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Sleep complaints are associated with reduced left prefrontal activation during a verbal fluency task in patients with major depression: A multi-channel near-infrared spectroscopy study

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ABSTRACT

Background: Recent studies have indicated the potential clinical use of near-infrared spectroscopy (NIRS) as a tool for assisting in the diagnosis of major depressive disorder (MDD). Although sleep complaints are often manifested in MDD, no study has elucidated the possible association between the objective evaluation of sleep and NIRS signals in MDD.

Methods: Fourteen patients with MDD and 15 healthy controls wore waist actigraphy equipment before the NIRS scan to investigate sleep parameters. We performed a 52-channel NIRS scan and measured changes in oxygenated hemoglobin ([oxy-Hb]) during a verbal fluency task.

Results: In patients with MDD, a significant negative correlation was observed between the 17-item Hamilton Depressive Rating Scale score and cerebral reactivity of the right temporal region (p_s:=−0.804 to −0.762; FDR-corrected; p=0.008–0.012). The Pittsburgh Sleep Questionnaire Index, which enables assessment of continuous sleep quality and disturbances, was negatively correlated with [oxy-Hb] changes in the left prefrontal cortex (p_s=−0.630 to −0.551; FDR-corrected; p=0.043–0.048). Actigraphic sleep variables prior to the NIRS measurement showed no significant correlation with [oxy-Hb] changes.

Limitations: The limitations were small sample size with the low severity of depression and the use of actigraphy for only one night.

Conclusion: Self-rated sleep disturbance were associated with decreased left prefrontal reactivity during a verbal fluency task in patients with MDD. Our result indicates that the reactivity of the prefrontal region is susceptible to sleep complaints, providing further evidence to support potential clinical application of NIRS.

1. Introduction

Major depressive disorder (MDD) is one of the most common psychiatric illnesses worldwide. MDD has a high lifetime prevalence of up to 20% (Kessler et al., 2005) and constitutes the leading cause of disability worldwide (Zhang et al., 2011). Affected individuals are at high risk for comorbid medical and psychiatric illnesses, have worse medical outcomes than the general population, and show a substantial correlation with suicidality (Krishnan et al., 2002; McIntyre and O'Donovan, 2004).

Sleep alterations are commonly observed in patients with MDD and form a crucial part of the diagnostic criteria. Patients with MDD frequently have difficulty in initiating sleep and experience frequent awakenings during the night, earlier than desired awakenings, and non-restorative sleep (Benca and Peterson, 2008; Ohayon, 2002, 2005). Several epidemiological studies demonstrated that patients with MDD have an increased frequency of sleep abnormalities that persist even during periods of remission (Li et al., 2012). In addition to a risk

Abbreviations: NIRS, Near-infrared spectroscopy; MDD, Major depressive disorder; VFT, Verbal fluency task; MRI, magnetic resonance imaging; HAM-D, Hamilton depressive rating scale; PSQI, Pittsburgh sleep quality index; ESS, Epworth sleepiness scale; TIB, Total time in bed; TST, total sleep time; [oxy-Hb], oxygenated hemoglobin; PSG, Polysomnography; REM, Rapid eye movement; DPF, differential pathlength factor; FDR, false discovery rate

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for relapse of MDD, patients with persistent insomnia but without depression show a higher risk of developing MDD than normal sleepers (Benca and Peterson, 2008).

A new and non-invasive neuroimaging method, near-infrared spectroscopy (NIRS), has the potential to identify the depressive state that accompanies various psychiatric disorders by measuring the spatiotemporal characteristics of brain function. Accumulating studies using NIRS have consistently reported that oxygenated hemoglobin ([oxy-Hb]) activation during a verbal fluency task (VFT) is significantly decreased in patients with MDD compared with healthy controls in fronto-temporal brain regions (Matsuo et al., 2002; Pu et al., 2008; Suto et al., 2004). A recent meta-analysis of NIRS studies further supports previous findings of hypofrontality in MDD (Zhang et al., 2015). Moreover, recent studies found that frontal hemodynamic patterns detected by NIRS accurately distinguish patients with MDD from patients with schizophrenia and bipolar disorder (Takizawa et al., 2014) and that NIRS signals before initiation of treatment may be useful for predicting the clinical response to antidepressant treatment (Tomioka et al., 2015). Taken together, NIRS-guided differential diagnosis of major psychiatric disorders manifesting with a depressive state may be promising for clinical application.

According to the above evidence, NIRS was approved as an insurance-covered auxiliary laboratory test for differential diagnosis of the depressive state by the Ministry of Health and Labour and Welfare in Japan in 2014 after a trial period as one of the Advanced Medical Technologies in 2009, costing 2000–4000 JPY according to one measurement (Fukuda, 2015). Although the use of NIRS has been gradually increasing at clinical sites in Japan, whether NIRS signal changes during a VFT are affected by the existing sleep disturbance that accompanies MDD is unclear. Magnetic resonance imaging (MRI) studies using a sleep deprivation paradigm revealed changes in brain metabolism and neural activation that involve various networks and connectivity (Basner et al., 2013). A previous NIRS study reported that decreased reactivity in the prefrontal region is related to daytime light sleepiness (Suda et al., 2008); however, this imaging study was limited to normal healthy volunteers.

