activations, although the exact regions involved and extent of signal reduction were different between these patient groups. This led us to expect that apparent similar PFC signal reductions observed for patients with SZ and MDD could be derived from differential neurophysiological findings. These functional brain abnormalities might be valuable for investigating differential brain pathophysiology in different psychiatric disorders. Furthermore, neuroimaging techniques could possibly be promising candidates for translation of imaging-guided differential diagnosis and evaluation into clinical settings.

Recently, the number of neuroimaging studies using near-infrared spectroscopy (NIRS), a relatively new method for investigating cerebral hemodynamic activity, has increased (Ferrari and Quaresima, 2012; Irani et al., 2007). NIRS involves irradiation of near-infrared light into the skull and measuring its reflection from oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) (Jobsis, 1977; Koizumi et al., 1999). Compared to other hemodynamic neuroimaging methods (fMRI or PET), NIRS has superior time resolution and inferior spatial resolution and lesser usefulness for detection of deep brain functions. NIRS has the benefits of producing no harmful radiation and being flexible because the NIRS device is compact and portable.

Few fMRI or PET studies have presented the time course of signal change; however, several previous NIRS-based studies have measured time-specific hemodynamic changes in patients with SZ, MDD, and bipolar disorder and clarified the abnormal time course of prefrontal activity in each major psychiatric disorder (Kameyama et al., 2006; Shimodera et al., 2012; Suto et al., 2004). Some of these NIRS studies have also elucidated the association between prefrontal NIRS signals and global functioning levels in psychiatric disorders (Pu et al., 2008; Takizawa et al., 2008). Thus, the specific spatiotemporal characteristics of brain activation patterns in each disorder might become candidate biomarkers of differential brain pathophysiology. However, the previous NIRS studies did not directly compare NIRS signal patterns among different disorders.

In this study, we measured hemodynamic changes during the VFT in patients with SZ and MDD and HCs using concise NIRS measurements in a natural setting. In expansion of a previous study that covered a limited PFC area (Suto et al., 2004), we investigated 3 groups including more subjects ($n = 32$ in each group) with comparable demographic characteristics using a multichannel NIRS machine with a wide coverage over the prefrontal cortical surface area (52 channels, ETG-4000 HITACHI Medical Co.). We also examined the relationship between hemodynamic changes and clinical scores. We hypothesized that the spatiotemporal characteristics of the time course in prefrontal activation patterns differentiate MDD from SZ and are related to global functioning levels in both disorders.

2. Methods

2.1. Participants

This study included 96 individuals: 32 patients with SZ, 32 patients with non-psychotic unipolar MDD, and 32 demographically matched HCs (Table 1). Patients with SZ or MDD did not have any psychiatric comorbidity. The diagnoses of the 2 disorders were established by well-trained psychiatrists (R.T. and K.K.) using DSM-IV criteria. Patients with drug or alcohol dependence and neurological disorders or other organic disorders were excluded. Written informed consent was obtained from all participants. This study was approved by the ethics committees of the University of Tokyo and JR Tokyo General Hospital.

All subjects were right-handed, according to the modified version of the Edinburgh Handedness Inventory (score > 70) (Oldfield, 1971). Participants of each group were matched for age ($F[2, 93] = 1.135$, $p = 0.33$), sex (male:female, 15:17; $p = 1.00$), task performance ($F[2, 93] = 0.113$, $p = 0.33$), and educational level ($F[2, 93] = 1.031$, $p = 0.36$) (Table 1). Hemodynamic response measured by NIRS varies according to the effects of age and sex (Herrmann et al., 2006; Kameyama et al., 2004). Thus, we matched the age and sex of each group to decrease these effects.

Table 1
Clinical characteristics of the study groups.[a]

	Healthy subjects ($n = 32$)	Patients with schizophrenia ($n = 32$)	Patients with depression ($n = 32$)	p value
Sex (male/female)	15/17	15/17	15/17	1.00
Age, years	45.7 ± 13.5	41.7 ± 10.1	44.8 ± 9.8	0.33
Education, years	15.1 ± 2.58	14.9 ± 2.37	14.3 ± 1.91	0.36
Task performance[b]	14.3 ± 3.3	14.8 ± 5.6	13.2 ± 4.7	0.33
PANSS				
Positive	–	15.7 ± 5.00	–	–
Negative	–	22.0 ± 7.11	–	–
General psychopathology	–	38.7 ± 8.47	–	–
HRS-D	–	–	19.6 ± 3.64	–
GAF	–	45.7 ± 14.0	53.3 ± 5.57	–
Medication	–	843 ± 707 (Cp eq. mg)	113 ± 65.7 (Imp eq. mg)	–

Abbreviations: Cp eq., chlorpromazine-equivalent; Imp eq., imipramine-equivalent.
[a] Chi-squared test was used to test group differences in sex distribution. Otherwise, a t test was used.
[b] Number of correct words generated (mean ± SD).

The exclusion criteria for all the 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 (Tess and Smetana, 2009), and alcohol/substance abuse or addiction that might be potential confounders for cognitive tasks. An additional exclusion criterion for the control group was a history of psychiatric disease or a family history of axis I disorders in any first-degree relatives. Any patients with MDD and SZ who had other psychiatric or physical comorbidities were excluded. All patients with SZ, a majority of whom had experienced the first or second episode of acute psychotic symptoms and had had the illness for <10 years, were taking various types of antipsychotic medication, including typical and newer atypical antipsychotics. The average dose of antipsychotic medication was 843 ± 707 mg, as a chlorpromazine-equivalent dose. None of the patients with SZ was in an acute phase, but all had some residual psychiatric symptoms at the time of NIRS measurement. Patients with MDD who also met the DSM-IV criteria for a major depressive episode unipolar type were diagnosed by the same well-trained psychiatrists. The total Hamilton Rating Scale for Depression (HRS-D; 17-item version) (Hamilton, 1960) scores of all patients with depression were above 15, which means in a "full symptomatic" state, to confirm the diagnosis and existence of symptoms (Frank et al., 1991). All, except 3, subjects with MDD were taking various types of antidepressants, such as selective serotonin reuptake inhibitors. The average dose of antidepressant medication was 113 ± 65.7 mg, as an imipramine-equivalent dose.

Psychiatric symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) in patients with SZ, the HRS-D in patients with MDD, and the Global Assessment of Functioning (GAF) scale in both groups of patients (Table 1).

2.2. Task design

We used the VFT (letter fluency version) as a cognitive task. Previous brain imaging studies have consistently shown abnormal brain activations during the VFT in various psychiatric disorders (Audenaert et al., 2000; Okada et al., 2003; Ragland et al., 2008; Videbech et al., 2003). Participants can be easily instructed on the VFT, and this task has a high successful execution rate for subjects, including psychiatric patients. Recent fMRI studies also used the VFT as a cognitive task; however, the noise in the environment in which the VFT is conducted may influence fMRI measurements. During NIRS measurements, participants are in a silent condition, and hence, observers can expect more natural measurements of cerebral activity induced by VFT using auditory stimuli and utterances.

The whole measurement time was 160 s, including 3 segments (30, 60, and 70 s). Concentration changes for the 2 types of hemoglobin molecules ([deoxy-Hb] and [oxy-Hb]) were measured according to our previous methods (Takizawa et al., 2008, 2009). During the first 30-s and last 70-s segments, participants vocalized 5 Japanese vowels repeatedly, which were used as control tasks. During the middle 60-s interval, the participants were instructed to pronounce in overt speech as many words as possible beginning with the letters indicated by a recorded human voice. To avoid a pause in thinking, the indicated letters were changed every 20 s. Thus, in this 60-s cognitive task period, 3 letters were counterbalanced. The number of words produced throughout the cognitive task period were recorded by an observer and counted as task performance.

2.3. NIRS measurements

The 52-channel NIRS machine (ETG-4000; Hitachi Medical Corporation) measures the relative changes in [oxy-Hb] and [deoxy-Hb] using 2 wavelengths (695 and 830 nm) of infrared light, based on the modified Beer–Lambert law. The distance between pairs of detector probes was set at 3.0 cm. A channel was defined as the measurement area between a pair of source–detector probes. [oxy-Hb] and [deoxy-Hb] changes measured by each of the 52-channel detectors were processed to a numerical value [mM · mm] and recorded on the machine every 0.1 s. Further details of the NIRS have been provided elsewhere (Yamashita et al., 1999).

Subjects placed the plastic frame with the injectors and detectors on their head, covering the bilateral prefrontal area. Using this arrangement, hemodynamic changes could be measured in approximate frontopolar PFC (FPPFC), DLPFC, and ventrolateral PFC (VLPFC) areas (Fig. 1), as corroborated by a multisubject study of anatomical cranio-cerebral correction using the international 10–20 system.

Furthermore, some studies (Kakimoto et al., 2009; Schecklmann et al., 2008), including ours (Kono et al., 2007), have supported the reliability of multiple NIRS measurements during VFT.

2.4. Statistical analyses

The pre- and post-task baselines were determined as the means across the last 10 s of the pre-task period and the last 5 s of the post-task period, respectively. Linear fitting was performed using the data obtained between the 2 baselines. Moving average methods were applied to remove short-term motion artifacts from the analyzed data (moving average window, 5 s). Since all artifacts were not removed using these methods, we used an algorithm developed previously to automatically reject data with artifacts (see supplementary information in our article Takizawa et al., 2008).

Grand mean waveforms averaged across subjects were created separately for the type of [Hb] and for each group. For parametric statistical tests, the measured [Hb] data from each channel were averaged across the 2 periods (pre-task baseline and 60-s task period).

First, to assess any significant increase in [Hb] associated with the task, we compared the mean [Hb] of the pre-task period and that of the task period at each channel by using Student's paired *t* tests. As we performed 52 paired *t*-tests, a correction for multiple comparisons was made using a false-discovery rate (FDR) [two-tailed; we set a value of q that specified the maximum FDR to 0.05, so that there were no more than 5% false-positive results on average (Singh and Dan, 2006)].

