a representative subject. Although the ECD for MMNm was located around the superior temporal area, there was no difference in the ECD localization among conditions (Fig. 9).

4 Discussion

The results suggested that feature of stimulus combined with simultaneous additional modality of stimuli could be a factor modulating MMNm, i.e., simultaneous visual stimulation affected the auditory MMNm, but somatosensory stimulation did not.

This Experiment 1 involved recording MMNm responses evoked by auditory stimulation, and the auditory MMNms were modified by accompanying visual stimulation. The results are summarized as follows: 1) auditory MMNm were enhanced under AV-S conditions, and 2) the difference in the peak latency of the N1m between deviant and standard stimuli was significantly smaller under AV-S than under other conditions. Estimated current for MMNm under the A-V condition was greater than that under the A-S condition in the right hemisphere in Experiment 2.

4.1 Enhanced auditory MMNm at synchronous visual stimulation

In experiment 1, auditory MMNms were reportedly obtained within a 100 to 200 msec interval after stimulus onset (Rinne et al., 2000), and the right-hemisphere predominance for non-verbal auditory stimulus was reported (Giard et al., 1990). These aspects of MMNm were similarly observed in this experiment.

The MMN reflects pre-attentive information processing comparing incoming stimuli and a sensory memory trace formed by preceding repetitive stimuli (Näätänen et al., 2005; Näätänen, 2008). A temporal sequence, or a time window, for standard and deviant stimulation is important for the detection process (Shiga et al., 2011; Yabe et al., 2001). To compare stimuli presented in a sequence, the preservation of stimulus-related information is essential. A memory trace, which is produced by sustained temporal plastic changes in a neuronal population, may play a principle role in the MMN production (Näätänen et al., 2005; Näätänen, 2008). Various types of deviant auditory stimulation elicited auditory MMNs, e.g., a change in the frequency (Sams et al., 1990), intensity (Näätänen et al., 1987), or duration (Näätänen et al., 1989). Shiga et al. (2011) stated that MMNs were not elicited depending on the amount of the physical energy at exposure to frequent stimuli, but they were elicited in response to changes in the features compared with frequent sounds (although their Experimental design was different from this study, involving sequential auditory stimulation).

In experiment 1, the difference in the physical energy between the auditory standard and deviant stimuli that enhanced MMNms was identical under all conditions. I consider that the above-described results indicate the following. The amount of auditory mismatch response is determined not only by a difference in the physical amount of auditory stimuli but also by the feature of the stimuli, i.e., total amount of stimuli combined with multimodal stimulation. Shiga et al. (2011) reported that deviant sounds including a couple of parts are processed as a single unit, and that a difference in the temporal features between standard and deviant stimuli affected the production of MMN. In experiment 1, auditory and visual stimuli were simultaneously presented under AV-S conditions, and the temporal feature of deviant stimulation was not different between A-0 and AV-S conditions. Therefore, I consider that the mismatch response was modified by the level of the changing stimulus or stimulus feature given in the course of standard and deviant stimulation.

It may be possible to consider factors regarding feature differences between stimuli (Fig. 1). When the standard and deviant stimuli are accompanied by a consistent stimulus of a different modality, two mismatch pairs exist when deviant stimulation is provided. One is the conventional auditory mismatch between frequent standard and rare deviant stimuli in a temporal sequence of auditory stimulation. Another mismatch is between auditory and visual stimuli. When frequent auditory stimuli are presented together with visual stimulation, the latter might be coded as frequent visual stimulation. When deviant auditory stimulation is accompanied by "frequent" visual stimulation coded with frequent auditory stimulation, a mismatch response between the auditory deviant and frequent visual stimuli might be superimposed with the conventional auditory mismatch response.

Several studies reported relationships between MMN and bimodal audio-visual and audio-somatosensory interaction (Kislyuk et al., 2008; Pantev et al., 2009; Stekelenburg et al., 2004). These studies investigated mismatch in the content of information under conditions of auditory and other-modality stimulation. Modification of MMN by bimodal stimuli in those studies is considered to be more complex than the stimulus combination in experiment 1, but fundamental factors during bi- and multimodal stimulation may be similar in this case.

