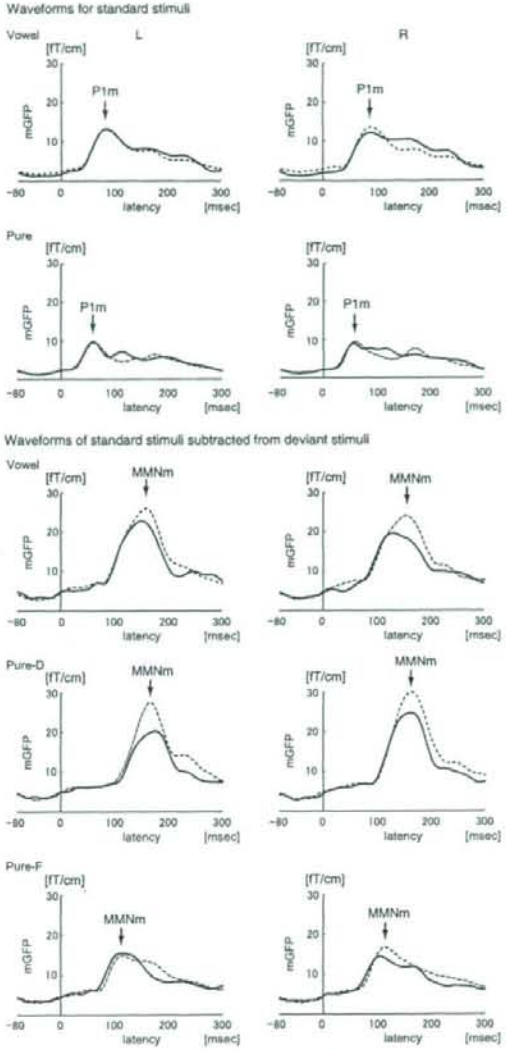

Figure 4. Grand mean mGFP waveforms of P1m (upper four panels) and MMNm (lower six panels) averaged for each group (major depressive disorder patients [solid line] and healthy volunteers [dashed line]), for each condition (vowel across-category change condition [Vowel], pure-tone [Pure], pure-tone duration change condition [Pure-D] and pure-tone frequency change condition [Pure-F]), and for each hemisphere (right [R], left [L]).

properties. They elicited MMNm in response to duration changes of pure-tone stimuli (standard: 100-ms duration, 1000-Hz frequency; duration deviant: 250-ms duration, 1000-Hz frequency), whereas we elicited MMNm in response to duration changes of pure-tone stimuli (standard: 50-ms duration, 1000-Hz frequency; duration deviant: 100-ms duration, 1000-Hz frequency). Without appropriate control conditions, exogenous/obligatory responses contributing differently to the repetitive standard stimulus and the rare deviant stimulus affect the results (Kujala, Tervaniemi, & Schröger, 2007). As in their studies, we did not control this effect; thus, the difference between our results and their results may be due to the non-MMN contribution such as offset-N1.

The absence of group differences in the mGFP powers and latencies of P1m in this study is also in disagreement with the results of Kähkönen et al. (2007). Whereas they found a shorter P1m latency in the major depressive disorder patients and its significant negative correlation with the HDRS scores, no such significant differences or correlations were obtained in this study. These differences cannot be explained by the differences in the

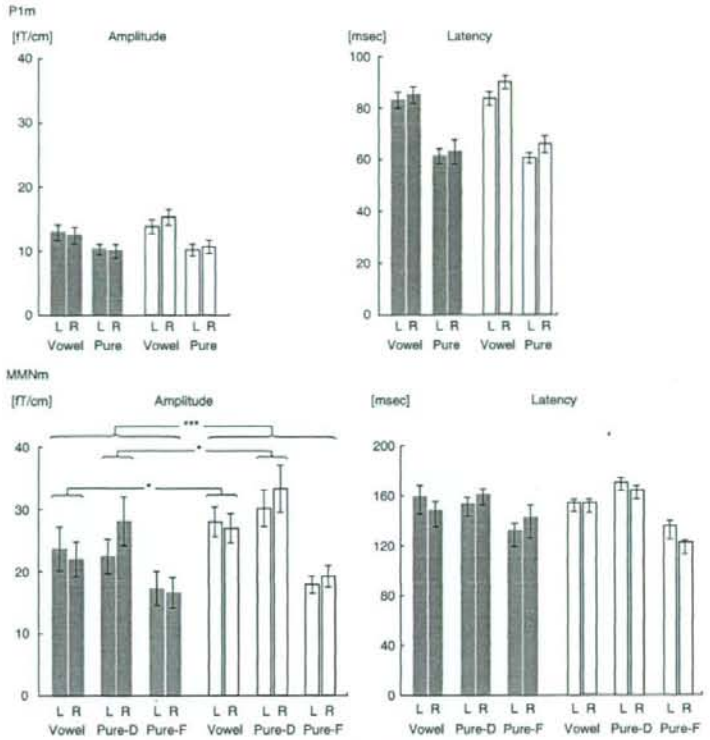

Figure 5. mGFP powers and latencies of P1m (upper panels) and MMNm (lower panels) averaged for each group (major depressive disorder patients [gray], healthy volunteers [white]), for each condition (vowel across-category change condition [Vowel], pure-tone duration change condition [Pure-D], and pure-tone frequency change condition [Pure-F]) and for each hemisphere (right [R], left [L]). Each error bar indicates standard error: $^{*}p < .1$; $^{**}p < .05$; $^{***}p < .01$.

task conditions described above. The differences in the severity of the depressive symptoms between the patients in the two studies may be one of the possible reasons for the difference in the results. The HDRS scores in this study were smaller those in the study by Kähkönen et al.

In the child subjects, Lepistö et al. (2004) found unchanged MMN amplitude and smaller MMN latency in major depressive disorder patients. In addition, Ogura et al. (1995) examined the N200 component in adult major depressive disorder and bipolar disorder and found small amplitudes of the early N200 component that is assumed to correspond to MMN. The results of this study are in agreement with those of Ogura et al. (1995) but not with those of Lepistö et al. Differences in task designs and in the age, severity of depressive symptoms, and medication status of the subjects may partly explain these discrepancies.

Relationship between MMN and Clinical Variables

The absence of significant correlations between MMNm power and doses of antidepressants, anxiolytics, and hypnotics in this study suggests that a smaller MMNm power in major depressive disorder patients is not due to the effects of psychotropic medication. In addition, although the MMN amplitude has been reported to be reduced in Alzheimer's disease and dementia (Pekkonen, 2000; Schroeder, Ritter, & Vaughan, 1995), MMNm power reduction in this study is not assumed to be due to intellectual decline in the subjects, because the subjects suspected of having dementia were excluded from our study on the basis of their MMSE scores.

The clinical significance of the MMNm power reduction in major depressive disorder patients can be speculated considering the lack of significant correlations of MMNm power with clinical variables. The lack of a significant correlation between MMNm power and clinical symptoms may suggest that the MMNm power reduction is not a state-dependent finding. The lack of a significant correlation between MMNm power and illness duration or age of onset may suggest its nonprogressive nature. Taken together, MMNm power reduction in major depressive disorder patients may be assumed to reflect the trait for developing major depressive disorder or the morbid process of developing major depressive disorder.

Shuchaku-Seikaku (*Shuchaku* the tendency for obsessive preoccupation with certain thoughts and affairs; *Seikaku* character) is a type of personality often observed as a premorbid personality of depression, particularly in Japan. MMN (N2a component) amplitude reduction in *Shuchaku-Seikaku* patients supports this interpretation (Ogura et al., 1991). This interpretation should be examined in future studies with more subjects and detailed personality assessments.

On the other hand, MMN amplitude for a pure-tone frequency change condition in schizophrenia was demonstrated to correlate with illness duration in a meta-analysis (Umbricht & Krljes, 2005), and MMN amplitude in schizophrenia was demonstrated to be reduced in recent-onset and chronic patients but not in first-episode patients (Umbricht, Bates, Lieberman, Kane, & Javitt, 2006). These findings support the deteriorating nature of MMN through the illness course. On the other hand, MMN amplitude has been reported to be reduced in adolescent-onset schizophrenia (Oades et al., 2006), which may suggest the trait-dependent or morbid-process-related nature of MMN reduction. Moreover, MMN amplitude reduction in schizophrenia may be interpreted to indicate state-dependent neurodegeneration based on the finding that MMN amplitude in a nonaffected member of twin pairs discordant for schizophrenia is unchanged when compared with that in healthy subjects (Ahveninen et al., 2006).

