



Research report

Association between longitudinal changes in prefrontal hemodynamic responses and social adaptation in patients with bipolar disorder and major depressive disorder



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ABSTRACT

Background: Patients with affective disorders exhibit changes in regional brain function and show abnormal social adaptation. However, to our knowledge, no near-infrared spectroscopy (NIRS) study has examined the relationship between these two phenomena longitudinally. This study examined the region-specific functional abnormality associated with bipolar disorder (BD) and major depressive disorder (MDD), and the association between particular longitudinal changes in regional activation and social adaptation.

Methods: We evaluated frontotemporal functioning during a verbal fluency test (VFT) for patients with BD ($N=18$), those with MDD ($N=10$), and healthy controls (HCs; $N=14$) using NIRS. NIRS measurements and the Social Adaptation Self-evaluation Scale (SASS) were administered twice with an interval of approximately 6 months.

Results: The BD and MDD groups showed lesser activation than the HCs in the bilateral ventro-lateral prefrontal cortex and the anterior part of the temporal cortex (VLPFC/aTC). Longitudinal changes in SASS scores were positively associated with the extent of change in left VLPFC/aTC activation in the BD group and with right VLPFC/aTC activation in the MDD group.

Limitations: Our small sample size limited statistical power, and the effect of medication and multiple comparisons cannot be excluded, although these effects were considered in the interpretation of the present results.

Conclusion: Longitudinal increases of VLPFC/aTC activation were associated with improvement in social adaptation in patients with BD and those with MDD. NIRS measurement could be a useful tool for objective evaluation of changes in social adaptation in BD and MDD.

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1. Introduction

Improving social functioning and quality of life are primary goals of clinical treatment. Cognitive function can be a major determinant of social functioning in patients with various psychiatric disorders (Pu et al., 2013). Cross-sectional studies have shown that patients with bipolar disorder (BD) typically exhibit deficits in executive function (Ancín et al., 2013; Martino et al., 2013). These deficits have been shown to improve with reductions

in symptom severity (Torres et al., 2014). Similarly, patients with major depressive disorder (MDD) also typically exhibit deficits in executive function (McIntyre et al., 2013; Schmid and Hammar, 2013). However, the results of longitudinal studies on cognitive functioning and MDD symptom severity have been inconsistent. Douglas and Porter (2009) suggested that verbal fluency is sensitive to the clinical state of patients with MDD. In contrast, Schmid and Hammar (2013) reported that patients with MDD exhibit prolonged poor performance in executive function, including semantic fluency, despite reductions in symptom severity.

Previous functional neuroimaging studies have suggested that in BD, the deficits in executive function are related to abnormal activation of the frontal and temporal regions (Altshuler and Townsend, 2012; Cerullo et al., 2014), and the same applies to

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MDD (Monks et al., 2004; Pu et al., 2008; Kikuchi et al., 2012). More specifically, the lateral prefrontal cortex, which contains the dorsolateral (DLPFC) and ventrolateral prefrontal cortices (VLPFC), is responsible for coordinating appropriate executive function (Robbins, 1998).

Multi-channel near-infrared spectroscopy (NIRS) can detect spatio-temporal functioning near the brain's surface non-invasively (Strangman et al., 2002a; Boas et al., 2004) without the habituation effects associated with repeated measurements (Kono et al., 2007; Schecklmann et al., 2008; Kakimoto et al., 2009). NIRS measures concentration of oxygenated ([oxyHb]) and deoxygenated hemoglobin ([deoxyHb]) in micro-blood vessels and estimates brain activation as an increase of [oxyHb] (Strangman et al., 2002a, 2002b).

NIRS has been used to assess brain function in many psychiatric disorders (Suto et al., 2004; Kameyama et al., 2006). Previous studies examining patients with BD have reported divergent results: hypo-frontality during the verbal fluency test (VFT) or working memory tasks (Matsuo et al., 2007; Schecklmann et al., 2011), and hyperfrontality during the VFT (Kubota et al., 2009). On the other hand, studies using NIRS to examine brain activity in patients with MDD have consistently reported hypoactivity during the VFT (Noda et al., 2012; Pu et al., 2012a, 2012b; Liu et al., 2014) and working memory tasks (Pu et al., 2012a, 2012b), compared to HCs. The divergence in results of studies of patients with BD might be caused by the mental state of the subject. Most NIRS studies have been conducted in patients with depression or euthymic individuals (Matsuo et al., 2007; Schecklmann et al., 2011; Kubota et al., 2009; Kameyama et al., 2006; Matsubara et al., 2013), or combined patients with different mental states (Kubota et al., 2009). Our group has focused on the hypomanic state of patients with BD, and has found significantly more left DLPFC activation in patients with hypomania than those in patients with depression. Follow-up measurements in patient with hypomanic BD revealed that prefrontal activation decreased with the disappearance of hypomanic symptoms (Nishimura et al., 2014). This showed the effect of mood states on prefrontal activation cross-sectionally and longitudinally in patients with BD.

