Dement Geriatr Cogn Disord Extra 2012;2:190–199
DOI: 10.1159/000338244
Published online: April 24, 2012

Introduction

With the substantial aging of the global population, the number of people with dementia will likely increase. Alzheimer's Disease International estimated the prevalence of dementia worldwide after conducting an evidence-based Delphi consensus study [1]. The Delphi study indicated that there were 24.3 million people with dementia in the world in 2001. The number of people with dementia is expected to increase to 42.3 million by 2020 and to 81.1 million by 2040. Life expectancy has been rising, and Japanese women have attained the longest life expectancy worldwide. Moreover, the speed of aging in the Japanese population is projected to be one of the fastest in the world. The identification of subjects at risk for dementia is important for the implementation of potential treatments that may delay or prevent cognitive decline. Mild cognitive impairment (MCI) is one of several terms describing a stage between normal cognitive changes in aging and dementia and is proposed to be prodromal to dementia in some elderly people [2]. Whereas several epidemiological studies on dementia have been conducted in Japan, scarce epidemiological data exist regarding MCI, especially in terms of the prevalence of MCI examined directly alongside the prevalence of dementia. In order to examine the prevalence of both MCI and dementia, we conducted a population-based study in Ama-cho, a rural island town in western Japan.

Methods

Subjects

This study was conducted in the municipality of Ama-cho, a rural island town located 70 km from Yonago City, in the northwestern part of Japan. For about 30 years, board-certificated neurologists have visited this town to examine dementia patients along with public health nurses. To be included in the study, subjects were required to be living and to be legally residing in the town on October 1, 2009. The total population of Ama-cho was 2,434 (1,197 men and 1,237 women). The number of elderly people aged 65 years or older was 924 (374 men, mean age ± SD 77.3 ± 7.8 years), which represented 38.0% of the total population.

The study was approved by the Committee for Medical Research Ethics at Tottori University following the principles outlined in the Declaration of Helsinki. Public health nurses supported us in the identification of participants, and all participants provided written informed consent to participate in the study.

Phase 1 Study

In phase 1 of the study, a screening of subjects aged 65 years or older was performed by 5 clinical psychologists in the town. The screening included an interview with both subjects and their families that surveyed cognitive changes, as well as the application of the Mini-Mental State Examination (MMSE) [3] and Clinical Dementia Rating (CDR) [4]. Subjects with an MMSE score under 27 points and/or CDR judged to be 0.5 or more were deemed positive.

Phase 2 Study

In phase 2 of the study, the subjects who screened positive in phase 1 were examined to confirm or exclude the presence of dementia or MCI and to classify the type of dementia or MCI. All subjects in phase 2 were examined by board-certificated neurologists. To confirm the diagnosis, neurologists met with the candidates and their family members at home or in official day care centers. Assessment of these subjects involved a careful study of the medical history, a physical examination, a drug inventory, a neurological examination, and a com-

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prehensive cognitive evaluation using the Psychogeriatric Assessment Scale (PAS) [5] and the Logical Memory Test of the Wechsler Memory Scale-Revised (WMS-R) [6].

Using magnetic resonance imaging (MRI; Philips Gyroscan Intera 1.5 Tesla), we evaluated hippocampal atrophy and cerebrovascular lesions since both are important criteria for a diagnosis of dementia.

Dementia was diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition revised (DSM-IV) [7]. For patients with dementia, we analyzed dementia-related disorders using the following criteria: (1) Alzheimer's disease (AD) was defined according to the criteria of the National Institute of Neurological and Communication Disorders Association [8]; (2) vascular dementia (VaD) was defined according to the criteria of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences [9]; (3) dementia with Lewy bodies (DLB) was defined according to the consensus guidelines for the clinical diagnosis of DLB [10]; (4) Parkinson's disease dementia (PDD) was defined according to the clinical diagnostic criteria for dementia-associated Parkinson's disease [11]; (5) progressive supranuclear palsy (PSP) was defined according to the National Institute of Neurological Disorders and the Society for PSP [12]; (6) frontotemporal lobar degeneration (FTLD) was defined according to international criteria [13], and (7) possible idiopathic normal pressure hydrocephalus (iNPH) was defined according to the clinical guidelines of the Japanese Society of Normal Pressure Hydrocephalus [14]. We excluded cases of cognitive decline secondary to major depression and other mental disorders such as schizophrenia only if these were proven to be the main cause for the cognitive decline through a psychiatric interview and the patients' medical history. The severity of dementia was assessed according to a functional assessment staging test (FAST) of AD and classified as follows: FAST4 = mild, FAST5 = moderate, and FAST6/7 = severe [15].

The diagnosis of MCI was given according to the International Working Group on MCI criteria [16]. The following criteria were obligatory for the diagnosis: (1) the subject or the informant had to express some concern about the subject's cognitive function (cognitive complaints); (2) there had to be evidence of a decline in cognitive function on administered objective cognitive tasks that were abnormal for the subject's age and education level; (3) the participant had to show no impairment of functional activities of daily living, and (4) the subject did not fulfill the DSM-IV dementia criteria. Among the subjects who met the criteria for MCI, subjects having a score 1.5 SD below average on the WMS-R were diagnosed as having amnestic MCI [17]. The other subjects who did not meet the amnestic MCI criteria were diagnosed as having non-amnestic MCI. We examined all the subjects directly in phase 2 of the study.

Data Analysis

The prevalence and 95% confidence intervals (CIs) were calculated for all types of dementia as well as for MCI. In order to identify subjects with dementia out of the non-responder pool, we used data from town medical records where the diagnosis of dementia was performed by board-certificated neurologists (K.W.-I., Y.U., K.N.) in our follow-up survey or using data from the Long-term Care Insurance System of Japan.

Results

Figure 1 shows the general design of the door-to-door two-phase prevalence survey. By the prevalence date of June 1, 2010, 24 subjects (2.7%) had deceased or migrated from the town. Of the remaining 900 subjects, 723 (80.3%) received a phase 1 test. Compared to phase

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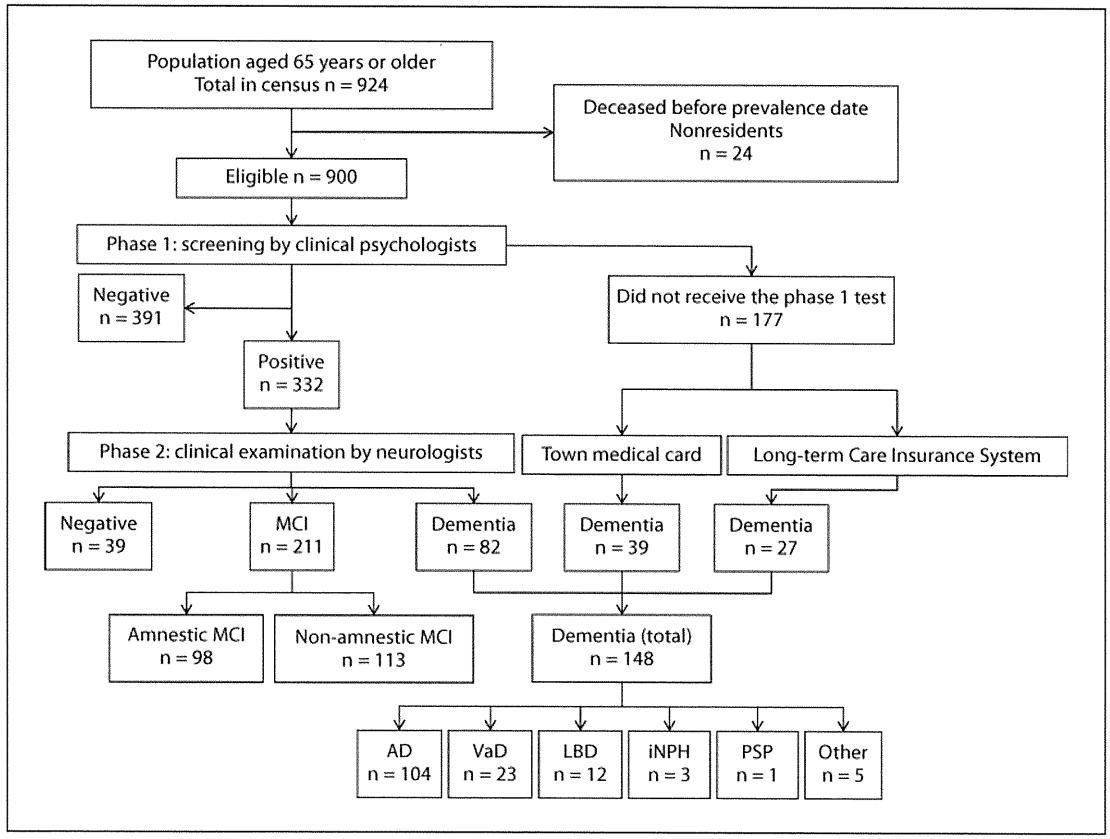