The results of the MMNm dipole location suggest an additional significance of MMNm abnormalities in major depressive disorder patients. The MMNm dipole has been estimated to be located more laterally in schizophrenia patients than in healthy volunteers in some studies (Kasai et al., 2003; Oades et al., 2006; Pekkonen et al., 2002), and the location shift is interpreted to reflect functional and structural abnormalities in the temporal lobe. The unchanged dipole location of MMNm in major depressive disorder patients in this study suggests that MMNm abnormalities in major depressive disorder patients are more functional than structural. However, this finding should be regarded as preliminary because correction for brain size was not considered. Preserved P1m power in this study also suggests additional significance of MMNm power reduction in major depressive disorder patients. Major depressive disorder patients may be relatively spared in sensory function (P1m) but more impaired in higher cognitive function, including preattentive level (MMNm), as compared with schizophrenia in which both P1m and MMNm powers are reduced (Ahveninen et al., 2006).

P1m Results

Some of the results obtained in this study are different among the three task conditions. As for P1m, both its mGFP and latency were significantly smaller in the pure-tone condition than in the vowel across-category change condition. As for MMNm, its mGFP and latency were significantly smaller in the pure-tone frequency change condition than in the pure-tone duration change condition and the vowel across-category change condition. These results suggest that P1m may be affected mainly by the physical property of the sound, whereas in the case of MMNm, it may be affected by the task conditions in a more complex manner.

This assumption is also supported by the estimated locations of the dipoles. Although the locations of the P1m dipole were not estimated differently across the task conditions, the locations of MMNm were estimated more anteriorly in the vowel across-category change condition than in the pure-tone duration change condition but not in the pure-tone frequency change condition. Comparison between P1m and MMNm resulted in the differences in the location: The MMNm dipole is located more superiorly than the P1m dipole. These results suggest again that the location of MMNm is affected not only by the physical property of the sound but also by the task condition.

Limitations of This Study

The limitations of this study are as follows: (1) The number of subjects is small; (2) the results were drawn from patients with mild to moderate symptoms; and (3) although we found no significant correlation of MMNm or P1m finding with psychotropic medication except mood stabilizers, the effect of psychotropic medication cannot be completely excluded because almost all the patients took psychotropic drugs. In the future, studies with more subjects in various mood states in a drug-free condition and longitudinal follow-up cohort studies including premorbid patients will be performed.

Conclusions

We investigated preattentive information processing in major depressive disorder patients by MEG using MMNm and P1m. The MMNm power was smaller in major depressive disorder patients than in healthy volunteers. This result suggests the functional dysfunction of preattentive information processing irrespective of clinical symptoms and psychotropic medication in major depressive disorder patients; this dysfunction is not due to the dysfunction at the lower level of information processing.

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Research Report

The influence of gender and personality traits on individual difference in auditory mismatch: A magnetoencephalographic (MMNm) study

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ABSTRACT

The mismatch negativity (MMN; and its magnetic counterpart, MMNm) is widely used to assess early-stage auditory cortical function in humans and its impairment in various neuropsychiatric disorders. To establish MMN as a useful clinical tool for objective monitoring of auditory cortical function in an individual, we investigated the effect of gender and personality traits on individual difference in MMNm in healthy subjects. Participants were 88 healthy adults (31 women and 57 men). The MMNm in response to the duration or frequency change of tones and those in response to across-phoneme change between vowels /a/ and /o/ were recorded using 204-channel whole-head magnetoencephalography. The temperament and character inventory (TCI) was used to assess individual personality traits. Women were associated with significantly delayed peak latency of phonetic MMNm for the right hemisphere compared with men. Men had greater strength of tonal duration MMNm for the left hemisphere than women. Additionally, the persistence score predicted the strength of phonetic MMNm for the left hemisphere in the combined sample and the tonal duration MMNm for the left hemisphere in men; reward dependence predicted the latency of the tonal duration MMNm for the left hemisphere in men; and cooperativeness predicted the strength of the tonal frequency MMNm for the right hemisphere in women. These results suggest that gender and personality traits have an effect on individual variability of the MMNm. Our observation may provide useful information to establish MMN/MMNm as a clinical tool for monitoring auditory cortical function on an individual basis.

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1. Introduction

The auditory mismatch negativity (MMN) is an event-related potential (ERP) component elicited at approximately 100–200 ms by infrequent, physically deviant stimuli in a sequence of identical, repeated sounds (standard stimulus) (Näätänen et al., 1993). Näätänen et al. (1993) noted that MMN (or its magnetic counterpart (MMNm) measured by magnetoencephalography (MEG)) represents human sensory memory function as it is generated by an automatic (attention-independent) neural mismatch process with a memory trace that encodes the physical features of the standard stimulus. MMN is also referred to as an index of preattentive processing as well as an auditory automatic change detection process, since it can be detected even in the passive condition when subjects entirely ignore stimuli. Recent findings have also suggested that the transient auditory sensory-memory representation underlying the MMN is facilitated by a long-term memory representation of the corresponding stimulus. This means that some characteristics of the sensory-memory traces involved in the elicitation of this component are stored in a more durable representation and that these memory traces can be reactivated (Winkler and Cowan, 2005). MMN(m) is also elicited by contrast between phonetic stimuli (for review, see Näätänen et al., 2007).

Tonal and phonetic MMN(m) is widely used to investigate the pathophysiological mechanisms of neuropsychiatric disorders, such as schizophrenia (for tonal MMN, see Umbricht and Krljes, 2005 for review; phonetic MMN(m), Kasai et al., 2002b, 2003), depression (Lepistö et al., 2004) and autism (Ferri et al., 2003, Kasai et al., 2005), where groups with neuropsychiatric disorders indicate lower amplitude or delayed latency of MMN(m) than psychiatrically healthy groups. In contrast, Morgan and Grillon (1999) reported that the amplitude of the MMN was significantly greater in women with posttraumatic stress disorder (PTSD) compared to the non-PTSD women. To establish MMN(m) as a useful clinical tool for estimating individual ability of auditory cortical function, two issues have to be assessed: one is diagnostic values; and the other is the sources of inter-individual difference. For the former issue, for example, Javitt et al. (1995) reported that they were able to identify 29 of 30 patients with schizophrenia and 5 of 10 controls with an MMN amplitude cutoff of −5.0 μV. For the latter issue, we need to clarify the effect of gender and personality traits on the inter-individual difference in MMN(m), which are the main purpose of the current study. In particular, observed gender differences in the prevalence and course of various psychiatric disorders makes it highly likely that gender is a factor in inter-individual differences (for example, Kessler et al., 1993; Smeeth et al., 2004). Improving our knowledge about sex differences will enhance our ability to develop sex-specific evaluation and treatments for neuropsychiatric brain disorders (Cosgrove et al., 2007).

Previous studies have investigated gender difference in electric MMN (Barrett et al., 1998; Kasai et al., 2002a; Kudo et al., 2004; Nagy et al., 2003; Schirmer et al., 2005), but the results were not conclusive. Barrett and Fulfs (1998) found a significant gender effect for tonal intensity MMN. Although the results of Schirmer et al. (2005) were preliminary, they reported gender difference in emotional phonetic MMN. In contrast, Kasai et al. (2002a) reported no gender effect for either tonal duration MMN or phonetic MMN. Kudo et al. (2004) similarly showed no gender effect for tonal duration MMN. Additionally, Nagy et al. (2003) found no gender effect for tonal frequency MMN. To our knowledge, however, no studies have investigated gender effects on MMNm.

In the current study, we also sought to investigate the effect of personality on individual variability of MMNm. Cloninger et al. (1993) proposed a psychobiological model of temperament and character and developed a self-report questionnaire consisting of 240 items, called Temperament and Character Inventory (TCI), to evaluate personality traits. The use of self-report questionnaires such as TCI has been well-established as a means to assess individual differences in behavioral traits (Cloninger, 1987; Cloninger et al., 1993). TCI is based on the hypothesis that personality consists of two components; temperament and character. Temperament (consisting of four dimensions: novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P)) is considered to be stable throughout life, and character (consisting of three dimensions: self-directedness (SD), cooperativeness (C), and self-transcendence (ST)) to be mature in adulthood (Cloninger et al., 1993). NS is defined as the tendency towards excitement in response to novel or rewarding stimuli; HA corresponds to the tendency toward an inhibitory response to signals of adverse stimuli; and RD

Table 1 – Mean peak ECD latencies for MMNm in female and male participants

Stimulus	Hemisphere	Male (n=44–53[a])		Female (n=25–27[a])		df[a]	t	P
		Mean	S.D.	Mean	S.D.			
Phonetic change	Left	143.4	28.4	144.7	35.1	76	−0.18	0.86
	Right	135.8	33.5	153.7	39.6	75	−2.08	0.041[b]
Tonal duration change	Left	166.0	22.1	159.9	18.5	76	1.22	0.23
	Right	151.3	27.4	152.1	27.1	78	−0.12	0.91
Tonal frequency change	Left	137.7	29.5	131.2	25.3	67	0.93	0.36
	Right	129.6	29.4	123.1	26.1	66	0.91	0.36

[a] Subjects N and degrees of freedom vary across stimuli since ECD was not successfully determined for some participants in some stimuli.
[b] Reached significance.

