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.

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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...
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 (hypoperfusion) 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; 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 ± 5.7 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 characteristics 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 University

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical variables of the participants.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patients (n = 29) (mean ± SD)</td>
</tr>
<tr>
<td>Age, years</td>
<td>72.4 ± 5.7</td>
</tr>
<tr>
<td>Gender, women/men</td>
<td>22/7</td>
</tr>
<tr>
<td>Handedness (%)</td>
<td>97.9 ± 6.2</td>
</tr>
<tr>
<td>Education, years</td>
<td>10.6 ± 1.9</td>
</tr>
<tr>
<td>Estimated premorbid IQ</td>
<td>97.1 ± 12.4</td>
</tr>
<tr>
<td>Duration of illness, years</td>
<td>4.7 ± 5.6</td>
</tr>
<tr>
<td>Number of words generated</td>
<td>10.7 ± 3.9</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.5 ± 1.9</td>
</tr>
<tr>
<td>HAMD</td>
<td>20.6 ± 5.2</td>
</tr>
<tr>
<td>SASS</td>
<td>28.7 ± 9.8</td>
</tr>
</tbody>
</table>

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