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Gray matter volume and dual-task gait performance in mild cognitive impairment

Takehiko Doi^{1,2,3,4}, Helena M. Blumen^{3,4}, Joe Verghese^{3,4}, Hiroyuki Shimada¹, Hyuma Makizako¹, Kota Tsutsumimoto¹, Ryo Hotta¹, Sho Nakakubo¹, and Takao Suzuki^{5,6}

¹Department of Preventive Gerontology, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, 7-430 Morioka-cho, Obu, Aichi, Japan

²Japan Society for the Promotion of Science, Chiyoda-ku, Tokyo, Japan

³Department of Neurology, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA

⁴Department of Medicine, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA

⁵National Center for Geriatrics and Gerontology, 7-430 Morioka-cho, Obu, Aichi 474-8511, Japan

⁶Graduate School of Gerontology, J.F. Oberlin University, Machida, Tokyo, Japan

Abstract

Dual-task gait performance is impaired in older adults with mild cognitive impairment, but the brain substrates associated with dual-task gait performance are not well-established. The relationship between gray matter and gait speed under single-task and dual-task conditions (walking while counting backward) was examined in 560 seniors with mild cognitive impairment (non-amnesic mild cognitive impairment: $n = 270$; mean age = 72.4 yrs., 63.6 % women; amnesic mild cognitive impairment: $n = 290$; mean age = 73.4 yrs., 45.4 % women). Multivariate covariance-based analyses of magnetic resonance imaging data, adjusted for potential confounders including single-task gait speed, were performed to identify gray matter patterns associated with dual-task gait speed. There were no differences in gait speed or cognitive performance during dual-task gait between individuals with non-amnesic mild cognitive impairment and amnesic mild cognitive impairment. Overall, increased dual-task gait speed was associated with a gray matter pattern of increased volume in medial frontal gyrus, superior frontal gyrus, anterior cingulate, cingulate, precuneus, fusiform gyrus, middle occipital gyrus, inferior temporal gyrus and middle temporal gyrus. The relationship between dual-task gait speed and brain substrates also differed by mild cognitive impairment subtype. Our study revealed a pattern of gray matter regions associated with dual-task performance. Although dual-task gait performance was similar in amnesic and non-amnesic mild cognitive impairment, the gray matter patterns associated with

Correspondence to: Takehiko Doi.

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Informed consent: Informed consent was obtained from all individual participants included in the study

dual-task gait performance differed by mild cognitive impairment subtype. These findings suggest that the brain substrates supporting dual-task gait performance in amnesic and non-amnesic subtypes are different, and consequently may respond differently to interventions, or require different interventions.

Keywords

Dementia; MCI; Brain atrophy; Mobility

Introduction

Gait requires adaptability to changing environments that are dependent on higher order cognitive systems (Yogev-Seligmann et al. 2008). Slowing of gait speed precedes declines in cognitive function (Mielke et al. 2013) and is a predictor for dementia (Verghese et al. 2007b). Gait impairment is also common in individuals with mild cognitive impairment (MCI) and slowing of gait speed precedes MCI (Montero-Odasso et al. 2014; Muir et al. 2012; Montero-Odasso et al. 2012; Verghese et al. 2008; Buracchio et al. 2010). Gait impairment in MCI is particularly pronounced under challenging dual-task gait conditions (Montero-Odasso et al. 2014) and is suggested to be related to an increased risk of fall among patients with MCI (Montero-Odasso et al. 2012).

