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Research report

Prefrontal cortex activation is associated with a discrepancy between self- and observer-rated depression severities of major depressive disorder: A multichannel near-infrared spectroscopy study

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ABSTRACT

Background: Studies on major depressive disorder (MDD) show that the degree of correlation between the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HAMD) varies widely. We aimed to determine whether this discrepancy reflects specific functional abnormalities in the frontotemporal cortex.

Methods: Mildly depressed or euthymic patients with MDD ($n=52$), including 21 patients with MDD with the discrepancy, i.e., those with low $HAMD_{17}$ scores (≤ 13) but high BDI-II scores (>28), and 31 patients without the discrepancy, i.e., those with low $HAMD_{17}$ scores and low BDI-II scores (≤ 28), participated in the study along with 48 control subjects. Regional changes of oxygenated hemoglobin (oxy-Hb) levels during a verbal fluency task (VFT) were monitored using a 52-channel near-infrared spectroscopy (NIRS) device.

Results: In the frontotemporal regions, mean oxy-Hb changes induced by the VFT were significantly smaller in patients with MDD than in control subjects. In 5 channels within frontal regions, the increase in mean oxy-Hb levels was significantly greater in MDD patients with the BDI–HAMD discrepancy than in those without the discrepancy. In 6 channels within the frontal region of the patients with MDD, significant positive correlations were observed between mean oxy-Hb changes and BDI total scores ($\rho=0.38$–0.59; $P<0.05$, false discovery rate corrected).

Limitations: Our findings required replication in severely depressed patients, particularly those with melancholia.

Conclusions: The distinct pattern of activation of the prefrontal cortex suggests that MDD with the BDI–HAMD discrepancy is pathophysiologically different from MDD without the discrepancy.

1. Introduction

The Beck Depression Inventory (BDI) (Beck et al., 1996) is the most widely used self-rated measure to evaluate the severity of depressive symptoms (Rush et al., 2008) and is a useful quantitative instrument. In addition, the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), which is an observer-rated measure, has been the gold standard for assessment of depression severity for more than 40 years (Bagby et al., 2004). Nonetheless, in terms of the relation between the BDI and HAMD scores, research on major depressive disorder (MDD) has demonstrated that the degree of correlation between those instruments varies rather widely, with correlation coefficients ranging from 0.20 to 0.89 (Bagby et al., 2004; Möller and von Zerssen, 1995; Richter et al., 1998).

One possible reason for this variation in the correlation is that these instruments measure different components of depression; BDI is focused mainly on depressive cognitions, and HAMD focuses on somatic/vegetative symptoms (Bagby et al., 2004; Uher et al., 2008). Another reason for the variation that can affect the correlation between self- and observer-rated depression severities are demographic factors such as age, the level of education (Corruble et al., 1999; Domken et al., 1994; Enns et al., 2000; Rane et al., 2010), clinical conditions such as anxiety (Corruble et al., 1999; Gartlehner et al., 2008), or a number of personality traits, such as high neuroticism (Duberstein and Heisel, 2007; Enns

Abbreviations: ANOVA, analysis of variance; BDI-II, Beck Depression Inventory, 2nd edition; DSM-IV, diagnostic and statistical manual of mental disorders, 4th edition; GAF, global assessment of functioning; $HAMD_{17}$, 17-item Hamilton Depression Rating Scale; MDD, major depressive disorder; MINI, mini-international neuropsychiatric interview; SIGH-D, structured interview guide for HAMD; SNR, signal-to-noise ratio; VFT, verbal fluency task

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et al., 2000), low extraversion (Enns et al., 2000; Schneibel et al., 2012), low agreeableness (Enns et al., 2000), low self-esteem (Domken et al., 1994), and comorbid personality disorder (Rane et al., 2010). Furthermore, several studies have demonstrated that the discrepancy between self- and observer-rated depression severities is linked to nonendogenous or nonmelancholic depression (Domken et al., 1994; Rush et al., 1987).

Recent studies showed that patients who overrate their depression severity in comparison with the clinicians' ratings exhibit slower improvement (Dunlop et al., 2011; Rane et al., 2010). In addition, we previously reported that the discrepancy between self- and observer-rated depression severities is associated with vulnerability to suicide among patients with MDD (Tsujii et al., 2014a). In this field, studies that have explored associations between the rating discrepancy and demographic or personality characteristics suggest that the discrepancy is trait-like rather than state dependent (Dunlop et al., 2011; Tsujii et al., 2014a). On the other hand, whether the rating discrepancy reflects specific neurobiological impairment in patients with MDD remains unclear.

