that plasma levels of BDNF were decreased in participants with type 2 diabetes independent of obesity (Krabbe et al., 2007). Plasma BDNF was inversely associated with fasting plasma glucose, but not with insulin. When plasma insulin was increased while maintaining normal blood glucose, the cerebral output of BDNF was not inhibited, indicating that high levels of glucose, but not insulin, inhibit the output of BDNF from the human brain. They concluded that the cerebral output of BDNF, which is negatively related to high plasma glucose levels and decreased BDNF, may be a pathogenetic factor involved not only in dementia, but also in type 2 diabetes. The results of our cohort support previous findings. Smoking was associated with higher BDNF levels; this finding is consistent with several studies. In animal studies, regional brain BDNF expression was altered by exposure to or withdrawal from nicotine (Kenny et al., 2000). In some human studies, smoking cessation increased BDNF serum levels over the span of several months (Kim et al., 2007; Bhang et al., 2010). A recent epidemiological study of 1168 subjects aged 18–65 years also reported an independent relationship between smoking and serum BDNF levels, with higher BDNF in former and current smokers compared to subjects who never smoked (Bus et al., 2011). The results of our study confirm this relationship between BDNF and smoking in adults 65 years of age and older. Nicotine has induced SH-SY5Y neuroblastoma cell proliferation through BDNF and its receptor, TrkB. The activation of nicotinic receptors has effects upon the BDNF–TrkB pathway, inducing cell proliferation by promoting the release of BDNF, which in turn activates TrkB receptors (Serres and Carney, 2006). Moreover, the beta-arrestin-2 protein is important in induction and expression of nicotine sensitization as well as nicotine's effects on accumbal BDNF (Correll et al., 2009).

Brain-derived neurotrophic factor is highly concentrated in the hippocampus (Phillips et al., 1990; Wetmore et al., 1990). A single nucleotide polymorphism in the BDNF gene affects the regulated secretion of BDNF in the hippocampus (Egan et al., 2003) and has been related to lower serum levels of BDNF (Ozan et al., 2010) and smaller hippocampal volumes (Pezawas et al., 2004; Szeszko et al., 2005), which can lead to deficits in executive function (Frodl et al., 2006) and memory function (Erickson et al., 2009). The hippocampus–orbitomedial prefrontal circuit integrates cognition, emotion, and behavior, thereby influencing working memory and executive functions (Wall and Messier, 2001). The observed relationship between lower serum BDNF and impaired memory and processing speed is consistent with previous studies. However, the relationships between serum BDNF and executive function, the Trail Making Test – Part B, did not reach significance ($P = 0.09$). Further studies will be needed to establish the relationships between serum BDNF and executive function in the elderly adults.

Serum BDNF values 1.5 SD lower than the age- and sex-adjusted mean were associated with MCI, whereas serum BDNF levels lower than 1.0 SD from age- and sex-adjusted mean serum BDNF values were not. These results suggest that the participants who had 1.5 SD lower than the mean age- and sex-adjusted BDNF values may pose a risk of cognitive impairment. BDNF supports cholinergic, dopaminergic, serotonergic, and neuropeptide-containing neurons (Hyman et al., 1991; Knusel et al., 1991; Mamounas et al., 1995) and may play an important role in AD-related pathophysiology. Animal studies found that Aβ disrupts BDNF signaling and that BDNF protects against Aβ toxicity via TrkB signaling (Tapia-Arancibia et al., 2008). Lower levels of both BDNF and TrkB have been found in postmortem brains of individuals with AD (Murer et al., 2001). BDNF levels are significantly reduced in the hippocampus and parietal cortex and BDNF/neurotrophin 3 ratios are lower in frontal and parietal cortices in patients with AD compared with age-matched controls (Hock et al., 2000). Higher serum levels of BDNF in individuals with AD are predictive of slower rates of decline (Laske et al., 2011). Peng et al. (2005) reported strong relationships between MMSE and Global Cognitive Score results and proBDNF and mature BDNF levels. Decreased serum BDNF in the preclinical stages of AD further suggests that BDNF and proBDNF deficiency play a pivotal role in cell atrophy, cell loss, and synaptic dysfunction, with a lack of trophic support contributing to the degeneration of specific neuronal subpopulations in the AD-affected brain (Hock et al., 2000; Laske et al., 2007).

Other studies have shown that BDNF serum levels increase in MCI and AD patients (Angelucci et al., 2010). This increase may reflect a compensatory repair mechanism in early and late neurodegeneration that is protective by contributing to Aβ degradation. Laske et al. (2006) found that patients in the early stages of probable AD with MMSE scores ≥21 (mean of 25.5) had significantly higher serum BDNF levels compared to patients in late-stage AD with MMSE scores <21 (mean of 13.3) and age-matched healthy controls. The study also showed a tendency toward lower BDNF levels in patients with late-stage AD and progressive dementia (mean MMSE: 13.3; range: 6–20). The mean MMSE scores of our MCI participants was 26.6 (range: 24–30), higher than that of patients in the early stages of probable AD in the Laske et al. (2006) study. Our MCI participants may have been at a stage earlier than the point at which the BDNF compensatory repair mechanism is triggered in early neurodegeneration.

The strengths of the present study include the large sample size and comprehensive measurement of cognitive function, which correlates closely with dementia. One limitation of the study is that the analysis is based on cross-sectional data. Although our study was population-based, further prospective investigations are needed to validate using 1.5 SD serum BDNF levels for discriminating the risk of cognitive decline and MCI in older people. Sensitivity of the 1.5 SD serum BDNF levels to discriminate MCI and healthy participants showed a very low value (6.4%). The result suggests that it is necessary to review the discrimination point to screen MCI in the community with high sensitivity. BDNF is reduced in elderly individuals with major depression and bipolar disorder, with distinct dynamics according to the disease stages, treatment, or the presence of cognitive impairment (Molendijk et al., 2011; McKinney and Sibille, 2013; Sibille, 2013). In a recently published study, Diniz et al. (2014) showed a significant decline in serum BDNF level over 2 years of follow-up only in those individuals with persistent cognitive decline (Diniz et al., 2014). Therefore, BDNF seems to be a non-specific marker for many neuropsychiatric disorders, thus, reducing its discriminative power to identify individuals with MCI. Our study also excluded older adults with neurological disorders and those adults who were certified for long-term care insurance due to functional

decline. Therefore, the study findings may not be generalized to these patient groups. It is likely that several clinical and etiological heterogeneities exist between subtypes of MCI (Petersen, 2004). Although amnestic MCI appears to be most closely linked with AD, there are many concomitant pathologic abnormalities, including argyrophilic grain disease, hippocampal sclerosis, and vascular lesions (Petersen et al., 2006). The findings of the study about the relationships between serum BDNF and MCI may change in further analyses of each subtype of MCI.

In conclusion, we provide preliminary evidence that serum BDNF can be associated with lower cognitive test scores in older people. In our cohort, serum BDNF was marginally associated with the presence of MCI when BDNF was 1.5 SD lower than the mean age- and sex-adjusted values. Future prospective studies should establish the discriminative value of serum BDNF for a risk of MCI and its validity as a screening test for this population.

AUTHOR CONTRIBUTIONS

Study concept and design: Hiroyuki Shimada, Takao Suzuki; acquisition of data: Hyuma Makizako, Takehiko Doi, Daisuke Yoshida, Kota Tsutsumimoto, Yuya Anan, Kazuki Uemura; analysis and interpretation of data: Sangyoon Lee; critical revision of the manuscript: Hyuma Makizako, Hyuntae Park; statistical analysis: Hyuntae Park; drafting of the manuscript: Hiroyuki Shimada; obtaining funding: Hiroyuki Shimada, Takao Suzuki, Hyuma Makizako; study supervision: Takao Suzuki.

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RESEARCH ARTICLE Open Access

Cognitive function and gait speed under normal and dual-task walking among older adults with mild cognitive impairment

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Abstract

Background: Gait ability and cognitive function are interrelated during both normal walking (NW) and dual-task walking (DTW), and gait ability is thus adversely affected by cognitive impairment in both situations. However, this association is insufficiently understood in people with mild cognitive impairment (MCI). Here, we conducted a study with MCI participants, to examine whether the association depends on walking conditions and MCI subtypes.

Methods: We classified 389 elderly adults into amnestic MCI (n = 191) and non-amnestic MCI (n = 198), assessed their cognitive functions, and administered gait experiments under NW and DTW conditions. Gait ability was defined as gait speed. Five aspects of cognitive function were assessed: processing speed, executive function, working memory, verbal memory, and visual memory.

