associated with tangle density in the entorhinal cortex and hippocampus (Wilson, Arnold, et al. 2007). Reduced brain density in these regions has been found to contribute to the prediction of conversion to AD (Jack et al. 1999; Devanand et al. 2007, 2012; Tapiola et al. 2008) among older individuals with MCI. Several previous cross-sectional studies reported a positive association between poor olfactory identification ability and AD (Doty et al. 1987; Serby et al. 1991). Olfactory function is thought to decrease with increasing age (Murphy et al. 2002; Mackay-Sim et al. 2006), and previous longitudinal studies have indicated that olfactory impairment is a predictor of increased risk for development of AD and incidence of cognitive impairment (Tabert et al. 2005; Devanand et al. 2008; Schubert et al. 2008). Schubert et al. (2008) reported that impaired odor identification was associated with global cognitive decline as assessed by changes in mini-mental state examination (MMSE) scores over a 5-year follow-up period. This suggests that olfactory identification testing performance may be an early indicator for cognitive impairment and that it could be associated with global cognitive function among older people. However, the associations between olfactory identification performance and neuropsychological measures in older adults with MCI remain unclear.

Therefore, we hypothesized that the decreased odor identification ability in subjects with MCI may be related to the memory impairment that reflects the early pathology of AD. If this hypothesis is supported, we can give elderly people information about the incidence of cognitive impairment and the risk of MCI converting to AD (Tabert et al. 2005; Devanand et al. 2008; Schubert et al. 2008) using an odor identification test. This may contribute to the early prevention of AD in elderly people with MCI. In the current study, to test this hypothesis, we investigated which aspects of neuropsychological measures are correlated with olfactory identification performance among older adults with MCI.

Materials and methods

Subjects

Subjects were recruited from a database of elderly individuals who met the criteria for MCI ($n = 945$) in a community-based survey, the Obu Study of Health Promotion for the Elderly (OSHPE) ($n = 5104$). Details of the OSHPE protocol and the criteria for MCI have been reported elsewhere (Shimada et al. 2013). In summary, MCI was defined as having subjective memory complaints, exhibiting intact general cognitive functioning [MMSE (Folstein et al. 1975) scores between 24 and 30], exhibiting age-adjusted objective cognitive impairment, exhibiting no use of Japanese long-term care insurance or no evidence of functional dependency (no need for supervision or external help to perform activities of daily living), and an absence of clinical criteria for dementia (Petersen and Knopman 2006). We determined age-adjusted objective cognitive impairment (age-adjusted score of ≤1.5 standard deviations [SDs] below average) using the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT) (Makizako et al. 2013). The NCGG-FAT consists of tasks to assess logical memory, word list memory, attention and executive, processing speed, and visuospatial skill. High test–retest reliability and moderate and high validity values for all task components of the NCGG-FAT have been confirmed in community-dwelling older adults (Makizako et al. 2013). We excluded subjects with a history of major psychiatric illness (e.g., schizophrenia or bipolar disorder), depression symptom (Geriatric Depression Scale 15-item short version score ≥6) (Mitchell et al. 2010), nose-related disease (e.g., empyema or sinusitis), and neurological or musculoskeletal conditions and those who were unable to complete the cognitive performance and olfactory identification tests in this study. Finally, 220 subjects with MCI (mean age 71.7 years, 50.9% women) were included in the present study and completed assessments of odor identification and neurocognitive function. This study was approved by the ethics committee of the National Center for Geriatrics and Gerontology. The purpose, nature, and potential risks of the experiments were fully explained, and all subjects gave written informed consent before participating in the study.

Assessment of odor identification

Odor identification was assessed using the Open Essence test (OE test, Wako Pure Chemical Industries) (Okutani et al. 2013). The OE test was developed as an odor identification assessment and is a card-type test for Japanese populations. In previous studies, the odor stick identification test for Japanese (OSIT-J) involved 13 different odorants familiar to the Japanese population and was reported to be an effective odor identification test for Japanese subjects (Kobayashi et al. 2006; Saito et al. 2006). The OE test, smell identification test cards, was modified from the OSIT-J. The OE test includes 12 odor items familiar to people in Japan (Indian ink, wood, perfume, menthol, orange, curry, cooking gas, rose, Japanese cypress "hinoki," sweaty smelling clothes, condensed milk, and roasted garlic). Each odorant was contained in 12 cards folded in two. In the center of the left half of the opened card, microencapsulated test odorants were applied instead of glue. On the opposite side, 6 choices (4 alternatives of odor name, as well as "detectable but not recognized" and "no smell detected") are printed in Japanese. Subjects opened each card and wrote their answer. The number of correct answers was defined as the OE test score. Subjects underwent an odor identification assessment, once, in a controlled environmental condition (mean temperature: 19 ± 2 °C, mean humidity: 62 ± 6%) between March and May 2012. Subjects wiped their fingers with an odorless wet tissue to remove the any smell before assessment.

Neurocognitive assessment

Subjects underwent comprehensive neurocognitive evaluation, including measures of verbal memory, visual memory,

working memory, attention/executive function, and processing speed. The neurocognitive assessment had a standardized format and was administered by licensed and well-trained clinical speech therapists in controlled environmental conditions. We created an assessment environment that enabled subjects to concentrate while performing cognitive assessments. Subjects were administered the neurocognitive assessment on 2 separate occasions between March and May 2012 to minimize errors due to fatigue.

Rey Auditory Verbal Learning Test

Rey Auditory Verbal Learning Test (RAVLT) performance was measured to assess subjects' verbal memory (Rey 1958). The test was administered according to its original standards: 15 nouns (list A) were read 5 times by the examiner. The subjects then conducted free recall 5 times consecutively (A1–A5). After the fifth recall period, the examiner read a second list (list B) of 15 new words, followed by free recall (B). Immediately after (A6) and 30 min later (A7), recall of list A was again assessed. In this test, a list, consisting of 15 words from list A mixed with 15 new words, was read to the subjects. Subjects were instructed to identify which words belonged to the original list and which were new. We analyzed subjects' performance in the last list A free recall trial (A5) and list A 30-min delayed recall (A7).

Wechsler Memory Scale-Revised visual reproduction subtest

Visual memory was examined using the visual reproduction subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler 1987). This test measures immediate (Visual Reproduction-I) and delayed retention (Visual Reproduction-II) of geometric figures.

Digit span test

We assessed working memory using the verbal digit span test (Wechsler 1981). The digit span test includes both forward and backward conditions, in which a subject is presented with a number sequence and asked either to repeat it as it was presented or to repeat it in the reverse order. The test includes 2 sequences of each length, and testing ceases when the subjects fail to recollect any 2 sequences with the same length. The subjects' score, ranging from 0 to 14, represents the number of successful sequences. The difference between the verbal digit forward test score and the verbal digits backward test score was used as an index of the central executive component of working memory. Smaller difference scores indicate better working memory.

The tablet version of the trail making test

Attention and executive function were assessed using the tablet version of the trail making test (TMT). This type of TMT consists of 2 parts (A and B), as in the original written version of TMT (Lezak 2004). In the tablet version of the TMT-A, subjects were required to touch the target numbers displayed randomly on the screen as rapidly as possible, in consecutive order (1–15). In the tablet version of TMT-B, subjects were required to touch target numbers or letters alternately between consecutive numbers and letters (Japanese Kana characters). We recorded the time (in seconds) taken to complete each task, within a maximum period of 90 s. Shorter time to complete the tasks represents better performance. A previous study confirmed that the tablet version of the TMT has excellent test–retest reliability and validated the test in comparison with the original written version of TMT (Makizako et al. 2013).

The tablet version of symbol digit substitution test

We used the tablet version of symbol digit substitution test (SDST) to assess processing speed. In this task, 9 pairs of numbers and symbols were presented at the top of the display. A target symbol was presented at the center of the display. Subjects then chose a number corresponding to a target symbol at the bottom of the display as rapidly as possible. The score was the number of correct numbers chosen within 90 s. One point was given for each correctly chosen number completed within the time limit. Higher scores represent better performance. The tablet version of the SDST has been found to exhibit excellent test–retest reliability and has been validated in comparison with the Digit Symbol-Coding subtest of the WAIS-III (Makizako et al. 2013).