Brain substrates that support dual-task gait performance in MCI are not well established. Imaging studies of single-task gait performance (i.e., normal gait speed) show associations with gray matter volume in the primary sensorimotor region, medial temporal area, cerebellum, basal ganglia, and prefrontal regions (Rosano et al. 2008; Rosano et al. 2010; Holtzer et al. 2014; Dumurgier et al. 2012; Rosano et al. 2007), cortical thinning (de Laat et al. 2012), and loss of white matter integrity (de Laat et al. 2011; Holtzer et al. 2014). MRI and magnetic resonance spectroscopy further reveal that the neurochemistry and volume of the primary motor cortex region are associated with gait performance in individuals with MCI (Annweiler et al. 2013). However, this study focused only on particular regions of interest and had a small number of samples ($n = 20$) due to the experimental design. Brain regions associated with dual-task gait were not examined across the whole brain, although gait, and particularly dual-task gait, is likely to engage both motor-related regions and other neural networks, such as those in the prefrontal cortex (PFC) region (Zwergal et al. 2012; Blumen et al. 2014).

To address the knowledge gap regarding brain substrates in dual-task gait in MCI patients, we examined patterns of gray matter volume in 560 seniors with MCI. Furthermore, since amnesic MCI (aMCI) and non-amnesic MCI (naMCI) subtypes, based on the types of cognitive impairment (Petersen 2004, 2011), may have different neuropathology (Fischer et al. 2007; Whitwell et al. 2007; Zanetti et al. 2006), we also examined gray matter associations with dual-task performance by MCI subtypes. Elucidation of the association between dual-task gait performance and brain substrates in MCI will contribute to understanding the specific nature of gait impairment in this population and help with development of interventions for improving mobility in MCI.

Materials and methods

Participants

Participants were recruited from the National Center for Geriatrics and Gerontology - Study of Geriatric Syndromes (Shimada et al. 2015). The overall goal of this study is to establish a screening system for geriatric syndromes and to validate evidence-based interventions for preventing these geriatric syndromes. The potential participants in the current sub-study were 1621 adults age 65 years old who were diagnosed with MCI using consensus diagnostic procedures. MCI criteria followed those established by Petersen (Petersen 2004, 2011) and included the following conditions: subjective memory complaints; objective cognitive decline; not meeting Diagnostic and Statistical Manual of Mental Disorders-IV clinical criteria for dementia; functionally independent in daily living activities; and intact general cognitive function, defined as a Mini-Mental State Examination (MMSE) score > 23 (Folstein et al. 1975). Objective cognitive decline was defined as cognitive function > 1.5 standard deviations lower than normal for an age-standardized battery of cognitive tests in memory, processing speed, attention/executive function and visuospatial skill (Shimada et al. 2013b) in the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al. 2013). Exclusion criteria were the presence of neurological disease (cerebrovascular disease, Parkinson's disease, depression), connective tissue disease, using a heart pacemaker, severe vision impairment, severe hearing impairment, depressive symptoms (15-item Geriatric Depression Scale > 5 (Yesavage 1988)), and unable to exercise due to a doctor recommendation or medical condition. Of 1169 participants who met MCI criteria and were invited to participate in this sub-study, 632 agreed to in-person assessments and 582 completed gait examination and MRI studies. Twenty-two participants diagnosed with bleeding, infarction, tumors, or cysts on brain MRI by a radiologist were not included in analyses. Following all exclusions, 560 MCI participants were eligible for analysis. Compared to those included in the study, the 72 participants excluded from this analysis were significantly older ($p < 0.001$), but sex ($p = 0.093$) and education ($p = 0.878$) were not significantly different. The ethics committee of the National Center for Geriatrics and Gerontology approved this study.

Gait procedure

Participants were instructed to walk on a level horizontal walkway of length 11 m that had buffer spaces of 2 m at both ends to account for initial acceleration and terminal deceleration. Two gait experiments were performed sequentially: single task walking, walking at preferred speed; and dual-task walking while counting backwards, starting from 100. In the dual-task gait condition, participants were instructed to pay equal attention to gait and the cognitive task to account for task prioritization effects (Verghese et al. 2007a). This type of arithmetic task is commonly used in dual-task walking studies and the effect of this task on gait has been confirmed in a meta-analysis (Al-Yahya et al. 2011). Time to walk the middle 5 m (steady state) was measured using a stopwatch and gait speed was expressed in m/s. The correct rate of backward counting was also monitored during the dual task gait condition. All participants completed both gait conditions, with three using walking aids during the assessment.

