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

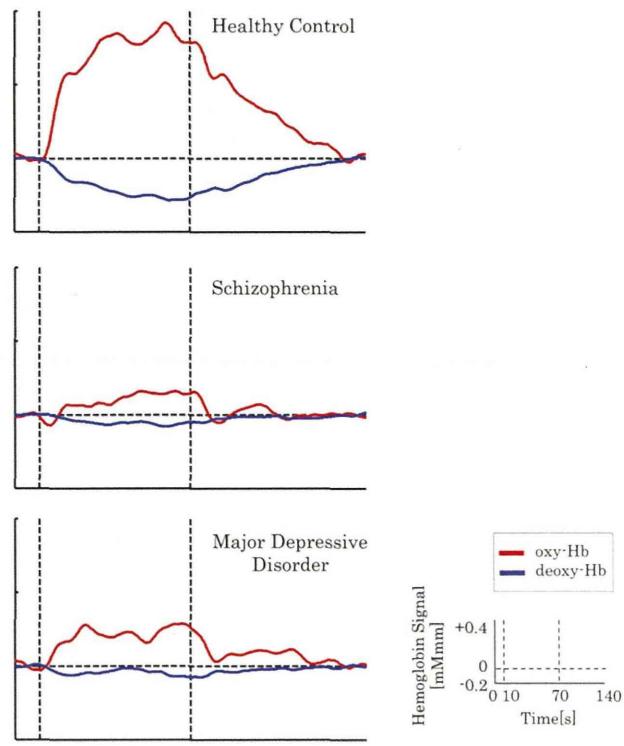

Fig. 2. Time course of [oxy-Hb] and [deoxy-Hb] changes in the FPPFC (channel 38).

