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Research paper

Correlation between frontal lobe oxy-hemoglobin and severity of depression assessed using near-infrared spectroscopy

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ABSTRACT

Introduction: The search for objective biomarkers of psychiatric disorders has a long history. Despite this, no universally accepted instruments or methods to detect biomarkers have been developed. One potential exception is near-infrared spectroscopy, although interpreting the measures of blood flow recorded with this technique remains controversial. In this study, we aimed to investigate the relationship between recorded blood flow and depression severity assessed using the Hamilton depression scale in patients with various psychiatric disorders.

Methods: Enrolled patients (n=43) had DSM-IV diagnoses of major depressive disorder (n=25), bipolar disorder I (n=5), schizophrenia (n=3), dysthymic disorder (n=3), psychotic disorder (n=3), panic disorder (n=2), and Obsessive Compulsive Disorder (n=2). The verbal fluency task was administered during blood flow recording from the frontal and temporal lobes.

Results: We found that severity of depression was negatively correlated with the integral value of blood flow in the frontal lobe, irrespective of psychiatric diagnosis ($F=5.94$, $p=0.02$).

Discussion: Our results support blood flow in the frontal lobe as a potential biomarker of depression severity across various psychiatric disorders.

Limitation: Limited sample size, no replication in the second set.

1. Introduction

In 2009, near-infrared spectroscopy (NIRS) was approved by the Ministry of Health, Labour and Welfare of Japan as an Advanced Medical Technology, for use in differential psychiatric diagnosis. This represented a radical change within clinical psychiatry, in which diagnosis had previously been made using only the subjective assessment of experienced clinicians. The approval recognized a role for NIRS in distinguishing amongst people experiencing depressive symptoms those with a diagnosis of schizophrenia, bipolar disorder, depression or no psychiatric diagnosis. This tool has come to the attention of patients, as well as being reported in the popular scientific press (Cyranoski, 2011). Since then, NIRS has been approved for use in clinical practice in over 25 institutions by the Ministry of Health, Labor and Welfare in Japan. Furthermore, in 2013, the technology was approved for use in the determination of healthcare insurance policies. Although many patients appear to have benefited from NIRS assessment, criticisms remain. One major concern about using NIRS as a clinical biomarker was the relatively small number of patients evaluated before the approval. Moreover, interpreting the signals derived using NIRS is controversial, as it has been reported that skin blood flow contributes to NIRS oxyhemoglobin (oxy-Hb) concentrations during tasks (Takahashi et al., 2011).

Other factors may further influence observations in studies using NIRS, including severity of depression. Noda et al. (2012) reported a highly significant negative correlation ($p<0.001$) between oxy-Hb and severity of depression symptoms, scaled according to the HAMD-21 (Hamilton depression scale) (Williams, 1988; Williams et al., 2008). However, this finding was observed

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only for channel 25, located on the dorsolateral prefrontal cortex (Bench et al., 1995; Kanazawa et al., 2008), during the verbal fluency task (VFT) (Pendleton et al., 1982).

We aimed to replicate and extend these findings by applying NIRS in patients with diagnoses other than just major depressive disorder (MDD). These patients were tested using the same task but at a different institution (the National Center of Neurology and Psychiatry in Japan) to the original report.

2. Materials and methods

2.1. Participants

We enrolled 43 patients with a range of psychiatric diagnoses (Table 1).

The majority of participants (n=25) had a diagnosis of MDD (The Diagnostic and Statistical Manual of Mental Disorders, 4th version DSM-IV TR code: 296.20-36). Further participants with other diagnoses were included in the analysis, including bipolar disorder (296.40-80), dysthymic disorder (300.4), schizophrenia (295), psychotic disorder (298.8–9), panic disorder (300.01, 21), and OCD (Obsessive Compulsive Disorder, 300.3).

All diagnoses were assessed using the SCID-I (Structured Clinical Interview for DSM-IV) (First et al., 2012) administered by an experienced clinician. Clinical diagnosis was based on the SCID-I assessment of the current complaint, as well as the recent clinical course. Clinical psychologists took a current and recent psychiatric history from patients. A team comprising independent clinical psychologists and psychiatrists then determined the clinical diagnosis.