Table 2 – Mean peak ECD strengths for MMNm in female and male participants

Stimulus	Hemisphere	Male (n=44–53[a])		Female (n=25–27[a])		df[a]	t	P
		Mean	S.D.	Mean	S.D.			
Phonetic change	Left	21.9	10.4	23.3	14.9	76	−0.51	0.62
	Right	19.7	13.0	25.0	19.7	75	−1.39	0.17
Tonal duration change	Left	24.5	14.2	18.3	7.7	76	2.10	0.039[b]
	Right	27.0	14.4	25.5	18.8	78	0.41	0.68
Tonal frequency change	Left	17.0	9.4	16.3	7.8	67	0.32	0.75
	Right	20.2	11.7	18.1	8.8	66	0.76	0.45

[a] Subjects N and degrees of freedom vary across stimuli since ECD was not successfully determined for some subjects in some stimuli.
[b] Reached significance.

reflects the tendency for a positive response to signals of reward to maintain behavioral extinction. According to Cloninger's model, the three dimensions are assumed to be inheritable and independent, and each dimension has been tied to a specific neurotransmitter; NS to dopaminergic activity; HA to serotonergic activity; and RD to noradrenergic activity.

Several reports have investigated the relationship between ERP measures and TCI scores. Hansenne (1999) reported that auditory P300 amplitude was negatively correlated with HA and positively with NS. Vedeniapin et al. (2001) showed that reduced amplitude of visual P300 was associated with lower scores on SD in healthy participants. Moreover, Kim et al. (2002) reported that the P300 amplitude at Fz was significantly positively associated with RD. To our knowledge, only two studies to date have been published in terms of MMN and personality correlations. Wang et al. (2001) showed that in healthy subjects, auditory MMN amplitude at Fz was positively correlated with neuroticism-anxiety, but negatively with experience seeking. Hansenne et al. (2003) reported no correlations between either tonal duration MMN amplitude or latency and TCI scores except for a significant negative correlation between MMN amplitude and HA. No study, however, has explored the relationship between MMNm and personality traits.

To summarize, although there have been a few studies on gender and personality effects on electric MMN, no studies to date have utilized MMNm. The electrophysiological signals measured in MMNm are not entirely equivalent to those in MMN, since MEG and EEG detect different components of mismatch response. First, MEG detects cortical magnetic fields that are not influenced by intervening tissues of different conductivities in contrast to electrical potentials (Hämäläinen et al., 1993). This enables an independent assessment of the left and right hemispheric functions. Next, MEG selectively detects electrical currents tangential to the scalp, whereas EEG detects both radial and tangential electrical currents (Hämäläinen et al., 1993). Thus, the MEG predominantly detects mismatch response generated in the superior temporal plane (Alho et al., 1998), which has more tangentially oriented currents, although it is less sensitive to that from other generators such as the frontal component, which has more radically oriented currents (Kasai et al., 1999). Thus, the purpose of this study was to evaluate the effect of gender and personality on MMNm, ultimately in order to establish MEG assessment of mismatch as a useful clinical assessment tool for auditory cortical function.

2. Results

2.1. *Task performance of visual target detection task*

The response time and the hit rate were not different between genders for either stimulus sequence (p's>0.5).

2.2. *Effect of gender*

Women had a significantly longer peak latency of MMNm under the phonetic change stimuli in the right hemisphere than men ($t[75]=-2.08$, $p=0.041$) (Table 1). Men had a significantly stronger ECD under the tonal duration stimuli in the left hemisphere than women ($t[76]=2.10$, $p=0.039$) (Table 2). There were no significant gender differences in TCI scores (Table 3).

2.3. *Relationships between MMNm and TCI scores*

We found a significant correlation between ECD strength for phonetic MMNm in the left hemisphere and persistence (gender collapsed), between ECD latency for tonal duration MMNm in left hemisphere and reward dependence (male), between ECD strength for tonal duration MMNm in left hemisphere and persistence (male), and between ECD

Table 3 – Mean scores of TCI in female and male participants

TCI items	Male (n=57)		Female (n=31)		df	t	P
	Mean	S.D.	Mean	S.D.			
NS	20.9	5.5	22.2	4.7	86	−1.11	0.27
HA	17.7	7.3	16.4	6.1	86	0.85	0.40
RD	15.4	3.2	16.1	3.3	86	−0.98	0.33
P	4.7	1.7	4.4	1.9	86	0.79	0.43
SD	29.5	8.2	30.8	8.2	86	−0.70	0.49
C	28.6	4.8	30.3	5.9	86	−1.43	0.16
ST	8.8	5.0	10.9	6.6	86	−1.70	0.09

None reached significance.

Table 4 – Regressional coefficients (beta) of simple linear regression analyses and correlation coefficients (r) of correlational analyses for the ECD values and TCI scores, in particular, significant correlations are summarized

Stimuli	Latency or Strength	Hemisphere	Gender	TCI	Simple linear		Correlation	
					B	p	R	P
Phonetic change	Strength	Left	Mix	Persistence	−0.318	0.005	−0.232	0.041
Tonal duration change	Latency	Left	Male	Reward Dependence	0.381	0.006	0.468	<0.001
Tonal duration change	Strength	Left	Male	Persistence	−0.316	0.024	−0.325	0.020
Tonal frequency change	Strength	Right	Female	Cooperativeness	−0.523	0.009	−0.481	0.017

strength for tonal frequency MMNm in right hemisphere and cooperativeness (female) (Table 4, Fig. 1).

3. Discussion

The findings of our study can be summarized as follows: 1) gender effects on MMNm: women showed significantly delayed peak latency of phonetic MMNm for the right hemisphere compared with men, while men had greater strength of tonal duration MMNm for the left hemisphere than women; 2) personality effects on MMNm: the persistence score predicted the strength of phonetic MMNm for the left hemisphere in the combined sample; the tonal duration MMNm for the left hemisphere in men; reward dependence predicted the latency of the tonal duration MMNm for the left hemisphere in men; and cooperativeness predicted the strength of the tonal frequency MMNm for the right hemisphere in women.

To our knowledge, this is the first study that provides information regarding gender and personality trait effects on latency and strength of phonetic and tonal MMNm in normal adults. The results of this study suggest that gender and personality may affect MMNm strength or latency, and that these effects vary depending on stimuli (tone-duration, tone-frequency, and phoneme). These results are of relevance to researchers who investigate the MMN/MMNm in healthy individuals and various clinical groups.

First, we interpret our findings of gender effects on MMNm. To date, several studies have reported gender differences in electric MMN (Barrett and Fulfs, 1998; Kasai et al., 2002a; Kudo et al., 2004; Nagy et al., 2003; Schirmer et al., 2005). Of these studies, only three (Kasai et al., 2002a; Kudo et al., 2004; Nagy et al., 2003) adopted similar conditions for eliciting MMN to those in our current study (i.e. use of auditory tonal or phonetic stimuli), but none of them found a gender effect on MMN. Kasai et al. (2002a) paper included 18 males and 10 females (age: male, 25.7 yrs, female, 27.0 yrs), while the current study included 57 males and 31 females (age: male, 30.6 yrs, female, 29.8 yrs). The characteristics of age range and sex distribution do not appear to significantly differ between the two studies. One possible reason why Kasai et al. (2002a) reported negative findings may be a lack of sufficient sample

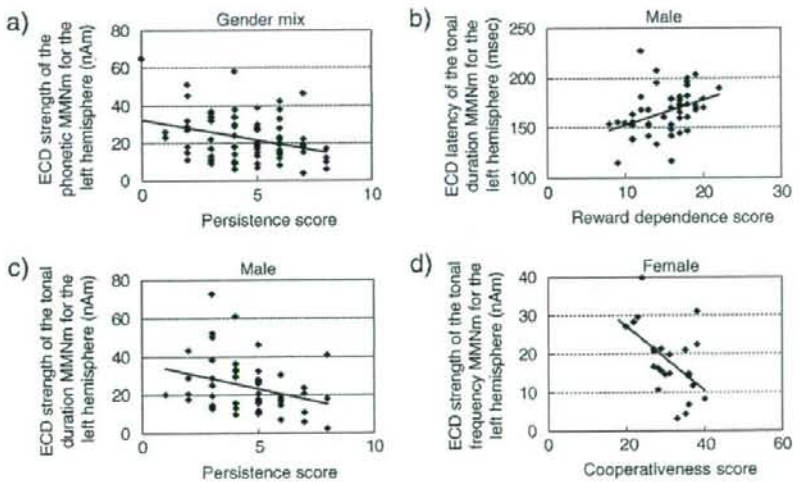

Fig. 1 – Scatterplots depicting significant correlations between ECD strength or latency for MMNm and TCI score, respectively; (a) a correlation between ECD strength for phonetic MMNm in the left hemisphere and persistence scores (gender collapsed), (b) between ECD latency for tonal duration MMNm in left hemisphere and reward dependence (male), (c) between ECD strength for tonal duration MMNm in left hemisphere and persistence (male), and (d) between ECD strength for tonal frequency MMNm in right hemisphere and cooperativeness (female).

