Published in final edited form as:

Am J Phys Med Rehabil. 2018 April ; 97(4): 229–235. doi:10.1097/PHM.0000000000000881.

Limbic and Basal Ganglia Neuroanatomical Correlates of Gait and Executive Function:

Older Adults With Mild Cognitive Impairment and Intact Cognition

Ellen L. McGough, PT, PhD,

Department of Rehabilitation Medicine, University of Washington, Seattle, Washington

Valerie E. Kelly, PT, PhD,

Department of Rehabilitation Medicine, University of Washington, Seattle, Washington

Kurt E. Weaver, PhD,

Department of Radiology, University of Washington, Seattle, Washington

Integrated Brain Imaging Center, University of Washington, Seattle, Washington

Rebecca G. Logsdon, PhD,

Psychosocial and Community Health, University of Washington, Seattle, Washington

Susan M. McCurry, PhD,

Psychosocial and Community Health, University of Washington, Seattle, Washington

Kenneth C. Pike, PhD,

Psychosocial and Community Health, University of Washington, Seattle, Washington

Thomas J. Grabowski, MD, and

Department of Radiology, University of Washington, Seattle, Washington

Integrated Brain Imaging Center, University of Washington, Seattle, Washington

Linda Teri, PhD

Psychosocial and Community Health, University of Washington, Seattle, Washington

Abstract

Objective: This study aimed to examine differences in spatiotemporal gait parameters between older adults with amnesic mild cognitive impairment and normal cognition and to examine limbic and basal ganglia neural correlates of gait and executive function in older adults without dementia.

Design: This was a cross-sectional study of 46 community-dwelling older adults, ages 70–95 yrs, with amnesic mild cognitive impairment ($n = 23$) and normal cognition ($n = 23$). Structural magnetic resonance imaging was used to attain volumetric measures of limbic and basal ganglia

All correspondence should be addressed to: Ellen L. McGough, PT, PhD, Department of Rehabilitation Medicine, University of Washington, 1959 NE Pacific St, Box 356490, Seattle, WA 98195.

Financial disclosure statements have been obtained, and no conflicts of interest have been reported by the authors or by any individuals in control of the content of this article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ajpmr.com).

structures. Quantitative motion analysis was used to measure spatiotemporal parameters of gait. The Trail Making Test was used to assess executive function.

Results: During fast-paced walking, older adults with amnesic mild cognitive impairment demonstrated significantly slower gait speed and shorter stride length compared with older adults with normal cognition. Stride length was positively correlated with hippocampal, anterior cingulate, and nucleus accumbens volumes ($P < 0.05$). Executive function was positively correlated with hippocampal, anterior cingulate, and posterior cingulate volumes ($P < 0.05$).

Conclusions: Compared with older adults with normal cognition, those with amnesic mild cognitive impairment demonstrated slower gait speed and shorter stride length, during fast-paced walking, and lower executive function. Hippocampal and anterior cingulate volumes demonstrated moderate positive correlation with both gait and executive function, after adjusting for age.

Keywords

Gait; Limbic System; Basal Ganglia; Magnetic Resonance Imaging; Quantitative Gait Analysis; Executive Function; Amnesic Mild Cognitive Impairment

Age-related impairments and neurodegenerative processes accelerate mobility-related decline in older adults. In amnesic mild cognitive impairment (aMCI) and Alzheimer's disease (AD), cognitive impairment is considered the primary function that declines; however, impairments in peripheral systems, including the motor system, are present during early stages of disease.¹ The worldwide prevalence of dementia has been projected to triple, increasing the number of cases to more than 106 million by 2050.² Older adults with aMCI are at high risk for AD, the most common form of dementia.³ Older adults with aMCI have demonstrated changes in mobility that may function as early markers of AD-related pathology.^{4,5}

Changes in gait performance often precede the onset of dementia and slowed gait speed, alone, is predictive of cognitive decline and future onset of dementia.^{6,7} Specific changes in spatiotemporal parameters related to walking pace and rhythm have been linked to distinct neurocognitive profiles in older adults.⁸ Unique motor phenotypes have also been described as being associated with neurodegenerative diseases, including Lewy body disease, Parkinson, and AD.⁹ Although a temporal relationship between cognitive and physical decline has been reported in preclinical, prodromal, and advancing stages AD,^{7,10} research is needed to examine underlying neural mechanisms.

Limbic system structures, including the hippocampus, amygdala, thalamus, and cingulate cortex, are known to play a functional role in memory formation, mood, and goal-directed behaviors and are impacted by AD pathology years or decades before the onset of cognitive impairment.^{11,12} Basal ganglia structures including the caudate, putamen, globus pallidus, and nucleus accumbens receive input from the motor cortex and cerebellum and provide adaptive movement control, especially when the gait pattern requires recalibration, such as in navigating different terrains and environments.¹³ Poor mobility outcomes are associated with reduced gray and white matter volume in older adults,⁵ and mechanisms beyond age-related decline, possibly early AD brain pathology, may be contributing to changes in gait speed. A prodementia syndrome characterized by slow walking and cognitive complaints is

reportedly a stronger predictor of cognitive decline than either slow gait speed or cognitive complaints alone.¹⁴ A better understanding of mechanisms that underlie a temporal relationship between cognitive and physical decline is important in identifying therapeutic targets and developing rehabilitation strategies to mitigate loss of mobility.