Fig. 1. General design of the door-to-door two-phase prevalence survey in Ama-cho. The number of subjects involved at each step is shown.

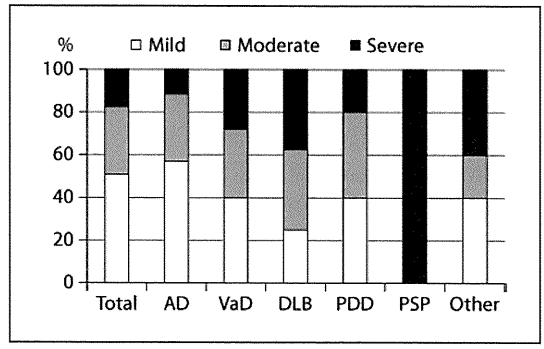

Fig. 2. Severity of dementia subtypes.

1 non-responders, responders were younger (mean 81.7 vs. 76.8 years, respectively) and were similar in gender (40.9% male vs. 37.4% male, respectively).

In total, 332 subjects were classified as having cognitive impairment in phase 1 of the study. In phase 2 of the study, 98 subjects were diagnosed with amnestic MCI, 113 subjects with non-amnestic MCI, and 82 subjects with dementia. Of the subjects who did not receive the phase 1 test, 39 subjects were diagnosed as having dementia according to data from their town medical records in our follow-up study, and 27 subjects were diagnosed as having dementia according to the Long-term Care Insurance System. The severity of dementia accord-

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Table 1. Age- and sex-specific prevalence of dementia

	Population at risk	All types of dementia		AD		VaD		DLB		PDD		iNPH		PSP		Others	
		n	prevalence	n	prevalence	n	prevalence	n	prevalence	n	prevalence	n	prevalence	n	prevalence	n	prevalence
Both genders																	
65–69 years	156	1	0.6	–	–	1	0.6	–	–	–	–	–	–	–	–	–	–
70–74 years	182	3	1.6	–	–	2	1.1	–	–	1	0.5	–	–	–	–	–	–
75–79 years	210	23	11.0	15	7.1	6	2.9	–	–	–	–	–	–	–	–	2	1.0
80–84 years	170	32	18.8	22	12.9	4	2.4	3	1.8	–	–	1	0.6	–	–	2	1.2
85–89 years	105	45	42.9	32	30.5	5	4.8	2	1.9	2	1.9	2	1.9	1	1.0	1	1.0
≥90 years	77	44	57.1	35	45.5	5	6.5	3	3.9	1	1.3	–	–	–	–	–	–
Total	900	148	16.4	104	11.6	23	2.6	8	0.9	4	0.4	3	0.3	1	0.1	5	0.6
Men																	
65–69 years	72	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
70–74 years	83	2	2.4	–	–	1	1.2	–	–	1	1.2	–	–	–	–	–	–
75–79 years	86	14	16.3	6	7.0	6	7.0	–	–	–	–	–	–	–	–	2	2.3
80–84 years	68	12	17.6	6	8.8	3	4.4	1	1.5	–	–	–	–	–	–	2	2.9
85–89 years	28	15	53.6	9	32.1	4	14.3	–	–	–	–	1	3.6	1	3.6	–	–
≥90 years	25	9	36.0	4	16.0	3	12.0	2	8.0	–	–	–	–	–	–	–	–
Total	362	52	14.4	25	6.9	17	4.7	3	0.8	1	0.3	1	0.3	1	0.3	4	1.1
Women																	
65–69 years	84	1	1.2	–	–	1	1.2	–	–	–	–	–	–	–	–	–	–
70–74 years	99	1	1.0	–	–	1	1.0	–	–	–	–	–	–	–	–	–	–
75–79 years	124	9	7.3	9	7.3	–	–	–	–	–	–	–	–	–	–	–	–
80–84 years	102	20	19.6	16	15.7	1	1.0	2	2.0	–	–	1	1.0	–	–	–	–
85–89 years	77	30	39.0	23	29.9	1	1.3	2	2.6	2	2.6	1	1.3	–	–	1	1.3
≥90 years	52	35	67.3	31	59.6	2	3.8	1	1.9	1	1.9	–	–	–	–	–	–
Total	538	96	17.8	79	14.7	6	1.1	5	0.9	3	0.6	2	0.4	–	–	1	0.2

Prevalence = Cases/100.

ing to FAST is shown in figure 2. Seventy-five individuals (50.7%) were at a mild stage, 47 (31.7%) at a moderate stage, and 26 (17.6%) at a severe stage of dementia. More than half of the subjects with AD were at a mild stage; however, more than half of the subjects with VaD were at a moderate or severe stage. Forty-five subjects with dementia were instituted in nursing homes in the town, while 16 subjects with dementia were instituted in nursing homes or hospitalized outside the town.

Prevalence of Dementia and MCI

Table 1 shows the number and prevalence of each dementia subtype. Overall, 148 subjects (52 men and 96 women) fulfilled the diagnostic criteria for dementia, yielding a crude prevalence for all dementia types of 16.4% (95% CI 14.0–18.9) in elderly individuals aged 65 years or older. The mean age was 83.1 ± 5.9 years (range 72–95) for men and 87.6 ± 6.8 years (range 68–102) for women. The age-specific prevalence of dementia displayed an exponential increase with advancing age for women. However, for men, the prevalence was highest between 85 and 89 years. The prevalence was higher in men than in women aged less than 90 years. The age-adjusted prevalence for dementia by the direct method in those aged 65 years and older compared with the population structure of Japan in 2008 was estimated to be 11.6% according to data from this study.

