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High-dose antidepressants affect near-infrared spectroscopy signals: A retrospective study

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ABSTRACT

Background: Recent studies have highlighted the clinical usefulness of near-infrared spectroscopy (NIRS) in psychiatry. However, the potential effects of psychotropics on NIRS signals remain unknown.
Methods: We conducted a systematic chart review of 40 depressed patients who underwent NIRS scans during a verbal fluency task to clarify the relationships between psychotropic dosage and NIRS signals. The dosage of psychotropic medications was calculated using defined daily dose (DDD). We investigated the associations between the DDD of psychotropic medications and oxygenated hemoglobin (oxy-Hb) in single channel levels.
Limitations: Retrospective study design and small sample size are the main limitations.
Results: Multiple regression analysis revealed that one channel in the right temporoparietal region had a significant association with antidepressant DDD controlling for age, sex, depression severity, and the DDD of antipsychotics and benzodiazepines. Moreover, high doses of antidepressants had significant effects on NIRS signals compared with low doses, in group comparisons.
Conclusions: The dose-dependent impact of antidepressants on NIRS signals should be taken into account when interpreting NIRS data.

1. Introduction

The diagnosis of psychiatric disorders, including major depressive disorder (MDD) and bipolar disorder, depends solely on clinical interviews according to the current diagnostic system such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2000) and International Classification of Diseases (ICD) (World Health Organization, 2016). An absence of objective diagnostic biomarkers for these disorders could lead to misdiagnosis. For example, only 20% of patients with bipolar disorder receive a correct diagnosis within the first year after the onset (Hirschfeld et al., 2003), and the latency from diagnosis to appropriate treatment averages from 5 to 10 years (Baldessarini et al., 2007). In addition, depressive symptoms that fulfill the operational diagnostic criteria for a major depressive episode can occur at any stage of schizophrenia (Heiden et al., 2005). Misdiagnosis of bipolar disorder or schizophrenia as MDD results in inappropriate treatment and hence a poor prognosis, as well as huge health-care costs (Hirschfeld et al., 2003).

Recent neuroimaging technologies have contributed to clarifying the pathophysiology of depression and exploring biomarkers for improving the accuracy of diagnosis and predicting treatment response (Mayberg, 2014). Neuroimaging studies using magnetic resonance imaging (MRI) and positron emission tomography (PET) have revealed structural and functional abnormalities in widely distributed brain regions in depressed patients (Mayberg, 2009; Price and Drevets, 2010). Moreover, recent MRI studies have also revealed structural and functional differences in widely distributed brain regions between MDD and bipolar disorder (De Almeida and Phillips, 2013; Wise et al., 2016), and between bipolar disorder and schizophrenia (Anticevic et al., 2015). While these neuroimaging techniques are powerful for examining the pathophysiology of psychiatric disorders, they are time-consuming and expensive, which may limit their clinical application.

Near-infrared spectroscopy (NIRS) is a comparably new neuroimaging technique that has received increasing attention in the field of neuroscience and psychiatry. NIRS detects changes in regional cerebral

Abbreviations: Anatomical Therapeutic Chemical, (ATC); defined daily dose, (DDD); Diagnostic and Statistical Manual of Mental Disorders, (DSM); Hamilton Rating Scale for Depression-17 item, (HRSD-17); International Classification of Diseases, (ICD); magnetic resonance imaging, (MRI); major depressive disorder, (MDD); Montgomery Asberg Depression Rating Scale, (MADRS); near-infrared spectroscopy, (NIRS); oxy-hemoglobin, (oxy-Hb); positron emission tomography, (PET); regional cerebral blood volume, (rCBV); verbal fluency task, (VFT); World Health Organization, (WHO).

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blood volume (rCBV) by measuring high temporal resolution (0.1 s) changes in the concentration of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb), using near-infrared light (Ohmae et al., 2006; Villringer and Chance, 1997). NIRS has several advantages over PET and MRI in that it is noninvasive, safe, and low in cost, and does not need to have subjects keep still in the scanner. This has made it feasible to perform NIRS in real-world clinical settings. So far, numerous studies, using multi-channel NIRS, have provided evidence that NIRS signals could work as promising diagnostic biomarkers for MDD, bipolar disorder, and schizophrenia. In fact, oxy-Hb activation during a verbal fluency task (VFT) (a straight-forward task for assessment of executive function) has consistently been reported to be decreased in MDD patients, compared with healthy controls (Matsuo et al., 2002, 2005; Suto et al., 2004; Takizawa et al., 2014; Tomioka et al., 2015; Usami et al., 2014; Zhang et al., 2015). In addition, a recent multi-site study found that frontal hemodynamic patterns detected with NIRS during a short VFT differentiated MDD patients from those with bipolar disorder or schizophrenia with >70% accuracy (Takizawa et al., 2014). Based on these findings, NIRS scans during VFT have been indicated to assist the determination of clinical diagnoses of MDD, bipolar disorder, and schizophrenia by the Japanese Ministry of Health, Labour and Welfare since 2014. The cost of this is now covered by the National Health Insurance scheme of Japan.

