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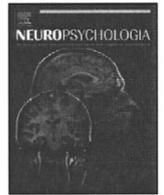
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IV. 研究成果の刊行物・別刷



Frontopolar activation during face-to-face conversation: An *in situ* study using near-infrared spectroscopy

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ABSTRACT

Near-infrared spectroscopy (NIRS) is a functional brain imaging technique for monitoring brain activation in a natural setting using near-infrared light, and hence, is considered to have some advantages for studies of brain function during social interactions such as face-to-face conversation compared with functional magnetic resonance imaging and positron emission tomography, which have methodological constraints for studying brain mechanisms underlying social interactions: subjects have to lie down on a bed in a small gantry during examination. The purpose of this study was to validate the possible use of NIRS as a functional brain imaging technique for studying social interactions in a natural setting; therefore, we investigated frontal and temporal lobe activation during face-to-face conversation in healthy subjects in the sitting position. The frontal and superior temporal regions were activated during face-to-face conversation, with higher activity in the speaking segments than in the mute segments during conversation particularly in frontopolar NIRS channels. The magnitude of frontopolar activity negatively correlated with the cooperativeness score of the subjects assessed using the temperament and character inventory. These results demonstrated the successful monitoring of brain function during realistic social interactions using NIRS and interindividual differences in frontopolar activity during conversation in relation to the cooperativeness of an individual.

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1. Introduction

The brain mechanisms underlying social interactions have recently been one of the most enthusiastically discussed topics in neuroscience, and the prefrontal cortex, superior temporal gyrus, and amygdalae have been implicated as the substrates of the “social brain” (Frith, 2001, 2007). These studies have been made possible by the development of functional brain imaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), and have focused on facial recognition, visual motion processing, and, recently, highly advanced social adaptation (Adolphs, 2003). However, both fMRI and PET have methodological constraints for studying brain mechanisms underlying social interactions: subjects have to lie down on a bed in a small noisy gantry during examination. Owing to such methodological constraints, social interactions have been studied mainly for their cognitive (input processing) aspects and have to be studied in an unusual and nonrealistic situation, such as using pictures or computer graphics shown on a PC monitor as task stimuli. Singer

et al. (2006) have taken up this issue and argued that truly interactive mind paradigms should be employed in, for instance, the fMRI setting. Such attempts have been made by Singer herself (Singer et al., 2006), but also in studies that make use of paradigms based on game theory (McCabe, Houser, Ryan, Smith, & Trouard, 2001). In other approaches, the use of virtual characters has also been suggested to be of particular interest and could be a useful tool for further investigations (Sanchez-Vives & Slater, 2005; Schilbach et al., 2006). Although these methods using virtual reality are useful for reproducing a social cognitive situation, a functional brain imaging methodology that enables the monitoring of brain activation in a more natural setting is expected to offer more informative data regarding social interactions in a real-life situation.

Near-infrared spectroscopy (NIRS) is one of the more recently available functional brain imaging techniques that employ near-infrared light emitted and detected on the skull skin (Boas, Dale, & Franceschini, 2004; Fallgatter, Ehlis, Wagnen, Michel, & Herrmann, 2004; Sato et al., 2007). It allows the monitoring of cerebral blood volume (CBV) changes in the neocortex, as an increase in oxygenated hemoglobin concentration ([oxy-Hb]) and a decrease in deoxygenated hemoglobin concentration ([deoxy-Hb]) using a small apparatus. It enables brain activity measurement in a more natural setting as compared with other functional brain imaging

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techniques: for example, subjects can undergo NIRS examination in the sitting position, with their eyes open, and while speaking. These characteristics of NIRS are considered to be particularly suitable for studies of social interactions. Thus far, NIRS has already been successfully used to monitor brain function for delicate subjective experiences in healthy subjects such as subjective sleepiness and subjective psychological fatigue (Suda et al., 2008, 2009) and of psychiatric patients who are sensitive to the experimental environment (Kameyama et al., 2006; Suto, Fukuda, Ito, Uehara, & Mikuni, 2004; Uehara et al., 2007).

Conversation with other people is one of the most frequent social interactions in the daily life of humans, and consists of verbal and nonverbal components. A number of functional brain imaging studies related to conversation have focused on speech perception, a verbal component of conversation. Studies in which speech stimuli were presented during passive listening tasks showed the prominent activation of bilateral superior temporal regions (Binder et al., 1994), and studies that used tasks similar to syllable discrimination or identification showed prominent activations of the left superior temporal regions (Demonet et al., 1992) and left inferior frontal lobe (Zatorre, Evans, Meyer, & Gjedde, 1992). As a non-verbal aspect, studies involving tasks such as facial recognition or eye gaze perception showed that the activation of the medial prefrontal cortex underlies both the perception of social communication indicated by facial expressions and the feeling of personal involvement indicated by eye gaze (Schilbach et al., 2006), and that the involvement of the medial prefrontal cortex associated with outcome monitoring and mentalizing indicates higher-order social cognitive processes related to the evaluation of the ongoing communicational input conveyed by direct gaze duration (Kuzmanovic et al., 2009). In addition, in some recent studies, the integration of information from face and voice has been investigated and found to be associated with nonverbal components (Campanella & Belin, 2007; Kang et al., 2006). During realistic conversations, the non-verbal components of communication are essential, and in some cases, might be more important than the verbal components. However, to the best of our knowledge, there are only a few functional brain imaging studies in which the brain substrate of a conversation that contains both verbal and nonverbal components was investigated as the procedural dynamics of social interaction as well as the reciprocity. The main reason is the limitation in the experimental setting of functional brain imaging, as described above.

In this study, by monitoring prefrontal and temporal lobe reactivities using NIRS in healthy subjects in the sitting position during their conversation opposite to another person, we investigated the possible applicability of NIRS as a functional brain imaging technique for studying social interactions that include both verbal and nonverbal components simultaneously in a natural setting. Such an approach could help enhance our understanding of brain activity during a social interaction in our everyday life and of the relationship between verbal and nonverbal communication from a new perspective. In addition, we investigated the relationship between these brain activation and personality traits in healthy subjects. We hypothesized that the face-to-face conversation is associated with prefrontal and superior temporal cortex activation, the brain areas implicated in social cognition, and a part of the personality traits of healthy subjects reflects interindividual variations in brain activation characteristics.

2. Materials and methods

2.1. Participants

Thirty healthy volunteers participated in this study (15 males and 15 females; average age, 26.7 years old, SD 3.3, range 23–36). All the subjects were right-handed. We had confirmed that they use the right hand when writing, drawing, using some tools, and throwing, and had never changed their hand dominance. They had no

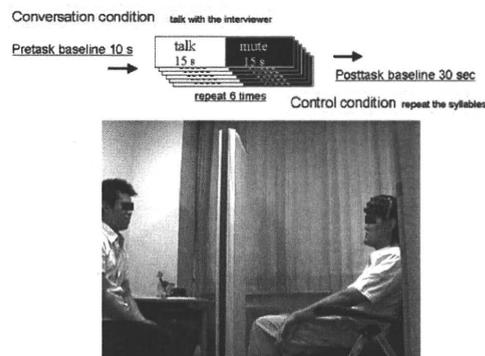


Fig. 1. Task procedures and picture of measurement settings. Two types of activation task, conversation condition and control condition, were employed in this study. Both tasks consisted of three segments, pretask, task, and posttask. Under the conversation condition, the subjects were required to talk with the interviewer facing them during the task segment. The task period consisted of six cycles of such a 30 s talk, with the total conversation lasting up to 180 s. Before starting and after finishing the experiment, the subject and interviewer were separated by a partition so that they could not see each other. Under the control condition, the subjects were instructed to repeat meaningless syllables during their turns to talk in the task period. As shown in the picture, the subject wearing the near-infrared spectroscopy probe on his forehead sat on the right side, whereas the interviewer sat on the left side. They faced each other and sat on chairs, and the partition was placed to separate them during the pretask and posttask segments.

history of any major psychiatric disorder, neurological disorder, substance abuse, head injury, or major physical illness, and they were not taking any psychotropic medications at the time of the study, although this had not been checked by brain CT or MRI. This study was approved by the Institutional Review Board of the Gunma University Graduate School of Medicine. Written informed consent was obtained from all the subjects prior to the study.

2.2. Activation tasks (Fig. 1)

We employed two types of activation task, namely, conversation condition and control condition. The order of the two tasks was counterbalanced among the subjects.

