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Depressive symptoms in older adults are associated with decreased cerebral oxygenation of the prefrontal cortex during a trail-making test

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ABSTRACT

Growing evidence supports the relationships between depressive symptoms, cognitive decline, and brain structural changes in older adults. The purpose of this study was to determine whether depressive symptoms are related to cerebral oxygenation during cognitive tasks in older adults. In this study, 80 elderly subjects (73.9 ± 5.4 years, 34 males) were evaluated using multi-channel Near-infrared spectroscopy. Concentration changes (mmol cm/l) in oxy-hemoglobin (oxy-Hb), as the most reliable available indicator of changes in regional cerebral blood flow, in the right and left prefrontal cortex were measured during the Trail Making Test Part B (TMT-B). Depressive symptoms were assessed using the short Geriatric Depression Scale (GDS). Subjects were divided into a depressive group (GDS greater than or equal to 6) and non-depressive group (GDS lower than 6). In results, Oxy-Hb activation during the TMT-B was significantly smaller in the depressive group ($n = 13$) than in the non-depressive group ($n = 67$) in both the right and left prefrontal cortex. In the multivariate analysis, GDS scores were significantly negatively correlated with oxy-Hb activation after adjusting for age, gender and educational history (right, $\beta = -0.32$, $p = 0.002$; left, $\beta = -0.25$, $p = 0.02$). Less prefrontal activation in older adults with depressive symptoms may account for decline in executive function. Further studies are needed to investigate the influence of the less brain activation associated with depressive symptoms on future cognitive decline and structural brain changes in older adults.

1. Introduction

In older adults, depression is often accompanied by marked disabilities, diminished quality of life, caregiver burdens, and mortality (Alexopoulos, 2005). Although depression is the most prevalent psychological disorder in senescence, it is still under-recognized, making it a significant health care issue (Charney et al., 2003). Depressive symptoms are common in older adults and are associated with cognitive deficits (Bennett, Wilson, Schneider, Bienias, & Arnold, 2004; Chuan, Kumar, Matthew, Heok, & Pin, 2008) and predict cognitive decline (Chodosh, Kado, Seeman, & Karlamangla, 2007), particularly in executive function (Royall, Palmer, Chiodo, & Polk, 2012). Depression in the non-demented aged has been identified as a possible risk factor for incident Alzheimer's disease (AD) (Green et al., 2003; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Furthermore, neuroimaging studies using magnetic resonance imaging (MRI) reported a relationship between depression and decreased regional volumes (e.g., prefrontal, frontal, and temporal regions) (Dotson, Davatzikos, Kraut, & Resnick, 2009; Kumar et al., 1997; Taki et al., 2005). These findings strongly support the link between depressive symptoms and age-related deterioration of cognitive function and brain structure.

Near-infrared spectroscopy (NIRS) was established as a tool for monitoring cortical activation during a task and has been applied to various fields of neurophysiological research since its introduction by Jobsis in the late 1970s (Jobsis, 1977). NIRS enables the non-invasive detection of spatiotemporal characteristics of brain function near the brain surface using near-infrared light

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(Strangman, Boas, & Sutton, 2002). NIRS has enabled bedside measurements of the concentrations of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) changes with a high temporal resolution. Concentrations of oxy-Hb and deoxy-Hb are assumed to reflect regional cerebral blood volume changes, as supported by a simultaneous NIRS and positron emission tomography (PET) study (Ohmae et al., 2006). Recent research supports the potential of NIRS as an early detection method for dementia (Herrmann, Langer, Jacob, Ehlis, & Fallgatter, 2008; Zeller, Herrmann, Ehlis, Polak, & Fallgatter, 2010). In contrast to other neuroimaging methodologies, such as functional MRI (fMRI), PET, electroencephalography and magnetoencephalography, NIRS can be measured easily and non-invasively, in a restraint-free environment, and rapidly, making it especially suitable for psychiatric patients. NIRS has been used to assess brain functions in older adults (Heinzel et al., 2013; Herrmann, Walter, Ehlis, & Fallgatter, 2006) and many psychiatric disorders, such as schizophrenia, depression, and bipolar disorders (Kameyama et al., 2006; Suto, Fukuda, Ito, Uehara, & Mikuni, 2004).

Pu et al. (2011) found that patients with major depressive disorder showed decreased activation in prefrontal cortex and worse task performance during engagement in working memory tasks than healthy controls. Moreover, frontal and right temporal activations correlate negatively with depression severity during verbal fluency tasks (Noda et al., 2012). These studies involved middle-aged subjects, and there are surprisingly few functional studies dealing with neural abnormalities in older adults with depressive symptoms. Although the presence of neural abnormalities seems plausible in the context of age-related brain changes (Raz et al., 1997; Vermeer, Longstreth, & Koudstaal, 2007), functional findings in younger adults may not generalize to older persons (Brassen et al., 2009). We expect that NIRS can be widely used to objectively assess depressive symptom severity as a clinical biomarker for early detection and prevention of geriatric depression. However, more studies of NIRS are required to clarify the relationship between depressive symptoms and brain activity in older adults.