Results: Regression analysis adjusted for covariates showed a significant association between cognitive functions and gait speed. Processing speed and executive function correlated with gait speed during both NW and DTW ($p < .05$). Gait speed during DTW was also significantly associated with working memory ($p < .001$). Visual memory was associated during NW and DTW, particularly for amnestic MCI participants ($p < .05$).

Conclusions: Our findings support the idea that the association between gait speed and cognitive function depends on walking condition and MCI subtypes. Additional studies are necessary to determine the neural basis for the disruption in gait control in older adults with MCI.

Background

Dementia is a notable health issue because of its extensive impact on the activities and quality of life of older adults. Given the current absence of disease-modifying treatments, as well as increasing awareness that symptoms develop over many years or even decades, there has been growing interest in early detection and effective strategies for prevention [1]. Mild cognitive impairment (MCI) is considered a clinical characteristic that typifies the prodromal phase of Alzheimer's disease (AD), the most common type of dementia [2]. Numerous studies have identified a wide range of potentially modifiable risk factors for AD and dementia, including cardiovascular risk factors, psychosocial factors, and health behaviors [1,3]. Gait impairment is a common characteristic in participants with cognitive impairments [4-6] and is a risk factor for developmental MCI and dementia [7,8]. Cognition and gait are thought to be strongly linked, a contention supported by findings from experimental studies using a dual-task paradigm to epidemiology.

Less is known about the relationships between specific cognitive functions and gait in people with MCI, though population studies have been conducted in older adults to examine this issue [9-14]. Prospective studies indicate that lower attention/executive function [9,13] or memory function [9,11] may lead to a decline in gait speed in older adults. Alternatively, a slow gait speed predicts deficits in the cognitive-processing speed [12] or in executive and memory functions [14]. Emerging evidence

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indicates that cognitive processes related to prefrontal lobe function such as attention and executive function are associated with slower gait and gait instability [15]. However, a consensus regarding the relationship between gait variables and memory deficits in particular has not yet been reached [9-11,14]. Mielke *et al.* has suggested that inconsistencies between studies may be partially due to variation in participant characteristics across studies, ranging from exclusively older adults with normal cognition to mixed participant pools that include those with MCI or AD [14]. In addition, the decline in cognitive function in people with MCI is not uniform, but rather depends on MCI subtype, i.e., amnestic (aMCI) or non-amnestic (naMCI) [2]. Furthermore, subtypes of MCI may potentially have different neuropathologies and courses of conversion, although the dependency of subtypes has not reached consensus [16-20]. Investigating cognitive function in MCI participants requires considering several cognitive function domains as well as these MCI subtypes.

The relationship between cognitive function and gait variables in conditions other than normal walking (NW) is insufficiently understood in people with MCI. Observing how people walk while they perform a secondary attention-demanding task, i.e., a dual-task paradigm, has been used to assess interactions between cognition and gait. Existing population studies have been conducted using both NW and dual-task paradigms with specific conditions [21-23], and gait coordination during dual-task walking (DTW) has been shown to be deteriorated [24,25] and to be associated with reduced executive function [21,22]. Although evidence is scarce, gait variables in older adults with MCI have been shown to be affected in both NW [6] and DTW [26]. Less focus has been given to the association between cognitive function and gait, and no strong conclusions can be drawn because of small MCI sample sizes, non-comprehensive cognitive measurements, or experiments that only examine NW. Thus, a large population study that combines comprehensive cognitive assessments with experiments that include DTW will contribute to a better understanding of the relationship between cognitive function and gait in people with MCI.

Untangling the relationship between early gait disturbances and early cognitive changes may be helpful in identifying older adults who are at risk of mobility decline, falls, and progression to dementia [15]. This study aimed to examine the association between cognitive function and gait speed in older people with MCI, and to examine whether these associations differed depending on walking condition (normal or dual-task) and subtypes of MCI. Gait ability was defined as gait speed following the standard method used in population studies of gait [14].

Methods

Participants

The study population and data were in a cohort study. Six hundred and forty-nine participants were selected as a potential study population from a cohort study (Obu Study of Health Promotion for the Elderly [27]) and met the following criteria: over 65 years old, diagnosed with MCI, no specific medical history of cerebrovascular disease, Parkinson's disease, connective tissue disease, or depression, no severe visual or auditory impairment, no current symptoms of depression (Geriatric Depression Scale ≥6 [28]), not part of other research projects, and not certified to receive support from the Japanese public long-term-care insurance system. As a result of recruitment, 409 responded and after giving their written informed consent 389 people completed the neuropsychological assessments and gait experiments. The ethics committee of the National Center for Geriatrics and Gerontology approved this study.

MCI criteria

MCI criteria followed those established and revised by Petersen [2], and in particular, participants satisfied the following conditions: 1) memory complaints; 2) objective cognitive decline; 3) intact general cognitive function; and 4) independent functioning in daily living activities. Intact general cognitive function was defined as a Mini-Mental State Examination score >23 [29]. Objective cognitive decline was defined as having cognitive function more than 1.5 standard deviations lower than normal. Normal scores were taken from the Obu Study of Health Promotion for the Elderly (OSHPE) database of healthy individuals [27]. Cognitive function was also assessed in multiple domains using the National Center for Geriatrics and Gerontology Functional Assessment Tool [30]. Participants who suffered from cognitive decline in the memory domain were classified as aMCI, while those who did not were classified as naMCI.

Gait measures

Participants wore the same type of appropriately sized shoes before each experiment. Participants were instructed to walk on a smooth 11-m horizontal walkway that had a 2-m buffer space at both ends for acceleration and deceleration. The time to walk 5 m to the mid-point of the walkway was measured, and gait speed was expressed in meters per second. Two gait experiments were performed sequentially: NW, in which participants walked at their preferred speed, was followed by DTW. Participants were instructed to walk while counting backward from 100 in DTW. This type of arithmetic task is commonly used in DTW investigations and its effects on gait have been confirmed in a meta-analysis [24].

Cognitive function

Cognitive function was evaluated by comprehensive neuropsychological assessment and conducted by a well-trained speech therapist. Processing speed was assessed using a tablet version of the Symbol Digit Substitution Task (SDST) [30], based on the Symbol Digit Modalities Test [31]. The score is the number of correct answers chosen within 90 s. Executive function was evaluated using a tablet version of the Trail Making Test Part B (TMT-B, 15 stimuli) [30]. We recorded the amount of time it took to complete each task, and results were excluded from analysis if this time was greater than 90 seconds. Working memory was assessed using the digit span backward test, a subset of the Wechsler Adult Intelligence Scale III [32]. Verbal memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT) [33]. Visual memory was examined using the visual reproduction subtest of the Wechsler Memory Scale-Revised (WMS-R) [34]. Better performance is represented by lower values in the TMT-B and higher values in the other tests.

Other covariates

Age, sex, body mass index (weight/height^2), and educational history were recorded as demographic data. Medical conditions and current medications were recorded. Apolipoprotein E (APOE) genotype was assessed using genomic DNA extracted from peripheral blood leukocytes or autopsy tissues using a standard method (SRL, Inc., Tokyo, Japan). The genotyped data were strictly controlled under condition of anonymity and blinded from the clinical information. Carrying ε4 is thought to be a strong factor related to deterioration of cognitive function in MCI participants [35]. To assess functional capacity, we used the Tokyo Metropolitan Institute of Gerontology Index of Competence [36] and activity level was measured using a life-space assessment [37].

Statistical analysis

We compared participant characteristics between MCI subtypes (aMCI and naMCI) using an unpaired *t*-test for continuous variables or a chi-square test for categorical variables. Before examining the association between cognitive functions and gait variables, we first compared cognitive functions and gait variables between aMCI and naMCI groups. To compare cognitive function, we used a general linear model adjusted for age, which is thought to be a strong covariate, and participant characteristics that differed significantly between MCI subtypes. For gait variables, we used a repeated-measures analysis of variance (ANOVA) (adjusted for the same variables as above) to test for the main effects of MCI subtype (aMCI or naMCI) and walking condition (NW or DTW). To examine whether cognitive functions were independently associated with gait speed, we used a multivariable regression analysis adjusted for age, sex, body mass index, education, medication, life space, functional capacity, and APOE status as potential covariates. This adjusted model is conducted against gait speed under NW and DTW (model 1). Additionally, to clarify the association between cognitive function and gait speed under DTW, model 2 adjusted variables using model 1 added to gait speed in NW was conducted (model 2). All analyses were performed using commercially available software (JMP 9.0 J for Windows; SAS Institute Japan, Tokyo, Japan). Statistical significance was set at $p < .05$.