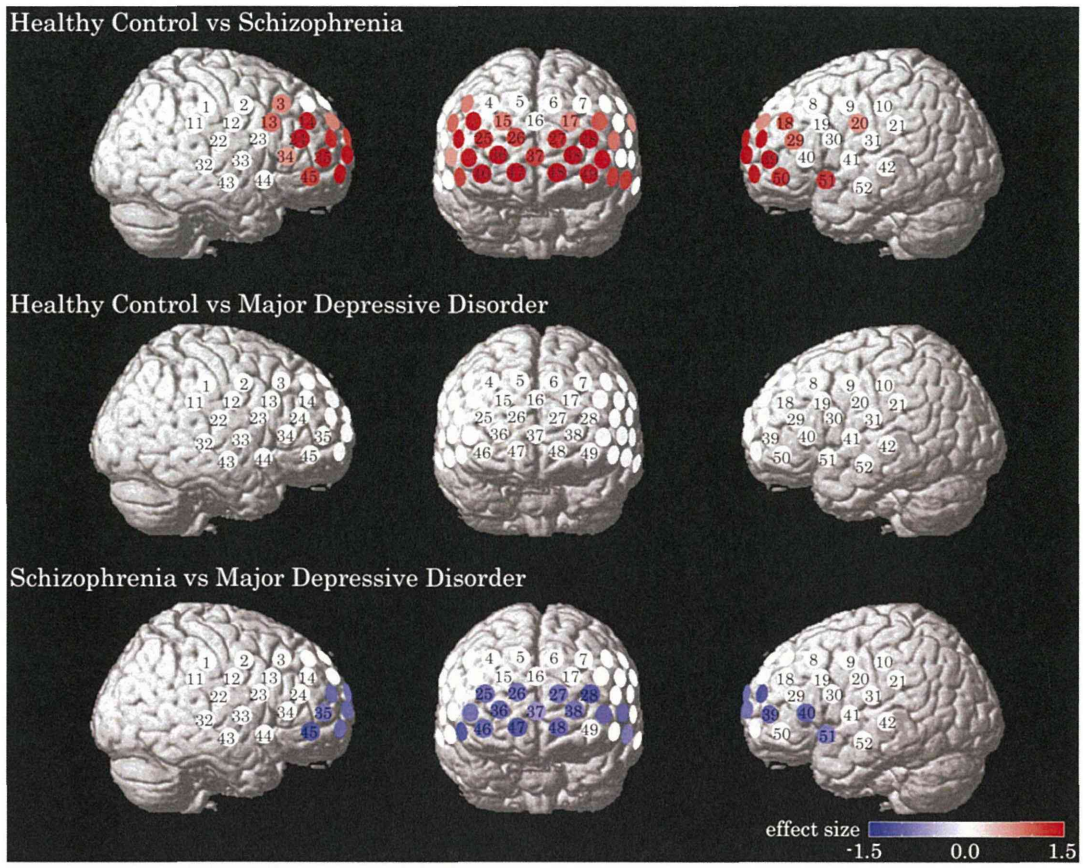

Fig. 3. Group differences in initial [oxy-Hb] slope. The effect sizes of the group differences are indicated by the color gradient. Channels that did not display significant differences among the 3 groups are colored in white.

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

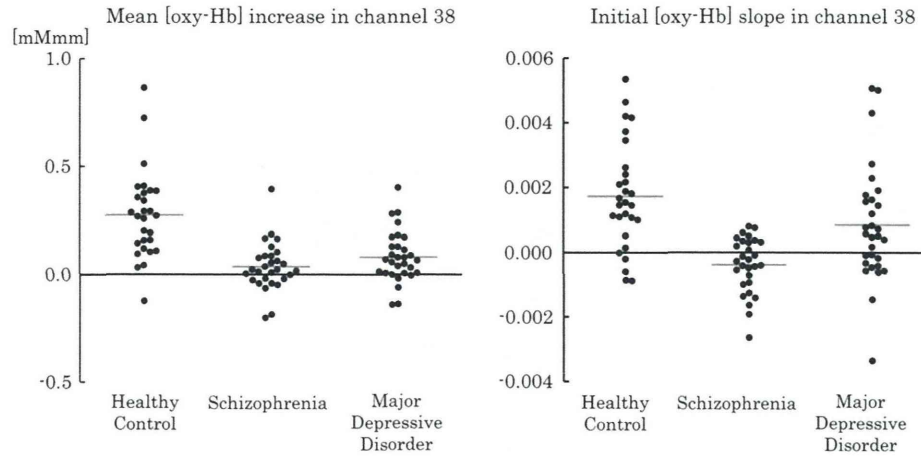

Fig. 4. Comparisons of mean [oxy-Hb] increase and initial [oxy-Hb] slope among the 3 groups. The bars indicate the mean ± 1 standard deviation.

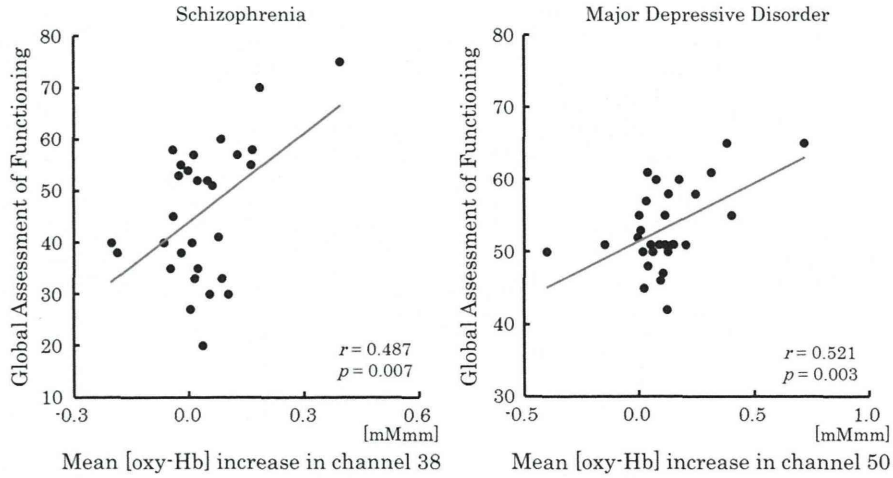

Fig. 5. Scatterplots for correlations between NIRS signal and GAF score in patients with schizophrenia and major depression.