2.2.1. Conversation condition

The conversation condition was designed to simulate usual conversations in everyday life in an experimental setting. Each subject and an interviewer sat facing each other one meter apart on comfortable chairs in a sunlit room with their eyes open, and the probes of the NIRS machine were placed on the subject's frontal and temporal regions. Before starting and after finishing the experiment, the subject and interviewer were separated by a partition so that they could not see each other, and the partition was removed during the experiment.

The experiment consisted of three periods: pretask, task, and posttask. During the task period, the subjects were required to talk with the interviewer facing them. To enable later data analyses, the subjects were instructed to carry out the conversation during the task period following two criteria as follows. First, the time course of the conversation was fixed a priori: the subject and interviewer were supposed to talk in turn in this order every 15 s, which was accomplished with cues provided by the experimenter's voice every 5 s. The task period consisted of six cycles of 30 s talk, with the entire conversation lasting up to 180 s. Second, the topic of the conversation was limited to anything related to food. The interviewers were selected from three male psychiatrists who were not acquainted with the subjects. During the pretask and posttask periods, the subjects were instructed to repeat the syllables /a/, /i/, /u/, /e/, and /o/ as the Japanese counterparts of A, B, and C in English to exclude the effect of phonation and hence to stabilize the baseline conditions. The images and voices of the subjects and interviewers were videotaped during the experiment for further analyses.

Task performances of the conversation were evaluated in two ways. First, the amount of talk by the subjects was evaluated quantitatively as talk time, which corresponded to the length of the subjects' talk measured using the recorded videotape. Second, the content of the talk was evaluated qualitatively in receiving and sending aspects. The receiving aspect indicates the appropriateness of the talk in the context of the conversation: the subjects' replies to the preceding interviewer's talk were scored as (1) inappropriate, (2) partially inappropriate, (3) partially appropriate, and (4) appropriate. The sending aspect indicates the productivity of new topics: the subjects' questions to the interviewer were scored as (1) no new topic, (2) nearly the same topic, (3) partially new topic, and (4) completely new topic. The raters were two psychiatrists who had 8 years of clinical experience each. They rated the contents individually at first, and then cross-checked the results.

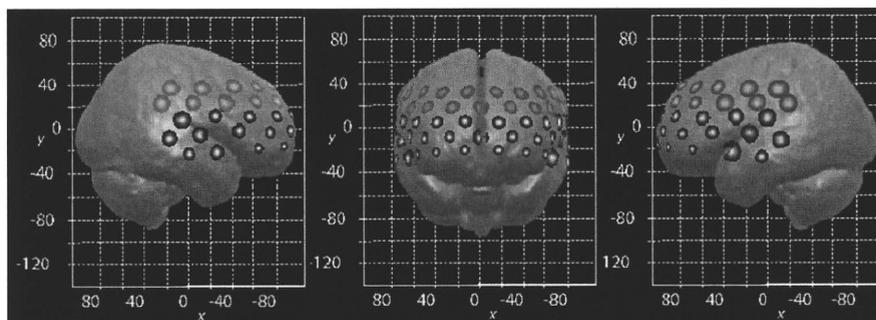


Fig. 2. The locations of NIRS channels were probabilistically estimated and anatomically labeled in the standard brain space in accordance with Tsuzuki et al. (2007). Shaded gray channels indicated the channels that were excluded because of clear motion artifacts.

2.2.2. Control condition

To examine brain activation and artifact contamination induced only by phonation, the control condition was used in addition to the experimental condition. The subjects were instructed to repeat meaningless syllables such as “a”, “ka”, “sa”, “ta”, and “na” during their turns to talk in the task period. All the subjects were able to repeat such syllables without interruption during their turns.

2.3. Assessments of personality of subjects

The personality of the subjects was assessed using the Japanese version of the temperament and character inventory (TCI; Cloninger, Svrakic, & Przybeck, 1993; Kijima, Tanaka, Suzuki, Higuchi, & Kitamura, 2000). The TCI is a self-questionnaire consisting of 240 items developed by Cloninger et al. The TCI assumes that personality consists of four biological dimensions (“temperament”) and three social dimensions (“character”). The four dimensions of temperament are novelty seeking, harm avoidance, reward dependence, and persistence. The three dimensions of character are self-directedness, cooperativeness, and self-transcendence.

2.4. NIRS measurement

In this study, changes in [oxy-Hb] and [deoxy-Hb] were measured using a 52-channel NIRS machine (Hitachi ETG-4000) at two wavelength of near-infrared light (i.e., 780 and 830 nm) whose absorption was measured, and [oxy-Hb] and [deoxy-Hb] were calculated. As an index of cerebral blood volume changes, [oxy-Hb] changes were evaluated. The distance between the pair of emission and detector probes was 3.0 cm, and it was considered that the machine measured points at a depth of 2–3 cm from the scalp, that is, the surface of the cerebral cortex (Hock et al., 1997; Toronov et al., 2001).

The probes of the NIRS machine were placed on the subject’s frontal region. The frontal probes measured [Hb] changes at 52 measurement points in a 6 cm × 30 cm area, with the lowest probes positioned along the Fp1–Fp2 line in accordance with the international 10/20 system used in electroencephalography. The measurement points were labeled Ch 1 to Ch 52 from top to bottom. The correspondence between the NIRS channels and the measurement points on the cerebral cortex was confirmed by a multisubject study of anatomical craniocerebral correlation (Okamoto et al., 2004) and was displayed on the basis of the results of the virtual registration method (Fig. 2; Tsuzuki et al., 2007).

The absorption of near-infrared light was measured with a time resolution of 0.1 s. The obtained data were analyzed using the “integral mode”. The pretask baseline was determined as the mean across the last 10 s of the 30-s pretask period, the posttask baseline was determined as the mean across the last 10 s of the 30-s post-task period, and linear fitting was applied to the data between these two baselines. The moving average method was used to exclude short-term motion artifacts in the analyzed data (moving average window: 5 s).

2.5. Data analyses

The waveforms of [Hb] changes in all 52 channels under the two conditions of tasks were calculated for all the subjects. The NIRS data of channels that clearly con-

tained motion artifacts, as determined by close observation of the subjects, namely, Chs 1–21, were excluded from further analyses. The most common cause of motion artifact is hair. The probe placed on an area with a lot of hair cannot be sufficiently fastened onto the head, and can be displaced easily.

[Hb] changes in the remaining 31 channels were analyzed in two steps. In the first step, the channels with significantly greater [Hb] changes under the conversation condition were identified. The individually averaged [Hb] data were divided into the following three time segments for each condition: the ‘pretask’ segment for 10 s before the task period, the ‘task segment’ for 180 s during the task period, and the ‘posttask’ segment for 30 s after the task period. The averages of [Hb] data of ‘task segment’ of each condition were calculated and analyzed using two-way repeated-measure analysis of variance (ANOVA) with “task” (conversation and control condition) and “channel” (31 channels) as independent variables, followed by a post hoc paired *t*-test for all the channels with Bonferroni correction of multichannel comparisons.

In the second step, the relationships of [Hb] changes during conversation with the personality of the subjects and task performances of the conversation were investigated. For the channels with significantly greater [Hb] increases under the conversation condition than under the control condition, as determined in the first step, multiple regression analysis (stepwise procedure) was conducted with Bonferroni correction: the averaged [Hb] changes in the task period as a dependent variable, and gender and the seven scores of items in the TCI, namely, novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness, and self-transcendence as independent variables. For the channels with significantly greater [Hb] increases under the conversation condition than under the control condition, as determined in the first step, multiple regression analysis was conducted with Bonferroni correction: the averaged [Hb] changes in the task period as a dependent variable, and three parameters for the conversation, namely, talk time, receiving score, and sending score for the content of the talk as independent variables.

3. Results

3.1. Characteristics of participants and behavioral data (Table 1)

The TCI scores and task performances of the participants are shown in Table 1. The scores of five out of the seven items in the TCI, except harm avoidance and self-transcendence, were within the standard values in the TCI (Cloninger et al., 1993). Among the scores of the seven items in the TCI and the three parameters for the conversation, namely, talk time, receiving score, and sending score for the content of the talk, significant correlations were obtained only between the TCI scores and the three parameters for the conversation.

Table 1
Characteristics of participants.