For the second analysis, to investigate intergroup differences among the significant channels, we compared the mean [Hb] changes during the task period among the 3 groups for each channel using one-way

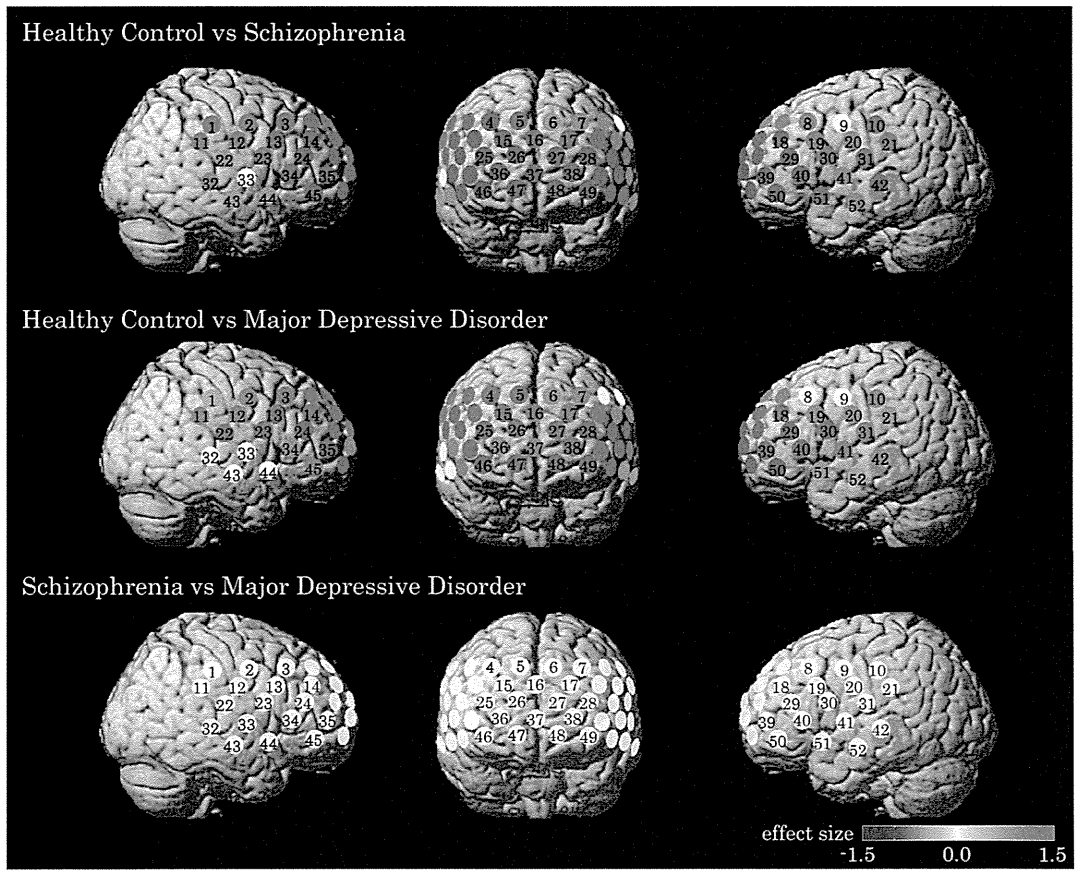

Fig. 1. Group differences in mean [oxy-Hb] increase during the task period. The effect sizes of the group differences are indicated by the color gradient. Channels that did not display significant differences among the 3 groups are colored in white.

analysis of variance (ANOVA); a correction for multiple comparisons was made using FDR.

Subsequently, as post-hoc analyses, we used Tukey's multiple comparison tests to compare the mean [Hb] changes during the task period for channels considered significant after ANOVA between each group (NC–SZ, NC–MDD, and SZ–MDD). A correction for multiple comparisons was made using FDR. To elucidate the spatiotemporal characteristics of NIRS signals, we calculated the effect size (Cohen, 1988) for each difference in these channels.

Next, we compared the time course of [Hb] changes. A previous NIRS study on difference between patients with SZ and MDD (Suto et al., 2004) did not mention statistical significance, but the figure included seemed to show an NIRS signal difference during the first period of the task in the frontopolar cortex area; therefore, we focused our attention on the initial slope of the task period as one of the parameters for the time-course change. To confirm the characteristics of the time course for each group, the initial 5-s slope of the task period was compared among the 3 groups for each channel, in a similar manner. In addition, we conducted similar analyses by using the other parameters for time-course change, which were introduced by Shimodera et al. (2012).

Finally, we analyzed the relationship between [Hb] changes and clinical characteristics, which included GAF, PANSS, and HRS-D scores, age, and dose of medication by calculating Pearson's correlation coefficients. Initially, we investigated the associations between mean NIRS signal change and the clinical characteristics. If any significant association was found, we confirmed the robustness of such associations by using the raw waveform data along the time course of the NIRS signal. According to the conservative method of Kameyama et al. (2006) and Marumo et al. (2009), in order to avoid multiple comparison errors, channels that yielded data with p values of <0.05 for more than 20 s consecutively (200 comparison time points in NIRS signals) during the measurement were considered to have a significant correlation.

Although we focused on [oxy-Hb] here, we have shown the analyses of [deoxy-Hb] data in Supplementary material (1). All data are expressed as means ± S.D. The significance level was set at alpha = 0.05. Statistical analyses were performed using the statistical packager for the Social Sciences ver. 20.0.0J (IBM, Corp., 2011, Chicago IL).

3. Results

3.1. Task performance

The mean number of correct words during the 60-s VFT was not significantly different among the 3 groups ($F[2, 93] = 1.11$, $p = 0.33$, Table 1).

3.2. NIRS [oxy-Hb] change during the VFT period

To assess the presence of significant activations, we compared the mean [oxy-Hb] change between the pre-task and 60-s task periods. HCs showed a significant increase in all channels of the PFC (FPPFC, DLPFC, and VLPFC) (channels 1–52; FDR $p < 0.05$, corrected for 52 channels). Patients with SZ exhibited a significant increase in the DLPFC and VLPFC (channels 24, 34, 35, 39, 41, 44, 45, 47, 49, 51, and 52; FDR $p < 0.05$, corrected for 52 channels), whereas patients with MDD showed a significant increase in the DLPFC, VLPFC, and part of the FPPFC (channels 1, 13, 14, 16–21, 24–29, and 32–52; FDR $p < 0.05$, corrected for 52 channels).

One-way ANOVA using group as a between-subject factor showed a significant main effect of group on the [oxy-Hb] increase during the 60-s task period in the following 50 channels: 1–8, 10–32, and 34–52 (FDR $p < 0.05$, corrected for 52 channels). An additional analysis was performed to compare the 3 groups within the above-mentioned 50 significant channels.

We found that in the widespread PFC, the [oxy-Hb] change in patients with SZ was significantly more reduced than that in HC (channels 1–8, 10–32, 34–52; FDR $p < 0.05$, corrected with 50 channels, Fig. 1).

Similarly, across the PFC, the [oxy-Hb] change was significantly more reduced in patients with MDD than in HCs (channels 1–7, 10–31, 34–42, and 45–52; FDR $p < 0.05$, corrected with 50 channels, Fig. 1).

Patients with SZ and MDD did not show significant difference in the mean [oxy-Hb] for any channel.

3.3. Time course of cognitive activation

The time-course patterns of [oxy-Hb] and [deoxy-Hb] changes in the left FPPFC (channel 38) vary according to diagnostic group (Fig. 2). The HC and MDD groups showed an immediate increase and regular decrease in [oxy-Hb] during the task. In contrast, the SZ group showed slow increase after the start of the task and immediate decrease after the end of the task period. In addition, this group showed a small increase in [oxy-Hb] during the post-task period.

One-way ANOVA using group as a between-subject factor showed a significant difference in the initial slope during the task period at 29 channels (channels 3, 8, 13–18, 20, 24–29, 34–40, and 45–51; FDR $p < 0.05$, corrected for 52 channels). Similar to the analysis of mean [oxy-Hb] change, an additional analysis to compare each group within these 29 significant channels was performed.

The initial slope for HCs was significantly steeper than that for patients with SZ at 26 channels (channels 3, 13–15, 17–18, 20, 24–29, 34–39, and 45–51; FDR $p < 0.05$, corrected for 27 channels, Fig. 3). However, the slope for patients with MDD was not significantly different from that for HCs at any channel (FDR $p > 0.05$, corrected for 27 channels, n.s.).

The slopes for patients with MDD were significantly steeper than those for patients with SZ at 15 channels located approximately in the FPPFC (channels 25–28, 35–40, 45–48 and 51; FDR $p < 0.05$, corrected for 27 channels, Fig. 3).

The comparisons of parameters between the 3 groups for channel 38 are summarized in Fig. 4.

In Supplementary material (2), we also show the results obtained using the indices that Shimodera et al. (2012) used. In brief, one of the

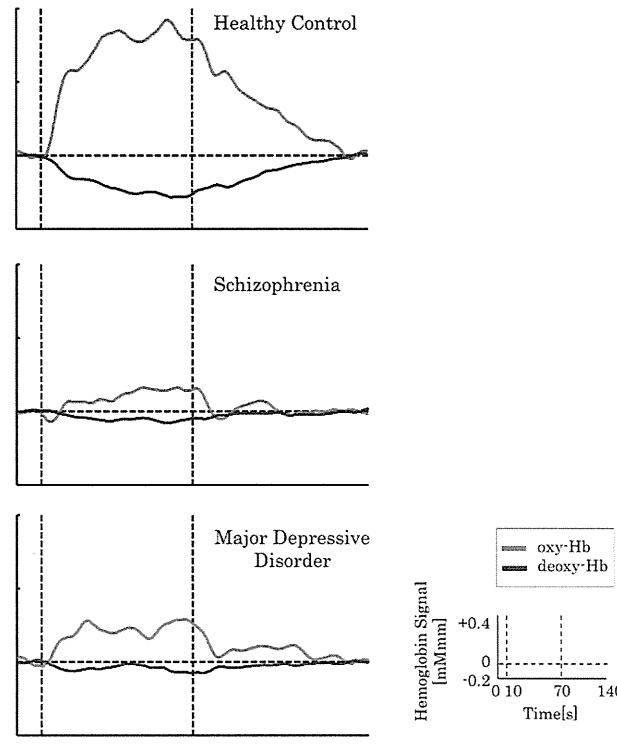

Fig. 2. Time course of [oxy-Hb] and [deoxy-Hb] changes in the FPPFC (channel 38).