MRI data acquisition

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 msec; echo time (TE)/repetition time (TR), 1.98 ms/1800 ms; 1.1-mm slice thickness). 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.

Image processing

T1-weighted images were pre-processed using SPM8 (Wellcome Department of Cognitive Neurology) with MATLAB R2011b (Mathworks, Natick, MA). Each structural image was analyzed using voxel-based morphometry using a unified segmentation procedure, diffeomorphic anatomical registration through exponentiated line algebra (Ashburner 2007; Ashburner and Friston 2005), a recently developed voxel-based morphometry technique that improves inter-subject alignment by modeling the shape of the brain using 3 parameters for each voxel. This program simultaneously aligns gray matter and white matter to produce a study-specific and increasingly crisp template, to which data are iteratively aligned. For each subject, this method produces a gray matter image, a white matter image and a cerebrospinal fluid image in the same space as the original T1-weighted image, with each voxel assigned a probability (Ashburner and Friston 2005, 2009). Each participant's data was then realigned and spatially normalized into Montreal Neurologic Institute space. Finally, images were spatially smoothed using an 8-mm full-width at half maximum of Gaussian smoothing kernel (Ashburner 2007; Ashburner and Friston 2005).

Covariates

Covariates for analysis were chosen based on biological plausibility or previously reported associations with dual task performance (Yogev-Seligmann et al. 2008; Zheng et al. 2012a; Zheng et al. 2012b). Age, sex, body mass index (BMI) (weight/height²), educational history, and chronic illnesses including hypertension, diabetes, hyperlipidemia, and osteoporosis were assessed. An association between white matter lesions and dual-task performance has been found in older adults (Zheng et al. 2012a). In our study, white matter lesions were identified as periventricular hyperintensities and deep and subcortical white matter hyperintensities according to the Fazekas scale (Fazekas et al. 1993), and participants were classified into groups with severe periventricular hyperintensities or deep subcortical white matter hyperintensities (grade III). A tablet version of the Symbol Digit Substitution Task (on which higher scores are better) in the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al. 2013) was used as a potential confounder for the association between dual-task gait and gray matter (Holtzer et al. 2014).

Statistical analysis

The decline in cognitive function in people with MCI is not uniform, but rather depends on MCI subtype, i.e., aMCI or naMCI (Petersen 2004). These two MCI subtypes may have different neuropathologies and courses of conversion to dementia (Zanetti et al. 2006;

Fischer et al. 2007; Albert et al. 2011). Thus, we conducted analyses in the total sample and stratified by MCI subgroups (aMCI and naMCI). Variables were compared between subgroups using an unpaired *t*-test or χ^2 test. Gait speed under single-task and dual-task conditions was compared by paired *t*-test. Analyses were performed using IBM SPSS ver. 20 (IBM Corp., Chicago, IL, USA). All tests were two-tailed and the significance level was set at $P < 0.05$.