	TCI							Task performances		
	NS	HA	RD	P	SD	C	ST	Time (s)	RS	SS
Mean	20.2	20.2	17.2	4.4	27.3	30.0	9.5	77.2	3.9	3.5
SD	4.4	5.6	3.5	2.0	7.3	4.3	5.4	5.6	0.3	0.7
Range	15–30	9–32	10–23	2–8	9–45	22–38	1–24	62–91	3–4	2–4
SV	19.2	12.6	15.5	5.6	30.7	32.3	19.2			

NS, novelty seeking; HA, harm avoidance; RD, reward dependence; P, persistence; SD, self-directedness; C, cooperativeness; ST, self-transcendence; time, speaking time; RS, scoring of qualitative evaluation of receiving aspects; SS, scoring of qualitative evaluation of sending aspects; SV mean scores of TCI of standard values.

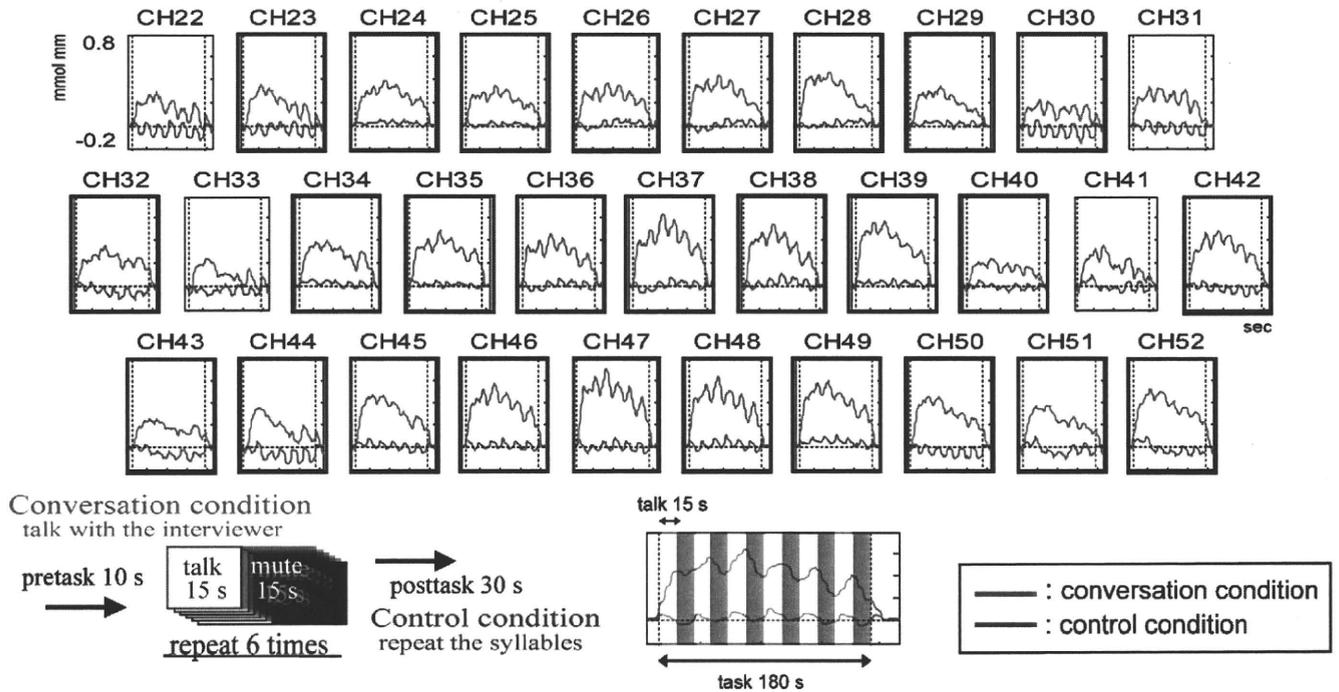


Fig. 3. Grand averaged waveforms of oxygenated hemoglobin concentrations ([oxy-Hb]) under conversation condition (red line) and under control condition (blue line) in 31 channels over frontal and temporal regions measured by NIRS. The channels framed in bold black indicate those channels that showed significantly larger activations under the conversation condition than under the control condition. Gray regions in a scale-up channel indicate the interval during which the subject kept silent under both conditions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

3.2. [Hb] changes during conversation and control tasks (Fig. 3, and see supplementary figure online)

As for [oxy-Hb] changes, the two-way repeated-measure ANOVA showed significant main effects of task ($F=5.5, P=0.019$) and channel ($F=2.1, P<0.001$), and significant two-way interactions for task by channel ($F=25.6, P<0.001$). The post hoc paired *t*-test of grand averaged [oxy-Hb] changes during 180-s task segments between the conversation and control conditions demonstrated significantly larger [oxy-Hb] increases under the conversation condition in 27 channels, namely, Chs 23–30, 32, 34–40, and 42–52 ($t=3.6–8.7, P<0.0016$), with Bonferroni correction of multichannel comparisons ($P<0.0016$). The robust activation was demonstrated over the frontal and superior temporal regions under the conversation condition, but not under the control condition. The channels without statistically significant differences between the conversation and control conditions (Chs 22, 31, 33, and 41) were located mainly around Broca's area.

As for [deoxy-Hb] changes, the two-way repeated-measures ANOVA showed the significant main effects of task ($F=50.4, P<0.001$) and channel ($F=1.5, P=0.037$), and the significant two-way interactions for task by channel ($F=2.1, P<0.001$). The post hoc paired *t*-test of grand averaged [oxy-Hb] changes during 180-s task segments between the conversation and control conditions demonstrated significantly larger [deoxy-Hb] decreases under the conversation condition in 5 channels, namely, Ch 24 ($t=4.0, P<0.001$), Ch 25 ($t=3.5, P=0.001$), Ch 27 ($t=3.7, P<0.001$), Ch 28 ($t=4.1, P<0.001$), and Ch 38 ($t=3.6, P<0.001$), with Bonferroni correction of multichannel comparisons ($P<0.0016$).

3.3. Relationship between personality or task performance and brain activation (Figs. 4 and 5)

The correlations between [oxy-Hb] changes during conversation and personality of the subjects were investigated. For the channels

with significantly greater [oxy-Hb] changes under the conversation condition than under the control condition determined in the first step analyses, multiple regression analysis was conducted with Bonferroni correction of multichannel comparisons ($P<0.0016$). [oxy-Hb] increases in Ch 37 during the task period significantly negatively correlated with the cooperativeness score in the TCI ($\beta=-0.550, P=0.0016$).

The scatter graph of averaged [oxy-Hb] changes during the task period in Ch 37 in relation to the cooperativeness score is shown

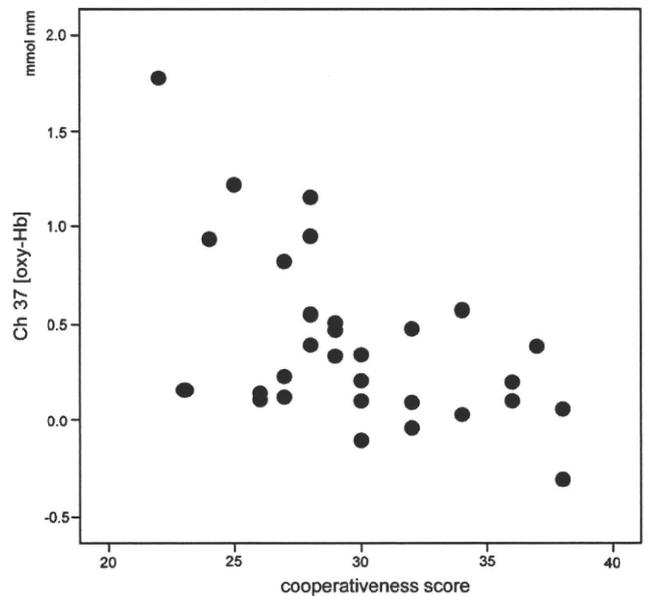


Fig. 4. Significant correlation between personality assessed by TCI and brain activation measured by NIRS: cooperativeness scores of TCI vs. oxygenated hemoglobin concentration ([oxy-Hb]) changes in Ch 37 over medial prefrontal cortex.