Results

The 389 participants (52% women, mean age: 71.6 years) were classified as either aMCI (n = 191) or naMCI (n = 198). Table 1 summarizes the demographic data including educational history, current medication, functional capacity, life space, and status of APOE. The proportion of women was significantly different between MCI groups (aMCI: n = 79, 41%; naMCI: n = 124, 63%; $p < .001$), while other demographic variables were not. Therefore, when comparing cognitive functions between MCI groups, we adjusted for age and sex. RAVLT scores were lower in aMCI participants, while SDST scores were lower in

Table 1 Subject characteristics

Variables	*M* ± *SD*
Age (years)	71.6 ± 4.9
Sex (women subjects (%))	203 (52)
Body mass index (kg/m^2)	23.4 ± 2.9
Educational history (years)	11.0 ± 2.4
TMIG (score)	12.4 ± 1.1
Life-space assessment (score)	90.2 ± 15.7
Current medications (numbers)	2.2 ± 2.0
Type of MCI (amnestic MCI (%))	191 (49)
Status of apolipoprotein E (ε4 carrier (%))	76 (20)
Cognitive tests	
MMSE (score)	26.7 ± 1.9
SDST (score)	38.9 ± 7.4
TMT-B (s)	43.5 ± 16.7
Digit span backward (score)	5.1 ± 1.6
RAVLT-delay (score)	7.3 ± 3.4
Visual reproduction (score)	21.9 ± 8.8
Normal walking	
Gait speed (m/s)	1.36 ± 0.22
Dual-task walking	
Gait speed (m/s)	1.23 ± 0.32

Note: TMIG: Tokyo Metropolitan Institute of Gerontology Index of Competence. MCI: mild cognitive impairment. SDST: Symbol Digit Substitution Task. TMT-B: Trail Making Test Part B. RAVLT: Rey Auditory Verbal Learning Test
Values are mean ± SD or numbers (proportion).

naMCI participants (RAVLT: $p < .001$, SDST: $p = .002$). No significant differences between groups were found for the other cognitive functions. A repeated-measures ANOVA adjusted for age and sex showed that gait speed was affected by walking condition (NW vs. DTW: $p = .042$), but not by MCI group (naMCI vs. aMCI: $p = .301$).

Simple correlation analysis showed a significant relationship between normal gait speed and all cognitive functions in all MCI participants (SDST: $r = .406$, $p < .0001$; TMT-B: $r = -.375$, $p < .0001$; digit span: $r = .122$, $p = .0166$; RAVLT: $r = .209$, $p < .0001$; visual reproduction: $r = 0.306$, $p < .0001$). DTW was also significantly associated with cognitive functions in all MCI participants (SDST: $r = .395$, $p < .0001$; TMT-B: $r = -.373$, $p < .0001$; digit span: $r = .307$, $p < .0001$; RAVLT: $r = .238$, $p < .0001$; visual reproduction: $r = .325$, $p < .0001$). Results from cognitive function tests are plotted against gait speed in Figure 1 (NW) and Figure 2 (DTW). A multivariate regression analysis adjusted for potential covariates was conducted and the results for gait variables during NW are summarized in Table 2. During NW, gait speed was associated with SDST scores in both MCI groups (aMCI: $p = .003$; naMCI: $p = .009$), with visual reproduction scores in aMCI participants ($p = .037$), and with TMT-B scores in naMCI participants ($p = .025$). Digit span and RAVLT were not significantly associated with gait speed during NW. Associations with gait speed during DTW are summarized in Table 3. Cognitive functions other than RAVLT correlated with gait speed in DTW even adjusted for normal gait speed in aMCI participants (all tests, $p < .05$), while only digit span did so in naMCI participants ($p < .001$).

Discussion

The results of this study indicate positive associations between cognitive functions and gait speed in MCI participants. The independent associations were revealed by a multivariate analysis adjusting for several potential confounding factors including the status of APOE. Processing speed and executive function correlated with gait speed during NW and DTW. Working memory was significantly associated with gait speed during DTW in both subtypes of MCI participants. Visual memory was also associated with gait speed in NW and DTW particularly in aMCI participants.

Our study showed that cognitive function in MCI participants is correlated with gait speed, and that this association differs depending on walking conditions (normal or dual-task). Indeed, some prospective studies have touched on this inter-relationship. Gait speed during NW has been shown to be related to cognitive decline [12], MCI [7], and risk of dementia [8], while impaired cognitive functions have been shown to be related to a decline in normal gait speed [9,11,13]. The majority of studies investigating this relationship have focused on normal gait speed and processing speed [12] or executive function [9,13], and have confirmed the relationship

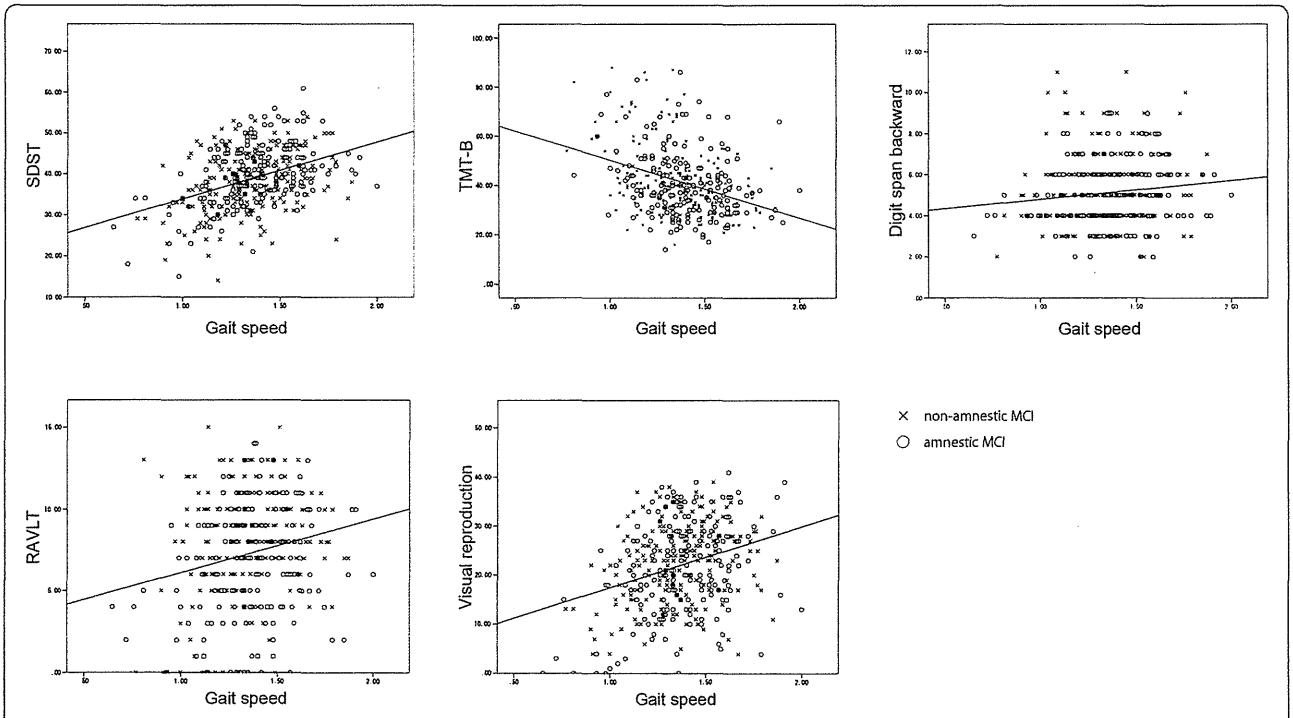

Figure 1 Cognitive measurements and gait speed during normal walking. Scatter plots showing scores of cognitive measurements and gait speed (m/s) during normal walking, grouped by MCI subtype. Lines indicate the resulting regression line for all participants.

