Effects of white matter lesions on trunk stability during dual-task walking among older adults with mild cognitive impairment

Takehiko Doi · Hiroyuki Shimada ·
Hyuma Makizako · Kota Tsutsumimoto · Ryo Hotta ·
Sho Nakakubo · Takao Suzuki

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Abstract The linkage between gait and cognition has been shown in cases of white matter lesion (WML) that affect gait in older adults. Dual-task walking is believed to be cognitively demanding and to alter trunk movement, and gait impairment in people with mild cognitive impairment (MCI) is highlighted under this condition. However, the association between dual-task walking and structural changes in the brain, particularly with WML, in people with MCI is still unclear. The aim of this study was to examine the association between trunk stability during dual-task walking and WML in 560 older adults with MCI. We measured magnetic reso-

nance imaging (MRI) and gait variables. Gait variables included harmonic ratio in vertical, mediolateral, and anteroposterior directions, analyzed using a tri-axial accelerometer attached to the lower trunk. Walking conditions were normal walking and dual-task walking (counting backwards while walking) conditions. Demographical data and brain atrophy were measured as covariates. Subjects were classified into non-severe WML ($n=451$, mean age=73.2 years) and severe WML ($n=109$, mean age=75.9 years) groups. Linear mixed-effects model analysis controlled for covariates showed dual-task-related changes in all harmonic ratios associated with WML ($p<0.05$). Even after adjustment for executive function, harmonic ratio in the mediolateral direction was significantly associated with WML ($p<0.05$). Our findings revealed that WMLs were associated with trunk stability in dual-task walking. Further studies are required to investigate the neural basis for deficits in gait ability among MCI subjects.

T. Doi (✉) · H. Makizako · K. Tsutsumimoto · R. Hotta ·
S. Nakakubo
Section for Health Promotion, Department of Preventive
Gerontology, Center for Gerontology and Social Science, National
Center for Geriatrics and Gerontology, Obu, Aichi, Japan
e-mail: take-d@ncgg.go.jp

T. Doi
Japan Society for the Promotion of Science, Tokyo, Japan

H. Shimada
Department of Preventive Gerontology, Center for Gerontology
and Social Science, National Center for Geriatrics and
Gerontology, Obu, Aichi, Japan

T. Suzuki
National Center for Geriatrics and Gerontology, Obu, Aichi, Japan

T. Suzuki
Department of Gerontology, J.F. Oberlin University Graduate
School, Tokyo, Japan

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Background

Gait and cognition are strongly related (Montero-Odasso et al. 2012b). Deficits in gait ability precede declines in cognitive function (Mielke et al. 2013) and are predictors for incidences of dementia (Verghese et al. 2007). Mild cognitive impairment (MCI) is considered a

clinical signature that represents a prodromal phase of dementia, and is defined as having cognitive ability lying between that of normal aging and that which fulfills the criteria for dementia (Petersen 2004; Petersen 2011). A deficit in gait performance is a clinical characteristic in older adults with MCI and even precedes MCI (Buracchio et al. 2010; Montero-Odasso et al. 2012a; Montero-Odasso et al. 2014; Muir et al. 2012; Verghese et al. 2008).

The link between gait and cognition is thought to depend on cognitive requirements during gait. To examine the requirement, numerous studies have used a dual-task paradigm, i.e., dual-task walking, that requires more attentional resources and executive functions than normal walking (for reviews, see Al-Yahya et al. 2011; Yogev-Seligmann et al. 2008). Executive function is achieved primarily through prefrontal cortex and refers to a variety of higher cognitive processes, including components of volition, planning, purposive action, and effective performance (Lezak 2004). Indeed, the performance on dual-task gait has been shown to be related to executive function (Doi et al. 2014; Hausdorff et al. 2008; van Iersel et al. 2008), requiring more brain activation in prefrontal cortex than was required by single-task walking among older adults with and without cognitive impairment (Doi et al. 2013b; Holtzer et al. 2015). Structural changes in the aging brain are related to gait performance (for reviews, see Holtzer et al. 2014a; Seidler et al. 2010). In particular, white matter hyperintensities or lesions (WMLs) have been linked to deficits in physical function among cognitively normal older adults (Bolandzadeh et al. 2014; Murray et al. 2010; Rosano et al. 2010; Silbert et al. 2008). WMLs were also shown to affect dual-task performance requiring executive function but not gait task among cognitively normal older adults (Zheng et al. 2012a). In MCI subjects, Annweiler et al. (2013) showed changes in neurochemistry and volume of the primary motor cortex associated with gait performance during dual-task walking (Annweiler et al. 2013). However, the associations between dual-task walking and WML among MCI subjects are still unclear. Examination of WML and dual-task gait may contribute to further understand the neural basis relating gait and cognition.