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,

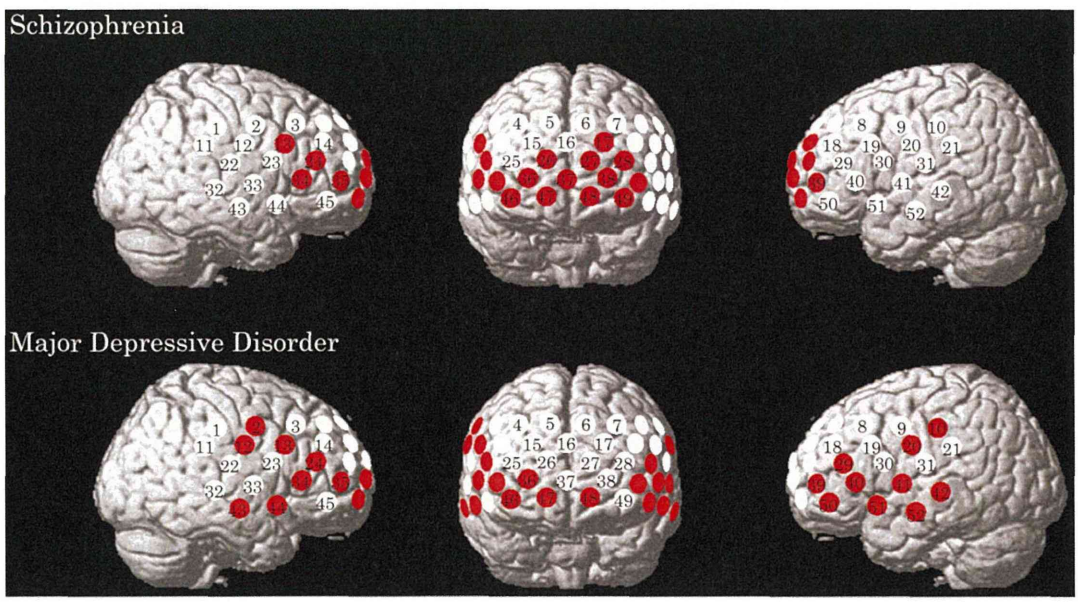

Fig. 6. Cerebral regions that exhibited a significant correlation between GAF score and mean [oxy-Hb] change.

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.

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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.

Beginning July 31, 2003, and continuing to the present, the University of Tokyo and the Hitachi Group (Advanced Research Laboratory, Hitachi Ltd. and The Research and Developmental Center, Hitachi Medical Corporation) have had an official contract for a collaborative study on the clinical applications of near-infrared spectroscopy (NIRS) in psychiatric disorders, which has been approved by the Research Promotion Office, University of Tokyo Hospital. The principal investigator of this study is Kiyoto Kasai. For this study, the Hitachi Medical Corporation provided a project grant (JPY 300,000 per year) and material support (temporary rental of a near-infrared spectroscopy machine (ETG-4000, Optical Topography)).

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Neuroimaging-aided differential diagnosis of the depressive state

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ABSTRACT

A serious problem in psychiatric practice is the lack of specific, objective biomarker-based assessments to guide diagnosis and treatment. The use of such biomarkers could assist clinicians in establishing differential diagnosis, which may improve specific individualised treatment. This multi-site study sought to develop a clinically suitable neuroimaging-guided diagnostic support system for differential diagnosis at the single-subject level among multiple psychiatric disorders with depressive symptoms using near-infrared spectroscopy, which is a compact and portable neuroimaging method. We conducted a multi-site, case–control replication study using two cohorts, which included seven hospitals in Japan. The study included 673 patients (women/men: 315/358) with psychiatric disorders (major depressive disorder, bipolar disorder, or schizophrenia) who manifested depressive symptoms, and 1007 healthy volunteers (530/477). We measured the accuracy of the single-subject classification in differential diagnosis among major psychiatric disorders, based on spatiotemporal characteristics of fronto-temporal cortical haemodynamic response patterns induced by a brief (<3 min) verbal fluency task. Data from the initial site were used to determine an optimal threshold, based on receiver-operator characteristics analysis, and to generate the simplest and most significant algorithm, which was validated using data from the remaining six sites. The frontal haemodynamic patterns detected by the near-infrared spectroscopy method accurately distinguished between patients with major depressive disorder (74.6%) and those with the two other disorders (85.5%; bipolar disorder or schizophrenia) that presented with depressive symptoms. These results suggest that neuroimaging-guided differential diagnosis of major psychiatric disorders developed using the near-infrared spectroscopy method can be a promising biomarker that should aid in personalised care in real clinical settings. Potential confounding effects of clinical (e.g., age, sex) and systemic (e.g., autonomic nervous system indices) variables on brain signals will need to be clarified to improve classification accuracy.