Statistics

Means, SDs, and proportions were calculated to describe the samples and provide summary information of the measures used. A P value of <0.05 was considered to indicate statistical significance. All data entry and analyses were performed using SPSS Windows 17.0. Student's t-tests and chi-square tests (to test for diagnosis and sex differences) were used to compare the demographic variables, neuropsychological measures, and cognitive performance scores between the subjects with severe hyposmia (OE test ≤ 4) and those without severe hyposmia (OE test ≥ 5) (Baba et al. 2012). Pearson correlation coefficients were calculated to assess simple relationships between OE test score and cognitive test performance. Linear regression analysis was used to assess the relationships between variables while controlling for age to minimize the confounding influence of age-related changes in olfactory identification performance, and standardized β values were calculated. We used univariate logistic regression analysis with severe hyposmia as the dependent variable (OE test ≤ 4) and RAVLT-A5 score, RAVLT-A7 score, Visual Reproduction-I score, and Visual Reproduction-II score as the independent variables to examine the associations between severe hyposmia and memory function. In addition,

the odds ratios (ORs) for severe hyposmia for memory performance tests were adjusted for demographic variables, attention, executive function, and processing speed using multivariable logistic regression models.

Results

Subjects with severe hyposmia (OE test ≤ 4) were significantly older, had lower education levels, reduced verbal and visual memory performance, decreased attention/executive function, and slower processing speed scores compared with those without severe hyposmia (OE test ≥ 5) (Table 1). There were no significant between-group differences in sex and diagnosis.

Verbal memory (RAVLT-A5, $r = 0.340$, $P < 0.001$; RAVLT-A7, $r = 0.302$, $P < 0.001$), visual memory (Visual Reproduction-I, $r = 0.265$, $P < 0.001$; Visual Reproduction-II, $r = 0.346$, $P < 0.001$), attention/executive function (tablet version of TMT-A, $r = -0.173$, $P = 0.010$; tablet version of TMT-B, $r = -0.188$, $P = 0.005$), and processing speed (tablet version of SDST, $r = -0.245$, $P < 0.001$) were significantly associated with OE test scores, but working memory (digit span, $r = -0.082$, $P < 0.225$) was not. Verbal memory (RAVLT-A5, $\beta = 0.265$, $P < 0.001$; RAVLT-A7, $\beta = 0.215$, $P = 0.002$) and visual memory (Visual Reproduction-I, $\beta = 0.169$, $P = 0.015$; Visual Reproduction-II, $\beta = 0.270$, $P < 0.001$) were significantly correlated with OE test scores, even after adjusting for age in the linear regression model (Table 2).

The univariate logistic regression analysis revealed that better performance on the RAVLT-A5 (OR 0.74, 95% confidence interval [CI] 0.64–0.86, $P < 0.001$), RAVLT-A7 (OR 0.81, 95%

Table 1 Characteristics and neurocognitive function in subjects with and without severe hyposmia

	Total (n = 220)	Severe hyposmia, OE test ≤ 4 (n = 36)	Nonsevere hyposmia, OE test ≥ 5 (n = 184)	P value
Characteristics				
Age (years)	71.7 (5.2)	75.8 (7.0)	70.9 (4.4)	<0.001
Sex, female (%)	112 (50.9)	16 (44.4)	96 (52.2)	0.396
Education (years)	11.0 (2.4)	9.7 (2.4)	11.2 (2.4)	0.001
Diagnosis[a], n (%)				
Hypertension	84 (39.1)	11 (31.4)	73 (40.6)	0.311
Diabetes mellitus	25 (11.6)	5 (14.3)	20 (11.1)	0.592
Odor identification				
OE test (score)	6.8 (2.4)	2.9 (1.3)	7.6 (1.7)	<0.001
General cognitive function				
MMSE (score)	26.6 (1.9)	25.4 (1.4)	26.8 (1.9)	<0.001
Verbal memory				
RAVLT-A5 (score)	9.6 (2.6)	7.9 (2.1)	9.9 (2.6)	<0.001
RAVLT-A7 (score)	7.0 (3.5)	4.8 (3.9)	7.4 (3.2)	<0.001
Visual memory				
WMS-R-Visual recall I (score)	30.5 (6.1)	28.3 (7.6)	30.9 (5.7)	0.019
WMS-R-Visual recall II (score)	22.1 (9.5)	15.7 (9.9)	23.3 (8.9)	<0.001
Working memory				
Digit span forward–backward (score)	2.6 (1.8)	3.0 (2.0)	2.6 (1.8)	0.178
Attention/executive function				
Tablet version of TMT-A (s)	22.8 (6.8)	25.4 (7.2)	22.3 (6.6)	0.013
Tablet version of TMT-B (s)	49.4 (19.7)	59.3 (22.3)	47.4 (18.7)	0.001
Processing speed				
Tablet version of SDST (score)	36.3 (8.3)	32.7 (9.4)	37.0 (7.9)	0.005

The data are expressed as the mean (SD) score unless otherwise indicated. Significance was indicated by P values <0.05 using the unpaired Student's t-test or chi-square test (for sex and diagnosis).
[a]One participant in the severe hyposmia group and 4 participants in the nonsevere hyposmia group did not report whether they had hypertension and diabetes mellitus.

CI 0.72–0.90, $P < 0.001$), Visual Reproduction-I (OR 0.94, 95% CI 0.89–0.99, $P = 0.021$), and Visual Reproduction-II (OR 0.92, 95% CI 0.88–0.95, $P < 0.001$) tests was significantly associated with decreased likelihood of severe hyposmia, but the digit span scores (OR 1.15, 95% CI 0.94–1.40, $P = 0.178$) was not. In the multivariable logistic regression models, better performance on the RAVLT-A5 (OR 0.78, 95% CI 0.66–0.94, $P = 0.007$), RAVLT-A7 (OR 0.87, 95% CI 0.76–0.99, $P = 0.029$), and Visual Reproduction-II (OR 0.93, 95% CI 0.89–0.98, $P = 0.006$) tests was significantly associated with decreased likelihood of severe hyposmia after adjusting for age, sex, education, and cognitive performance scores, including the tablet TMT-A, TMT-B, and SDST scores, except for memory tests (Table 3).

Discussion

The present results revealed that olfactory identification performance was associated with verbal and visual memory performance in older adults with MCI. This association remained significant after controlling for age, sex, education, and cognitive function, including attention, executive function, and processing speed.

Previous cross-sectional and epidemiological studies indicated that olfactory function was impaired in individuals with MCI compared with normal controls (Eibenstein et al. 2005; Djordjevic et al. 2008), and olfactory impairment was associated with the incidence of MCI (Wilson et al. 2006; Wilson, Arnold, et al. 2007). In addition, poor odor identification performance in MCI individuals has been shown to predict conversion to dementia (Devanand et al. 2000; Djordjevic et al. 2008; Fusetti et al. 2010). In a longitudinal cohort study with annual follow-up evaluations for up to 5 years, impaired odor identification was also associated with a lower level of global cognition at baseline and more rapid decline in episodic memory, semantic memory, and perceptual speed (Wilson, Schneider, et al. 2007). Djordjevic et al. (2008) examined the relationship between olfactory ability and cognitive impairment in patients with AD, patients with MCI, and in normal elderly control subjects. They reported that olfactory identification was associated with cognitive performance, especially verbal, visual, and working memory, and verbal fluency performance among older participants including AD and MCI patients, and healthy subjects. Although this previous study used a relatively small sample, testing only 51 MCI subjects, interestingly, the results of the subanalysis of MCI subjects showed that odor identification ability was associated with memory assessed by the RAVLT-5 (verbal immediate memory). The present findings revealed that poor odor identification performance

Table 2 Correlation between the odor identification test and neurocognitive performance tests after controlling for age

Neurocognitive tests	Simple correlation (r)	P value	Age controlled (standardized β)	P value
RAVLT-A5	0.340	<0.001	0.265	<0.001
RAVLT-A7	0.302	<0.001	0.215	0.002
WMS-R-Visual recall I	0.265	<0.001	0.169	0.015
WMS-R-Visual recall II	0.346	<0.001	0.270	<0.001
Digit span	−0.082	0.225	−0.063	0.332
Tablet version of TMT-A	−0.173	0.010	−0.065	0.349
Tablet version of TMT-B	−0.188	0.005	−0.058	0.416
Tablet version of SDST	−0.245	<0.001	0.125	0.083