Dual-task walking was shown to affect aspects of gait including gait speed, variability in lower limb movement, and trunk stability (de Hoon et al. 2003; Doi et al. 2012; van Iersel et al. 2007; van Iersel et al. 2008). Control of trunk movement is prioritized to maintain

gait stability (Winter 1995). Thus, assessing trunk stability during gait could be useful for capturing age-related changes and the risk of falling among older adults (Doi et al. 2013a; Menz et al. 2003). Although dual-task walking highlighted deficits in gait speed in MCI (Montero-Odasso et al. 2014), the effects of dual-task gait on trunk stability in MCI are still unclear. The aim of this study was to examine the dual-task-related changes in trunk stability and the association with WML among older adults with MCI. To assess trunk stability, we measured lower trunk acceleration during gait according to previous studies (Doi et al. 2013a; Menz et al. 2003).

Methods

Participants

The study population and data were obtained from a cohort study. Potential participants were 1621 older adults (65 years or older) diagnosed with MCI as part of the National Center for Geriatrics and Gerontology-Study of Geriatric Syndromes (NCGG-SGS) (Shimada et al. 2015). The overall goal of the NCGG-SGS was to establish a screening system for geriatric syndromes and to validate evidence-based interventions for preventing geriatric syndromes. The NCGG-SGS participants were from a community setting and recruited from Nagoya and Obu cities in Japan by mail. MCI criteria followed those established by Petersen (Petersen 2004; Petersen 2011), and in particular, participants satisfied the following conditions: (1) subjective memory complaints, (2) objective cognitive decline, (3) intact general cognitive function, and (4) functioned independently in daily living activities. Intact general cognitive function was defined as a Mini-Mental State Examination score >23 (Folstein et al. 1975). Objective cognitive decline was defined as cognitive function more than 1.5 standard deviations lower than normal (Shimada et al. 2013). Cognitive function was assessed in multiple domains (memory, attention and executive function, processing speed, and visuospatial function) using the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al. 2013). Exclusion criteria in this study were having cerebrovascular disease, Parkinson's disease, depression, a connective tissue disease, using a heart pacemaker, and having a severe vision impairment, a severe hearing impairment, depressive symptoms (15-item Geriatric Depression

Scale >5 (Yesavage 1988)), or contradiction of exercise by a doctor. A total of 1169 MCI participants met these criteria and were invited to participate by mail. Six hundred and thirty-two responded and 582 received a complete gait examination and MRI without missing data. Additionally, participants diagnosed as having bleeding, infarction, tumors, or cysts based on the brain images and diagnosed by a radiologist were excluded. In the final group, we analyzed 560 MCI participants. Participants were given examinations after providing informed consent in accordance with the ethical policy. The ethics committee of the National Center for Geriatrics and Gerontology approved this study.

Gait analysis

The gait protocol was described in detailed elsewhere (Doi et al. 2012). 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. Two gait experiments were performed sequentially: normal walking (NW): walking at their preferred speed, and dual-task walking (DTW): walking while counting backwards starting from 100. This type of arithmetic task is commonly used among dual-task walking investigations, and the effect on gait was confirmed in a meta-analysis (Al-Yahya et al. 2011). The mid 5-m walking time was measured, and gait speed was expressed in meters per second. A miniature sensor (MVP-RF8, size 45 mm wide×45 mm deep×18.5 mm high, weight 60 g, sampling rate 200 Hz; MicroStone, Nagano, Japan) with included accelerometer and gyroscope was attached to the L3 spinous process using a Velcro™ belt to measure trunk acceleration. The other sensor attached to the posterior surface of the right heel with surgical tape to define each stride supplementally.