I consider that an additional stimulation modality provides another dimension for mismatch detection. Sequential auditory stimulation provides a temporal dimension, while simultaneous visual and auditory stimuli yield another plane of dimension at one time (Fig. 1). Since more deviant sensory information would elicit larger MMN, as Näätänen et al. (1987) pointed out, a greater number of dimensions for mismatch might produce larger MMN on presenting deviant stimulation. To explain such multidimensional processes, the contribution of bi- or multimodal sensory systems to the generation of a mismatch response is essential (Besle et al., 2009; Kayser et al., 2007; Lehmann et al., 2005). I think that my findings indicated one of the basic bimodal contributions to MMN. In the conventional method to record MMN, the visual condition (reading sentences during passive auditory stimulation) could be asynchronous visual stimulation with respect to the auditory stimulation. In such a sense, A-0 and AV-R may be similar conditions on visual stimulation for MMNm recording, in which there was no specific difference in MMNms.

4.2 N1m modified by simultaneous visual stimulus

I would like to add a short discussion regarding N1m changes. The difference in the peak latency of N1m between deviant and standard stimuli was shorter under AV-S conditions, which elicited a larger amplitude of MMNm than the other conditions. As described above, the level of physical deviation of the auditory stimulation was similar under A-0 and AV-S conditions. An anticipatory effect guided by visual stimulation should be considered under AV-S condition. According to previous reports, the peak latency of N1m was shorter when a visual anticipatory stimulus was presented (Vroomen et al., 2010; van Wassenhove et al., 2005). If the synchronous visual stimulation enhanced the process for deviant stimulus in its time course, the difference in the peak latency between standard and deviant stimuli might be less under AV-S conditions compared to other conditions, although the mechanism could not be confirmed regarding the latency change of N1m from those results.

Therefore, I investigated modulation of auditory MMNm by synchronous visual stimulation, which was similarly applied with standard and deviant auditory stimulation. The above-described results suggest that the mismatch response could be evoked not only by the temporal dimension of stimulus deviation but also by a deviated feature generated by two stimulation modalities applied at one time.

4.3 The different effect of adding synchronous stimulation between visual and somatosensory on auditory MMNm

The aim of experiment 2 was to investigate the effects of adding synchronous stimulation of another modality on auditory MMNm. The results indicated that the effects of synchronous stimulation differ between visual and somatosensory modalities on the auditory evoked MMNm in the right hemisphere.

In experiment 2, the differences in physical stimuli between standard and deviant stimuli and temporal features were not changed among A-0, A-V, and A-S conditions, but the total amount of the stimulus, or a feature of stimulation, at the timing of stimulation was different among the conditions.

Previous studies reported a bimodal interaction of audio-visual (Colin et al., 2002a, 2002b; Kislyuk et al., 2008; Rahne et al., 2007; Sams et al., 1991) and audio-somatosensory stimuli (Pantev et al., 2009) on MMN production. These studies investigated MMN produced by incongruence between stimuli of different modalities. Their results suggested that the detection of a deviant stimulation was not based on only one dimension of a sequential stimulation, but also on another dimension produced by additional stimulation at the time of stimulation, i.e., deviant stimulation produced by incongruent combination of two modality of stimulation. I considered that the deviant stimulation produced by one of the bimodal stimuli involved two dimensions of difference of stimulation from the standard stimulus (Fig. 1). One was physical difference of frequency between standard and deviant auditory stimulation (D1 in Fig. 1), as in the conventional A-0 condition. The other was difference in stimulus feature produced by combination of two modalities of stimulus (D2 in Fig. 1). For example, at the auditory deviant stimulation in the A-V condition, the stimulus feature produced by the visual with auditory deviant was different from that produced by the visual and auditory standard stimulation. In Figure 1, D2 included not only physical auditory difference as in D1, but the feature of combination of two modalities was difference in D2. I considered that the feature of combined stimulation affected the effect of physical amount of deviation on MMNm.

The effect of the feature might not simple, but interaction, suppression, or facilitation on MMNm production might occur, as seen in the difference of MMNm between the A-V and A-S conditions in experiment 2.

As described above, there were two dimensions of deviance at the time of deviant stimulation under A-V and A-S conditions. One dimension of deviance for mismatch response production was conventional deviance in the auditory temporal sequence between standard and deviant tones (Näätänen et al., 1978). The other dimension was a deviance in the combination of two stimuli given at one time, i.e., between visual-standard and visual-deviant tones, and between somato-standard and somato-deviant tones.