Introduction

Among non-communicable diseases, neuropsychiatric conditions, including depression, contribute most significantly to overall disability-adjusted life years (DALYs), surpassing both cardiovascular disease and cancer (Mathers and Loncar, 2006; Prince et al., 2007). Therefore, early and accurate diagnosis and treatment are critical in psychiatric disorders, for which the development of specific biomarkers is of special importance. Currently, however, the diagnostic process in psychiatry is mainly based on patients' reports of symptoms, observed behaviours and disease course. Overcoming the limitations of relying on clinical interviews alone for the diagnosis of psychiatric disorders has been a great challenge.

To complicate this issue further, the manifestation of only a major depressive episode hampers the reliable differentiation of major depressive disorder (MDD) from bipolar disorder (BP) or

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schizophrenia (SZ) based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria alone (Zimmermann et al., 2009). Although many clinical symptoms are common to various psychiatric disorders, depressive symptoms are particularly ubiquitous in the disease process or clinical staging of various psychiatric disorders (Hafner et al., 2005). For instance, differentiation between BP presenting with depressive symptoms and unipolar MDD is a topical issue (Akiskal et al., 1995). Indeed, most patients with BP with depressive symptoms are initially diagnosed with and treated for MDD (Akiskal et al., 1995; Goldberg et al., 2001). Therefore, biomarkers that can facilitate early and accurate differentiation of BP with depressive symptoms from MDD are necessary.

In addition, depressive symptoms that fulfil the operational diagnostic criteria for a depressive episode/major depression can also occur at any stage of SZ and can contribute substantially to its associated morbidity and even mortality (an der Heiden et al., 2005). The differentiation of SZ from MDD, especially in the early stages, is also important because patients with SZ also exhibit non-psychotic and non-specific prodromal symptoms (e.g., depressive or negative symptoms and cognitive deficits) for several years before the onset of full-blown psychosis (McGorry et al., 2008). Therefore, the availability of clinically useful and cost-effective biomarkers for the differential diagnosis of major psychiatric disorders would likely enhance patient management, improve treatment/therapeutic response and lead to targeted therapies tailored to the individual (Holsboer, 2008). Despite their potential, to date, no such biomarkers have been established.

Functional imaging studies are one source of potential biomarkers (Gur et al., 2007; Phillips and Vieta, 2007); these studies have previously elucidated subtle brain abnormalities in patients with major psychiatric disorders relative to healthy control (HC) individuals and have been applied to the differential diagnosis of psychiatric disorders (e.g., to differentiate MDD from SZ, Barch et al., 2003 or BP, Almeida et al., 2009). However, some functional neuroimaging techniques are limited by the fact that, during the procedure, the individuals need to be placed in an uncomfortable or unnatural setting (e.g., lying in a supine position in a narrow gantry with the head fixed during the entire examination), for accurate measurement.

In contrast, multi-channel near-infrared spectroscopy (NIRS) using near-infrared light provides a completely non-invasive measurement of the spatiotemporal characteristics of brain function in ordinary clinical settings and allows patients to be comfortably seated in a well-lit room; therefore, it is considered a method for 'real-world neuroimaging'. Additionally, NIRS has relatively low maintenance costs and does not involve ionising radiation or objectionable noise; thus, it can be repeated as needed even for patients with psychiatric disorders. The utility and limitations of NIRS have been discussed extensively in previous reports (Ferrari and Quaresima, 2012; Obrig and Villringer, 2003; Strangman et al., 2002a). NIRS allows the measurement of haemoglobin concentration changes (1) only in the cortical surface area located immediately beneath the probes, but not in deeper brain structures, and (2) with limited spatial resolution, although it has a high temporal resolution. In NIRS, typical cortical activation represents not only decreased concentration of deoxy-haemoglobin ([deoxy-Hb]), which is considered the main source of blood oxygenation level-dependent (BOLD) contrast increase in functional magnetic resonance imaging (fMRI), but also a relatively larger increase in oxy-haemoglobin concentration ([oxy-Hb]) (Fig. 1).