Signal processing was performed using commercially available software (MATLAB, Release 2012b, The MathWorks Japan, Tokyo, Japan); detailed analysis was performed as described previously (Doi et al. 2012). The person who analyzed the acceleration data was blinded to any other results. Before analysis, all acceleration data were low-pass filtered (dual pass zero lag Butterworth filtered) with a cutoff frequency of 20 Hz. The harmonic ratio (HR) was used to evaluate the smoothness and stability of trunk movement during gait, as reported elsewhere (Doi et al. 2012; Menz et al. 2003; Yack and Berger 1993). HR was computed separately in each direction (vertical direction (VT), mediolateral direction

(ML), and anteroposterior direction (AP)), and higher HR values indicate greater gait stability.

MRI

A detailed MRI protocol was described in our previous study (Doi et al. 2015). MRI was performed on a 3-T system (TIM Trio, Siemens, Germany), and 3-D volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (inversion time [TI], 800 ms; echo time (TE)/repetition time (TR), 1.98 ms/1800 ms; 1.1-mm slice thickness). Then, axial T2-weighted SE images (TR, 4200 ms; TE, 89.0 ms; 5-mm slice thickness) and axial FLAIR images (TR, 9000 ms; TE, 100 ms; TI, 2500 ms; 5-mm slice thickness) were obtained for diagnosis. WML were identified as periventricular hyperintensity or deep and subcortical white matter hyperintensity. Participants were classified into non-severe or severe WML groups, based on Fazekas scale grade (Fazekas et al. 1993). Severe WML was defined as having grade-III WML in either the periventricular hyperintensity or in the deep and subcortical white matter hyperintensity (Fazekas et al. 1993). Brain atrophy was one of the potential confounding factors for associating WML with gait (Seidler et al. 2010). Therefore, we evaluated brain atrophy using validated software, the voxel-based, specific regional analysis system for advance Alzheimer's disease (Hirata et al. 2005; Matsuda et al. 2012).

Other covariates

Age, sex, body mass index (weight/height²), and educational history were recorded as demographic data. Participants who suffered from a cognitive decline in memory domain were classified as amnesic MCI, while those who did not were classified as non-amnesic MCI. Medication use and illness including hypertension, diabetes, hyperlipidemia, and osteoporosis were assessed. Previous studies reported that cognitive functions such as executive function and processing speed that rely on the prefrontal cortex were mediated by the association of WML with gait and dual-task performances (Bolandzadeh et al. 2014; Zheng et al. 2012a). We used a tablet version of the Symbol Digit Substitution Task as a measure of executive function (Makizako et al. 2013).

Statistical analysis

We classified participants into non-severe or severe WML groups and compared participant characteristics between groups using an unpaired *t* test for continuous variables or a chi-square test for categorical variables. Additionally, we first compared gait variables in NW and DTW between groups using an unpaired *t* test. Then, a general linear model was used to compare between groups adjusting for age, sex, education, medication, MCI subtype, significant differences in illness between groups, and the degree of brain atrophy. To examine the association between dual-task effects on gait variables and WML, we used a linear mixed-effects model as has been used elsewhere (Holtzer et al. 2014b), showing that the dual-task effect is operationalized as the difference in gait variables in the two-level repeated measure. The walking condition (single or dual-task) and WML groups (non-severe or severe) were set as explanatory variables in model 1, and model 2 was the same, but with the addition of Symbol Digit Substitution Task (SDST). Covariates were age, sex, education, medication, MCI subtype, significant differences in illness between groups, and degree of brain atrophy. Variables in HR analyses were further adjusted for changes in gait speed between conditions. All analyses were performed using commercially available software (IBM SPSS statistics software, version 20; IBM Corp., Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

Results

The 560 MCI participants were classified into non-severe WML ($n=451$) or severe WML ($n=109$) groups. Demographical data and brain atrophy were compared between groups (Table 1). The severe WML group was older (non-severe WML 73.2 ± 4.7 years, severe WML 75.9 ± 5.6 years, $p < 0.001$) and had higher atrophy rate (non-severe WML 1.7 ± 1.1 %, severe WML 2.8 ± 1.8 %, $p < 0.001$), higher proportion of hypertension (non-severe WML 40.6 %, severe WML 53.2 %, $p = 0.017$), and lower performance in SDST (non-severe WML 43.5 ± 9.7 , severe WML 40.6 ± 8.9 , $p = 0.004$). Table 2 shows gait variables under NW and DTW conditions. All gait variables under both normal walking and dual-task walking conditions showed significant difference between groups. While severe WML was associated with slower gait speed and lower values in HR under both walking conditions (all $p < 0.05$), no significant differences between groups were observed after adjustment with covariates (all $p > 0.05$).