Table 2 shows demographic data for all included patients with a diagnosis of MDD. All participants were right-handed, and their native language was Japanese. They underwent MRI scans (3 T) and endocrine testing to detect any clinical abnormalities. All patients were recruited from the outpatient service at the Neuropsychiatry Department of Osaka Medical College.

This study was carried out in accordance with the latest version or the Declaration of Helsinki, and was approved by the ethical committee of Osaka Medical College. Written informed consent was obtained for all participants following an explanation of the NIRS procedure.

2.2. Clinical assessments

Depression severity was assessed using the HAMD scale administered by a trained psychiatrist blinded to the NIRS data. HAMD-17 and 21 were originally designed to assess depressive symptoms within major depression. However, there is a need for the scale to be adapted for use in other psychiatric disorders. We assessed the intelligence quotient (IQ) of participants using the Wechsler Adult Intelligence Scale-III, and excluded participants with a total score below 80.

Table 1
Psychiatric diagnoses of study participants.

Psychiatric diagnosis	n
Major depressive disorder	25
Bipolar disorder I	5
Dysthymic disorder	3
Schizophrenia	3
Psychotic disorder	3
Panic disorder	2
OCD	2
Total	**43**

Table 2
Demographic data for patients with MDD (n=25).

Variable	Mean (SD)
Age	44.1 (9.3)
WAIS-IV	94.2 (20.5)
SDS	54.0 (8.9)
WHO-QOL	2.5 (0.6)
STAI/SA score	56.6 (12.0)
STAI/TA score	53.5 (10.4)
SASS	29.2 (7.3)
HAMD-17	13.1 (6.5)
HAMD-21	14.4 (7.2)
BMI	25.3 (6.0)

WAIS-IV: Wechsler Adult Intelligence Scale IV; SDS: Self-rating Depression Scale; WHO-QOL: World Health Organization Quality of Life; STAI-SA: State-Trait Anxiety Inventory, State Anxiety; STAO-TA: State-Trait Anxiety Inventory, Trait Anxiety; SASS: Social Adaptation Self-Evaluation Scale; HAMD: Hamilton Rating Scale for Depression; BMI: Body Mass Index.

2.3. NIRS device

Twenty-two channel NIRS (ETG-4000; Hitachi Medical, Tokyo, Japan) was used to derive values for oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb). We placed 18 channels over the frontal cortex and four channels over the temporal cortex. The NIRS device settings were similar to those in previous studies (Matsuo et al., 2002; Takizawa et al., 2008; Noda et al., 2012), although we used fewer probes (22 compared with 52 channels in previous reports).

Briefly, participants sat comfortably in a quiet, day-lit room. The task procedures were explained by a clinical laboratory technician, who subsequently monitored head movement during the procedure. To avoid the effect of motion artifacts, data with clear evidence of head movement were omitted from further analysis. Moreover, we employed an automatic algorithm to exclude channels contaminated with rhythmic signals, which indicates noise and body-movement artifacts. This algorithm recognizes that frequencies with no signal represent no change in oxy-Hb or deoxy-Hb concentrations at any time point. Therefore, channels in which the standard deviation of all measurement points was zero were deemed to be artifact channels. Further details of this algorithm are reported elsewhere (Takizawa et al., 2014).

2.4. Activation task

During the procedure, participants were instructed to look at a monitor. A demonstration of the VFT procedure accompanied by instructions from external speakers surrounding the monitor was provided after an explanation by a clinical laboratory technician. The task is the same as that administered in previous studies (Pu et al., 2008; Takizawa et al., 2008).

The full task procedure included a 30 s pre-task baseline, a 60 s VFT, and a 70 s post-task baseline. For the pre- and post-task baseline periods, participants were instructed to repeat aloud the five Japanese vowels ('a', 'i', 'u', 'e', 'o'). The subtraction method (task minus pre- and post-task baseline) minimized vocalization effects during the VFT. During the task, participants were instructed to generate as many Japanese words beginning with a designated syllable as possible. The three sets of initial syllables (1. /to/,/se/,/o/; 2. /a/,/ki/,/ha/; 3. /na/,/i/,/ta/) were presented in counterbalanced order among the subjects, and each syllable changed every 20 s during the 60 s task (Fig. 1).