Regarding the reason for a large MMNm under the A-V condition, the summation of MMNm by two dimensions of deviance could be considered. When the summation of two dimensions of MMNm occurs, MMNm under the A-S condition might be larger than that under the A-0 condition. However, since there was no significant difference in MMNm between A-0 and A-S, and also between A-0 and A-V conditions, I could not state that the large MMNm under the A-V condition was caused by the summation of MMNm caused by two deviances. In addition, I could not conclude regarding the A-0 condition. Since the MMNm in the A-0 condition did not differ statistically from the A-V and A-S conditions, it remained unclear whether the A-0 stimulation was null for stimulation of other modality or included some referential feeling at the time of auditory stimulation, compared to the A-V and A-S conditions.

I have to consider the reasons why MMNm was different between A-V and A-S conditions. To evoke MMN or MMNm by somatosensory stimulation, specific stimulus conditions were needed in previous studies (Akatsuka et al., 2005, 2007). The contribution of somatosensory signals to the mismatch response might not be greater than that of visual input. I also considered the difference in the attentional condition between A-V ands A-S conditions. Subjects read sentences during MMNm recording with no specific attention to the additional stimulation, nor to the auditory stimuli. When the attention condition was changed by additional stimulation, the temporal component of MMN was not affected, but the frontal component might have been modified (Restuccia et al., 2005). I considered that the change in MMNm in experiment 2 was mainly caused in the production of MMNm, and not by the modulation of attention. However, although MMN/MMNm was pre-attentive response, I could not exclude completely the effects of difference in stimulus feature, i.e., difference of standard stimulation between A-V and A-S conditions, on prior response to the MMNm, such as N1 (Horváth et al., 2008; Näätänen et al., 2005).

The ECDs for auditory MMNm in experiment 2 were located around the supra-temporal area, similarly to the results of a previous study (Restuccia et al., 2005), but a difference in the ECD localization was not obtained among stimulus conditions. Nyman et al. (1990) reported that auditory MMN was probably specific to the auditory modality. In experiment 2, the localization of the mean ECD was not different among conditions. But, the inter-individual difference of the ECD localization was large as shown in Figure 9, and a possibility of the mixture of a visual-related activity with the MMNm response remained from the results with the single dipole analysis for MMNm.

Other technical reasons could not be excluded. The stimulus timing relative to the auditory stimulation was different between visual and somatosensory stimuli. Visual and auditory stimuli caused primary cortical responses in a similar period between 50-100 msec, while that for somatosensory stimuli was 20 msec. Since simultaneous auditory stimuli within 150-200 msec could be integrated into a unitary event in a conscious state (van Wassenhove et al., 2007) and in the window of MMN (Yabe et al., 1998), the difference in the stimulus timing between visual and somatosensory stimuli might not be a major reason. However, regarding the temporal window of integration, auditory (Yabe et al., 2001) and somatosensory (Yamashiro et al., 2011) modalities were separately investigated and the temporal window of integration for bimodal stimulation remains unclear.

4.4 Clinical implications for OT

Patients diagnosed with schizophrenia, dementia and developmental disorders have difficulty in paying attention or awareness to stimulation in daily life. There were few reports regarding practical intervention of OT for attention disturbance.

This impairment was revealed by MMN studies for those disorders (Lepistö et al., 2007; Näätänen et al., 2009; Pekkonen et al., 1994). Sensory memory was formed by the function of NMDA (N-methyl-d-aspartic acid) receptor (Garrido et al., 2009). Dysfunction of NMDA receptor was reported in those disorders (Näätänen et al., 2009). Those results were suggested that simultaneous stimulation could effect on other primary and secondary cortex. It could be efficacy that the intervention for sensory memory dysfunction by bimodal stimulation. While sensory memory formed in early information processing, later process such as conscious awareness, attention switching, and motor performances could be changed by bimodal stimulation in clinical OT practice.

Physiological study indicated that cross-modal interaction occurred in relative timing of both stimulus, spatial congruency of sensory stimuli, and related to the strength of stimulus (Kayser et al., 2007). In clinical practice, it is important to consider the timing of stimulation and the combination of modalities for improving the intervention regarding attention disturbance or awareness. This study may be a basic knowledge about the effect of a bimodal intervention on attention disturbance or awareness.

4.5 Conclusion

This article discussed that the effects of bimodal stimulation on pre-attentive brain information processing. The present results suggested that feature of stimulus combined with simultaneous additional modality of stimuli could be a factor modulating MMNm, i.e., simultaneous visual stimulation affected the auditory MMNm, but somatosensory stimulation did not. This study suggested that the effects on pre-attentive information process differed from the combination of modalities.

It is suggested to be important for clinical OT intervention to clarify how the way of presenting sensory stimuli effects on information processing.