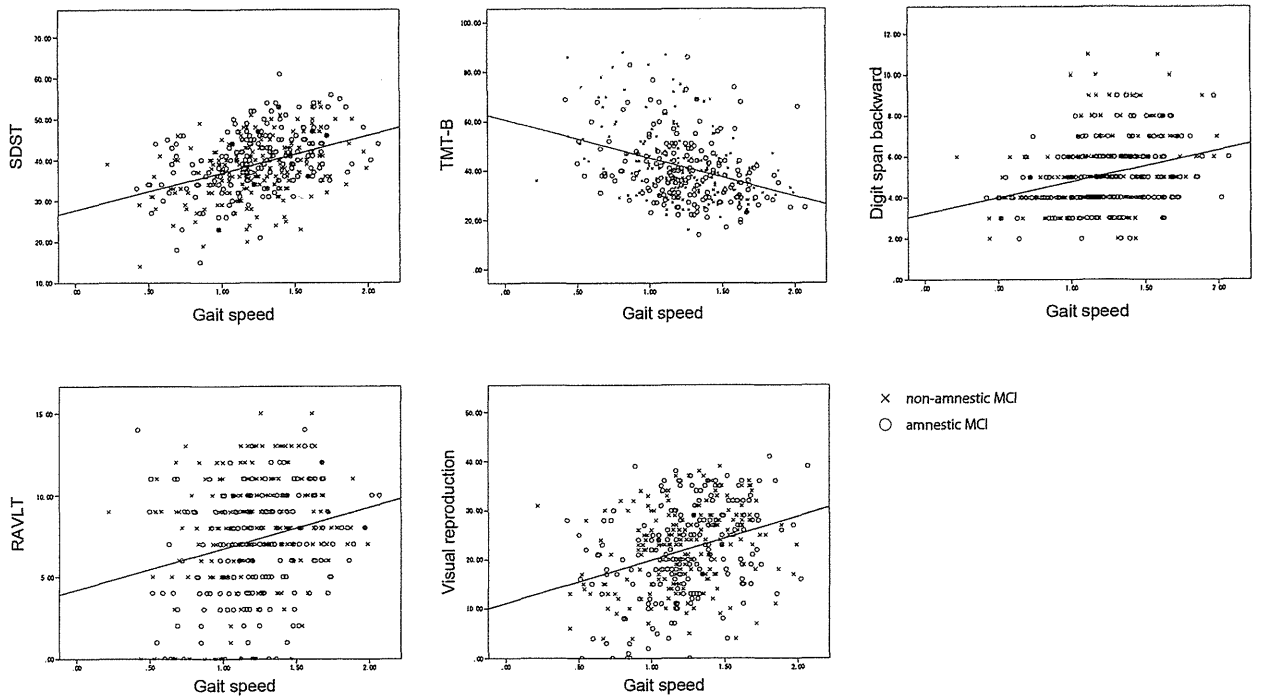

Figure 2 Cognitive measurements and gait speed during dual-task walking. Scatter plots showing scores of cognitive measurements and gait speed (m/s) during dual-task walking grouped by MCI subtype. Lines indicate the resulting regression line for all participants.

in older adults. Consistent with our results in MCI participants, McGough *et al.* have reported that physical performance is associated with executive function after adjusting for age, sex, and age-related factors in sedentary older adults with aMCI [38]. Here, we show that in addition to processing speed and executive function, gait speed during DTW is also associated with working memory in MCI participants, even after adjusting for normal gait speed. The effect of DTW on gait variables [24,25] and the requirement for executive function in older adults have been reported [21,22], and cognitive impairment (e.g., MCI) has been shown to have an impact on DTW performance. Montero-Odasso *et al.* [26] suggested that gait speed in MCI participants is related to working memory ability, and that the relationship is exaggerated during DTW. Our results partially agree with their study in that working memory was correlated with gait variables during DTW but not NW. Executive function is thought to be dominant in prefrontal lobe function. Processing speed has been reported to correspond to prefrontal lobe function, a region also thought to have a role in gait control [39]. Working memory systems are believed to be dominated and require similar neural resources in prefrontal cortex [40], although the resources for these functions are not fully identical. Our study supports the idea that prefrontal lobe function is required for gait in MCI participants.

Table 2 Multivariable regression results between cognitive function and gait speed during normal walking

Cognitive measures	Cognitive domain	Coefficients (SE)		
		aMCI	naMCI	Total
		(n = 191)	(n = 198)	(n = 389)
SDST	Processing speed	.216 (0.002)†	.202 (0.002)†	.209 (0.002)‡
TMT-B	Executive function	-.095 (0.001)	-.287 (0.001)‡	-.180 (0.001)‡
Digit span backward	Working memory	.013 (0.009)	.006 (0.009)	.006 (0.006)
RAVLT-delay	Verbal memory	.087 (0.004)	.025 (0.005)	.036 (0.003)
Visual reproduction	Visual memory	.142 (0.002)*	.066 (0.002)	.111 (0.012)*

Note: aMCI: amnestic mild cognitive impairment. naMCI: non-amnestic mild cognitive impairment. SDST: Symbol Digit Substitution Task. TMT-B: Trail Making Test Part B. RAVLT: Rey Auditory Verbal Learning Test.
Multivariable regression was adjusted for age, sex, body mass index, education, medication use, life space, functional capacity, and apolipoprotein E status.
*$p < .05$. †$p < .01$. ‡$p < .001$.

Table 3 Multivariable regression results between cognitive function and gait speed during dual-task walking

Cognitive measures	Cognitive domain	Coefficients (SE)					
		Model 1			Model 2		
		aMCI (n = 191)	naMCI (n = 198)	Total (n = 389)	aMCI (n = 191)	naMCI (n = 198)	Total (n = 389)
SDST	Processing speed	.349 (0.004)‡	.214 (0.003)†	.269 (0.002)‡	.195 (0.003)†	.093 (0.003)	.134 (0.002)†
TMT-B	Executive function	-.203 (0.002)*	-.265 (0.002)†	-.237 (0.001)‡	-.148 (0.001)*	-.092 (0.001)	-.121 (0.001)†
Digit span backward	Working memory	.234 (0.015)†	.214 (0.013)†	.227 (0.010)‡	.226 (0.012)‡	.210 (0.009) ‡	.223 (0.007)‡
RAVLT-delay	Verbal memory	.174 (0.007)*	.047 (0.007)	.101 (0.005)	.120 (0.006)	.032 (0.005)	.079 (0.004)
Visual reproduction	Visual memory	.252 (0.003)‡	.109 (0.003)	.196 (0.002)‡	.166 (0.002)†	.068 (0.002)	.128 (0.002)†

Note: aMCI: amnestic mild cognitive impairment. naMCI: non-amnestic mild cognitive impairment. SDST: Symbol Digit Substitution Task. TMT B: Trail Making Test Part B. RAVLT: Rey Auditory Verbal Learning Test.
Model 1: Multivariable regression was adjusted for age, sex, body mass index, education, medication use, life space, functional capacity, and apolipoprotein E status. Model 2: adjusted for variables in model 1 and gait speed in normal walking.
*$p < .05$. †$p < .01$. ‡$p < .001$.

The associations between cognitive function and gait speed differed depending on MCI subtype. To our knowledge, this is the first report showing that memory function requiring free recall is correlated with gait variables specifically in aMCI participants. Although a consensus regarding the relationship between memory function and gait ability has not been reached in studies of healthy older adults, our results are in line with prospective studies of healthy older adults [9,11]. Memory function in MCI, particularly aMCI, is a clinical signature of developing AD [2]. However, whether or not memory function relates to gait variables remains an open debate even when including studies using neuroimaging [41,42]. Unlike executive function, investigations focusing on the connection between memory and gait ability are few, and those that do have used variable measures of memory (e.g., verbal memory or visual memory). We examined verbal memory (RAVLT) and visual memory (visual reproduction subtest of the WMS-R) separately. Gait speed during both NW and DTW conditions correlated with visual memory functions in aMCI participants, while verbal memory function never correlated with gait speed. This result may reflect the fact that visual memory is required for visuospatial processing in addition to simple memory functions. In fact, cortical thickness [43] and gray matter [41] in visual processing regions are correlated with gait variables during NW. Further study is required to clarify the relationship between memory function and gait performance.

Our study had several strengths and limitations. We used a large cohort with a sufficient sample size. Additionally, our analysis included adjustments for several potential covariates, such as the status of APOE, that affect not only pathogenesis (e.g., Aβ aggregation or neural toxicity) [44] but cognitive decline [35]. However, some limitations must be noted. Because a cross-sectional design was used, the causal relationship between cognitive function and gait is still unclear in people with MCI. Further prospective studies are required to address this issue. Additionally, the type and/or difficulty of the cognitive task used for DTW could have affected the results. While the mental tracking task we adopted (counting backwards) is widely used, the effects of dual tasking on gait may depend on the cognitive task [24]. Hence, DTW using other types of cognitive tasks (e.g., verbal fluency) should be investigated. Finally, neuroimaging methods have recently been used to clarify the cortical control of gait. Further evidence using imaging techniques should be gathered to clarify the association between cognitive function and gait ability under varied conditions.