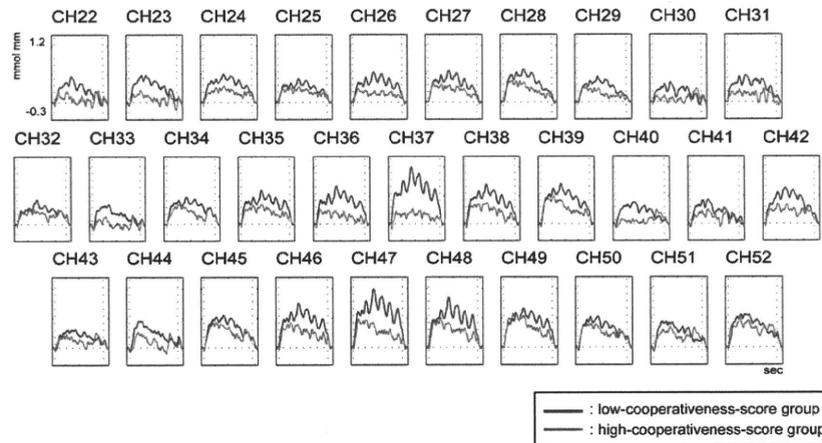


Fig. 5. Contrast of the differences in cooperativeness score. The subjects were divided into high- and low-cooperativeness-score subgroups using 30 as the cut-off score, the mean of the cooperativeness score of TCI: high-score group (more than 30 points, 14 subjects, mean 33.5, SD 3.1) and low-score group (less than 30 points, 16 subjects, mean 26.6, SD 2.2). Pink lines indicate the grand averaged waveforms of [oxy-Hb] during conversation of the high-score group, and red lines indicate those of the low-score group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

in Fig. 4, and the averaged [oxy-Hb] waveforms are shown in Fig. 5 dividing all the subjects into high- and low-cooperativeness-score subgroups employing a cut-off score of 30, the mean of cooperativeness.

There were no significant correlations between [oxy-Hb] changes during conversation and the three scores of task performances. [deoxy-Hb] changes during conversation did not significantly correlate with the seven scores of items in the TCI and the three scores of task performances.

4. Discussion

4.1. Summary of obtained results

In this study, in which brain activation during conversation was examined, the obtained results demonstrated that (1) brain activation can be monitored time-dependently during a real face-to-face conversation in a natural setting using a multichannel NIRS machine; (2) the face-to-face conversation was accompanied by a robust activation, [oxy-Hb] increases, over the frontal and superior temporal regions compared with the control condition; and (3) such [oxy-Hb] increases negatively correlated with the cooperativeness score in the TCI in the frontopolar channel.

4.2. *In situ* monitoring of brain function during conversation

In this study, and to the best of our knowledge for the first time, we can monitor brain function during conversation in a natural setting. Such *in situ* functional brain imaging during conversation was possible owing to the features of NIRS in which the subjects are not obliged in this context to lie motionless in a gantry as opposed to those of functional MRI, PET, and SPECT. Although NIRS has a limitation, that is, it can be used to investigate only cerebral cortex activation, it has been shown to be advantageous for elucidating brain function during conversation, and hence, during more complicated social interactions *in situ*.

In addition, NIRS is also useful for monitoring activation in the frontopolar region. The monitoring of the frontopolar region by fMRI and PET is considered difficult because of artifacts due to the skull bone and frontal sinus. NIRS is assumed to be less affected by such bone and frontal sinus artifacts and is suitable for the measurement of the frontopolar region.

4.3. Brain activation during conversation

The face-to-face conversation was accompanied by a robust activation over the frontal and superior temporal regions, including the medial prefrontal and superior temporal cortices, which are the brain areas implicated in social cognition. These findings are consistent with previous findings. The medial prefrontal cortex plays a unique role in social interaction (Amodio & Frith, 2006). It is suggested that the anterior region of the rostral medial prefrontal lobe has access to information about both actions and outcomes. The characterization of this area comprises roughly three different categories: self-knowledge, person knowledge, and mentalizing. At the same time, the anterior temporal region is also considered to be related to social cognition such as mentalizing (Kampe, Frith, Dolan, & Frith, 2001) and social concepts (Zahn et al., 2007). A face-to-face conversation must require such social cognitive function, because it is impossible to act and adapt to circumstances without mentalizing, i.e., the ability to think about others' thoughts and mental states to predict their intentions and actions.

There was one functional brain imaging study in which the neural substrate of conversation was examined (Sassa et al., 2007). They used functional MRI to compare cortical activation while normal subjects casually talked to an actor with that while describing an action performed in video clips. Significantly larger activations in the medial prefrontal cortex and bilateral anterior superior temporal gyri were observed during the former communication task than during the latter description task. The authors considered that these regions are important in the behavioral aspects of communicative speech production. These results are in good agreement with our results, that is, activation of the frontal and temporal regions during the conversation. In addition, the channels over the dorso-lateral prefrontal regions were also significantly activated under the conversation condition in this study. These additional activations shown in our NIRS study might be associated with some sort of nonverbal component of conversation, because of the difference in the experimental setting (facing a gantry vs. face-to-face).

Differences between [oxy-Hb] changes under the conversation and control conditions showed no statistically significant differences in the two channels located around Broca's area, as shown in Fig. 3. Because both conditions were similar in their composition of alternating repetition of 15 s talk and 15 s mute phases, these brain areas were considered to reflect Broca's area function activated by phonation.

4.4. Frontopolar activation along the time course of speaking and listening phases

In addition to the blockwise activations of the frontal and temporal lobes during the 180-s conversation, rhythmic activations superimposed them: accumulating activation during the talk subsegment and its resolution during the mute subsegment in the conversation task, as shown in Fig. 3. Such 30-s-cycled rhythmic frontal activation across the talk and mute subsegments was successfully clarified owing to the high time resolution of NIRS. These additional rhythmic activations were more prominent over the frontopolar region than over other brain regions such as superior temporal regions. Such frontopolar dominant activation may reflect a realistic nature of face-to-face conversation that requires multitasking and ambiguous and uncertain judgments all the time, because the frontal pole is assumed to be involved in high-level judgment and intention decision (Koechlin & Hyafil, 2007), multitasking (Burgess, 2000), working with ambiguity or uncertainty (Yoshida & Ishii, 2006), and hence, possibly in conversation.

4.5. Cooperativeness

High-cooperativeness-scores in the TCI are considered to reflect social acceptance, empathy, helpfulness, compassion, and pure-heartedness (Cloninger et al., 1993). In this study, the cooperativeness scores significantly negatively correlated with the anterior medial prefrontal activation during conversation. There is one structural MRI study (Yamasue et al., 2008) and one functional MRI study (Decety, Jackson, Sommerville, Chaminade, & Meltzoff, 2004) that found a brain correlation of cooperativeness in the TCI. In the structural MRI study, the cooperativeness score positively correlated with the anterior medial prefrontal cortex volume. In the functional MRI study in which the effects of cooperation and competition with another player in a computer game were examined, the anterior medial cortex activation was larger under the cooperation condition than under the competition condition. These results are apparently inconsistent with those of the present study showing the relationship between high-cooperativeness-score and small brain activation. This discrepancy may be explained by the feature of the task design in this study: the subjects were forced to talk in turn in accordance with the experimenter's cue, instead of a spontaneous natural conversation. Such an unusual setting of the conversation may result in subjects with a low-cooperativeness-score requiring larger brain activation because they had difficulty in talking with others cooperatively.

Moreover, the "default system" of the brain, which has been described as a set of regions that are 'activated' during rest and 'deactivated' during cognitively demanding tasks (Raichle, 2001), and its putative role in social cognition related to the medial prefrontal lobe (Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008) might be useful to explain these findings. The findings on the relative small activations over the medial prefrontal lobe of the subjects with a high-cooperativeness-score might be explained using this "default system", that is, the physiological 'baseline' of the brain might not be equal for minds at rest, but might be linked with a psychological 'baseline' related to social cognition such as self-consciousness and other-person perception. A highly cooperative subject might already activate a larger social cognitive function at rest; therefore, his/her brain activation during social cognitive tasks might be less affected by such factors as the "ceiling effect".