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7 Figures and Tables

	Left hemisphere		Right hemisphere	
Condition	Standard	Deviant	Standard	Deviant
A-0	98.0 (±10.8)	103.5 (±10.5) *	92.0 (±5.2)	99.4 (±7.0) *
AV-S	96.8 (±8.0)	107.2 (±10.6)	93.9 (±7.0)	92.9 (±7.9)
AV-R	102.6 (±11.3)	109.3 (±11.8)	94.2 (±5.6)	99.3 (±6.5)

(* $P < 0.05$, vs standard stimulation)

Table 1: Mean peak latency (msec, mean ±SD) for the N1m component among conditions.

	Left hemisphere		Right hemisphere	
Condition	Standard	Deviant	Standard	Deviant
A-0	64.9 (±36.2)	80.6 (±32.6) *	80.8 (±40.3)	97.5 (±40.8) *
AV-S	79.9 (±21.0)	88.8 (±34.65)	84.0 (±29.2)	97.4 (±49.3)
AV-R	63.6 (±28.7)	75.0 (±35.4)	72.9 (±34.3)	83.9 (±43.0)

(* $P < 0.05$, vs standard stimulation)

Table 2: Root mean square (R.M.S.) values (fT/cm, mean ±SD) at the peak latency of N1m.

Condition	Hemisphere	GOF (%)	Latency (msec)
A-0	Left	93.5±5.1	177.1±25.6
	Right	92.0±5.3	173.6±34.1
A-V	Left	94.7±3.3	173.8±20.3
	Right	94.9±3.7	171.5±25.6
A-S	Left	92.3±4.5	183.0±30.7
	Right	94.7±3.3	171.9±32.7

Table 3: Mean (±SD) GOF, peak latencies, GOF of ECDs for the MMNm.

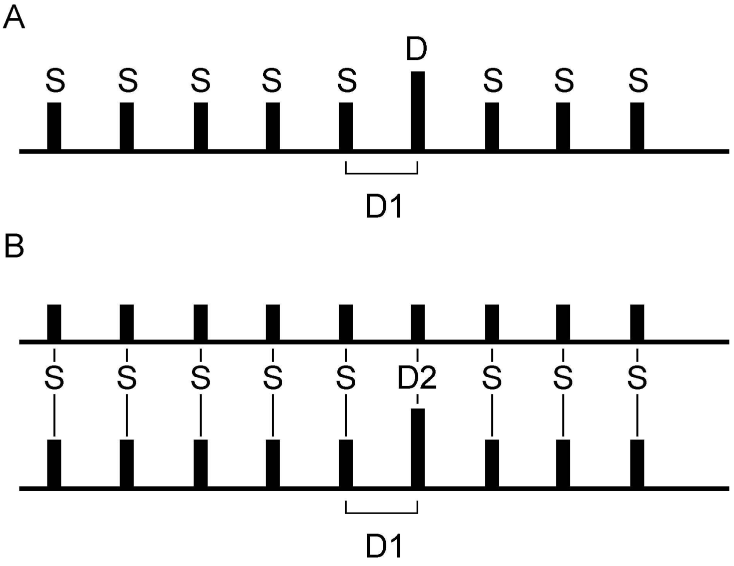

Fig. 1: Scheme of experimental and stimulus conditions. Conventional auditory MMN production on standard (S) and deviant (D) stimulation in a temporal sequence. Under the A-0 condition (A), one dimension of deviation (D1) evoked MMNm. Under the AV-S condition (B), accompanying visual stimuli were presented synchronously with auditory stimuli; at deviant stimulation under these conditions, deviation due to a combined feature of stimuli (D2) was added to D1 to produce MMNm. Under AV-R conditions, visual stimulation was irrelevant to the auditory timing thus, there was one dimension of deviant stimulation.