Table 3 Association between memory performance and olfactory impairment (severe hyposmia, OE test ≤ 4) based on multivariate logistic regression analyses

Memory performance	Crude			Model 1			Model 2		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
RAVLT-A5	0.743	0.640–0.862	<0.001	0.787	0.665–0.932	0.005	0.784	0.656–0.936	0.007
RAVLT-A7	0.806	0.723–0.899	<0.001	0.861	0.761–0.974	0.018	0.865	0.760–0.985	0.029
WMS-R-Visual recall I	0.936	0.885–0.990	0.021	0.997	0.931–1.067	0.927	1.009	0.934–1.089	0.822
WMS-R-Visual recall II	0.916	0.879–0.954	<0.001	0.940	0.898–0.983	0.007	0.933	0.888–0.981	0.006
Digit span	1.148	0.939–1.404	0.178	1.136	0.905–1.427	0.273	1.126	0.896–1.416	0.309

Model 1: adjusted for age, sex, and education. Model 2: adjusted for Model 1 plus the tablet version of TMT-A, TMT-B, and SDST.

was related to lower memory function in an aged population of people with MCI, testing more than 200 individuals. The results of our study including only MCI subjects also indicated that severe hyposmia was associated with memory rather than attention/executive function and processing speed. In addition, the relationships between olfactory function and memory remained significant after controlling for age, sex, education, and cognitive function (except for memory), including attention, executive function, and processing speed. These results suggest that olfactory identification performance is more closely related to memory than to other aspects of cognitive functioning in older adults with MCI. Because the present study included only MCI subjects, further research in a large cohort including older, cognitively intact individuals will be needed to clarify these points.

A large number of previous studies have reported that severe memory loss can progress to AD (Petersen et al. 2001; Levey et al. 2006). Accelerated atrophy of the medial temporal lobe, including the entorhinal cortex, hippocampus, and parahippocampal gyrus, is reported to be related to an increased risk of developing AD (Devanand et al. 2007, 2012; Spulber et al. 2012). In this study, odor identification ability was found to be related to verbal and visual memory, but not to working memory. In general, working memory is considered to be a function of the frontal lobe (Haxby et al. 2000). The results of the current study suggest that odor identification in subjects with MCI is decreased owing to an effect on olfactory processes excluding frontal lobe function. In a previous study using clinicopathological analyses of an aging population in the Rush Memory and Aging Project (Wilson, Arnold, et al. 2007), odor identification was associated with tangle density in the entorhinal cortex and hippocampus, and components of the central olfactory system are thought to be among the first sites of pathological changes in AD (Kesslak et al. 1991; Braak and Braak 1997; Killiany et al. 2002). Therefore, the odor identification disability revealed in this study might be related to a disorder of the inside temporal lobe, where the initial pathological changes of AD occur, in support of our hypothesis. Impaired odor identification has been associated with more rapid cognitive decline (Graves et al. 1999; Royall et al. 2002; Swan and Carmelli 2002; Wilson et al. 2006) and an increased risk of conversion to AD (Devanand et al. 2000; Tabert et al. 2005). Although the present study did not produce neuroimaging data, the poor olfactory identification performance we observed is likely to be related to the hippocampus and associated structures of the medial temporal lobe, which are recruited during memory performance. On the other hand, a previous study suggested that the anosmia in dementia was associated with Lewy bodies rather than Alzheimer's pathology (McShane et al. 2001). Lewy bodies are found in the olfactory bulb early in dementia with Lewy bodies (DLB) (Braak et al. 2003). The present study may include MCI subjects with a high risk of developing not only AD but also DLB, especially in those showing severe hyposmia. To determine the effects of hyposmia on differences in risk of dementia type, DLB or AD, it will be necessary to design future studies including neuropathological testing and long-term follow-up observation.

Olfactory performance is easily assessed using the OE test, and it is not necessary for assessors to have thorough specific knowledge; it also seems that the OE test requires a lower mental workload than memory tests. Therefore, it can be performed in the community and nonclinical settings by nonspecialized persons. If the decreased odor identification ability of MCI subjects is associated with a memory impairment, as the results of this study show, odor identification tests, which we can conduct easily, may provide information to more many elderly people about the incidence of MCI and the risk of converting to AD. Elderly people may receive a preventive intervention in the earlier stage of MCI. MCI is considered a suitable target for therapeutic intervention (Petersen et al. 2001), and several nonpharmacological interventions are currently used to maintain cognitive function and brain health in older people (Teixeira et al. 2012). Interestingly, one study reported increased activation in the entorhinal cortex, right hippocampus, and posterior parahippocampal gyri during correct odor identification (Kjelvik et al. 2012). This finding suggested that these brain regions can be activated during an odor identification task. It might be important to examine the effect of interventions on memory function using odor identification tasks in the future because of the association between odor identification ability and memory impairment in MCI subjects shown in this study.

Several limitations of the current study must be considered. Our data were collected using a cross-sectional design. In addition, some factors—e.g., time of day (Lotsch et al. 1997; Higuchi et al. 2000) and food intake (Kaplan et al. 2000; Stafford and Welbeck 2011)—that may have affected cognitive and odor identification performances were not controlled. Further experiments using longitudinal and interventional designs will be required for more accurately defining the associations between olfactory function and cognition, particularly memory function, in the processes of cognitive change. In addition, we did not collect data from healthy older persons or patients with AD in the present study. Additional analyses, including comparisons of nonimpaired and severe cognitive impairment groups, may be needed to clarify the associations between olfactory identification and memory function. Future studies examining cognitively healthy controls and patients with AD will be needed to determine the relationships between olfactory function and memory in AD-related processes.

In conclusion, we observed significant associations between olfactory identification and memory performance in older adults with MCI. These findings suggest that olfactory impairment may be more closely associated with memory loss compared with the other aspects of cognitive functioning in MCI subjects. Therefore, the assessment of olfactory function may enable early detection of memory

decline. Investigation of an effect of MCI on brain health (in particular, memory function and odor identification) is needed in the near future.

Further longitudinal and intervention studies with adequate adjustment for potential confounders (e.g., brain structure changes) are required to examine the effects of olfactory function on memory function and cognition among older adults at risk of dementia.

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Conflict of interest

There are no financial and personal relationships with other people or organizations that may lead to a conflict of interest.

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The combined status of physical performance and depressive symptoms is strongly associated with a history of falling in community-dwelling elderly: Cross-sectional findings from the Obu Study of Health Promotion for the Elderly (OSHPE)

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ABSTRACT

The purpose of this study was to examine whether the combined factors of physical performance, depressive symptoms and cognitive status are significantly associated with a history of falling in community-dwelling elderly. We performed a cross-sectional community-based survey, the OSHPE, from August 2011 to February 2012. In total, 5104 community-dwelling older adults aged 65 years and older (mean age 72.0) participated in the OSHPE. Participants underwent a grip strength (GS) test, chair stand test (CST), Timed Up & Go (TUG) test, Geriatric Depression Scale (GDS), and Mini-Mental State Examination (MMSE). Of the 4481 participants who met our requirements, 645 (14.4%) participants reported falling at least once in the past year. In a signal detection analysis (SDA), we found that the combination of GDS (≥6 points) and TUG (≥10.6 s) had the highest fall rate (36.4%), and the combination of GDS (<6 points) and CST (<11.1 s) had the lowest fall rate (11.7%). The highest fall rate group had a significantly higher odds ratio (OR) compared with the lowest fall rate group after adjusting for other potentially confounding variables [OR 3.12 (95% confidence interval (CI) 2.08–4.68) $p < 0.001$]. The combination of depressive symptoms, TUG, and CST performance was strongly associated with a history of falling in community-dwelling elderly.

1. Introduction

Falls, fall-related fractures, and fear of falling are a major cause of public health problems and common causes of long-term care enrollment in older populations (Gillespie & Friedman, 2007; Masud & Morris, 2001). There are many distinct causes of falls in older people. Fall risk factors are frequently classified as intrinsic (e.g., physical frailty and sensory deficits) or extrinsic (e.g., home hazards and footwear) factors (Fabre, Ellis, Kosma, & Wood, 2010).

