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

Akihiro Takamiya[a], Jinichi Hirano[a,*], Yuki Ebuchi[a], Satoyuki Ogino[a], Kenichi Shimegi[a], Hiroyuki Emura[a], Kyoko Yonemori[a], Akiko Shimazawa[a], Gentaro Miura[a], Ayako Hyodo[a], Sari Hyodo[a], Tunetaka Nagai[a], Madoka Funaki[a], Masako Sugihara[a], Mitsuhiro Kita[b], Bun Yamagata[a], Masaru Mimura[a]

[a] Department of Neuropsychiatry, Keio University School of Medicine, 35, Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
[b] Brain Energy, 1-28-5, Komaba, Meguro-ku, Tokyo 153-0041, Japan

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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).

* Corresponding author.
E-mail address: hjinichi@z7.keio.jp (J. Hirano).

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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

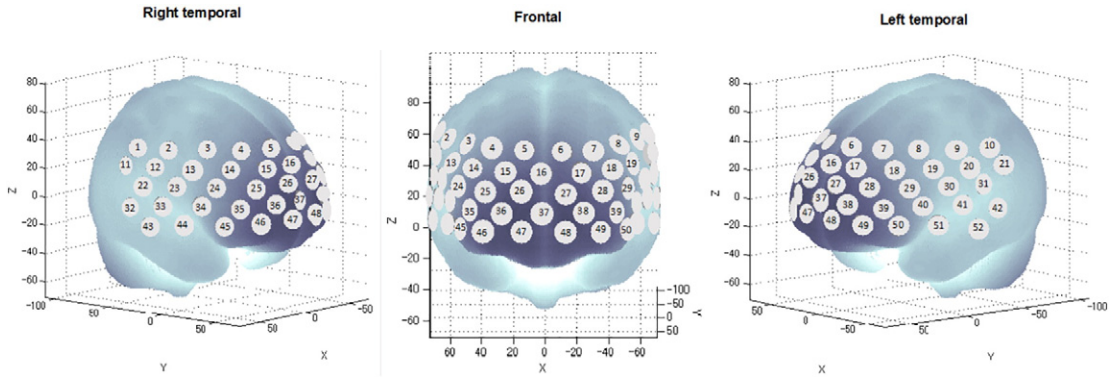


Fig. 1. Measurement points of 52 channels for near-infrared spectroscopy (NIRS). All 52 measuring positions of the NIRS system are superimposed on the 3D-reconstructed cerebral surface. The 52 measuring positions are labeled as ch1 to ch52, from right temporal to left temporal regions. Channels 1, 11, 12, 22, 32, 33, and 43 are located over the right superior temporal gyrus (Brodmann area (BA) 21, 22, and 38). Channels 10, 20, 21, 31, 41, 42, and 52 are located over the left superior temporal gyrus (BA 21, 22, and 38). Channels 2–5, 14, 24, 25, 35, and 46 are located over the right dorsal prefrontal cortex (BA 9 and 46). Channels 6–9, 18, 28, 29, 39, and 49 are located over the left dorsal prefrontal cortex (BA 9 and 46). Channels 13, 23, 34, 44, and 45 are located over the right ventrolateral prefrontal cortex (BA 44, 45, and 47). Channels 19, 30, 40, 50, and 51 are located over the left ventrolateral prefrontal cortex (BA 44, 45, and 47). Channels 15–17, 26, 27, 36–38, 47, and 48 are located over the frontal polar region (BA 10).

base curve from the original data (linear fitting), to derive integral data for subsequent analyses (Supplementary Fig. 1). A moving average method using a window width of 5 s was applied to remove any short-term motion artifacts. A channel was rejected if artifact waveforms were visible (Takizawa et al., 2014).

2.5. NIRS data

When analyzing NIRS data, we focused on [oxy-Hb] because its correlation with rCBV is stronger than its association with [deoxy-Hb] (Strangman et al., 2002). Mean [oxy-Hb] concentration was calculated during the 60-s task period. As [oxy-Hb] changes typically have a positive direction, only data with positive [oxy-Hb] changes were used. NIRS data from the 21 channels in the upper two rows were excluded from statistical analyses because they tended to contain artifacts. Additionally, after visual inspection of the waveforms, channels with a low signal-to-noise ratio were excluded from statistical analyses (Noda et al., 2012). The frontal centroid value (FCV) was calculated (as described below) using the same letter VFT NIRS scan. Takizawa et al. developed a "centroid value" that serves as an index of time-course change, and is indicated by the time shown with a perpendicular line from the centroid of the NIRS signal change area (calculated as positive change) throughout the task period (Supplementary Fig. 2). Takizawa et al. (2014) stated that the FCV (11 channels: ch25–28, ch35–39, and ch46–49) could be used to distinguish MDD from bipolar disorder or schizophrenia with >70% accuracy (FCV ≤ 54 s for MDD; FCV > 54 s for bipolar disorder or schizophrenia). In Japan, this FCV cut-off value is used as a biological maker to assist in the diagnosis of major psychiatric disorders with depressive symptoms.