The verbal fluency task (VFT) is a cognitive task that is used as a neuropsychological test or a neuroimaging task. The VFT elicits different abnormalities relevant to each diagnostic group of major psychiatric disorders (Curtis et al., 2001; Zanelli et al., 2010). We previously developed a very brief (<3 min) VFT and used it to investigate the differential fronto-temporal haemodynamic pattern between MDD and SZ (Suto et al., 2004) or MDD and BP (Kameyama et al., 2006), as well as the relationship between NIRS signals and functional impairment in SZ (Takizawa et al., 2008). We also found functional NIRS abnormalities in individuals at ultra-high risk for SZ and patients with first-episode psychosis (Koike et al., 2011). However, the clinical applicability of NIRS to the differential diagnosis of individuals remains uncertain. In this study, we extended our translational approach to replicate our previous findings (Kameyama et al., 2006; Suto et al., 2004) in a seven-site collaborative study using a large, fully independent sample set, and to evaluate the application of NIRS to psychiatric differential diagnosis in natural clinical settings.

Specifically, we used NIRS with wide coverage of the prefrontal and temporal cortices to investigate whether the frontal and temporal brain haemodynamic responses induced by cognitive activation could serve as biomarkers of underlying major psychiatric disorders with depression. To validate the reproducibility and generalisability of the results, we applied an algorithm developed using the data generated at the initial site to the test data derived from the remaining 6 sites. We hypothesised that the spatiotemporal characteristics of the haemodynamic responses detected by NIRS would not only differentiate patients with psychiatric disorders from HCs with acceptable sensitivity and specificity, but would also differentiate correctly and with a high concordance rate patients with MDD from patients with bipolar disorder and schizophrenia who present with depressive symptoms.

Material and methods

Participants

This multi-site study was performed in 7 hospitals: 6 were affiliated with universities (Fukushima, Gunma, Mie, Tokyo, Showa, and Tottori) and one was affiliated with the National Centre of Neurology and Psychiatry of Japan. The sites were situated in the Tokyo metropolitan area and in moderate-scale prefectural capital cities (Fukushima, Maebashi, Tsu and Yonago). The participants were recruited from June 2004 to June 2009, with the exception of recruitment at the initial site (Gunma University Hospital in Maebashi City), which was conducted over 6 years (March 2003 to March 2009). The ethics committees of the participating hospitals approved this collaborative study. In accordance with the Declaration of Helsinki, all participants gave written informed consent after receiving a complete explanation of the study.

Six hundred and seventy-three in-patients and out-patients with psychiatric disorders (MDD, BP and SZ), in addition to 1007 HC volunteers (Flow diagram (1)), were initially enrolled. Of note, these individuals were not the same as those included in our previous studies (Kameyama et al., 2006; Suto et al., 2004). The patients were diagnosed by experienced psychiatrists based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1997). The HC volunteers were hospital staff members, university students and members of the general population who responded to website or newspaper advertisements in each city. The SCID non-patient edition was used to screen HC individuals. The exclusion criteria of the initial enrolment were neurological illness, traumatic brain injury with any known cognitive consequences and alcohol/substance abuse or addiction. All participants were native Japanese speakers who were capable of performing a Japanese version of the VFT easily.

On the day of NIRS measurement, the depressive symptoms of participants were evaluated using the 17-item Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960) and their psychotic and manic symptoms were evaluated using both the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1991) and the Young Mania Rating Scale (YMRS) (Young et al., 1978), respectively, by well-trained psychiatrists with no knowledge of the NIRS data. During the study, all patients with psychiatric disorders were medicated with one or more agents (anti-psychotics, anti-depressants, anxiolytics and/or anti-parkinsonian agents), with the exception of 10 drug-free patients with MDD and 5 drug-free patients with SZ.