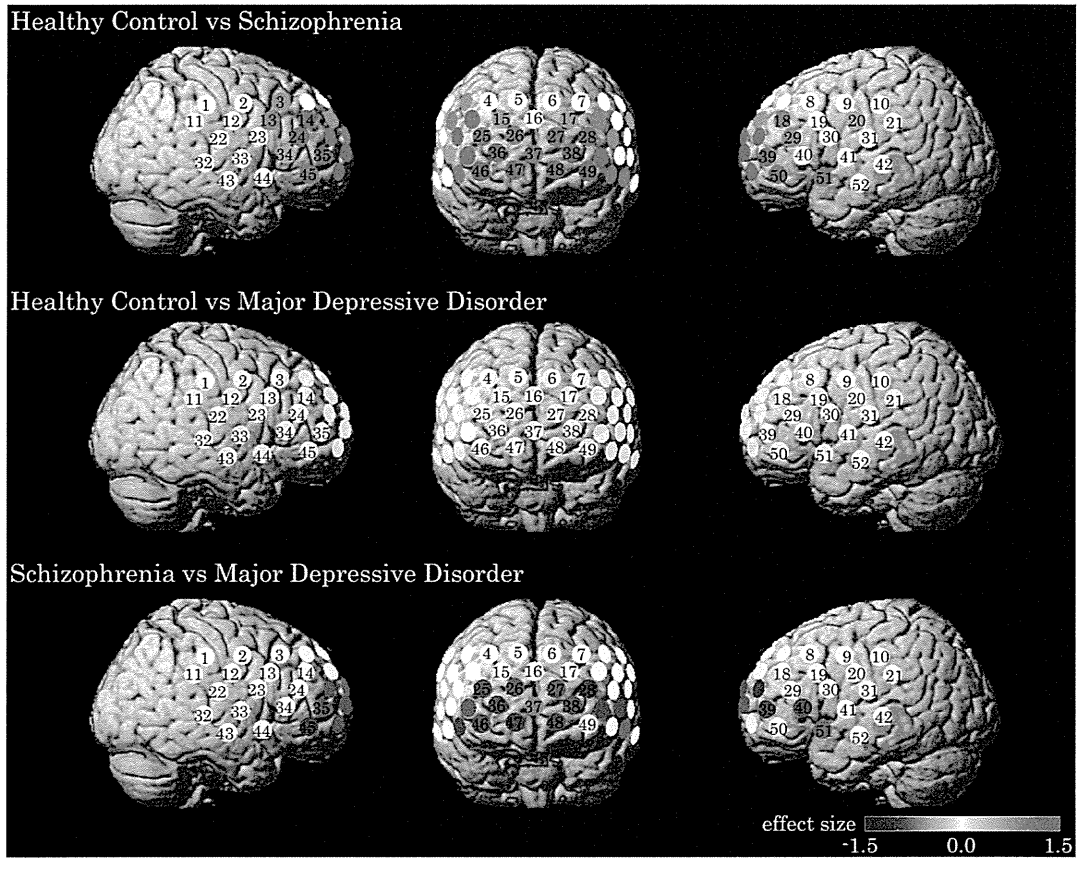

Fig. 3. Group differences in initial [oxy-Hb] slope. The effect sizes of the group differences are indicated by the color gradient. Channels that did not display significant differences among the 3 groups are colored in white.

2 parameters that Shimodera et al. (2012) employed for time-course analysis was significantly different between the patient groups (MDD and SZ) and healthy controls, but not significantly different between the patients with MDD and SZ.

3.4. Correlation with clinical characteristics

For analyzing the correlation between PFC response and clinical characteristics, GAF scores were calculated and found to exhibit significant positive correlations with the mean [oxy-Hb] change of the 60-s task period in patients with SZ at 7 channels ($r = 0.377–0.487$) and in patients with MDD at 23 channels ($r = 0.451–0.610$) (SZ: channels 27–28, 36–39, and 46, located mainly in the FPPFC; MDD: channels 2, 10, 12, 13, 20, 24, 25, 30, 34–37, 39–41, 43, 44, 46–48, and 50–52, located mainly in the DLPFC and VLPFC), which means that the more severe the GAF scores were the more reduced the NIRS changes were (Fig. 5). Additionally, to confirm the robustness of such associations, the time-course analysis of the associations revealed that there were significant associations in the latter half of the time course of the NIRS measurement (SZ: channels 13, 17, 24, 26–28, 34–39, and 46–49, located mainly

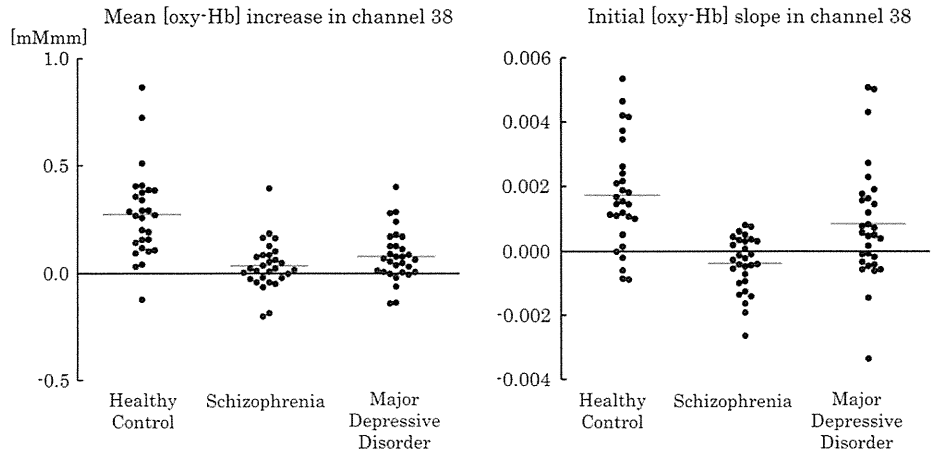

Fig. 4. Comparisons of mean [oxy-Hb] increase and initial [oxy-Hb] slope among the 3 groups. The bars indicate the mean ± 1 standard deviation.

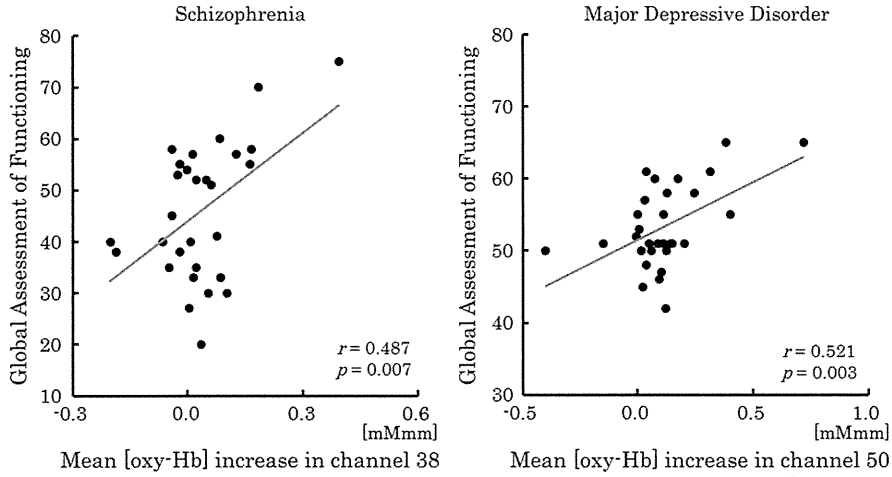

Fig. 5. Scatterplots for correlations between NIRS signal and GAF score in patients with schizophrenia and major depression.

in the FPPFC; MDD: channels 2, 10, 12–13, 20, 24, 29, 34–36, 39–44, 46–48, and 50–52, located mainly in the DLPFC and VLPFC) ($p < 0.05$, with 200 consecutive time points) (Fig. 6).

Other clinical characteristics, including age, dose of medication, and PANSS and HRS-D scores were not significantly correlated with mean [oxy-Hb] change in the 60-s task period at any channel in any group. Moreover, no clinical characteristic showed significant correlation with the initial [oxy-Hb] slope of the task period at any channel in any group.

4. Discussion

These results suggest the presence of a significant difference in the time-course patterns of prefrontal activations in a VFT among HCs, patients with SZ, and patients with MDD matched for age, sex, task performance, and education years. Compared to HCs, patients with SZ and those with MDD showed a significant task-associated reduction in mean [oxy-Hb]. In addition, the initial slope was significantly steeper for patients with MDD and HCs than for patients with SZ. Furthermore, in patients with SZ, the mean [oxy-Hb] change in the area approximately located in the FPPFC was significantly correlated with the GAF score; this is similar to our previous finding (Takizawa et al., 2008), whereas patients with MDD exhibited a significant correlation between mean [oxy-Hb] change and GAF scores in the areas approximately located in the DLPFC and VLPFC. These findings may help understand the differential brain pathophysiology of SZ and MDD better.

4.1. Functional prefrontal abnormality in patients with SZ and MDD

Compared with HCs, patients with SZ and those with MDD showed a reduced NIRS [oxy-Hb] increase in the 60-s task period at the PFC. This result agrees with those of previous NIRS studies (Kameyama et al., 2006; Suto et al., 2004; Takizawa et al., 2008) and other neuroimaging studies.

The 2 patient groups had an [oxy-Hb] reduction compared to that of HCs in FPPFC and DLPFC; however, patients with MDD showed no significant [oxy-Hb] reduction in VLPFC, whereas patients with SZ did, i.e., compared to patients with MDD, those with SZ had reduced NIRS signals in a wider area (Fig. 1). However, patients with SZ and MDD did not show significant difference in mean [oxy-Hb] change at all channels; this suggests that differentiating between these 2 disorders using only the mean change in NIRS signal is difficult.