Conclusion

Successful DTW for those with MCI may require adequate cognitive function, processing speed, executive function, working memory and visual memory. The association between cognitive functions and gait variables partially depends on the MCI subtype. Gait speed in both NW and DTW are associated with memory performance particularly in MCI participants whose memory performance has declined (aMCI) compared with those with relatively intact memory functions (naMCI). Further studies are needed to clarify the effects of cognitive function on gait in MCI participants.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TD substantially contributed to the conception of the methods used, participant recruitment, analysis and writing the manuscript. HS and HM made substantial contributions to conception and design, participant recruitment, and writing the manuscript. KT and KU were involved in the acquisition, analysis and interpretation of data. YA contributed to the acquisition of data. TS made substantial contributions to the conception and design and writing the manuscript. All authors read and approved the final manuscript.

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Objectively measured physical activity, brain atrophy, and white matter lesions in older adults with mild cognitive impairment

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ABSTRACT

Physical activity may help to prevent or delay brain atrophy. Numerous studies have shown associations between physical activity and age-related changes in the brain. However, most of these studies involved self-reported physical activity, not objectively measured physical activity. Therefore, the aim of this study was to examine the association between objectively measured physical activity, as determined using accelerometers, and brain magnetic resonance imaging (MRI) measures in older adults with mild cognitive impairment (MCI). We analyzed 323 older subjects with MCI (mean age 71.4 years) who were recruited from the participants of the Obu Study of Health Promotion for the Elderly. We recorded demographic data and measured physical activity using a tri-axial accelerometer. Physical activity was classified as light-intensity physical activity (LPA) or moderate-to-vigorous physical activity (MVPA). Brain atrophy and the severity of white matter lesions (WML) were determined by MRI. Low levels of LPA and MVPA were associated with severe WML. Subjects with severe WML were older, had lower mobility, and had greater brain atrophy than subjects with mild WML (all $P < 0.05$). Multivariate analysis revealed that more MVPA was associated with less brain atrophy, even after adjustment for WML ($\beta = -0.126$, $P = 0.015$), but LPA was not ($\beta = -0.102$, $P = 0.136$). Our study revealed that objectively measured physical activity, especially MVPA, was associated with brain atrophy in MCI subjects, even after adjusting for WML. These findings support the hypothesis that physical activity plays a crucial role in maintaining brain health.

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1. Introduction

Alzheimer disease (AD) is a serious health problem, and its prevalence is dramatically increasing worldwide. Because of the absence of disease-modifying treatments, numerous studies have sought to identify potentially modifiable risk factors for AD (Barnes and Yaffe, 2011). In particular, physical inactivity has been recognized as a significant risk factor for cognitive decline (Sofi et al., 2011) and cognitive impairments, including AD and mild cognitive impairment (MCI) (Barnes and Yaffe, 2011; Lautenschlager et al., 2010),

MCI is considered to be a clinical feature that typifies the prodromal phase of AD and most types of dementia (Petersen, 2004). MCI is associated with a relatively high rate of conversion to dementia, but may also revert to a healthy cognitive state (Brodaty et al., 2013). Physical activity (PA)-based interventions were tested to improve cognitive function in people with MCI, and studies have suggested associations between PA and preservation of cognitive function. However, a meta-analysis revealed some inconsistencies in the effects of PA (Gates et al., 2013). Thus, better understanding of the association between PA and cognition should allow us to refine PA interventions.

Emerging evidence also suggests that PA could protect against age-related changes in the brain, including structural changes observed on magnetic resonance imaging (MRI). Several studies have shown that greater PA is associated with larger brain volume or less atrophy (Benedict et al., 2013; Erickson et al., 2010; Flöel et al., 2010; Gow et al., 2012). Brain atrophy is strongly associated with the presence of white matter lesions (WML), but the association between WML and PA is still debated (Burzynska et al., 2014; Kooistra et al., 2014; Podewils et al., 2007; Wirth et al., 2014). The coexistence of WML and brain atrophy was thought to depend on underlying vascular risk factors

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; WML, white matter lesions; LPA, light-intensity physical activity; METs, multiples of the resting metabolic rate; MVPA, moderate-to-vigorous intensity physical activity; PA, physical activity; TE, echo time; TI, inversion time; TR, repetition time; TUG, timed up and go test

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or on a contribution of altered white matter integrity to the pathogenesis of brain atrophy, although the mechanisms were unclear (Appelman et al., 2009). The severity of WML was also associated with brain atrophy in older adults, including those with cognitive impairment (Appelman et al., 2009). However, it is still unclear whether the association between PA and brain atrophy is independent of the severity of WML. It is also notable that, in these earlier studies, PA was assessed using self-reported questionnaires. An earlier study reported that objectively measured PA was associated with cognitive function, but self-reported PA was not (Buchman et al., 2008). Even young adults had difficulty in evaluating PA because of recall bias with subjective assessments, and over- or under-estimated PA (Hagstromer et al., 2010).

Thus, we examined whether objectively measured PA is associated with brain atrophy, independent of WML, in older adults with MCI. Studies using objectively measured PA have revealed that the intensity of PA, rather than the amount of PA, is associated with cognitive performance in older people (Brown et al., 2012; Kerr et al., 2013). Therefore, we also examined whether the intensity of PA has an impact on the association between PA and brain atrophy. In this study, we objectively measured PA using tri-axial accelerometers and calculated the mean daily duration of PA for several intensity levels.

2. Materials and methods

2.1. Subjects

Overall, 649 subjects participating in the Obu Study of Health Promotion for the Elderly (Shimada et al., 2013) were considered for this study, and met the following criteria: age > 65 years; diagnosis of MCI; no specific medical history of cerebrovascular disease, Parkinson disease, connective tissue disease, or depression; no severe visual or auditory impairment; no current symptoms of depression defined as Geriatric Depression Scale ≥ 6 (Yesavage, 1988); not participating in other research projects; and not receiving support from the Japanese public long-term-care insurance system, which certifies a person as "Support Level 1 or 2" if they need support for daily activities or "Care Level 1, 2, 3, 4, or 5" if they need continuous care (Tsutsui and Muramatsu, 2007). MCI was defined based on the criteria established and revised by Petersen (2004) as follows: 1) subjective memory complaints; 2) objective cognitive impairment; 3) no dementia; and 4) independent function in daily life activities. The subjects with MCI included in our study were not diagnosed with dementia and their general cognitive function was considered intact with a Mini-Mental State Examination score of >23 (Folstein et al., 1975). Objective cognitive impairment was defined as a cognitive function score at least 1.5 standard deviations below the normal score (Shimada et al., 2013). Cognitive function was assessed in multiple domains (attention, executive function, processing speed, visuospatial skill, and memory) using the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al., 2013). Subjects with cognitive impairment in the memory domain were classified as having amnestic MCI; the remaining subjects were classified as having non-amnestic MCI. Overall, 409 people responded to the invitation to participate, 400 participated after providing informed consent in accordance with the ethical policy, and 336 completed all examinations and the MRI analysis. The ethics committee of the National Center for Geriatrics and Gerontology approved this study.

2.2. MRI

MRI was performed on a 3T system (TIM Trio; Siemens, Berlin, Germany). Three-dimensional volumetric acquisition of a T1-weighted gradient-echo sequence produced a gapless series of thin sagittal sections using a magnetization preparation with rapid-acquisition (inversion time [TI], 800 ms; echo time [TE], 1.98 ms; repetition time [TR], 1800 ms; slice thickness, 1.1 mm). Then, axial T2-weighted, spin-echo images (TR, 4200 ms; TE, 89.0 ms; slice thickness, 5 mm) and axial fluid-attenuated inversion recovery images (TI, 2500 ms; TR, 9000 ms; TE, 100 ms; slice thickness, 5 mm) were obtained for diagnosis. WML were assessed based on periventricular hyperintensity and deep and subcortical white matter hyperintensity. Subjects were classified as having severe WML if periventricular hyperintensity or white matter hyperintensity was classified as grade III (Fazekas et al., 1993).

Brain atrophy was evaluated using the voxel-based, specific regional analysis system for Alzheimer's disease advance, which has been validated and described in more detail elsewhere (Hirata et al., 2005; Matsuda et al., 2012). Normalized MRI images were segmented into gray matter, white matter, cerebrospinal fluid, and other components. The segmented gray matter images were then subjected to affine and non-linear anatomical standardization using a gray matter template established a priori. Then, gray matter images were smoothed with an isotropic Gaussian kernel with a full-width-at-half-maximum of 12 mm. We compared the gray matter images of each subject with the mean and standard deviation of gray matter images obtained from healthy older adults using voxel-by-voxel Z-score analysis (Hirata et al., 2005; Matsuda et al., 2012). Regions of brain atrophy were defined as voxels with a Z-score >2. A brain atrophy index was defined as the proportion of atrophic voxels relative to the total number of voxels for the entire brain.