Of the 148 demented subjects, 104 (70.3%) were diagnosed with AD (25 men, 79 women), 23 (15.5%) with VaD (17 men, 6 women), 8 (5.4%) with DLB (3 men, 5 women), 4 (3.4%)

Dement Geriatr Cogn Disord Extra 2012;2:190–199
DOI: 10.1159/000338244
Published online: April 24, 2012

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Table 2. Age- and sex-specific prevalence of MCI

	Population at risk	All types of MCI		Amnestic MCI		Non-amnestic MCI	
		n	prevalence	n	prevalence	n	prevalence
Both genders							
65–69 years	156	26	16.7	8	5.1	18	11.5
70–74 years	182	38	20.9	18	9.9	20	11.0
75–79 years	210	56	26.7	23	11.0	33	15.7
80–84 years	170	59	34.7	33	19.4	26	15.3
85–89 years	105	25	23.8	13	12.4	12	11.4
≥90 years	77	7	9.1	3	3.9	4	5.2
Total	900	211	23.4	98	10.9	113	12.6
Men							
65–69 years	72	17	23.6	4	5.6	13	18.1
70–74 years	83	20	24.1	9	10.8	11	13.3
75–79 years	86	19	22.1	10	11.6	9	10.5
80–84 years	68	20	29.4	13	19.1	7	10.3
85–89 years	28	7	25.0	4	14.3	3	10.7
≥90 years	25	5	20.0	3	12.0	2	8.0
Total	362	88	24.3	43	11.9	45	12.4
Women							
65–69 years	84	9	10.7	4	4.8	5	6.0
70–74 years	99	18	18.2	9	9.1	9	9.1
75–79 years	124	37	29.8	13	10.5	24	19.4
80–84 years	102	39	38.2	20	19.6	19	18.6
85–89 years	77	18	23.4	9	11.7	9	11.7
≥90 years	52	2	3.8	–	–	2	3.8
Total	538	123	22.9	55	10.2	68	12.6

Prevalence = Cases/100.

with PDD (1 man, 3 women), 3 (2.0%) with iNPH (1 man, 2 women), and 1 (0.7%) with PSP (1 man). Five (3.4%) were diagnosed with mixed or other dementias not classifiable (4 men, 1 woman). The overall crude prevalence was 11.6% (95% CI 9.5–13.6) for AD and 2.6% (95% CI 1.5–3.6) for VaD. The prevalence of AD was three times higher in women than in men, while that of VaD was almost three times higher in men than in women. The AD/VaD ratio was 13.2 in women and 1.5 in men. Crude prevalences were 0.89% (95% CI 0.28–1.5) for DLB and 0.56% (95% CI 0.07–0.10) for PDD. The AD/DLB ratio in both sexes was 13.0.

Table 2 shows the number and prevalence of MCI cases. In total, 211 subjects (88 men and 123 women) fulfilled the diagnostic criteria for MCI, yielding a prevalence of 23.4% (95% CI 20.7–26.2) in elderly individuals aged 65 years or older. Crude prevalences were 10.9% (95% CI 8.9–12.9) for amnestic MCI and 12.6% (95% CI 10.4–14.7) for non-amnestic MCI. The mean age of the subjects with amnestic MCI was 78.7 ± 7.7 years for men and 78.7 ± 5.5 years for women. The mean age of the subjects with non-amnestic MCI was 74.4 ± 6.9 years for men and 78.1 ± 5.7 years for women. Whereas there was no significant difference in the mean age of the subjects with amnestic MCI between men and women, the mean age of the subjects with non-amnestic MCI was lower for men than women.

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Discussion

We conducted a population-based study on dementia and MCI in Ama-cho, a rural island town in western Japan. Ama-cho has evidently a stable population in terms of elderly population due to very low levels of migration. Three public health nurses working as permanent care providers had kept detailed information about the physical and mental health of the entire town for about 30 years. Almost all of the subjects with dementia lived in their own home or were instituted in a nursing home within the town. Thus, these features proved suitable for investigations into the prevalence of dementia.

We previously reported the crude prevalence of dementia to be 11.0% in elderly individuals aged 65 years or older [18]. In that study, screening for dementia depended upon information collected by public health nurses in the town. The screening included an interview with both subjects and their families and surveyed cognitive changes, psychiatric symptoms, personality changes, problem behaviors, activities of daily living, and psychological and medical symptoms. Recorded subjects with dementia were limited to people who were actually living in the town, meaning that people with dementia who were institutionalized in nursing homes outside the town or lived with their families outside the town were excluded. In comparison, in the present study, the screening of subjects displaying cognitive impairment based on MMSE and CDR by clinical psychologists in a phase 1 study allowed us to detect individuals with mild dementia who had not been recognized by public nurses or doctors in the town. This might account for the greater prevalence of dementia reported in this study compared to the values presented in our previous study. Further, we examined the state of cognitive function in survey non-responders according to data from their town medical card or the Long-term Care Insurance System of Japan. We could also extensively examine subjects suffering from various stages of cognitive impairment ranging from mild to severe.

This study suggests that AD is the most common and VaD is the second most common subtype of dementia in elderly individuals. We also examined the prevalence of dementia subtypes other than AD and VaD. The proportion of patients with DLB (among patients with any type of dementia) was 5.4%, while the proportion of patients with PDD was 2.7%. These values are consistent with previous estimates reported in systematic reviews [19, 20]. We did not discover any patients with FTLD in this study, although a larger number of subjects may be needed to examine the exact prevalence of FTLD in the elderly via community-based studies.

Previous reports have demonstrated the prevalence of MCI to be 4.9 and 5.3% in Japanese communities [21, 23]. Our estimate of the crude prevalence of MCI (23.4%) was higher compared to these previous reports. The non-amnestic type of MCI was included in the construct of MCI in the current study but not in previous studies, and this might account for the greater estimated prevalence of MCI. However, the crude prevalence of amnestic MCI (10.6%) in the current study is also higher compared to previous reports. Recently, Sasaki et al. [23] reported a prevalence of all types of MCI of 18.9% when using a –1.5 SD cut-off level. Taken together with our results, around 20% of elderly people aged 65 years or older might suffer from MCI in Japan. In comparison, the prevalence of MCI has also been reported in areas outside of Japan. A previous review showed that the prevalence of MCI in the general elderly population (older than 65 years) was between 3.1 and 19% in the United States and Europe [24]. The prevalence of MCI among Koreans aged 65 years or older was estimated to be 24.1% (95% CI 21.0–27.2) in a nationwide survey [25]. A systematic analysis of 22 studies in China described a pooled prevalence of MCI in elderly populations of 12.7% (95% CI 9.7–16.5) [26]. One of the challenges of studying the prevalence of MCI in population-based studies is that the reported prevalence of MCI varies between reports due to different diagnostic criteria as well as disparate assessment procedures. Another confound is that up to 44% of subjects with

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MCI at their first visit were estimated to return to normal after a year [24, 27]. Apart from neurodegeneration, numerous factors including vascular risk factors, education, psychiatric status, genetic background, use of anticholinergic drugs, and hormonal changes can affect cognitive function in elderly populations [28]. Recently, the National Institute on Aging-Alzheimer's Association workgroup (NIA-AA) and the American Heart Association/American Stroke Association have published a diagnostic recommendation of MCI due to AD [29] and a statement on vascular cognitive impairment [30], respectively. It will be important to incorporate these new criteria for MCI in future population-based studies.

There are some limitations regarding our measurements of MCI prevalence. First, we did not conduct cognitive tests in subjects who did not answer the survey. A recent community-based study describing a 2.3-fold increase in the prevalence of MCI in delayed responders compared to quick responders forces us to consider the possibility of undetected MCI in our non-responder subjects [31]. Therefore, the prevalence of MCI reported in this study likely represents a minimum value. Second, we did not perform more extensive tests measuring other cognitive domains aside from memory due to the time limitations for assessing community residents, and we classified MCI into only amnestic and non-amnestic types.

We conducted a door-to-door epidemiological study on the prevalence of mild to severe cognitive impairment in a rural island town in western Japan. With the striking increase in the elderly population, the number of individuals with dementia or preclinical stages of dementia would appear to be increasing in Japan.

Acknowledgments

This work was supported by Grants-in-Aid from the Ministry of Health, Labour and Welfare of Japan, and the Ministry of Education, Culture, Sports, Science and Technology of Japan. We thank all the inhabitants of Ama-cho for their participation in the present study. We also thank Dr. Sakakibara, Dr. Kitagawa, Ms. Hamami, Ms. Nakagawa, Ms. Hayashi, and Mr. Maeda for collecting and providing clinical information.