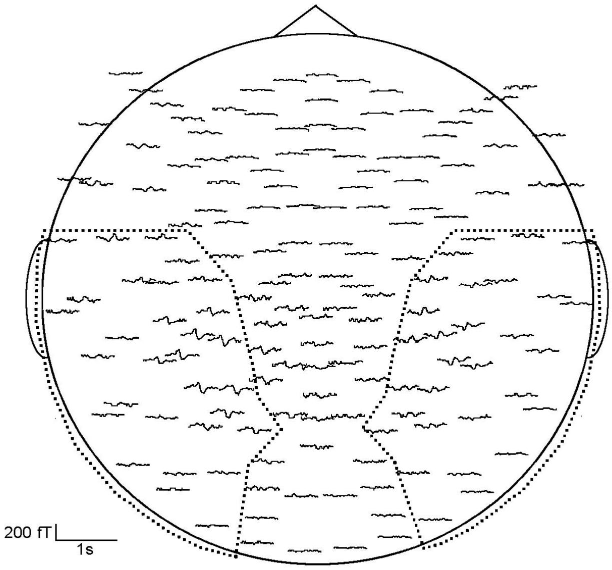

Fig. 2: Sensor layout of the gradiometer of the MEG system. Dashed lines indicate 30 channels selected for MMNm and N1m recordings.

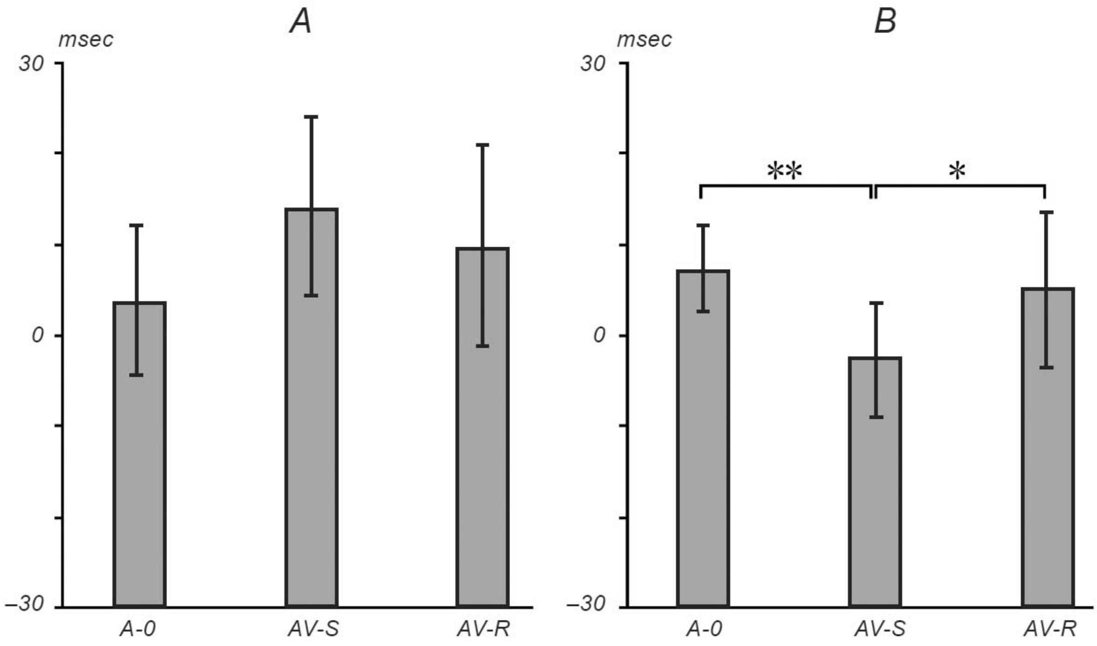

Fig. 3: Differences of the N1m peak latency, msec, between deviant and standard responses under each stimulation condition in the left and right hemisphere (A and B respectively). The difference in the N1m peak latency between standard and deviant stimulation was in the right hemisphere greater (* $P < 0.05$, ** $P < 0.01$, ANOVA) for the auditory-only condition (A-0) and auditory stimulation with asynchronous visual stimulation (AV-R) than the synchronous visual stimulation condition (AV-S).