The aim of this study was to investigate the association between sleep disturbance and NIRS signals in MDD. We hypothesized that the severity of sleep disturbance may affect [oxy-Hb] changes during a VFT as observed with NIRS, because a previous report indicated that a decreased [oxy-Hb] change is correlated with the sleep-related items in the Hamilton Depressive Rating Scale (HAM-D) (Noda et al., 2012). Thus, we used multi-channel NIRS to investigate the relationship between [oxy-Hb] changes and sleep disturbance in inpatients with MDD. We evaluated sleep disturbance in MDD not only with questionnaires, but also with the use of waist actigraphy, which involves use of a non-invasive, restraint-free, wearable device that enables objective assessment of sleep. In addition, we hypothesized that the prefrontal region may be more vulnerable to sleep disturbance in MDD compared to normal controls, suggesting an impaired hemodynamic response in those with MDD.

2. Material and methods

2.1. Participants (Table 1)

The patient group was composed of 14 inpatients (7 males, 7 females, age: 46.2 ± 11.9 years, mean ± standard deviation (SD)), and the control group was composed of 15 healthy adults (8 males, 7 females, age: 45.5 ± 10.9 years, mean ± SD). The participants with MDD were diagnosed by experienced psychiatrists based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV-TR American (American Psychiatric Association., 2000). To rule out any psychiatric conditions, experienced psychiatrists examined all participants using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998).

Based on medical history and clinical examination, none of the participants had clinical evidence of other psychiatric conditions, central nervous system disorders, or drug or substance abuse. MRI of the brain was performed for all patients with MDD, and those with abnormalities such as cortical atrophy, or ischemic regions indicative of previous cerebral infarctions were excluded from this study. In addition, subjects who manifested with obvious symptoms of circadian rhythm disorder, parasomnia, narcolepsy, or other primary sleep disorders as defined by the International Classification of Sleep Disorders, Second edition (American Academy of Sleep Medicine, 2005) were excluded from this study after examination by sleep medicine experts.

All participants were confirmed to be right-handed and native Japanese speakers. After providing comprehensive information about the study, written informed consent for the study protocol was obtained from all study participants. This study was performed in accordance with the Helsinki Declaration, as revised in 1989, and was approved by the ethics committee of Jichi Medical University (Shimotsuke, Tochigi, Japan).

2.2. Clinical assessment

All participants were clinically assessed prior to the NIRS measurement. Severity of depression was evaluated with the 17-item HAM-D (Hamilton, 1960) by trained psychiatrists who were involved in this study. All patients with MDD were in a depressed mood state (HAM-D score > 7). To assess self-rated sleep quality and disturbances (equivalent to sleep complaints) over approximately 1 month prior to the measurement, the Pittsburgh Sleep Quality Index (PSQI) (s) (Buysse et al., 1989) was assessed for the participants by sleep medicine experts. In addition, sleepiness was also scored on the Epworth Sleepiness Scale (ESS) (Johns, 1991). All participants were prohibited from consuming any alcohol or caffeine during the study period.

Daily doses of all antidepressants, anxiolytics, and hypnotics were converted to an equivalent dose of imipramine, diazepam, and flunitrazepam, respectively (Inagaki and Inada, 2006). Medication was kept stable for at least 1 week before the NIRS measurement.

2.3. Sleep evaluation

2.3.1. Sleep setting

The patients in the ward were asked to get into bed at 22:00 when the lights were turned off the night before the experiment and to get out of bed when the lights were turned on at 7:00 the next morning. The normal controls at home were requested to adhere to a similar sleep schedule as the patients.

2.3.2. Actigraphy measurement

To obtain objective sleep variables, waist-worn actigraphy with the FS-750 (Estera Corporation, Saitama, Japan) was used to record sleep parameters. All participants were instructed to wear the FS-750 before going to bed prior to the day of the NIRS measurement and to continue wearing the device until they got out of bed. This small, light, rectangular device (external dimensions: 75×33.5×10.8 mm (width × height × depth); weight, 26 g including the battery) records the amount of activity by using an internal three-axis accelerometer (electrostatic capacity sensor). Every 0.125 s, the number of times that acceleration exceeded a reference value was summed, and the value was recorded as the activity value over 2-min bins. The activity intensity is calculated from the activity value as a value from 0 to 31 (32 levels). An activity intensity of 0 means the subject did not move, and larger values indicate higher amounts of activity.

An algorithm for the FS-750 that determines sleep and wakefulness was included in the SleepSignAct software (Kissei Comtec Co. Ltd., Matsumoto, Japan) and validated in previous studies for use in polysomnography (PSG) (Enomoto et al., 2009; Nakazaki et al.,