Disclosure Statement

The authors declare no conflicts of interest

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ARTICLE IN PRESS
PSYN-09915; No of Pages 8
Psychiatry Research: Neuroimaging xxx (2012) xxx–xxx
Contents lists available at SciVerse ScienceDirect
Psychiatry Research: Neuroimaging
journal homepage: www.elsevier.com/locate/psychresns

Reduced prefrontal cortex activation during the working memory task associated with poor social functioning in late-onset depression: Multi-channel near-infrared spectroscopy study

Shenghong Pu [a,*], Takeshi Yamada [a], Katsutoshi Yokoyama [a], Hiroshi Matsumura [a], Hideaki Mitani [b], Akiko Adachi [b], Koichi Kaneko [a], Kazuyuki Nakagome [c]

[a] Division of Neuropsychiatry, Department of Brain and Neuroscience, Tottori University Faculty of Medicine, 36-1 Nishi-cho, Yonago, Tottori, 683-8504, Japan
[b] Division of Technical Support, Tottori University Faculty of Medicine, 36-1 Nishi-cho, Yonago, Tottori, 683-8504, Japan
[c] National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo, 187-8551, Japan

ARTICLE INFO

Article history:
Received 5 July 2011
Received in revised form 27 November 2011
Accepted 29 January 2012
Available online xxxx

Keywords:
Working memory
Late-onset depression
Near-infrared spectroscopy
Social Adaptation Self-Evaluation Scale
Prefrontal cortex
Biological marker

ABSTRACT

A number of studies have demonstrated impairment of working memory (WM) in patients with major depressive disorder (MDD). However, the relationship between the underlying brain activity associated with impairment of WM function in MDD patients and their clinical characteristics is not yet clear. The objective of this study is to evaluate prefrontal hemodynamic response related to a WM task in patients with late-onset depression (LOD) and to assess the relationship between activation in the prefrontal cortex and clinical characteristics. Thirty-six patients with LOD and age- and gender-matched 35 healthy controls were recruited for the present study. We measured hemoglobin concentration changes in the prefrontal and temporal regions during a WM (2-back, letter version) task using 52-channel near-infrared spectroscopy (NIRS). LOD patients were associated with reduced increase in prefrontal and temporal activation compared with healthy controls. Moreover, reduced activation in the prefrontal and temporal regions was significantly related with lower scores in Social Adaptation Self-Evaluation Scale (SASS) in the patient group. More specifically, the reduced hemodynamic response in frontopolar region was associated with functional impairment related to interpersonal relationship factor scores of SASS. These findings suggest that hemodynamic response in prefrontal and temporal regions during a WM task may act as a biological marker of social functioning in LOD patients.

1. Introduction

Major depressive disorder (MDD) is characterized by marked deterioration in affect as well as significant impairment in cognitive function (Veiel, 1997; Austin et al., 1999), especially for older patients (Veiel, 1997; Zakzanis et al., 1998). Cognitive dysfunction has a severe impact on the patient's ability to cope with the demands of daily living. One major aspect of cognition relevant to social functioning is working memory. Working memory is an extensively researched psychological concept related to the temporary storage and processing of information (Baddeley, 1992; Baddeley, 2003). Intact working memory is essential for everyday functioning.

Many neuropsychological studies demonstrated impairment of working memory in patients with MDD (Channon et al., 1993; Beats et al., 1996; Elliott et al., 1996; Nebes et al., 2000; Landro et al., 2001; Porter et al., 2003; Harvey et al., 2004; Rose and Ebmeier, 2006). MDD patients perform poorly in the n-back task, a working memory task, compared with healthy controls, and their performance on the n-back task is inversely correlated with the severity of depressive symptoms (Harvey et al., 2004). The n-back task performance of either depressed or remitted elderly MDD patients is significantly inferior to that of control subjects, suggesting that the impairment of working memory is a trait marker of geriatric depression (Beats et al., 1996; Nebes et al., 2000).

The neural basis of working memory appears to lie in the prefrontal cortex, a region also involved in other high-level cognitive functions. Considering the significance of social functioning in psychiatric patients, elucidation of the relationship between the neural activity in prefrontal cortex underlying the working memory processes and clinical characteristics including social functioning in depression is a worthwhile focus of study.

Multi-channel near-infrared spectroscopy (NIRS) (ETG-4000, Hitachi Medical Co.), a recently developed functional neuroimaging technology, enables the non-invasive detection of spatiotemporal characteristics of brain function near the brain surface using near-infrared light (Strangman et al., 2002a; Boas et al., 2004). NIRS has enabled bedside measurement of the concentrations of oxygenated ([oxy-Hb]) and

* Corresponding author. Tel.: +81 859 6547; fax: +81 859 6549.
E-mail address: pshh0517@yahoo.co.jp (S. Pu).

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doi:10.1016/j.pscychresns.2012.01.007

deoxygenated hemoglobin ([deoxy-Hb]) in micro-blood vessels. Assuming that hematocrit is constant, the changes in [oxy-Hb], [deoxy-Hb] and also [total Hb] (summation of [oxy-Hb] and [deoxy-Hb]) are correlated with the changes in the regional cerebral blood volume (rCBV) as shown by simultaneous NIRS and positron emission tomography (PET) measurements (Hock et al., 1997; Villringer et al., 1997; Ohmae et al., 2006). In contrast to other neuroimaging methodologies, NIRS can be measured under a more restraint-free environment that is especially suitable for psychiatric patients. Indeed, NIRS has been used to assess brain functions in many psychiatric disorders (Matsuo et al., 2003; Suto et al., 2004; Kameyama et al., 2006). Recently, we showed reduced [oxy-Hb] activation of the prefrontal cortex during working memory task (2-back, letter version) in patients with major depressive disorder using NIRS, but the relationship between the hemodynamic response and severity of depressive symptoms has not been clarified. One of the possibilities is that the hemodynamic response elicited by working memory task may tap the neuronal activity in prefrontal cortex, which may be closely linked to social functioning rather than mood symptomatology per se. Assuming that [oxy-Hb] activation in the frontal and temporal regions reflects the neural activity underlying the cognitive process during 2-back task, it may not relate to depressive symptomatology straightforwardly considering the previous studies that suggest patients with depression present cognitive impairment even in their remitted stage (Kennedy et al., 2007). Moreover, cognitive impairment is acknowledged as one of the major factors that affect poor social functioning of patients with depression in their remitted stage (Kennedy et al., 2007). Accordingly it seems reasonable to consider that the [oxy-Hb] activation in the frontal and temporal regions is relevant to social functioning apart from mood symptomatology.

One of the candidate tools for assessing social functioning is Social Adaptation Self-Evaluation Scale (SASS). SASS is a 21-item scale developed for the evaluation of patients' social motivation and behavior in depression by Bosc et al. (1997); the reliability and validity of its Japanese version have already been confirmed (Goto et al., 2005). Each item is scored from 0 to 3, corresponding to minimal and maximal social adjustment, with a total score range of 0 to 60. We have demonstrated the association of reduced [oxy-Hb] activation induced by verbal fluency task in the frontopolar region with functional impairment assessed by SASS in patients with geriatric depression using 52-channel NIRS (Pu et al., 2008). It is of interest to test whether similar findings could be obtained for other cognitive tasks, which may indicate universal relevance of the prefrontal hemodynamic response to social functioning.

Previous studies, using principal component analysis, demonstrated that the 21 items in SASS could be summarized into 3 factors: interpersonal relations, interest and curiosity, and self-perception (Goto et al., 2005). One of the primary objectives of the present study was to investigate more precisely the relationship between hemodynamic response in the prefrontal cortex and clinical characteristics including total SASS scores as well as the 3 factors' scores in unmedicated patients with geriatric depression, using a 52-channel NIRS machine (ETG-4000, Hitachi Medical Co.). Taking into consideration the putative relationship between cognitive function and social functioning, and also our previous findings that failed to find significant relationship between mood symptomatology and [oxy-Hb] activation induced by 2-back task in patients with depression, although not late-onset, we hypothesized that activity in the prefrontal cortex associated with working memory process is related to social functioning rather than depressive symptoms' severity in patients with geriatric depression.