Guidelines for the prevention of falls in older persons compiled by the Panel on Falls Prevention of the American and British Geriatrics Society identified the major fall risk factors and their relative importance (2001). One of the strongest risk factor domains is muscle weakness and problems with gait and balance. These are key risk factors for falls and present with high OR (values ranging from 3.0 to 4.9) (Rubenstein, 2006).

One of the complications of falls in older people is the post-fall anxiety syndrome; an older individual refrains from activity because of fear of falling. Falls in older people are associated not only with physical functions such as muscle weakness, balance impairment, and gait dysfunction (Masud & Morris, 2001), but also psychological factors, e.g., depressive symptoms (Somadder, Mondal, Kersh, & Abdelhafiz, 2007). A higher prevalence of depression has been reported in fallers than in non-fallers (Wada et al., 2008), and depressive symptoms have been shown to be a

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risk factor for falls among older people (Anstey, Burns, von Sanden, & Luszcz, 2008; Deandrea et al., 2010; Kwan, Lin, Close, & Lord, 2012). Additionally, the risk of falls is proportional to the number itself of fall-related risk factors (Tinetti, Williams, & Mayewski, 1986). Previous studies suggest that the combined status of declining physical functions and psychological status such as depression may be related to falling. However, little studies have reported that which combination of modifiable factors has most impact for falling and its optimal cut-off points are unclear.

Measures of lower extremity function, balance, and gait performance have been recommended as a screening for fall risk in older people (Rubenstein & Josephson, 2006; Scott, Votova, Scanlan, & Close, 2007; Shimada et al., 2009). Previous studies using instruments of physical function assessment as related to falls have provided potential cut-off scores to identify increased fall risks among community-dwelling older people (Fabre et al., 2010; Scott et al., 2007). For instance, the TUG test is a relatively simple screening test and a specific indicator of whether falls are likely to occur in older adults. A previous study indicated that a cut-off time of 10–12 s separated fallers from non-fallers in a group of community-dwelling older adults (Trueblood, Hodson-Chennault, McCubbin, & Youngclarke, 2001). In another study, community-dwelling older adults who took 13.5 s or longer to perform the TUG were classified as fallers with an overall correct prediction rate of 90% (Shumway-Cook, Brauer, & Woollacott, 2000). These studies demonstrate differences in the cut-off points for falling risk. One reason for these different cut-off points may be a limited sample size. Furthermore, even though there studies focused on community-dwelling older people, the participant characteristics were different (e.g., physical function and psychological status). Therefore, the combined status of risk for falling should be considered to identify risks for falls in a large population-based study. Such information would be useful because factors related to falls may be different in older people with or without depressive symptoms.

The aim of this study was to examine which combination of modifiable factors, such as physical performance, depressive symptoms, and cognitive status were closely associated with a history of falling in community-dwelling elderly. This investigation may be critical to the exploration of the combined classification of modifiable factors for fall risk screenings, in order to develop future risk assessments and prevention programs.

2. Participants and methods

2.1. Participants

We performed a cohort study entitled OSHPE (Shimada et al., 2013) from August 2011 to February in 2012. Individuals selected for participation in the OSHPE were chosen from the 15,974 older people living in Obu, Japan. Inclusion criteria required that the participant was aged 65 years or older at the time of examination in 2011 or 2012, and living in Obu. Prior to recruitment, we excluded 1661 individuals who had participated in another study, needed hospitalization or residential care, and required support or care by the Japanese public long term care insurance system (Care Level $\geq$ 3/5). Recruitment involved sending mail messages to 14,313 people; 5104 people underwent a health check. We excluded participants who reported a history of stroke, Parkinson's disease, Alzheimer's disease, other serious neurologic diagnoses, and those who could not complete the physical performance tests. Finally, 4481 participants (mean age 72.0) were included in the present study, and their data were analyzed. Informed consent was obtained from all participants prior to their inclusion in the study. The Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol.

2.2. Fall interview

Fall history was assessed using face-to-face interviews. A fall was defined as "an unexpected event in which the person comes to rest on the ground, floor, or lower level" (Lamb, Jorstad-Stein, Hauer, & Becker, 2005). The question "Do you have any history of a fall within the past year?" was used for detecting fallers. Participants who answered yes to the question were considered to be fallers (Wada et al., 2008).

2.3. Measurement of depressive symptoms

The 15-item GDS was administered to assess presence depressive symptoms (Yesavage, 1988). The GDS is unique because it was specifically developed for use in geriatric patients, and it contains fewer somatic items. The participants were required to respond to each question with only a "yes" or "no". The sum of GDS scores ranges from 0 to 15; higher scores indicate a greater likelihood of depression in an older adult.

2.4. Physical and cognitive assessments

The following physical performance tests were conducted: GS, CST (Hirsch et al., 1997), and the TUG (Podsiadlo & Richardson, 1991). All physical performance tests were performed by licensed and well-trained physical therapists. The MMSE (Folstein, Folstein, & McHugh, 1975), administered by well-trained examiners, assessed global cognitive function. GS was measured in kilograms with participants' dominant hand using a portable grip strength dynamometer (GRIP-D; Takei Ltd., Niigata, Japan). The measurement was taken once and in the standing position. CST involved standing up and sitting down five times from a sitting position as quickly as possible (Hirsch et al., 1997). In CST, physical therapists recorded the time needed to perform five consecutive chair-stands (timed to 0.1 s) from a seated position on a 45-cm tall chair, with arms folded across the chest. General mobility was assessed using the TUG. TUG involves the participant rising from a standard armchair, walking a distance of 3 m at a normal and safe pace, turning around, walking back to the chair and sitting down again (Podsiadlo & Richardson, 1991). TUG is measured in seconds using a stopwatch. The time taken to complete TUG was measured twice and the best-timed trial was used for each participant's score.

2.5. Statistical analysis

Student's t test for differences in means and chi-square tests for differences in proportions were used to compare group differences in characteristics between the faller and non-faller groups. The SDA determined, through creation of a decision tree, the most sensitive and specific algorithm to categorize subgroups with a shared association with a history of falling. The SDA was performed with ROC4 software (Department of Veterans Affairs, Mental Illness Research, Education, and Clinical Centers, 2002) including GS, CST, TUG, GDS, and MMSE as independent variables. The merits of SDA have been summarized in a previous article (Agras et al., 2000). SDA is a form of recursive partitioning that considers at each step all possible predictors (at every possible cut point), with the optimal predictor and optimal cut point chosen in terms of their sensitivity and specificity. The cut point was set in advance because no optimal predictor was associated with an outcome at $p < 0.01$. Furthermore, simple (univariate) and multiple (multivariate) logistic regression analyses were per-

formed to assess the association between a history of falling and combined status determined by SDA. The crude and adjusted OR and 95% CIs were calculated adjusting for important potentially confounding variables including age, sex, body mass index (BMI), medication, severe visual or auditory disturbance, and frequency of going out. Data were analyzed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) and p-values less than 0.05 were considered significant.

3. Results

3.1. Demographic characteristics of the sample

Of the 4481 participants who met our requirements, 645 (14.4%) participants reported falling at least once in the past year. Table 1 summarizes the characteristics of the faller and non-faller groups. The faller group had a statistically significantly higher age, number of medications, frequency of going out, female and osteoporosis population, and lower education level compared with the non-faller group ($p < 0.05$). In addition, the faller group exhibited statistically significant lower GS ($p < 0.001$), CST ($p < 0.001$) and TUG ($p < 0.001$) performance, and MMSE score ($p = 0.020$) and higher GDS score ($p < 0.001$) compared with the non-faller group. There were no statistically significant between-group differences in BMI ($p = 0.240$) and the proportion of severe visual or auditory disturbance ($p = 0.536$).

3.2. Sample divided into subgroups associated with a history of falling

Participants were categorized into four subgroups whose fall rate varied 11.7–36.4% by SDA (Fig. 1). Group-I had the lowest fall rate at 11.7%. This group consisted of participants who did not have symptoms of clinical depression (GDS < 6 points) and exhibited better chair stand performance (CST < 11.1 s). Group-II had the next lowest fall rate at 18.8%. Participants in Group-II did not have symptoms of clinical depression (GDS < 6 points), but exhibited poor chair stand performance (CST ≥ 11.1 s). Group-III had a fall rate of 21.6%. Group-III was characterized by reported symptoms of clinical depression (GDS ≥ 6 points) and better mobility performance (TUG < 11.6 s). The highest fall rate of 36.4% was confirmed in Group-IV. Group-IV consisted of participants who had symptoms of clinical depression (GDS ≥ 6 points) and exhibited poor mobility performance (TUG ≥ 11.6 s).