2.6. NIRS data and clinical data analysis

Demographic and clinical variables were compared, using two-tailed *t*-tests or chi-squared tests. For simplicity, we abbreviated "mean [oxy-Hb] concentration during the 60-s task period" to "[oxy-Hb] values".

First, Spearman correlation analysis between the [oxy-Hb] values of each channel and the DDD of each psychotropic was performed to determine which channels were associated with each psychotropic DDD (antidepressant, benzodiazepine, or antipsychotic).

Second, a multiple linear regression analysis (forced entry model) with the channels with significant associations as dependent variables, and age, sex, HRSD-17 total score, antidepressant DDD, antipsychotic DDD, and benzodiazepine DDD as independent variables, was performed to investigate the effects of other clinical characteristics on [oxy-Hb] values.

Third, the impact of antidepressant dosage on NIRS signals was also investigated. Patients were divided into two dose groups according to DDD (i.e., standard or low-dose group [≤1 DDD] and high-dose group [>1 DDD]) for each psychotropic (antidepressant, benzodiazepine, or antipsychotic), and [oxy-Hb] values of each channel were compared between these two groups, using Student's *t*-test.

Furthermore, the effects of psychotropic dose on the usefulness of NIRS as a tool for assisting in diagnosing psychiatric disorders were also investigated. The odds ratio was calculated as an estimate of relative risk of bipolar disorder or schizophrenia diagnosis based on FCV (FCV ≤ 54 s for MDD; FCV > 54 s for bipolar disorder or schizophrenia) in association with each psychotropic DDD (i.e., standard or low-dose group and high-dose group).

All statistical analyses were performed using SPSS ver. 22.0 (IBM Inc., Armonk, NY, USA). Waveform illustration was performed, using Brain Energy Analyzer ver. 1.0 (Brain Energy, Japan, Tokyo: https://brainenergy.jp/). A false discovery rate (FDR)-based procedure was adopted for multiple testing correction (Benjamini and Hochberg, 1995; Singh and Dan, 2006). Statistical significance was defined by a p-value of <0.05 (two-tailed). Values are shown as means (±standard deviations, SD).

3. Results

3.1. Demographic characteristics

Data were collected from 137 patients. Ninety-seven patients were excluded due to other diagnoses (n = 3), younger or older age (n = 28), lower HRSD-17 or MADRS scores (n = 7), missing HRSD-17 or MADRS data (n = 43), or lack of any positive wave (n = 16). Data from the remaining 40 patients were included in further analyses. The demographic and clinical characteristics of the patients and NIRS variables are summarized in Table 1. Participants took the following antidepressants: mirtazapine (n = 6); sertraline (n = 4); trazodone (n = 4); duloxetine (n = 3); escitalopram (n = 3); nortriptyline (n = 2); paroxetine (n = 1); mianserin (n = 1); amoxapine (n = 1); imipramine (n = 1); amitriptyline (n = 1).

3.2. Correlation analysis of [oxy-Hb] values and psychotropic medications

There were significant associations between [oxy-Hb] values and antidepressant DDD on five channels (ch22 (rho = −0.462, df = 35, p = 0.004), 44 (rho = −0.435, df = 35, p = 0.007), 46 (rho = −0.431, df = 35, p = 0.007), 49 (rho = −0.445, df = 35, p = 0.006), and 52 (rho = −0.492, df = 35, p = 0.002)) after FDR correction (Fig. 2).

Table 1
Baseline characteristics.

