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Prefrontal activation predicts social functioning improvement after initial treatment in late-onset depression

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ABSTRACT

The activation of oxygenated hemoglobin (oxy-Hb) has been shown to be lacking in the prefrontal cortex (PFC) of patients with late-onset depression (LOD), in verbal fluency task (VFT)-related near-infrared spectroscopy (NIRS). In our previous studies, we have emphasized the connection between the lack of activation in the frontopolar cortex and social functioning disorder in patients with LOD. In this study, we investigated whether the responsiveness to medical treatment of untreated patients with LOD, particularly social functioning improvements, could be predicted by NIRS findings at the initial examination. The subjects were 29 patients with LOD who were diagnosed with major depression at 65 years or older at the initial examination (mean age ± standard deviation, 72.4 ± 5.71 years). We measured the changes in hemoglobin concentration in the prefrontal and temporal cortex regions during a VFT by using 52-channel NIRS. In addition, depression status and social functioning were evaluated with the Hamilton Depression Rating Scale and the Social Adaptation Self-evaluation Scale, respectively, at the initial examination and 8 weeks after the treatment. A negative correlation was found between the NIRS activation in the right ventrolateral PFC region before treatment and the improvement in social functioning. These results suggested that the social functioning improvements were greater in LOD with initially lower NIRS activation in the right ventrolateral PFC region. NIRS is a simple technique that can be used before treatment to evaluate the social functioning levels of patients with LOD, and predict social functioning improvement after treatment.

1. Introduction

As the aging of populations continues in society, there has been a growing interest in psychiatric disorders in the elderly (WHO, 2008). Depression, which is a disease with a high prevalence, is common in the elderly in the general population (Blazer, 1989; NIH consensus conference 1992). In recent years, increased knowledge of the disease and the increased use of pharmacotherapy with new-generation antidepressants such as selective serotonin reuptake inhibitors and selective serotonin noradrenaline reuptake inhibitors have resulted in improved treatment effects in patients with depression. However, social functioning disorder remains despite improvements in the depression symptoms (Hirschfeld et al., 2002). It has been suggested that improvements in social functioning are important for patients with depression to be able to adapt to society. Thus, social functioning is being taken into consideration in the treatment of patients with depression. Social functioning is instrumental to the quality of life, and it requires complex operations of various executive functions that include monitoring, reasoning, organizing, selecting, and planning. Depression and schizophrenia cause severe impairments in social functioning (WHO, 2004). Social functioning has received widespread attention as one of the most important outcomes in psychiatric disorders and has been related to cognitive functioning and the underlying brain activity.

The dysfunction of the prefrontal cortex (PFC) in patients with depression has been reported in previous studies that used neuropsychological tests (Beats et al., 1996; Degl'Innocenti et al., 1998; Moritz et al., 2002). This PFC dysfunction in patients with depression has been increasingly clarified by functional brain imaging

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studies (Baker et al., 1997; Baxter et al., 1989; Drevets et al., 1997; Nobler et al., 2002; Okada et al., 2003, 2009). To date, it has been widely reported that cerebral blood flow and glucose metabolism are decreased in the dorsolateral prefrontal cortex and increased in the ventrolateral and ventromedial prefrontal cortex in patients with depression (Drevets, 2000). The medial prefrontal cortex has dense reciprocal connections with the amygdala and is presumed to inhibit the abnormally increased amygdala activity in patients with depression (Etkin et al., 2011). The medial prefrontal hyperactivity may indicate the need for stronger control in patients with depression compared to healthy controls. By contrast, lateral prefrontal area has primarily been associated with cognitive functions. However, recent studies suggest that the cognitive control functions may also pertain to emotion. Specifically, functional imaging studies demonstrate the recruitment of the lateral prefrontal area during the regulation of negative emotion through reappraisal/suppression strategies (Eippert et al., 2007; Levesque et al., 2003; Ochsner et al., 2002, 2004; Phan et al., 2005). Thus, a defect in the regulation of negative affect due to lateral prefrontal dysfunction is indeed a plausible mechanism for causing depression.