Of note, in many NIRS studies, probes have been arranged to measure functional activities in the bilateral prefrontal cortex (i.e., dorsolateral [Brodmann areas (BAs) 9 and 46], ventrolateral [BAs 44, 45, and 47] and frontopolar [BA 10] regions) and the superior and middle temporal cortical surface regions. This method has been corroborated by a multi-individual study of anatomical craniocerebral correction via the international 10–20 system (Tsuzuki et al., 2007). However, retest reliability was unsatisfactory at the single-individual and single-channel levels, and studies of repeated NIRS measurements have only demonstrated acceptable reliability at the group and cluster levels (Schecklmann et al., 2008). Thus, in the present study, we performed an analysis of NIRS signals at the group and cluster levels. The Social Adaptation Self-evaluation Scale (SASS) is a self-rating questionnaire for assessing social functioning. The reliability and validity of the Japanese version of the SASS have been confirmed (Goto et al., 2005). Reduced activation in the prefrontal and temporal regions during cognitive tasks has been associated with the lower SASS scores in patients with late onset major depression (Pu et al., 2012a, 2012b). To our knowledge, no NIRS study has examined the association between this regional brain activation and social functioning assessed by SASS in patients with BD.

We hypothesized that the deficits in executive function that affect social functioning can be detected by reduced activation in the prefrontal and temporal regions during cognitive tasks using NIRS, and such abnormally low levels activation can change over time, reflecting improvement in social functioning, including social adaptation in patients with BD and MDD. In the present study, we analyzed regional activation associated with cognitive tasks in three frontal brain regions of interest (ROIs) defined by

Takizawa et al. (2014). Furthermore, we examined the correlation between longitudinal changes of activation in those regions that show abnormal activation compared to HCs and the longitudinal change in SASS scores for the patients with BD and MDD. The aim of the present study was to test our hypothesis and examine whether NIRS can be a biomarker of longitudinal changes in social functioning. This study is, to our knowledge, the first longitudinal NIRS study examining the association between regional brain activation and social functioning in patients with BD and MDD.

2. Methods

2.1. Participants

Participants included 18 patients with BD, 10 with MDD, and 14 healthy controls. Patients were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Ed.* (DSM-IV-TR) (APA, 2000). Patients with BD and MDD were recruited from inpatient and outpatient units of Tokyo Metropolitan Matsuzawa Hospital. HCs were volunteers. All three groups were matched for gender, age, years of education, and estimated intelligence (IQ) (Table 1). Exclusion criteria were as follows: left-handedness, history of major physical illness, neurological disorder, substance use, alcohol abuse, and any loss of consciousness due to head injury.

Participant IQ was estimated using the Japanese version of the National Adult Reading Test (JART) (Matsuoka et al., 2006). Social functioning of patients with BD and MDD was evaluated using the 21-item SASS (Bosc et al., 1997). Participants were asked to answer either item 1 or item 2, in accordance with their occupational status (item 1) or other types of primary activities such as housework (item 2), and then answer the other 20 items. Each item is scored from 0 to 3, corresponding to minimal and maximal social adjustment, with a total score range of 0–60. The reliability and validity of this Japanese version have been confirmed (Goto et al., 2005). Using principal component analysis, previous studies demonstrated that the 20 SASS items can be classified into three factors: interpersonal relations, interest and motivation, and self-perception (Goto et al., 2005). Of note, the interpersonal relations factor can be scored as the sum of the items: “family seeking behavior,” “family relationship quality,” “gregariousness,” “relationship seeking behavior,” “external relationship quality,” “external relationship appreciation,” “social attractiveness,” and “social compliance.” The interest and motivation factor can be scored as the sum of the items: “job interest or homework interest,” “work enjoyment,” “interest in hobbies,” “quality of spare time,” “community involvement,” “social inquisitiveness,” “intellectual interest,” and “control of surroundings.” In addition, to confirm the effect of overall symptom severity on brain function and social functioning, affective symptom severities were evaluated by well-trained psychiatrists (KT, TO, RI) using Japanese versions of the Hamilton Rating Scale for Depression (HAM-D) 17-item version (Hamilton, 1960) and Young Mania Rating Scale (YMRS; Young et al., 1978). The SASS, HAM-D, and YMRS were administered less than 1 week before each NIRS measurement. Patient medications are listed in Tables 1 and 2. Written informed consent was obtained from all participants prior to participation. This study was approved by the Research Ethics Committee of Tokyo Metropolitan Matsuzawa Hospital.

2.2. Activation task

We used the letter version of the VFT of one block design model to measure the regional activation of the frontal and temporal brain regions. The cognitive activation task included a 30 s

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