2.3. Physical activity

To objectively measure PA, we used a small tri-axial accelerometer (74 × 46 × 34 mm; modified HJA-350IT, Active style Pro; Omron Healthcare Co., Ltd., Kyoto, Japan) (Kim et al., 2013; Oshima et al., 2010) according to a previously described protocol (Makizako et al., 2014). The number of steps and the intensity of PA were measured every 4 s throughout each day. The intensity of PA was calculated in multiples of the resting metabolic rate (METs). Subjects were instructed to wear the accelerometer on an elastic band on their hip at all times for 2 weeks. To assess normal daily activity, the displays of the accelerometers were masked to the subjects. We excluded the data for 13 subjects lacking activity data for ≥75% of the daytime period (6 am to 6 pm) on 7 days or more in the 2-week period. Accelerometer data were classified as light-intensity physical activity (LPA; 1.5–2.9 METs) or moderate-to-vigorous physical activity (MVPA; more than 3.0 METs), which were calculated from the mean duration of each intensity of PA in min/day.

2.4. Other covariates

Age, sex, and body mass index (weight/height^2) were recorded as demographic characteristics. Comorbidities including hypertension, diabetes mellitus, lipidemia, and current medications were also recorded.

Table 1
Characteristics of subjects according to the severity of white matter lesions.

Variables	Non-severe WML ($n = 263$)	Severe WML ($n = 60$)	P
Age, years	70.7 ± 4.1	74.3 ± 5.2	<0.001
Sex (women), %	54.7	50.0	0.499
BMI, kg/m^2	23.3 ± 2.9	23.6 ± 2.5	0.509
Subjects with non-amnestic MCI, %	48.2	54.8	0.343
Hypertension, %	39.2	43.5	0.528
Diabetes mellitus, %	10.3	12.9	0.544
Lipidemia, %	28.6	24.2	0.487
Number of medications	2.0 ± 1.9	2.4 ± 1.8	0.143
TUG, s	8.4 ± 1.7	9.0 ± 1.7	0.013
LPA, min/day	353.6 ± 96.0	324.4 ± 96.7	0.035
MVPA, min/day	24.1 ± 18.7	18.6 ± 17.5	0.039
Brain atrophy, %	1.6 ± 1.0	2.7 ± 1.6	<0.001

Values are means ± standard deviation or % of subjects.
WML: white matter lesions; BMI: body mass index; MCI: mild cognitive impairment; TUG: timed up and go test; LPA: low-intensity physical activity. MVPA: moderate-to-vigorous intensity physical activity.

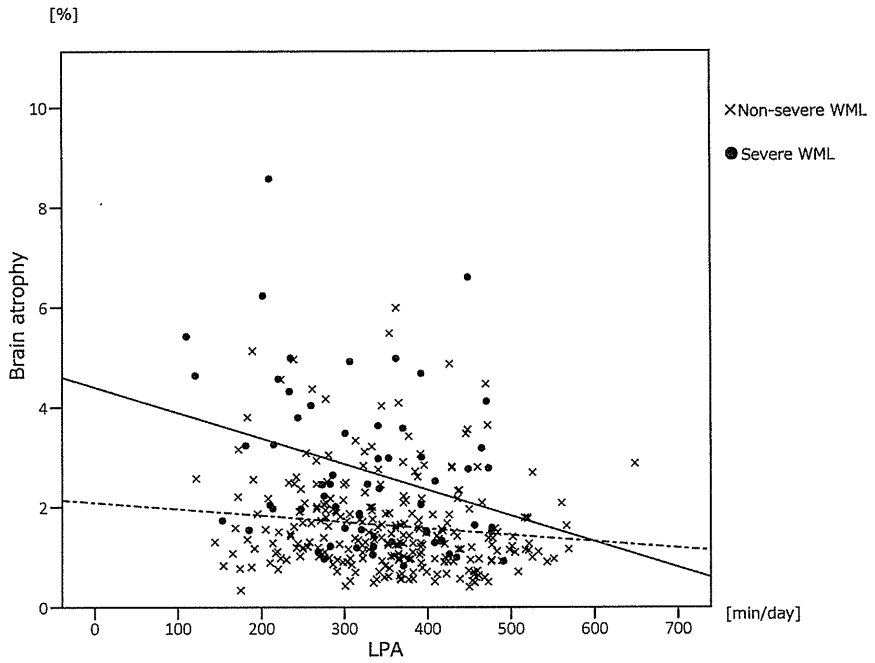

Fig. 1. Scatterplot showing the relationship between LPA and brain atrophy in subjects divided according to the severity of WML as severe or non-severe. Regression lines are drawn for each group (*solid line*, severe WML group; *dashed line*: non-severe WML group).

Mobility was assessed using the Timed Up and Go test (TUG) (Podsiadlo and Richardson, 1991). The TUG is a mobility test in which subjects are asked to walk 3 m then turn around and walk back 3 m at their self-selected normal pace in a well-lit environment.

2.5. Statistical analysis

We compared subject characteristics, including brain atrophy and PA, between the WML groups using Student's *t* test for continuous variables or χ^2 tests for categorical variables. To examine the association between PA and brain atrophy, we first conducted a simple correlation analysis and a partial correlation analysis (controlling age, sex, and TUG). Next, multiple regression analysis was used to determine independent associations between PA and brain atrophy. Brain atrophy was used as the dependent variable. Explanatory variables included LPA or MVPA. To determine the effects of WML on the association between PA and brain atrophy, we established three models. Model 1 was limited to the PA measures. Model 2 included the variables in Model 1 plus demographic data and physical function as covariates. In Model 3, we also added WML to Model 2. The change in R^2 between

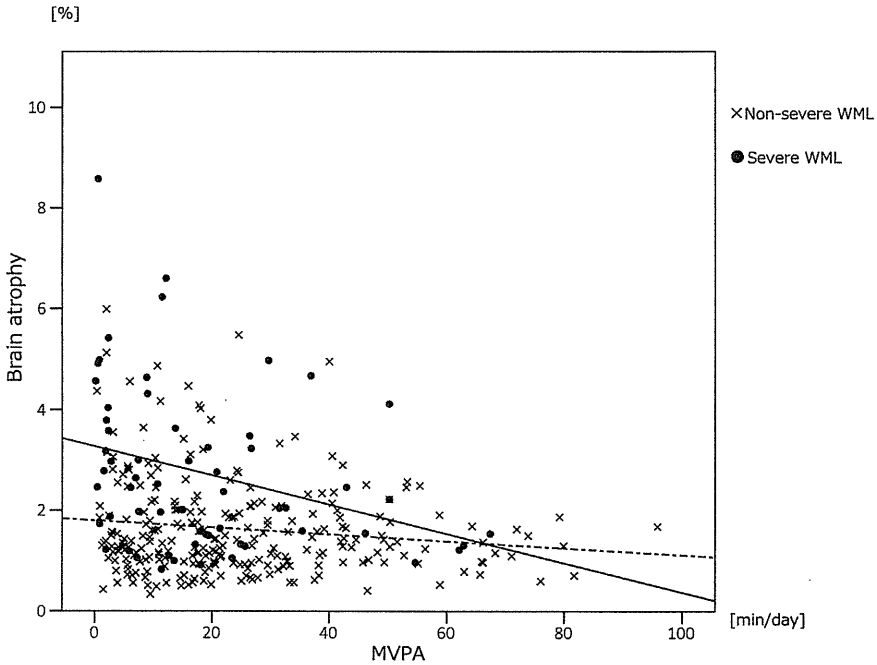

Fig. 2. Scatterplot showing the relationship between MVPA and brain atrophy in subjects divided according to the severity of WML as severe or non-severe. Regression lines are drawn for each group (*solid line*, severe WML group; *dashed line*: non-severe WML group).

Table 2
Linear regression analysis of the association between brain atrophy and low-intensity physical activity.

Variables	Model 1		Model 2		Model 3	
	β	P	β	P	β	P
LPA	−0.209	<0.001	−0.120	0.062	−0.102	0.136
Age	–	–	0.206	0.001	0.116	0.048
Sex	–	–	0.110	0.089	0.115	0.065
BMI	–	–	−0.030	0.584	−0.034	0.528
MCI subtype	–	–	−0.008	0.887	0.015	0.766
Hypertension	–	–	0.065	0.233	0.055	0.295
Diabetes mellitus	–	–	0.049	0.356	0.037	0.473
Lipidemia	–	–	−0.021	0.692	−0.017	0.736
TUG	–	–	0.164	0.006	0.166	0.003
WML	–	–	–	–	0.287	<0.001
ΔR^2	–		0.111		0.073	
R^2	–	–			0.228	

LPA: low-intensity physical activity; BMI: body mass index; MCI: mild cognitive impairment; TUG: timed up and go test; WML: white matter lesions.

each model was calculated. All analyses were performed using commercially available software (IBM SPSS statistics software, Version 20; IBM Corp., Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

3. Results

Overall, 323 subjects fulfilled with the eligibility criteria and were divided into those with severe WML ($n = 60$) or non-severe WML ($n = 263$). The characteristics of each group are summarized in Table 1. Age, TUG, and brain atrophy were significantly different between the two groups ($P < 0.05$). The proportions of time in LPA and MVPA were also significantly different between the two WML groups ($P < 0.05$).