Group-level covariance analyses

Multivariate covariance-based analyses were performed to identify brain patterns of gray matter related to single-task and dual-task gait using a principal components analysis toolbox (http://www.nitrc.org/projects/gcva_pca) (Habeck et al. 2005; Habeck and Stern 2007). This toolbox was used to extract a linear combination of principal components associated with single and dual-task gait. All images were masked using a group level gray matter mask supplied by SPM8, including only voxels with >20 % probability of being gray matter. The resultant masked images from all participants in each image modality were subjected to analyses in subsequent fits of behavioral variables. The detailed protocol has been described elsewhere (Steffener et al. 2013). In summary, principal components analysis was performed after participant means were subtracted from each voxel to generate a set of principal components and their associated pattern expression scores. The covariance patterns relating gray matter to gait speed were calculated by regression. The gray matter covariance patterns associated with single-task and dual-task gait speed were computed by regressing the participant-specific factor scores from the first 12 principle components, using Akaike information criteria (Burnham 2002). First, we analyzed the total sample and compared the patterns between gait speed in single-task and dual-task conditions. Each model was adjusted by a set of covariates. For single-task gait speed, these covariates were age, sex, education, subtypes of MCI and white matter lesions (model 1). For dual-task gait speed, the covariates were age, sex, education, subtypes of MCI, white matter lesions and cognitive performance during gait (model 2). Cognitive performance (correct rating) during dual-task gait was added as a covariate because the cognitive performance during the dual task could potentially affect gait performance (Kelly et al. 2010). To clarify differences between single-task and dual-task gait speed, single-task gait speed was added to the covariates in model 2 to give a fully adjusted model (model 3). Then, a sub-analysis of dual-task gait speed, stratified by subtypes of MCI (aMCI and naMCI) was conducted, adjusted for age, sex, education, white matter lesions, cognitive performance during the dual task, and single-task gait speed (model 3). For the results of all models, the stability of the voxels within the resultant covariance patterns were tested using 1000 bootstrap resamples.

A covariance pattern was applied to the resampled data and a Z value was computed. The resulting Z map was thresholded at $Z > 2.3$ ($P < 0.0215$, two-tailed) with a cluster threshold of 50 voxels. Significant regions indicate a positive association with gait speed. Anatomical labels for cluster maxima in the covariance pattern were determined using WFU PickAtlas (Maldjian et al. 2004; Maldjian et al. 2003) and Talairach Daemon (Lancaster et al. 1997; Lancaster et al. 2000). Results of images were overlaid with MRICron (<http://www.mccauslandcenter.sc.edu/CRNL/>).

Results

Characteristics and behavioral data

The 560 MCI subjects were classified as naMCI ($n = 270$) or aMCI ($n = 290$) following consensus diagnostic procedures. Individuals with naMCI were younger ($P = 0.021$) and included a higher proportion of women ($P < 0.001$) (Table 1). As expected, naMCI subjects had lower performance on the Symbol Digit Substitution Task (naMCI: 41.8 ± 9.5 vs. aMCI: 44.0 ± 9.6 , $P = 0.007$), while MMSE scores were not different. Education, BMI, chronic diseases and white matter lesions did not differ significantly between the two groups.

Gait and cognitive performance during the dual-task condition are also shown in Table 1. Gait speed significantly slowed from the single-task to dual-task conditions (dual task effect) in all subjects and in the aMCI and naMCI groups ($P < 0.001$). Gait speed under single- and dual-task conditions did not differ significantly between the two groups. Backward counting performance during dual-task gait also did not differ between aMCI and naMCI groups.

Total sample

The gray matter patterns associated with single-task and dual-task gait had shared and non-overlapping/unique regions. The results for model 1 (single-task gait) and model 2 (dual-task gait) overlaid on the same template are shown in Fig. 1. Dual-task gait shared many regions with single-task gait, including the inferior frontal gyrus, medial frontal gyrus, superior frontal gyrus, precentral gyrus, fusiform gyrus, cingulate gyrus, including the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC), and the occipital and middle temporal gyrus. The gray matter pattern associated with single-task gait also encompassed regions that were not associated with dual-task gait, including the supplementary motor cortex, primary motor cortex and thalamus. Model 3 (adjusted for covariates including single-task gait speed) also revealed a pattern specific in dual-task gait that comprised the medial frontal gyrus, superior frontal gyrus, anterior cingulate, cingulate, precuneus, fusiform gyrus, middle occipital gyrus, inferior temporal gyrus and middle temporal gyrus (Table 2 and Fig. 2).