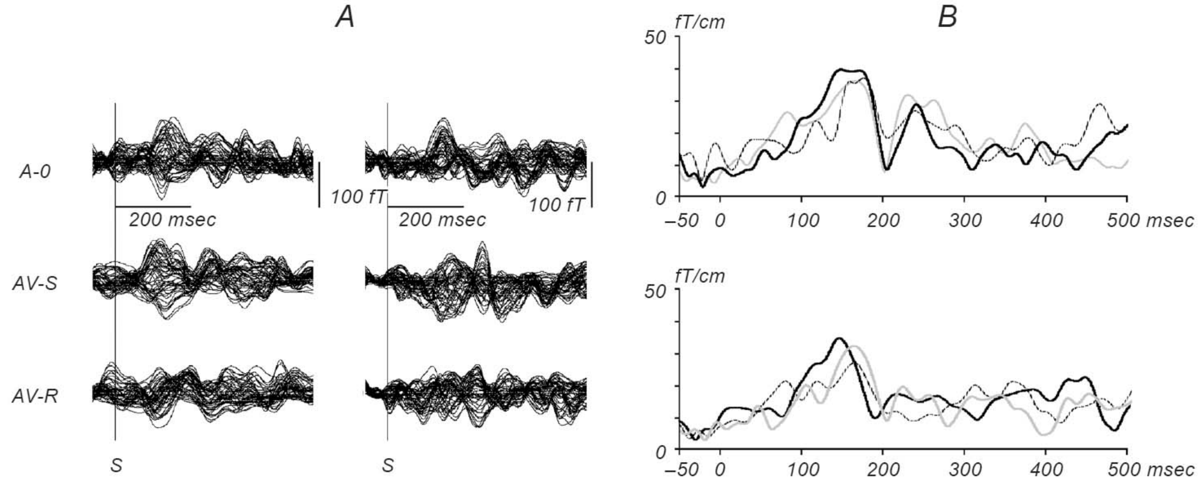

Fig. 4: MMNm waveforms (subtraction waveforms). A) MMNms recorded from a representative subject. Deflections within a 100 to 200 msec window after stimulus onset (S) were recognized under each condition (A-O, AV-S, and AV-R). B) Grand average of the R.M.S. (fT/cm) of MMNms observed under each condition (gray, solid, and doted lines, A-O, AV-S, and AV-R, respectively). The R.M.S. value for the MMNm response at auditory stimulation with synchronous visual stimulation (AV-S condition) is greater than under other conditions (auditory-only, A-0, and auditory stimulation with asynchronous visual stimulation, AV-R).

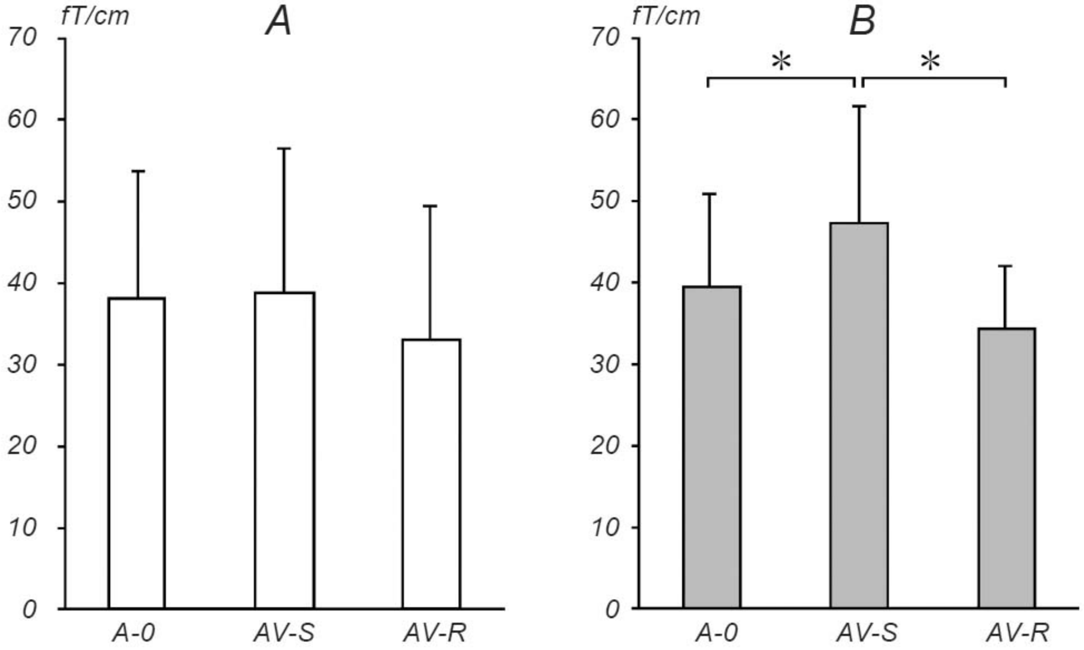

Fig. 5: Root mean square (R.M.S.) values (fT/cm) of the MMNm responses under each condition. Values of R.M.S. for the MMNm response in the right hemisphere are greater (*$P < 0.05$, ANOVA) at auditory stimulation with synchronous visual stimulation (AV-S condition) than under other conditions (auditory-only, A-0, and auditory stimulation with asynchronous visual stimulation, AV-R).