The VFT recruits not only a single specific cognitive domain, but also some integrated cognitive dimensions, such as working memory,

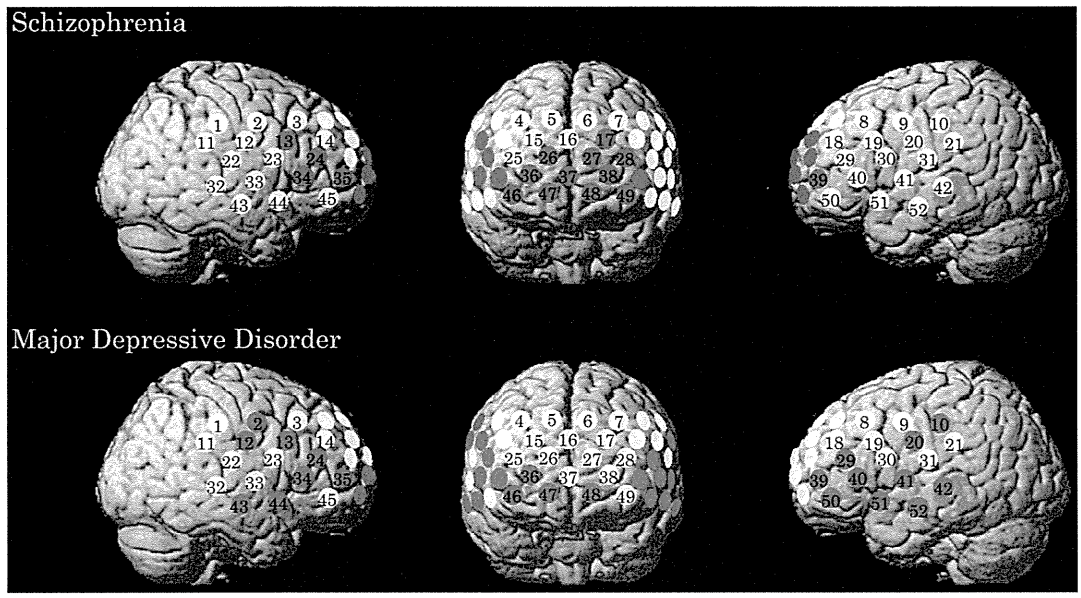

Fig. 6. Cerebral regions that exhibited a significant correlation between GAF score and mean [oxy-Hb] change.

selection of appropriate words, inhibition of inappropriate words, and maintenance of attention (Ruff et al., 1997). For this reason, our "hypofrontality" result during the VFT could not clarify the specific deficit of neural networks in each patient group. However, the difference in mean [oxy-Hb] change during the VFT between patients and HCs may reflect a common impairment, such as executive dysfunction. In addition, from the perspective of the area that showed a group difference (Fig. 1), the brain pathophysiology involving this impairment in SZ might be severer than that of MDD.

4.2. Differential spatiotemporal characteristics of prefrontal activation

The comparison of the time course of [oxy-Hb] signal between the 3 groups (Fig. 2) revealed that the SZ group showed a more gradual slope than the MDD or NC groups, whereas the MDD and HC groups showed no significant difference in the initial slope, immediately after the task started.

Despite the fact that the 2 patient groups had a similar reduced [oxy-Hb] change, there was a difference in the time course of NIRS [oxy-Hb] signal between them. Several previous functional neuroimaging studies based on fMRI also reported a difference in cognitive activation, and the possibilities of qualitative changes, between patients with SZ and MDD (Holmes et al., 2005; Hugdahl et al., 2004). In our study, we replicated this qualitative difference between the disorders based not only on the activation of the PFC region, but also on the comparison of the time course of frontal activation. These findings suggest that the brain pathophysiology of SZ might be severer than that of MDD.

Furthermore, the initial rise rate of the prefrontal hemodynamic response to the task stimulus in patients with MDD was similar to that of HCs, but the response did not continue to increase throughout the task period (Fig. 2), which means that, despite the fact that the load of the task continued, the prefrontal hemodynamic response in these patients did not follow. This discontinuance in the frontal hemodynamic response may reflect symptoms of depression, such as impaired concentration and psychomotor slowing (Hickie et al., 2007). Conversely, patients with SZ appeared to have an inefficient small reactivation or a delay of baseline reversion after the task period (Fig. 2), similar to the results of previous NIRS studies (Suto et al., 2004; Takizawa et al., 2008). As was also discussed for the abnormal time course of patients with SZ observed in a recent NIRS study (Shimodera et al., 2012), only its reduced mean signal change does not seem to represent their functional dysfunctions. The time-course analyses of cognitive activation according to patient groups need to be replicated in future NIRS studies.

4.3. Association between functional impairment and PFC subregions

In this study, we found a significant correlation between the mean [oxy-Hb] change of the task period in specific cerebral regions and the GAF score. However, the correlated cerebral regions were spatially different between patients with SZ (mainly in the FPPFC) and patients with MDD (mainly in the VLPFC/DLPFC) (Fig. 6).

Recent neuroimaging studies reported that the regions activated in patients with SZ were different from those activated in patients with MDD for the same cognitive task, suggesting that the abnormal neural correlates and compensatory mechanisms might be different between patients with SZ and MDD (Barch et al., 2003; Holmes et al., 2005; Hugdahl et al., 2004). Thus, in the present study, the activated regions that correlated to GAF might be variable in each patient group.

Our previous study (Takizawa et al., 2008) was replicated regarding the relationship between GAF score and NIRS [oxy-Hb] increase in the FPPFC and DLPFC. As was discussed in Takizawa et al. (2008), this relationship suggests that reduced frontopolar cortical activations may be associated with functional impairment in patients with SZ.

Regarding patients with MDD, a previous NIRS study using the same VFT (Pu et al., 2008) showed that the mean [oxy-Hb] change in the right DLPFC was significantly associated with scores on the Social Adaptation Self-Evaluation Scale, which evaluates social motivation and behavior (Bosc et al., 1997). This measure should be strongly related with global social functioning, which is similar to what was measured by the GAF scale in the current study. Therefore, here we replicated part of the Pu et al. (2008) regarding the correlations between the DLPFC signal and the generalized scores of social functioning in patients with MDD.

Studies based on nonhuman primates reported that the VLPFC receives projections from the orbitofrontal cortex and subcortical areas, such as the midbrain and amygdala, which are involved in processing motivational and emotional information. The VLPFC might integrate cognitive and motivational information to guide flexible goal-directed behavior (Sakagami and Pan, 2007). In mood disorders, a deficit in the VLPFC observed in emotion tasks reflected the impairment in processing motivational and emotional information in this area (Johnstone et al., 2007; Taylor Tavares et al., 2008). These VLPFC functions may be factors that influence the extent of social functioning in patients with depression. Thus, our results of increasing severity in functional impairments with the reduction of VLPFC signals might be justified. However, the global role of the VLPFC and its relation to social impairment in patients with MDD remains to be elucidated. Our results regarding the VLPFC warrant further investigation.

The correlation between lateral PFC activation and GAF score in patients with MDD suggests that this region plays a key role in maintaining social function in these patients; however, these PFC areas seemed to be different from those observed in patients with SZ, for some reason (e.g., compensatory or abnormal mechanisms). These findings suggest not only differential brain pathophysiology, but also differential symptomatology between patients with MDD and SZ. Further detailed investigations need to be performed in the future.

4.4. Limitations

Some methodological limitations need to be addressed. First, all patients were taking medication at the time of NIRS measurement. Some authors have mentioned an absence of significant effects of psychotropic medications on abnormal structural and functional neuroimaging measures (Phillips et al., 2008). Moreover, similar to what was observed in previous NIRS studies (Shimodera et al., 2012; Takizawa et al., 2008), psychotropic medication dose was not related to [oxy-Hb] change at any channels in the present study. However, the effect of antidepressants or antipsychotics on neuroimaging studies could not be entirely ruled out. In addition, we confirmed that the significant findings were unchanged if either or medication or task performance was included as a covariate in the analyses. Second, in the current study, NIRS measurements were made once throughout the stages of the disease. To repeat the NIRS measurements during the treatment of patients, the actual state of activation patterns throughout the process of recovery may become clear (Walsh et al., 2007). A longitudinal study is needed to replicate our findings. Third, NIRS has a low spatial resolution, and its accuracy in the estimation of measurement positions is limited. According to the virtual registration method (Tsuzuki et al., 2007; Tzourio-Mazoyer et al., 2002), which estimates the cortical localization of each channel. We interpreted that the correlated cerebral area (including channel 24 or 29, and more lateral channels) in patients with MDD was located mainly in the bilateral VLPFC and right DLPFC (Fig. 6).

4.5. Conclusions and future implications

In conclusion, we investigated the hemodynamic changes using the LFT in patients with MDD and SZ and in HCs by using 52-channel NIRS with a wide coverage over the prefrontal cortical surface area. The comparison between patients with SZ and MDD revealed a difference in the time course of the NIRS signal. We also observed a correlation between the GAF score and the mean [oxy-Hb] change at the FPPFC in patients with SZ, and at the DLPFC and VLPFC in patients with MDD. These

results suggest the presence of differential prefrontal abnormalities in each disease, despite a similar reduction in the magnitude of hemodynamic activations between them. These findings may lead to a better understanding of the different brain pathophysiology of SZ and MDD. Finally, these results, if replicated using large-scale or longitudinal studies, suggest that NIRS could potentially be used as an aid for the diagnosis and clinical evaluation of SZ and MDD.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.08.026.

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Contributors

Masato Fukuda, Ryu Takizawa, and Kiyoto Kasai designed the study and wrote the protocol. Ryu Takizawa, Masaru Kinou, and Shingo Kawasaki performed the statistical analysis. Masaru Kinou, Ryu Takizawa, Marumo Kohei, and Yuki Kawakubo carried out data acquisition. Ryu Takizawa and Masaru Kinou wrote the first draft of the manuscript, and the other authors revised it critically for important intellectual content. All authors have approved the final version of the manuscript.

Conflict of interest

Regarding financial and material support for the present study, Dr. Kasai has a potential conflict of interest (see below for details). All other authors have no relevant conflicts of interest.

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Electrophysiological and neuropsychological predictors of conversion to schizophrenia in at-risk subjects

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Patients with schizophrenia show neurophysiological and psychological disturbances before the onset of the illness. Mismatch negativity (MMN), an event-related potential, has been shown to be associated with cognitive function. Specifically, duration MMN (dMMN) amplitudes have been indicated to predict progression to overt schizophrenia in subjects with at-risk mental state. The aim of this article is to provide a hypothesis that a combined assessment of dMMN and neuropsychological performance would enhance accuracy for predicting conversion to schizophrenia in at-risk subjects. Data from these neurocognitive modalities in subjects with first-episode schizophrenia (FES) are also presented. There is accumulated evidence that converters to schizophrenia among at-risk subjects show significantly smaller dMMN amplitudes than those in healthy control (HC) subjects at the frontal lead before the onset. In fact, the amplitudes in these converters have been reported to be similar to those in FES to begin with. dMMN current source density, by means of low-resolution brain electromagnetic tomography, was significantly lower in FES than HC subjects, especially in some medial temporal regions which are implicated in the pathophysiology of schizophrenia. Importantly, dMMN current density in the frontal lobe was positively correlated with working memory performance in FES subjects. These findings indicate the utility of the combination of electrophysiological/neuropsychological assessments for early intervention into patients with schizophrenia and high-risk people.