	Total	Major depressive disorder	Bipolar disorder	Schizophrenia
Number of patients	40	33	5	2
Sex				
Male	23 (58%)	17 (52%)	4 (80%)	2 (100%)
Female	17 (42%)	16 (48%)	1 (20%)	0 (0%)
Age (year-old)	46.7 ± 11.5	46.4 ± 11.7	47.6 ± 13.8	48.5 ± 6.4
Age at onset (years-old)	37.7 ± 11.7	39.1 ± 11.3	26.0 ± 9.8	45.5 ± 4.9
Number of words generated	13.8 ± 5.1	13.8 ± 5.1	14.4 ± 6.3	11.5 ± 6.3
Number of depressive episodes	2.2 ± 1.6	1.9 ± 1.3	4.4 ± 1.8	1.0 ± 3.5
HRSD-17 total score	19.2 ± 6.9	19.2 ± 6.4	20.2 ± 9.9	17.0 ± 9.8
Antidepressant (DDD)	0.67 ± 1.00	0.82 ± 1.05	0.00 ± 0.00	0.00 ± 0.00
Antipsychotics (DDD)	0.24 ± 0.53	0.22 ± 0.56	0.38 ± 0.31	0.25 ± 0.36
Benzodiazepine (DDD)	1.11 ± 1.27	1.27 ± 1.33	0.48 ± 0.50	0.00 ± 0.00

Data are number (percentage) or mean ± standard deviation unless stated otherwise. Abbreviations: HRSD-17, Hamilton rating scale for depression 17 items; DDD, defined daily dose.

Only ch48 had a significant correlation between [oxy-Hb] values and benzodiazepine DDD, after FDR correction (rho = −0.501, df = 36, p = 0.001). In contrast, there were no significant correlations between [oxy-Hb] values and antipsychotic DDD after FDR correction.

3.3. Multiple linear regression analysis

In the multiple linear regression analysis, we included [oxy-Hb] values for each channel (ch22, 44, 46, 48, 49, 52) as dependent variables, and age, sex, HRSD-17 total score, antidepressant DDD, antipsychotic DDD, and benzodiazepine DDD as independent variables. Antidepressant DDD was significantly related to [oxy-Hb] values on ch22 ($\beta = -0.57$, $p = 0.002$), while other independent variables did not show any significant associations (age: $\beta = 0.09$, $p = 0.56$; sex; $\beta = -0.20$, $p = 0.20$; HRSD-17 total score; $\beta = -0.04$, $p = 0.84$; antipsychotic DDD; $\beta = -0.15$, $p = 0.37$; benzodiazepine DDD; $\beta = 0.18$, $p = 0.31$) (Table 2). Conversely, there were no significant factors associated with NIRS signals on ch44, 46, 48, 49, 52 (Supplementary Table 1).

3.4. Dose group comparison

The high-dose antidepressant group showed significantly attenuated [oxy-Hb] activation compared with the standard or low-dose antidepressant group only on ch22 after FDR correction ($t = 3.48$, $df = 35$, $p = 0.001$) (Fig. 3). There were no significant differences in age, sex, age at onset, and HRSD-17 total score between the high-dose antidepressant and the standard or low-dose antidepressant groups (Table 3). In contrast, in the benzodiazepine and antipsychotic analysis, there were no significant differences between high-dose and the standard or low-dose groups after FDR correction.

3.5. FCV and psychotropic drugs

Although failing to reach statistical significance, the high-dose antidepressant group showed a tendency towards a bipolar or schizophrenia pattern (odds ratio: 7.88; 95% CI: 0.88–70.2) (Fig. 4), as did the high-dose benzodiazepine group (odds ratio: 4.33; 95% CI: 0.80–23.5). We could not calculate an odds ratio related to antipsychotic dose because there was only one patient in the high-dose antipsychotic group.

4. Discussion

The main finding of our study is that antidepressant dose is negatively correlated with [oxy-Hb] values in the right temporoparietal region. To the best of our knowledge, this is the first study to systematically examine the effects of psychotropic drugs on NIRS signals. These results emphasize the need for caution when analyzing NIRS signals in patients receiving high doses of antidepressants.