Despite the clinical usefulness of NIRS, only a few studies have investigated effects of psychotropic drugs on NIRS signals. Previous studies including healthy volunteers have shown the significant effects of antidepressants on NIRS signals (Tsujii et al., 2007, 2009; Kohmura et al., 2013), although studies including patients with psychiatric disorders have shown inconsistent results (Noda et al., 2012; Takizawa et al., 2014). Moreover, investigations of the effects of other psychotropic drugs, such as benzodiazepines and antipsychotics, on NIRS signals are rare. Given that a significant proportion of depressed patients are receiving psychotropic medications, it is critically important to examine those effects for the appropriate interpretation of NIRS signals. Therefore, in the present study, we performed a retrospective chart review of patients with depressive symptoms who underwent a 52-channel NIRS scan during a VFT task.

2. Material and methods

2.1. Patients

A systematic chart review was performed for in- and outpatients who underwent a 52-channel NIRS scan during a VFT task at Keio University Hospital, Tokyo, Japan, between 2012 and 2015. The study protocol was approved by the Ethics Committee of Keio University School of Medicine. Data from patients fulfilling the following criteria were included: (i) clinical diagnosis of MDD according to DSM-IV-Text-Revision (TR) codes: 296.2, 296.3, bipolar disorder according to DSM-IV-TR codes: 296.5, 296.89, or schizophrenia according to DSM-IV-TR codes: 295.9 (American Psychiatric Association, 2000); (ii) ages of 20 to 65; (iii) a Hamilton Rating Scale for Depression-17 item (HRSD-17) total score of >7 (Hamilton, 1960), or a Montgomery Asberg Depression Rating Scale (MADRS) total score of >10 (Montgomery and Asberg, 1979); and (iv) presence of a positive average wave in the NIRS scan (a positive wave indicates successful activation of the cortex by the task). Patients meeting the following criteria were excluded: (i) clinical diagnosis of other major psychiatric disorders (e.g. delusional disorder, alcohol dependence); (ii) past history of head trauma; and (iii) symptom remission. These assessments of symptomatology were routinely conducted by psychiatrists in charge at Keio University Hospital. The following information was also collected: age, sex, diagnosis, comorbidity, current medications, duration of illness, HRSD-17 total score, and MADRS total score. MADRS total scores were converted to HRSD-17 total scores based on Carmody's conversion data (e.g. a MADRS total score of 27 = a HRSD-17 total score of 20) (Carmody et al., 2006) to use these variables to indicate the severity of depression in the statistical analyses.

2.2. Defined daily dose calculation

The Anatomical Therapeutic Chemical (ATC) classification system and defined daily dose (DDD) as a measuring unit are recommended by the World Health Organization (WHO) for drug utilization studies (http://www.whocc.no/atc_ddd_index/). DDD is defined as an assumed average maintenance dose per day for a drug used for its main indication in adults. Based on the ATC classification system with drug nomenclature defined by WHO, each drug has an ATC code and its DDD. Psychotropic medications were classified into three groups according to ATC classification: antipsychotics (ATC code: N05A), antidepressants (ATC code: N06A), and benzodiazepine derivatives (ATC code: N003AE, N05B, N05C). When patients received two or more drugs in each category, a summed DDD was calculated. As blonanserin, perospirone, and etizolam were not included in the ATC system, DDDs of these drugs were defined as mean values of the minimum and maximum doses specified on their package inserts.

2.3. Activation task (verbal fluency task)

The task procedure in this study was similar to that used by Takizawa et al. (2014). Patients sat in a comfortable chair and were instructed to relax and avoid any major body movements to prevent artifacts. The letter VFT was used as an activation task. The task procedure consisted of a 30-s pre-task baseline, 60-s VFT, and 70-s post-task baseline. For the pre- and post-task baseline periods, patients were instructed to consecutively repeat aloud the five Japanese vowels ("a", "i", "u", "e", and "o"). During the activation period, patients were instructed to say as many words with specific initial syllables as they could. The three sets of initial syllables (A: /to/, /se/, /o/; B: /a/, /ki/, /ha/; C: /na/, /i/, /ta/) were presented in a counterbalanced order among the subjects, with each syllable changed every 20 s during the 60-s task. The subtraction method (task minus pre- and post-task baseline) minimized vocalization effects during the VFT. The number of words generated during the task was used as a measure of task performance.

2.4. NIRS measurement

A 52-channel NIRS system (ETG-4000; Hitachi Medical Co., Tokyo, Japan) was used (Fig. 1). The NIRS system measures relative changes in [oxy-Hb] and [deoxy-Hb], using two wavelengths (695 nm and 830 nm) of infrared light, based on the modified Beer-Lambert law (Obrig and Villringer, 2003). This system measures relative changes in absorbed near-infrared light with a temporal resolution of 0.1 s. The distance between a pair of source-detector probes was set at 3.0 cm, and the area measured between a pair of source-detector probes was defined as a 'channel'. The NIRS device is assumed to measure 'channels' at 2–3 cm depth from the scalp, i.e., at the surface of the cerebral cortex.

In total, 33 probes consisting of 16 light emitters and 17 detectors with interoptrodes were used. Thus, the probe set consisted of 52 channels and covered the bilateral prefrontal and temporal cortical surface regions. Correspondence between probe position and measurement area on the cerebral cortex was confirmed from a previous multi-subject study of anatomical craniocerebral correction using the International 10–20 system (Okamoto et al., 2004; Tsuzuki et al., 2007).

The obtained data were analyzed using the "integral mode": the pre-task baseline was determined as the mean over a 10-s period immediately prior to the task period, while the post-task baseline was determined as the mean over the last 5 s of the post-task period. First, we calculated the linear function (base curve) between the pre- and post-task baseline average. This inclination of linear function was thought to originate from NIRS signal fluctuations. We then subtracted the