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Research paper

Severity-dependent and -independent brain regions of major depressive disorder: A long-term longitudinal near-infrared spectroscopy study

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ARTICLE INFO

Abbreviations: MDD, major depressive disorder
NIRS, near-infrared spectroscopy
DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
HAMD, Hamilton Rating Scale for Depression
IFG, inferior frontal gyrus
ICCs, intra-class correlation coefficients
MRI, magnetic resonance imaging
PFC, prefrontal cortex
VFT, verbal fluency test
SCID, Structured Clinical Interview for DSM-IV
IQ, Intelligence Quotient
JART, Japanese Adult Reading Test
GAF, Global Assessment of Functioning
FDR, false-discovery rate
CH, channel
MFG, middle frontal gyrus
PET, positron emission tomography
CBF, cerebral blood flow

Keywords:
Near-infrared spectroscopy (NIRS)
Major depressive disorder (MDD)
Mood disorder
Long-term longitudinal study
Biological marker

ABSTRACT

Background: Long-term longitudinal studies are necessary to establish neuroimaging indicators which contribute to the detection of severity changes over time in patients with major depressive disorder (MDD).
Methods: One hundred sixty-five patients with MDD underwent clinical assessments and near-infrared spectroscopy (NIRS) examination at the initial evaluation (T0). After 1.5 years, 45 patients who visited for the follow-up evaluation (T1.5) were included in the analysis. The authors conducted analyses using the 17-item Hamilton Rating Scale for Depression (HAMD) scores and mean oxy-hemoglobin concentration ([oxy − Hb]) changes during a cognitive task in NIRS at T0 (T0_HAMD, T0_[oxy − Hb]) and at T1.5 (T1.5_HAMD, T1.5_[oxy − Hb]), and their intra-individual longitudinal changes (ΔHAMD = T1.5_HAMD − T0_HAMD, Δ[oxy − Hb] = T1.5_[oxy − Hb] − T0_[oxy − Hb]).
Results: For severity-dependent regions, the Δ[oxy − Hb] in the right inferior frontal gyrus (IFG) was negatively correlated with the ΔHAMD. For severity-independent regions, the intra-class correlation coefficients between T0_ and T1.5_[oxy − Hb] were moderate in the bilateral middle frontal gyri (MFG).
Limitations: The percentage of patients included in the follow-up examination was relatively small.
Conclusions: Brain activation in the right IFG and the bilateral MFG as measured by NIRS may differentially indicate clinical severity and trait-related abnormalities in MDD.

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1. Introduction

To establish neuroimaging biomarkers for major depressive disorder (MDD), investigations into longitudinal relationships with symptomatology are important. Previous studies using structural or functional MRI (fMRI) demonstrated the cross-sectional association between depression severity and neuroimaging indicators (Hall et al., 2014; Zhang et al., 2016). However, no studies on neuroimaging in MDD have followed clinical outcomes and brain functions over a longer period of time (1–2 years).

Near-infrared spectroscopy (NIRS) is a non-invasive neuroimaging modality that can easily be performed in a natural environment and is applicable to patients with psychiatric disorders. The blood oxygenation signal patterns as measured by NIRS during cognitive tasks have been reported to be different among major psychiatric disorders, which enables individual-level discrimination of MDD from bipolar disorder and schizophrenia (Takizawa et al., 2013). As a result, NIRS has officially been approved as an auxiliary test for the differential diagnosis of psychiatric disorders exhibiting depressive symptoms by the Ministry of Health, Labor and Welfare of Japan (Fukuda, 2015).

Previous NIRS literature has repeatedly shown that brain activation measured as oxygenated hemoglobin (oxy–Hb) signals in the prefrontal cortex (PFC) during the verbal fluency test (VFT) in patients with MDD was smaller than that in healthy subjects (Ehlis et al., 2014). However, it remains unclear whether the decreased brain activation reflects state- or trait-related characteristics of MDD. A cross-sectional study found that depression severity was negatively correlated with the increase of oxy–Hb signals during VFT in the right dorsolateral PFC (Noda et al., 2012). In contrast, Tomioka et al. followed up on patients with MDD for 12 weeks before and after the initiation of pharmacotherapy and found that the changes in depression severity were not correlated with those of the NIRS signal (Tomioka et al., 2015). Again, however, no NIRS study in MDD to date has followed brain functions over a longer period of time ($>$ 1 year).