size to yield significance. However, a major reason for the discrepancy between past studies and the present study may stem from the technical difference between EEG and MEG. While EEG detects mismatch response generated in both the frontal lobe and the superior temporal plane (Näätänen and Alho, 1995), MEG predominantly detects signals in the superior temporal plane due to detectable vectors of neural activities. In fact, Kudo et al. (2006) found no meaningful correlation between MMN amplitude and MMNm strength data obtained in a group of healthy subjects. We therefore interpreted our findings of gender effects on MMNm in relation to brain structure, particularly concerning gender difference in superior temporal plane. Within the superior temporal plane, tonal MMN has been shown to be generated from Heschl's gyrus (Javitt et al., 1994) and phonetic MMN could possibly be generated from the planum temporale, which is located posterior (caudal) to Heschl's gyrus (Tervaniemi et al., 2000). These areas have been reported to display sexual dimorphism. For example, Good et al. (2001) suggested that women had greater gray matter volume of right posterior superior temporal gyrus than male, whereas men had greater gray matter volume of left anterior superior temporal gyrus than women. Im et al. (2006) data suggested that women have a thicker right caudal superior temporal gyrus than that of men. Although speculative, it is possible that sexual dimorphism in brain structure may influence our findings that women had longer latency of phonetic MMNm for the right hemisphere than men and that men had greater strength of tonal duration MMNm for the left hemisphere than women.

Second, we discuss the relationships between MMNm and TCI scores. To our knowledge, only one previous study has reported relationships between mismatch response and TCI score (Hansenne et al. 2003). They reported a significant negative correlation between tonal duration (electric) MMN amplitude and HA, while our results suggested that P, RD and C scores may impact on MMNm values. One of the major reasons for this discrepancy may be the technical difference between EEG and MEG, as discussed above. Additionally, the SOA used in Hansenne et al. study was longer (800 ms) than those used in standard paradigms (about 500 ms), which resulted in overall amplitudes of MMN being relatively small. Iidaka et al. (2006) reported a significantly positive correlation between RD and right caudate nucleus volume using voxel-based morphometry which survived small volume correction. They also found a trend-level positive correlation between RD and volumes of right inferior temporal gyrus and superior temporal gyrus (uncorrected $p<0.001$). However, we found that higher score on RD was associated with longer tonal MMNm latency in the LEFT hemisphere. Thus, Iidaka et al. data are not necessarily compatible with ours.

Some comment on the methodological issues of the current study is required. First, the tonal stimuli and the phoneme stimuli were not matched for duration of the stimuli (50–100 ms duration for tonal MMNm; 250 ms duration for phonetic MMNm). However, we chose the physical features of the stimuli so that each of the stimuli would be similar to standard methods used in the literature, since we ultimately sought to establish optimal MMN methods for clinical application. Second, we did not measure EEG in the present study participants. Further studies will be necessary to concurrently evaluate both MEG and EEG to investigate how the relationship between gender and personality traits and auditory mismatch differs between MEG and EEG.

In summary, the present study suggests that gender and personality traits have an effect on individual variability of the MMNm. Our observation may provide useful information to establish MMN/MMNm as a clinical tool for monitoring auditory cortical function on an individual basis.

4. Experimental procedures

4.1. Subjects

Participants were 88 healthy individuals (31 women and 57 men; mean=30.1 yrs [SD=7.3; range: 20–56]; women: mean=30.6 [SD=8.4]; men: mean=29.8 [SD=6.7]). All participants were right-handed (determined using the Edinburgh inventory (Oldfield, 1971) and gave informed consent before the experiment in accordance the protocol approved by the Ethics Committee of the University of Tokyo and the Institutional Research Board of Gunma University Graduate School of Medicine.

4.2. TCI assessment

Personality traits were assessed using the Temperament and Character Inventory (TCI)— Japanese version (Kijima et al., 2000). Each participant completed the 240 item self-questionnaire TCI within three months after the MEG measurements.

4.3. Tasks

The subjects were presented with auditory stimuli (80 dB SPL and a rise/fall time of 10 ms) through ear tubes to both ears. To keep attention away from auditory stimuli, they were instructed to ignore the stimuli and to perform a visual target detection task. In the visual target detection task, the subjects pressed a button when the target stimuli (e.g., animal) were presented on a screen in front of the subject. The target stimuli were presented randomly (not being synchronized with auditory sequence for eliciting auditory MMNm) and the probability of the appearance was 30%.

The experiment consisted of two separate sequences. The first sequence was to elicit MMNm in response to duration and frequency change of pure-tone stimuli (standard, 1000 Hz, 50 ms, 83%; duration-deviant, 1000 Hz, 100 ms, 8.3%; frequency-deviant, 1200 Hz, 50 ms, 8.3%). The sequence lasted until 120 duration-deviant and 120 frequency-deviant stimuli were presented. The second was to elicit MMNm in response to phonemic change (standard, Japanese vowel /a/, 250 ms, 90%; deviant, Japanese vowel /o/, 250 ms, 10%). These vowel stimuli were spoken by a native-Japanese-speaking actor, digitized using the NeuroStim system (NeuroScan Inc., U.S.A.). The stimulus sequence lasted until 120 deviant stimuli were presented. The SOA was set at 445+/−15 ms for cancelling the offset response to affect averaged evoked magnetic fields. The order of the two sequences was counterbalanced across the participants.

4.4. MEG recordings and analysis

MEG signals were recorded in a magnetically shielded room using VectorView (Elekta Neuromag, Helsinki, Finland), which has 204 first-order planar gradiometers at 102 measuring sites on a helmet-shaped surface that covers the entire scalp. The position of the magnetometer with respect to the head was determined at the beginning of the task by recording 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 before the start of the experiment with an Isotrak 3D-digitizer (Polhemus TM, U.S.A.).The recorded data were filtered online with a band-pass filter of 0.03–100 Hz, digitalized at a sampling rate of 512 Hz, and averaged online separately for standard and deviant stimuli. The duration of the averaging period was 400 ms, including a 80-ms prestimulus baseline. The measurement data coinciding with electrooculogram (EOG) movement exceeding 150 μV or MEG exceeding 3000 fT/cm were also excluded from averaging. The EOG was measured above the outer canthus of the left eye. We used signal space separation filtering (signal-space projections; SSP) for cancellation of external noise and correction of movement and DC measurements. Averaging was conducted separately for deviant and standard stimuli. The number of deviant stimuli was above 100 for all stimulus sequences. The averaged data were further filtered offline with a band-pass filter of 1–20 Hz.

For each subject under each stimulus, equivalent current dipoles (ECDs) for MMF were calculated primarily according to the method of Alho et al. (1998). Briefly, the MMNm was determined from the difference curves obtained by subtracting the response to standard stimuli from that to deviant stimuli. Then, ECDs were determined using a single-dipole model (least-squares fit) at 2-ms intervals from 100 to 250 ms. The calculation, using a spherical head model, was performed using a subset of 54 channels over the temporal brain areas separately for each hemisphere. The sphere was individually fitted to the scalp of each participant using a magnetic resonance image of each participant. The average of goodness-of-fit for the dipole estimation was 86.0% (SD=8.1).

4.5. Statistical analysis

Initially, Student's t-test was used to investigate the gender difference in MMNm values (ECD strength, peak latency) under each stimulus and in scores on each item of the TCI. Second, simple linear regression and correlational analyses were performed to investigate the relationships between each MMNm value (ECD strength, latency) and each TCI score separately for each gender. Finally, two additional analyses were performed to test for gender specificity in the correlation between MMNm values and TCI scores observed in the second (correlational) analysis. One analysis tested if the regression slopes for male and female were significantly different. The other analysis tested if the correlation coefficients for male and female were significantly different using Fisher's r to z transformation. If both analyses were significant, the correlation was regarded as gender-specific. Otherwise, the relationship between MMNm value and TCI score was reanalyzed after the data were collapsed across gender. $p<0.05$ (two-tailed) was considered significant for all analyses.