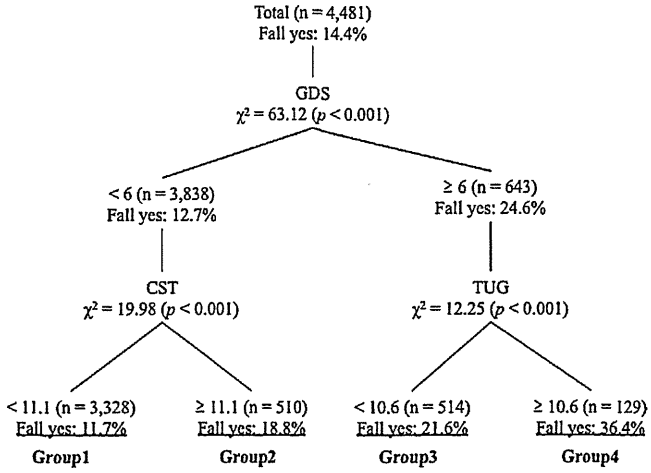

Fig. 1. Results of SDA for the participants' performance on the following measures: GDS; CST; TUG test.

3.3. Relationship between a history of falling and combined status determined by SDA

In the logistic regression analyses, compared with Group-I (the lowest fall rate group), the other three groups had significantly higher ORs after adjusting for age, sex, BMI, medication (number per day), severe visual or auditory disturbance, frequency of going out (days per week), GS, and MMSE score. In model 3 adjusting for these confounding variables, ORs (95% CI, p-value) of Group-II, Group-III, and Group-IV were 1.47 (1.14–1.91, $p = 0.003$), 1.92 (1.51–2.45, $p < 0.001$), and 3.12 (2.08–4.68, $p < 0.001$), respectively (Table 2).

4. Discussion

The results of this study including 4481 community-dwelling older adults indicated that the combination of GDS (≥6 points) and TUG (≥10.6 s) was the highest (36.4%), and GDS (<6 points) and CST (<11.1 s) was the lowest in term of fall rate (11.7%). Groups with a combined status of GDS, TUG, and CST had statistically significantly higher ORs compared with the lowest fall rate group (Group-I: GDS < 6 points and CST < 11.1 s), after adjusting for age, sex, BMI, medication (number per day), severe visual or auditory disturbance, frequency of going out, GS, and MMSE score.

Table 1
Demographic details and characteristics for the non-fallers and fallers.

Variables	All (n = 4481)	Non-fallers (n = 3836)	Fallers (n = 645)	p-Value
Age, years	72.0 ± 5.5	71.8 ± 5.4	73.2 ± 6.1	<0.001
Female, n (%)	2320 (51.8)	1926 (50.2)	394 (61.1)	<0.001
BMI, kg/m^2	23.2 ± 3.7	23.2 ± 3.6	23.4 ± 3.9	0.240
Education, years	11.4 ± 2.5	11.4 ± 2.5	11.0 ± 2.5	0.001
Medical history (self-reported), n (%)				
Cardiac disease	723 (16.1)	610 (15.9)	113 (1735)	0.303
Diabetes	578 (12.9)	487 (12.7)	91 (14.1)	0.322
Osteoporosis	483 (10.8)	377 (9.8)	1.6 (16.4)	<0.001
Cancer	437 (9.8)	368 (9.6)	69 (10.7)	0.383
Medication, number/day	2.0 ± 2.1	1.9 ± 2.0	2.4 ± 2.4	<0.001
Severe visual or auditory disturbance, n (%)	15 (0.3)	12 (0.3)	3 (0.5)	0.536
Frequency of going out, days/week	5.8 ± 1.7	5.8 ± 1.7	5.7 ± 1.8	0.014
GS, kg	26.8 ± 8.0	27.2 ± 8.0	24.8 ± 7.5	<0.001
CST, s	8.7 ± 2.9	8.6 ± 2.8	9.3 ± 3.4	<0.001
TUG test, s	8.4 ± 1.9	8.3 ± 1.8	8.9 ± 2.5	<0.001
GDS, score	2.8 ± 2.6	2.7 ± 2.5	3.7 ± 3.0	<0.001
MMSE, score	26.2 ± 2.7	26.3 ± 2.7	26.0 ± 3.0	0.020

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

Table 2
Logistic regression summary for participants groups classified by the SDA on falls.

Variable	Fallers, no. (%)	Crude		Model 1		Model 2		Model 3	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Group I: GDS < 6 and CST < 11.1 (n = 3328)	391 (11.7)	1.00 [Reference]	–	1.00 [Reference]	–	1.00 [Reference]	–	1.00 [Reference]	–
Group II: GDS < 6 and CST ≥ 11.1 (n = 510)	96 (18.8)	1.74 (1.36–2.23)	<0.001	1.55 (1.20–2.00)	0.001	1.52 (1.17–1.96)	0.002	1.47 (1.14–1.91)	0.003
Group III: GDS ≥ 6 and TUG < 10.6 (n = 514)	111 (21.6)	2.07 (1.64–2.62)	<0.001	2.02 (1.59–2.56)	<0.001	1.96 (1.54–2.48)	<0.001	1.92 (1.51–2.45)	<0.001
Group IV: GDS ≥ 6 and TUG ≥ 10.6 (n = 129)	47 (36.4)	4.31 (2.96–6.26)	<0.001	3.60 (2.43–5.33)	<0.001	3.30 (2.21–4.91)	<0.001	3.12 (2.08–4.68)	<0.001

Model 1: adjusted for age, sex, and BMI.
Model 2: adjusted for Model 1 plus medication (number/day), and severe visual or auditory disturbance.
Model 3: adjusted for Model 2 plus frequency of going out (days/week), GS, and MMSE.

Depressive symptoms have been related to incident falls in prospective studies (Eggermont, Penninx, Jones, & Leveille, 2012; Kwan et al., 2012) and cross-sectional studies with large samples (Halil et al., 2006; Lawlor, Patel, & Ebrahim, 2003). One of the problems associated with falling in older people is a post-fall psychological reaction. A prospective cohort-study reported that depression at 1 year post-injury due to falling was higher than at the pre-injury baseline (Scaf-Klomp, Sanderman, Ormel, & Kempen, 2003). Although the present study included community-dwelling older people with and without fall-related injury and differences between with them were not compared, depressive symptoms were identified as being strongly associated with a history of falling. A cut-off score of 6 or greater on the GDS was used to divide the first two groups. A score of 6 or more symptoms on the GDS has been reported as an optimal cut-off point with comparison to a structural clinical interview for depression (Friedman, Heisel, & Delavan, 2005). Thus, depressive symptoms were also thought to be associated with falls in our large sample study.

To screen for fall risk among older people, measures of lower extremity function, balance, and gait performance have been recommended (Rubenstein & Josephson, 2006; Scott et al., 2007; Shimada et al., 2009). The TUG has been recommended as a key test for detecting fall risk in community-dwelling older adults. Many retrospective studies have found a significant positive association between the time taken to perform the TUG and a history of falls (Beauchet et al., 2011). However, the cut-off time separating non-fallers and fallers was varied and inconsistent. For instance, Shumway-Cook et al. (2000) demonstrated that older adults who required 13.5 s or longer to perform the TUG were classified as fallers, with an overall prediction rate of 90%. In another prospective study, a cut-off score of 10 s on the TUG yielded high sensitivity (71%) and specificity (89%) to discriminate between older adult fallers and non-fallers (Rose, Jones, & Lucchese, 2002). The cut-off time established for separating non-fallers and fallers in a study including day hospital patients was considerably longer than 30.2 s (Thomas & Lane, 2005). The different cut-off values among these previous retrospective studies may be the results of a variation in participants' physical function characteristics. Additionally, cut-off values may related to different definitions of fallers (e.g., single and recurrent fallers, or only recurrent fallers). Furthermore, these studies that demonstrated cut-off times for TUG had limited findings with a relatively small cohort (less than 200 participants). Thus, a consensus for an accurate cut-off score for TUG has not yet been established. The results of our large cohort study with an aged population (n = 4481) demonstrate that older adults with the highest fall rate (36.4%) required more than 10.6 s to perform the TUG and had depressive symptoms (GDS ≥ 6 points). According to a combination fall risk assessment, renewed cut-off values are required and further prospective studies are needed to identify high-risk groups and the predictive value for future falls in community-dwelling older adults.