Accordingly, we conducted a longitudinal NIRS study in which we recorded clinical variables and brain functions both at baseline and after 1.5 years. Our purpose was to segregate brain regions into (i) severity-dependent regions, where the NIRS signals reflect the change in the severity of depressive symptoms in a state-related manner, and (ii) severity-independent regions, where the NIRS signals are stable over time.

2. Methods

2.1. Participants

Participants were recruited in outpatient and inpatient units of the University of Tokyo Hospital from September 2009 to November 2012 for the initial evaluation (time 0: T0). Most participants were referred to the hospital from other clinics for a 4-day psychiatric assessment program consisting of various psychological and neuroimaging tests including NIRS. After the program was completed, they returned to their original clinic for further follow-ups. We included the patients who met the diagnostic criteria for MDD using the Structured Clinical Interview for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) Axis I Disorders (SCID-I) (American Psychiatric Association., 1994; First, 1997). We excluded individuals with neurological diseases including dementia, traumatic brain injury with loss of consciousness for more than 5 min, low premorbid Intelligence Quotient (IQ) (less than 70) as estimated using the Japanese Adult Reading Test (JART) (Matsuoka and Kim, 2006; Matsuoka et al., 2006), and a history of substance abuse or dependence. This study was approved by the ethics committee of the University of Tokyo Hospital (certification no. 3202). All participants gave written informed consent in accordance with the Declaration of Helsinki after a complete explanation of the study.

One hundred sixty-five patients underwent clinical assessments and NIRS examinations at T0. After about 1.5 years (time 1.5: T1.5), we contacted these patients by mail, telephone or e-mail and asked if they could participate in the second evaluation. As a result, 54 patients (32.7%) visited our hospital again for the second NIRS measurement and a face-to-face interview including the SCID-I. Among these, 45 patients (27.3%) met the above criteria both at T0 and T1.5 and were thus included in the analysis (Figure S1 in Supplementary materials). The proportion of females was significantly larger in the 45 patients analyzed in this study than in the remaining 120 subjects that were not included. There was no significant difference in other indicators (Table S1 in Supplementary materials).

2.2. Clinical assessment

At T0 and T1.5, we indexed depression severity by using the total score on the 17-item Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960). Additionally, the Global Assessment of Functioning (GAF) (American Psychiatric Association. Task Force on DSM-IV., 2000) was also evaluated. We recorded medication information for each patient by calculating doses of antidepressants, anxiolytics, neuroleptics, and anti-parkinsonian drugs (imipramine, diazepam, chlorpromazine, and biperiden-equivalent doses, respectively) and the use of mood stabilizers.

2.3. Cognitive activation task

We used the block-designed VFT as a cognitive task (Takizawa et al., 2013). The task consisted of three periods: the 30-s pre-task, the 60-s task, and the 55-s post-task period. During the task period, the participant was instructed to say as many words as possible starting with the indicated syllables. The total number of appropriate words was defined as their task performance.

2.4. Changes in demographic characteristics and clinical indices at two evaluation points

Changes in demographic characteristics and clinical indices between T0 and T1.5 are shown in Table 1. HAMD decreased significantly from T0 to T1.5 (paired-t test, $p < 0.001$). GAF also indicated improvement ($p < 0.001$). Furthermore, we indicated the number of patients in depressive state (HAMD $>$ 7; DEP) or remission state (HAMD $\leq$ 7; REM) (Frank et al., 1991) in Table 1. At T1.5 compared to T0, the proportion of patients in REM was significantly greater (McNemar test, $p < 0.05$). Although the equivalent doses (imipramine, diazepam, chlorpromazine, and biperiden) and the use of mood stabilizers were not different significantly between T0 and T1.5, dosages of antidepressants and psychotropics were changed in 35 and 43 patients, respectively. There were no significant differences in other indices.

2.5. NIRS measurements and indicators of brain activation

We used a 52-channel NIRS machine (ETG-4000, Hitachi Medical Co., Japan) to measure relative changes in oxy-hemoglobin concentration ([oxy − Hb]) and deoxy-hemoglobin concentration ([deoxy − Hb]) at the surface of the bilateral prefrontal and temporal regions. The time resolution of NIRS was set at 0.1-s. A linear fitting method was performed using the pre-task and post-task baselines to exclude task-unrelated changes. Then, a moving average with a window of 5-s was applied to the signals to remove higher frequency components. Furthermore, an automatic rejection of data with artifacts was performed separately for each channel (Koike et al., 2011). In the same way as in previous studies (Takizawa et al., 2013, 2008), we calculated mean [oxy − Hb] changes during the 60-s task period for each channel, which was defined as the task related brain activation. (See details about NIRS data processing in Methods S2 in Supplementary materials).