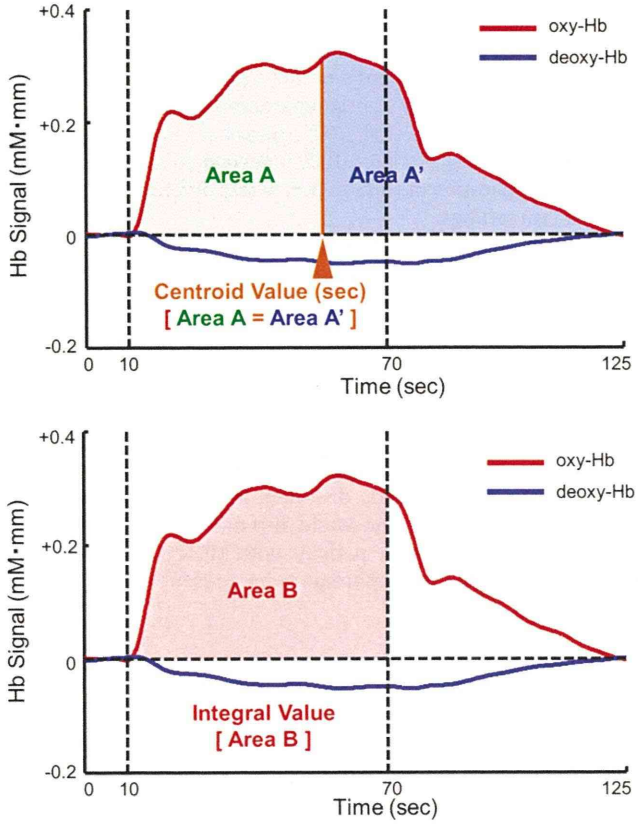

Fig. 1. Typical time-course pattern of near-infrared spectroscopy (NIRS) signals coupled with the verbal fluency task. The 'centroid value' is indicated by the time [s], which is indicated by a perpendicular line from the centroid of an NIRS signal-change area (calculated with positive change) throughout all the task periods. Oxy-Hb: oxygenated haemoglobin signal; deoxy-Hb: deoxygenated haemoglobin signal.

To minimise the influence of confounding factors, we performed group matching for age and gender among the 4 diagnostic groups using one-way analysis of variance (ANOVA) and a chi-squared test, which excluded randomly selected individuals and brought the mean age of the HC individuals and patients with MDD or SZ in closer alignment with that of the patients with BP (44.0 ± 14.9 years old (y.o.)), which was the group with the fewest individuals (Table 1 and Flow diagram (2)). For confirmation, we also analysed demographically non-matched samples that are identified in the Supplementary Material (I). The overall results were the same as those described in the main manuscript and the reduction in the total number of study participants after demographical matching did not appear to have an influence on the development of the algorithm (see Supplementary Material (I)).

Because our clinically valuable target were help-seeking unremitted patients, subsequently we excluded study participants with extremely mild symptoms (HAMD score ≤ 5, PANSS depression item score ≤ 1, PANSS negative symptom score ≤ 11, PANSS general psychopathology score ≤ 21, or PANSS positive symptom score − negative symptom score ≤ 11; the latter 3 criteria were based on the criteria from the PANSS manual for the 5th percentile of patients with mild SZ, Kay et al., 1991). We also excluded patients in a manic phase (YMRS score > 10) from the NIRS measurement; rather, we focused on patients with BP who were in the depressive phase because the different phases may produce different brain dysfunctions in patients with BP (Phillips and Vieta, 2007), and manic patients with BP were diagnosed without apparent difficulty (Flow diagram (3)).

Activation task

The activation task used in this study was similar to that used in our previous studies (Kameyama et al., 2006; Suto et al., 2004; Takizawa et al., 2008). Briefly, a VFT (letter version) was administered and NIRS signal ([oxy-Hb] and [deoxy-Hb]) changes were measured during a 10 s pre-task baseline period, a 60 s activation period and a 55 s post-task baseline period. During the activation period, the participants were instructed to utter as many Japanese words beginning with a designated syllable as possible. For the pre- and post-task baseline periods, the individuals were instructed to simply repeat Japanese vowels out loud. The total number of correct words generated during the 60 s activation period was used as the measure of task performance (Table 1).

Among the many neuropsychological tasks used for detecting neurocognitive deficits in patients with major psychiatric disorders (Barrett et al., 2009; Zanelli et al., 2010), we selected the VFT because it is an executive task that exhibits distinct differences in performance and neuroimaging data among each diagnostic group of major psychiatric disorders (Costafreda et al., 2006; Curtis et al., 2001; Zanelli et al., 2010). In addition, the VFT is easy to understand and execute; in fact, all participants generated more than one word during the VFT. Therefore, this task is suitable for translational research aimed at identifying practical biomarkers.