4.6. Limitations

This study has some methodological limitations. First, the task design was still unnatural and did not sufficiently reproduce an ordinary social communication situation. We imposed unnatural

regulations such as a conversation cycle of 15 s and the topic of conversation being limited to food. Such regulations were required to control the task conditions to analyze and examine the methodological adequacy. The average time of the conversation task was 77.2 s; however, it was 12.8 s shorter than the set time segment, i.e., minus 2.1 s every 15-s turn. Such reduction in the speaking time might also be caused by unnatural regulations such as a conversation cycle of 15 s. It might be attributable to the subject's difficulty to speak for 15 s in every 15-s speaking segment during the interactive conversation, because some subjects might think of the next topic before opening their mouth and others might come up with a topic before the end of the 15-s speaking segment. In addition, the evaluation of the contents of the conversation was a bit subjective, such as having only four levels of rating. However, in future studies, we will develop a more sophisticated task design. Second, the control condition that we employed was only performing phonation. We interpreted the difference in [Hb] changes between the conversation and control conditions as brain activation for conversation. However, such a task design cannot exclude the in-depth effects other than the conversation such as nonverbal communication. In future studies, other additional conditions, such as a conversation via telephone or a face-to-face situation without speaking, will be helpful in examining the effects of nonverbal communication in detail. Third, NIRS has some methodological limitations, such as a low spatial resolution of approximately 3 cm, i.e., nearly equal to one gyrus of the brain, and ineffectiveness to assess deep brain structures. When placing a NIRS probe on a head in accordance with 10–20 standard positions, the cerebro-cranial correlation is considered to vary within the range of 1 cm; therefore, the correspondence at the level of the gyrus is not affected by it (Okamoto et al., 2004). NIRS methodology is still a developing technology; thus, there is a problem related to interindividual spatial normalization. One of the major impediments is the difficulty in determining the exact path length for each subject. In activation studies, it is important to define a relationship between NIRS data and fMRI data, which have the advantage of a standardized anatomical reference frame. In that case, there is a major concern about differences in analyzing brain activation, in addition to the correspondence of anatomical references. fMRI is based on BOLD fMRI, a method of observing which areas of the brain are active at any given time. In contrast, most NIRS studies have not employed a hemodynamic response model hypothesis such as BOLD fMRI, but only the calculation of [Hb] changes. In addition, in this study, NIRS probes covered only around the frontal area. The involvement of other cortical areas and deep brain structures that might be particularly important for social cognition cannot be determined, owing to the ineffectiveness of the NIRS methodology to assess deep brain structures. Fourth, assessments of the behavioral data of the tasks and personality traits of the participants were inadequate. The behavioral aspects of the conversation were assessed only in terms of its verbal component. Other aspects such as eye movement or facial expression should be assessed in future studies. In addition, the personality of the participants was assessed using only the TCI. Some reports demonstrated racial differences in the standard scores of the TCI; Japanese subjects scored lower in cooperativeness than American subjects (Kijima et al., 2000). Because this problem arises from the self-administered nature of the TCI, an objective evaluation of the personality of the subjects should be carried out in future studies.

4.7. Conclusion

In summary, we monitored the frontal lobe activation during face-to-face conversation *in situ* by NIRS, and demonstrated the relationship between brain activation and the cooperativeness of the subjects. Because other functional brain imaging modalities such as fMRI, PET, and SPECT suffer from methodological limita-

tions in experimental settings, studies in which brain function *in situ* under natural conditions is examined by NIRS may deepen our understanding of social and interpersonal cognition and behavior.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2009.09.036.

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Preattentive dysfunction in major depression: A magnetoencephalography study using auditory mismatch negativity

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Abstract

Information processing deficits in major depressive disorder have been infrequently examined electrophysiologically. Its preattentive and sensory information processing was examined using mismatch field (MMNm) and P1m components, respectively, by magnetoencephalography. Fourteen major depressive disorder patients and 19 healthy volunteers participated in the study. MMNm was elicited in response to duration and frequency changes of pure-tone stimuli and in response to a vowel across-category change. The magnetic global field power (mGFP) of MMNm was significantly smaller in the major depressive disorder patients than in the healthy volunteers, although that of P1m did not differ between the two groups. Information processing at the preattentive level is impaired functionally in major depressive disorder, and this dysfunction is not due to the dysfunction at the lower level of information processing.

Descriptors: MEG, Mismatch negativity, Major depressive disorder, MMN, Magnetoencephalography, Attention

Cognitive dysfunctions are assumed to underlie clinical symptoms in major depressive disorder patients and have been included in the criteria for establishing diagnosis: For example, a diminished ability to think or concentrate during a major depressive episode is included as an item in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*). Cognitive dysfunctions in major depressive disorder patients have been experimentally demonstrated in many neuropsychological studies. During a depressive episode of major depressive disorder patients, neuropsychological deficits have been demonstrated in memory, learning, attention, alertness, and executive functions (Austin et al., 1992; Veiel, 1997; Zakzanis, Leach, & Kaplan, 1998). In addition, a number of recent studies have shown that some of these cognitive deficits persist during the euthymic state and symptomatological remission (Austin et al., 1992; Tham et al., 1997).

Information processing deficits underlying these cognitive dysfunctions in major depressive disorder patients can be examined electrophysiologically using event-related potentials (ERPs). For example, among late ERPs, the P300 component has often been reported to be reduced in amplitude and delayed in peak latency in major depressive disorder patients (Karaaslan, Gonul, Oguz, Erdinc, & Esel, 2003; Kawasaki, Tanaka, Wang, Hokama, &

Hiramatsu, 2004; Papageorgiou et al., 2004; Roschke & Wagner, 2003; Urretavizcaya et al., 2003), and the results are interpreted as reflecting abnormalities in the capacity of attentional operation resource (Kok, 2001). However, because late ERPs such as P300 are often vulnerable to motivational factors and task involvement of the participants, the interpretation of these findings in major depressive disorder patients is difficult.

Among the earlier components of ERPs, mismatch negativity (MMN) has been the most extensively investigated to elucidate preattentive cognitive function. MMN and its magnetic counterpart (MMNm) are considered to reflect preattentive information processing and are elicited approximately 150–200 ms after the onset of physically deviant auditory stimuli in identical and repeated stimulus sequences (Hari et al., 1984; Näätänen, Gaillard, & Mäntysalo, 1978). Although there is some evidence for attentional modulation of MMN (Trejo, Ryan-Jones, & Kramer, 1995; Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998), MMN is elicited even when attention is directed away from the auditory input. Thus, the significance of MMN results can be more easily interpreted than that of P300 results if the motivational factor of the subjects cannot be controlled, as in the case of psychiatric patients. This automatic mismatch process might have an important role in initiating an involuntary switching of attention to an auditory stimulus change occurring outside the focus of attention (Giard, Perrin, Pernier, & Bouchet, 1990; Lyytinen, Blomberg, & Näätänen, 1992; Näätänen, 1992).

Among various psychiatric disorders, MMN has been studied mainly in schizophrenia. In a meta-analysis of MMN (Umbricht & Krljes, 2005), it was concluded that MMN deficits are a robust

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feature of chronic schizophrenia and represent the underlying mechanism of attention dysfunction in schizophrenia. Studies of MMNm in schizophrenia also indicated an MMNm amplitude decrease in schizophrenia and changes in the equivalent current dipole (ECD) location (Kasai et al., 2003; Kreitschmann-Andermahr et al., 1999; Oades et al., 2006; Pekkonen et al., 2002).

There have been few studies of MMN in major depressive disorder patients. Umbricht et al. (2003) examined MMN generated in response to a pure-tone duration and a frequency change in major depressive disorder patients, bipolar disorder patients, schizophrenia patients, and in healthy volunteers and found no significant differences in MMN amplitude between major depressive disorder patients and healthy volunteers. Ogura, Nageishi, and Omura (1995) investigated major depressive disorder patients and bipolar disorder patients in the depressive state using the oddball paradigm of a tone-burst frequency change. They reported that the mean amplitude of the early N200 component (N2a), which corresponds to the MMN component, of the patients in the depressive state was smaller than that of the healthy volunteers. Lepistö et al. (2004) investigated MMN using a consonant sound change and a novel sound and found a short MMN latency and an unchanged MMN amplitude in children with major depressive disorder patients compared with those in healthy children. Taken together, these previous studies of MMN in major depressive disorder patients have not yielded sufficiently consistent results.

Another earlier ERP component, P1, often called P50, and its magnetic counterpart P1m are considered to reflect earlier stages of auditory information processing and, in accordance with the assumption, its dipole is located in the primary auditory cortex. This component is employed in studies of auditory information processing in psychiatric disorders. For example, Ahveninen et al. (2006) reported a significant P50 amplitude reduction and a marked deviation of P50m dipole sources in a twin study of schizophrenia, and assumed that a P50 amplitude reduction and a P50m dipole deviation might be a marker of brain function changes related to the genetic predisposition to schizophrenia and that these changes might be inherited as morphological changes in auditory cortex neurons. In fact, from these findings, the left superior temporal gyrus and left medial temporal lobe are considered to be key regions of structural difference in patients with schizophrenia (Honea, Crow, Passingham, & Mackay, 2005).