MCI subtypes

Table 3 displays a gray matter pattern associated with dual-task gait speed in naMCI (Model 3), comprising the inferior frontal gyrus, medial frontal gyrus, middle frontal gyrus, superior frontal gyrus, and extranuclear and middle temporal gyrus. In contrast, the gray matter pattern associated with dual-task gait speed in aMCI comprised the occipital gyrus, parahippocampal gyrus, fusiform, middle temporal gyrus, cuneus, precuneus, and cingulate gyrus (Table 4). To simplify comparisons and interpretation, results from the naMCI and aMCI subgroups are overlaid on the same figure (Fig. 3).

Discussion

This study identified gray matter patterns associated with dual-task gait performance in a large number of older adults with MCI. There were shared and unique regions in patterns associated with single-task and dual-task gait. Regions that were uniquely associated with

dual-task gait were identified after accounting for several confounders, including single-task gait speed. Even though the behavioral data during the dual task were similar in both MCI subgroups, gray matter patterns associated with dual-task gait differed between aMCI and naMCI. These results suggest that different brain mechanisms may be involved in maintaining dual-task performance in the two MCI subtypes.

Brain regions associated with single-task and dual-task gait

The gray matter pattern associated with single-task and dual-task gait speed in our sample was composed of many different regions, including the inferior frontal gyrus, medial frontal gyrus, superior frontal gyrus, precentral gyrus, fusiform gyrus, cingulate gyrus including the ACC and PCC, and the occipital and middle temporal gyrus. Most of these regions have also been identified in previous studies, even though participant characteristics varied in these studies. Normal gait speed (single-task gait), for example, has been associated with gray matter volume in the frontal lobe, particularly the PFC (Rosano et al. 2012) and hippocampus (Ezzati et al. 2015), in healthy older subjects. Gait speed has also been associated with cortical thinning in frontal regions (inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus), precentral gyrus, cingulate, temporal lobe (middle temporal gyrus, inferior temporal gyrus and fusiform gyrus), occipital region and limbic system (ACC, PCC and parahippocampal gyrus) in older adults with small vessel disease (de Laat et al. 2012). We did not find a significant pattern associated with dual-task gait in the cerebellum, which has been linked to balance control. A previous whole brain analysis of gray matter, as performed in the current study, also showed no significant association between gait and the cerebellum (Rosano et al. 2008). However, the posterior and lateral regions of the cerebellum, which are associated with cognition, rather than being sensorimotor or vestibular regions, have been shown to be associated with gait speed and information-processing ability (Nadkarni et al. 2014). Rosano et al. (2008) suggested that the association between the cerebellum and gait was masked in healthy subjects due to the cerebellum not being impaired for balance control in the absence of a neurological disease such as stroke, while Nadkarni et al. (2014) suggested that the association with gait depended on connectivity between the lateral region of the cerebellum (cognition) and the frontal lobe. The requirement of the cerebellum in balance control might not have been impaired in the subjects in the current study. Lesions in the cerebellum that cause impaired balance are mostly due to neurological diseases such as stroke or trauma, and subjects with these diseases were excluded from the study. In this context, our findings expand knowledge about brain structural relationships with gait to the MCI population and to the dual-task condition.

Most neuroimaging studies of dual-task gait performance have shown brain activation patterns using different modalities. Based on the structure–function relationship in which local gray matter volume is related to functional activation in the brain (Kalpouzos et al. 2012; Johnson et al. 2000), the evidence from these activation studies of dual-task gait are important to consider. PFC activation during dual-task gait has been observed in cognitively healthy older adults (Holtzer et al. 2015) and in individuals with MCI (Doi et al. 2013) using functional near-infrared spectroscopy, a portable optical imaging technique that permits imaging during actual locomotion, but is limited to recording brain activation close to the