Keywords: event-related potentials, mismatch negativity, dMMN, schizophrenia, cognition, early intervention

INTRODUCTION

Shorter duration of untreated psychosis (DUP) has been associated with better prognosis in schizophrenia (Jackson and McGorry, 2009). Also, early intervention into individuals who are at risk of developing psychosis is important to attain better long-term outcome (Jackson and McGorry, 2009). There is a suggestion that brain-related markers, such as subtle morphological changes revealed by magnetic resonance imaging, may provide a tool to identify at-risk people vulnerable to schizophrenia (Takahashi et al., 2009). Accordingly, we reported the utility of electrophysiological measures, such as event-related potentials (ERPs), as a sensitive and feasible biomarker for the detection of individuals who later developed schizophrenia (Higuchi et al., 2013b) and early intervention into the illness (Higuchi et al., 2013a).

In this paper, we provide a theory for electrophysiological and neuropsychological predictors of outcome in early psychosis. The topics include: (1) cognitive function in prodromal phase psychosis, as measured by neuropsychological performance; (2) the role for mismatch negativity (MMN), a component of ERPs, in early detection of schizophrenia; and (3) three-dimensional current source imaging of MMN and its relation with cognitive performance in early schizophrenia.

THE PSYCHOSIS HIGH-RISK STATE

The concept of the psychosis high-risk state has been reported in several ways (e.g., Fusar-Poli et al., 2013). Starting treatment in the early phase of psychosis, or minimizing DUP, is important to improve long-term outcome for patients. If we can start intervention in the prodromal phase, it may prevent progression to psychosis. For this purpose, there have been efforts to establish biological or neuropsychological markers to identify high-risk people who are likely to develop schizophrenia later, which is the main focus of this article.

COGNITIVE FUNCTION BASED ON NEUROPSYCHOLOGICAL MEASURES

There is abundant evidence that cognitive function is impaired in patients with schizophrenia. Usually, the deficit is measured by neuropsychological test batteries, such as the MATRICS Comprehensive Cognitive Battery (Green et al., 2004; Nuechterlein and Green, 2006). In schizophrenia and related psychoses, several domains of cognitive function are disturbed with a 1–2 standard deviation decline. The cognitive deficit has been reported to provide a vulnerability marker of schizophrenia, so one would expect similar disturbances in high-risk people for the disease. In fact, a recent meta-analysis of cognitive functioning in people at risk for psychosis indicates impairments in almost all cognitive domains which are typically affected in schizophrenia, i.e., executive function, verbal fluency, attention, visual memory, verbal memory, working memory, and social cognition, with a milder degree (Fusar-Poli et al., 2012).

The Brief Assessment of Cognition in Schizophrenia (BACS) battery (Keefe et al., 2004) is one of the most frequently used tests to evaluate cognitive impairment of schizophrenia in Japan. It takes only approximately 30 min to complete, and covers key cognitive domains specifically impaired in schizophrenia (Keefe et al., 2004; Kaneda et al., 2007). We recently investigated performance on the BACS in people with at-risk mental state (ARMS), and compared baseline data between subjects who later developed schizophrenia and those who did not (Higuchi et al., 2013b). As demonstrated in **Figure 1**, the two groups performed differently in working memory, verbal fluency, and attention. These results are generally consistent with the literature (Fusar-Poli et al., 2012), and indicate impairment of frontal lobe function in vulnerable people plays a role in the progression to schizophrenia (Higuchi et al., 2013b; Miyanishi et al., 2013). Specifically, a recent meta-analytic study (De Herdt et al., 2013) reports worse working memory and visual (learning) memory for converters compared to non-converters, supporting the above concept based on results from a larger number of subjects.

MISMATCH NEGATIVITY

As discussed, data from neuropsychological performance may provide some information to identify high-risk individuals who later develop psychosis. However, the sensitivity of neuropsychological evaluation to predict conversion to schizophrenia may be less than that of negative symptoms (Riecher-Rossler et al., 2009). This prompts the search for neurocognitive markers from other modalities, such as ERPs and other electrophysiological paradigms.

MMN is a pre-attentive component of ERPs. When auditory cortex automatically detects a change of stimuli, attention shifting occurs in frontal cortex (Jahshan et al., 2012a,b). This neural process generates MMN. For the measurement of MMN, auditory stimuli were delivered to subjects. Standard and target tones with different durations were randomly presented in the case for duration MMN (dMMN). During the measurement, subjects are requested to pay attention to a silent animation movie and ignore the tones. MMN is obtained by subtracting standard waveforms from target waveforms.

One of the strength of MMN is the limited number of generators, in contrast to the case for P300, another component of ERPs (**Figure 2**). The generators for MMN are assumed to be located mainly on superior temporal gyrus and prefrontal cortex. This facilitates functional imaging evaluation. Importantly, MMN amplitudes have been shown to be decreased in schizophrenia with a large effect size (Umbricht and Krljes, 2005). Specifically, dMMN amplitudes have been found to be decreased also in ARMS subjects (e.g., Jahshan et al., 2012a).

Figure 3 demonstrated MMN waveforms at the frontal lead for healthy controls (HCs), ARMS subjects, and first-episode schizophrenia (FES). Converter subjects showed reduction in the amplitudes before the onset, similar to patients with FES. By contrast, MMN amplitudes of non-converters resembled those of HCs (Higuchi et al., 2013b). These results are consistent with some recent reports from other groups of investigators (Bodatsch et al., 2011; Atkinson et al., 2012; Jahshan et al., 2012a; Shaikh et al., 2012). A novel finding in our study was a positive correlation between MMN amplitudes and verbal fluency in ARMS subjects (Higuchi et al., 2013b). This indicates word production during a given time would provide an estimate of an electrophysiological activity which is predictive of progression to overt schizophrenia.

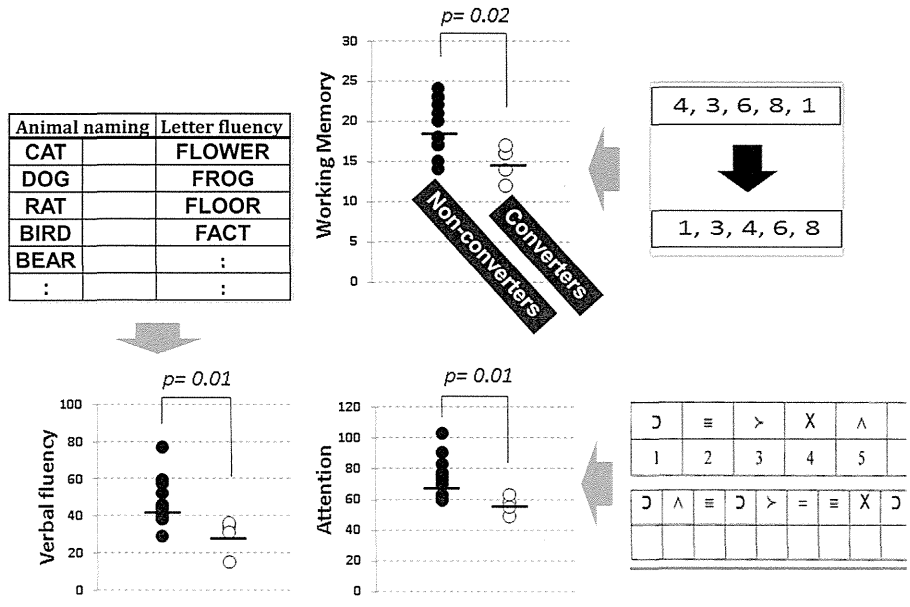

FIGURE 1 | Neuropsychological performance, as evaluated by the BACS, in subjects with at-risk mental state. Transition to overt schizophrenia was predicted by working memory (top), verbal fluency (bottom left), and attention (bottom right) before the onset of illness (extracted from Higuchi et al., 2013b).

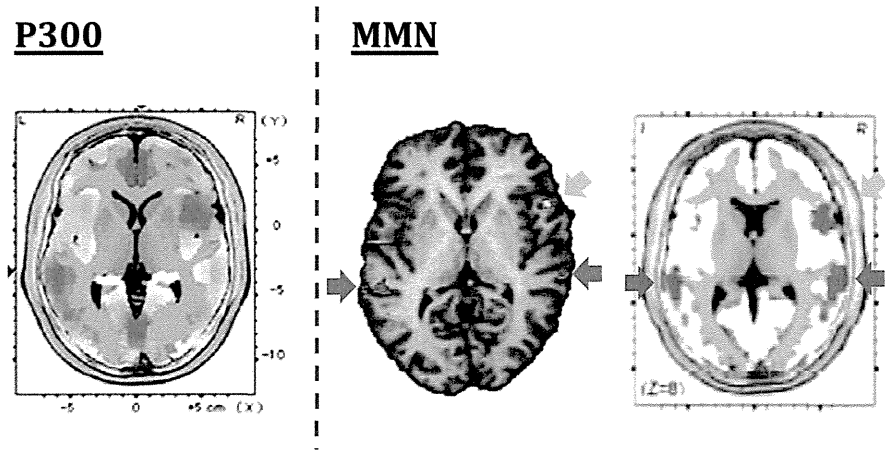

FIGURE 2 | The generators of ERPs. In contrast to multiple generators for P300 (left), putative generators for MMN are limited to superior temporal gyrus and prefrontal cortex, as demonstrated by fMRI (center) and EEG-LORETA (right) methods. Images are extracted from Higuchi et al. (2008) (left), Opitz et al. (2002) (center), and Marco-Pallares et al. (2005) (right), respectively.

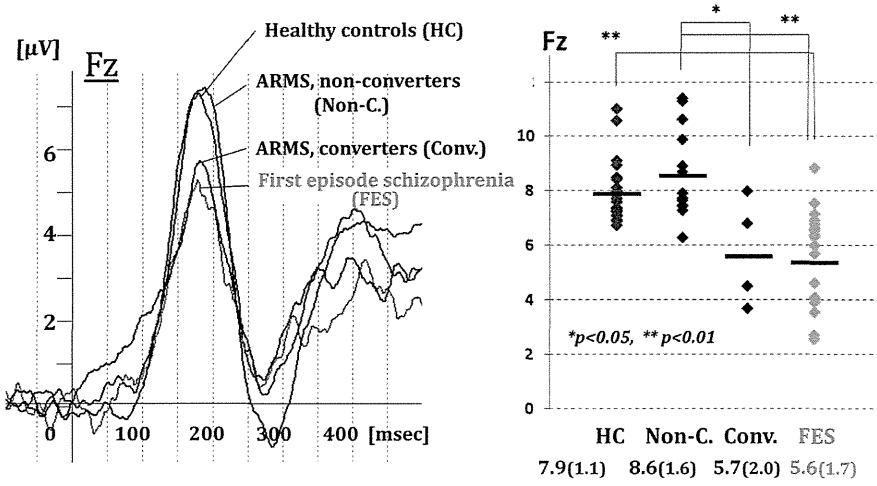

FIGURE 3 | Prediction of transition to schizophrenia by dMMN in ultra-high risk subjects. MMN waveforms at the frontal lead are shown for healthy controls, ARMS subjects, and first-episode schizophrenia. Converter subjects showed reduction in the amplitudes before the onset, similar to patients with first-episode schizophrenia. By contrast, MMN amplitudes of non-converters resembled those of healthy controls (Higuchi et al., 2013b).