Correlations between PA and brain atrophy in each WML group are shown in Fig. 1 for LPA and Fig. 2 for MPA. The simple correlation analysis revealed that more LPA ($r = -0.20$, $P < 0.001$) and MVPA ($r = -0.20$, $P < 0.001$) correlated with a lower rate of atrophy. Partial correlation analysis that controlled age, sex, and TUG showed that LPA was not significantly associated with brain atrophy ($pr = -0.10$, $P = 0.069$), but that MVPA was ($pr = -0.15$, $P = 0.006$). The results of the regression analysis of LPA against brain atrophy are shown in Table 2. In Model 1, brain atrophy was negatively associated with LPA ($\beta = -0.209$, $P < 0.001$). However, adjusting for demographic data in Model 2 and WML in Model 3 revealed that LPA itself was not independently correlated with atrophy (Model 2: $\beta = -0.120$, $P = 0.062$; Model 3: $\beta = -0.092$, $P = 0.136$). In contrast, MVPA was significantly associated with brain atrophy in Model 1 ($\beta = -0.202$, $P < 0.001$, Table 3), and remained so in Model 2 ($\beta = -0.148$, $P = 0.007$) and Model 3 ($\beta = -0.126$, $P = 0.015$).

Table 3
Linear regression analysis of the association between brain atrophy and moderate-to-vigorous intensity physical activity.

Variables	Model 1		Model 2		Model 3	
	β	P	β	P	β	P
MVPA	−0.202	<0.001	−0.148	0.007	−0.126	0.015
Age	–	–	0.206	<0.001	0.117	0.045
Sex	–	–	0.182	0.001	0.170	0.002
BMI	–	–	−0.020	0.713	−0.027	0.608
MCI subtype	–	–	−0.009	0.871	0.014	0.784
Hypertension	–	–	0.064	0.233	0.054	0.295
Diabetes mellitus	–	–	0.054	0.304	0.041	0.420
Lipidemia	–	–	−0.020	0.704	−0.017	0.744
TUG			0.135	0.025	0.142	0.014
WML	–	–	–	–	0.284	<0.001
ΔR^2	–		0.103		0.072	
R^2	–		–		0.213	

MVPA: moderate-to-vigorous intensity physical activity; BMI: body mass index; MCI: mild cognitive impairment; TUG: timed up and go test; WML: white matter lesions.

4. Discussion

The proportions of time spent in LPA and MVPA were lower in subjects with severe WML than in those without severe WML. Subjects with severe WML were older, had less mobility and more extensive brain atrophy. Our study revealed that in this cohort of subjects with MCI, objectively measured PA was associated with brain atrophy, independent of WML. Specifically, multivariate regression models showed that greater MVPA was associated with less extensive brain atrophy, even after adjusting for WML. In contrast, the amount of LPA could not explain the amount of brain atrophy better than the other covariates.

The results of studies using objectively measured PA, including our study, provide evidence for sustained protective effects of PA in preserving brain health. Some studies have shown that PA is associated with macrostructural brain measures (Benedict et al., 2013; Burzynska et al., 2014; Erickson et al., 2010; Flöel et al., 2010; Gow et al., 2012). Most of those studies assessed PA using questionnaires. For example, it was found that the self-reported duration and frequency of PA were associated with gray matter and white matter volume (Benedict et al., 2013) and greater walking distance at baseline was related to greater gray matter volume 9 years later in older adults (Erickson et al., 2010). In contrast, there is less evidence of a relationship between objectively measured PA and brain health. Burzynska et al. (2014) focused on the association between white matter and PA among low-fit older adults. Their findings showed that more MVPA was associated with a smaller volume of white matter hyperintensities and that sedentary time was associated with lower white mater integrity. In contrast, the LPA was less associated with these brain measures than with other covariates. Additionally, they reported that the correlation between PA and brain health depended on the intensity of the PA. However, these studies did not investigate the effects of PA among older adults with MCI. Thus, our results provide further insight into the benefits of PA on maintaining brain health, even among subjects with MCI.

Based on the hypothesis that PA has a positive impact on brain health, several intervention studies have examined the effects of introducing exercise or enhancing PA on improving cognition in subjects with MCI (Gates et al., 2013). However, a consensus has not been reached, partly because the intensity of the interventions varied among studies. An intervention aimed at promoting PA helped to maintain cognitive function, although the effect was dependent on the severity of cognitive impairment (Lautenschlager et al., 2008). By contrast, a walking program aimed at enhancing PA had limited effects on cognition in subjects with MCI (van Uffelen et al., 2008). In other studies, aerobic exercise at moderate to high intensities had a positive impact on hippocampus volume in older adults (Erickson et al., 2011) and cognitive function in subjects with MCI (Baker et al., 2012). Thus, our results suggest that the benefits of PA, especially MVPA, on brain health extend to older adults with MCI.

The strength of our study is that we performed multivariate analysis, which included WML. WML are thought to represent the loss of myelin, axons, oligodendrocytes, and other glial cells in the subcortical white matter because of ischemic damage caused by underlying small-vessel disease (Brun and Englund, 1986) or other explanations, such as Wallerian degeneration (Leys et al., 1991). The presence of WML is thought to be a strong mediating factor for brain atrophy. The coexistence of WML and brain atrophy is a common age-related change in the brain, even in people without overt diseases, because disturbances in white matter integrity contributes to the pathogenesis of brain atrophy (Appelman et al., 2009). Additionally, WML may be associated with PA, although the results published to date are conflicting (Gow et al., 2012; Podewils et al., 2007; Wirth et al., 2014). Thus, when investigating the factors associated with brain atrophy, it is important to consider the

severity of WML. Additionally, neuroimaging studies have revealed that brain atrophy and white matter lesions are typical age-related structural changes in the brain (Seidler et al., 2010), while physical performance, particularly mobility, is correlated with gray matter volume and WML (de Laat et al., 2012; Rosano et al., 2010). Based on this evidence that brain structure is associated with age and mobility, we included age, TUG, and other demographic data as covariates in this study. Higher age, being male, and low mobility were associated with more brain atrophy. Results of the partial correlation and multivariate analysis indicated that age and TUG could explain atrophy better than LPA, but also supported the association between MVPA and brain measures even after adjusting for other factors.

Some limitations must be mentioned. Because of the cross-sectional design, we could not assess the causal relationship between PA and brain structure in these subjects with MCI. Further prospective studies are required to address this issue. In addition, other brain measures including Aβ burden and white matter integrity might mediate the association between PA and MCI. Additionally, we used a voxel-based analysis to assess gray matter atrophy of the entire brain. The possibility that PA has differential effects depending on brain region should be investigated in future studies.

5. Conclusion

Our study showed that PA, particularly MVPA, was negatively associated with the extent of brain atrophy in older adults with MCI. This association was independent of the severity of WML. These results support the possibility that enhancing PA could contribute to brain health. Further studies, including interventions, are needed to confirm the benefits of PA on cognition and brain health.

Conflict of interest

The authors declare that they have no competing interests.

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Association of insulin-like growth factor-1 with mild cognitive impairment and slow gait speed

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ABSTRACT

The decrease in serum insulin-like growth factor-1 (IGF-I) with aging is related to the neurobiological processes in Alzheimer's disease. IGF-1 mediates effects of physical exercise on the brain, and cognition has a common pathophysiology with physical function, particularly with gait. The aim of this study was to examine whether mild cognitive impairment (MCI) and slow gait are associated with the serum IGF-1 level. A population survey was conducted in 3355 participants (mean age, 71.4 years). Cognitive functions (attention, executive function, processing speed, visuospatial skill, and memory), gait speed, and demographic variables were measured. All cognitive functions and gait speed were associated with the IGF-1 level ($p < 0.001$). The association of IGF-1 with slow gait was weakened by adjustment for covariates, but MCI and the combination of MCI and slow gait were independently related to the IGF-1 level in multivariate analysis ($p < 0.05$). Our findings support the association of a low IGF-1 level with reduced cognitive function and gait speed, particularly with a combination of MCI and slow gait.