Multichannel near-infrared spectroscopy (NIRS), a functional neuroimaging technology widely used in recent years, can measure the hemodynamics over the surface of the cortices of the bilateral frontotemporal regions (Heinzel et al., 2013; Strangman et al., 2002a). This technique enables the detection of spatiotemporal characteristics of brain function by measuring the concentrations of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb), which are assumed to reflect the regional cerebral blood volume as demonstrated by good correlations with functional MRI (fMRI) signals (Sato et al., 2013). NIRS has several advantages over existing imaging techniques, such as positron emission tomography (PET), Single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), because it is noninvasive, without using any radioactive substances, and is easy to administer, tolerates small movements, is inexpensive, and provides excellent time resolution (Ferrari and Quaresima, 2012). Meanwhile, it also contains disadvantages such as its poor spatial resolution, and the fact that it could not measure the deeper layer of the brain. Indeed, NIRS has been used to assess brain functions in many psychiatric disorders (Kameyama et al., 2006; Matsuo et al., 2003; Pu et al., 2008; Takizawa et al., 2014). In addition, NIRS was approved for application in clinical practice by the Ministry of Health, Labor, and Welfare of Japan in April 2009 as a clinical evaluation method for the differential diagnosis assistance of depression symptoms in psychiatric treatment in Japan. NIRS, which is a simple and noninvasive technique that can analyze the temporal course of brain function changes over a short period and in a natural position, allows for a relatively convenient examination that can be conducted in the outpatient clinic. In particular, it is a functional brain imaging examination that poses relatively little burden on elderly patients.

There have been several reports on the use of NIRS in patients with late-onset depression (LOD). A consistently reduced oxy-Hb activation in the PFC (hypoactivation) has been observed in patients with LOD according to NIRS findings in a study using a verbal fluency task (VFT) with the initial sounds of words, which is most commonly employed (Matsuo et al., 2000, 2005; Pu et al., 2008). However, there have only been a few reports on the connection between therapeutic responses in patients with LOD and NIRS findings. An objective diagnostic method for the prediction of depression treatment responses has yet to be established in other studies of neurological functional imaging as well.

There are still some debates as to what clinical aspects the NIRS signal actually reflects. One study by Noda et al. (2012) has demonstrated a significant negative correlation between NIRS signal activations in the frontal and right temporal regions and depression severity. However, in our previous study, we found a stronger cross-sectional correlation between NIRS signal activations in the PFC during the verbal fluency task and social functioning rather than the depressive symptom severity (Pu et al., 2008). In the present study, we performed pretreatment NIRS measurements in untreated patients with LOD and investigated the relationship between the treatment response of these patients, particularly the degree of improvement in social functioning, and the pretreatment NIRS findings. We hypothesized that pretreatment activity in the PFC is related to both pretreatment and degree of improvement in social functioning in patients with LOD.

2. Materials and methods

2.1. Participants (Table 1)

The subjects were 29 patients [7 males, 22 females, mean ± standard deviation (SD) age: 72.4 ± 5.71 years] who were diagnosed with major depressive disorder based on the DSM-IV (American Psychological Association, 1994) using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). None of the patients had clinical evidence of other central nervous system disorders based on medical history and examination. They visited the outpatients ward of Tottori University Hospital for the first time between September 2006 to July 2010 with an initial onset episode at an age of 65 years or older. The control group comprised of 29 healthy adults [7 males, 22 females, mean ± standard deviation (SD) age: 71.6 ± 5.57 years] matching the patients in terms of age and sex, with no history of neuropsychiatric diseases. The NIRS data of 7 out of 29 patients had been reported in our previous study (Pu et al., 2008) but not about their relationship with treatment response. All the patients with LOD were in a depressed mood state (Hamilton Depression Rating Scale [Hamilton Depression Rating Scale (HAM-D) score ≥15; 17 items; mean ± SD HAM-D score: 20.6 ± 5.22]. All the participants were right-handed with criteria of more than 80% by the Edinburgh

Table 1
Demographic and clinical variables of the participants.

Demographics	Patients (n = 29) (mean ± SD)	Healthy controls (n = 29) (mean ± SD)	t	df	Group difference
Age, years	72.4 ± 5.7	71.6 ± 5.6	−0.605	56	0.548
Gender, women/men	22/7	22/7	$X^2 = 0$	1	1.000
Handedness (%)	97.9 ± 6.2	97.9 ± 6.4	−0.042	56	0.925
Education, years	10.6 ± 1.9	11.6 ± 2.0	2	56	0.071
Estimated premorbid IQ	97.1 ± 12.4	92.6 ± 28.1	−0.782	56	0.437
Duration of illness, years	4.7 ± 5.6	–	–	–	–
Nuber of words generated	10.7 ± 3.9	12.2 ± 3.2	1.621	56	0.111
MMSE	27.5 ± 1.9	27.4 ± 2.4	−0.189	56	0.851
HAMD	20.6 ± 5.2	–	–	–	–
SASS	28.7 ± 9.8	41.0 ± 6.3	7.680	56	<0.001

Abbreviations: IQ, Intelligence Quotient; MMSE, Mini-Mental State Examination; HAMD, Hamilton Rating Scale for Depression; SASS, Social Adaptation Self-Evaluation Scale.