OTHER ELECTROPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL BIOMARKERS

There is evidence that amplitudes of P300, another component of ERPs reflecting attentive cognitive abilities, are reduced in at-risk subjects (e.g., Nagai et al., 2013). As noted above, visual memory has been reported to differentiate between converters and non-converters in individuals vulnerable to developing schizophrenia (De Herdt et al., 2013). Further efforts are required to refine the use of these biomarkers for early detection of psychosis.

THREE-DIMENSIONAL IMAGING OF dMMN CURRENT DENSITY

Localization of generators for ERPs provides valuable information. For this purpose, the low-resolution brain electromagnetic tomography (LORETA) methods have been used (Pascual-Marqui, 1999, 2002). In these analyses, current source density of electrical activity is calculated from scalp EEG. Specifically, the LORETA methods can perform voxel-by-voxel comparisons of current source density.

Recently, researchers from the University of California San Diego conducted three-dimensional imaging of dMMN current density in control subjects and patients with chronic schizophrenia (Takahashi et al., 2012). In that study, the mean duration of illness was 24 years, which was lengthy. The comparison between the two groups indicates reduced activations in the cingulate gyrus and medial frontal gyrus in patients (Takahashi et al., 2012).

Regarding the *early* phase of schizophrenia, we recently reported data from patients whose mean duration of illness was

	Healthy controls (n=20)	Early schizophrenia (n=20)	Significance
Male/Female	14/6	9/11	n.s.
Age (years)	25.4 (6.9)	27.2 (7.3)	n.s.
Education (years)	15.1 (2.9)	13.2 (2.1)	< 0.05
Age at onset (years)	-	26.5 (7.1)	
Duration of illness (years)	-	0.6 (0.5)	

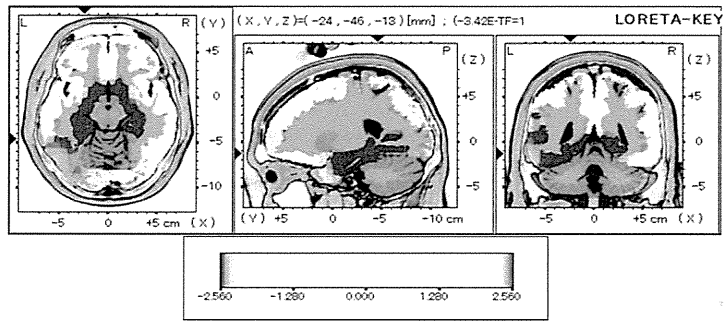

FIGURE 4 | Three-dimensional imaging of dMMN current density in *early* schizophrenia. Duration of illness was <1 year for all patients. Comparison between healthy subjects and patients showed decreased current density in such brain regions as bilateral parahippocampal gyrus, left fusiform gyrus, right hippocampus, and left anterior cingulate gyrus (data extracted from Miyanishi et al., 2013).

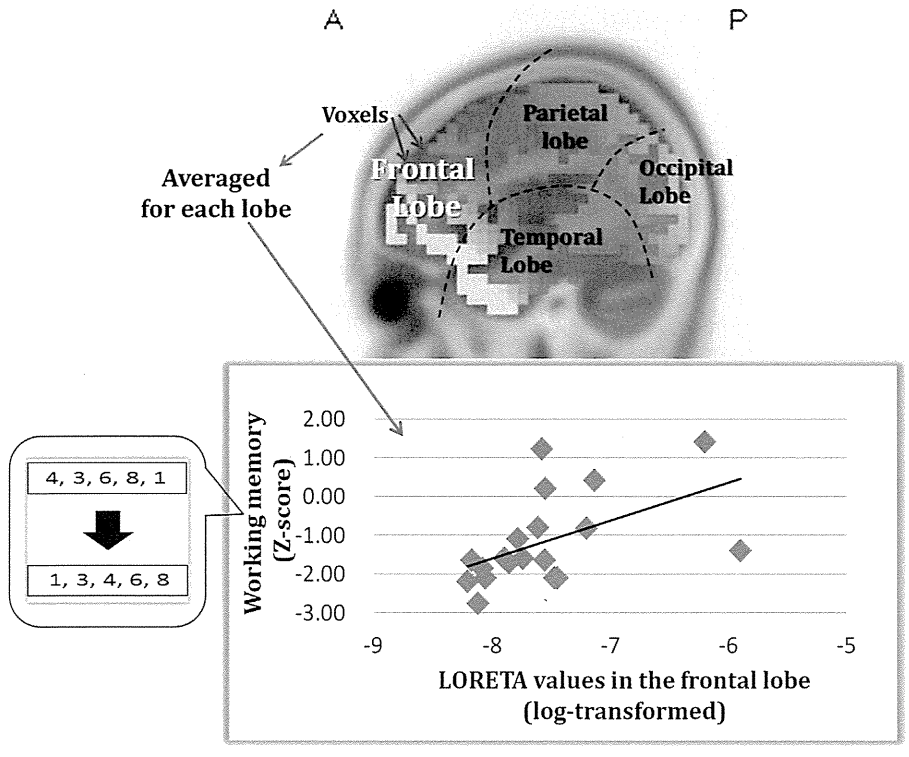

FIGURE 5 | Correlation between dMMN current density in the frontal lobe and working memory, as evaluated by the BACS-J, in patients with *early* schizophrenia. (Miyanishi et al., 2013).

<1 year (Miyanishi et al., 2013). **Figure 4** demonstrates the comparison of dMMN current density between healthy subjects and patients. Early schizophrenia patients showed decreased current density in medial temporal lobe structures and anterior cingulate gyrus, i.e., brain areas related to the pathophysiology of schizophrenia (Jensen et al., 2004; Hao et al., 2009).

An important part of our study was to determine if the change in dMMN activations is associated with neuropsychological performance. As demonstrated in **Figure 5**, dMMN current density in the frontal lobe is positively correlated with working memory, as measured by the BACS, in early schizophrenia patients (Miyanishi et al., 2013). These findings are consistent with the concept that the prefrontal cortex plays a major role in this cognitive domain. Further study is warranted to see if the association between dMMN current density in the frontal lobe and working memory is specific to schizophrenia, but not HCs, and if dMMN current density predicts progression to schizophrenia in at-risk people.

CONCLUSION

This paper provided a hypothesis regarding a role for neuropsychological and electrophysiological markers in intervention into early psychosis and high-risk subjects. The combination of these modalities of neurocognition would be expected to facilitate early detection of subjects who are likely to develop psychosis, and identification of those who need immediate treatment.

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PLOS ONE

LORETA Current Source Density for Duration Mismatch Negativity and Neuropsychological Assessment in Early Schizophrenia

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Abstract

Introduction: Patients with schizophrenia elicit cognitive decline from the early phase of the illness. Mismatch negativity (MMN) has been shown to be associated with cognitive function. We investigated the current source density of duration mismatch negativity (dMMN), by using low-resolution brain electromagnetic tomography (LORETA), and neuropsychological performance in subjects with early schizophrenia.

Methods: Data were obtained from 20 patients meeting DSM-IV criteria for schizophrenia or schizophreniform disorder, and 20 healthy control (HC) subjects. An auditory odd-ball paradigm was used to measure dMMN. Neuropsychological performance was evaluated by the brief assessment of cognition in schizophrenia Japanese version (BACS-J).

Results: Patients showed smaller dMMN amplitudes than those in the HC subjects. LORETA current density for dMMN was significantly lower in patients compared to HC subjects, especially in the temporal lobes. dMMN current density in the frontal lobe was positively correlated with working memory performance in patients.

Conclusions: This is the first study to identify brain regions showing smaller dMMN current density in early schizophrenia. Further, poor working memory was associated with decreased dMMN current density in patients. These results are likely to help understand the neural basis for cognitive impairment of schizophrenia.

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Introduction

Schizophrenia is a chronic and progressive psychotic disorder that emerges mainly in late adolescence or early adulthood. Patients with the illness exhibit positive symptoms and negative symptoms, as well as disturbances of various domains of cognitive function, e.g. verbal memory, working memory, executive function, and attention [1,2]. In particular, cognitive impairments have been shown to disturb their social activities, work outcome, and quality of life. Recent studies [3,4] report that mild cognitive deficits already exist before the onset of schizophrenia, or "at risk mental state" (ARMS). The neural substrates for cognitive deficits may include some brain regions, such as hippocampus and parahippocampal gyrus [5–8].

Mismatch negativity (MMN) is one of the event-related potentials (ERPs) generated by a deviant (infrequent) stimulus. MMN is elicited even under pre-attentive conditions, and reflects an automatic pre-attention process. Generation of the MMN is an indicator of auditory sensory memory, and represent information processing dependent on some components of the auditory cortex, e.g. superior temporal gyrus [9–11]. Previous studies using low-resolution brain electromagnetic tomography (LORETA), fMRI, and other procedures have demonstrated that MMN reflects activities of a neural network involving several brain structures. Among them, the auditory cortex plays a key role in the complex neural architecture of sensory discrimination [12–14].

The feature of MMN waveforms varies according to type of deviant stimuli, i.e. frequency, duration, intensity, and location. For example, diminished MMN amplitudes reflect cognitive decline in psychiatric conditions [15]. In schizophrenia, smaller amplitudes of MMN, especially duration MMN (dMMN), have been reported [3,16–19].

Several attempts have been made to relate MMN amplitudes and neuropsychological performance [17–21]. Lin et al. used predictive multivariate logistic regression model, and demonstrated dMMN and performance IQ, evaluated by the Wechsler Adult Intelligence Scale-Third Edition, can distinguish between schizophrenia patients and healthy control (HC) subjects [22].