NIRS measurement

The NIRS apparatus and measurement procedure were described in full previously (Takizawa et al., 2008). Briefly, we used a 52-channel NIRS system (ETG-4000; Hitachi Medical Co., Tokyo, Japan). The preparation of the apparatus, including the audiovisual on-screen instructions, usually took less than 7 min and our brief version of the VFT took less than 3 min, which is less demanding for participants (10–15 min is necessary for the entire procedure).

NIRS is based on the principle that near-infrared light is preferentially absorbed by haemoglobin and less so by other tissues. Near-infrared light emitted from the skin travels into the body, is reflected and absorbed by the internal tissues and reappears on the skin. Thus, the absorption of near-infrared light reflects haemoglobin concentration ([Hb]) in the tissue placed beneath emission and detection probe pairs. Measurements taken using 2 or more wavelengths of near-infrared light enable the determination of [oxy-Hb] and [deoxy-Hb] changes because their absorptions are different at different wavelengths. The ETG-4000 system measures 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.(Yamashita et al., 1996) In this continuous-wave NIRS system, these [Hb] values include a differential pathlength factor (DPF); therefore, the unit of this form of NIRS measurement is mM·mm. The distance between pairs of source-detector probes was set to 3.0 cm and each measurement area located between pairs of source-detector probes was defined as one 'channel'. It is assumed that a machine in which the source-detector spacing is 3.0 cm measures points at a depth of 2–3 cm from the scalp (i.e., the surface of the cerebral cortex) (Okada and Delpy, 2003). The temporal resolution of NIRS was set to 0.1 s.

The arrangement of the probes measured relative [oxy-Hb] and [deoxy-Hb] signal changes in the bilateral prefrontal cortical area (i.e., dorso-lateral [Brodmann areas (BAs) 9 and 46], ventro-lateral [BAs 44, 45, and 47] and fronto-polar [BA 10] regions) and in the superior and middle temporal cortical surface regions, which was corroborated by a multi-individual study of anatomical cranio-cerebral correction via the international 10–20 system (Fig. 2 and Table S1) (Tsuzuki et al., 2007). However, in the 10–20 system, the anterior parts of the probes (e.g., Fpz) can be positioned precisely, whereas the position errors of more lateral probes might be increased due to inter-individual head size variability. In addition, although we initially aimed to analyse single-individual and single-channel levels in this study, studies of repeated NIRS measures have demonstrated acceptable reliability of the NIRS signal at the group and cluster levels, whereas retest reliability was unsatisfactory at the single-individual and single-channel levels (Schecklmann et al., 2008).

Table 1
Demographic and clinical characteristics of the 4 age- and gender-matched diagnostic groups at all 7 study sites.

	Major depressive disorder		Schizophrenia		Bipolar disorder		Healthy control		Group difference
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p*-Value
n	153		136		134		590		
Age years	43.8	12.7	43.7	12.1	44.0	14.9	43.9	15.7	0.99
Gender, women/men	77/76		67/69		69/65		314/276		0.81[a]
Education, years	14.0	1.9	15.2	2.0	15.6	2.0	16.1	2.4	<0.01
Estimated premorbid IQ	106.0	10.1	103.7	11.2	106.9	8.6	107.2	10.1	0.23
Task performance	13.0	3.8	13.6	4.4	12.0	3.6	15.3	4.8	<0.01
Age at onset, years	39.2	11.3	23.4	7.4	32.9	12.4	–		
PANSS									
Positive	–		16.3	5.0	–		–		
Negative	–		21.0	6.0	–		–		
General psychopathology	–		37.0	7.6	–		–		
HAM-D	14.1	6.7	–		8.4	7.0	–		
YMRS	–		–		4.7	5.9	–		
GAF	53.9	9.7	47.3	11.4	55.5	13.3	–		

Abbreviations: IQ, intelligence quotient; PANSS, Positive and Negative Syndrome Scale; GAF, global assessment of functioning.
[a] Chi-square test was used for testing group difference. Otherwise, one-way ANOVA was used.

Therefore, instead of undertaking a full analysis at the single-individual and single-channel levels, here we performed an analysis of NIRS signals at the single-individual and cluster levels. A principal component analysis (PCA) of NIRS [oxy-Hb] signal changes in targeted fronto-temporal channels was performed at the initial study site as a preliminary analysis to capture a channel cluster of the analogous time-course pattern in HC individuals. Subsequently, the weight maps of the first and second principal component graphs were used to identify 2 cluster components.