2. Subjects and methods

2.1. Subjects

Antidepressant-naïve patients with geriatric depression were recruited among outpatients of Tottori University Hospital in Tottori, Japan. The inclusion criteria were a diagnosis of a first episode of major depressive disorder and age of onset older than 65 years (LOD; late onset depression) according to DSM-IV criteria. The diagnosis was obtained using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). None of the subjects had clinical evidence of other central nervous system (CNS) disorders based on history and medical examination. Mental status was examined using the Mini-Mental State Examination (MMSE; Folstein et al., 1975) with a cut-off point of 24. Patients with previous head trauma, stroke, electroconvulsive therapy, current or previous substance abuse and psychotic symptoms were excluded from participation. We excluded patients with psychotic symptoms because those patients show a distinct cognitive profile compared to nonpsychotic depression, which is more similar to that of schizophrenia (Reichenberg et al., 2009). Thirty-six individuals (9 males, 27 females) meeting these criteria participated in the investigation.

Healthy individuals who were appropriate age, gender and MMSE matches for the LOD patients participated as controls in the present study. Inclusion criteria for controls were the same as those for the patient sample, although control participants were additionally required to have no previous or current psychiatric illness. Thirty-five individuals (11 males, 24 females) meeting these criteria participated in the study. All participants were right-handed with a value of more than 80% by the Edinburgh Inventory Index (Oldfield, 1971). Sociodemographic and clinical details are summarized in Table 1. Age, sex, educated years and MMSE scores were comparable between the two groups.

All subjects provided written consent after receiving comprehensive information on the study protocol. The study was approved by the ethics committee of Tottori University Faculty of Medicine.

2.2. Clinical evaluation

Prior to NIRS measurement, all the subjects undertook self-assessments of depression severity and the level of social functioning: the Beck Depression Inventory (BDI, Beck et al., 1961) and Social Adaptation Self-Evaluation Scale were used (SASS, Bosc et al., 1997). In addition, only patients were assessed for depression severity using the Hamilton Rating Scale for Depression (HAMD, Hamilton, 1960) by two trained psychiatrists.

2.3. Activation task

We used a 2-back task with a blocked periodic BAB design (Fig. 1) to activate brain regions specialized for maintenance components of verbal working memory, as originally described by Cohen et al. (1994). Two contrasting conditions were visually presented in 60-s

Table 1

Demographic and clinical indices	Depression ($n=36$)	Controls ($n=35$)	Group difference
	Mean (S.D.)	Mean (S.D.)	
Age (years)	71.8 (5.1)	70.9 (4.3)	NS
Gender (% females)	75.0	68.6	NS[a]
Education (years)	10.5 (2.0)	11.43 (2.1)	NS
Duration of illness (months)	4.6 (4.8)	N/A	
MMSE	27.2 (1.9)	27.8 (1.9)	NS
HAMD	19.6 (3.7)	N/A	
BDI	20.1 (8.8)	5.4 (3.9)	$P<0.001$
SASS	30.4 (6.2)	40.1 (7.2)	$P<0.001$
Task performance			
(0-back task) reaction time (RT; ms)	699.6 (173.7)	646.6 (130.2)	NS
(0-back task) sensitivity A′	0.98 (0.03)	0.99 (0.02)	NS
(2-back task) reaction time (RT; ms)	823.2 (240.2)	758.3 (232.8)	NS
(2-back task) sensitivity A′	0.72 (0.37)	0.93 (0.08)	$P<0.01$

Clinical characteristics and task performance of the study groups.
[a] Fisher's exact test.

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periods to subjects on a computer screen placed approximately one meter away from the subjects' eyes. During the period of the baseline (B) condition, subjects viewed a series of figures (0–9), which appeared one at a time, and were required to press a button with their right index finger whenever the figure "9" appeared. During the period of the activation (A) condition (2-back), subjects again viewed a series of figures (0–9) and were required to press a button with their right index finger if the currently presented figure was the same as that presented two trials previously (e.g., 5-1-5, but not 2-6-3-2 or 2-7-7). The working memory task consisted of a 60-s pre-task period (baseline (B) condition), a 60-s 2-back task period (activation (A) condition) and a 60-s post-task period (baseline (B) condition). Each period comprised 25 stimuli (5 targets, stimulus duration 1.8 s, stimulus onset asynchrony (SOA) = 2.3 s). Behavioral performance on 2-back task during measurement was monitored in terms of reaction time (RT) to target figures and sensitivity A′ (Grier, 1971). Sensitivity A′ is an index of information processing ability using both "hit rate (HR)" and "false alarm rate (FAR)" for calculation, which is expressed as below;

$$A' = 0.5 \pm (HR - FAR)(1 \pm HR - FAR)/4HR(1 - FAR).$$

High A′ implies high information processing ability. All subjects received a brief period of identical training to ensure that they understood the rule of the task prior to measurement.

2.4. NIRS measurements

The 52-channel NIRS machine (ETG-4000) measures relative changes of [oxy-Hb] and [deoxy-Hb] using two wavelengths (695 and 830 nm) of infrared light on the basis of the modified Beer–Lambert law (Yamashita et al., 1996). In this system, these [Hb] values include differential pathlength factor (DPF). The distance between pairs of source-detector probes was set at 3.0 cm and each measuring area between pairs of source-detector probes was defined as 'channel'. It is considered that the machine measures points at 2–3 cm depth from the scalp, that is, the surface of the cerebral cortex (Toronov et al., 2001; Okada and Delpy, 2003). The probes of the NIRS machine were fixed with thermoplastic 3×11 shells, with the lowest probes positioned along the T3–Fp1–Fp2–T4 line according to the international 10–20 system used in electroencephalography. The arrangement of the probes enabled the measurement of [Hb] values from bilateral prefrontal and superior temporal cortical surface regions. The correspondence of the NIRS channels and the measurement points to the cerebral cortex was confirmed by a multi-subject study of anatomical craniocerebral correlation (Okamoto et al., 2004) and was presented on the basis of the results of the virtual registration method (Tsuzuki et al., 2007).

The rate of data sampling was 0.1 s. The obtained data were analyzed using the "integral mode"; the pre-task baseline was determined as the mean over a 10-s period just prior to the task period, and the post-task baseline was determined as the mean over the last 5 s of the post-task period; linear fitting was applied to the data between these two baselines. A moving average method using a window width of 5 s was applied to remove any short-term motion artifacts. However, a moving average method alone could not remove all the artifacts and, thus, we applied a semi-automatic method for removing those data with significant artifacts. First, we applied the algorithm developed by Takizawa et al. (2008) that enables a fully automatic rejection of data with artifacts separately for each channel using quantitative evaluation, although in some cases, the algorithm appeared to even reject data without artifacts. Therefore, in the next step, two researchers, who were both blind to the clinical background of the data, judged whether or not to save those data rejected by the algorithm through consultation.

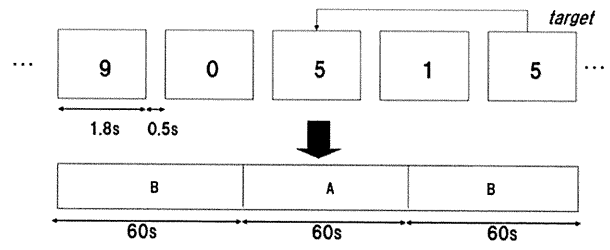

Fig. 1. The task design of 2-back task.A: Activation condition: 2-back.B: Baseline condition: 0-back, "9" as target.

Although the criteria for quantifying artifacts have not been clarified, experience shows that there are three kinds of noise artifacts (high frequency noise, low frequency noise and no signal) and body-movement artifacts show sharp signal changes compared with those of normal hemodynamics.

High frequency noise is caused by insufficient intensity of the detection light in the OT system and the digital gain and the analog gain are taken to the maximum value. Therefore, the channel(s) in this maximum value gain state are determined as artifact channel(s).

Low frequency noise has excessive FFT (Fast Fourier Transform) power in the 0.1–1 [Hz] spectrum of the oxy-Hb and the deoxy-Hb (OT system sampling rate is 10 [Hz]). In such cases we applied the FFT (Fast Fourier Transform) to the oxy-Hb(xoxy(t)) and the deoxy-Hb(xdeoxy(t)), and the FFT power is calculated (Poxy(t) and Pdeoxy(t)).

$$P_{oxy}(t) = \sqrt{\mathrm{real}\left(\sum_{j=1}^{N} x_{oxy}(t)e^{-jwt}\right)^2 + \mathrm{imag}\left(\sum_{j=1}^{N} x_{oxy}(t)e^{-jwt}\right)^2} \quad (1)$$

$$P_{deoxy}(t) = \sqrt{\mathrm{real}\left(\sum_{j=1}^{N} x_{deoxy}(t)e^{-jwt}\right)^2 + \mathrm{imag}\left(\sum_{j=1}^{N} x_{deoxy}(t)e^{-jwt}\right)^2} \quad (2)$$

We calculated the maximum value of 0.1–1 [Hz] spectrum from the Poxy(t) and Pdeoxy(t), the channel(s) above this threshold are determined as an artifact channel(s).

$$\max\left(P_{oxy}(N/100 : N/10)\right) > 15 \quad (3)$$

$$\max\left(P_{deoxy}(N/100 : N/10)\right) > 6 \quad (4)$$

Where N is the number of OT measurement points.

The no signal has no change in the concentration of oxy-Hb and deoxy-Hb in all measurement time-points. Therefore, the channel(s) in which the standard deviation value of all the measurement points is 0 are determined as an artifact channel(s).

The body-movement artifacts are sharp changes. Therefore, the channel(s) that have body-movement artifacts with oxy-Hb and total-Hb changes over 0.15 [mMmm] in over 20 successive samples (during 2 [s]) are determined as an artifact channel(s).

Consequently, the number of averaged data for each channel did not vary widely within and between the two diagnostic groups (LOD: $N = 33$–36 [mean = 35.4, S.D. = 0.85]; control: $N = 34$–35 [mean = 34.9, S.D. = 0.14]; percentage: LOD, 98.4%; control, 99.4%, n.s.).

2.5. Statistical analysis

First, the performance level (reaction time, sensitivity A′) was compared between the two groups using Wilcoxon rank sum test.

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Performance level, in case there was a significant difference between the 2 groups, was used as a covariate in the following analyses of between-group comparison. Next, for the analysis of the hemodynamic response data, [Hb] variables, which are specifically [oxy-Hb], [deoxy-Hb] and [total Hb] concentrations, of each channel were averaged for the two time segments (pre- and post-task baseline and task period). We focused on [oxy-Hb] concentrations, since [oxy-Hb] change (task period − pre- and post-task baseline period) is assumed to more directly reflect cognitive activation than [deoxy-Hb] change as shown by a stronger correlation with blood-oxygenation level-dependent signal measured by fMRI (Strangman et al., 2002b). The mean [oxy-Hb] changes were compared between the two groups (LOD and control) for each channel using Student's *t*-test. Since this amounts to 52 *t*-tests, correction for multiple comparisons was made using false discovery rate (FDR). We set the value of q specifying the maximum FDR to 0.05, so that there were no more than 5% false-positives on average (Singh and Dan, 2006). In case there was a significant between-group difference in the performance level (sensitivity A′), we performed additional analyses of co-variance (ANCOVA) using the performance level (sensitivity A′) as a covariate to the [oxy-Hb] changes, also applying FDR correction.

For LOD patients, Pearson's product moment correlation coefficients were calculated for testing the relationship between the mean [oxy-Hb] changes during the task period and the clinical characteristics such as HAMD, BDI and SASS scores for each channel. We again adopted an FDR-based procedure for the multiple testing correction in correlational analyses for 52 channels and identified those channels for which r values reached a significance level of $P<0.05$ (FDR-corrected). In accordance with a previous study (Goto et al., 2005), 21 items in SASS were separated into 3 subgroups, which represent interpersonal relations, interest and curiosity, and self-perception factors. We summed the scores of the items involved in each factor as representing "factor scores". We then examined the relationship between [oxy-Hb] changes and each factor score of SASS. Additionally, we investigated the relationship between [oxy-Hb] changes and performance level (reaction time, sensitivity A′), age and duration of illness in LOD patients using Spearman's rho because these variables did not show normal distribution. Statistical analyses were performed using SPSS 17.0 software.

3. Results

3.1. Task performance

The response sensitivity A′ ($P<0.01$) on the 2-back task during NIRS measurement was significantly worse in the LOD group than in the healthy controls. There was no significant between-group difference in reaction time (Table 1).

3.2. Cognitive activation

LOD patients were associated with a significantly smaller increase in [oxy-Hb] than controls at 31 channels (ch6–12, ch14–15, ch18, ch20–21, ch23–25, ch28–29, ch31–34, ch36, ch39, ch41–45, ch47, ch51–52; FDR-corrected *P*: 0.0005 to 0.030), distributed predominantly in the dorsolateral prefrontal and temporal regions (Fig. 2).

The between-group differences in the [oxy-Hb] changes remained significant after correcting for performance level in 27 channels (ch6–10, ch12, ch14–15, ch18, ch20–21, ch23–25, ch29, ch31–34, ch39, ch41–45, ch51–52; FDR-corrected *P*: 0.001 to 0.042) with ANCOVA using sensitivity A′ as a covariate to the [oxy-Hb] changes.

3.3. Correlation analyses (Fig. 3)

In LOD patients, the mean [oxy-Hb] changes did not show any significant correlation with demographic and clinical variables, such as age, duration of illness, BDI and HAMD in LOD patients. As for performance level, sensitivity A′ showed a significant positive correlation with the mean [oxy-Hb] changes in 16 channels (ch28, ch30, ch33–35, ch39–42, ch45–46, ch48–52; *Rho*: 0.41 to 0.55; FDR-corrected *P*: 0.001 to 0.015) located around left ventral frontal and temporal regions (Fig. 3a). There was no significant correlation between [oxy-Hb] changes and reaction time.

The mean [oxy-Hb] changes showed a significantly positive correlation with SASS total scores in 35 channels (ch1–2, ch11–13, ch16–17, ch21–28, ch30–32, ch34–36, ch38–51; *R*: 0.36 to 0.63; FDR-corrected *P*: 0.001 to 0.034), distributed extensively in the prefrontal and temporal regions.

Moreover, the mean [oxy-Hb] changes showed a significantly positive correlation with interpersonal relationship factor scores of SASS in 13 channels (ch1–2, ch5, ch15–17, ch25–27, ch30, ch36, ch39, ch47; *R*: 0.41 to 0.52; FDR-corrected *P*: 0.001 to 0.013) located predominantly in the frontopolar region (Fig. 3b), but did not show any significant relationship with other factors' scores.

In addition, sensitivity A′ showed a significant correlation with SASS total scores but not with SASS interpersonal relationship factor scores. In order to partial out the effect of variance of sensitivity A′ from the relationship between SASS total scores and NIRS data, we performed additional partial correlation analyses between SASS total scores and NIRS data using sensitivity A′ as a control variable. As a result, correlations between SASS total scores and NIRS data remained significant in 24 channels (ch1–2, ch12–13, ch16–17, ch21–22, ch25–28, ch30–32, ch36, ch38–39, ch42–43, ch45–47, ch49; *R*:0.40–0.59; *P*: 0.001–0.02; FDR-corrected), suggesting that the relationship between SASS total scores and NIRS data cannot be fully explained by the variance of sensitivity A′.

In healthy controls, the mean [oxy-Hb] changes did not show any significant correlation with age (*R*: −0.08–0.39), SASS scores (*R*: −0.28–0.07), sensitivity A′ (*Rho*: −0.16–0.29).

4. Discussion

In the present study, it was shown that [oxy-Hb] activation in the prefrontal and temporal regions during working memory task was significantly smaller in LOD patients than in age- and gender-matched healthy controls, which was in accordance with our previous study (Pu et al., 2011). However, other studies suggest increased dorsolateral prefrontal cortex activation induced by n-back working memory task (Harvey et al., 2005; Matsuo et al., 2007; Walsh et al., 2007; Fitzgerald et al., 2008), especially in conditions with high cognitive demands. On the other hand, in a recent study using n-back tasks by Garrett et al. (2011), nonpsychotic major depression patients showed lower right dorsolateral prefrontal activation than psychotic depression patients and healthy controls. The discrepancy among the studies may arise from patient characteristics, age or severity of illness as well as the amount of cognitive load upon processing the task. For example, the 2-back task adopted in the present study is expected to impose relatively small cognitive load than the n-back task used in those studies that showed hyperfrontalities in depression patients, regarding the high performance level of the normal controls, and that the 2-back task using numerical figures in the present study may well be relatively simple compared to that using letters adopted in most studies showing hyperfrontalities, and also the relative short task period of 60 s. It is also possible that the LOD patients in the present study failed to recruit additional neural resources to compensate for the impaired working memory performance because of poor vasomotor function associated with presumably higher incidence of microvascular dysregulation associated with aging, although the view is not supported by the fact that we found similar findings even in middle-aged patients that are presumed to be less affected regarding vasomotor function in our previous study (Pu et al., 2011). Among the LOD patients adopted in the present study, 24 out of 36 patients

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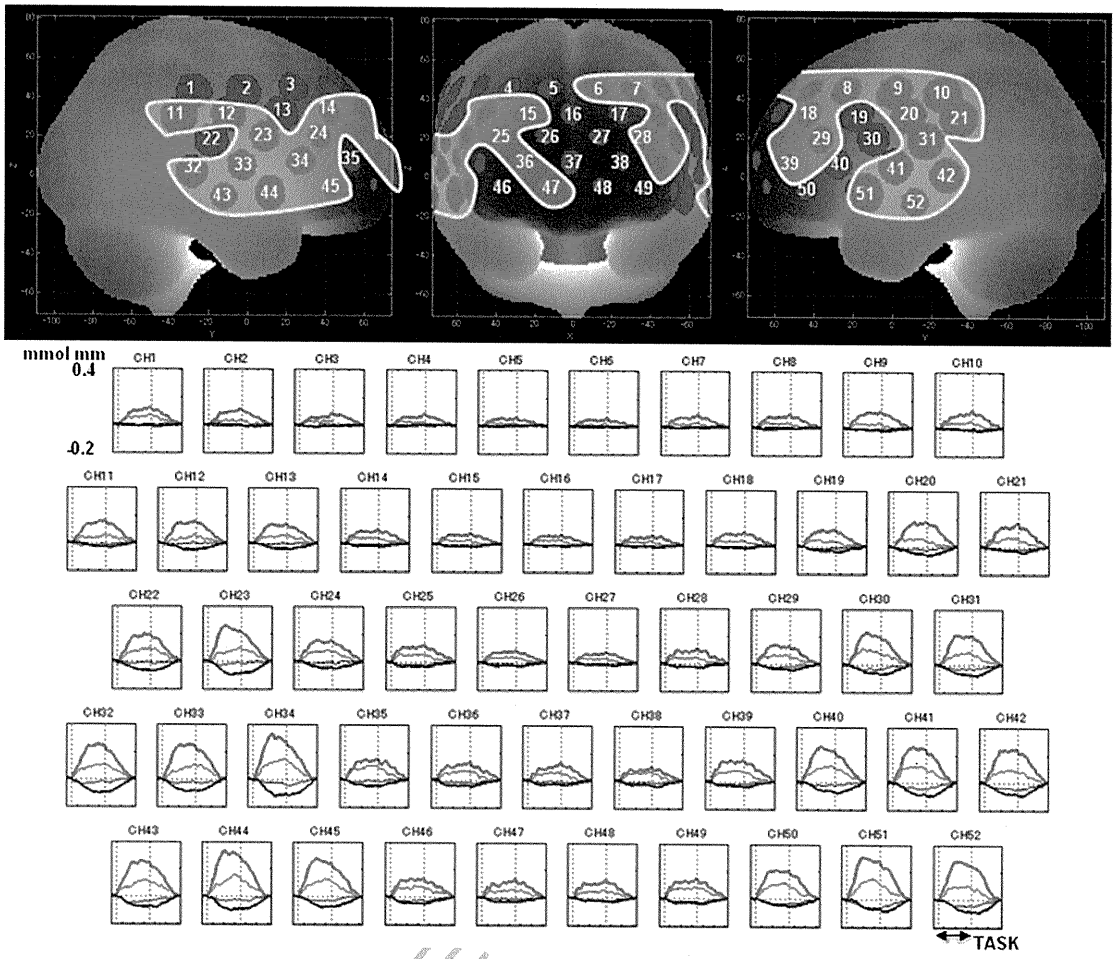

Fig. 2. Below: Grand averaged waveforms of oxygenated hemoglobin ([oxy-Hb], red line) and deoxygenated hemoglobin ([deoxy-Hb], blue line) during 60-s 2-back task (between two dotted vertical lines in each graph) in 52 channels over frontal and temporal regions measured by near-infrared spectroscopy (NIRS). Thick and thin red lines represent LOD and control groups, respectively.Above: Brain area in yellow corresponds to the NIRS channels with significantly lower levels of activation in the LOD group than in the control group. The locations of NIRS channels were probabilistically estimated and anatomically labeled in the standard brain space in accordance with Tsuzuki et al. (2007). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

fulfilled the criteria for vascular depression according to the clinical definition by Alexopoulos et al. (1997). If the poor vasomotor function in LOD patients was the main reason for the attenuated [oxy-Hb] activation, smaller activation in vascular depression patients subgroup, which was presumed to be more extensively affected regarding vasomotor function, should be observed compared to non-vascular depression patients subgroup. However, we found no significant difference between vascular and non-vascular patients subgroups in [oxy-Hb] activation in either channel, indicating that altered vasomotor function could not fully explain the group difference (P:0.08–0.99).

Moreover, we found a significant positive relationship between performance level (sensitivity A′) and hemodynamic response near left ventral prefrontal and temporal regions. Although the regions partially overlapped with those where significant hypoactivation was observed for the LOD patients compared with that for healthy controls, they were shifted more to the ventral site and were more predominant in the left hemisphere. The finding suggests that the relatively strong left ventral prefrontal and temporal activation in patients with higher performance level reflect the compensation for functional impairment in an extended area of prefrontal and temporal regions, including dorsolateral prefrontal cortex. A similar finding in schizophrenia patients was reported in a study using fMRI during n-back tasks by Tan et al. (2006), which showed that, while reduced dorsal prefrontal activation was observed in schizophrenia patients, they showed greater activation in the left ventral prefrontal cortex than healthy controls, which also correlated with accuracy. In addition, the correlations between prefrontal activation and performance accuracy occurred at the *dorsal* prefrontal cortex but not at the *ventral* prefrontal cortex in healthy controls. Similar to the schizophrenia patients in their study, it was suggested that the LOD patients in the present study required additional activation from the left ventral prefrontal cortex to improve the working memory performance, albeit inefficiently.

Interestingly, the smaller [oxy-Hb] change in the extended area including prefrontal and temporal regions induced by cognitive activation was significantly associated with severer social functioning impairment in LOD patients, even after controlling for the variance of performance level (sensitivity A′), which also showed significant correlations with both SASS total scores and NIRS data in multiple channels. The finding was similar to that obtained in our previous study using verbal fluency task (Pu et al., 2008). The 2-back task poses heavier load on working memory including more frequent context updating than verbal fluency task and verbal fluency task requires process using lexical dictionary, while both tasks require processing speed and attention concentration. Compared to our previous findings using verbal fluency task, our present findings show

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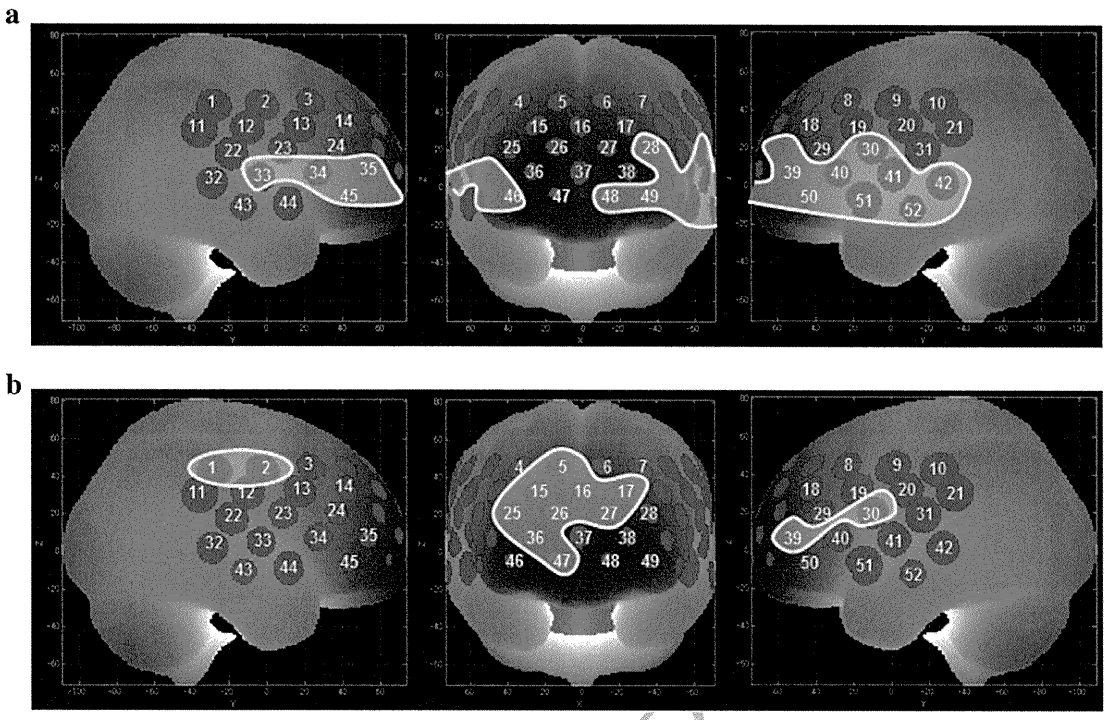

Fig. 3. a) Cortical distribution of the area where significant correlation between [oxy-Hb] changes and sensitivity A′ was suspected. Brain area in yellow corresponds to the NIRS channels, [oxy-Hb] changes of which showed significant correlation (Spearman's rho; FDR-corrected $P<0.05$) with sensitivity A′.b) Cortical distribution of the area where significant correlation between [oxy-Hb] changes and SASS factor (interpersonal relationships) scores was suspected. Brain area in yellow corresponds to the NIRS channels, [oxy-Hb] changes of which showed significant correlation (Pearson's product moment correlation; FDR-corrected $P<0.05$) with SASS factor (interpersonal relationships) scores. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

broader region of activation that significantly correlated with SASS total scores. Moreover, although we did not present the finding in our previous paper, we did not find any significant relationship between NIRS data using verbal fluency task and SASS factor scores. These discrepancies suggest that although neural activation in prefrontal and temporal regions appears to be related to social functioning irrespective of the task, working memory function may be more relevant to social functioning. Moreover, the area of activation that showed significant association with the interpersonal relationship factor scores of SASS was localized predominantly in the frontopolar region, which also showed a significant association with social functioning level in our previous study using [oxy-Hb] changes induced by verbal fluency task (Pu et al., 2008). Furthermore, Takizawa et al. (2008) similarly demonstrated the association of reduced [oxy-Hb] activation in the frontopolar region induced by verbal fluency task with functional impairment assessed by global assessment of functioning scores in schizophrenia patients. These findings taken together suggest that reduced frontopolar cortical activity may be associated universally with functional impairment in a psychiatric population with a wide diagnostic range. Although frontopolar cortex is one of the least well understood regions of the human brain, it has been suggested to provide a higher level of control to coordinate ventrolateral and dorsolateral functions in order to maximize task performance (Koechlin et al., 1999; Fletcher and Henson, 2001). One important feature of the frontopolar cortex is that the number of dendritic spines per cell and the spine density are higher than in other regions of prefrontal cortex (Jacobs et al., 2001). This indicates that the functional properties of the frontopolar cortex are more likely than those in other prefrontal regions to be involved in the integration process.

One of the shortcomings of the present study is that NIRS cannot measure the hemodynamic response in deeper regions of the brain such as dorsal cingulate and medial prefrontal cortex as well as medial temporal regions and we also did not take into consideration the neural activity in the posterior parietal cortices, which are all major constituents of the network contributing to working memory process (Owen et al., 2005). Previous fMRI studies using a cognitive challenge showed decreased activity in medial prefrontal cortex while dorsolateral prefrontal cortex and other cognitive regions were activated (Pochon et al., 2002). Harvey et al. (2005) demonstrated a trend for a greater decrease of activity in medial prefrontal cortex in control subjects compared with that in patients with major depressive disorder; they suggested that the activity gap between dorsolateral and medial prefrontal cortices may affect the processing efficiency. In addition, there have been at least two studies that suggest increased activation in the parahippocampal cortex during the working memory task compared with that in healthy controls (Walsh et al., 2007; Garrett et al., 2011). Finally, functional connectivity analyses between prefrontal and parietal cortices, which may provide important clues to clarify the network activity related to working memory process, were not conducted because we focused on the anterior regions of the brain and dismissed the posterior regions. These shortcomings should be covered by using other functional imaging techniques, although we believe that the present study using NIRS also provides a significant clinical finding that hemodynamic response in prefrontal and temporal regions during a working memory task may act as a biological marker of social functioning in LOD patients.

Another limitation arises from the possibly too low MMSE cutoff score used for excluding dementia from the depression subjects in the study. Although we adopted a traditional MMSE cutoff score of 24, which had been used in previous studies (Lincoln and Flannaghan, 2003; Rapaport et al., 2003; Schneider et al., 2003), more recent studies suggest that the score is too low to gain enough sensitivity in detecting those with cognitive impairment within geriatric depression subjects

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and that the cutoff score should be increased to 27 (Rajji et al., 2009). According to the recent report, it is possible that some of the depression patients in the present study were suffering from dementia.

In conclusion, our study suggested reduced hemodynamic response in an extended area including prefrontal and temporal regions during a working memory task in patients with LOD and compensation activation for impaired working memory performance appeared in the left ventral prefrontal and temporal regions. Moreover, the hypoactivation in prefrontal and temporal regions was associated with impaired social functioning. More specifically, the reduced hemodynamic response in frontopolar region was associated with functional impairment related to interpersonal relationships. Finally, NIRS may be an efficient clinical tool for monitoring these characteristics.

Acknowledgment

The authors thank all the participants in this study. The authors also thank the Hitachi Medical Corporation for providing us with technical advice.

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Please cite this article as: Pu, S., et al., Reduced prefrontal cortex activation during the working memory task associated with poor social functioning in late-onset..., Psychiatry Research: Neuroimaging (2012), doi:10.1016/j.pscychresns.2012.01.007

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