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Reduced frontopolar activation during verbal fluency task in schizophrenia: A multi-channel near-infrared spectroscopy study

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Abstract

Functional neuroimaging studies to date have shown prefrontal dysfunction during executive tasks in schizophrenia. However, relationships between hemodynamic response in prefrontal sub-regions and clinical characteristics have been unclear. The objective of this study is to evaluate prefrontal hemodynamic response related to an executive task in schizophrenia and to assess the relationship between activation in the prefrontal sub-regions and clinical status. Fifty-five subjects with schizophrenia and age- and gender-matched 70 healthy subjects were recruited for this case-control study in a medical school affiliated hospital in the Tokyo metropolitan area, Japan. We measured hemoglobin concentration changes in the prefrontal (dorsolateral, ventrolateral, and frontopolar regions) and superior temporal cortical surface area during verbal fluency test using 52-channel near-infrared spectroscopy, which enables real-time monitoring of cerebral blood volumes in the cortical surface area under a more restraint-free environment than positron emission tomography or functional magnetic resonance imaging. The two groups showed distinct spatiotemporal pattern of oxy-hemoglobin concentration change during verbal fluency test. Schizophrenia patients were associated with slower and reduced increase in prefrontal activation than healthy controls. In particular, reduced activations of the frontopolar region, rather than lateral prefrontal or superior temporal regions, showed significant positive correlations with lower global assessment of functioning scores in the patient group, although task performance was not significantly associated with the scores. These results suggest that reduced frontopolar cortical activation is associated with functional impairment in patients with schizophrenia and that near-infrared spectroscopy may be an efficient clinical tool for monitoring these characteristics.

Keywords: Schizophrenia; Near-infrared spectroscopy (NIRS); Frontopolar prefrontal cortex; Verbal fluency test; Global assessment of functioning (GAF)

1. Introduction

Neuroimaging studies have identified schizophrenia as being associated with dysfunction of the prefrontal cortex (Callicot et al., 2000; Carter et al., 1998; Curtis et al., 1998), an area involved in almost all high-level cognitive functions such as working memory, memory

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retrieval, executive function, and language (Cabeza and Nyberg, 2000). Moreover, recent advances in neuroscience have sought to clarify functional segregation in the prefrontal cortical surface areas such as dorsolateral, ventrolateral, and frontopolar (anterior frontal) regions (Daw et al., 2006; Fletcher and Henson, 2001; Fox et al., 2006). The ventrolateral and dorsolateral sub-regions are involved in the updating/maintenance of information and to the selection/manipulation/monitoring of that information, respectively (Fletcher and Henson, 2001). In contrast, frontopolar cortex (BA 10), which has been suggested to have enlarged and become specialized during hominid evolution (Semendeferi et al., 2001), provides higher level of control to coordinate ventrolateral and dorsolateral functions in order to maximize task performance (Koechlin et al., 1999; Fletcher and Henson, 2001; Braver and Bongiolatti, 2002), which has led to the idea that frontopolar region is likely to have a vital role in achieving high-order executive control in everyday life (Burgess et al., 2000). However, it remains unclear which specific sub-regions of the prefrontal cortex is most directly associated with clinical characteristics in schizophrenia.

An independent line of work has suggested that cognitive deficits as indexed by neuropsychological assessments are more tightly coupled with social functioning in patients with schizophrenia than positive or negative symptoms (Green, 1996; Green et al., 2000; Green et al., 2004; Flashman and Green, 2004). Whereas progress has been made for an association between psychosocial impairment and electrophysiological measures such as P300, N200b, and mismatch negativity event-related potentials (Ikebuchi et al., 1996; Iwanami et al., 1999; Kawakubo and Kasai, 2006; Light and Braff, 2005; Ohno et al., 2000) and brain morphological measures (Ho et al., 2003; Milev et al., 2003; Prasad et al., 2005; Staal et al., 2001; Wassink et al., 1999), the relationships between functional hemodynamic response in the sub-regions of the prefrontal cortex and clinical characteristics in schizophrenia has been unclear. These research questions may be an important step towards developing an objective monitoring tool and ultimately an effective intervention strategy for cognitive and social dysfunction in schizophrenia.

Multi-channel near-infrared spectroscopy (NIRS), a recently developed functional neuroimaging technology, enables the non-invasive detection of spatiotemporal characteristics of brain function (Strangman et al., 2002a, 2003; Boas et al., 2004; Huppert et al., 2006). NIRS has enabled non-invasive and bedside measurement of the concentrations of oxy-hemoglobin ([oxy-Hb]) and deoxy-hemoglobin ([deoxy-Hb]), which are assumed to reflect the regional cerebral blood volume (rCBV). While functional brain imaging methodologies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have an excellent spatial resolution, they are limited in that they require large apparatuses which prevents their use in a bedside setting for diagnostic and treatment purposes. In contrast, NIRS is a neuroimaging modality that, for the following reasons is especially suitable for psychiatric patients (Matsuo et al., 2003a). First, because NIRS is relatively insensitive to motion artifact, it can be applied to experiments that might cause some motion of the subjects such as vocalization. Second, the subject can be examined in a natural sitting position, without any surrounding distraction. Third, the cost is much lower than other neuroimaging modalities and the set-up is very easy. Fourth, the high temporal resolution of NIRS is useful in characterizing the time course of prefrontal activity of psychiatric disorders (Kameyama et al., 2006; Suto et al., 2004). Accordingly, NIRS has been used to assess brain functions in many psychiatric disorders, including schizophrenia, bipolar disorder, depression, dementia, post traumatic stress disorder, and pervasive developmental disorders (Fallgatter et al., 1997; Hock et al., 1997; Kameyama et al., 2006; Kubota et al., 2005; Kuwabara et al., 2006; Matsuo et al., 2003a, b, 2004; Shinba et al., 2004; Suto et al., 2004).

A previous study (Suto et al., 2004) showed reduced [oxy-Hb] changes in the prefrontal cortex during verbal fluency task in patients with schizophrenia using a NIRS machine with insufficient coverage of important sub-regions of the prefrontal cortex such as ventrolateral portions. The purpose of the present study was to use an NIRS machine with a wide coverage of the prefrontal cortex in order to investigate more precisely the relationship between activity in the prefrontal sub-regions and the clinical characteristics in a larger group of patients with schizophrenia.

2. Materials and methods

2.1. Subjects

Fifty-five patients with schizophrenia and 70 age- and gender-matched healthy subjects participated in the study (Table 1). All the participants were right-handed according to the Edinburgh Inventory (Oldfield, 1971) and were native Japanese speakers.

The patients were recruited among outpatients and inpatients at the University of Tokyo Hospital. Diagnosis of schizophrenia was made through the Structured Clinical Interview for DSM-IV Axis I Disorders (First

Table 1
Clinical characteristics of the study groups

	Patients with schizophrenia (N=55)		Healthy subjects (N=70)		Group difference P value
	Mean	SD	Mean	SD	
Age, year	40.1	11.1	37.4	13.6	.22
Gender, women/men	26/29		34/36		.89[a]
Handedness	92.4	17.3	92.9	16.3	.85
Education, year	14.7	2.5	15.6	2.0	.022
Self socio-economic status (SES)	3.4	1.1	2.0	.6	<.001
Parental SES	2.5	.7	2.3	.7	.18
Estimated premorbid IQ	102.3	12.2	108.3	9.8	.006
Number of words generated	14.3	4.6	17.3	4.4	<.001
Age at onset, years	26.4	8.7	NA		
Duration of illness, years	13.8	10	NA		
PANSS					
Positive	16.7	5.6	NA		
Negative	21.6	6.4	NA		
General psychopathology	38.2	7.9	NA		
Global Assessment of Functioning (GAF)	47.2	12.9	NA		
Medication					
Chlorpromazine equivalent dose, mg/day	778	655	NA		
Diazepam equivalent dose, mg/day	13.4	18.5	NA		
Biperiden equivalent dose, mg/day	3.2	2.3	NA		

Abbreviations: IQ, Intelligence Quotient; PANSS, Positive and Negative Symptom Scale; NA, not applicable.
[a] Chi-square test was used for testing group difference. Otherwise, t-test was used.

et al., 1997) by an experienced psychiatrist (K.K.). For screening of healthy subjects, SCID non-patient edition (SCID-NP) was used. On the same day as the near-infrared spectroscopy (NIRS) experiment, psychiatric symptoms and the level of social functioning were evaluated by one psychiatrist (K.K.) using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Global Assessment of Functioning scores (GAF) (American Psychiatric Association, 1994), respectively, without knowledge of the NIRS data. At the time of the study, the patients with schizophrenia were on medication with antipsychotics and/or anxiolytics and/or antiparkinsonian agents. Socioeconomic status (SES) and parental SES were assessed using the Hollingshead scale (Hollingshead, 1965). Premorbid IQs were estimated using Japanese version of the National Adult Reading Test (Matsuoka et al., 2006) (Table 1). The reliability of the GAF as an assessment of social functioning was confirmed based on the high correlation between GAF scores and total scores on the Japanese version of Life Skills Profile (N=55, r=.61, P<.001) (Parker et al., 1991; Japanese version, Hasegawa et al., 1997).