surface of the skull, e.g. the PFC. Another study of cognitively healthy older adults examined mental imagery of dual-task walking (walking while reciting alternate alphabetical letters) with functional MRI and showed that dual-task gait engaged not only PFC regions, but also cerebellar, precuneus and supplementary motor regions (Blumen et al. 2014). A study using PET showed adaptability for treadmill walking, i.e., challenging gaits like dual-task gait, require a neuronal network involving the frontal, hippocampus, primary motor area, supplementary motor area, occipital, cerebellum, and PCC (Shimada et al. 2013a). Collectively, these studies in cognitively intact older adults link the cerebellar, precuneus, primary motor, supplementary motor and PFC regions to dual-task gait performance. These regions were overlaid with our results in MCI. Thus, gray matter of regions requiring functional activation during dual-task gait may have a crucial role in MCI.

Other neuroimaging studies have linked functional brain networks during rest with single-task gait (Sakurai et al. 2014) and dual-task gait (Yuan et al. 2015). The first study found that cerebral glucose metabolism in the PFC, PCC, and parietal cortex was associated with single-task gait and these regions were thought to be constitutive parts of the default mode network (Sakurai et al. 2014). The second study found that dual-task gait was associated with greater connectivity in dorsolateral prefrontal regions of the left fronto-parietal resting state network (Yuan et al. 2015). Our results showing gray matter overlaid with these regions linked to single- and dual-task gait are in accordance with these findings. The default-mode network is more active when individuals are not engaged in particular tasks and is thought to play a role in vigilance, readiness, or monitoring (Raichle et al. 2001). Alzheimer pathology disrupts the default-mode network and the abnormality in the network manifests as MCI and Alzheimer's disease (Dickerson and Sperling 2008). Thus, specificity of impaired brain function in MCI may contribute to the association of the gray matter pattern with dual-task gait. A further multimodal neuroimaging study is required to clarify the association between pathological changes in MCI that account for impaired dual-task gait performance.

Among dual-task gait studies, the type of cognitive task used as the secondary task is a key issue. We used an arithmetic task as the cognitive task during dual tasking. Arithmetic tasks have been reported to result in brain activation in the middle-temporal (Ueda et al. 2015) and occipito-temporal (Kawashima et al. 2004) regions. Furthermore, older adults have an activated middle temporal gyrus during dual-task using an arithmetic task (Van Impe et al. 2011). The task-specific activation could affect the association between dual-task gait and brain pattern. Brain patterns in MCI associated with other types of secondary tasks, e.g., verbal tasks, should also be investigated.

MCI subtypes

The pattern of brain regions associated with dual-task gait performance differed between aMCI and naMCI, while the gait speed under both single- and dual-task conditions and cognitive performances during dual-task gait were similar in these subtypes. This finding implies that dual-task gait performance in MCI may depend on the type of MCI. In other words, these differences may relate to brain regions, risk factors or physiology that are unique to each MCI subtype. Gray matter atrophy patterns in MCI subtypes are different compared to healthy subjects (Whitwell et al. 2007; Zhang et al. 2012): aMCI has more

atrophy in the hippocampus, parahippocampus and temporal lobes, while naMCI has reduced atrophy in the inferior and medial frontal gyrus, anterior cingulate gyrus, superior temporal gyrus and insula (Zhang et al. 2012). Risk factors vary among MCI subtypes that may also affect brain activation during dual tasks. Individuals with aMCI also have a higher proportion of APOE4 (He et al. 2009; Sasaki et al. 2009) and risk of conversion to Alzheimer's disease (Palmer et al. 2008), whereas naMCI has more vascular risk factors (Knopman et al. 2009; Reitz et al. 2007) and cortical infarcts (Kantarci et al. 2008) than aMCI. There are different activation patterns during a memory task between MCI subtypes: compared to a control group, naMCI has diminished parietal and frontal activation during an encoding task, while aMCI has less activation in parietal, parietooccipital, insula and posterior temporal regions (Machulda et al. 2009). Our findings raise the possibility that the compensatory mechanisms employed to maintain dual task performance may differ in the two MCI subtypes. That is, dual-task gait performances in naMCI may compensate in areas (e.g., hippocampus, PCC) other than the frontal network because differences of results from the total population and naMCI were observed in regions other than the frontal network. On the contrary, aMCI may compensate in areas (e.g., frontal circuit) other than the impaired memory network. This possibility requires further exploration to develop new interventions to maintain mobility in patients with MCI.