CST is a valid measure of lower extremity strength and function. Several studies have suggested that a slower CST performance is useful for the detection of older adults at higher risk for falls, independent of other prominent risk factors (Buatois et al., 2008; Tiedemann, Shimada, Sherrington, Murray, & Lord, 2008). In a previous prospective cohort study involving 362 subjects aged 74–98 years, a cut-off point of 12 s on the CST was associated with an increased fall risk, with 66% sensitivity and 55% specificity regarding the identification of multiple fallers (Tiedemann et al., 2008). Data from a prospective population-based study involving 1958 subjects aged 65 years and older found that the ideal cut-off time for performing the CST for use in predicting recurrent fallers was 15 s (sensitivity 55%, specificity 65%) (Buatois et al., 2008). The present data provide a cut-off point of 11.1 s on the CST for separating non-fallers and fallers among older adults without depressive symptoms (GDS < 6 points). Moreover, a combined status of a lower GDS score (<6 points) and better CST time (<11.1 s) demonstrated the lowest fall rate (11.7%). The results of this study, however, may indicate a shorter CST cut-off point compared with previous studies as we defined participants who had had at least one fall within the past year as fallers and we analyzed cross-sectional data.

One key finding was a strong association between a history of falls and combined status using the GDS, TUG, and CST in a large aged population sample. This is the first study to suggest the validity of a combined classification of both physical and psychological factors. Multi-dimensional measures may be important to assess fall risks. Additionally, studies including longitudinal data are needed to confirm whether these combined statuses of the GDS, TUG, and CST predict future falls in older people.

Our study has several limitations. Our data were collected using a cross-sectional design. Participants who had had at least one fall in the past year were categorized as fallers in this study. A previous study has found that single fallers are more similar to non-fallers than to recurrent fallers on a range of medical, physical, and psychological risk factors (Lord, Ward, Williams, & Anstey, 1994). Other researchers define fallers as people who have had at least one injurious or two non-injurious falls (Delbaere et al., 2010; Zheng et al., 2012). In addition, one-year memory recall on falls may be long and the accuracy of self-reported falls for older adults, especially those with severe depression, may results over- or under-reported the number of falls. Therefore, future research with a longitudinal design and different definitions of fallers are needed to supplement the present results.

5. Conclusions

This study found that a combination of the GDS, TUG, and CST performance was strongly associated with a history of falling in community-dwelling elderly. In particular, the group with depressive symptoms (GDS ≥ 6 points) and lower mobility

function (TUG ≥ 10.6 s) had the highest fall rates. Multi-dimensional measures may be important to assess fall risks. Future studies including longitudinal data are needed to confirm whether the combination of using the GDS, TUG, and CST measures predicts future falls in older people.

Conflict of interest statement

None.

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RESEARCH ARTICLE Open Access

Poor balance and lower gray matter volume predict falls in older adults with mild cognitive impairment

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Abstract

Background: The risk of falling is associated with cognitive dysfunction. Older adults with mild cognitive impairment (MCI) exhibit an accelerated reduction of brain volume, and face an increased risk of falling. The current study examined the relationship between baseline physical performance, baseline gray matter volume and falls during a 12-month follow-up period among community-dwelling older adults with MCI.

Methods: Forty-two older adults with MCI (75.6 years, 43% women) underwent structural magnetic resonance imaging and baseline physical performance assessment, including knee-extension strength, one-legged standing time, and walking speed with normal pace. 'Fallers' were defined as people who had one or more falls during the 12-month follow-up period.

Results: Of the 42 participants, 26.2% (n = 11) experienced at least one fall during the 12-month follow-up period. Fallers exhibited slower walking speed and shorter one-legged standing time compared with non-fallers (both $p < .01$). One-legged standing time (sec) (standardized odds ratio [95% confidence interval]: 0.89 [0.81, 0.98], $p = .02$) was associated with a significantly lower rate of falls during the 12-month follow-up after adjusting for age, sex, body mass index, and history of falling in the past year at baseline. Voxel-based morphometry was used to examine differences in baseline gray matter volume between fallers and non-fallers, revealing that fallers exhibited a significantly greater reduction in the bilateral middle frontal gyrus and superior frontal gyrus.

Conclusions: Poor balance predicts falls over 12 months, and baseline lower gray matter densities in the middle frontal gyrus and superior frontal gyrus were associated with falls in older adults with MCI. Maintaining physical function, especially balance, and brain structural changes through many sorts of prevention strategies in the early stage of cognitive decline may contribute to decreasing the risk of falls in older adults with MCI.

Background

Falls and fall-related injuries are a common healthcare problem, and represent important causes of morbidity and mortality in older populations. One-third of all community-dwelling adults age 65 years and older experience at least one fall annually [1]. Many distinct causes for falls in older people have been reported by a large number of studies [1-4]. Impaired physical function, particularly muscle weakness and problems with gait and balance, are the most important contributors to the risk of falling [5]. The ageing of the worldwide population in recent decades has resulted in an increasing number of older adults with cognitive decline [6], and cognitive impairment has also been found to increase the risk of falling [7-10]. As such, correctly identifying the risk factors for falling among older adults with cognitive impairment is an important research question. In addition, people with cognitive impairment recover less well after a fall than those without cognitive impairment [11]. Therefore, the falling may have negative impact on health in older people with cognitive

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impairment compare with those without cognitive impairment. In older individuals with mild cognitive impairment (MCI) in particular, consideration of a broad range of causes of falls could play a role in reducing the fall risk and providing strategies to prevent falls among the high-risk population.

Several studies have examined falling in older adults with dementia, such as Alzheimer's disease [11,12]. However, little research has focused on falling among people with MCI, even though mild declines in cognitive function have been reported to be an important factor associated with falling [13]. Liu-Ambrose et al. demonstrated that older community-dwelling people with MCI but not dementia were at greater risk of falling than those without MCI [14]. Brain structural changes represent one of the key clinical features associated with MCI, including gray matter volume loss [15] and white matter hyperintensities (WMH) [16]. A recent prospective study indicated that greater WMH burden predicts falls over 12 months in non-demented community-dwelling older adults [17].

Although prospective evidence suggests that WMH are an important risk factor for falls in community-based older populations [17,18], it remains unclear whether gray matter volume predicts falls and which regions are related to a greater risk of falls in older adults with MCI. Structural changes in the brain have been linked to motor performance deficits [19]. WMH was reported to exhibit a negative correlation with postural stability involved balance, stepping and gait [20], while reduced gray matter density is associated with impaired gait performance [21-23] and postural instability [24]. Kido et al. [24] suggested that postural instability is associated with gray matter volume loss, and is related to pathological cognitive decline, such as MCI and AD. Lower gray matter volume has been found to be related not only to cognitive decline, but also to decreased physical function. Thus, gray matter volume loss may increase the risk of falls in older adults with MCI. In particular, a smaller volume of the prefrontal area might be associated with poor physical performance [22,23], such as slower gait and poor balance, but no evidence has been reported that smaller brain volume of specific regions is related to the occurrence of subsequent falls in older adults with MCI. In the current study, we sought to examine whether physical performance and gray matter volume were related to falls during a 12-month follow-up period among community-dwelling older adults with MCI.

Methods

Participants

The sample for this longitudinal study consisted of 42 community-dwelling older adults with MCI who completed a randomized controlled trial (RCT) (trial registration: UMIN-CTR UMIN000003662) evaluating the effects of multicomponent exercise on cognitive function. The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol. The study design and the primary results of the RCT have been described previously [25]. All participants gave written informed consent prior to taking part in the study. Briefly, participants enrolled in the RCT were: aged 65 years and over, community dwelling, and did not suffer from dementia. All participants met the Petersen criteria for MCI [26]. Participants who had a Clinical Dementia Rating (CDR) = 0, or a CDR of 1–3, a history of neurological, psychiatric, or cardiac disorders or other severe health issues, use of donepezil, impairment in basic activities of daily living (ADL), and participation in other research projects were excluded from the RCT study. A total of 100 participants took part in the RCT and completed neuropsychological assessments including language, memory, attention, and executive function tests. All subjects in this study had objective impairments at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. The participants were classified to an amnestic MCI (aMCI) group (n = 50) with neuroimaging measures, and other MCI group (n = 50) before the randomization. The subjects in each group were then randomly assigned to either a multicomponent exercise group or an education control group using a ratio of 1:1. The sample for this longitudinal study involved participants in a control group. Of the 50 participants in the control group, 42 completed fall follow-up assessments during the 12-month follow-up period.