The exclusion criteria for both groups were neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, and alcohol/substance abuse or addiction. An additional exclusion criterion for the control group was a history of psychiatric disease in themselves or a family history of axis I disorder in their first-degree relatives. The ethical committee of the Hospital of Tokyo University approved this study. All subjects gave written informed consent according to the Declaration of Helsinki after a complete explanation of the study.

2.2. Activation task

[Hb] changes were measured during a cognitive activation task. Each participant sat on a comfortable chair with their eyes open throughout the measurements. The subjects were instructed to minimize movement such as head movements, strong biting and eye blinking during the NIRS measurements, for they can produce artifacts or changes in cerebral perfusion unrelated to the task.

The cognitive activation task included a 30-s pre-task baseline, a 60-s verbal fluency task (letter version), and a 70-s post-task baseline. The verbal fluency test was chosen, because it has been often used for cognitive activation in NIRS studies, and previous reports showed measurable prefrontal activation during the letter fluency task in healthy subjects (Herrmann et al., 2003, 2006; Kameyama et al., 2004). This procedure was similar to that of Suto et al. (2004), Ito et al. (2005) and Kameyama

et al. (2006) except for the use of a 70-s post-task baseline instead of their 60 s, to enable a more complete return of [Hb] change to the baseline in the post-task period.

For the pre- and post-task baseline periods, the subjects were instructed to repeat Japanese vowels (/a/, /i/, /u/, /e/ and /o/) aloud. This was intended to correct the data during the fluency task for activation due to vocalization.

During the verbal fluency task period, they were instructed to generate as many Japanese words beginning with a designated syllable as possible, which is commonly used in Japanese letter version of the verbal fluency task since Japanese words inevitably begin with a vowel or consonant-vowel syllable. The three initial syllables (first; /to/, /a/, or /na/, second; /i/, /ki/, or /se/, third; /ta/, /o/, or /ha/) were presented in the order which was counterbalanced among the subjects and changed every 20 s during the 60-second task to reduce the time during which the subjects remained silent. The subjects were instructed by an auditory cue at the start and end of the task and when the syllable was changed. Because the number of words generated was not significantly different among the three initial syllables (one-way repeated measures ANOVA; $F[2, 123]=1.28$, $P=.28$, n.s.), the total of correct words generated during verbal fluency tasks was defined as a measure of task performance (Table 1).

2.3. NIRS measurement

The 52-multi-channel NIRS machine (ETG-4000, Hitachi Medical Co.) measures relative changes of [oxy-Hb] and [deoxy-Hb] using two wavelengths (695 nm and 830 nm) of infrared light based on the modified Beer–Lambert law (Yamashita et al., 1996). The [total-Hb] was calculated as the sum of [oxy-Hb] and [deoxy-Hb]. In this system, these [Hb] values include differential pathlength factor (DPF). The distance between pairs of source-detector probes was set at 3.0 cm and we defined each measuring area between pairs of source-

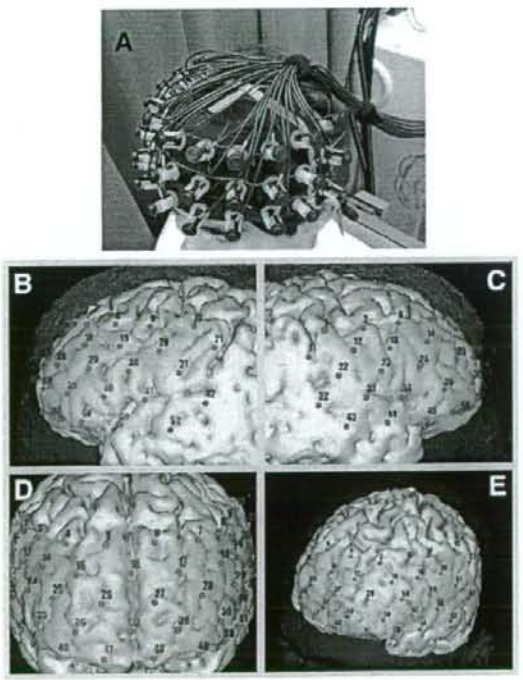

Fig. 1. The probe setting and measurement points of 52-channel near-infrared spectroscopy (NIRS). Panel A: the probes with thermoplastic 3 × 11 shells were placed over a subject's bilateral frontal regions. Panels B–E: the 52 measuring positions of the NIRS machine are superimposed on 3D-reconstructed cerebral cortical surface from magnetic resonance imaging of a representative subject. The channel numbers are indicated above the measuring points.

detector probes as 'channel'. It is supposed that the machine, in which the source-detector spacing is 3.0 cm, measures points at 2–3 cm depth from the scalp, that is, the surface of the cerebral cortex (Hock et al., 1997; Okada and Delpy, 2003a,b; Toronov et al., 2001). The probes of the NIRS machine were fixed with thermoplastic 3 × 11 shells, with the lowest probes positioned along the Fp1-Fp2 line according to the international 10–20 system used in electroencephalography. The time needed for this fixation is usually less than 5 min, which is less-demanding for the subjects. The 52 measuring areas are labeled ch1-ch52 from the right-posterior to the left-anterior. This arrangement of the probes can measure [Hb] from bilateral prefrontal (approximately dorsolateral [Brodmann's area (BA) 9, 46], ventrolateral [BA 44, 45], and frontopolar [BA 10]) and superior temporal cortical surface regions (Fig. 1, panel A). The correspondence of the probe positions and the measuring areas on the cerebral cortex was confirmed by superimposing the measuring positions on a magnetic resonance image of a three-dimensionally reconstructed cerebral cortex of a representative subject (Fig. 1, panels B–E).

The time resolution of the NIRS machine was set at .1 s. [Hb] changes were analyzed using the first-order correction to exclude task-unrelated changes during the verbal fluency task. The pre-task baseline was determined as the mean across the last 10 s of the pre-task period and the post-task baseline was determined as the mean across the last 5 s of the post-task period, and a linear fitting was performed based on the data between the two baselines. Moving average methods were applied to remove short-term motion artifacts in the analyzed data (moving average window: 5 s). Grand mean waveforms averaged across subjects were created separately for type of [Hb] and for each group. The moving average methods cannot correct all the artifacts and the most researchers qualitatively judge and remove the data with significant

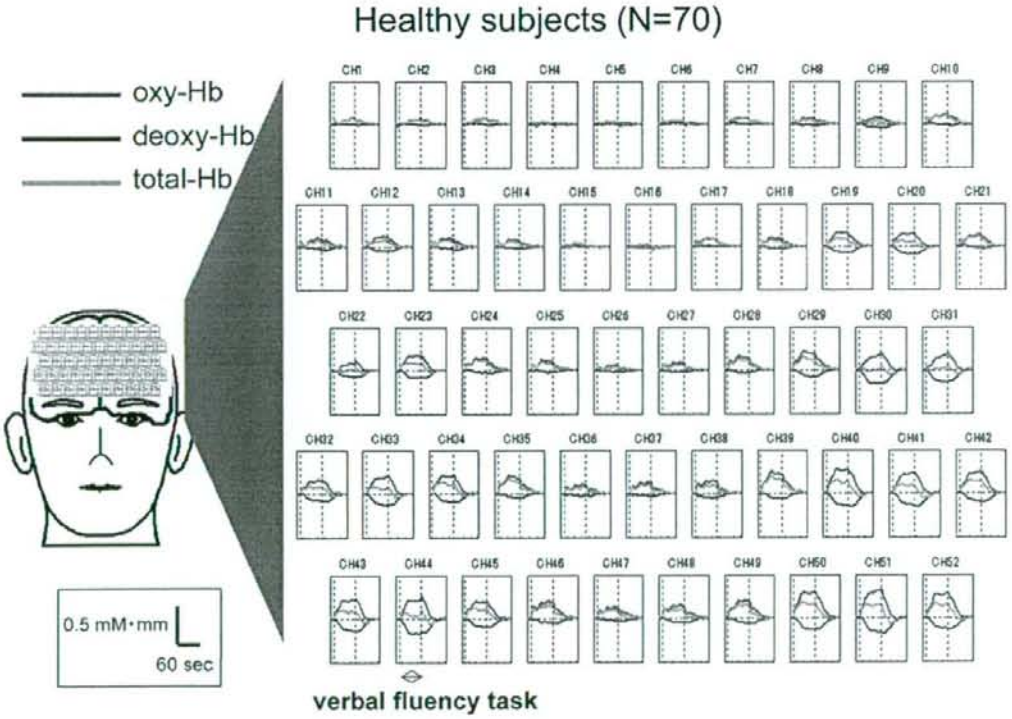

Fig. 2. Grand average waveforms in healthy subjects ($N = 70$). Oxy-, deoxy-, and total-hemoglobin concentration changes during cognitive activation are presented as grand average waveforms in 52 channels in red, blue, and green lines, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

artifacts; however, it remains subjective (Sato et al., 2006). Thus, we developed an algorithm to quantitatively evaluate the artifacts which enables a fully automatic rejection of data with artifacts (see Supplementary material I for details) separately for each channel; i.e., the number of averaged subjects varied across channels (schizophrenia: N=30–53 [mean, 43.8; SD, 5.4]; healthy subjects: N=34–67 [mean, 58.1; SD, 6.7]; percentage: schizophrenia, 80.7%; healthy subjects, 84.4%, n.s.).