Analysis using a linear mixed-effects model is shown in Table 3. Gait speed and HRs in all directions were significantly associated with dual-task-related changes controlled for other variables (all $p < 0.001$). In dual-task walking, participants had slower gait speed and lower HRs. WML was significantly associated with dual-task-related changes in HR-VT ($p = 0.027$), HR-ML ($p = 0.007$), and HR-AP ($p = 0.047$), even adjusted for gait speed (model 1). In model 2 (in which SDST was

Table 1 Subject characteristics in non-severe and severe WML groups

Variables	Non-severe WML ($n=451$)	Severe WML ($n=109$)	<i>p</i>
Age, years	72.2 (4.7)	75.9 (5.6)	<0.001
Sex (women), %	46.3	46.8	0.933
Education, years	11.2 (2.5)	11.0 (2.7)	0.471
Body mass index, kg/m ²	23.3 (3.0)	23.4 (2.8)	0.691
MCI subtypes (naMCI), %	51.8	51.4	0.940
Hypertension, %	40.6	53.2	0.017
Diabetes, %	10.0	9.2	0.800
Hyperlipidemia, %	31.5	30.3	0.807
Osteoporosis, %	11.8	18.3	0.066
Medication, number	2.6 (2.5)	3.0 (2.2)	0.226
Brain atrophy, %	1.7 (1.1)	2.8 (1.8)	<0.001
Symbol Digit Substitution Task, score	43.5 (9.7)	40.6 (8.9)	0.004

Values are mean (SD) or proportion. The comparison between groups was by *t* test or chi-square test

WML white matter lesions, naMCI non-amnesic mild cognitive impairment

Table 2 The comparison of gait variables between WML groups

Variables	Non-severe WML (<i>n</i> =451)	Severe WML (<i>n</i> =109)	<i>p</i> value
Normal walking condition			
Gait speed	1.36 (0.21)	1.27 (0.21)	<0.001
HR-VT	3.22 (0.81)	3.02 (0.82)	0.024
HR-ML	2.33 (0.64)	2.19 (0.59)	0.036
HR-AP	3.69 (1.03)	3.46 (1.02)	0.039
Dual-task walking condition			
Gait speed	1.23 (0.32)	1.14 (0.27)	0.007
HR-VT	2.65 (0.85)	2.44 (0.81)	0.017
HR-ML	1.97 (0.61)	1.83 (0.50)	0.029
HR-AP	3.01 (0.99)	2.78 (0.94)	0.030

Values are mean (SD). *p* values were obtained by comparing groups using a *t* test

WML white matter lesions, HR harmonic ratio, VT vertical, ML mediolateral, AP anteroposterior

included as a covariate), the association between HRs and WML was weaker and HR-ML was still significantly related to WML ($p=0.013$).

Discussion

Our study revealed significant dual-task-related changes of trunk stability among MCI participants. All measured gait variables including gait speed and trunk stability showed significant differences between WML groups, but covariates attenuated these associations. Severe WML groups had higher age, higher proportion in the presence of hypertension, higher rate of brain atrophy, and lower performances in executive function. Even after adjusting for covariates including these variables,

dual-task-related changes in trunk stability were associated with WML levels.