Multichannel near-infrared spectroscopy (NIRS) is a noninvasive optical technique that allows monitoring of 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 high temporal resolution (0.1 s) for measuring time-specific characteristics of dynamic frontotemporal cortical functions. Recently, several studies involving multichannel NIRS demonstrated that the increase in oxy-Hb within the frontotemporal regions during a verbal fluency task (VFT) is significantly smaller in patients with MDD than in control subjects (Kameyama et al., 2006; Noda et al., 2012; Suto et al., 2004; Tsujii et al., 2014b).

Nevertheless, to the best of our knowledge, there are no neuroimaging studies that assessed whether the discrepancy between self- and observer-rated depression severities reflects specific functional abnormalities in the frontotemporal cortex. In the present study, we hypothesized that depressed patients who overrate their depression severity in comparison with the clinicians' ratings are pathophysiologically and biologically distinct from those who rate their depression severity in concordance with the clinicians' ratings, even if the patients have an objective rating of *mildly depressed* or *euthymic*. Thus, we used multichannel NIRS to test whether oxy-Hb changes induced by the VFT can objectively distinguish between patients with MDD with and without the rating discrepancy.

2. Methods

2.1. Subjects

Fifty-two mildly depressed or euthymic patients with MDD (20 females) and 48 control subjects (27 females) were enrolled in the study after they provided written informed consent; the study protocol was approved by the Ethics Committee of Kinki University Faculty of Medicine. The diagnosis was made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) using the Mini-International Neuropsychiatric Interview (MINI; Japanese version 5.0.0) (Otsubo et al., 2005). Eligible subjects had 17-item HAMD ($HAMD_{17}$) scores of ≤ 13 at enrollment. The patients were subdivided into the following two groups: (1) patients with MDD with the discrepancy ($n=21$), i.e., those with low $HAMD_{17}$ scores (≤ 13) but high BDI-II scores (>28) and (2) patients with MDD without the discrepancy ($n=31$), i.e., those with low $HAMD_{17}$ scores and low BDI-II scores (≤ 28). Daily doses of all antidepressants were converted to an equivalent dose of imipramine (Inagaki and Inada, 2006). Control subjects were screened using the MINI and were excluded if there was any history of psychiatric disorders or heritable neurological diseases among the immediate or second-degree family members.

The exclusion criteria for all participants were the following: a serious suicide risk, a current diagnosis of a DSM-IV bipolar disorder (any history of a manic, hypomanic, or mixed episode) or an anxiety disorder, a history of head injury or a neurological disorder, a history of a DSM-IV substance abuse disorder, significant drug and/or alcohol use, current treatment with electroconvulsive therapy (or during the 6 months preceding the study), or current or past endocrinological disease.

2.2. Clinical assessment

Objectively, the depressive symptoms were evaluated using the structured interview guide for HAMD (SIGH-D) (Williams, 1988); patients with scores ranging from 0 to 7 were considered not depressed (i.e., the diagnosis was a euthymic phase of MDD), with scores from 8 to 13 were considered mildly depressed (i.e., the diagnosis was mild MDD), those with scores from 14 to 18 were considered moderately depressed, those with scores from 19 to 22 were considered severely depressed, and those with scores ≥ 23 were considered very severely depressed (Rush et al., 2008). Subjectively, the depressive symptoms were assessed using the BDI, 2nd edition (BDI-II) (Beck et al., 1996); patients with scores ranging from 0 to 13 were considered not depressed, those with scores from 14 to 19 were considered mildly depressed, those with scores from 20 to 28 were considered moderately depressed, and those with scores from 29 to 63 were considered severely depressed (Rush et al., 2008).

In addition, the level of social functioning was evaluated by means of the Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994).

2.3. NIRS

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 concentrations using two wavelengths (695 nm and 830 nm). Optical data were analyzed using the modified Beer–Lambert Law (Cope et al., 1988). This method enables the calculation of signals reflecting changes in Hb levels, which were calculated in arbitrary units (mM–mm). The sampling rate was set to 100 ms.

The distance between the source and detector probe was set to 3.0 cm, and the measurement area 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 in 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 changes in oxy-Hb and deoxy-Hb signals in the bilateral prefrontal cortex area (i.e., the frontopolar region of the prefrontal, dorsolateral prefrontal, and ventrolateral prefrontal regions) and in the superior and middle temporal cortical surface regions; this experimental setup was corroborated by means of a multi-individual study of the anatomical craniocerebral correction using the international 10–20 system (Fig. 1; see Supplementary Table 1) (Lancaster et al., 2000; Singh et al., 2005; Tsuzuki et al., 2007).

The data were analyzed using the integral mode; the pre-task baseline period was defined as the mean oxy-Hb and deoxy-Hb