2.4. Statistical analysis

For data analysis using parametric statistical tests, obtained [Hb] data of each channel were averaged across the two time segments (pre-task baseline and task period). We focused on [oxy-Hb] here, since [oxy-Hb] change is assumed to more directly reflect cognitive activation than [deoxy-Hb] change as shown by a stronger correlation with blood-oxygenation level-dependent signal measured by fMRI (Strangman et al., 2002b), although the analysis of [deoxy-Hb] was also shown (see Supplementary material II for details). First, at each channel, the mean [Hb] for the pre-task baseline period and that for the task period were compared using Student's paired t-test in order to confirm the statistically significant increase associated with the verbal fluency task. Since we performed 52 paired t-tests, the correction for multiple comparisons was made using false discovery rate (FDR) (two-tailed; we set the value of q specifying the maximum FDR to .05, so that there are no more than 5% false positives on average (Singh and Dan, 2006)). Next, the mean [Hb] changes during the 60-s task period were compared between the two groups for each channel by Student's t-test (two-tailed was used since task-load-dependent hypo- or hyperperfusion of prefrontal cortex in schizophrenia was found in previous literature; FDR correction for multiple comparisons [52 channels] was applied). As a confirmatory analysis, we performed the same group comparison of the performance-matched (50 healthy controls: mean, 15.8 [SD=3.5]; 50 schizophrenia patients: mean, 15.0 [SD=4.1]; t[2,98]=1.02, P=.31, n.s.) and premorbid

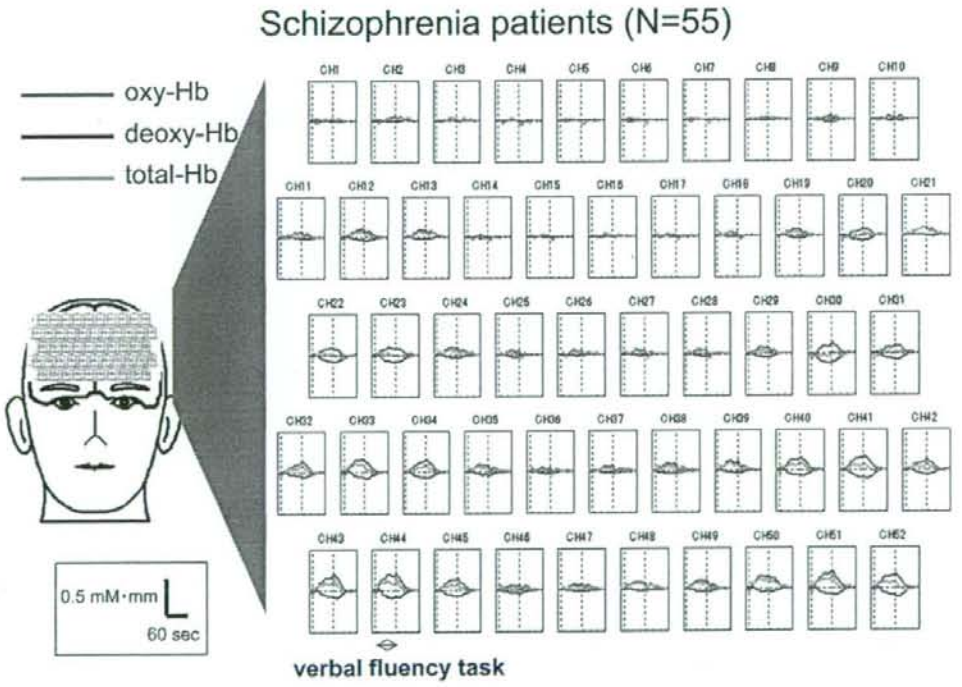

Fig. 3. Grand average waveforms in schizophrenia patients (N=55). Oxy-, deoxy-, and total-hemoglobin concentration changes during cognitive activation are presented as grand average waveforms in 52 channels in red, blue, and green lines, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

IQ-matched (48 healthy controls: mean, 106.8 [SD= 9.0]; 48 schizophrenia patients: mean, 104.9 [SD=10.1]; $t[2,94]=.96$, $P=.34$, n.s.) samples. Third, for analysis in time course of [Hb] change, the slope of the first 5-s during the task period were compared between the two groups for each channel by Student's paired t-test (two-tailed; FDR correction for multiple comparisons [52 channels] was applied).

For the schizophrenia group, Pearson's correlation coefficients were calculated for a relationship between the mean [Hb] changes during the task period and the GAF and PANSS scores for each channel. Degrees of freedom varied across the channels due to the artifact rejection procedure explained above. Since we sought to explore which regions of the brain showed more association with clinical assessment, we did not use the multiple correction; rather, we performed multiple correlational analyses for each channel and evaluated the graduation of the r values that reached a significance level of $P<.05$ over the frontotemporal regions (Fig. 5).

Additionally, we performed correlational analysis of [Hb] and age, duration of illness, dose of medication in the schizophrenia group. Statistical analysis was performed using SPSS 10.1.3J software (Tokyo, Japan).

3. Results

3.1. Test for significance in [Hb] change during activation period relative to baseline

The grand averaged waveforms of [oxy-Hb], [deoxy-Hb], and [total-Hb] during cognitive activations in healthy controls and schizophrenia patients were shown in Figs. 2 and 3.

A significant increase in [oxy-Hb] changes occurred during the task period relative to the pre-task baseline at 43 channels (ch7-14, ch17-25, ch27-52; FDR-corrected P: .001 to .041) in healthy controls and at 23 channels (ch12-13, ch19, ch24, ch29, ch32-35, ch37-45, ch48-52;

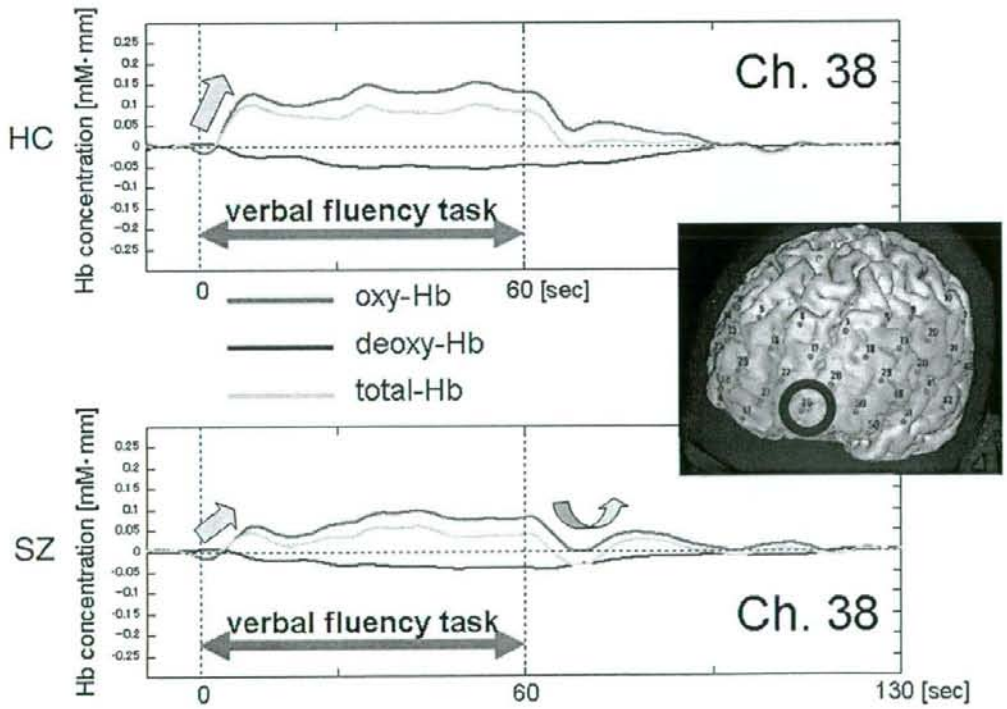

Fig. 4. The differential time course of [Hb] changes in healthy subjects and schizophrenia patients. The differential time course of [Hb] changes between healthy controls (HC; $N=70$) and schizophrenia patients (SZ; $N=55$) were indicated in a representative channel (channel 38; left frontopolar region).

FDR-corrected P: .001 to .022) in schizophrenia patients.