These analyses suggested that 2 cluster components were identified and that the 2 clusters included the frontal region (11 channels) and the bilateral temporal region (10 channels each) (see Supplementary Material (II) and eFig. S1). The channels in these 2 respective regions of interest were averaged and transformed into representative 'Region 1 (R1)' and 'Region 2 (R2)' NIRS signals for each individual (Fig. 3). According to registration into the LONI Probabilistic Brain Atlas 40 (LBPA40) (Fig. 2) (see Supplementary Table S1 for LBPA40 anatomical labels) (Shattuck et al., 2008), the R1 NIRS signal consisted of signals from channels located approximately in the fronto-polar and dorsolateral prefrontal cortical regions (i.e., superior and middle frontal gyri), whereas the R2 NIRS signal consisted of signals from channels located approximately in the ventro-lateral prefrontal cortex and the superior and middle temporal cortical regions (i.e., inferior frontal gyrus and superior and middle temporal gyri).

An automatic artefact-rejection procedure (see Supplementary Material (III)) was followed and individual data were excluded when there were fewer than 6 remaining channels from each of the 2 cluster regions (Flow diagram (4)).

Statistical analyses

Taking into consideration the potential application of the technique in ordinary clinical settings and personalised care, a conservative receiver operating characteristic (ROC) analysis was performed and used to generate simple indices of NIRS signal patterns, to aid individual diagnoses.

The spatiotemporal characteristics of the frontal and temporal haemodynamic responses induced by VFT were assessed and subsequently applied to an algorithm using the simplest and fewest variables for differential diagnosis. Because previous studies have shown that the best way to differentiate patients with MDD from those with BP or SZ is to describe the time-course of changes in the NIRS signal associated with the VFT (Kameyama et al., 2006; Suto et al., 2004), we chose to create 2 simple visual indices, referred to here as 'integral value' and 'centroid value', to capture these time-course changes.

The integral value describes the size of the haemodynamic response during the 60 s activation task period, whereas the centroid value serves as an index of time-course changes throughout the task, with periods representing the timing of the haemodynamic response. The centroid value is indicated by a time shown with a perpendicular line from the centroid of the NIRS signal change area (calculated as a positive change) throughout the task periods (from 0 [s] to 125 [s]

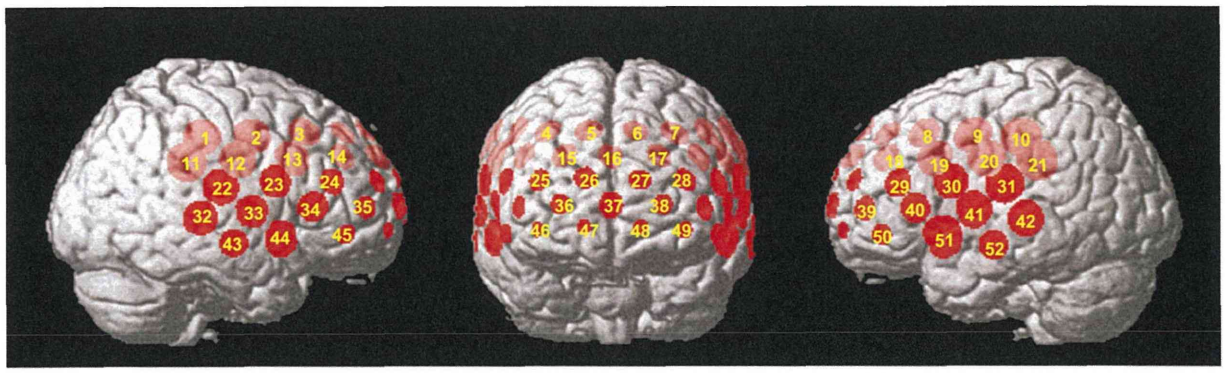

Fig. 2. Regions of interest (Regions 1 and 2) of the near-infrared spectroscopy (NIRS) signals. The locations of near-infrared spectroscopy (NIRS) measurements were probabilistically estimated and anatomically labelled in the standard brain space (LBPA40) according to Tsuzuki et al. (2007). Region 1: (ch 25–28, ch 36–38 and ch 46–49); Region 2, Right: (ch 22–24, ch 32–35 and ch 43–45); Left: (ch 29–31, ch 39–42 and ch 50–52).