Whole-head magnetoencephalography (MEG) has advantages over scalp electroencephalography (EEG) in terms of its higher spatial resolution with many recording channels and its more accurate estimation of MMNm dipole locations. These advantages are due to the fact that magnetic fields are less affected by intervening tissues of different conductivities than electrical fields. To the best of our knowledge, there has been only one study of MMNm and P1m in major depressive disorder patients using MEG (Kähkönen et al., 2007). They used a pure-tone frequency deviant to elicit MMNm and found no significant differences in MMN amplitude or latency between major depressive disorder patients and healthy volunteers. In this study, we recorded MMNm and P1m by MEG in major depressive disorder patients in the passive oddball paradigms of vowel sounds as well as pure tone and examined their power and latency in relation to clinical symptoms and psychotropic medications. We also estimated the current dipoles of MMNm and P1m. Our hypotheses are as follows: (1) Preattentive information processing deficits are revealed as reduced MMNm power and/or delayed MMNm latency in major depressive disorder patients and (2) the locations of estimated current dipoles do not differ

between major depressive disorder patients and healthy volunteers because most voxel-based morphometry studies showed no anatomical differences in temporal structures between major depressive disorder patients and healthy volunteers (Beyer & Krishnan, 2002).

Methods

Participants

Fourteen major depressive disorder patients and 19 healthy volunteers participated in this study (Table 1). The major depressive disorder patients were recruited from the Department of Psychiatry, Gunma University Hospital, Japan. Each patient was diagnosed as having major depressive disorder in accordance with *DSM-IV* (American Psychiatric Association, 1994).

The major depressive disorder patients included 9 men and 5 women (age: mean, 41.4 years; *SD*, 10.2; range, 25–60). Major depressive disorder patients over 60 years old were not included in this study to eliminate the effects of additional pathophysiological factors on major depressive disorder such as aging and vascular changes.

During this study, all the subjects were euthymic or depressive, as indicated by their 17-item Hamilton Rating Scale for Depression (HRSD) scores (mean, 10.7; *SD*, 4.1; range, 5–19; Hamilton, 1960). According to the minimal state examination (MMSE) scores, there were no patients with dementia in the major depressive disorder group. However, 13 of the 14 patients were on medication with antidepressants, mood stabilizers, antipsychotics, anxiolytics, or hypnotics during this study. The imipramine equivalent dose of antidepressants, the diazepam equivalent dose of anxiolytics, and the flunitrazepam equivalent dose of hypnotics were calculated for each patient (Inagaki & Inada, 2006).

The healthy volunteers included 13 men and 6 women (age: mean, 37.7 years; *SD*, 10.0; range, 26–56). They had no history of any major psychiatric disorders or major physical illnesses and were not on any major psychiatric medications during this study. The mean age and sex ratio did not significantly differ between the two groups, $F(1,31) = 1.0$, $p = .32$; $\chi^2(1) = 0.62$, $p = .80$. All the subjects were right-handed as indicated by their Edinburgh inventory scores (mean, 96.8; *SD*, 6.0; range, 80–100; Oldfield, 1971). Their sleepiness scores at the time of MEG examination were assessed using the Stanford sleepiness scale. The sleepiness scores before, $F(1,31) = 0.29$, $p = .59$, and during the task performance, $F(1,31) = 1.52$, $p = .23$, did not differ significantly between the two groups.

For both the patients and healthy volunteers, Japanese was the first language. The exclusion criteria for both groups included clear abnormality of MRI results, neurological illness, traumatic brain injury with any of the known cognitive consequences or loss of consciousness for more than 5 min, substance use or addiction, and presence of hearing or vision impairment. This study was approved by the Institutional Review Board of Gunma University Hospital, and written informed consent was obtained from all the participants prior to the study.

Task Procedures

P1m and MMNm were recorded during an auditory task while the subjects were instructed to perform another visual task and to ignore the auditory stimuli.

Table 1. Characteristics of Participants

Case	Age (years)	Sex	Age of onset (years)	MMSE score	HRSD score	Total imipramine equivalent dose (mg/day)	Antidepressant (imipramine equivalent dose)	Mood stabilizer (mg/day)	Others (mg/day)
Major depressive disorder (<i>n</i> = 14)									
1	41	M	39	29	10	25	Sulpiride 50(25)		Zopiclone 7.5, Loflazepate 1
2	37	M	34	30	10	72.9	Milnacipran 100(66.7), Trazodone 25(12.5)		Nitrazepam 5
3	31	F	28	29	8	0			Loflazepate 1
4	37	M	24	29	6	75	Amitriptyline 75(75)	Lithium 600	Lorazepam 1, Zolpidem 5
5	37	M	36	30	13	60	Maprotiline 60(60)	Lithium 600	Lorazepam 1
6	54	F	24	30	9	112.5	Milnacipran 75(50), Sulpiride 100(50), Trazodone 25(12.5)		Clonazepam 1, Etizolam 1.5
7	58	M	57	29	7	25	Sulpiride 50(25)		Loflazepate 1
8	34	M	33	30	9	37.5	Paroxetine 10(37.5)		Levothyroxine 25
9	48	F	45	29	19	150	Paroxetine 40(150)		Quetiapine 100, Clonazepam 1.5, Nitrazepam 20, Quazepam 15, Flunitrazepam 2, Levothyroxine 25
10	42	F	20	30	12	125	Milnacipran 75(50),		Etizolam 1.5
11	25	F	24	28	13	82.5	Amoxapine 75(75) Milnacipran 30(20), Trazodone 125(62.5)	Valproate 200	Levomepromazine 5
12	40	M	34	30	11	300	Imipramine 150(150), Setiptiline 6(150)		Methylphenidate 10, Brotizolam 0.25, Triazolam 0.5, Flunitrazepam 2
13	60	M	34	30	18	141.7	Sulpiride 150(75), Maprotiline 25(25), Trazodone 25(12.5), Paroxetine 20(75)		
14	35	M					Sulpiride 150(75), Milnacipran 100(66.7)		Etizolam 1.5
Mean	41.4	M9/F5	34.6	29.5	10.7	99.6			
SD	10.2		10.9	0.7	4.1	79			
Healthy control (<i>n</i> = 19)									
Mean	37.7	M13/F6							
SD	10.0								

Note: M: male; F: female; HRSD: 17-item Hamilton Rating Scale for Depression.

Auditory mismatch negativity task. In the auditory task, the subjects were presented with sequences of auditory stimuli consisting of standard and deviant stimuli delivered randomly. The interstimulus interval was 445 ± 15 ms. The stimuli were delivered binaurally through plastic tubes. The experiment consisted of two conditions. The first condition was designed to elicit MMNm in response to duration and frequency changes of pure-tone stimuli (standard: 50-ms duration, 1000-Hz frequency, probability = 83%; duration deviant: 100-ms duration, 1000-Hz frequency, probability = 8.5%; frequency deviant: 50-ms duration, 1200-Hz frequency, probability = 8.5%). The second condition was designed to elicit MMNm in response to a vowel across-category change condition (standard, Japanese vowel sound/a/, probability = 90%; deviant, Japanese vowel sound/o/, probability = 10%). These vowel stimuli were spoken by a native Japanese, digitized using the NeuroStim system (NeuroScan, USA), and edited to have a loudness of 80 dB SPL and a rise/fall time of 10 ms. The frequency spectra for the vowels were as follows./a/: formant (F) 0 = 140, F1 = 760, F2 = 1250,

F3 = 2750, and F4 = 3600 Hz;/o/: F0 = 140, F1 = 480, F2 = 770, F3 = 2820, and F4 = 3600 Hz. The frequency of the pure-tone stimuli was 1000 Hz, nearly equal to the central frequency of the formants of the vowel stimuli. The order of the two conditions was counterbalanced across the subjects.

Visual task. The subjects performed a visual task while ignoring the auditory stimuli during MMNm measurement. The visual stimuli consisted of three sequences. Sequence 1 consisted of pictures of animals, flowers, buildings, and fruits. Sequence 2 consisted of pictures of sweets, flowers, animals, insects, castles, festivals, stone lanterns, and fruits. Sequence 3 consisted of pictures of birds, landscapes, flowers, and roads. The target pictures of Sequence 1 were animals, those of Sequence 2 were sweets, and those of Sequence 3 were birds. In each sequence, the target pictures were randomly presented with a probability of 30%. The pictures were sequentially presented at 2000-ms duration on a screen placed 1.7 m from the subjects. The subjects were instructed to press a button immediately after a target

picture was presented. The order of the three sequences was counterbalanced across the subjects.