Physical performance measures

At baseline, all participants underwent an extensive assessment of measures by licensed and well-trained physical therapists.

Knee-extension strength

Isometric knee extension strength was tested twice using a dynamometer (Model MDKKS, Molten Co Ltd, Hiroshima, Japan) from the dominant leg (self-reported side they would use to kick a ball as far as possible). Knee extension was measured while the participant was sitting on a chair with a backrest and the knee flexed to 90°. A testing pad was attached to the front lower leg of the participant and strapped to the leg of the chair. The participant was instructed to push the pad with maximal strength. Licensed and well-trained physical therapists confirmed compensatory movement and assessed muscle strength. Participants practiced several times before data collection. Two trials were conducted,

and the maximal isometric strength was determined as the peak torque (Nm) in the data analysis.

One-legged standing (OLS) test

The OLS test is a commonly used balance assessment of postural stability. For the OLS test, we asked participants to look straight ahead at a dot 50 cm in front of them, then to stand on their preferred leg with their eyes open and hands down alongside the trunk. OLS balance was measured as the length of time (0–60 s) participants were able to stand on one leg. The better of the two trials was used for statistical analysis.

Walking speed

WS was measured using a 5-m walking test. The participants' usual WS was measured over an 11-m straight and level path. The time taken (in seconds) to pass the 5-m mark on the path was used as the participant's score. A 3-m approach was allowed before the starting marker, and an additional 3 m of space was provided after the end marker of the 5-m path to ensure a usual walking pace throughout the task. Participants were instructed to walk the 11-m path at their usual walking pace. The time to complete the 5-m walking test was measured once and was used to calculate walking speed (m/min).

Falls follow-up

Fall frequency during the 12-month follow-up period was measured with two face-to-face interviews at 6 months and 12 months after baseline measurements. A fall was defined as "an unexpected event in which the person comes to rest on the ground, floor, or lower level" [27]. In this study, 'fallers' were defined as people who had at least one fall during the 12-month follow-up period [28].

Magnetic resonance imaging (MRI) procedure

Magnetic resonance imaging (MRI) was performed using a 1.5-T system (Magnetom Avanto, Siemens, Germany). Three-dimensional volumetric acquisition of a T1-weighted gradient-echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (repetition time, 1,700 ms; echo time, 4.0 ms; flip angle 15°, acquisition matrix 256 × 256, 1.3-mm slice thickness). Tissue segmentation, regulation, registration, and normalization were conducted in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/), which is incorporated in the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/), running on MATLAB R2010a (Mathworks). Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) [29] was conducted for the image analysis. The normalized images were transformed into Montreal Neurological Institute space. The gray matter images were then smoothened using a Gaussian kernel of 12-mm full-width at half-maximum.

Statistical analysis

For baseline comparisons, basic characteristics and physical performance tests including knee-extension strength, OLS, and WS were compared between fallers and non-fallers using *t*-tests. Chi-square tests for differences in proportions were used to compare differences in sex and history of falling in the past year at baseline between the faller and non-faller groups. To describe variations in different physical performance factors related to falls, multivariate logistic regression analyses were performed to reveal the physical performance factors independently related to falls during the 12-month follow-up after adjusting for age, sex, body mass index (kg/m^2), and history of falling in the past year at baseline. We calculated the odds ratios (OR) with 95% confidence intervals (CI). These statistical analyses were calculated using SPSS for Windows version 19.0 (SPSS Inc., Chicago, IL).

In the voxel-based morphometry (VBM) analysis, data preprocessing and analysis was performed with the VBM8 toolbox, which is incorporated in the SPM8 software. VBM [30] was used to examine differences in baseline gray matter volume between fallers and non-fallers. We used unpaired t-tests in SPM8 to identify the locations of smaller gray matter volume in fallers compared to non-fallers during the 12-month follow-up period using MRI data at baseline. Age and sex were included as covariates. The statistical threshold selected for these analyses was $P < .001$ (uncorrected), with an extent threshold of 100 voxels.

Results

The characteristics and physical performance tests at baseline are presented in Table 1. Over the 12-month follow-up period, 11 of the 42 participants (26.2%) experienced at least one fall. Fallers exhibited poorer one-legged standing time ($p < .01$) and slower walking speed ($p < .01$) compared with non-fallers. In addition, the faller group had a significantly higher rate of fall history at baseline compared with the non-faller group ($p < .01$). In the multivariate logistic regression, OLS time (sec) (OR [95% CI]: 0.89 [0.81, 0.98], $p = .02$) was associated with a significantly lower rate of falls during the 12-month follow-up after adjusting for age, sex, body mass index, and history of falling in the past year at baseline. There was no statistical evidence of associations between falls and knee-extension strength (Nm) (1.02 [0.96, 1.08], $p = .59$) and walking speed (m/min) (0.91 [0.81, 1.03], $p = .13$) (Table 2).

Table 1 Comparison of characteristics and physical performance tests between non-fallers and fallers at baseline

	Total (n = 42)	Non-fallers (n = 31)	Fallers (n = 11)	P-value
Age, years	75.6 ± 6.3	75.2 ± 6.5	76.8 ± 5.9	0.462
Female, n (%)	18 (42.9)	12 (38.7)	6 (54.4)	0.362
History of falling in the past year, n (%)	13 (31.0)	6 (19.4)	7 (63.6)	0.006
Knee-extension strength, Nm	60.5 ± 26.8	63.4 ± 23.3	52.3 ± 34.7	0.242
One-legged standing time, sec	32.3 ± 24.2	38.9 ± 22.3	13.8 ± 19.7	0.002
Walking speed, m/m	66.7 ± 12.6	70.0 ± 11.8	57.5 ± 10.4	0.004
Mini-mental state examination, score	26.3 ± 2.7	26.6 ± 2.0	25.5 ± 3.9	0.112

The gray matter density profiles used for examining differences between fallers and non-fallers at baseline are shown in Figure 1. VBM analysis revealed that fallers exhibited lower gray matter density compared with non-fallers in the bilateral middle frontal gyrus and superior frontal gyrus (Table 3). These regions correspond to the premotor cortex and supplementary motor area.

Discussion

The present study examined whether baseline physical performance and gray matter volume are related to falls during a 12-month follow-up period in community-dwelling older adults with MCI. Our results indicated that older adults with MCI exhibiting poor balance had a greater risk of falls during the 12-month follow-up period, while adjusting for age, sex, body mass index, and history of falling at baseline. In addition, baseline lower gray matter volume in the middle frontal gyrus and superior frontal gyrus was associated with the occurrence of subsequent falls. To our knowledge, this is the first study to examine the association between lower gray matter density and risk of falls in older adults with MCI.

Problems with gait and balance have been reported to have the strongest association with falling [2,31]. Slower walking speed has been found to be an independent predictor of falling [32,33]. Poor balance represented by increased postural sway and gait asymmetry has been reported to approximately triple the risk of falling [2]. A previous systematic review and meta-analysis provided a summary estimate for falls due to balance impairment at a relative risk of 1.42 [34]. Therefore, an assessment of balance and gait for older adults, particularly those without a history of falling, has been recommended [35]. Moreover, cognitive impairment has been associated with the risk of falls as well as deficits of physical function [2]. A recent systematic review and meta-analysis confirmed that cognitive deficits detected in clinical assessment are associated with an increased fall risk in community and institution-dwelling older adults [36]. A number of studies have examined the risk of falls in older adults with dementia [37]. However, little research has focused on individuals with MCI. MCI is increasingly recognized as a substantial clinical problem in older populations [38], so it is important to determine risk factors for falling among older individuals with MCI, and to develop effective fall-prevention strategies. A previous study showed that older women with MCI demonstrated a greater number of risk factors for falling compared with older women without MCI [14]. The results of the present study indicate that poor balance assessed by one-legged standing time predicts falls in people with MCI prospectively over 12 months. Although fallers exhibited slower walking speed compared with non-fallers, walking speed was not associated with the occurrence of subsequent falls after adjusting for age, sex, body mass index, and history of falling at baseline. There was no difference in the extension strength between fallers and non-fallers. The results of this study indicate that poor balance is the important factor related to an increased risk of falling among people with MCI. Muscle weakness and problems with mobility had been considered to be the important contributors to the risk of falling in older people [5], and there are presumably some relationships. In study cohorts including older people with MCI and similar lower muscle strength, like the present study, poor balance may have a greater impact on increased risk of falling

Table 2 Multivariate logistic regression summary for physical performance on falls (n = 42)

Variables	Odds ratio	95% confidence intervals	*p* Value
Knee-extension strength, Nm	1.017	0.957-1.080	0.588
One-legged standing time, sec	0.891	0.809-0.981	0.019
Walking speed, m/m	0.911	0.806-1.029	0.133

Notes: Age, sex, body mass index (kg/m^2) and history of falling in the past year at baseline were included as covariates.