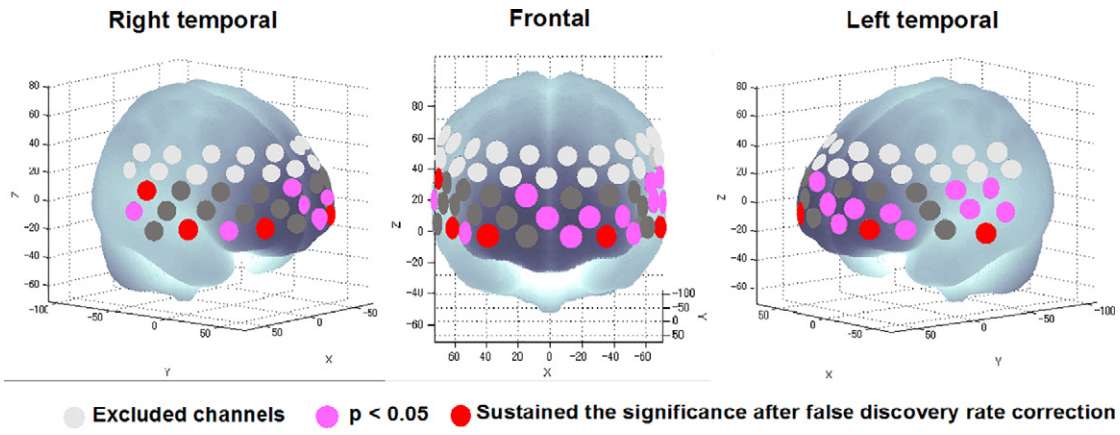
4.1. Psychotropic medications and NIRS signal

Antidepressant dosage was negatively correlated with [oxy-Hb] values in a dose-dependent manner in the present study. Previous longitudinal and cross-sectional studies have been inconsistent regarding the effects of psychotropic drugs on NIRS signals. Noda et al. (2012) examined the correlation between the severity of depression and [oxy-Hb] values during VFT. In their cross-sectional study, they found negative correlations between [oxy-Hb] values and antidepressant doses in several channels located in the left temporal regions. However, the authors concluded that the antidepressant effect on [oxy-Hb] values was minor because these channels did not overlap with the channel showing a significant correlation between [oxy-Hb] values and the depression severity. Takizawa et al. (2014) conducted a step-wise regression analysis in their cross-sectional study to explore any confounding factors affecting FCV. None of the medications and clinical variables showed any association with FCV. However, antidepressant effects on NIRS signals were not evaluated at any single channel level in their study. The results of these previous studies appear to be inconsistent with our results. The most important difference between previous studies and ours is that we investigated the effects of antidepressants on NIRS signals at the single channel level and performed a regression analysis to consider the effects of confounding factors.

In contrast, recent cohort studies of healthy subjects have consistently reported significant effects of medication on NIRS signals. For example, Kohmura et al. (2013) examined the effects of sedative antidepressants on NIRS signals in a randomized controlled trial. They found that the administration of mirtazapine (15 mg for 8 consecutive days) increased [oxy-Hb] values during VFT, whereas trazodone (25 mg for 8 days) and a placebo did not have any significant effects on NIRS signals. Tsujii et al. (2007, 2009) investigated the effects of antihistamines on NIRS signals, and found that first-generation histamine H1-receptor antagonists significantly attenuated [oxy-Hb] activation in the lateral prefrontal cortex compared with second-generation H1 blockers.

Moreover, in the current study, the high-dose antidepressant group showed an inverted waveform in the group comparison (Fig. 3). The current results might indicate that high-dose antidepressants contribute to the negative conversion of the NIRS waveform in single channel levels. However, a certain portion of unmedicated cases in this study show negative conversion of the NIRS waveform in single channel levels (data not shown). Our results are not conclusive in terms of NIRS negative waveforms and further studies are required to investigate this phenomena.

A) Channels with significant correlations between [oxy-Hb] value and antidepressant DDD.



B) Relationship between antidepressant dosage and [oxy-Hb] value in ch22.