In particular, our results among MCI participants showed that trunk stability represented by HR was significantly deteriorated in dual-task gait. Trunk stability assessed by HR was shown to have dual-task-related changes in cognitively normal older adults (de Hoon et al. 2003; Doi et al. 2012; van Iersel et al. 2007; van Iersel et al. 2008). Among MCI participants, studies have shown dual-task-related changes in gait speed and variability (Doi et al. 2014; Montero-Odasso et al. 2012a; Montero-Odasso et al. 2014; Muir et al. 2012). Our study adds further evidence along these lines, showing that trunk stability in people with MCI is affected during dual-task walking. Dual-task-related changes in gait performance were thought to occur because gait control requires cognition (Al-Yahya et al. 2011; Yogev-Seligmann et al. 2008). Dual-task walking has been shown to be associated with cognitive function, particularly executive function, among cognitively normal older adults and those with cognitive impairment (Doi et al. 2014; Hausdorff et al. 2008; van Iersel et al. 2008). Furthermore, brain activation in prefrontal cortex during dual-task walking occurred in MCI participants (Doi et al. 2013b) as well as among cognitively healthy older adults (Holtzer et al. 2015).

Emerging evidence indicates that gait ability is associated with structural changes in the brain among older adults (Holtzer et al. 2014a; Seidler et al. 2010). A systematic review revealed that WML affected physical function and elevated fall risk (Zheng et al. 2011). Our study also supports other studies showing that WML were associated with gait variables (Bolandzadeh et al. 2014; Murray et al. 2010; Rosano et al. 2010; Silbert et al. 2008). Furthermore, WML induced deficits in

Table 3 Results of linear mixed-effects model for trunk stability

Variables	HR-VT		HR-ML		HR-AP	
	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Model 1						
Task	152.0	<0.001	104.1	<0.001	144.7	<0.001
WML	4.9	0.027	7.2	0.007	3.9	0.047
Model 2						
Task	137.8	<0.001	99.9	<0.001	133.5	<0.001
WML	3.5	0.063	6.2	0.013	2.2	0.136
SDST	9.1	0.003	10.8	0.001	11.1	0.001

The model 1 was adjusted for age, sex, education, medication uses, hypertension, subtypes of MCI, brain atrophy, and gait speed. The model 2 was added SDST to covariates in model 1

WML white matter lesions, SDST Symbol Digit Substitution Task, HR harmonic ratio, VT vertical, ML mediolateral, AP anteroposterior

dual-task performance and elevated the risk of falling (Zheng et al. 2012a; Zheng et al. 2012b). Additionally, the association between WML and dual-task performance was mediated by cognitive function (Zheng et al. 2012a). Hypertension has been recognized as a strong risk for WML (van Dijk et al. 2004). Hypertension induced slower gait speed, while WML attenuated the association between hypertension and gait speed (Dumurgier et al. 2010). Thus, we adjusted for covariates including these variables. As a result, we showed that SDST mediates the association between WML and dual-task-related changes in gait variables. The mediating effects of executive function on the association between dual-task performance and WML were in accordance with another study of healthy older adults (Zheng et al. 2012a). The association between WML and HR-ML remained even after adjusting for covariates that included cognitive function. WML may cause postural instability represented by trunk sway among older adults (Sullivan et al. 2009). Stability in ML during gait was required for successful locomotion in older adults and directly linked to fall risk (Maki 1997). Thus, WML may independently affect the dual-task-related changes in trunk stability. Further studies were required to clarify the effects of WML.

Although cross-sectional in design, our study had several covariates and a sufficient number of participants that allowed us to conduct multivariate analysis; however, there were several limitations. The evaluation of WML was based on the degree of severity according to Fazekas' criteria (Fazekas et al. 1993). Recent studies that used quantitative assessment of WML and a regional analysis have also been conducted (Bolandzadeh et al. 2014; Ogama et al. 2014). Quantitative assessments of WML and consideration of their regions in further studies may help to enhance our findings. Other limitations were the effects of type and/or difficulty of dual-task walking. Although we used an arithmetic task, one of the major tasks used in dual-task walking experiments (Al-Yahya et al. 2011), other types of cognitive tasks should also be examined. WML affected improvement in gait ability by an intervention such as rehabilitation among older adults (Nadkarni et al. 2013). Further studies should also investigate the effects of WML on improvement of dual-task performances.

In conclusion, WML affected dual-task-related changes in gait, particularly trunk stability, in older adults with MCI. This study supports the notion that

there is a link between gait and cognition. Further study will be required to examine the effects of WML on gait.

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

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

Ethics approval The ethics committee of the National Center for Geriatrics and Gerontology approved this study.

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