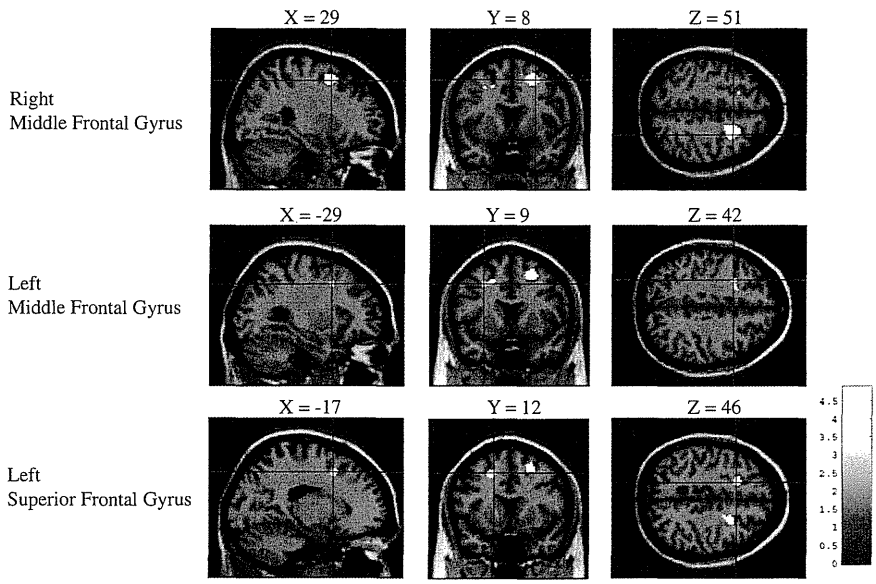

Figure 1 Gray matter density in fallers versus non-fallers. Regions of gray matter reduction in fallers compared to non-fallers ($p < 0.001$, uncorrected). Fallers exhibited a greater reduction of gray matter loss in the bilateral middle frontal gyrus and superior frontal gyrus.

than walking performance. Certainly, poor balance could be one of the predictors of walking decline among older people [39]. Balance ability may be an important dimension of physical functioning to predict the occurrence of subsequent falls among older people with MCI, as well as those with intact cognition. The present study has advantages including the examination of occurrence of subsequent falls during a 12-month follow-up period and neuroimaging assessments in older adults with MCI. However, our sample was not large, and selection bias may affect the results of the relationships between physical performance and occurrence of subsequent falls. Therefore, future studies with larger numbers of MCI subjects and a longitudinal design are needed to add evidence to the present results.

Unlike previous investigations, the current study included MRI scanning and a follow-up assessment of falls in community-dwelling older adults with MCI. The results provide the first evidence that lower gray matter volume in the middle and superior frontal gyrus is related to the occurrence of subsequent falls among older adults with MCI. Age-related changes in the brain may contribute to the subtle onset of motor disturbances in older people. Previous brain-imaging studies of older adults have reported that age-related changes in the brain, such as lower global brain volume, WMH, and microbleeds, are associated with clinical measures of poor balance and slow gait [40-43]. The association between MRI-detected lower brain volume and falls in older adults with MCI has not been examined longitudinally. In the present study, fallers exhibited decreased gray matter density compared with non-fallers in the bilateral middle frontal gyrus and superior frontal gyrus corresponding to premotor cortex and supplementary motor area. These particular regions are likely to play an important role in predicting fall-risk because the middle frontal gyrus is involved in controlling behavior with spatial and sensory guidance.

Growing evidence suggests that brain function is associated with physical function, as confirmed by neuroimaging techniques. Structural changes of the brain in older people are reported to be related to physical performance, such as gait dysfunction [44,45], postural instability [24], and lack of cardiorespiratory fitness [46].

Table 3 VBM results including age and sex as covariates

Location	Cluster size (K)	Peak T	Z score	P (uncorrected)	MNI coordinates		
					X	Y	Z
Right middle frontal gyrus	594	4.87	4.27	< 0.001	29	8	51
Left middle frontal gyrus	165	4.35	3.90	< 0.001	−29	9	42
Left superior frontal gyrus		4.78	4.20	< 0.001	−17	12	46

Note: *VBM* voxel-based morphometry.

Activation in the frontal cortex, including the premotor cortex and the supplementary motor areas, have been reported to increase during human gait by studies using near-infrared spectroscopic imaging [47-50]. Previous studies have reported that lower brain volume in the prefrontal areas is associated with slower gait in high-functioning or cognitively normal older adults [23,40,51]. Other neuroimaging studies have indicated that 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 region [52-54]. The middle frontal gyrus is involved in motor output and the direct control of behavior, as well as planning, spatial guidance, and sensory guidance of movement [55]. Lower gray matter volume in the premotor cortex and supplementary motor area may be risk factors for falls in older adults. Falls often occur when older individuals attempt to avoid an obstacle in their path, requiring the control of behavior and the planning of movement under sensory guidance. The premotor cortex and supplementary motor area may play an important role in preventing falls when spatial and sensory guidance are required for movement.

Several limitations of the current study should be noted. First, fall experience during the 12-month follow-up period were confirmed with two face-to-face interviews at 6-months and 12-months after baseline, while previous studies have reported that monthly fall diaries and follow-up telephone calls provide more accurate measures of fall frequency [56,57]. Second, participants who had at least one fall during the 12-month follow-up period were categorized as fallers in this study. A previous study reported that single fallers are more similar to nonfallers than to recurrent fallers on a range of medical, physical, and psychological risk factors [58]. Other studies defined fallers as people who had at least one injurious or two non-injurious falls [17,59]. In addition, our MRI scans were performed using a 1.5-T system with relatively low resolution. We performed the VBM analysis to identify the locations of group differences in gray matter volume. Therefore, we consider that our results cannot provide evidence for whether the effects of physical performance are independent of the gray matter volume or whether the latter confounds the association between the former and the fall risk. Although it is unclear whether lower gray matter volume is related to poor balance in older adults with MCI, the current study revealed that poor balance and lower gray matter volume in the middle frontal gyrus and superior frontal gyrus were associated with falls. To clarify these points, we consider that future studies including larger numbers of subjects and countable data for structural changes in the brain (e.g., described volumes in cubic millimeters) are needed.

Conclusions

The current findings indicate that poor balance predicts falls over a 12-month period, and that lower gray matter volume in the middle frontal gyrus and superior frontal gyrus was associated with falls in older adults with MCI. Maintaining physical function, especially balance, and brain structural changes through many sorts of prevention strategies in the early stage of cognitive decline may contribute to decreasing the risk of falls in older adults with MCI.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HM has made substantial contributions to conception and design, subject recruitment, analysis and interpretation of data, and writing the manuscript. HS has made substantial contributions to conception and design, subject recruitment, interpretation of data, and writing the manuscript. TD has made substantial contributions to subject recruitment, acquisition of data, interpretation of data, and manuscript preparation. HP has made substantial contributions to conception and design, interpretation of data, and writing the manuscript. DY contributed subject recruitment and manuscript preparation. KU and KT contributed subject recruitment and acquisition of data. TLA has been involved in drafting the manuscript or revising it critically for important intellectual content. TS has made substantial contributions to conception and design and writing the manuscript. All authors read and approved the final manuscript.

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