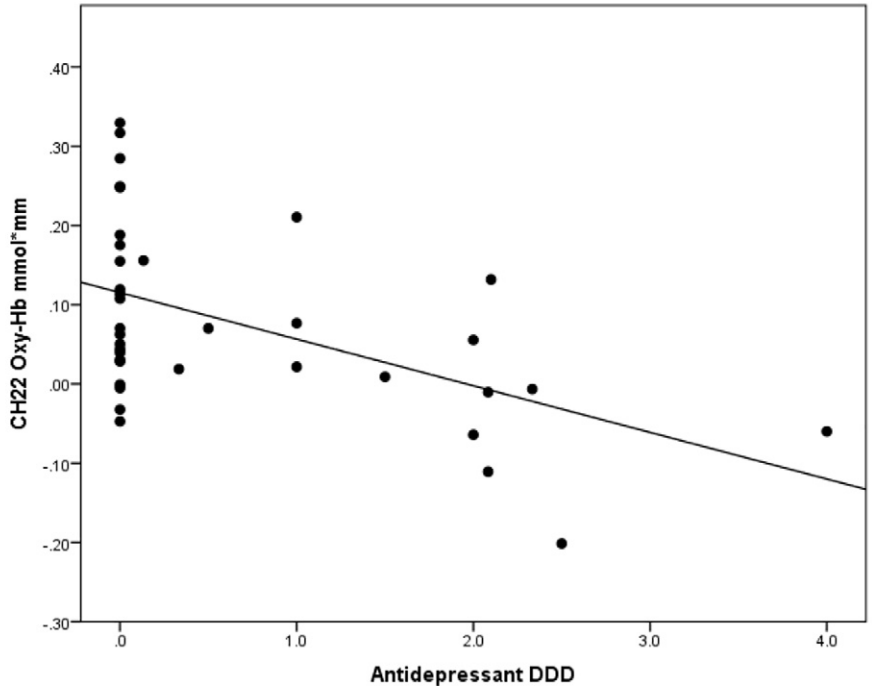


Fig. 2. Correlation between [oxy-Hb] values and antidepressant DDD. Abbreviations: DDD, defined daily dose.

Table 2
Factors associated with Ch22 [oxy-Hb] value.

Variables	B	β	95% CI	p-Value
Age, years	0.001	0.093	−0.002–0.004	0.559
Sex	−0.046	−0.196	−0.119–0.026	0.203
HRSD-17 total score	−0.001	−0.036	−0.006–0.005	0.837
Antidepressant DDD	**−0.065**	**−0.565**	**−0.105** to **−0.026**	**0.002***
Benzodiazepine DDD	0.016	0.175	−0.016–0.048	0.312
Antipsychotic DDD	−0.033	−0.151	−0.107–0.041	0.368

$R = 0.585$, $R2 = 0.342$, $p = 0.038$*. p-Values of <0.05 was shown in bold and *. Abbreviations: B, non-standardized coefficient: β, standardized coefficient: CI, confidence interval: R, multiple correlation coefficient: R^2, coefficient of determination: HRSD, Hamilton rating scale for depression: DDD, defined daily dose.

Overall our findings suggest that the effects of medication on NIRS signals should be taken into account when interpreting data.

4.2. Antidepressants and cerebral perfusion

Previous neuroimaging studies of depression have revealed a general pattern of increased activity in the limbic regions, including the amygdala, with reduced activity of the prefrontal regions, particularly the lateral prefrontal cortex. Reversal or normalization of these processes has also been demonstrated following antidepressant use (Fitzgerald et al., 2008; Delaveau et al., 2011). In this study we found that high-doses of antidepressants are associated with attenuated cortical activation during a cognitive task. This seems inconsistent with previous studies, however, these might have included state-

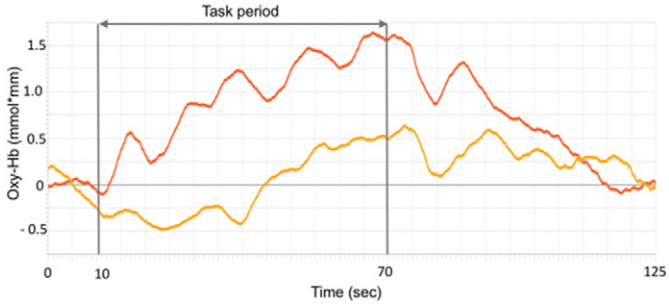


Fig. 3. Average waveforms on ch22. The orange line represents low-dose group (≤1 antidepressant DDD), and the yellow line represents high-dose group (>1 antidepressant DDD). Abbreviations: DDD, defined daily dose.

dependent changes with a clinical response per se, as well as changes in antidepressants. In contrast, we excluded patients in remission, and our results might therefore be restricted to the effects of antidepressants.

The patients taking high-dose antidepressants exhibited attenuated activation during VFT in the right temporoparietal junction region in this study. Previous fMRI studies have consistently shown that the temporoparietal junction is involved in reorienting attention to salient stimuli (Corbetta and Shulman, 2002). This region is considered to be a part of the ventral frontoparietal system, which is distinct from the dorsal attention system that prepares and applies goal-directed, top-down selection of task-relevant stimuli and responses. In addition, a recent study found that the right temporoparietal junction is functionally connected to the left dorsolateral prefrontal cortex, which is strongly associated with working memory (Garrett et al., 2011). Based on these previous results, the temporoparietal junction region may function to reorient attention to the cognitive task, and high-dose antidepressants may attenuate this function.