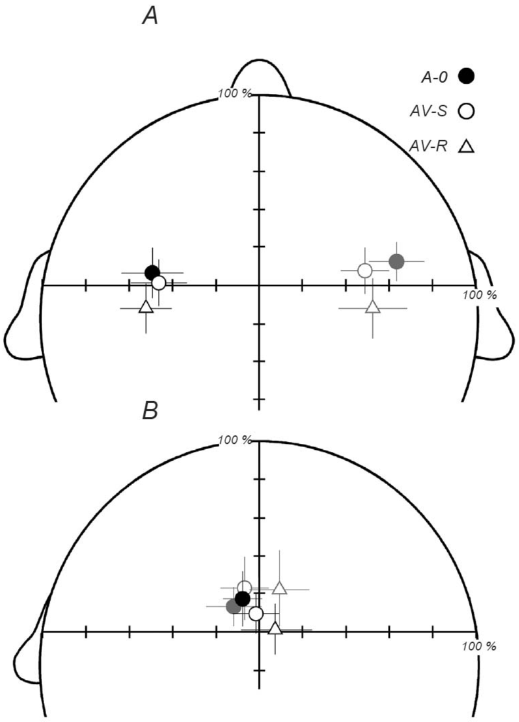

Fig. 6: Standardized localization of equivalent current dipoles (ECDs; eight subjects) of the MMNms shown on the horizontal (A) and side view (B) planes. Relative localizations of ECDs are shown as percentages from the center of the spherical model (0) to the scalp surface (100%). Dipoles in the left and right hemispheres are shown in filled and gray symbols, respectively. The x axis is defined by the line connecting the left and right pre-auricular points, the y axis points toward the nasion from the midpoint of the x axis, and the z axis points vertically from the y axis. The horizontal and vertical bars indicate standard deviations of the mean. There was no significantly difference in the ECD localization among stimulation conditions.