Limitations

We had a large sample of individuals with MCI who underwent gait and MRI studies, but the study still has several limitations. The cross-sectional design limits causal inferences, and longitudinal studies are required to examine causal associations between brain structural changes and dual-task gait performance. The physiology and architecture of the brain regions identified also needs to be studied to clarify differences in dual-task associated networks between subtypes in MCI and potential compensatory mechanisms.

Conclusion

Our whole brain analysis study showed distinct gray matter regions in the brain associated with dual-task gait performance. The pattern of regions related to dual-task gait performance differed between subtypes of MCI. Clarifying the underpinnings of gait impairment in MCI will contribute to a better understanding of cognitive control processes for gait and aid in the development of interventions to prevent mobility loss.

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Fig. 1.

Brain regions associated with single-task and dual-task gait in all subjects. Analysis of single-task gait (red) adjusted for covariates of age, sex, education, subtype of MCI, and white matter lesions (model 1) and for dual-task gait speed (blue) adjusted for covariates of age, sex, education, subtype of MCI, white matter lesions, and cognitive performance during gait (model 2). The results are overlaid and regions indicated in purple are associated with both single-task and dual-task gait. Threshold: $Z > 2.3$ and $k = 50$

Fig. 2.

Brain regions associated with dual-task gait speed after adjustment for single-gait speed in all subjects. Results for dual-task gait speed adjusted for covariates of age, sex, education, subtype of MCI, white matter lesions, cognitive performance during gait, and single-task gait speed (model 3). Threshold: $Z > 2.3$ and $k = 50$

Fig. 3.

Brain regions associated with dual-task gait speed in aMCI and naMCI subjects. Results for each MCI subtype are shown for dual-task gait speed adjusted for covariates of age, sex, education, subtype of MCI, white matter lesions, cognitive performance during gait, and single-task gait speed (model 3). Threshold: $Z > 2.3$ and $k = 50$

Table 1
Characteristics of subjects with non-amnestic and amnestic MCI

Variables	Mean (SD) or %			p
	naMCI (n = 270)	aMCI (n = 290)	Total (n = 560)	
Age (yrs)	72.9 (5.1)	72.4 (4.5)	73.4 (5.6)	0.021
Education (yrs)	11.2 (2.5)	11.1 (2.5)	11.2 (2.5)	0.732
Body mass index (weight/height ²)	23.3 (3.0)	23.3 (2.8)	23.3 (3.1)	0.705
Sex, women (%)	53.6	63.6	45.5	< 0.001
Hypertension (%)	43.0	39.6	46.2	0.116
Diabetes (%)	9.8	8.1	11.4	0.199
Hyperlipidemia (%)	31.2	31.1	31.4	0.945
Osteoporosis (%)	13.0	14.4	11.7	0.339
Severe white matter lesions (%)	19.5	19.6	19.3	0.924
Mini-Mental State Examination (score)	26.7 (1.8)	26.7 (1.9)	26.6 (1.7)	0.499
Gait speed				
Single-task condition (m/s)	1.35 (0.22)	1.35 (0.21)	1.35 (0.22)	0.975
Dual-task condition (m/s)	1.21 (0.31) *	1.22 (0.30) *	1.20 (0.32) *	0.446
Backward counting				
Correct rating during dual-task condition (%)	89.5 (18.0)	89.8 (18.2)	89.3 (17.8)	0.729

Values are mean (SD) or proportion. MCI: mild cognitive impairment

Comparison between groups by unpaired-t-test or chi-square test

Comparison of gait speed between single- and dual-task conditions by paired-t-test

