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Differential spatiotemporal characteristics of the prefrontal hemodynamic response and their association with functional impairment in schizophrenia and major depression

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ABSTRACT

Recent neuroimaging studies have shown similarities and differences in prefrontal abnormalities between patients with schizophrenia (SZ) and major depressive disorder (MDD). However, the differential spatiotemporal characteristics of these abnormalities and their association with functional impairment remain unclear. To elucidate differential brain pathophysiology in these disorders, we used multichannel near-infrared spectroscopy (NIRS) to measure the spatiotemporal characteristics of prefrontal activation and investigated their association with global functioning levels. The study included 96 individuals: 32 patients with SZ, 32 patients with MDD, and 32 demographically matched healthy subjects. During a verbal fluency task, the changes in oxygenated and deoxygenated hemoglobin ([oxy-Hb] and [deoxy-Hb]) signals over the prefrontal cortex (PFC) were measured using 52-channel NIRS and compared among the 3 groups. Patients with SZ and MDD showed lesser-than-normal [oxy-Hb] activation during the task, whereas the initial slope of [oxy-Hb] activation was steeper for patients with MDD than for patients with SZ. The reduced hemodynamic response was associated with lower global functioning, and the correlative regions were different between the 2 disorders (frontopolar PFC in SZ; dorsolateral and ventrolateral PFC in MDD). The hypofrontality observed in patients with SZ and MDD is consistent with the findings of previous neuroimaging studies. Moreover, the spatiotemporal characteristics and the functional significance of the prefrontal hemodynamic response could differentiate the 2 psychiatric disorders. These results suggest a differential brain pathophysiology between SZ and MDD. Future large-scale studies are needed to determine the practical applicability of these findings for clinical diagnosis and evaluation.

1. Introduction

Psychiatric studies using neuroimaging techniques (functional magnetic resonance imaging [fMRI] and positron emission tomography [PET]) performed during cognitive activation tasks, such as the verbal fluency task (VFT) (Yurgelun-Todd et al., 1996), n-back task (Driesen et al., 2008; Manoach et al., 1999), and mental arithmetic task (Hugdahl et al., 2004), have consistently shown abnormalities in task-associated activation of the prefrontal cortex (PFC) in patients with schizophrenia (SZ) compared with healthy controls (HCs).

Reduced prefrontal activation during cognitive activation tasks has been observed in patients with major depressive disorder (MDD). However, the abnormal increase or decrease in PFC activation in these patients seems to depend on the type of cognitive task and experimental design. Compared to HCs, patients with MDD were shown to have reduced PFC activation in the VFT (Okada et al., 2003), digit-sorting task (Siegle et al., 2007), AX continuous performance task (Holmes et al., 2005), and emotional task (Liotti and Mayberg, 2001; Mayberg et al., 1999). Conversely, patients with MDD have been reported to have increased activation in the bilateral dorsolateral PFC (DLPFC) during the mental arithmetic task (Hugdahl et al., 2004) and in the left DLPFC during the high-loaded working memory task (Harvey et al., 2005).

Some researchers have compared the functional neuroimaging differences in impaired brain functions between SZ and MDD (Barch et al., 2003; Berman et al., 1993; Holmes et al., 2005; Hugdahl et al., 2004; Walter et al., 2007). Holmes et al. (2005) suggested that patients with SZ and MDD exhibit decreased PFC

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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.