3.2. Group comparison

Schizophrenia patients were associated with significantly lower [oxy-Hb] increase than healthy subjects at 20 channels (ch 17-18, ch24-25, ch28-29, ch 35-40, ch42, ch46-52; FDR-corrected P: .001 to .019). The statistical conclusion did not significantly change when the task-performance-matched sample (significance found at 37 channels [ch1, ch3, ch7-8, ch10, ch14, ch17-21, ch24-25, ch27-32, ch34-43, ch45-52; FDR-corrected P: .001 to .036) or the premorbid IQ-matched sample [significant found at 33 channels (ch7-10, ch14, ch17-21, ch24-25, ch28-29, ch31-32, ch34-43, ch45-47, ch49-52; FDR-corrected P: .001 to .031) were compared.

3.3. Time course of [oxy-Hb] change

The [oxy-Hb] slope of the first 5-s in the task period was significantly steeper in healthy subjects than those in schizophrenia patients at 33 channels (ch1, ch3, ch5, ch10, ch12-13, ch17-18, ch20-21, ch23-25, ch28-32, ch34-35, ch38-47, ch49-52; FDR-corrected P: .001 to .031). Fig. 4 indicates the differential time course between healthy subjects and schizophrenia patients in a representative channel (ch38; left frontopolar region). In healthy subjects, the [oxy-Hb] rapidly increased at the beginning of the verbal fluency task, remained at the activated level during the task and gradually decreased after the end of the task. In contrast, the [oxy-Hb] in schizophrenia patients showed more gradual and lower increase during the task period, and began to decrease immediately after the end of the task, then followed by an inefficient re-increase during the post-task period. These differential patterns were similar to the findings reported by Suto et al. (2004) using a similar protocol.

3.4. Correlational analysis

In schizophrenia patients, the mean [oxy-Hb] changes showed a significantly positive correlation with GAF scores in 10 channels (ch13: r=.34, P=.04; ch16: r=.29, P=.05; ch24: r=.29, P=.04; ch25: r=.40, P=.004; ch26: r=.32, P=.02; ch27: r=.30, P=.04; ch36: r=.38, P=.007; ch37: r=.29, P=.05; ch38: r=.38, P=.007; ch47: r=.32, P=.04), with the highest correlations located approximately in the frontopolar (BA 10) and right dorsolateral (BA 9, 46) regions (Fig. 5), although task performance during verbal fluency test was not significantly correlated with GAF scores.

The mean [oxy-Hb] changes during the task period were not significantly correlated with premorbid IQ or task performance for any channels in either group. The mean [oxy-Hb] changes also showed no significant correlation with clinical variables including duration of illness or dose of medication in the schizophrenia group, except for a significant correlation with age at channel 21 (r=−.35, P=.02). Correlations with PANSS scores were found in a few channels: positive (ch23: r=.37, P=.03; ch33: r=.38, P=.01; ch38: r=.33, P=.02; ch49: r=.31, P=.03); negative (none); general psychopathology (ch12: r=−.32, P=.04; ch25; r=−.36, P=.01; ch27: r=−.32, P=.03; ch36: r=−.35, P=.01; ch47: r=−.32, P=.03), which did not converge on specific sub-regions or in consistent directions.

3.5. Comparison between high- and low-social functioning group in schizophrenia

To confirm the relationship between prefrontal cortical activation and social functioning, we divided patients with schizophrenia into high- and low-social functioning groups by the GAF median value of 52. Student's t-test was used to compare [Oxy-Hb] change between 28 high social functioning group (14 male and 14 female) and 27 low-social functioning group (15 males and 12 females). Potential confounding factors such as age, gender, task performance and premorbid IQ were matched between the two condition groups (not

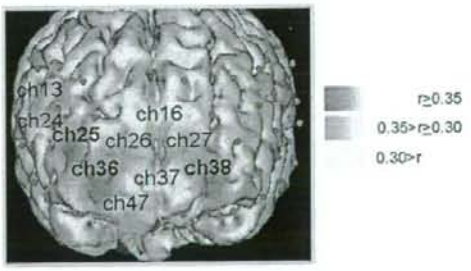

Fig. 5. The cortical distribution of a significant correlation between oxy-hemoglobin changes and global assessment of functioning (GAF) scores. The channels with a significant correlation (Pearson's correlation; P<.05) between the mean [oxy-Hb] changes and GAF scores were indicated with colored area. To illustrate the graduation of the correlation coefficients over the prefrontal cortical surface area, channels with $r \geq .35$ were colored in red, $.35 > r \geq .30$ in orange, and r<.30 in yellow. These areas approximately correspond to frontopolar region (BA 10) and right dorsolateral region (BA 9 and 46). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

described). We found a significant difference in the [oxy-Hb] change between the two groups in the channels located in frontopolar and right dorsolateral prefrontal regions (A significant difference at 5 channels; ch13 (right DLPFC), $P=.018$; ch25 (right DLPFC), $P=.037$; ch26 (right FPPFC), $P=.048$; ch38 (left FPPFC), $P=.029$; ch39 (left FPPFC), $P=.050$).

4. Discussion

Using a 52-channel NIRS with a wide coverage over the prefrontal cortical surface area, it was shown that [oxy-Hb] change during verbal fluency test was significantly slower and smaller in schizophrenia patients as compared with age- and gender-matched healthy subjects, which was not explained by difference in task performance or premorbid IQ. Furthermore, this smaller [oxy-Hb] change following cognitive activation was significantly associated with severer functional impairment in the schizophrenia patients, although the relationship between GAF score and verbal fluency task performance was not significant. And, the regions that showed significant association with the global assessment of functioning were relatively localized in frontopolar regions (BA 10). These results suggest that reduced frontopolar cortical activation associated with executive tasks may be associated with functional impairment in schizophrenia and that NIRS may offer promise as a non-invasive clinical method for evaluating these differential patterns in schizophrenia patients.

4.1. Prefrontal sub-regions

The present study has segregated specific regions in the prefrontal cortex associated with functional impairment in patients with schizophrenia. Petrides' model proposed that ventrolateral prefrontal regions (BA 44/45) are involved in simple short-term operation, whereas middorsal regions perform high-level executive or working memory operations, such as monitoring, reasoning and planning (Petrides, 1994; 1995; Owen, 1997). Fletcher and Henson (2001) attributed ventrolateral and dorsolateral activations to the updating/maintenance of information and to the selection/manipulation/monitoring of that information, respectively. In contrast, recent studies have shed light upon an important role of frontopolar regions (also known as anterior prefrontal cortex) (BA 10), which has been relatively less recognized in functional neuroimaging studies, in higher-order integrative prefrontal function (Ramnani and Owen, 2004). Interestingly, area 10 has been suggested to have enlarged and become specialized during hominid evolution by comparative studies of humans and apes (Semendeferi et al., 2001). Frontopolar regions might provide higher level of control to coordinate ventrolateral and dorsolateral functions in order to maximize task performance, or to achieve these goals (Koechlin et al., 1999; Fletcher and Henson, 2001; Braver and Bongiolatti, 2002). Christoff and Gabrieli (2000) proposed that frontopolar activations become recruited when internally generated information needs to be evaluated. Areas 9/10 are also involved in selecting among competing candidate responses (Desmond et al., 1996; Thompson-Schill et al., 1997).

4.2. Verbal fluency task and prefrontal cortex

In the present NIRS study, the verbal fluency test recruited widespread regions of the prefrontal cortical surface area and superior temporal regions, which is in accordance with previous studies using fMRI and PET (Elfgren and Risberg, 1998; Cabeza and Nyberg, 2000). The verbal fluency test not only requires retrieval of items from long-term memory storage but also concurrently requires working memory capacity to hold the already-generated words, maintenance of cognitive effort, and inhibition of inappropriate response (Henry and Crawford, 2004). This characteristic of the task demands may recruit frontopolar regions as well as lateral prefrontal cortex. Social daily activities require complex operations of working memory, executive function and memory retrieval that including monitoring, reasoning, organizing, selecting and planning, rather than simple short-term operations. Burgess et al. (2000) noted that the high-level of executive control associated with the frontopolar region is likely to be a vital component of everyday life. Considering these observations together, it may be reasonable to postulate that the smaller activations observed in the frontopolar regions during verbal fluency test in the present study were associated with severer functional impairment in schizophrenia.

Our study replicated the findings of reduced prefrontal activation during the letter version of the verbal fluency test in schizophrenia patients (Curtis et al., 1998; Suto et al., 2004). However, neuropsychological studies on Western populations have suggested that the category version of the verbal fluency test is more severely impaired than the letter version of the verbal fluency test in schizophrenia (Bokat and Goldberg, 2003). However, Japanese patients with schizophrenia have been shown to have a similar degree of impairments in both tasks (Sumiyoshi et al., 2004). Future studies should conduct an NIRS measurement during letter and category fluency test and investigate the relationship with functional outcome in Japanese patients with schizophrenia.