4.3. NIRS signal as a biomarker

In this study, we investigated the relationships between the dose of antidepressant drugs and FCV, which is used as a biological maker for assisting in diagnosis of major psychiatric disorders with depressive symptoms in Japan. We reanalyzed our data after excluding patients with bipolar disorder and schizophrenia, and found similar results. Although these failed to reach statistical significance, we revealed that MDD patients taking more than one DDD of psychotropics were more likely to exhibit signs of bipolar disorder or schizophrenia than those taking less than one DDD (antidepressant: odds ratio: 8.25; 95% CI: 0.89–76.1; benzodiazepine: odds ratio: 4.55; 95% CI: 0.80–26.0) (Supplementary Fig. 3, Supplementary Table 2). These results indicate that MDD patients taking more than the standard dose of psychotropics might be at risk of being diagnosed with bipolar disorder or schizophrenia due to a higher FCV (FCV ≤ 54 s for MDD; FCV > 54 s for bipolar disorder or schizophrenia) (Takizawa et al., 2014).

As some treatment-resistant depression patients administered high-dose antidepressants may have a diagnosis of bipolar disorder (Parker et al., 2005), MDD patients with more than one DDD in this study are potentially bipolar disorder individuals. Another interpretation of our result is that antidepressant medications truly affect FCV. In fact, Rizvi et al. (2014) reported that treatment-resistant depression patients are more likely to receive polypharmacy and receive higher doses of psychotropic medications than the non-treatment-resistant depression group. Therefore, it is possible that MDD patients with high-dose antidepressants may be misdiagnosed with bipolar disorder or schizophrenia based on NIRS assessment, regardless of their clinical diagnosis. Thus, attention should be paid to antidepressant dosage when NIRS is used as a tool to assist in diagnosing psychiatric disorders.

Table 3
Baseline characteristics of standard or low-dose group (≤1 antidepressant DDD) and high-dose group (>1 antidepressant DDD).

	Low dose group: ≤1 DDD	High dose group: >1 DDD	p value
Number of patients	30	10	
Diagnosis[a]			
Major depressive disorder	23 (77%)	10 (100%)	0.24
Bipolar disorder	5 (17%)	0 (0%)	
Schizophrenia	2 (6%)	0 (0%)	
Sex[a]			0.58
Male	12 (40%)	5 (50%)	
Female	18 (60%)	5 (50%)	
Age (year-old)[b]	46.5 ± 12.2	47.1 ± 9.9	0.88
Age at onset (years-old)[b]	37.1 ± 12.3	43.7 ± 12.0	0.15
Number of depressive episodes[b]	2.1 ± 1.7	2.3 ± 1.3	0.66
Number of words generated[b]	13.5 ± 4.1	14.4 ± 7.3	0.71
HRSD-17 total score[b]	19.2 ± 6.8	20.2 ± 9.9	0.43
Antidepressant (DDD)[b]	0.17 ± 0.35	2.2 ± 0.7	< 0.001
Antipsychotics (DDD)[b]	0.81 ± 0.26	0.44 ± 0.95	0.42
Benzodiazepine (DDD)[b]	0.82 ± 0.91	1.98 ± 1.79	0.08

Data are number (percentage) or mean ± standard deviation unless stated otherwise. Abbreviations: HRSD-17, Hamilton rating scale for depression 17 items; DDD, defined daily dose.
[a] Pearson χ^2 test.
[b] Independent student's *t*-test.

4.4. Limitations

The results of our study must be interpreted with caution owing to the following limitations. First, because of the cross-sectional study design, we did not examine any causality between the use of antidepressants and NIRS signals. Second, owing to concomitant usage of each psychotropic and small sample size, there is the possibility that we overlooked the effects of antipsychotics and benzodiazepines on NIRS signals. Nevertheless, we systematically evaluated the effects of each psychotropic on NIRS signals, and only antidepressants showed significant results. However, further prospective studies using each psychotropic medication alone need to be performed to replicate our findings. Third, the sample size was small. We tried to minimize effects of confounding factors, by adopting strict inclusion criteria, and as a result two-thirds of the patients who were identified through the initial systematic chart review were excluded. Nevertheless, we strictly adhered to the criteria that the Japanese Ministry of Health, Labour and Welfare provided in 2014 for the use of NIRS. Additionally, we excluded one-third of our data because of lack of assessment using a depression rating scale. Fourth, participants in this study were diagnosed based on unstructured clinical interviews. Therefore, they may have several comorbidities, including anxiety disorders or personality disorders, which could affect the NIRS assessment results. Fifth, we may have overlooked unknown confounding factors such as autonomic nervous function, scalp–cortex distance, and frontal sinus volume. Further studies to explore the effects of these potential confounders on NIRS signals are needed. Sixth, our findings might be specific to changes in NIRS signal during VFT. To generalize our results, analyses during other activation tasks are needed. However, VFT is the most common activation task for NIRS and is always used in clinical practice.