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1. Introduction

Insulin-like growth factor-1 (IGF-1) is an important mediator of growth hormone effects in body growth and tissue remodeling (Nishijima et al., 2010) and contributes to the promotion of neuronal plasticity and skeletal muscle (Clegg et al., 2013; Florini et al., 1991; van Dam et al., 2000). IGF-1 also has protective effects on the neurobiological processes that are compromised by aging and Alzheimer's disease (AD), including those with potent neurotrophic and neuroprotective actions (Baker et al., 2012; de la Monte and Wands, 2005; Deak and Sonntag, 2012; Sonntag et al., 2005). A decrease in IGF-1 may be related to the pathology of AD because IGF-1 increases clearance of amyloid beta (Aβ) in the brain and upregulates Aβ carriers and transport of Aβ-carrier protein complexes (Carro et al., 2002, 2006). In humans, low levels of serum IGF-1 are a risk for AD and dementia (Watanabe et al., 2005; Westwood et al., 2014).

Mild cognitive impairment (MCI) is a prodromal status in the course of AD. Subjects with MCI have characteristics between healthy subjects and AD, including pathology, biomarkers, brain function, and cognitive function (Petersen, 2004, 2011). The common features of MCI, particularly in cases showing progression to AD, are higher levels of Aβ42 and tau, brain atrophy, and reduced cognitive function (Petersen, 2011). Subcutaneous injections of growth hormone–releasing hormone enhances the IGF-1 level and improves cognitive function in MCI subjects (Baker et al., 2012), but it is unclear whether lower levels of serum IGF-1 are a characteristic of MCI.

Cognitive impairment has a strong link with physical frailty, especially with slow gait linked with worsening of cognitive function. Slow gait has been associated with the cognitive decline (Mielke et al., 2013) and with accumulation of brain pathology related to AD at autopsy (Buchman et al., 2013), whereas longitudinal studies indicate that slow gait precedes MCI and dementia (Buracchio et al., 2010; Solfrizzi et al., 2013). Importantly, a combined status of slow gait and cognitive impairment increases the risk for dementia compared with each status alone (Waite et al., 2005). The mechanism of the association between physical and cognitive impairment was not examined, but IGF-1 may mediate this association.

The mechanism underlying the benefit of exercise on cognition is also thought to involve IGF-1 (Liu-Ambrose et al., 2012). Exercise-dependent stimulation of angiogenesis and neurogenesis seems to

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be regulated by IGF-1 (Cotman et al., 2007), whereas a peripheral increase in IGF-1 appears to be required for exercise-induced neurogenesis in the brain (Trejo et al., 2001). IGF-I is also an important modulator of muscle mass and function (Barbieri et al., 2003). Low IGF-I levels may also be associated with physical frailty represented by muscle weakness and slow gait speed (Cappola et al., 2001; Onder et al., 2006). Therefore, an improved understanding of the association of IGF-1 with physical and cognitive functioning may contribute to the clarification of mechanisms associated with aging.

The aim of this study was to examine the association between serum IGF-1 and MCI and to determine whether slow gait affects this association. We hypothesized that lower levels of serum IGF-1 are associated with reduced cognitive function and gait speed and that a combined status of MCI + slow gait speed would be sensitively associated with a lower IGF-1 level. Assessments of cognitive function require the use of a variety of cognitive domains (Albert et al., 2011) because there is some debate over which cognitive functions are related to IGF-1 levels (Dik et al., 2003; Sanders et al., 2014). In contrast, confirmed covariates in older adults, such as age and body mass index (BMI), are known to weaken the association between mobility and IGF-1 (Cappola et al., 2001; Kaplan et al., 2008; Sanders et al., 2014). Thus, we conducted a population survey in a large cohort with adjustment for covariates in multivariate analysis.

2. Material and methods

2.1. Participants

Subjects eligible for this study were participants in the population-based cohort of the Obu Study of Health Promotion for the Elderly (OSHPE), which was conducted from August 2011 to February 2012. Inclusion criteria for the OSHPE required each participant to be 65 years or older at the time of examination and to reside in Obu city; a total of 15,974 individuals were eligible for participation. Before recruitment, 1661 people were excluded because they had participated in other similar studies, were hospitalized or in residential care, or were certified at levels 3–5 to require support or care by the Japanese public long-term care insurance system. Recruitment was conducted via a letter sent to 14,313 individuals, and 5104 of these individuals participated in the OSHPE. In the present study, we included participants who were independent for basic activities of daily living, as confirmed by interview, and not certified by long-term care insurance, and were cognitively normal (no objective cognitive impairment and Mini-Mental State Examination [MMSE] score >23, Folstein et al., 1975) or met the criteria for MCI. MCI criteria followed those established and revised by Petersen (2004); in particular, subjects satisfied the following conditions: subjective memory complaints, objective cognitive impairment, no dementia, and independent in activity of daily living. No dementia was defined as not meeting clinical criteria for dementia, and intact global cognitive function was defined as an MMSE score >23 (Folstein et al., 1975). Cognitive function was also assessed in multiple domains using the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al., 2013), and objective cognitive impairment was defined as having a cognitive function of >1.5 standard deviation lower than the normal data (Shimada et al., 2013a). Subjects were classified into subtypes of amnestic MCI (aMCI) and nonamnestic MCI (naMCI). Those with objective cognitive impairment in memory were defined as aMCI and others were defined as naMCI, based on the published criteria (Petersen, 2004). Participants were excluded based on a history of cerebrovascular disease, Parkinson disease, depression or dementia, or an MMSE score of ≤23 (Folstein et al., 1975). Finally, 3355 participants were judged to be eligible for the study and completed all assessments, including blood tests. The Ethics Committee of the National Center for Geriatrics and Gerontology approved this study.

2.2. Gait speed

Gait speed was measured as an indicator of motor function. Participants were asked to walk on a straight walkway of 6.6 m in length on a flat floor under their usual gait speed. Gait duration was measured using a stopwatch over a 2.4-m distance between marks at 2.1 and 4.5 m from the start of the walkway, and the mean gait speed (minute per second) was calculated. The measurement protocol of using a stopwatch has been validated elsewhere (Peters et al., 2013). The cutoff value (1.0 m/s) for a slow gait speed was based on the threshold value for discrimination of functional decline found in a previous study (Shimada et al., 2013b).

2.3. Cognitive function

Cognitive function was assessed using the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al., 2013). The test consists of tasks to assess memory, processing speed, attention and executive function, and visuospatial cognition (Figure Selection Task). Memory was assessed using word and story tests. Both tests have 2 sessions (an immediate session and a delayed session). Processing speed was assessed using a tablet version of the Symbol-Digit Substitution Task (Makizako et al., 2013), based on the Symbol-Digit Modality Test (Shum et al., 1990). The score is the number of correct answers chosen within 90 seconds. Attention and executive functions were evaluated using a tablet version of the Trail-Making Test Part A (TMT-A) and Part B (TMT-B, 15 stimuli) (Makizako et al., 2013). The amount of time taken to complete each task was recorded. In the Figure Selection Task, participants were required to select the same figure from 3 choices shown at the bottom of the display (Makizako et al., 2013). This task consists of 9 questions and 1 point is given for each correctly selected figure, with the score being the number of correct answers (0–9). Better performance is represented by lower values on the TMT-A and TMT-B and higher values on the other tests.

2.4. IGF-1

To obtain serum, whole blood samples were allowed to coagulate at room temperature for 30 minutes and then centrifuged at room temperature for 15 minutes at 1000 × g. The collected serum was stored in polypropylene tubes at −80 °C until assayed. IGF-1 was quantitatively determined using an IGF-1 Immunoradiometric assay "Daiichi" (TFB Inc, Tokyo, Japan). Measurements were performed in duplicate and averaged to give a value in nanograms per milliliter. The assay was performed by SRL Inc (Tokyo, Japan).

2.5. Demographic and lifestyle data

Demographic data were collected for age, sex, BMI (weight/height^2), educational history, and medication use in a face-to-face interview. Information on lifestyle was also obtained, and sleep quality was assessed using the question "How would you rate your sleepiness in daytime?" on a 4-point scale ranging from "never," "very little," and "sometimes" to "almost always". Subjects who answered never or very little were judged to have good quality of sleep. Depressive symptoms were evaluated using the 15-item Geriatric Depression Scale (Yesavage, 1988). The total amount of time spent walking in a day was used to assess physical activity using a subscale of the International Physical Activity Questionnaire (Murase et al., 2003).