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Research report

Left temporal activation associated with depression severity during a verbal fluency task in patients with bipolar disorder: A multichannel near-infrared spectroscopy study

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ABSTRACT

Background: Neuroimaging studies using multichannel near-infrared spectroscopy (NIRS) have provided compelling evidence about the dysfunction of the frontotemporal cortices in patients with bipolar disorder (BD). However, it remains unclear whether the dysfunction is associated with mood state or symptom severity. Using NIRS, we aimed to clarify differences in oxygenated hemoglobin (oxy-Hb) activation between depressive and euthymic states as well as regional brain dysfunction in relation to symptom severity in BD.

Methods: Fifty-five patients with BD, including 30 with bipolar depression (BPD) and 25 with euthymic bipolar disorder (BPE), and 28 healthy controls (HCs) participated in the study. Regional hemodynamic changes during a verbal fluency task (VFT) were monitored using a 52-channel NIRS apparatus.

Results: The mean oxy-Hb changes induced by VFT were significantly smaller in the BD patients than in the HCs in 18 channels in the frontotemporal regions (false-discovery rate $p < 0.05$, $p = 0.000–0.011$). The BPD group exhibited significantly smaller changes in mean oxy-Hb compared with the BPE group in three channels of the left temporal region ($p = 0.005–0.014$). In the BD patients, significant negative correlations were observed between mean oxy-Hb changes in the left temporal regions and the severity of depression.

Limitations: Our sample size was small, making the results susceptible to type II errors.

Conclusions: BD patients have persistent hypofunction of the frontotemporal cortical regions. Moreover, the hemodynamic response in the left temporal regions is associated with symptom severity.

1. Introduction

Bipolar disorder (BD) is a chronic and recurrent mental illness that causes unusual mood shifts associated with significant morbidity and suicide rates (Phillips and Kupfer, 2013; Townsend and Altshuler, 2012). Because individuals with BD spend the majority of their time in episodes of depression (Judd et al., 2002; Kupka et al., 2007), and because this phase is associated with high levels of morbidity and mortality across the life span, efforts aimed at identifying biological mechanisms that contribute to BD are imperative (Townsend and Altshuler, 2012).

Neuroimaging studies in BD patients have documented structural and functional abnormalities in the dorsolateral and lateral prefrontal cortex (PFC) and the temporal areas known to be involved in emotional regulation, attention, learning and memory, and the anticipation and interpretation of complex information (Chen et al., 2011; Malhi and Yatham, 2004; Townsend and Altshuler, 2012). Recent reviews of functional magnetic resonance imaging (fMRI) that focused on the processing of emotions in BD concluded that the limbic, frontal, and occipitotemporal regions were affected (Malhi and Yatham, 2004; Strakowski et al., 2005; Yurgelun-Todd, 2007). These findings are largely consistent with those for a model in which impaired prefrontal (cognitive) modulation of the anterior limbic (emotional) networks underlay mood symptoms in BD (Blumberg et al., 2000; Malhi and Yatham, 2004; Strakowski et al., 2005, 2010; Yurgelun-Todd, 2007). Strakowski et al. suggested a diminished prefrontal modulation of the subcortical and medial temporal structures that resulted in mood dysregulation (Strakowski et al., 2005).

Multichannel near-infrared spectroscopy (NIRS) is a noninvasive optical technique that monitors hemodynamic changes related to cortical neural activity by measuring relative changes in oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb). NIRS has an advantage over other neuroimaging techniques because it has a high temporal resolution (0.1 s) for measuring time-specific characteristics of dynamic frontotemporal cortical functions. The high temporal resolution of NIRS may allow

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for not only the detection of regional functional abnormalities (i.e., hypofrontality) but also the capture of time-specific hemodynamic activation (Takizawa et al., 2014).

Recent neuroimaging studies using NIRS have provided compelling evidence about the dysfunction of the frontotemporal cortices in BD patients. Matsuo et al. reported that the increase in oxy-Hb induced by a verbal fluency task (VFT) in the frontal regions was significantly smaller in patients with euthymic BD than in controls (Matsuo et al., 2002, 2004, 2007). In the study by Kubota et al. (2008), patients with euthymic or depressed BD exhibited lower oxy-Hb levels during VFT compared with the controls. Kameyama et al. (2006) found that the increase in oxy-Hb in the frontal and left anterior temporal lobes during the early phase of a VFT (i.e., first 20 s) was smaller in the patients with euthymic or subclinically depressed BD than in controls.

However, these previous reports using NIRS, which included relatively small sample sizes and primarily focused on the dysfunction of prefrontal regions, could find no significant correlations between changes in oxy-Hb levels and depression severity (Kameyama et al., 2006; Kubota et al., 2008; Matsuo et al., 2007). We hypothesized that depressive and euthymic states in BD patients can be distinguished by the level of oxy-Hb activation in the frontotemporal regions. Furthermore, the dysfunction in those regions may be associated with symptom severity. This study aimed to clarify differences in the level of oxy-Hb activation between depressive and euthymic states using NIRS and regional brain dysfunction in relation to symptom severity in BD patients.