Data Acquisition

MEG. Magnetic fields were recorded in a magnetically shielded room (JFE Mechanical Co., Japan) with a 306-channel magnetometer (Knuutila et al., 1993). This whole-head magnetometer consisted of 102 triple-sensor units, each with two orthogonal planar gradiometers and one magnetometer that records maximal signals directly above the source (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). We used a 204-channel gradiometer for data analysis except for a 102-channel magnetometer, because we could not record the data obtained with the 102-channel magnetometer for all subjects. A subject was instructed to sit on a chair with his/her head inside the helmet-shaped magnetometer. The position of the magnetometer with respect to the head was determined at the beginning of the task under each condition according to the magnetic fields produced by currents fed into three indicator coils at predetermined locations on the scalp. The locations of these coils in relation to the preauricular points and nasion were determined with an Isotrak 3D digitizer (Polhemus TM, USA) before the start of the experiment.

MEG epochs were averaged separately for standard and deviant stimuli. The duration of the averaging period was 420 ms, including a 100-ms prestimulus baseline. The recording bandpass range was 0.1–100 Hz, with a sampling rate of 512 Hz. The first 10 stimuli were automatically excluded from averaging. MEG epochs exceeding 3000 fT/cm were also excluded from averaging. Data collection under each condition lasted until 100 deviant stimuli that did not generate artifacts were presented. This number for averaging was adopted according to those adopted in previous studies (Alho et al., 1998; Kasai et al., 2003) and considering the balance between the signal-to-noise ratio and a possible habituation effect of MMN in response to speech sound (McGee et al., 2001). Average responses were digitally filtered in the bandpass range of 1–20 Hz.

Magnetic resonance imaging (MRI) of brain. In all the major depressive disorder patients and volunteers, a set of 2-mm-thick, sagittal MRI slices were acquired with 1.5-T equipment (MAGNETOM Symphony Maestro Class, Siemens Medical Solutions, Erlangen, Germany) using a three-dimensional (3D) fast spoiled gradient recalled acquisition in the steady state (FSPGR). The MEG coordinate system was aligned with the MRI-based coordinates by identifying the left and right preauricular points, as well as the nasion, from the MRI slices.

Data Analysis

Magnetic counterpart of global field powers (mGFPs) of P1m and MMNm. The mismatch reaction is defined as the difference between the magnetic field of the standard tone and the evoked field of the deviant tone. The magnetic fields of standard tones were subtracted from those of deviant tones for each channel, and the root mean squares of the differences over the 54 channels positioned over the temporal region (Figure 1) were calculated for each subject as the magnetic counterpart of the global field power (mGFP) of the mismatch reaction, separately for each condition and hemisphere, using the formula shown in Figure 2 (Kreitschmann-Andermahr et al., 1999; Lehmann & Skrandies, 1980). The peak latency of P1m was determined as the maximum amplitude of the individual mGFP curve of standard stimuli for

$$\text{mGFP (fT/cm)} = \sqrt{\frac{1}{n} \cdot \sum_{i=1}^n \left(U_i - \frac{\sum_{j=1}^n U_j}{n} \right)^2}$$

Figure 1. Grand mean waveform of magnetic fields for MMNm response to duration changes of pure-tone stimuli in major depressive disorder patients and healthy volunteers. Thick circles indicate selected channels. Thin circle indicates an enlarged picture of part of the channels. Left side: focused parts of the left hemisphere. Solid lines, major depressive disorder patients; dashed lines, healthy volunteers.

each condition between 40 and 100 ms (Tervaniemi et al., 1999). The individual curves of MMNm were calculated by subtracting the wave at each channel elicited in response to the standard tone from that elicited in response to deviant tones under the same experimental condition (Alho et al., 1998). The peak latency of MMNm was determined as the maximum amplitude of the individual mGFP curves between 100 and 250 ms (Kasai et al., 2003; Tervaniemi et al., 1999). The individual curve whose peak amplitude could not be found in the designated periods of those of P1m and MMNm was excluded from analysis.

Dipole analysis. Under each condition and for each subject, equivalent current dipoles for P1m and MMNm were calculated separately for each hemisphere, utilizing a spherical head model constructed on the basis of an individual MRI and a subset of 54 channels over the temporal brain areas (Figure 3). ECD of P1m was calculated from standard stimuli for each condition. ECD of MMNm was calculated from the deviant-stimulus response wave minus the standard-stimulus response wave. ECDs of MMNm and P1m were calculated at the same latency determined by mGFP analysis. The ECDs with a goodness of fit (GOF) greater than 70% were included in the analysis. In this procedure, we reduced the number of channels to 32–49 when the dipole was not calculated or a certain channel had a considerable number of artifacts. The mean GOFs for P1m under the two conditions and in the two hemispheres ranged from 85.7% to 90.6% for the major depressive disorder patients and from 85.5% to 90.4% for the healthy volunteers. The mean GOFs for MMNm under the three conditions and in the two hemispheres ranged from 84.4% to 88.1% for the major depressive disorder patients and from 82.4% to 85.8% for the healthy volunteers. Whenever available, the ECD locations for each subject were superimposed on his/her 3D-reconstructed MRI. The *x*-axis defined the right and left directions, the *y*-axis defined the anterior and posterior directions, and the *z*-axis defined the superior and inferior directions.

Statistical Analyses

The reaction time and correct answer rate during the visual task performance, age, and sleepiness scores before and during the task performance were compared between groups by one-way analysis of variance (ANOVA). We excluded the data of the visual task performance (reaction time and correct answer rate) over 3 SDs lower or higher than the average. The mGFP peak latencies and powers of P1m and MMNm were analyzed using three-way ANOVA with group (major depressive disorder patients and healthy volunteer), condition (pure-tone frequency change condition, pure-tone duration change condition, and vowel across-category change condition) and hemisphere (left and right) as independent variables, followed by Scheffe's post hoc test where appropriate. Spearman's rho was calculated in exploratory analyses of the relationships among the visual task

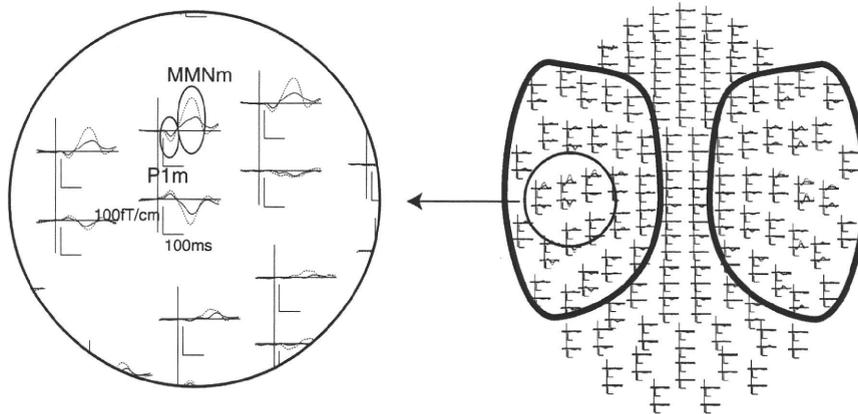


Figure 2. Formula for calculating mGFP. In this formula, n is the number of channels and u is the amplitude.

performance, clinical measures, and medications (reaction time, correct answer rate, age, HRSD score, age of onset, illness duration, and doses of antidepressants, anxiolytics, and hypnotics) and the mGFP power/peak latency or dipole location of P1m and MMNm.

The ECD locations of P1m and MMNm were compared between the two groups separately for each hemisphere using three-way ANOVA with group (major depressive disorder patients and healthy volunteer) and condition (pure-tone frequency change condition, pure-tone duration change condition, and vowel across-category change condition) as independent variables, followed by Scheffé's post hoc test where appropriate. The ECD location between P1m and MMNm was also compared separately for each hemisphere using one-way ANOVA. The statistical results were considered significant if $p < .05$ for the ANOVA of mGFP and the dipole analyses and $p < .01$ for the correlational analyses to avoid false positive findings in multiple correlation calculations.

Results

Behavioral Data

The reaction time during the visual task did not differ between the groups (major depressive disorder patients: mean, 588.3 ms; SD , 111.5; healthy volunteers: mean, 546.0 ms; SD , 70.6; $F[1,28] = 1.61$, $p = .22$). The correct answer rates in the visual task did not differ between the two groups (major depressive disorder patients: mean, 99.4%; SD , 0.5%; healthy volunteers: mean, 98.8%; SD , 1.3%). The Stanford sleepiness scores before and during the task did not significantly differ between the two groups.