5. Conclusion

The present study suggests that the dose-dependent impact of antidepressants on NIRS signals should be taken into account when NIRS signals are analyzed. Additionally, the dose-dependent impact of antidepressants on FCV may result in misdiagnosis of MDD as bipolar disorder or schizophrenia. Given that many psychiatric patients are receiving multiple and sometimes high-dose psychotropic drugs, sufficient attention should be paid to the dosage of antidepressant medication when NIRS is utilized.

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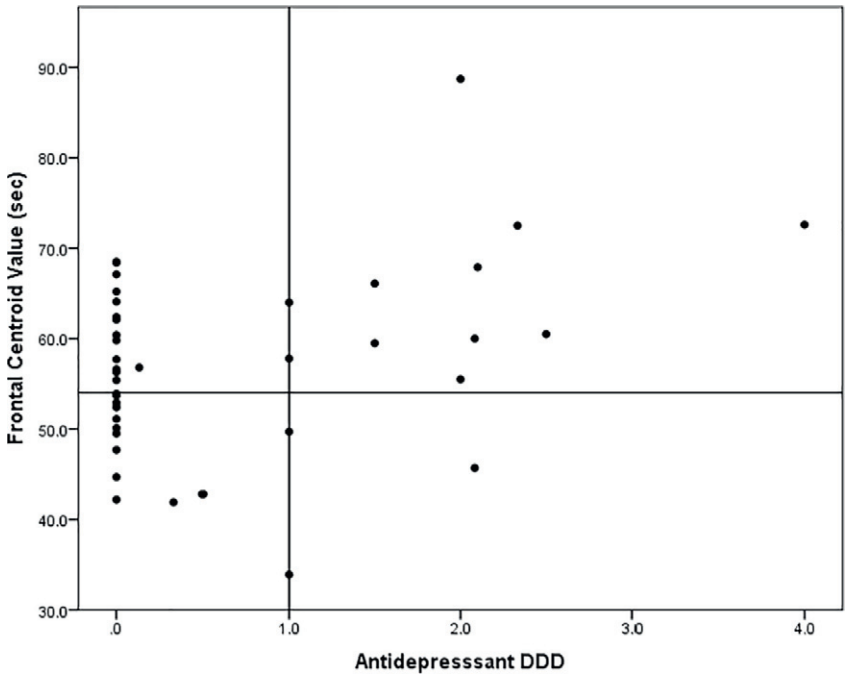

		Antidepressant DDD	
		≤ 1	1<
FCV	>54.0sec	16	9
	≤54.0sec	14	1

Fig. 4. Scatter graph showing the relationship between antidepressant DDD and frontal centroid value. Twenty-five (62.5%) patients had FCV responses > 54.0 s (indicating schizophrenia or bipolar disorder) and 15 (37.5%) patients had responses < 54.0 s (indicating MDD). Patients taking more than one DDD showed a tendency towards a bipolar disorder or schizophrenia pattern (FCV > 54.0 s) (odds ratio: 7.88; 95% CI: 0.88–70.2). Abbreviations: DDD, defined daily dose DDD; FCV, frontal centroid value.

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The other authors do not have any conflicts of interests to declare.

Contributors

A. Takamiya and J. Hirano designed the study, wrote the protocol, searched the literature, statistically analyzed the data, and wrote the first draft of the manuscript. Y. Ebuchi, S. Ogino, K. Shimegi, H. Emura, K. Yonemori, A. Shimazawa, G. Miura, A. Hyodo, S. Hyodo, T. Nagai, M. Funaki, and M. Sugihara were involved in data collection. M. Kita supported figure illustrations. B. Yamagata and M. Mimura wrote the final version of the manuscript. All authors contributed to and have approved the final manuscript.

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