* $p < 0.001$ vs. single-task gait speed (paired-t-test)

Table 2
Local maxima in patterns of brain regions associated with dual-task gait in all subjects

Region	Hem	X	Y	Z	k	z-value (maximum)
Middle temporal gyrus	R	64	-26	-4	8632	3.20
Fusiform gyrus	L	-36	-16	-32	142	2.54
Middle temporal gyrus	L	-60	-38	-4	8198	3.19
Parahippocampal gyrus	L	-30	-33	-22	2226	2.62
Inferior temporal gyrus	R	46	-42	-20	73	2.63
Parahippocampal gyrus	R	26	-44	-14	237	2.80
Medial frontal gyrus	L	-8	46	-8	972	2.61
Superior frontal gyrus	R	18	63	2	372	2.64
Lingual gyrus	L	-24	-78	-12	50	2.62
Middle occipital gyrus	R	34	-87	2	182	2.82
Precuneus	R	4	-63	16	5011	3.28
Insula	L	-36	-22	15	1141	3.24
Middle temporal gyrus	R	34	-81	16	142	2.54
Anterior cingulate	R	9	33	28	108	2.65
Cingulate gyrus	L	-8	6	42	422	2.80
Cingulate gyrus	R	9	2	42	50	2.62

The model was adjusted for age, sex, education, subtypes of mild cognitive impairment, white matter lesions, cognitive performance during gait, and single-gait speed. Threshold: $Z > 2.3$ and k

Table 3
Local maxima in patterns of brain regions associated with dual-task gait in naMCI subjects

Region	Hem	X	Y	Z	k	z-value (maximum)
Inferior frontal gyrus	L	-27	8	-18	5486	2.55
Inferior frontal gyrus	R	36	26	-3	5304	2.56
Medial frontal gyrus	R	4	52	-4	2655	2.46
Middle temporal gyrus	L	-60	-10	-9	236	2.42
Middle frontal gyrus	L	-33	36	-16	157	2.37
Inferior frontal gyrus	R	34	33	-14	191	2.41
Middle temporal gyrus	R	63	-10	-9	251	2.50
Superior frontal gyrus	R	28	60	-2	1059	2.44
Superior frontal gyrus	L	-26	58	2	285	2.40
Extra-Nuclear	L	-4	-14	16	658	2.46
Inferior frontal gyrus	L	-42	38	16	157	2.35
Inferior frontal gyrus	L	-51	9	24	111	2.36

Model adjusted for age, sex, education, subtypes of mild cognitive impairment, white matter lesions, cognitive performance during gait, and single-gait speed. Threshold: $Z > 2.3$ and $k \geq 50$

Table 4
Local maxima in patterns of brain regions associated with dual-task gait in aMCI subjects

Region	Hem	X	Y	Z	k	z-value (maximum)
Middle temporal gyrus	R	42	3	-45	57	2.45
Parahippocampal gyrus	L	-33	-15	-32	332	2.64
Fusiform gyrus	R	60	-9	-33	210	2.58
Inferior temporal gyrus	L	-57	-28	-26	354	2.55
Fusiform gyrus	R	45	-40	-20	602	2.75
Middle temporal gyrus	R	52	-66	15	1298	2.69
Middle occipital gyrus	L	-45	-69	-8	707	2.91
Middle occipital gyrus	L	-33	-93	0	2203	2.93
Cuneus	L	-6	-98	6	751	2.75
Parahippocampal gyrus	R	16	-46	-3	51	2.44
Middle occipital gyrus	R	38	-87	2	85	2.52
Posterior cingulate	R	2	-54	20	5271	3.19
Cingulate gyrus	L	-8	6	46	66	2.61

Model adjusted for age, sex, education, subtypes of mild cognitive impairment, white matter lesions, cognitive performance during gait, and single-gait speed. Threshold: $Z > 2.3$ and $k \geq 50$