2. Patients and Methods

2.1. Patients

Fifty-five BD patients and 28 HCs matched by age, gender, handedness, and years of education were enrolled in this study. The diagnosis was made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (American Psychiatric Association, 1994) using the Mental Illness Neuropsychiatric Interview (MINI, Japanese version 5.0.0) (Otsubo et al., 2005). Among the BD patients, 28 had bipolar I disorder and 27 had bipolar II disorder. The HCs were screened using the MINI and were excluded if there was any history of psychiatric disorders or heritable neurological diseases in the immediate or second-degree family members. The exclusion criteria were the following: history of head trauma with loss of consciousness, current or previous neurological diseases, current or previous endocrine diseases, history of electroconvulsive therapy, and alcohol/substance abuse or addiction. After the study procedures had been fully explained, written informed consent was obtained from every participant. This study was approved by the Ethics Committee of Kinki University Faculty of Medicine.

On the day of scanning, mood symptoms were evaluated in the BD patients using the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Structured Interview Guide for the Hamilton Depression Rating Scale (HAM-D) (Williams, 1988). The patients were divided into a group with bipolar depression (BPD) and euthymic bipolar disorder (BPE). On the basis of self-reports and the MINI, the BPD patients had a 17-item HAM-D score of >7 and a YMRS score of <10, while the BPE patients had a 17-item HAM-D score of ≤ 7 and a YMRS score of <10 and had been euthymic for at least 2 months before scanning. There were no differences among groups in age, gender, handedness, and years of education [chi-squared test, analysis of variance (ANOVA), or Kruskal–Wallis nonparametric ANOVA]. There were no differences between the BPD and BPE groups with regard to the following: age of illness onset, duration or age of illness onset, daily doses of all antipsychotics, and daily doses of all antidepressants (chi-squared test or the Mann–Whitney U test). Thirty-eight patients were taking psychotropic medication at the time of participation in the study; 17 were taking lithium (BPD, $n=8$; BPE, $n=9$), 13 anticonvulsants (BPD, $n=5$; BPE, $n=8$), 16 antipsychotics (BPD, $n=7$; BPE, $n=9$), and 33 antidepressants (BPD, $n=21$; BPE, $n=12$). The daily doses of all antidepressants were converted to an equivalent dose of imipramine (Inagaki and Inada, 2006), and the daily doses of all antipsychotics were converted to those of chlorpromazine (Inagaki and Inada, 2006).

2.2. Assessment of symptoms

Depressive signs/symptoms (objective) and the level of social functioning were evaluated using HAM-D and Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994), respectively. Depressive symptoms (subjective) were assessed using the Beck Depression Inventory, second edition (BDI-II) (Beck et al., 1996), and handedness was assessed using the Edinburgh handedness inventory (Oldfield, 1971).

2.3. NIRS measurements

We used a 52-channel NIRS device (ETG-4000 Optical Topography System; Hitachi Medical Co., Tokyo, Japan) that measures relative changes in oxy-Hb and deoxy-Hb levels using two wavelengths (695 nm and 830 nm). Optical data were analyzed using the modified Beer–Lambert Law (Cope et al., 1988). This method allows for the calculation of signals reflecting changes in Hb levels, which were calculated in arbitrary units (mM–mm). The sampling rate was set at 100 ms.

The distance between the source and detector probe was set at 3.0 cm, and the area measured between the probes was defined as a channel. The NIRS probes were fixed using 3×11 thermoplastic shells, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10–20 system. The probes can measure Hb values bilaterally from the prefrontal and temporal surface regions at a depth of 2–3 cm from the scalp, i.e., near the surface of the cerebral cortex (Hock et al., 1997; Okada and Delpy, 2003; Toronov et al., 2001). The arrangement of the probes measured relative oxy-Hb and deoxy-Hb signal changes in the bilateral prefrontal cortical area (i.e., frontopolar region of the prefrontal, dorsolateral prefrontal, and ventrolateral prefrontal regions) and in the superior and middle temporal cortical surface regions, which was corroborated by a multi-individual study of anatomical craniocerebral correction via the international 10–20 system (Fig. 1; see Supplementary Table S1) (Lancaster et al., 2000; Singh et al., 2005; Tsuzuki et al., 2007).

Data were analyzed using the integral mode with the pre-task baseline defined as the mean oxy-Hb and deoxy-Hb levels measured 10 s immediately before the task period; the post-task baseline was defined as the mean oxy-Hb and deoxy-Hb levels during the last 5 s in the post-task period (Suto et al., 2004; Takizawa et al., 2008). Linear fitting was then applied to the data between these baseline levels. A 5 s moving average was calculated to remove any short-term motion artifacts. Moreover, Hb channels with a low signal-to-noise ratio (SNR) and significant motion artifacts were excluded; data displaying artifacts were excluded separately in each channel using an automatic artifact rejection procedure described previously by Takizawa et al. (2014). To acquire more reliable data, they developed a new algorithm to exclude channels contaminated with rhythmic signals that indicated noise artifacts (high-frequency noise, low-frequency noise, and no signal) and body movement artifacts.