LORETA provides three-dimensional images of brain electrical activity [23]. There are only a few reports on LORETA analysis of MMN in schizophrenia. Park et al. (2002) [24] observed a significant decrease in the current density for frequency MMN in the left superior temporal gyrus and left inferior parietal gyrus in patients with schizophrenia. Recently, Takahashi et al (2013)

report reduced dMMN current density at right medial frontal gyrus, right cingulate gyrus, and right paracentral lobule in patients with chronic schizophrenia [12]. To our knowledge, there is no report on LORETA analysis of dMMN in early psychosis.

The above considerations indicate the ability of the combination of neuropsychological tests and dMMN to provide an objective measure to diagnose schizophrenia. So far, no study has investigated the correlation between MMN current density in some brain regions, e.g. frontal lobe, and neuropsychological performance.

Therefore, this study was conducted to test the hypotheses that 1) patients with schizophrenia would exhibit decreased dMMN current density in brain areas relevant to the pathophysiology of the illness, such as some temporal lobe structures [25], and 2) reduced dMMN current density in the frontal lobe would be associated with impairment of neuropsychological performance, such as working memory.

Methods

Ethics Statement

This protocol was approved by the Committee on Medical Ethics of the University of Toyama. After a complete and detail description of the study was given, subjects provided written informed consent. Clinical staff explained the nature of the study to the subjects, the risks and benefits, and the option not to participate in this research. If the mental status of a subject was impaired to the point where s/he could not understand these issues, the subject was not asked to participate in this research. If there was a possibility that the capacity of a participant to consent was compromised, an additional consent form was obtained from the next of kin, care takers, or guardians of such subjects.

Participants

Subjects were diagnosed by experienced psychiatrists, based on the Structured Clinical Interview for DSM-IV (SCID) for schizophrenia or schizophreniform disorder. Twenty patients (male/female, 9/11; mean [S.D.] age, 27.2 [7.3]) participated in this study. Their duration of illness was less than 2 years. Twenty HC participants (male/female, 14/6; mean [S.D.] age, 25.4 [6.9]) were also recruited. They had no personal history of psychiatric illnesses, including schizophrenia and other psychotic disorders. All participants were right-handed. Psychiatric and treatment histories were obtained from the subjects, family members, and medical records. Subjects with a current history of substance abuse or dependence, seizure, or head injury were excluded from the study. Complete physical examination revealed no neurological illness for all subjects. Demographic data at baseline evaluation are shown in Table 1.

Clinical and neurocognitive assessment

The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) [26] were administered by an experienced psychiatrist. These data are shown in Table 1.

Neuropsychological performance, measured by the brief assessment of cognition in schizophrenia Japanese version (BACS-J) [27], was evaluated by experienced psychiatrists or psychologists. The BACS-J uses the following assessments in the respective targeted domains; list learning (verbal memory), digit sequencing task (working memory), token motor task (motor function), category fluency and letter fluency (verbal fluency), symbol coding (attention and processing speed), and the Tower of London test (executive function) [27], as shown in Table 1. These scores were transformed into Z-scores using data from healthy volunteers, as previously reported [27,28]. Raters were not informed of subjects' profiles or their diagnoses.

Table 1. Demographic and clinical data.

	Healthy controls (n = 20)	Early schizophrenia (n = 20)
Male/Female	14/6	9/11
Age (years)	25.4 (6.9)	27.2 (7.3)
	range, 16–45	range, 16–38
Education (years)	15.1 (2.9)	13.2 (2.1) *
Age at onset (years)	-	26.5 (7.1)
Duration of illness (years)	-	0.6 (0.5)
Antipsychotic dose (Risperidone equivalent mg/day)	-	2.1 (2.4)
SAPS	-	16.5 (13.2)
SANS	-	53.9 (25.2)
BACS-J (Z-score)#		
Verbal memory		−1.22 (1.59)
Working memory		−1.16 (1.18)
Motor function		−2.52 (1.07)
Verbal fluency		−1.12 (0.77)
Attention		−1.65 (0.75)
Executive function		−0.40 (1.89)

Values represent means (SD).
SAPS, Scale for the Assessment of Positive Symptoms.
SANS, Scale for the Assessment of Negative Symptoms.
BACS-J, Brief Assessment of Cognition in Schizophrenia, Japanese version.
*$p<0.05$, significantly smaller than healthy controls.
SD unit compared to reported values (ref. [27,28]).
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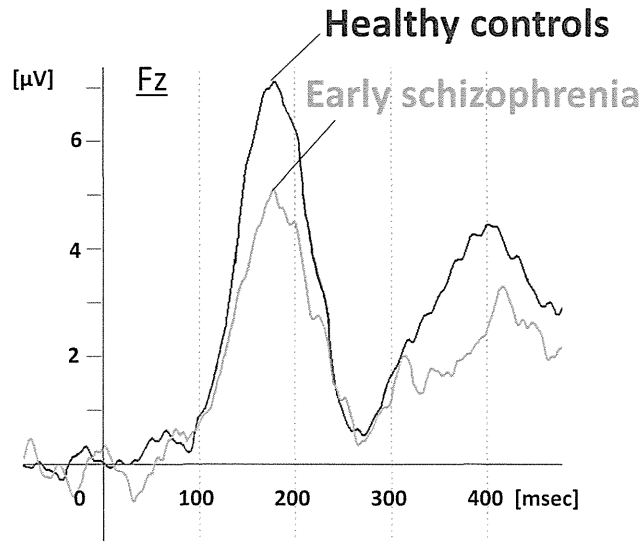

Figure 1. Duration mismatch negativity (dMMN) waveforms at the Fz lead. dMMN waveforms for healthy controls (N = 20, blue line) and early schizophrenia (N = 20, light green line) are shown.
doi:10.1371/journal.pone.0061152.g001

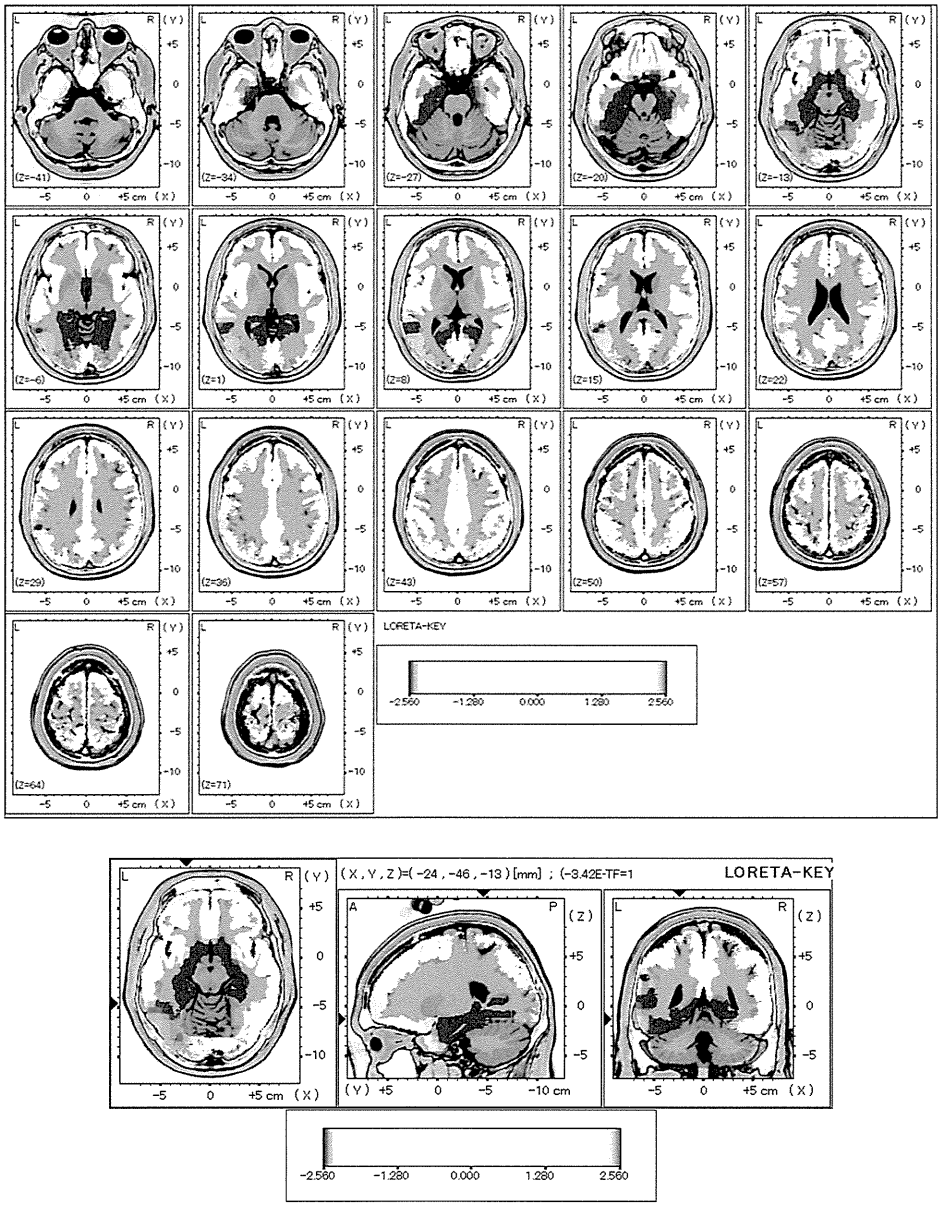

Figure 2. LORETA images for dMMN. Comparison of LORETA current density for dMMN between early schizophrenia (N = 20) and healthy control (N = 20, HC) subjects, as revealed by statistical non-parametric mapping voxel-wise comparison for independent samples. Blue areas represent brain regions showing significantly lower LORETA values for early schizophrenia subjects in comparison with HC subjects.
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Electroencephalographic recording

Electroencephalograms (EEGs) were recorded based on previous reports from our laboratory [29–34]. A 32-channel DC-amplifier (EEG-2100 version 2.22J, Nihon Kohden Corp., Tokyo, Japan), according to the international 10–20 system, was used. Recordings were performed using an electro cap (Electro cap Inc., Eaton, OH) in a sound-attenuated room. Data were collected with a sampling rate of 500 Hz. All electrodes were referred to the average amplitude of the ear electrodes (bandwidth, 0.53–120 Hz, 60 Hz notch filter). Electrode impedance was less than 5 kΩ. Measurements of dMMN were based on our previous report [33]. One thousand auditory stimuli were delivered binaurally through headphones with inter-stimulus intervals of 500 ms. Standard/target tones of 50/100 ms duration were randomly presented with a presentation probability of 0.9/0.1. All tones were 60 dB, 1000 Hz and with a rise-fall time of 10 ms. Subjects were requested to watch a silent animated movie (Tom and Jerry®), and to pay attention to the monitor and ignore the tones. Averaging of ERP waves and related procedures were performed using Vital Tracer and EPLYZER II software (Kissei Comtec, Co. Ltd. Nagano, Japan). Epochs were 600 ms, including a 100-ms pre-stimulus baseline. Eye movement artifacts (blinks and eye movements) were manually rejected. MMN waveforms were obtained by subtracting the standard waveforms from the target waveforms. ERP component peaks were identified within the fixed search windows between 100–250 ms. We confirmed the presence of the peaks of MMN in all subjects.