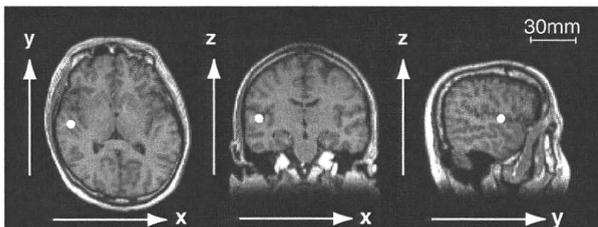


Figure 3. ECD location of MMNm of healthy volunteers for the pure-tone duration change condition in the left hemisphere. The arrows in this figure indicate each axis. The x -axis defines the right and left directions, the y -axis defines the anterior and posterior directions, and the z -axis defines the superior and inferior directions.

Magnetic Counterpart of Global Field Power (Table 2, Figures 4 and 5)

P1m. A three-way ANOVA of the mGFP power of P1m with group, condition, and hemisphere as independent variables revealed a significant effect of condition, $F(1,121) = 20.67$, $p < .01$, but not of group, hemisphere, or any interaction. A three-way ANOVA of the mGFP latency of P1m also revealed a significant effect of condition, $F(1,121) = 126.40$, $p < .01$, but not of group, hemisphere, or any interaction. Larger power and prolonged latency of mGFP in the vowel across-category change condition than in the pure tone condition were revealed.

MMNm. A three-way ANOVA of the mGFP power of MMNm with group, condition, and hemisphere as independent variables revealed significant effects of group, $F(1,186) = 7.01$, $p < .01$, and condition, $F(2,186) = 16.52$, $p < .01$, but not of hemisphere or any interaction. The mGFP powers of MMNm in the major depressive disorder patients were significantly smaller than those in the healthy volunteers. The Scheffé's post hoc test clarified that the mGFP powers of MMNm for pure-tone frequency change condition were significantly smaller than those for pure-tone duration change condition, $t(130) = 11.12$, $p < .01$, and vowel across-category change condition, $t(130) = 7.68$, $p < .01$. A post hoc two-way ANOVA of the mGFP power of MMNm with group and hemisphere as independent variables for each condition revealed trend-level significant effects of group in the vowel across-category condition, $F(1,62) = 3.04$, $p = .09$, and in the pure-tone duration change condition, $F(1,62) = 3.52$, $p = .07$, but not in the pure-tone frequency change condition, $F(1,62) = 0.61$, $p = .44$.

A three-way ANOVA of the mGFP latency of MMNm with group, condition, and hemisphere as the independent variables revealed a significant main effect of condition, $F(2,186) = 19.75$, $p < .01$, but not of group, hemisphere, or any interaction. The Scheffé's post hoc test clarified that the MMNm latencies were smaller in the pure-tone frequency change condition than in the pure-tone duration change condition, $t(135) = 30.46$, $p < .01$, and the vowel across-category change condition, $t(135) = 21.35$, $p < .01$.

Dipole Analysis

P1m. Reliable ECDs of P1m were successfully estimated in both the left and right hemispheres in 16 out of the 19 healthy

Table 2. Three-Way Factorial ANOVA of mGFP Amplitudes of MMNm and P1m with Group, Condition, and Hemisphere

		Group	Task	Hemisphere	Group × Task	Group × Hemisphere	Task × Hemisphere
MMNm	mGFP (fT/cm)	7.0**	16.5**	0.5	0.8	0.0	0.2
	mGFP latency (ms)	0.1	19.7**	0.3	1.8	1.2	0.2
P1m	mGFP (fT/cm)	2.2	20.7**	0.2	1.2	0.9	0.1
	mGFP latency (ms)	0.9	126.4**	3.5	0.1	1.0	0.0

Note: Group (major depressive disorder patients and healthy volunteers); Condition (vowel across-category change, pure-tone duration change, and frequency change); Hemisphere (right and left):

** $p < .01$.

subjects and in 12 out of 14 major depressive disorder patients and were estimated either in the left or the right hemisphere in 3 out of the 19 healthy subjects and in 3 out of the 14 major depressive disorder patients. A three-way ANOVA of x/mm , y/mm , and z/mm of estimated ECD locations with group, condition, and hemisphere as independent variables demonstrated a significant effect of hemisphere in y/mm , $F(1,118) = 31.93$, $p < .01$, and in z/mm , $F(1,118) = 13.13$, $p < .01$, but not of group, condition, or any interaction. These results indicate that the ECDs were located more anteriorly and superiorly in the left hemisphere than in the right hemisphere.

MMNm. Reliable ECDs of MMNm were successfully estimated both in the left and right hemispheres in 15 out of the 19 healthy subjects and in 8 out of the 14 major depressive disorder patients, and were estimated either in the left or the right hemisphere in only 4 out of the 19 healthy subjects and in 6 out of the 14 major depressive disorder patients. A three-way ANOVA of x/mm , y/mm , and z/mm of estimated ECD locations with group, condition, and hemisphere demonstrated a main effect of condition in y/mm , $F(2,174) = 4.59$, $p = .01$, and hemisphere in y/mm , $F(1,174) = 26.69$, $p < .01$, but not of group or any interaction. The Scheffé's post hoc test clarified that the ECDs were located more anteriorly in the vowel across-category change condition than in the pure-tone duration change condition, $t(126) = 4.55$, $p = .02$, and also were located more anteriorly in the right hemisphere than in the left hemisphere.

Comparison between P1m and MMNm. A one-way ANOVA of x/mm , y/mm , and z/mm of estimated ECD locations with component (P1m and MMNm) in each hemisphere revealed a significant main effect of component in z/mm , $F(1,154) = 4.61$, $p = .03$: The MMNm dipole is located inferiorly to the P1m dipole in the left hemisphere.

Correlational Analysis

In the healthy volunteers, the MMNm power in the right hemisphere in the pure-tone duration change condition significantly correlated with age ($\rho = -0.64$, $p < .01$) and the reaction time ($\rho = 0.61$, $p < .01$). The MMNm duration in the left hemisphere in the pure-tone duration change condition significantly correlated with the reaction time ($\rho = -0.71$, $p < .01$). In the major depressive disorder patients, there was no significant correlation of P1m or MMNm power/latency with age, HRSD score, age of onset, reaction time, correct answer rate, or doses of antidepressants, anxiolytics, and hypnotics. The P1m latency in the left hemisphere under the pure-tone condition significantly correlated with illness duration ($\rho = 0.73$, $p < .01$).

Discussion

Summary of Results

In this study, we investigated MMNm and P1m responses in major depressive disorder patients and healthy volunteers. The results are summarized as follows: (1) mGFP of MMNm was significantly smaller in the major depressive disorder patients than in the healthy volunteers; (2) mGFP of P1m did not differ between the two groups; (3) mGFP of MMNm did not correlate with depressive symptoms, psychotropic medication, age of onset, or illness duration; and (4) the locations of the estimated MMNm and P1m dipoles did not significantly differ between the two groups. These results suggest impaired preattentive information processing in major depressive disorder patients irrespective of the depressive state and psychotropic medication.

Comparison with Previous Studies

As described in the introduction, there has been only one study of MMNm and P1m in major depressive disorder patients using MEG (Kähkönen et al., 2007), and there has been only one study that directly examined MMN in major depressive disorder patients using EEG (Umbricht et al., 2003). Kähkönen et al. found no significant differences in MMN amplitude or latency between major depressive disorder patients and healthy volunteers using pure-tone frequency deviant to elicit MMNm. Umbricht et al. (2003) found no significant differences in MMN amplitude or latency between major depressive disorder patients and healthy volunteers using pure-tone frequency deviant and pure-tone duration deviant to elicit MMNm. In our results, a three-way ANOVA of the mGFP power of MMNm with group, condition, and hemisphere as independent variables revealed significant effects of group, and a post hoc two-way ANOVA of the mGFP power of MMNm with group and hemisphere as independent variables for each condition revealed trend-level significant effects of group in the vowel across-category condition and in the pure-tone duration change condition but not in the pure-tone frequency change condition. This result is partly replicated in previous studies in the sense that the mGFP power and latency of MMNm were not significantly different between the major depressive disorder patients and the healthy volunteers in the pure-tone frequency change condition. However, our results were in disagreement with those of Umbricht et al. (2003) as well in the sense that the mGFP power of MMNm in the pure-tone duration change showed the trend-level significant effects in our study. There was a study showing that attention affects MMN power (Yucel, Petty, McCarthy, & Belger, 2005); thus, the difference in the methods of distracting the subjects' attention from the auditory stimuli may also be responsible for the difference between our results and Umbricht's results, because of the difference in the visual task procedure. However, an obvious difference between our study and their studies was in the physical