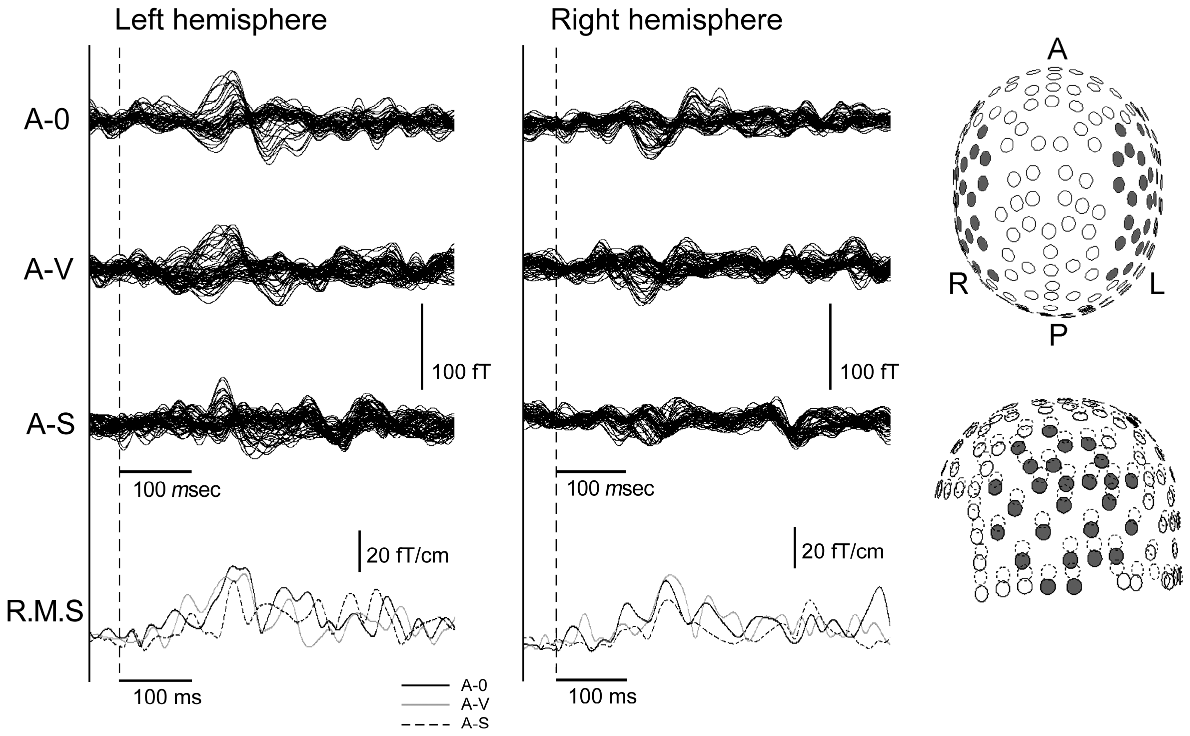

Fig. 7: Mismatch fields (upper) and R.M.S. (lower) waveforms recorded from a representative subject in each stimulus condition (gray, solid, and doted lines, A-O, A-V, and A-S, respectively). Dashed vertical lines indicate the onset of the stimulus. Sensor layouts of gradiometer of the MEG system were shown in the right; top view (right top) and the left-side view (right bottom). Gray sensors indicate 26 channels selected for MMNm recordings. A: anterior, P: posterior.

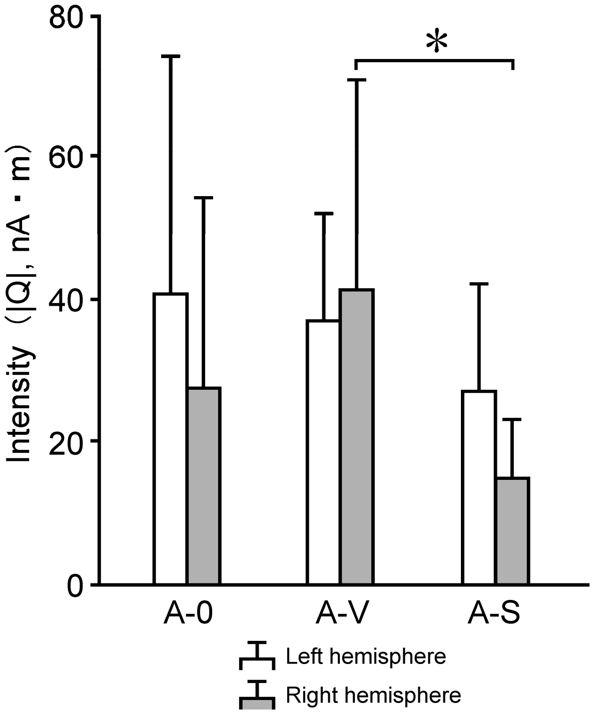

Fig. 8: Current intensity for MMNm under each condition. The intensity was greater under the auditory and synchronous visual stimulus condition (A-V) than under the condition with auditory and somatosensory stimuli (A-S) in the right hemisphere (gray columns, *$P < 0.05$, ANOVA). A-0: Auditory only with no additional stimulation. Each vertical line indicated a standard deviation.

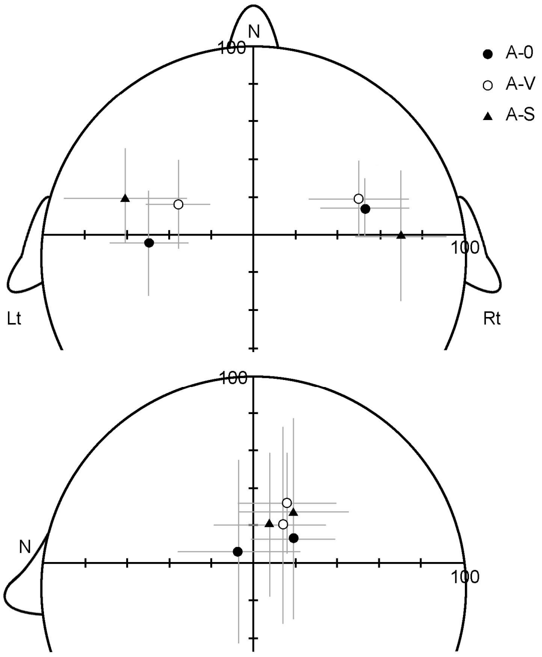

Fig. 9: Grand-average of equivalent current dipole (ECD) localizations (eight subjects) of MMNm shown on the horizontal (top) and side view (bottom) planes. Relative localizations of ECD are shown as percentages from the center of the spherical model (0) to the scalp surface (100%). Dipoles in the left and right hemispheres are shown in black and gray, respectively. The x-axis is defined by the line connecting the left and right pre-auricular points. The y-axis points toward the nasion from the midpoint of the x-axis, and z-axis points vertically from the y-axis. The horizontal and vertical gray bars indicate the standard deviations of the mean. There was no difference in dipole localization among stimulus conditions.