LORETA analysis

LORETA images were obtained by estimating the current source density distribution for epochs of brain electric activity on a dense grid of 2394 voxels at 7-mm spatial resolution applied to the digitized Talairach and Tournoux (1988) [35], based on the established method [23]. LORETA made use of the three-shell spherical head model registered to the Talairach atlas available as a digitized MRI from the Brain Imaging Centre, Montreal Neurologic Institute. Registration between spherical and realistic head geometry used EEG electrode coordinates reported by Towle et al (1993) [36]. The solution space was restricted to cortical gray matter and the hippocampus, as determined by the corresponding digitized Probability Atlas also available from the Brain Imaging Centre. A voxel was labeled as gray matter if it met the following three conditions: its probability of being gray matter was higher than that of being white matter, its probability of being gray matter was higher than that of being cerebrospinal fluid, and its probability of being gray matter was higher than 33% [23]. We used the original LORETA version reported by Pascual-Marqui et al [23]. We calculated LORETA images for each subject in the fixed time frame between the 100–250 ms post-stimulus period to obtain the LORETA value for each voxel. Additionally, we averaged LORETA value containing the following brain regions of interest (ROI): frontal lobe, temporal lobe, parietal lobe, and occipital lobe.

Data analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20 (SPSS Japan Inc., Tokyo, Japan). To investigate differences between groups, dMMN amplitudes at the Fz lead were assessed by independent t-test. Comparisons between early schizophrenia and HC on LORETA source imaging were conducted using voxel-by-voxel unpaired *t*-statistics after logarithmic transformation of the data. Holmes' non-parametric correction for multiple comparisons was applied [37]. Relationships of LORETA current density with BACS-J domain scores, SAPS total scores, and SANS total scores were analyzed using Spearman rank correlations. Bonferroni correction was applied for multiple comparisons. LORETA current density for dMMN did not show a uniformly normal distribution. Therefore, dMMN current density was subjected to natural logarithmic transformation to obtain a more normal distribution. The significance level for all statistical tests was set at $p<0.05$ (two-tailed).

Results

Subjects' profiles

Demographic data of participants are shown in Table 1. The female to male ratio and age were not significant between patients and HC (data not presented). Education level was significantly lower in patients than in HC subjects ($t=2.29$; $p=0.028$).

Neuropsychological assessments

BACS data for patients are shown in Table 1. Except for executive function, the Z-scores of the other domains were below −1.0. Especially motor function was severely impaired.

Comparisons of dMMN amplitudes between HC and early schizophrenia

Figure 1 shows the overall average dMMN waveforms in the Fz lead. dMMN amplitudes in HC and patients (mean ± SD) were 7.9±1.1 μV and 5.6±1.7 μV, respectively. Patients showed significantly smaller dMMN amplitudes than did HC subjects ($t=4.97$; $p<0.01$).

Table 2. Coordinates for brain areas showing the largest differences (top five) between healthy controls and early schizophrenia in dMMN current density.

		(X,Y,Z)	P-value
①	left parahippocampal gyrus	−24, −46, −13	<0.01
②	left fusiform gyrus	−31, −46, −6	<0.01
③	right parahippocampal gyrus	11, −39, 1	<0.05
④	right hippocampus	25, −39, 1	<0.05
⑤	left anterior cingulate	−3, −11, −6	<0.05

doi:10.1371/journal.pone.0061152.t002

Comparison of LORETA images for dMMN between HC and early schizophrenia

We compared LORETA current source density of dMMN between HC and early schizophrenia. Compared to HC subjects, patients elicited a significantly lower current density in several brain regions, especially those in the temporal lobes, such as parahippocampal gyrus and hippocampus (Figure 2). Additionally, dMMN current density in the frontal structures, such as anterior cingulate, was significantly lower for early schizophrenia. Table 2 demonstrates brain areas showing the largest difference in dMMN current density.

Relationship between psychotic symptoms and LORETA current density for dMMN

There was no significant correlation between the SAPS or SANS score vs. LORETA current density for dMMN in any brain region (data not presented).

Relationship between neuropsychological assessment and dMMN current density

Table 3 demonstrates the relationships between BACS-J domain scores and LORETA current density for dMMN. dMMN current density in the frontal lobe was positively correlated with working memory in patients with early schizophrenia (Table 3,

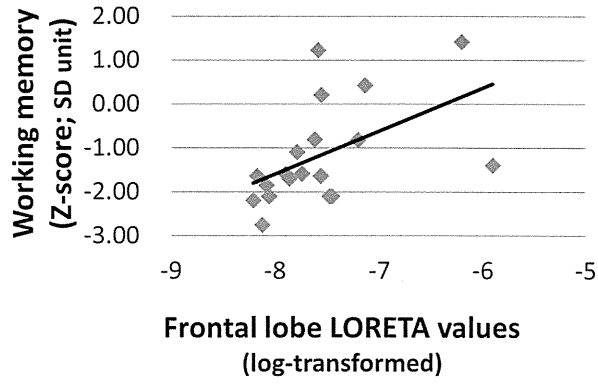

Figure 3. Correlations between dMMN current density and working memory. Scatterplots and least squares regression lines are shown for the correlations between LORETA current density for dMMN (log-transformed) and neuropsychological performance in early schizophrenia.
doi:10.1371/journal.pone.0061152.g003

Table 3. Spearman correlation coefficients between dMMN current density (log-transformed) in discrete brain regions and BACS-J scores in early schizophrenia.

	verbal memory		working memory		motor function		verbal fluency		attention		executive function	
	r	P	r	P	r	P	r	P	r	P	r	P
Frontal lobe	0.308	0.199	0.587	**0.008**	−0.102	0.678	−0.275	0.254	0.097	0.691	−0.092	0.707
Temporal lobe	0.259	0.285	0.448	0.055	−0.220	0.366.	−0.244	0.314	0.116	0.637	−0.108	0.659
Parietal lobe	0.110	0.655	0.274	0.257	−0.146	0.551	−0.256	0.290	0.150	0.540	−0.221	0.364
Occipital lobe	0.072	0.770	0.336	0.160	−0.100	0.683	0.107	0.663	0.372	0.117	0.028	0.909

doi:10.1371/journal.pone.0061152.t003

Figure 3). The correlation remained significant even after Bonferroni correction was applied. There were no such correlations for temporal, parietal, and occipital lobes.

Discussion

To our knowledge, this is the first study to report three-dimensional distribution patterns of dMMN current density and neuropsychological performance in early schizophrenia in comparison with healthy controls. LORETA images demonstrated a decreased dMMN current density in brain areas known to be associated with the pathophysiology of the illness, e.g. parahippocampal gyrus, hippocampus, fusiform gyrus, and anterior cingulate [5,6,38,39]. We also observed positive correlations between dMMN current density in the frontal lobe and working memory performance in patients with early schizophrenia.

Reductions in the volume of several brain regions, including frontal cortex and temporal cortex, in schizophrenia subjects and individuals vulnerable to developing the illness have been reported [40–42]. Reduced dMMN current density in the temporal lobe of patients, observed in this study, is consistent with these morphological findings. Specifically, MMN has been considered to be generated by neural activities in the superior temporal cortex and frontal cortex [9–11]. The present data from a more feasible and non-invasive methodology (i.e. EEG) add support to these lines of evidence for the potential role of several discrete brain regions in the pathophysiology of schizophrenia.

Takahashi et al. (2013) report schizophrenia patients demonstrated a smaller dMMN current density in the right medial frontal gyrus [12]. Compared with our data, their results indicate more frontal regions are affected in patients [12]. The discrepancy may be due to the difference in duration of illness. The subjects of Takahashi's study were chronic schizophrenia, with a mean duration of illness of 23.6 years, while that of our subjects was shorter, i.e. less than 2 years. It is possible that the electrophysiological impairment, e.g. dMMN, becomes more extensive as psychosis progresses. In this context, further study is needed to examine a longitudinal course of dMMN in schizophrenia.

Correlations between MMN amplitudes and neuropsychological performance have been an issue for intensive investigations. Several [17–21], but not all [3,22] studies found MMN amplitudes to be related to cognitive function. The present study revealed, for the first time, that dMMN current density in early schizophrenia was correlated with working memory. Perlstein et al. [43] report that this cognitive domain was associated with dorsolateral prefrontal cortex function, as measured by fMRI, consistent with our electrophysiological findings. Further study should clarify sub-region(s) of the frontal cortex whose dMMN current density is specifically associated with working memory.

The limitations of the present study should be noted. Patients with early schizophrenia were taking antipsychotic drugs which are agonists at dopamine receptors, although modulations of dopaminergic transmission have been shown to exert little effect on dMMN [44,45]. Another limitation may be the use of the original version of LORETA. Further study is warranted to examine dMMN in drug-naïve subjects using an updated version of LORETA (e.g. eLORETA, sLORETA), which would be more advantageous for sub-region analyses and/or multiple comparisons.

In conclusion, this study provides, for the first time, information on the brain regions responsible for diminished dMMN amplitudes in subjects with early schizophrenia. Further, we have found associations between poor working memory and decreased dMMN current density in these patients. These results are likely to help understand the neural basis for cognitive impairment of schizophrenia.

Author Contributions

Conceived and designed the experiments: TM T. Sumiyoshi YH. Performed the experiments: TM YH T. Seo. Analyzed the data: TM T. Sumiyoshi YH. Contributed reagents/materials/analysis tools: TM T. Sumiyoshi YH T. Seo MS. Wrote the paper: TM T. Sumiyoshi YH.

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