We hypothesized that if depressive symptoms impair brain activation and cognitive functions and alter brain structures, depressive symptom severity and oxy-Hb changes during cognitive tasks are also inter-related in older adults. Oxy-Hb changes in the prefrontal cortex during the TMT-B (Kortte, Horner, & Windham, 2002) were investigated because cognitive assessments in geriatric depression show a pattern of impairment in executive tasks and slower information processing speed, suggesting prefrontal cortex dysfunction (Butters et al., 2004; Royall et al., 2012). Indeed, NIRS has confirmed blood flow increases in the prefrontal cortex during the performance of Trail Making Test (TMT) in healthy young adults (Kubo et al., 2008). We aimed to determine whether depressive symptoms in older adults affect cerebral oxygenation during cognitive tasks using NIRS. Clarifying the relationship between depressive symptoms and brain activity may elucidate the mechanisms underlying the relationship between cognitive impairments and depression.

2. Methods

2.1. Subjects

In this study, 80 elderly subjects (mean age = 73.9 ± 5.4 years, range 65–86 years, proportion of males: 42.5%) were investigated. Medical condition and medication use were individually interviewed by a trained public health nurse using a structured check sheet. The inclusion criteria required that they speak Japanese, did not use of psychotropic drugs, have adequate hearing and visual acuities, be able to participate in the examinations, a Mini-Mental State Examination score greater than 23 (Folstein, Folstein, & McHugh, 1975), and not have a severe neurological disorder (such as AD or Parkinson's disease) or major depressive disorders (MDDs). Written informed consent was obtained from the participants in accordance with the guidelines approved by the National Center for Geriatrics and Gerontology and the Declaration of Human Rights, Helsinki, 1975. Table 1 summarizes the characteristics of the subjects of the individual groups.

Depressive symptoms were assessed using the short GDS (Burke, Roccaforte, & Wengel, 1991). GDS scores range from zero to 15. Higher scores indicate worse depression. A cut-point of 5/6 best discriminates between clinically depressed and non-depressed older adults (Dennis, Kadri, & Coffey, 2012). Subjects were divided into a depressive group (GDS greater than or equal to 6) and non-depressive group (GDS lower than 6).

2.1.1. Activation task

We used a design with four blocks consisting of the pre-task period of 10 s, task period of 20 s, resting period of 20 s, and post-task period of 10 s (Fig. 1). After the montage of the sensors, measurements were initiated to control whether the sensors were placed correctly without any artifacts. Thereafter, the participants were told to relax with their eyes opened and stare fixedly at a circle displayed on a tablet PC, which was set 40 cm in front of the participants at eye level. After the participants seemed to relax, a pre-task period of 10 s was conducted. During the task period, the tablet version of the TMT-B (Makizako et al., 2012) was conducted. In the tablet version of the TMT-B, subjects are required to touch target numbers or letters alternately between consecutive numbers and letters (Japanese Kana characters) with a touch pen (1 to/a/to 2 to/i/to 3, and so on, to 13) (Fig. 1). The color of the circle automatically changed from white to red once the subject touched the correct circle. Before NIRS, the subject was instructed how to perform the task. In the pre-task, resting, and post-task periods, participants were instructed to repeat consecutive numbers (i.e., 1–5) in their heads to stabilize the baseline conditions. Additionally, they were required to fixate a circle at the center of the screen and tap the touch pen on the table at a uniform pace. This was repeated over three trials. Numbers and letters were displayed randomly on the panel in each trial. Task performance was evaluated as average number of correct answers for consecutive numbers and letters during the task period.

Table 1
Characteristics of the study participants.

	Non-depressive group ($n = 67$)	Depressive group ($n = 13$)	p-Value
Age (years)	73.8 ± 5.3 (65–86)	74.5 ± 5.8 (68–84)	0.69
Gender (males)	28 (41.8)	6 (46.2)	0.77
MMSE (points)	26.9 ± 1.8 (24–30)	27 ± 1.7 (24–29)	0.98
GDS (points)	2.4 ± 1.6 (0–5)	9.2 ± 2.7 (6–14)	<0.001
No. of medication	2.0 ± 2.2 (0–8)	2.8 ± 2.1 (0–6)	0.28
Task performance (points)	4.6 ± 1.4 (2–8.7)	4.5 ± 1.6 (1.7–6.3)	0.77

Note: Values represent the mean ± SD or n (%). MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale.