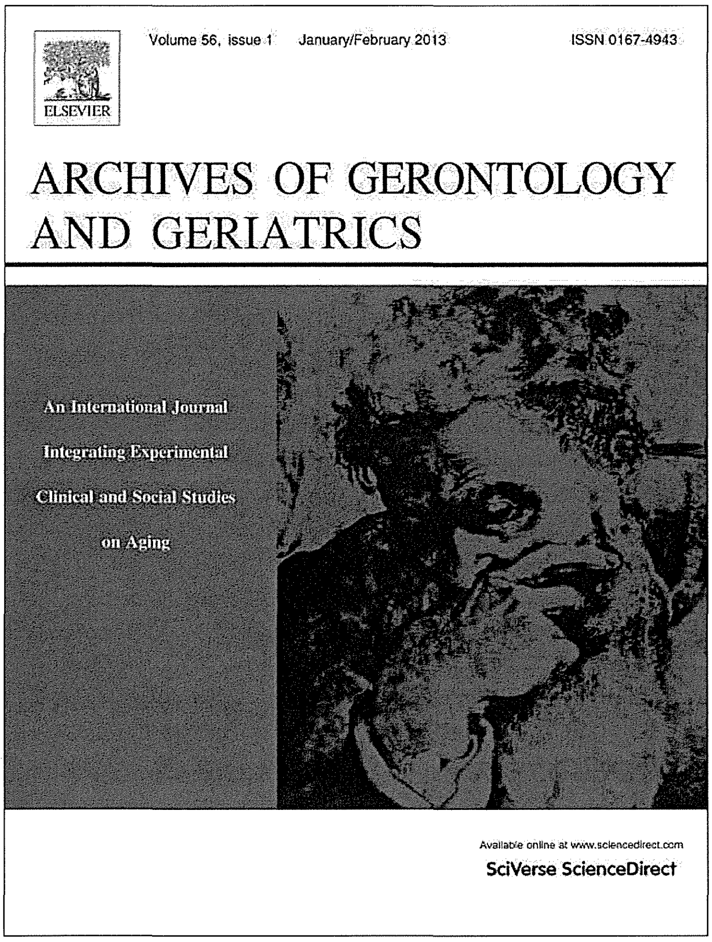


Volume 56, issue 1 January/February 2013 ISSN 0167-4943

ELSEVIER

ARCHIVES OF GERONTOLOGY AND GERIATRICS

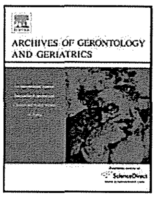
An International Journal
Integrating Experimental
Clinical and Social Studies
on Aging

Archives of Gerontology and Geriatrics 56 (2013) 118–123

Contents lists available at SciVerse ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger



Relationship between going outdoors daily and activation of the prefrontal cortex during verbal fluency tasks (VFTs) among older adults: A near-infrared spectroscopy study

Hyuma Makizako [a,b,*], Takehiko Doi [a], Hiroyuki Shimada [a], Hyuntae Park [c], Kazuki Uemura [a,b], Daisuke Yoshida [a], Kota Tsutsumimoto [a], Yuya Anan [a], Takao Suzuki [d]

[a] *Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu, Aichi 474-8511, Japan*
[b] *Japan Society for the Promotion of Science, Sumitomo-Ichibancho FS Bldg., 8 Ichibancho, Chiyoda-ku, Tokyo 102-8472, Japan*
[c] *Section for Physical Functioning Activation, Department of Functioning Activation, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu, Aichi 474-8511, Japan*
[d] *Research Institute, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu, Aichi 474-8511, Japan*

ARTICLE INFO

Article history:
Received 10 April 2012
Received in revised form 28 August 2012
Accepted 30 August 2012
Available online 17 September 2012

Keywords:
Aging
Cerebral oxygenation
Life-space
Cognition

ABSTRACT

This study sought to investigate the relationship between going outdoor daily and prefrontal cortex activation during execution of the VFT using near-infrared spectroscopy (NIRS) in community-dwelling older adults. Blood oxygenation changes in left and right prefrontal cortices were measured in twenty older adults (mean age 76.1 ± 6.7 years) by NIRS during VFT performance. In this task, participants were required to pronounce as many nouns as possible beginning with the letters "*Shi*," "*I*," and "*Re*." Changes in oxygenated hemoglobin (oxy-Hb) levels during the VFT were compared between two groups defined by the frequency of going outdoors: daily or non-daily within a week. Participants in both groups exhibited significantly increased oxy-Hb levels in the left and right prefrontal cortices during the VFT compared to a resting baseline condition. After controlling for age and gender, there were significant group-by-condition interactions on oxy-Hb levels with less activation during the execution of the VFT over both cortices in the non-daily group (left: $F = 4.76$, $p = 0.04$; right: $F = 6.32$, $p = 0.02$). These findings indicate that going outdoors daily is associated with increased activation in the prefrontal cortices during VFT performance in community-dwelling older adults.

1. Introduction

For older people, getting outdoors requires a certain level of physical and cognitive functioning. A low frequency of going out has been found to predict functional and intellectual decline among frail older adults, whereas going out frequently corresponded with improvement of baseline self-efficacy for both daily activities and health promotion (Kono, Kai, Sakato, & Rubenstein, 2004). In a recent longitudinal study, with a mean follow-up of 4.4 years, constricted living space was found to lead to decreased physical activity and social engagement, and was associated with increased risk of Alzheimer disease (AD), mild cognitive impairment (MCI), and a faster rate of global cognitive decline among older adults (James, Boyle, Buchman, Barnes, & Bennett, 2011). Thus, going out into the life-space seems to play an important role in maintaining physical and cognitive function among older adults.

Older adults with cognitive impairment, such as AD patients, demonstrate diminished activation of the prefrontal cortex during cognitive tasks compared to those who are cognitively healthy (Herrmann, Langer, Jacob, Ehlis, & Fallgatter, 2008; Li, Zheng, Wang, & Gui, 2009; Richter, Herrmann, Ehlis, Plichta, & Fallgatter, 2007). Cognitive decline is thought to be a consequence of neurodegeneration in the brain, and abnormal activation during cognitive task performance has been found to precede decline of cognitive function (Clark et al., 2012; O'Brien et al., 2010). A previous functional neuroimaging study used near-infrared spectroscopy (NIRS) to investigate the oxygenation of brain tissue during the VFT in dementia patients (Herrmann et al., 2008). The results revealed that dementia patients exhibited reduced brain activation during VFT performance, as indicated by significantly lower oxygenated hemoglobin (oxy-Hb) levels compared to control subjects. The VFT is a neuropsychological task with category-fluency and letter-fluency versions. The VFT allows an

---

* Corresponding author at: Section for Health Promotion, Department of Health and Medical Care, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu, Aichi 474-8551, Japan. Tel.: +81 562 44 5651x5082; fax: +81 562 46 8294.
E-mail address: makizako@ncgg.go.jp (H. Makizako).

0167-4943/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.archger.2012.08.017

assessment of a subject's ability to retrieve a series of nouns based on a common criterion. Performance in the VFT has been found to decline according to cognitive dysfunction, and VFT is one of the most effective neuropsychological tests to assess the risk of AD (Laws, Duncan, & Gale, 2010). The frontal lobe is essential for a range of important cognitive functions, including executive function and memory. In particular, performance in the letter version of the VFT is thought to be closely associated with frontal lobe function (Herrmann, Ehlis, & Fallgatter, 2003; Kitabayashi et al., 2001). Decreased neural activation may be a suitable predictor for the risk of cognitive decline.

Going outdoors daily is beneficial for older people, and is correlated with reduced functional decline (Jacobs et al., 2008). However, the influence of frequently going outdoors on brain activation during cognitive tasks is unknown. An increased outdoor activity, such as walking, recreation, and sport, is associated with slower age-related cognitive decline and brain atrophy in older people (Erickson et al., 2010; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001). Therefore, we hypothesized that the frequency of going outdoors may be related to age-related decline of brain activation. We aimed to test the hypothesis that going outdoors daily would exert positive effects on functional brain activation during performance of the letter version of the VFT among older adults.

2. Subjects and methods

2.1. Subjects

Twenty right-handed older adults (10 females; aged 66–89 years) living independently in the community participated in this study after giving written informed consent. None of the participants had a previous history of major psychiatric illness (e.g., schizophrenia or bipolar disorder), other serious neurological or musculoskeletal diagnoses, or clinical depression. We also excluded participants if they had a diagnosis of dementia, exhibited moderate to severe cognitive decline, were taking anti-Alzheimer's drugs, or required long-term care. This study was approved by the ethics committee of the National Center for Geriatrics and Gerontology.

2.2. Frequency of going outdoors

The frequency of going outdoors was assessed using a sub question item of the life-space assessment scale (Baker, Bodner, & Allman, 2003), which asked participants whether they had been to places in their neighborhood, and within their town during the past four weeks. The available responses were daily, four to six times a week, one to three times a week, less than once a week, or none. Participants were classified into the daily ($n = 7$) and non-daily ($n = 13$) groups based on their responses.

2.3. Other variables

Functional capacity was measured using the Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG-IC), a self-report questionnaire (Koyano, Shibata, Nakazato, Haga, & Suyama, 1991). The TMIG-IC is a multi-dimensional 13-item index developed to assess the functional capacity of older people with intact activities of daily living according to their abilities in complex activities. The total score on this index ranges from 0 to 13 points, with higher scores indicating higher functional capacity. General cognitive function was examined using the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). The MMSE was assessed by licensed and experienced clinical speech therapists.

2.4. Verbal-fluency task and procedure

For the letter version of the VFT, we used a block design with three 140-s blocks consisting of a 10-s pre-resting period, a 60-s activation period, and a 70-s post-resting period (Fig. 1). We began recording after fitting the montage of sensors to determine whether they were placed correctly, without artifacts. Participants were then told to relax with their eyes open and fixate on a circle displayed in front of them. When participants seemed to be relaxed, a baseline measurement of 10 s was conducted. In the phonemic VFT task, the participant was instructed to retrieve as many words as possible beginning with the Japanese syllabic characters (hiragana) "*Shi*," "*I*" and "*Re*," respectively, in a 60-s period (Takahashi et al., 2008). Each of these three conditions (different starting letters) lasted 60 s. There was a 70-s post-resting period after each 60-s activation period during each VFT.

2.5. NIRS measurements

Changes in oxy-Hb levels were recorded using the Spectratech OEG-16 system (Spectratech Inc., Yokohama, Japan) with 16 channels. The NIRS system used two wavelengths (approximately 770 and 840 nm) of near-infrared light, and absorption was

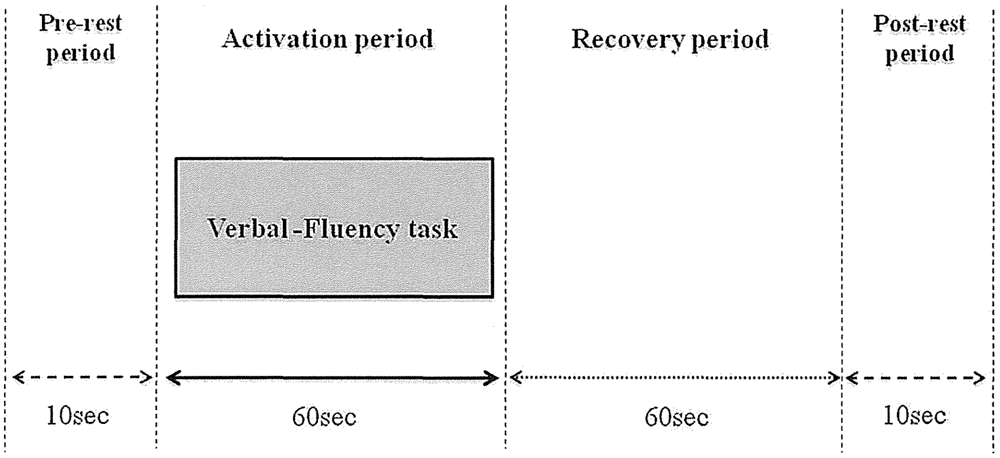


Fig. 1. Time course of one block. Total time of one block is 140 s. Each block contained a 10-s pre-resting period, a 60-s activation period, and a 70-s post-resting period. NIRS data were collected in three blocks (beginning with the Japanese syllabic characters "*Shi*," "*I*" and "*Re*," respectively).

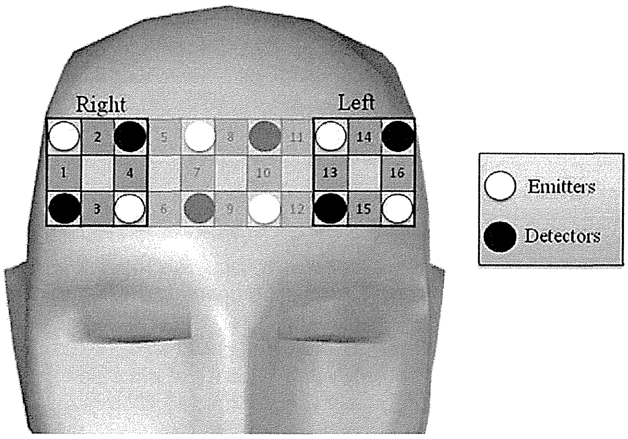


Fig. 2. Location of NIRS probes and channels. The NIRS system in this study consisted of six light sources (white) and six detector fibers (black), resulting in 16 channels of source-detector pairs. nROIs were arranged into two regions: RIFG (channels 1, 2, 3, and 4), and LIFG (channels 13, 14, 15, and 16).

recorded to estimate oxy-Hb levels. The temporal resolution was set at 650 ms. The emission probes were located 3.0 cm apart from the detector probes. This system could measure changes in oxy-Hb levels at a depth of approximately 3 cm below the scalp. Six emission and six detector probes were arranged in a 6 (wide) × 2 (long) matrix on the participant's forehead. Thus, cortical responses were obtained from a total of 16 locations. The center of the probe matrix was placed on Fpz (midpoint between Fp1 and Fp2) in accordance with the international 10/20 system used in electroencephalography. In this study, we analyzed NIRS data for the following measurement points, which were labeled as Ch1–4 for right frontal channels and Ch13–16 for left frontal channels, approximately covering the anterior and ventrolateral prefrontal cortices (Fig. 2).

2.6. Data analysis

Student's t tests and chi-square tests (to test for gender differences) were used to compare demographic characteristics between the daily and non-daily groups. For the NIRS data, a low-pass filter was set at 0.05 Hz using a fast Fourier transform (FFT) to exclude artifacts caused by minor movements of the participant, and a baseline correction was performed using linear fitting based on two baseline data: the mean across a 10-s-period just before the VFT section, and the mean across a final 10-s period of 70 s after the VFT section (Fig. 1). To determine oxy-Hb levels in the specific region of the lateral prefrontal cortex related to changes of activation during the VFT (Kameyama, Fukuda, Uehara, & Mikuni, 2004; Kameyama et al., 2006; Suto, Fukuda, Ito, Uehara, & Mikuni, 2004), regions of interest for NIRS data (nROIs) were arranged into two regions: (1) right inferior frontal gyrus (RIFG: channels 1, 2, 3, and 4); and (2) left inferior frontal gyrus (LIFG: channels 13, 14, 15, and 16) (Fig. 2) (Kita et al., 2011). Changes in oxy-Hb levels in each nROI were averaged in each participant. NIRS data were compared between the daily and non-daily groups defined by the frequency of going outdoors. The delta oxy-Hb levels during the execution of the VFT were expressed relative to that during the rest condition in each nROI, and were compared between groups using student's t tests. A repeated-measures analysis of covariance (ANCOVA) model adjusted for age and gender was used to evaluate group differences on changes in oxy-Hb levels during the VFT. Post hoc analyses were conducted using Bonferroni comparisons to compare oxy-Hb levels between resting and VFT conditions in each group. Statistical analyses were performed using SPSS for Windows, version 19.0 (SPSS, Chicago, IL, USA). Statistical significance was set at 0.05 for all analyses.

3. Results

Table 1 summarizes the characteristics of the daily and non-daily groups. There were no significant between-group differences in the characteristics, TMIG-IC, MMSE, and VFT performance. During the VFT, we found a significant increase of oxy-Hb levels over both inferior frontal gyri compared to a resting baseline condition in the daily (RIFG: baseline, −0.004 ± 0.008 mM mm; VFT, 0.258 ± 0.234 mM mm, $p = 0.03$; LIFG: baseline, −0.001 ± 0.005 mM mm; VFT, 0.275 ± 0.256 mM mm, $p = 0.02$) and non-daily (RIFG: baseline, 0.001 ± 0.003 mM mm; VFT, 0.087 ± 0.091 mM mm, $p < 0.01$; LIFG: baseline, 0.000 ± 0.006 mM mm; VFT, 0.094 ± 0.122 mM mm, $p = 0.02$) groups. The delta oxy-Hb of LIFG in the daily group was significantly higher than that in the non-daily group in the RIFG (daily, 0.262 ± 0.233 mM mm; non-daily, 0.086 ± 0.091 mM mm, $p = 0.03$) and LIFG (daily, 0.276 ± 0.253 mM mm; non-daily, 0.093 ± 0.119 mM mm, $p = 0.04$) (Fig. 3). In both inferior frontal gyri, there was a significant group-by-condition interaction on oxy-Hb levels, with higher levels in the daily group (RIFG: $F = 6.32$, $p = 0.02$; LIFG: $F = 4.76$, $p = 0.04$) even after adjusting for age and gender.

4. Discussion

The current results indicate that going outdoors daily is associated with activation in the prefrontal cortices. Subjects who go outdoors daily exhibited greater activation in the prefrontal cortices during the execution VFT performance compared to subjects who do not. These findings suggest that going outdoors may contribute to successful oxygenation during the performance of cognitive tasks.

The frequency of going outdoors is a component of the life-space and could be a useful and simple indicator for predicting changes in functional capacity among older adults (Kono et al., 2004), and walking outside the home is important for maintaining functional independence in frail older adults (Shimada et al., 2010; Simonsick, Guralnik, Volpato, Balfour, & Fried, 2005). Previous findings indicate that functional level is related to the frequency of going outside in older adults, especially frail older people (Ganguli, Fox, Gilby, & Belle, 1996; Kono & Kanagawa, 2001). Several longitudinal studies (Fujita, Fujiwara, Chaves, Motohashi, &

Table 1
Participant characteristics.

	All participants ($n = 20$)	Daily ($n = 7$)	Non-daily ($n = 13$)	p
Age, years	76.1 ± 6.7	75.6 ± 7.0	76.3 ± 7.0	0.83
Sex, %female	50.0	42.9	53.8	0.63
Body mass index, kg/m^2	24.0 ± 3.0	25.0 ± 3.3	23.5 ± 2.8	0.30
Education, years	10.7 ± 2.6	11.3 ± 2.4	10.3 ± 2.7	0.43
TMIG, score	12.2 ± 0.9	12.4 ± 0.8	12.0 ± 1.0	0.34
MMSE, score	26.1 ± 2.6	27.0 ± 2.8	25.6 ± 2.5	0.24

Note: Data are presented as mean ± SD, unless otherwise indicated.

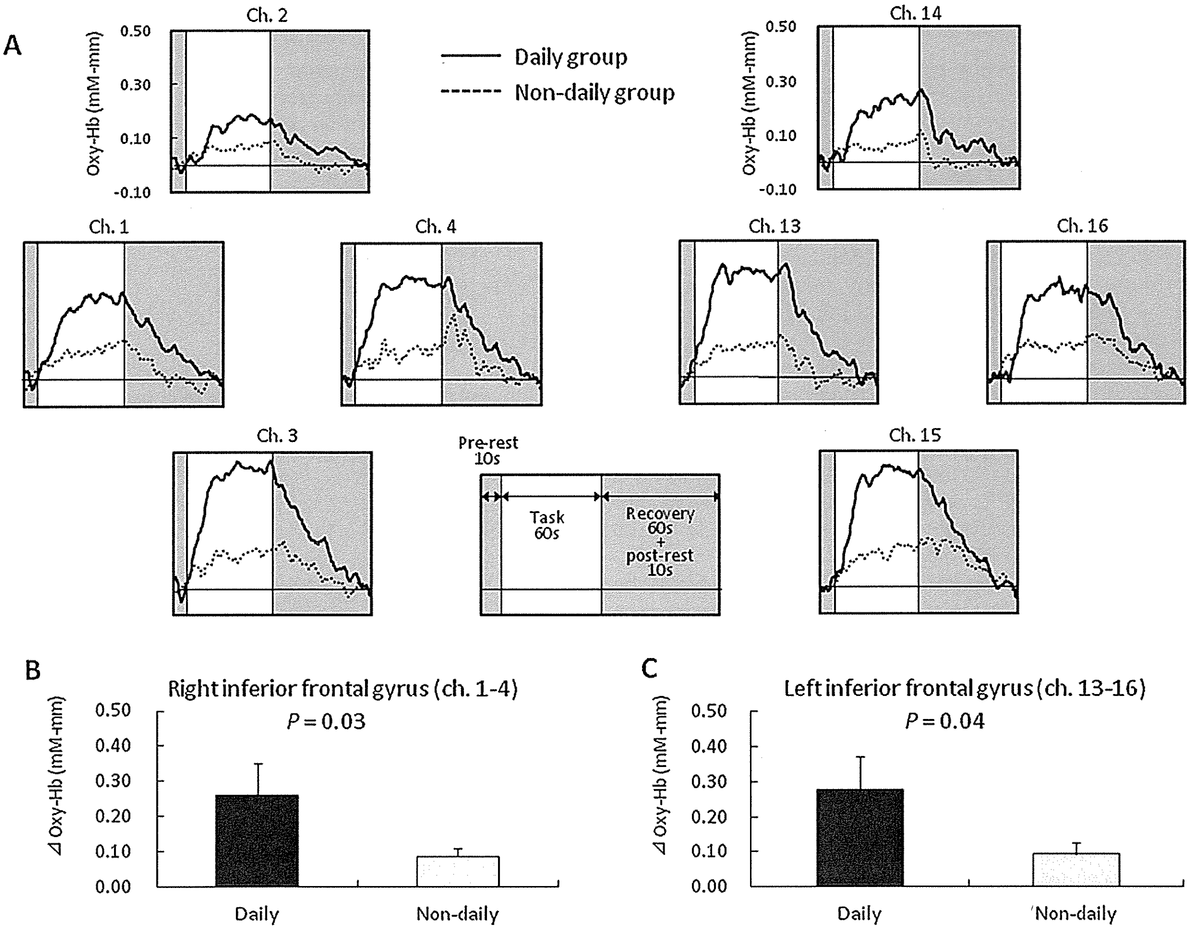


Fig. 3. Oxy-Hb values averaged for the daily (solid line) and non-daily (dotted line) groups for the RIFG (channels 1, 2, 3, and 4) and LIFG (channels 13, 14, 15, and 16) (A). Comparisons of the delta oxy-Hb (changes of oxy-Hb levels during the execution of the VFT compared with the rest condition) between the daily and non-daily groups in the RIFG (B) and the LIFG (C). Error bars represent 1 SE.

Shinkai, 2006; James et al., 2011) have indicated that a low frequency of going out predicts functional decline, even when there are no differences on physical and cognitive function at baseline. In the current study, all participants were living independently in the community with relatively good health status, and there were no differences in functional capacity and general cognitive function between the daily and non-daily groups. VFT performance did not differ between the groups. However, there was a significant group-by-condition interaction in oxy-Hb levels, with higher levels in the daily group VFT performance. These results indicate that going outdoors daily might have a positive effect on brain activation, despite some specific differences in the VFT performance. Reduced brain activation during cognitive tasks may be associated with functional decline in the future as well as a lower frequency of going outside. The current cross-sectional study is not able to answer these questions conclusively.

Rosano et al. investigated the relationship between physical activity and brain activation using functional magnetic resonance imaging (fMRI) during cognitive tasks requiring the prefrontal lobe (i.e., digit symbol substitution test). The researchers suggested that engagement in physical activity increased task-induced activation and had beneficial effects on cognitive health (Rosano et al., 2010). Indeed, recent longitudinal studies suggest that reduced life-space is related to future cognitive decline and increased risk of AD and MCI among community-dwelling older adults (Crowe et al., 2008; James et al., 2011). Frequency of attainment is included as an important factor for assessing life-space (Baker et al., 2003). A previous study indicated that greater activity levels in youth reduced the risk of cognitive impairments in aging, and that involvement in certain activities may contribute to cognitive "reserve" (Fritsch et al., 2005). In addition, an epidemiological study suggested that participation in cognitively stimulating leisure activity (e.g., attending a class, lecture, or public meeting; and participating in community, church, or social clubs) may attenuate the effects of brain lesion pathology on cognitive performance in older adults (Saczynski et al., 2008). Taken together, these findings indicate that maintaining a high frequency of outdoor activities, consequently extending the life-space, could have positive effects on brain health, preventing future cognitive decline among independent older adults.

Previous studies using NIRS have investigated the functional brain oxygenation correlates of locomotion (Holtzer et al., 2011; Miyai et al., 2001; Suzuki, Miyai, Ono, & Kubota, 2008). These studies have revealed that walking itself is associated with oxy-Hb levels in the prefrontal, primary sensorimotor, and supplementary motor areas (Holtzer et al., 2011; Miyai et al., 2001). A recent NIRS study provided surprising evidence that moderate exercise immediately increased both cognitive performance and dorsolateral prefrontal activation while executing cognitive tasks (Yanagisawa et al., 2010). These results suggest that physical activity itself may increase brain oxygenation in the frontal region, and have beneficial effects on cognitive health. Moreover, increased oxy-Hb levels in the prefrontal cortex during walking while talking were found to be greater than normal walking in both young and old individuals (Holtzer et al., 2011). In daily life, multi-task conditions are common while performing outdoor activities. To produce appropriate behavior in these situations, older adults require significantly more overall attentional resources as the difficulty of locomotion is increased compared to young adults (Lajoie, Teasdale, Bard, & Fleury, 1993; Sparrow, Bradshaw, Lamoureux, & Tirosh, 2002). Frequently going outdoors may require an increased attentional capacity for locomotor tasks, and exerting positive effects on brain activation among older adults.

Furthermore, going outdoors more frequently may also enhance a person's engagement in social interaction and activity. For example, engaging in conversation with other people is a common activity in the daily lives of most people. A previous study using NIRS reported that the frontal and superior temporal regions were activated during face-to-face conversation, with stronger activity during speaking segments in a conversation (Suda et al., 2010). Outdoor activities including walking under multi-task conditions and meeting other people and engaging in face-to-face conversation may increase brain activation, particularly in the prefrontal cortex, among older adults.

Some methodological limitations of this study should be considered. Our investigation was conducted under experimental conditions, and used a cross-sectional design. We classified participants into daily and non-daily groups based on their responses to a sub-question item of the life-space assessment scale. The group sizes were small and a relevant frequency of going outdoors was unclear. Future studies including a large sample size, longitudinal design, and regression analyses may be needed to further clarify the relationship between the frequency of going outdoors and brain activation among older adults. Despite these limitations, the results indicate that going outdoors, frequent walking, and increased physical activity are likely to be beneficial for preventing age-related decline in brain activations. Future longitudinal studies should investigate whether going outdoors has a causal role on brain health in older adults. A second limitation is that our NIRS probes only recorded from the frontal area, particularly the prefrontal cortices, meaning that the activation of other cortical areas and deep brain structures was not observed. Gait requires complex visuo-sensorimotor coordination and is associated with activation of the medial frontoparietal region, e.g., the primary sensory and motor areas, supplementary motor area, lateral premotor cortex, cingulate cortex, superior parietal lobule, precuneus, and the infratentorial region including the dorsal (Fukuyama et al., 1997; Hanakawa et al., 1999; la Fougere et al., 2010). Future research should examine the relationship between the activation of other cortical areas and the frequency of going outdoors, and should use other neuroimaging techniques (e.g., positron emission tomography, single photon emission tomography, and fMRI) to further investigate whether going outdoors daily is a beneficial behavior for neural health among the aged population. In addition, the current study included no measure of physical activity, such as a self-report inventory or a pedometer, so we were unable to accurately quantify the amount of exercise undertaken. Furthermore, the sample size of the current cross-sectional study was relatively small, limiting the generalizability of the results. Further experiments using longitudinal and interventional designs will be required for more rigorously defining the effect of going outdoors daily on aging in the brain.

5. Conclusion

Older adults in both the going outdoors daily and non-daily groups exhibited significantly increased oxy-Hb levels in the left and right prefrontal cortices during VFT performance compared to a resting baseline condition. After controlling for age and gender, there were significant group-by-condition interactions on oxy-Hb levels, with less activation during VFT performance over both cortices in the non-daily group. These findings demonstrated that going outdoors daily was associated with increased activation in the prefrontal cortices during VFT performance in community-dwelling older adults.

Conflict of interest statement

None.

Acknowledgements

This work was supported in part by a grant from the Japanese Ministry of Health, Labor and Welfare (Project for optimizing long-term care, B-3) and a Grant-in-Aid for JSPS Fellows (23-9862) from the Japan Society for the Promotion of Science.

References

Baker, P. S., Bodner, E. V., & Allman, R. M. (2003). Measuring life-space mobility in community-dwelling older adults. *Journal of the American Geriatrics Society, 51*, 1610–1614.

Clark, V. H., Resnick, S. M., Doshi, J., Beason-Held, L. L., Zhou, Y., Ferrucci, L., et al. 2012. Longitudinal imaging pattern analysis (SPARE-CD index) detects early structural and functional changes before cognitive decline in healthy older adults. *Neurobiology of Aging*, http://dx.doi.org/10.1016/j.neurobiolaging.2012.01.010, in press.

Crowe, M., Andel, R., Wadley, V. G., Okonkwo, O. C., Sawyer, P., & Allman, R. M. (2008). Life-space and cognitive decline in a community-based sample of African American and Caucasian older adults. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 63*, 1241–1245.

Erickson, K. I., Raji, C. A., Lopez, O. L., Becker, J. T., Rosano, C., Newman, A. B., et al. (2010). Physical activity predicts gray matter volume in late adulthood: The Cardiovascular Health Study. *Neurology, 75*, 1415–1422.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189–198.

Fritsch, T., Smyth, K. A., McClendon, M. J., Ogrocki, P. K., Santillan, C., Larsen, J. D., et al. (2005). Associations between dementia/mild cognitive impairment and cognitive performance and activity levels in youth. *Journal of the American Geriatrics Society, 53*, 1191–1196.

Fujita, K., Fujiwara, Y., Chaves, P. H., Motohashi, Y., & Shinkai, S. (2006). Frequency of going outdoors as a good predictors for incident disability of physical function as well as disability recovery in community-dwelling older adults in rural Japan. *Journal of Epidemiology, 16*, 261–270.

Fukuyama, H., Ouchi, Y., Matsuzaki, S., Nagahama, Y., Yamauchi, H., Ogawa, M., et al. (1997). Brain functional activity during gait in normal subjects: A SPECT study. *Neuroscience Letters, 228*, 183–186.

Ganguli, M., Fox, A., Gilby, J., & Belle, S. (1996). Characteristics of rural homebound older adults: A community-based study. *Journal of the American Geriatrics Society, 44*, 363–370.

Hanakawa, T., Katsumi, Y., Fukuyama, H., Honda, M., Hayashi, T., Kimura, J., et al. (1999). Mechanisms underlying gait disturbance in Parkinson's disease: A single photon emission computed tomography study. *Brain, 122*, 1271–1282.

Herrmann, M. J., Ehlis, A. C., & Fallgatter, A. J. (2003). Frontal activation during a verbal-fluency task as measured by near-infrared spectroscopy. *Brain Research Bulletin, 61*, 51-56.

Herrmann, M. J., Langer, J. B., Jacob, C., Ehlis, A. C., & Fallgatter, A. J. (2008). Reduced prefrontal oxygenation in Alzheimer disease during verbal fluency tasks. *American Journal of Geriatric Psychiatry, 16*, 125–135.

Holtzer, R., Mahoney, J. R., Izzetoglu, M., Izzetoglu, K., Onaral, B., & Verghese, J. (2011). fNIRS study of walking and walking while talking in young and old individuals. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 66*, 879–887.

Jacobs, J. M., Cohen, A., Hammerman-Rozenberg, R., Azoulay, D., Maaravi, Y., & Stessman, J. (2008). Going outdoors daily predicts long-term functional and health benefits among ambulatory older people. *Journal of Aging and Health, 20*, 259–272.

James, B. D., Boyle, P. A., Buchman, A. S., Barnes, L. L., & Bennett, D. A. (2011). Life space and risk of Alzheimer disease, mild cognitive impairment, and cognitive decline in old age. *American Journal of Geriatric Psychiatry, 19*, 961–969.

Kameyama, M., Fukuda, M., Uehara, T., & Mikuni, M. (2004). Sex and age dependencies of cerebral blood volume changes during cognitive activation: A multichannel near-infrared spectroscopy study. *Neuroimage, 22*, 1715–1721.

Kameyama, M., Fukuda, M., Yamagishi, Y., Sato, T., Uehara, T., Ito, M., et al. (2006). Frontal lobe function in bipolar disorder: A multichannel near-infrared spectroscopy study. *Neuroimage, 29*, 172–184.

Kita, Y., Gunji, A., Inoue, Y., Goto, T., Sakihara, K., Kaga, M., et al. (2011). Self-face recognition in children with autism spectrum disorders: A near-infrared spectroscopy study. *Brain and Development, 33*, 494–503.

Kitabayashi, Y., Ueda, H., Tsuchida, H., Iizumi, H., Narumoto, J., Nakamura, K., et al. (2001). Relationship between regional cerebral blood flow and verbal fluency in Alzheimer's disease. *Psychiatry and Clinical Neurosciences, 55*, 459–463.

Kono, A., Kai, I., Sakato, C., & Rubenstein, L. Z. (2004). Frequency of going outdoors: A predictor of functional and psychosocial change among ambulatory frail elders living at home. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 59*, 275–280.

Kono, A., & Kanagawa, K. (2001). Characteristics of housebound elderly by mobility level in Japan. *Nursing & Health Sciences, 3*, 105–111.

Koyano, W., Shibata, H., Nakazato, K., Haga, H., & Suyama, Y. (1991). Measurement of competence: Reliability and validity of the TMIG Index of Competence. *Archives of Gerontology and Geriatrics, 13*, 103–116.

la Fougere, C., Zwergal, A., Rominger, A., Forster, S., Fesl, G., Dieterich, M., et al. (2010). Real versus imagined locomotion: A [18F]-FDG PET-fMRI comparison. *Neuroimage, 50*, 1589–1598.

Lajoie, Y., Teasdale, N., Bard, C., & Fleury, M. (1993). Attentional demands for static and dynamic equilibrium. *Experimental Brain Research, 97*, 139–144.

Laws, K. R., Duncan, A., & Gale, T. M. (2010). 'Normal' semantic–phonemic fluency discrepancy in Alzheimer's disease? A meta-analytic study. *Cortex, 46*, 595–601.

Li, C., Zheng, J., Wang, J., & Gui, L. (2009). An fMRI stroop task study of prefrontal cortical function in normal aging, mild cognitive impairment, and Alzheimer's disease. *Current Alzheimer Research, 6*, 525–530.

Miyai, I., Tanabe, H. C., Sase, I., Eda, H., Oda, I., Konishi, I., et al. (2001). Cortical mapping of gait in humans: A near-infrared spectroscopic topography study. *Neuroimage, 14*, 1186–1192.

O'Brien, J. L., O'Keefe, K. M., LaViolette, P. S., DeLuca, A. N., Blacker, D., Dickerson, B. C., et al. (2010). Longitudinal fMRI in elderly reveals loss of hippocampal activation with clinical decline. *Neurology, 74*, 1969–1976.

Richter, M. M., Herrmann, M. J., Ehlis, A. C., Plichta, M. M., & Fallgatter, A. J. (2007). Brain activation in elderly people with and without dementia: Influences of gender and medication. *World Journal of Biological Psychiatry, 8*, 23–29.

Rosano, C., Venkatraman, V. K., Guralnik, J., Newman, A. B., Glynn, N. W., Launer, L., et al. (2010). Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 65*, 639–647.

Saczynski, J. S., Jonsdottir, M. K., Sigurdsson, S., Eiriksdottir, G., Jonsson, P. V., Garcia, M. E., et al. (2008). White matter lesions and cognitive performance: The role of cognitively complex leisure activity. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 63*, 848–854.

Shimada, H., Ishizaki, T., Kato, M., Morimoto, A., Tamate, A., Uchiyama, Y., et al. (2010). How often and how far do frail elderly people need to go outdoors to maintain functional capacity? *Archives of Gerontology and Geriatrics, 50*, 140–146.

Simonsick, E. M., Guralnik, J. M., Volpato, S., Balfour, J., & Fried, L. P. (2005). Just get out the door! Importance of walking outside the home for maintaining mobility: Findings from the women's health and aging study *Journal of the American Geriatrics Society, 53*, 198–203.

Sparrow, W. A., Bradshaw, E. J., Lamoureux, E., & Tirosh, O. (2002). Ageing effects on the attention demands of walking. *Human Movement Science, 21*, 961–972.

Suda, M., Takei, Y., Aoyama, Y., Narita, K., Sato, T., Fukuda, M., et al. (2010). Frontopolar activation during face-to-face conversation: An in situ study using near-infrared spectroscopy. *Neuropsychologia, 48*, 441–447.

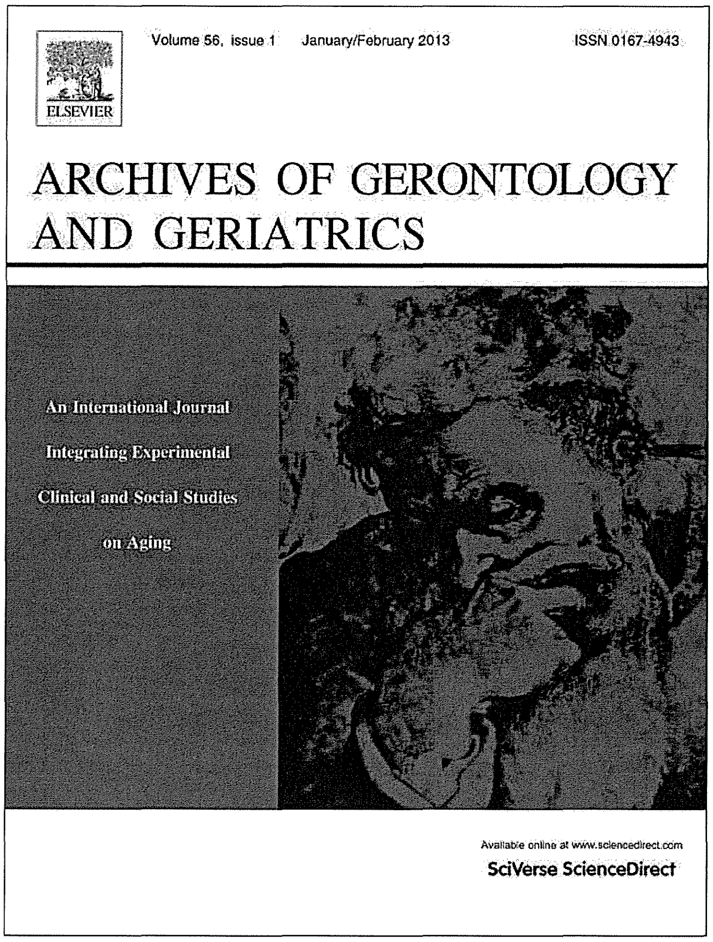
Suto, T., Fukuda, M., Ito, M., Uehara, T., & Mikuni, M. (2004). Multichannel near-infrared spectroscopy in depression and schizophrenia: Cognitive brain activation study. *Biological Psychiatry, 55*, 501–511.

Suzuki, M., Miyai, I., Ono, T., & Kubota, K. (2008). Activities in the frontal cortex and gait performance are modulated by preparation. An fNIRS study. *Neuroimage, 39*, 600–607.

Takahashi, H., Kato, M., Takano, H., Arakawa, R., Okumura, M., Otsuka, T., et al. (2008). Differential contributions of prefrontal and hippocampal dopamine D(1) and D(2) receptors in human cognitive functions. *Journal of Neuroscience, 28*, 12032–12038.

Yaffe, K., Barnes, D., Nevitt, M., Lui, L. Y., & Covinsky, K. (2001). A prospective study of physical activity and cognitive decline in elderly women: Women who walk. *Archives of Internal Medicine, 161*, 1703–1708.

Yanagisawa, H., Dan, I., Tsuzuki, D., Kato, M., Okamoto, M., Kyutoku, Y., et al. (2010). Acute moderate exercise elicits increased dorsolateral prefrontal activation and improves cognitive performance with Stroop test. *Neuroimage, 50*, 1702–1710.



Volume 56, issue 1 January/February 2013 ISSN 0167-4943

ELSEVIER

ARCHIVES OF GERONTOLOGY AND GERIATRICS

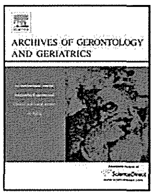
An International Journal
Integrating Experimental
Clinical and Social Studies
on Aging

Archives of Gerontology and Geriatrics 56 (2013) 104–108

Contents lists available at SciVerse ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger



Effects of multicomponent exercise on spatial–temporal gait parameters among the elderly with amnestic mild cognitive impairment (aMCI): Preliminary results from a randomized controlled trial (RCT)☆

Takehiko Doi [a,b,*], Hyuma Makizako [a], Hiroyuki Shimada [a], Daisuke Yoshida [a], Kota Tsutsumimoto [a,b], Ryuichi Sawa [c], Shogo Misu [b], Takao Suzuki [d]

[a] *Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, Japan*
[b] *Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Japan*
[c] *Department of Community Health Science, Kobe University Graduate School of Health Sciences, Japan*
[d] *Research Institute, National Center for Geriatrics and Gerontology, Japan*

ARTICLE INFO

Article history:
Received 31 July 2012
Received in revised form 18 September 2012
Accepted 18 September 2012
Available online 11 October 2012

Keywords:
Mild cognitive impairment (MCI)
Alzheimer's disease (AD)
Gait
Exercise
RCT

ABSTRACT

Exercise training has been shown to increase physical function in the elderly. However, the effects of exercise on elderly individuals with amnestic aMCI are unclear. The aim of this RCT was to investigate the effect of multicomponent exercise on gait in the elderly. Fifty elderly individuals with aMCI (age: 65–92 years) participated in the study and were randomly allocated to a multicomponent exercise or control group. Multicomponent exercise training was performed for 90 min, twice a week over six months. Gait was analyzed at baseline and after the six month intervention. Gait analysis was performed on an eleven meter walkway at each subject's comfortable walking speed. A miniature tri-axial accelerometer was attached to the L3 spinous process and was used to analyze gait speed, stride length, stride time, and the harmonic ratio (HR) (representing the smoothness of trunk movement). There were no differences in the participant characteristics or gait parameters between the groups at baseline. After adjustment for covariates the multicomponent exercise program had a significant ($p < 0.05$) effect on gait speed, stride length, and the vertical HR. Through improving gait, multicomponent exercise training improves the physical health of the elderly with aMCI.

1. Introduction

Worldwide, AD is one of the most important health issues and is therefore the focus of numerous research projects investigating the impact of interventions for preventing the progression of the disease (Ballard et al., 2011). MCI is considered a prodromal AD (Petersen, 2004; Winblad et al., 2004) and aMCI, in particular, is likely to convert to AD (Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006). Early detection of MCI and treatment interventions are important components of an AD prevention strategy (Albert et al., 2011). The decline of cognitive function is a dominant characteristic in MCI, while cognitive function is associated with physical activity or performance. Epidemiological studies demonstrated that reduced physical activity, including walking, was a risk factor for cognitive decline and dementia (Abbott et al., 2004; Weuve et al., 2004), and that motor dysfunction among people with MCI was a risk for progression to AD (Aggarwal, Wilson, Beck, Bienias, & Bennett, 2006). In addition, poor gait performances were a feature among older adults with MCI (Gillain et al., 2009; Muir et al., 2012), aMCI (Beauchet et al., 2011; Verghese et al., 2008) and AD (Allan, Ballard, Burn, & Kenny, 2005; Nadkarni, Mawji, McIlroy, & Black, 2009), and a risk factor for cognitive decline (Buracchio, Dodge, Howieson, Wasserman, & Kaye, 2010; Deshpande, Metter, Bandinelli, Guralnik, & Ferrucci, 2009; Verghese, Wang, Lipton, Holtzer, & Xue, 2007).

Exercise training is an intervention that enhances physical function among the elderly. A systematic review revealed that exercise training enhances physical function, including gait, among the elderly (Howe, Rochester, Jackson, Banks, & Blair, 2007). The positive effect of exercise training on physical performances among elderly individuals, even with cognitive impairments was confirmed in a meta-analysis (P. Heyn, Abreu, & Ottenbacher, 2004; P.C. Heyn, Johnson, & Kramer, 2008). However, the meta-analysis indicated limitations in previous

---

☆ *Clinical trial registration number: UMIN000003662.*

* Corresponding author at: Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka, Obu, Aichi 474-8511, Japan. Tel.: +81 562 44 5651;
fax: +81 562 46 8294.
E-mail address: take-d@ncgg.go.jp (T. Doi).

0167-4943/$ – see front matter. Crown Copyright © 2012 Published by Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.archger.2012.09.003

research. These included the examination of various degrees of cognitive impairment in the same study, for example, mild, moderate, and severe impairment, as well as the use of several designs of study, for example, RCT or no-RCT. Another review concluded that exercise interventions had a limited effect on physical performance (Hauer, Becker, Lindemann, & Beyer, 2006). A recent exercise training RCT reported improvements in gait among elderly individuals with dementia (Hauer et al., 2012), but limited effects on mobility among individuals with MCI (Varela, Ayan, Cancela, & Martin, 2011). Whether exercise training has positive effects on physical performances, particularly gait, among MCI is unclear. Maintenance of gait ability was shown to have beneficial effects on several health conditions as well as survival rate among the elderly (Studenski et al., 2011). In addition, walking was the dominant activity performed by the elderly and gait ability was directly related with level of physical activity (Eyler, Brownson, Bacak, & Housemann, 2003). Lower physical activity was a major risk factor for cognitive decline (Sofi et al., 2011), as well as lower gait ability (Buracchio et al., 2010; Deshpande et al., 2009; Verghese et al., 2007). Improving gait ability may play an important role in the promotion of health in elderly individuals with MCI.

The aim of this RCT was to investigate the effects of multicomponent exercise on gait in the elderly with aMCI. The reason for examining this elderly group was because longitudinal studies have suggested that patients with aMCI are more likely to progress to AD compared with patients who have non-amnestic MCI (Yaffe et al., 2006). The multicomponent exercise program included aerobic exercise, muscle strength training, walking training, and postural balance retraining, because previous reviews have suggested that multiple exercise interventions improve mobility among older adults (Howe, Rochester, Neil, Skelton, & Ballinger, 2011). Gait ability was assessed using trunk acceleration data that was acquired from miniature sensors that are feasible for use in a clinical setting (Kavanagh & Menz, 2008).

2. Materials and methods

2.1. Participants and study design

The study was a RCT conducted over six months. Participants were allocated to a multicomponent exercise intervention group (MEG; $n = 25$) or a control group (CG; $n = 25$). The allocation occurred after completion of all baseline testing. The study protocol was approved by the ethics committee of the National Center for Geriatrics and Gerontology. All subjects gave written, informed consent before participating in the study.

An initial 1543 subjects were recruited for the study from two volunteer databases using either random sampling or when they attended a medical check-up in Obu, Japan. The flow of the study is shown in Fig. 1. Assessments to determine eligibility for the study included cognitive and physical performances tests. Inclusion criteria for the study were that the participant was 65 years and older, had sufficient hearing and visual acuity to participate in the examinations, and met the conditions of aMCI. The criterion of aMCI, using the most international consensus criteria (Petersen, 2004), are summarized as follows; living independently in the community (i.e., no impairment of activities of daily living), to be intact in general cognitive function, Mini-Mental State Examination (MMSE) scores between 24 and 30 (Folstein, Folstein, & McHugh, 1975), and having memory impairment (assessed via education-adjusted scores on the Wechsler Memory Scale-Revised (WMS-R) Logical Memory II) (Wechsler, 1987). Exclusion criteria included a history of major psychiatric illness (e.g., schizophrenia or bipolar disorder), other serious neurological or musculoskeletal diagnoses. After eligibility assessments, 68 subjects did not meet the criteria (29 subjects were non-aMCI, 21 subjects did not complete all the assessments of eligibility 2, and 18 subjects did not meet the inclusion criteria other than the type of MCI), five subjects had medical problems that did not allow them to participate in the study, and 12 subjects refused to participate. Finally, 50 participants (age: 65–92 years, women: $n = 23$, 46%)

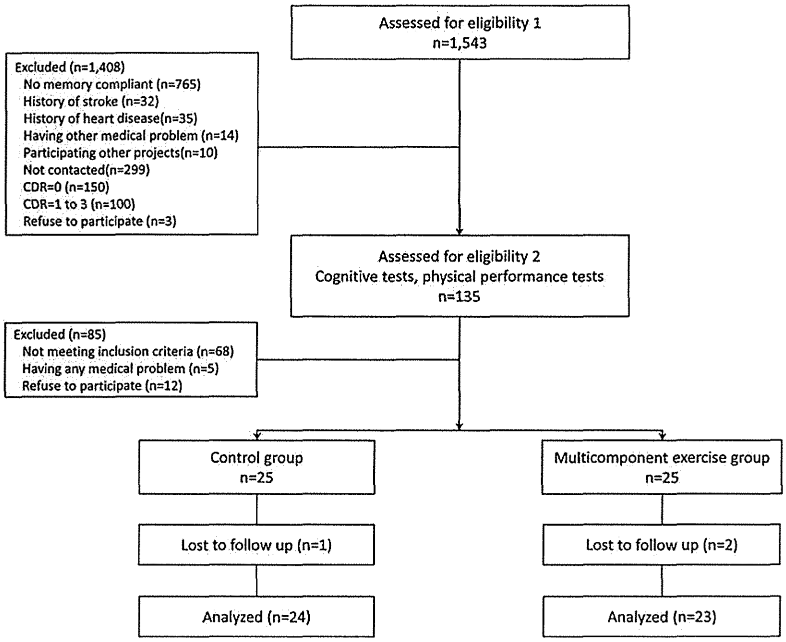


Fig. 1. The flow of the randomized controlled study.

satisfied the inclusion criteria and were allocated to either the MEG or CG.

2.2. Intervention

The six-month, multicomponent exercise program, consisted of 90-min sessions performed twice a week. The sessions included combinations of aerobic exercise, endurance walking, muscle strength training, postural balance retraining, and gait training. The average intensity of the aerobic exercise was 60% of aged-predicted maximal heart rate. Heart rate was monitored during the aerobic sessions using portable heart rate monitors (Pulse Plus, TRYTECH Co. Ltd., Tokyo, Japan). Eleven of the 40 classes during the six month intervention period included 20–30 min of consecutive outdoor walking. Postural balance exercises, such as tandem walking and side walking on balance boards, were also included in the sessions. Gait training was conducted at the same intensity as the aerobic exercise and included dual-task walking, e.g., walking whilst conducting a conversation or creating a poem. For the ladder training exercise, subjects learned to step into consecutive square segments, and were instructed to step as quickly and accurately as possible. In addition, participants performed combined exercises, e.g., circuit training including stair stepping, ladder training and endurance walking. The exercise program also included a focus on promoting exercise and behavior change. Two trained physiotherapists, with geriatric rehabilitation experience, supervised and conducted the sessions.

Each session began with a 10 min warm-up period that included dynamic and static stretching, followed by 20 min of strength training and then combinations of aerobic exercise, gait training, postural balance training for an additional 60 min. The participants were provided with an exercise and physical activity logbook and were required to perform and record daily home-based exercises and walking. To promote exercise and behavior change, the subjects were required to self-monitor their own physical activity levels using a pedometer. Participants in the CG attended two education classes about health promotion during the six month study period. The class provided information regarding healthy diet, oral care, prevention of urinary incontinence, and health checks. However, the group did not receive specific information regarding exercise, physical activity, or cognitive health.

2.3. Outcome measures

Participants were checked before each gait assessment to ensure that they were wearing appropriate size shoes. The assessment required the subjects to walk at their preferred speed on an 11-m smooth, horizontal walkway. The walkway had a two meter space at either end that allowed for acceleration and deceleration. The mid five meter walking time was measured, and gait speed was expressed in meters per second. A tri-axial accelerometer (sampling rate: 200 Hz; MVP-RF8, MicroStone, Nagano, Japan) was attached to the L3 spinous process using a belt and surgical tape. This apparatus set-up was described in detail in a previous study (Doi et al., 2012). Before measurement proceeded, the accelerometer was calibrated statically against gravity. After analog to digital transformation, signals were immediately transferred to a laptop PC (Let's Note CF-W5, Panasonic, Osaka, Japan) via a Bluetooth Personal Area Network. The working range of the accelerometer to the PC was approximately 50 m. Signal processing was performed using commercially available software (MATLAB, Release 2008b, The MathWorks Japan, Tokyo, Japan). The person processing the acceleration data was blinded to any other results. Before analysis, all acceleration data were low pass filtered (dual pass zero lag Butterworth filtered) with a cutoff frequency of 20 Hz. Stride time was recorded as the interval from an initial contact event to the next ipsilateral event. The mean stride time was calculated from five consecutive stride times. This method of determining stride time was validated previously (Zijlstra, 2004). The average stride length was determined by multiplying gait speed by mean stride duration. The HR was used to evaluate the smoothness and stability of trunk movement during gait, and the procedure for calculating HR was reported elsewhere (Menz, Lord, & Fitzpatrick, 2003; Yack & Berger, 1993). Higher HR values indicated greater stability during walking. HR was computed separately in each direction (vertical direction: VT, mediolateral direction: ML and anteroposterior direction: AP) using digital Fourier transformations.

2.4. Statistical analysis

All analyses were performed using commercially available software, IBM SPSS statistics software (Version 19; SPSS Inc., Chicago, IL, USA). The spatial–temporal gait parameters data were found to be normally distributed. The baseline spatial–temporal gait parameters for each group were compared using *t*-tests. A multivariate repeated measure analysis of variance was used to determine between group differences relating to the intervention effect, for each gait parameter, adjusting for sex and gait speed, thought to be potential confounders for the majority of the spatial–temporal gait parameters. However, for gait speed, only sex was the factor adjusted in the analysis. Statistical significance was set at $p < 0.05$ a priori.

3. Results

Of the 50 individuals enrolled in the study, 47 (94%) completed the six month follow-up and complete assessment after the intervention (24 in the MEG (96%) and 23 in the CG group (92%)). Mean adherence to the exercise program in the MEG, for the 24 participants, was 86.9%, and 19 participants displayed a greater than 80% adherence to the exercise program.

There were no significant differences ($p > 0.05$) in subject characteristics between the two groups at baseline (Table 1). Table 2 shows the results of the gait analyses at baseline and after the intervention. There were no significant differences in the gait variables between the two groups at baseline. Gait speed and stride length were increased, and stride time was shortened in both groups, after the intervention period (gait speed: $p < 0.001$, stride time: $p < 0.001$ stride length: $p < 0.001$). HR in VT was significantly improved in the MEG (VT: $p < 0.01$), while there were no significant

Table 1
Characteristics of the control and exercise groups.

	Mean (SD)	
	CG (n = 25)	MEG (n = 25)
Age, years	76.8 (6.8)	75.3 (7.5)
Men, No. (%)	14 (56.0)	13 (52.0)
Educational level, years	10.8 (2.7)	11.1 (2.4)
Diagnosis, No. (%)		
Hypertension	11 (46)	13 (52)
Heart disease	0 (0)	2 (8)
Diabetes Mellitus	3 (12)	5 (20)
Medication, 3 and over	11 (46)	10 (40)
IADL subscale of TMIG index, score	4.9 (0.3)	5.0 (0.2)
Cognitive functions		
MMSE, score	26.6 (1.6)	26.8 (1.8)
Logical Memory IIA, score	3.3 (2.7)	4.0 (2.6)

Values are numbers (proportion). IADL subscale of TMIG index = instrumental activities of daily living subscale of Tokyo Metropolitan Institute of Gerontology index.

Table 2
Effects of intervention on spatial–temporal gait parameters.

Gait parameters	Mean (SD)				Mean differences (95% CI)		Group × Time[a]	
	Baseline		After intervention		Change after intervention			
	CG	MEG	CG	MEG	CG	MEG	F	p
Gait speed	1.10 (0.20)	1.10 (0.32)	1.26 (0.21)	1.38 (0.32)	0.16 (0.10, 0.22)	0.28 (0.18, 0.38)	4.629	0.037[b]
Stride time	1.02 (0.10)	1.04 (0.11)	0.96 (0.08)	0.96 (0.09)	−0.06 (−0.08, −0.04)	−0.08 (−0.11, −0.04)	1.262	0.268
Stride length	1.12 (0.15)	1.13 (0.31)	1.20 (0.17)	1.31 (0.28)	0.09 (0.04, 0.13)	0.18 (0.11, 0.24)	7.085	0.011
HR-VT	3.04 (0.65)	2.63 (0.88)	3.05 (0.64)	3.15 (0.88)	0.01 (−0.30, 0.33)	0.52 (0.19, 0.84)	5.272	0.027
HR-ML	2.06 (0.60)	2.11 (0.67)	2.21 (0.61)	2.32 (0.79)	0.15 (−0.05, 0.36)	0.20 (−0.05, 0.46)	0.110	0.741
HR-AP	3.32 (0.83)	2.89 (1.03)	3.43 (0.71)	3.34 (1.03)	0.12 (−0.35, 0.58)	0.45 (−0.004, 0.90)	1.163	0.287

CI, confidential interval.

[a] This is the interaction effect (group × condition) using a multivariate repeated measure analysis of variance. The value of the gait variables were analyzed at baseline and after intervention using a multivariate repeated measure analysis of variance, adjusting for sex and gait speed as covariances.

[b] Adjustment for sex as a covariance against gait speed.

changes in HR in the CG in all directions. In a multivariate repeated measure analysis of variance, multicomponent exercise was associated with significant group differences in gait speed and stride length, but not stride time (gait speed: $F = 4.629$, $p = 0.037$; stride length: $F = 7.085$, $p = 0.011$), and HR in VT ($F = 5.272$, $p = 0.027$).

4. Discussion

The primary finding of our study was that a multicomponent exercise program improved gait ability among elderly individuals with aMCI. Multicomponent exercise improved gait speed, stride length, and trunk smoothness during gait, but not stride time.

This is the first study to demonstrate that an exercise program improves gait ability among elderly individuals with aMCI. Previously, age-related changes and physical functional decline were shown to decrease gait ability (Menz et al., 2003). The maintenance of gait ability was beneficial for several health conditions among the elderly (Studenski et al., 2011). In addition, lower gait ability was a risk factor for cognitive decline or dementia (Buracchio et al., 2010; Deshpande et al., 2009; Verghese et al., 2007), and a feature among older adults with aMCI (Beauchet et al., 2011; Verghese et al., 2008) and AD (Allan et al., 2005; Nadkarni et al., 2009), although the characteristic gait variables most likely to be affected in cognitively impaired individuals remains unclear. The improvement of gait ability in individuals with aMCI may have a crucial role not only for functional improvements, but also for decreasing the risk of progression to AD. Furthermore, multicomponent exercise could improve trunk smoothness during gait. Trunk movement control during gait has a crucial role for successful locomotion among the elderly. Age-related deficits or having increased fall risk was associated with decreased trunk smoothness during walking (Menz et al., 2003; Yack & Berger, 1993). Additionally, cognitive impairment was one of the major fall risks and falling incidents are a serious health problem among older adults with or without cognitive impairment (Ganz, Bao, Shekelle, & Rubenstein, 2007). Therefore, enhanced trunk smoothness may contribute to successful locomotion and be important for the elderly with aMCI.

Exercise training was shown to improve physical performances among cognitively impaired elderly individuals (P. Heyn et al., 2004; P.C. Heyn et al., 2008). However, there were several limitations of these studies, including the study sample or design of the RCT. These may have masked the benefits of exercise in for the cognitive impaired study populations (Hauer et al., 2006). Varela et al. (2011) performed a RCT study on MCI subjects and showed that aerobic exercise at different intensities did not have a significant effect on physical performance, compared to recreational therapy. In contrast, the training in the present study consisted of numerous modes of exercise in addition to aerobic exercise. In a RCT, Hauer et al. (2012) reported beneficial effects of combined physical training on motor performances, including gait ability, among individuals with dementia. The intervention was a combination of several types of training, including resistance and functional motor training as well as walking. Our results therefore support the findings of previous studies that reported positive effects of combined exercise training on physical performance, suggesting that multicomponent exercise training could improve gait ability among individuals with aMCI.

A systematic review concluded that multidimensional exercise interventions had beneficial effects on physical function such as gait ability (Howe et al., 2007). However, the content of programs and the exercise modality used varied across studies. The multicomponent exercise program developed in the present study also included gait training that may have played an important role in improving physical function, in particular the gait ability of the subjects. In addition, exercise training or enhanced physical activity has been shown to have several neuroprotective effects (Kaliman et al., 2011), and engaging in physical exercise is associated with reduced biomarkers of AD pathology, i.e., low level of Pittsburgh compound-B and cerebrospinal fluid Aβ42 (Liang et al., 2010). Therefore, a multicomponent exercise program may be a useful intervention for promoting health among elderly individuals with MCI.

There was a high level of adherence to the exercise program in the present study (mean adherence was 86.9%). This value is comparable to, as well as better than, previous exercise intervention studies on elderly individuals with MCI (Baker et al., 2010; Lautenschlager et al., 2008) or AD (Hauer et al., 2006, 2012). Only a few participants (three out of 50 participants) dropped out due to individual medical problems or refusal to participate. The exercise program was shown to be safe and no injuries were reported. Therefore the exercise program is feasible and can be supervised by physiotherapists. It is also associated with a low drop-out rate and is safe.

Our study had several limitations. First, this is a preliminary study and no follow-up data was collected after the initial post-intervention testing was performed. Second, the participants were limited to aMCI to avoid heterogeneity. To generalize the effects of multicomponent exercise among elderly with cognitive impairments, the investigation among other types of MCI, i.e., non-aMCI, or AD should be investigated further. A previous study reported that different intensities of aerobic exercise had no significant effects on individuals with MCI (Varela et al., 2011). Future research should investigate the effects of different combinations of duration and/or intensity of exercise interventions to determine the most beneficial exercise training for elderly individuals with aMCI. Additionally, methodology used in gait analysis using an accelerometer is variable in previous studies, with variations in the length of walkway, amount of data, and/or sampling rate used. Further study is required to determine the optimal methodology to evaluate the effects of intervention on gait. Finally, outcomes other than gait ability, such as the health benefits of increasing physical activity, should be investigated among elderly individuals with MCI.

5. Conclusions

In conclusion, a multicomponent exercise program had positive effects on gait ability, including trunk smoothness during walking, among elderly individuals with aMCI. Additional studies are required to clarify the effects of exercise training on gait ability including the control of trunk movement.

Conflicts of interest

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

Acknowledgments

This work was supported by a grant from the Japanese Ministry of Health, Labour and Welfare (Project for optimizing long-term care; B-3) to T.S. and Grant-in-Aid for Research Activity Start-up (22800093) to T.D. in Japan. The authors wish to acknowledge Dr. Soichiro Hirata and Dr. Hiroshi Ando for their valuable advice on methodology and data analysis.

References

Abbott, R. D., White, L. R., Ross, G. W., Masaki, K. H., Curb, J. D., & Petrovitch, H. (2004). Walking and dementia in physically capable elderly men. *Journal of the American Medical Association, 292*, 1447–1453.

Aggarwal, N. T., Wilson, R. S., Beck, T. L., Bienias, J. L., & Bennett, D. A. (2006). Motor dysfunction in mild cognitive impairment and the risk of incident Alzheimer disease. *Archives of Neurology, 63*, 1763–1769.

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers & Dementia, 7*, 270–279.

Allan, L. M., Ballard, C. G., Burn, D. J., & Kenny, R. A. (2005). Prevalence and severity of gait disorders in Alzheimer's and non-Alzheimer's dementias. *Journal of the American Geriatrics Society, 53*, 1681–1687.

Baker, L. D., Frank, L. L., Foster-Schubert, K., Green, P. S., Wilkinson, C. W., McTiernan, A., et al. (2010). Effects of aerobic exercise on mild cognitive impairment a controlled trial. *Archives of Neurology, 67*, 71–79.

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. *Lancet, 377*, 1019–1031.

Beauchet, O., Thiery, S., Gautier, J., Fantino, B., Annweiler, C., & Allali, G. (2011). Association between high variability of gait speed and mild cognitive impairment: A cross-sectional pilot study. *Journal of the American Geriatrics Society, 59*, 1973–1974.

Buracchio, T., Dodge, H. H., Howieson, D., Wasserman, D., & Kaye, J. (2010). The trajectory of gait speed preceding mild cognitive impairment. *Archives of Neurology, 67*, 980–986.

Deshpande, N., Metter, E. J., Bandinelli, S., Guralnik, J., & Ferrucci, L. (2009). Gait speed under varied challenges and cognitive decline in older persons: A prospective study. *Age and Ageing, 38*, 509–514.

Doi, T., Makizako, H., Shimada, H., Yoshida, D., Ito, K., Kato, T., et al. (2012). Brain atrophy and trunk stability during dual-task walking among older adults. *Journal of Gerontology Series A: Biological Science and Medical Science, 67*, 790–795.

Eyler, A. A., Brownson, R. C., Bacak, S. J., & Housemann, R. A. (2003). The epidemiology of walking for physical activity in the United States. *Medicine and Science in Sports and Exercise, 35*, 1529–1536.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189–198.

Ganz, D. A., Bao, Y., Shekelle, P. G., & Rubenstein, L. Z. (2007). Will my patient fall? *Journal of the American Medical Association, 297*, 77–86.

Gillain, S., Warzee, E., Lekeu, F., Wojtasik, V., Maquet, D., Croisier, J. L., et al. (2009). The value of instrumental gait analysis in elderly healthy, MCI or Alzheimer's disease subjects and a comparison with other clinical tests used in single and dual-task conditions. *Annals of Physical and Rehabilitation Medicine, 52*, 453–474.

Hauer, K., Becker, C., Lindemann, U., & Beyer, N. (2006). Effectiveness of physical training on motor performance and fall prevention in cognitively impaired older persons: A systematic review. *American Journal of Physical Medicine & Rehabilitation/Association of Academic Physiatrists, 85*, 847–857.

Hauer, K., Schwenk, M., Zieschang, T., Essig, M., Becker, C., & Oster, P. (2012). Physical training improves motor performance in people with dementia: A randomized controlled trial. *Journal of the American Geriatrics Society, 60*, 8–15.

Heyn, P., Abreu, B. C., & Ottenbacher, K. J. (2004). The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis. *Archives of Physical Medicine and Rehabilitation, 85*, 1694–1704.

Heyn, P. C., Johnson, K. E., & Kramer, A. F. (2008). Endurance and strength training outcomes on cognitively impaired and cognitively intact older adults: A meta-analysis. *Journal of Nutrition, Health and Aging, 12*, 401–409.

Howe, T. E., Rochester, L., Jackson, A., Banks, P. M., & Blair, V. A. (2007). Exercise for improving balance in older people. *Cochrane Database of Systematic Reviews*, CD004963.

Howe, T. E., Rochester, L., Neil, F., Skelton, D. A., & Ballinger, C. (2011). Exercise for improving balance in older people. *Cochrane Database of Systematic Reviews, 11*, CD004963.

Kaliman, P., Parrizas, M., Lalanza, J. F., Camins, A., Escorihuela, R. M., & Pallas, M. (2011). Neurophysiological and epigenetic effects of physical exercise on the aging process. *Ageing Research Reviews, 10*, 475–486.

Kavanagh, J. J., & Menz, H. B. (2008). Accelerometry: A technique for quantifying movement patterns during walking. *Gait and Posture, 28*, 1–15.

Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J. G., et al. (2008). Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease – A randomized trial. *Journal of the American Medical Association, 300*, 1027–1037.

Liang, K. Y., Mintun, M. A., Fagan, A. M., Goate, A. M., Bugg, J. M., Holtzman, D. M., et al. (2010). Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Annals of Neurology, 68*, 311–318.

Menz, H. B., Lord, S. R., & Fitzpatrick, R. C. (2003). Age-related differences in walking stability. *Age and Ageing, 32*, 137–142.

Muir, S. W., Speechley, M., Wells, J., Borrie, M., Gopaul, K., & Montero-Odasso, M. (2012). Gait assessment in mild cognitive impairment and Alzheimer's disease: The effect of dual-task challenges across the cognitive spectrum. *Gait & Posture, 35*, 96–100.

Nadkarni, N. K., Mawji, E., McIlroy, W. E., & Black, S. E. (2009). Spatial and temporal gait parameters in Alzheimer's disease and aging. *Gait and Posture, 30*, 452–454.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*, 183–194.

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., et al. (2011). Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *Journal of Internal Medicine, 269*, 107–117.

Studenski, S., Perera, S., Patel, K., Rosano, C., Faulkner, K., Inzitari, M., et al. (2011). Gait speed and survival in older adults. *Journal of the American Medical Association, 305*, 50–58.

Varela, S., Ayan, C., Cancela, J. M., & Martin, V. (2011). Effects of two different intensities of aerobic exercise on elderly people with mild cognitive impairment: A randomized pilot study. *Clinical Rehabilitation, 26*, 442–450.

Verghese, J., Robbins, M., Holtzer, R., Zimmerman, M., Wang, C., Xue, X. N., et al. (2008). Gait dysfunction in mild cognitive impairment syndromes. *Journal of the American Geriatrics Society, 56*, 1244–1251.

Verghese, J., Wang, C. L., Lipton, R. B., Holtzer, R., & Xue, X. N. (2007). Quantitative gait dysfunction and risk of cognitive decline and dementia. *Journal of Neurology, Neurosurgery and Psychiatry, 78*, 929–935.

Wechsler, D. (1987). *Wechsler memory scale-revised manual.* San Antonio, TX: The Psychological Corporation.

Weuve, J., Kang, J. H., Manson, J. E., Breteler, M. M., Ware, J. H., & Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *Journal of the American Medical Association, 292*, 1454–1461.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., et al. (2004). Mild cognitive impairment-beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine, 256*, 240–246.

Yack, H. J., & Berger, R. C. (1993). Dynamic stability in the elderly: Identifying a possible measure. *Journal of Gerontology, 48*, M225–M230.

Yaffe, K., Petersen, R. C., Lindquist, K., Kramer, J., & Miller, B. (2006). Subtype of mild cognitive impairment and progression to dementia and death. *Dementia and Geriatric Cognitive Disorders, 22*, 312–319.

Zijlstra, W. (2004). Assessment of spatio-temporal parameters during unconstrained walking. *European Journal of Applied Physiology, 92*, 39–44.

Geriatrics Gerontology INTERNATIONAL Medline Indexed

Geriatr Gerontol Int 2013; **13:** *83–89*

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Characteristics of cognitive function in early and late stages of amnestic mild cognitive impairment

Takehiko Doi,[1,7] Hiroyuki Shimada,[1] Hyuma Makizako,[1] Daisuke Yoshida,[1] Hiroshi Shimokata,[2] Kengo Ito,[3] Yukihiko Washimi,[4] Hidetoshi Endo[5] and Takao Suzuki[6]

[1]Section for Health Promotion, Department of Health and Medical Care, [2]Department for Development of Preventive Medicine, [3]Department of Clinical and Experimental Neuroimaging, Center for Development of Advanced Medicine for Dementia, Departments of [4]Cognitive Disorders and [5]Comprehensive Geriatric Medicine, Hospital of National Center for Geriatrics and Gerontology, [6]Research Institute, National Center for Geriatrics and Gerontology, Obu, Aichi, and [7]Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Hyogo, Japan

Aim: The detection of the early stages in amnesic mild cognitive impairment (aMCI) is considered important in diagnosing progression to Alzheimer's disease. The current study sought to investigate differences in cognitive function between control subjects with no memory loss (control), and subjects in the early stage of aMCI (EMCI) and late stage of aMCI (LMCI).

Methods: A total of 100 community-dwelling older adults aged 65 years and over were recruited from 1543 potential subjects. Subjects were classified into three groups based on the degree of objective memory impairment; control ($n = 29$), EMCI ($n = 34$) and LMCI ($n = 37$). Multiple neuropsychological tests were carried out to examine cognitive function.

Results: The EMCI individuals showed lower cognitive function relative to controls; not only in logical memory, but also in letter fluency ($P < 0.05$). There were no significant differences in neuropsychological scores between the EMCI and LMCI groups, except for category fluency and logical memory. In addition, the EMCI subjects' logical memory score showed a significant relationship with letter fluency, category fluency and digit span backward test performance ($P < 0.05$).

Conclusions: These results suggest that the application of multiple neuropsychological tests might be useful in diagnosing older adults with EMCI and LMCI. **Geriatr Gerontol Int 2013; 13: 83–89.**

Keywords: cognitive function, dementia, executive function, memory, mild cognitive impairment.

Introduction

Mild cognitive impairment (MCI) is a prodromal condition of Alzheimer's disease (AD). It is a reversible state that can improve or progress to AD. Indeed, amnestic MCI (aMCI) has a particularly high risk of progression to AD compared with normal aging.[1–3] MCI has become increasingly well understood in the past decade, although some studies have produced inconsistent results.[4] This variation in results might a result of the heterogeneity of MCI, particularly of aMCI.[4–6] To detect the earlier stages of aMCI, the severity of clinical impairment and pathology of this condition need to be clarified. To characterize an extended range of MCI to broaden the understanding of the early stages of AD, conventional stages of aMCI are considered to represent a late stage of aMCI (LMCI), and the gap between cognitively normal and LMCI is considered to represent the early stage of aMCI (EMCI).[7]

Memory deterioration is the core characteristic of both MCI and AD, and is strongly related to pathology in the medial temporal lobe (MTL).[6,8,9] Although the volume in the MTL can show decreases according to the spectrum of AD, predicting conversion to AD, the functional changes in the brain are thought to proceed non-linearly. MCI patients with some atrophy have been reported to show hyperactivation in the MTL compared with normal controls during a memory task, whereas MCI patients whose conditions were closer to AD showed hypoactivation similar to that found in AD

Accepted for publication 8 March 2012.

Correspondence: Dr Takehiko Doi PhD, Section for Health Promotion, Department of Health and Medical Care, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, 35 Gengo Morioka, Obu, Aichi 474-8511, Japan. Email: take-d@ncgg.go.jp

doi: 10.1111/j.1447-0594.2012.00865.x

patients.[5,6] These abnormal activations were found to correspond with the severity of memory decline in MCI, and compensation in the brain network might affect the severity of cognitive decline in MCI. However, the characteristics of cognitive function in the earlier stages of MCI, such as EMCI, have not been clarified.

Etiological data have confirmed not only a functional decline of memory in aMCI, but also other cognitive functional decline; for example, executive dysfunction in aMCI has been described as a risk factor for conversion to AD.[10–12] The declines of memory and other cognitive functions in MCI might reflect the abnormal activity of multiple domains in the brain. Memory is not only dependent on the pathology in MTL, but also on the connectivity of the MTL with the cingulate gyrus, frontal lobe and prefrontal lobe.[13–16] The loss of this connectivity in this neural network is linked to decreased cognitive function in aMCI.[13,17] Furthermore, in addition to the contribution of the MTL regions, decreased thickness in the prefrontal cortex and the posterior cingulate cortex has strong associations with lower memory and executive function in aMCI,[18] and lower executive function interfaces with memory performance in aMCI.[19] However, the characteristics of cognitive function, including executive function in EMCI, and the relationships between memory loss and other cognitive dysfunctions in EMCI remain unclear.

In the current preliminary study, we sought to compare cognitive function between EMCI and LMCI subjects. In addition, we wanted to determine the association between memory and other cognitive functions in elderly adults with EMCI or LMCI. Multiple neuropsychological tests measuring attention, verbal fluency, visual memory and logical memory were used to examine cognitive function.

Materials and methods

Participants

Participants were recruited from two volunteer databases ($n = 1543$), which included elderly adults aged 65 years and over who were selected by random sampling or who attended a health check carried out at a health center in Obu in 2009. The strata used for the stratified random sampling were age and sex. In the first eligibility assessment for the present study, 528 potential participants with a Clinical Dementia Rating of 0.5, or reporting memory complaints, were enrolled. A total of 165 participants responded to the second eligibility assessment, whereas 100 completed the assessment and met the inclusion criteria. To meet the inclusion criteria, participants had to be living independently in the community, be Japanese-speaking, possess adequate hearing and visual acuity, and be able to participate in the examinations. Additionally, general cognitive function was found to be intact in participants who had Mini-Mental State Examination (MMSE) scores between 24 and 30.[20] The exclusion criteria were: a history of major psychiatric illness, other serious neurological or musculoskeletal diagnoses and depression (Geriatric Depression Scale [GDS] score ≥10[21]). The core concepts of aMCI in the present study were according to the Peterson's internationally accepted criteria:[22] having memory complaints and objective memory impairment, being independent in activities of daily living, preserved general cognitive function, and no dementia. The definition of objective memory impairment varies among previous reports. In the current study, we defined objective memory impairment using memory scores in the Wechsler Memory Scale-Revised (WMS-R) Logical Memory II,[23] based on the criteria of the Alzheimer's Disease Neuroimaging Initiative Grand Opportunity protocol.[24] In addition, we used cut-off scores in a modification of the category of educational history suited to the Japanese educational system to divide the aMCI stages as follows: EMCI (between 0.5 and 1.5 SD below the mean of normative data adjusting for educational history) and LMCI (more than 1.5 SD below the mean of normative data adjusting for educational history). Participants were classified into three groups; control subjects without significant objective cognitive impairments (control: $n = 29$); EMCI: $n = 34$; and LMCI: $n = 37$. The present study was approved by the ethics committee of the National Center for Geriatrics and Gerontology. All participants provided written informed consent.

Measurements

Demographic data were recorded, including age, sex and educational history. All neuropsychological tests were carried out by well-trained speech therapists, and each score was rechecked by a single therapist who was blinded to the other data of the participants in the present study. General cognitive function was evaluated using MMSE.[20] The WMS-R Logical Memory II was carried out to examine logical memory. Visual memory was assessed using the Rey–Osterrieth Complex Figure Test (RCFT; 3 min and 30 min delay).[25,26] At the beginning of the test, participants were provided with a complex figure for the first time. Then, after 3 min and 30 min, these participants were asked to recall and draw, as accurately as possible, the original figure. Verbal fluency is composed of letter fluency and category fluency.[27] Participants were asked to generate as many words as possible within 1 min consisting of an initial letter (letter fluency) and an animal name (category fluency).[28] The verbal fluency test provides an evaluation of expressive language

Table 1 Comparison of neuropsychological tests between groups

Variables	Control ($n = 29$)	MCI EMCI ($n = 34$)	LMCI ($n = 37$)	F	P-value
Mini-Mental State Examination (score)	27.6 (2.0)	26.6 (1.9)	27.0 (1.9)	2.28	0.107
WMS-R Logical Memory II (score)	10.8 (2.4)	5.5 (1.6)[†]	1.2 (1.3)[†‡]	230.7	<0.0001
RCFT 3 min (score)	18.6 (5.6)	15.0 (6.0)[†]	14.0 (5.5)[†]	5.57	0.005
RCFT 30 min (score)	17.6 (5.5)	15.1 (5.8)	13.0 (6.5)[†]	4.81	0.01
DS forward (score)	8.3 (2.3)	7.8 (2.2)	7.4 (2.4)	1.28	0.283
DS backward (score)	5.9 (1.6)	5.4 (1.6)	4.6 (1.6)[†]	4.82	0.01
Letter fluency (numbers)	6.9 (3.1)	5.2 (2.0)[†]	5.3 (1.6)[†]	5.13	0.008
Category fluency (numbers)	16.6 (5.0)	15.8 (4.9)	12.9 (3.5)[†‡]	6.49	0.002

[†] Compared with normal for post-hoc analyses at $P < 0.05$. [‡] Compared between EMCI and LMCI for post-hoc analyses at $P < 0.05$. Values are means (SD) or proportion. Group differences were tested in all data using ANOVA. The statistical data are presented as F and P-value. Control, control subjects without objective memory impairments; DS, digit span; EMCI, the early stage in amnesic mild cognitive impairment; LMCI, the late stage in amnesic mild cognitive impairment; MCI, mild cognitive impairment; RCFT, Rey–Osterrieth complex figure test; WMS-R, Wechsler Memory Scale-Revised.

ability and executive function.[25,27,28] We carried out a digit span forward test (DSF) and a digit span backward test (DSB). Both tests are subsets of the Wechsler Adult Intelligence Scale III, and require participants to repeat a series of verbally-presented digits of increasing length in forward and backward order.[25] Performance on the digit span task strongly depends on working memory, cognitive regulation and manipulation, all of which are components of executive function.

Statistical analyses

Analyses of variance (ANOVA) or χ^2-tests (for sex) were carried out to determine the differences in demographic data between the control, EMCI and LMCI groups. The comparison of each neuropsychological test between groups was analyzed using ANOVA and Tukey–Kramer honestly significant difference post-hoc tests. In addition, logistic regression analysis was carried out to identify the relationship between neuropsychological tests and cognitive impairment status. Crude odds ratios were calculated for each test (model 1) and logistic regression analysis was carried out, adjusted for age and sex (model 2). To examine the association between verbal memory and other neuropsychological tests, Pearson's correlation coefficients were calculated. We also used linear regression to assess the relationships between neuropsychological variables while controlling for age and sex. Statistical significance was set at $P < 0.05$. All analyses were carried out using commercially available software (JMP8.0J, SAS Institute Japan, Tokyo, Japan) for Windows.

Results

Demographic characteristics (control: age = 72.8 ± 4.7, proportion of women = 62%, educational history = 10.3 ± 2.3; EMCI: age = 75.4 ± 7.2, proportion of women = 56%, educational history = 10.4 ± 2.1; LMCI: age = 76.8 ± 7.5, proportion of women = 41%, educational history = 11.3 ± 2.9) were not different between groups (age: $F = 2.62$, $P = 0.08$; sex: $\chi^2 = 3.35$, $P = 0.19$; educational history: $F = 1.69$, $P = 0.19$). The results of the neuropsychological measures are presented in Table 1. MMSE scores did not differ between groups. Group effects were observed in the RCFT (3 min: $P < 0.01$, 30 min: $P = 0.01$), DSB ($P = 0.01$), letter fluency ($P < 0.01$) and category fluency ($P < 0.01$). Both EMCI and LMCI showed lower function of letter fluency ($P = 0.01$) and WMS than the control ($P < 0.01$). DSB significantly decreased in LMCI compared with the control ($P = 0.01$), but not between other groups. DSF was not significantly different between groups. Scores in the neuropsychological tests, other than category fluency ($P = 0.02$) and logical memory ($P < 0.01$), did not differ between EMCI and LMCI. Table 2 shows the results of logistic regression analysis of the neuropsychological test results, discriminating EMCI subjects from control or LMCI subjects. In the control and EMCI groups, the RCF 3 min (model 1: $P = 0.02$, model 2: $P = 0.04$) and letter fluency (model 1: $P = 0.03$, model 2: $P = 0.04$) showed significant associations, whereas only category fluency (model 1: $P < 0.01$, model 2: $P < 0.01$) showed a significant difference between the EMCI and LMCI groups.

Table 3 shows the relationships of WMS-R Logical Memory II test with the neuropsychological tests. Over all participants, the WMS-R Logical Memory II test was significantly associated with RCFT 3 min, RCFT 30 min, DSB, letter fluency and category fluency scores, even after controlling for age and sex. In the EMCI group, DSB, letter fluency and category fluency were significantly related to WMS-R Logical Memory II test scores. However, there were no significant relationships

Table 2 The results of logistic regression in neuropsychological tests for discriminating early stage in amnesic mild cognitive impairment subjects from control or late stage in amnesic mild cognitive impairment subjects

Variables	Control and EMCI (n = 63) Odds ratio (95% CI)		EMCI and LMCI (n = 71) Odds ratio (95% CI)	
	Model 1	Model 2	Model 1	Model 2
RCFT 3 min	0.90 (0.82–0.99)*	0.91 (0.83–0.99)*	0.97 (0.89–1.05)	0.97 (0.89–1.06)
RCFT 30 min	0.92 (0.84–1.01)	0.94 (0.85–1.03)	0.94 (0.87–1.02)	0.94 (0.87–1.02)
DS forward	0.89 (0.71–1.12)	0.89 (0.70–1.12)	0.93 (0.76–1.15)	0.92 (0.74–1.15)
DS backward	0.82 (0.60–1.14)	0.87 (0.62–1.22)	0.75 (0.55–1.02)	0.74 (0.54–1.03)
Letter fluency	0.91 (0.83–0.99)*	0.91 (0.83–0.99)*	1.00 (0.92–1.09)	0.99 (0.91–1.09)
Category fluency	0.97 (0.88–1.07)	0.99 (0.89–1.10)	0.84 (0.74–0.96)**	0.82 (0.71–0.94)**

*$P < 0.05$; **$P < 0.01$. Model 1 is a crude model and model 2 was conducted adjusting for age and sex. CI, confidential interval; Control, control subjects without objective memory impairments; DS, digit span; EMCI, the early stage in amnesic mild cognitive impairment; LMCI, the late stage in amnesic mild cognitive impairment; RCFT, Rey–Osterrieth complex figure test.

Table 3 Relationships between the Wechsler Memory Scale-Revised Logical Memory II test and neuropsychological tests

Variables	Total		EMCI		LMCI	
	r	β	r	β	r	β
RCF 3 min	0.36**	0.30**	0.04	−0.0002	0.11	0.21
RCF 30 min	0.33**	0.26**	0.05	−0.01	0.03	0.10
DS forward	0.13	0.08	0.28	0.16	−0.09	−0.07
DS backward	0.35**	0.29**	0.64**	0.59**	−0.20	−0.18
Letter fluency	0.32**	0.28**	0.48**	0.39*	−0.19	−0.22
Category fluency	0.39**	0.35**	0.43*	0.35*	0.20	0.16

*$P < 0.05$; **$P < 0.01$. Pearson r-values represent the simple correlation between the Wechsler Memory Scale-Revised Logical Memory II test and the dependent variables. A standardized beta (β) represents the correlation between logical memory and each dependent variable after controlling for age and sex. Control, control subjects without objective memory impairments; DS, digit span; EMCI, the early stage in amnesic mild cognitive impairment; LMCI, the late stage in amnesic mild cognitive impairment; RCFT, Rey–Osterrieth complex figure test.

between the WMS-R Logical Memory II test and the other neuropsychological measurements in the LMCI group.

Discussion

The present preliminary study shows the characteristics of cognitive function in EMCI and LMCI participants. We classified the participants into three groups by the stage of aMCI, showing group differences in cognitive decline. Significantly lower neuropsychological performance scores in RCFT, DSB, letter fluency and category fluency were found in the LMCI group compared with control participants. The EMCI group also showed significantly lower cognitive performance in the letter fluency and RCFT compared with the control group, whereas significant differences in cognitive function between the EMCI and LMCI groups were only found in the category fluency and in the WMS-R Logical Memory II test. These group differences remained after adjusting for age and sex. These findings suggest that this method is useful in distinguishing EMCI from other groups. The correlational analysis further examined the characteristics of EMCI. A significant relationship between WMS-R Logical Memory II test with verbal fluency and DSB was confirmed in the EMCI participants, but not LMCI participants, after adjusting for age and sex.

Decline in cognitive function was mainly observed in memory, and other cognitive functions also deteriorated in elderly participants with MCI. The present results in LMCI participants are consistent with other studies in which aMCI subjects showed lower performance in the RCFT,[29] DSB[30] and verbal fluency test[30-33] compared with control subjects. The decline of RCFT and letter fluency performance also occurred in EMCI individuals in the present study. RCFT performance reflects the visual memory involved in both encoding and retrieval tasks, and EMCI individuals showed lower performance than the control group in the 3-min task, but not in the 30-min task. This discrepancy in RCFT was likely a result of task difficulty. The degree of task difficulty for cognitive dysfunction subjects (e.g. MCI or AD patients) affects neuropsychological performance, and overly difficult tasks are not useful for assessing these disorders.[34] Digit span performance also differed between tasks in the current study. The DSF and DSB tests evaluate executive function, including attention, and the DSB further requires working memory.[25] These differences might have played a role in the differing results between the two digit span tests.

Verbal fluency assessed the ability to express language and executive function.[25,27,28] The present results were also consistent with the decline of both letter and category fluency, which were observed in LMCI.[32] In addition, the decline of letter fluency occurred in EMCI individuals, whereas category fluency did not differ between control and EMCI subjects, but was different between EMCI and LMCI subjects. These letter fluency and category fluency results show a discrepancy in verbal fluency ability. This discrepancy might be based on the differences of the neuronal requirements of these tasks. Letter fluency is thought to rely on a neural network involving the left prefrontal and inferior parietal cortex, whereas category fluency involves the frontal and temporal regions.[35] Although it is unclear which tasks of letter fluency and category fluency are most useful for detection of MCI, the present results indicate that both letter fluency and category fluency might depend on the severity of memory impairment in aMCI. Although category fluency is generally more frequently impaired in AD, worse letter fluency has also been reported.[35] The present results indicate that impairments of letter fluency may be a characteristic of EMCI. However, the sample size or study design of the present study might have limited the generalizability of these findings. The etiological data confirmed that the decline of cognitive function in aMCI, but not memory, was also a risk for conversion to AD.[10–12] The present results indicate that screening for EMCI should not only involve a verbal memory test, but also measurements of other domains.

The correlation analysis shows characteristics of cognitive function in EMCI. A variety of executive functions, including verbal fluency and DSB performance, were associated with logical memory in the EMCI group. However, there was no significant relationship in the LMCI group. These results remained after controlling for age and sex. Many neuroimaging studies have shown that memory impairment in aMCI and AD is induced by structural and functional changes in the MTL region.[6,8,9] Activation in the MTL region during MCI transforms from hyperactivation to hypoactivation according to the severity of cognitive function during the progression of MCI to AD, and hyperactivation in the MTL confirms a functional compensatory mechanism in very early MCI.[5,6] This compensation might occur as a result of an abnormal functional connectivity or network within the brain.[13–16] Activation of the MTL alone is not sufficient for successful memory function, and the MTL region shows strong connectivity with the cingulate cortex and frontal lobe within the memory network, which is decreased in aMCI and AD.[13,17,36] DSB performance has been found to activate the frontal lobe,[37] whereas verbal fluency tests activate in the prefrontal lobe, parietal lobe, frontal lobe and temporal lobe.[38,39] Additionally, the frontal lobe is a key region involved in human memory processing. Large cortico-cortical direct reciprocal connections exist between the frontal lobe and the MTL.[40] The characteristic relationship between logical memory and a part of executive function in EMCI patients might be caused by a functional abnormality in the brain network. Further studies should be carried out to confirm this hypothesis, using neuroimaging methods, such as functional magnetic resonance imaging.

Several limitations of the current study must be considered. First, the sample size was relatively small, introducing potential difficulties in avoiding heterogeneity in the MCI subjects. Second, the study was cross-sectional. The association between memory function and other cognitive domains should be investigated in prospective and neuroimaging studies. MCI is a reversible state in the spectrum of normal aging-MCI-AD. Clarifying the characteristics of cognitive function in EMCI during conversion to AD is important, and requires a longitudinal study. Finally, the present study did not include data involving apolipoprotein E ε4, amyloid status and cerebrospinal fluid biomarkers. These limitations should be taken into consideration when interpreting the current findings.

In conclusion, elderly adults with MCI showed deterioration not only in memory, but also in executive function, and the memory decline corresponded with poorer performance in executive function. The present preliminary results show that comprehensive assessments that include memory and executive functions might be required to distinguish elderly adults with MCI from cognitively normal elderly adults. Future research is required to determine appropriate neuropsychological tests for predicting the conversion of EMCI and LMCI to AD.

Acknowledgments

This work was supported by a grant from the Japanese Ministry of Health, Labour and Welfare (project for optimizing long-term care; B-3 to T. S.). We thank the Obu city office for the help provided in

participant recruitment, and the speech therapists of the Ukai rehabilitation hospital for assistance with data collection.

Disclosure statement

The authors have no financial or any other kinds of conflicts with this paper.

References

1 Petersen RC, Doody R, Kurz A *et al.* Current concepts in mild cognitive impairment. *Arch Neurol* 2001; **58**: 1985–1992.

2 Winblad B, Palmer K, Kivipelto M *et al.* Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004; **256**: 240–246.

3 Gauthier S, Reisberg B, Zaudig M *et al.* Mild cognitive impairment. *Lancet* 2006; **367**: 1262–1270.

4 Petersen RC, Roberts RO, Knopman DS *et al.* Mild cognitive impairment: ten years later. *Arch Neurol* 2009; **66**: 1447–1455.

5 Dickerson BC, Sperling RA. Large-scale functional brain network abnormalities in Alzheimer's disease: insights from functional neuroimaging. *Behav Neurol* 2009; **21**: 63–75.

6 Pihlajamaki M, Jauhiainen AM, Soininen H. Structural and functional MRI in mild cognitive impairment. *Curr Alzheimer Res* 2009; **6**: 179–185.

7 Weiner MW, Aisen PS, Jack CR Jr *et al.* The Alzheimer's disease neuroimaging initiative: progress report and future plans. *Alzheimers Dement* 2010; **6**: 202 e7–211 e7.

8 Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004; **256**: 183–194.

9 Wolf H, Jelic V, Gertz HJ, Nordberg A, Julin P, Wahlund LO. A critical discussion of the role of neuroimaging in mild cognitive impairment. *Acta Neurol Scand Suppl* 2003; **179**: 52–76.

10 Blacker D, Lee H, Muzikansky A *et al.* Neuropsychological measures in normal individuals that predict subsequent cognitive decline. *Arch Neurol* 2007; **64**: 862–871.

11 Rozzini L, Chilovi BV, Conti M *et al.* Conversion of amnestic Mild Cognitive Impairment to dementia of Alzheimer type is independent to memory deterioration. *Int J Geriatr Psychiatry* 2007; **22**: 1217–1222.

12 Tabert MH, Manly JJ, Liu X *et al.* Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. *Arch Gen Psychiatry* 2006; **63**: 916–924.

13 Bai F, Zhang Z, Watson DR *et al.* Abnormal functional connectivity of hippocampus during episodic memory retrieval processing network in amnestic mild cognitive impairment. *Biol Psychiatry* 2009; **65**: 951–958.

14 Davidson PS, Troyer AK, Moscovitch M. Frontal lobe contributions to recognition and recall: linking basic research with clinical evaluation and remediation. *J Int Neuropsychol Soc* 2006; **12**: 210–223.

15 Trivedi MA, Murphy CM, Goetz C *et al.* fMRI activation changes during successful episodic memory encoding and recognition in amnestic mild cognitive impairment relative to cognitively healthy older adults. *Dement Geriatr Cogn Disord* 2008; **26**: 123–137.

16 Fouquet M, Desgranges B, Landeau B *et al.* Longitudinal brain metabolic changes from amnestic mild cognitive impairment to Alzheimer's disease. *Brain* 2009; **132**: 2058–2067.

17 Bai F, Liao W, Watson DR *et al.* Abnormal whole-brain functional connection in amnestic mild cognitive impairment patients. *Behav Brain Res* 2011; **216**: 666–672.

18 Chang YL, Jacobson MW, Fennema-Notestine C *et al.* Level of executive function influences verbal memory in amnestic mild cognitive impairment and predicts prefrontal and posterior cingulate thickness. *Cereb Cortex* 2010; **20**: 1305–1313.

19 Chen TF, Chen YF, Cheng TW, Hua MS, Liu HM, Chiu MJ. Executive dysfunction and periventricular diffusion tensor changes in amnesic mild cognitive impairment and early Alzheimer's disease. *Hum Brain Mapp* 2009; **30**: 3826–3836.

20 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–198.

21 Yesavage JA. Geriatric depression scale. *Psychopharmacol Bull* 1988; **24**: 709–711.

22 Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol* 2005; **62**: 1160–1163; discussion 67.

23 Wechsler D. *Wechsler Memory Scale-Revised Manual.* San Antonio, TX: The Psychological Corporation, 1987.

24 Alzheimer's Disease Neuroimaging Initiative. Alzheimer's Disease Neuroimaging Initiative Grand Opportunity. 2010. [Cited 1 Aug 2011.] Available from URL: http://www.adni-info.org/Scientists/AboutADNI.aspx

25 Lezak MD. *Neuropsychological Assessment*, 4th edn. New York: Oxford University Press, 2004.

26 Meyers JE, Meyers KR. *Rey Complex Figure Test and Recognition Trial.* Odessa, TX: Psychological Assessment Resources, 1995.

27 Benton AL. Differential behavioral effects in frontal lobe disease. *Neuropsychologia* 1968; **6**: 53–60.

28 Nemoto T, Kashima H, Mizuno M. Contribution of divergent thinking to community functioning in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31**: 517–524.

29 Kasai M, Meguro K, Hashimoto R, Ishizaki J, Yamadori A, Mori E. Non-verbal learning is impaired in very mild Alzheimer's disease (CDR 0.5): normative data from the learning version of the Rey-Osterrieth Complex Figure Test. *Psychiatry Clin Neurosci* 2006; **60**: 139–146.

30 Muangpaisan W, Intalapaporn S, Assantachai P. Digit span and verbal fluency tests in patients with mild cognitive impairment and normal subjects in Thai-community. *J Med Assoc Thai* 2010; **93**: 224–230.

31 Murphy KJ, Rich JB, Troyer AK. Verbal fluency patterns in amnestic mild cognitive impairment are characteristic of Alzheimer's type dementia. *J Int Neuropsychol Soc* 2006; **12**: 570–574.

32 Nutter-Upham KE, Saykin AJ, Rabin LA *et al.* Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. *Arch Clin Neuropsychol* 2008; **23**: 229–241.

33 Duff K, Hobson VL, Beglinger LJ, O'Bryant SE. Diagnostic accuracy of the RBANS in mild cognitive impairment: limitations on assessing milder impairments. *Arch Clin Neuropsychol* 2010; **25**: 429–441.

34 Small GW, Bookheimer SY, Thompson PM *et al.* Current and future uses of neuroimaging for cognitively impaired patients. *Lancet Neurol* 2008; **7**: 161–172.

35 Laws KR, Duncan A, Gale TM. "Normal" semantic-phonemic fluency discrepancy in Alzheimer's disease? A meta-analytic study. *Cortex* 2010; **46**: 595–601.
36 Choo IH, Lee DY, Oh JS *et al.* Posterior cingulate cortex atrophy and regional cingulum disruption in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 2010; **31**: 772–779.
37 Owen AM. The role of the lateral frontal cortex in mnemonic processing: the contribution of functional neuroimaging. *Exp Brain Res* 2000; **133**: 33–43.
38 Hirono N, Mori E, Ishii K *et al.* Neuronal substrates for semantic memory: a positron emission tomography study in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2001; **12**: 15–21.
39 Pihlajamaki M, Tanila H, Hanninen T *et al.* Verbal fluency activates the left medial temporal lobe: a functional magnetic resonance imaging study. *Ann Neurol* 2000; **47**: 470–476.
40 Rempel-Clower NL, Barbas H. The laminar pattern of connections between prefrontal and anterior temporal cortices in the Rhesus monkey is related to cortical structure and function. *Cereb Cortex* 2000; **10**: 851–865.