Purpose

The aims of this study were (1) to examine differences in spatiotemporal gait parameters in older adults with aMCI and normal cognition (NC) and (2) to examine limbic and basal ganglia neural correlates of gait and executive function. The overall objective was to gain insight into the neural mechanisms common to gait performance and executive function in older adults without dementia.

METHODS

This study was a cross-sectional examination of relationships between spatiotemporal gait parameters, executive function, and magnetic resonance imaging (MRI) volumetric measures of limbic and basal ganglia structures. Participants were community-dwelling older adults recruited from independent retirement homes and enrolled between October 2009 and March 2012 as part of ongoing studies of older adults with aMCI and NC (2R01 AG14777–06A2 [PI: LT]; 1RCA NS073008 01 [PI: TJG]). Forty-six community-dwelling older adults with a mean age of 83.7 yrs (SD = 4.9; range = 73.9–94.3) were included in this study.

Study Inclusion and Exclusion Criteria

Inclusion criteria were (1) ages of 70–95 yrs and (2) completing less than 150 mins of moderate intensity exercise per week. Exclusion criteria were the following: (1) dementia, as evidenced by a diagnosis of dementia, a Clinical Dementia Rating¹⁵ score of 1.0 or higher or a Mini-Mental Status Examination (MMSE)¹⁶ score of less than 20; (2) unable to walk independently without an assistive device; (3) a known terminal illness or uncontrolled medical condition; (4) actively suicidal, hallucinating, or delusional; (5) hospitalized within the past 12 mos; (6) blind or deaf; (7) a known central nervous system condition; or (8) a metal implant or any other contraindication to MRI. The University of Washington Institutional Review Board approved study procedures, and all participants provided written consent. This study conforms to all Strengthening the Reporting of Observational Studies in Epidemiology Checklist guidelines and reports the required information accordingly (see Checklist, Supplemental Digital Content, <http://links.lww.com/PHM/A540>).

Classification (aMCI vs. NC)

After study enrollment, participants were classified into aMCI or NC groups. The classification of aMCI was determined with the application of the Petersen criteria (single or multiple domain MCI)¹⁷ including the following: (1) memory complaint; (2) objective evidence of memory impairment; (3) preserved general cognitive function; (4) essentially preserved activities of daily living; and (5) no diagnosis of dementia. Neuropsychological tests, to confirm memory impairment for the purpose of aMCI versus NC classification,

included the the following: (1) MMSE for global cognition¹⁶; (2) AD Assessment Scale-Cognitive Subscale for severity of cognitive decline¹⁸; (3) Wechsler Memory Scale-Revised Logical Memory I and II for immediate and delayed recall¹⁹; and (4) Clinical Dementia Rating severity rating of cognitive impairment (Clinical Dementia Rating of 0 = no cognitive impairment; Clinical Dementia Rating of 0.5 = mild cognitive impairment).¹⁵ Objective memory impairment was determined by a score on the Wechsler Memory Scale-Revised Logical Memory II that was one standard deviation below age and education adjusted norms,²⁰ problems on memory recall items of the MMSE, and/or observed difficulty with everyday recall during the assessment interview.

Demographics and Baseline Characteristics

Co-morbid health conditions were identified from a self-report questionnaire of health conditions and a medications questionnaire. The short-form Geriatric Depression Scale (range = 0–15) was used to screen for symptoms of depression.²¹ A brief musculoskeletal screening examination was conducted by a licensed physical therapist to determine whether there were impairments in lower-limb sensation (light touch, protective, or vibration) or joint range of motion. Protective sensation was assessed using a Semmes Weinstein 5.07 monofilament at eight sites on the dorsal and plantar surface of each foot.²² Vibration sensation was tested with a 128- or 256-Hz tuning fork over the metatarsal phalangeal joint and the medial malleolus.²²

Magnetic Resonance Imaging

Structural magnetic resonance imaging (T1 MRI) was used to measure region of interest (ROI) brain volumes and intracranial volume (ICV). A Philips 3.0T Achieva system with an eight-channel SENSE head coil was used to acquire a high-resolution T1-weighted three-dimensional Magnetization-Prepared Rapid Gradient-Echo (170 sagittal slices; in-plane resolution = 256×256 ; field of view = 240×256 ; echo time = 3.01 milliseconds; repetition time, 6.491 milliseconds; flip angle = 8.0 degrees) for each participant.

Structural MRI Analysis

To obtain volume measures from subcortical and cortical regions, cortical reconstruction and volumetric segmentation of the Magnetization-Prepared Rapid Gradient-Echo scans was performed using FreeSurfer Version 5.1.²³ Default parameters were used except where adjustment to the watershed threshold was needed to refine skull stripping. Reported cortical grey matter volumes are based on the Desikan-Killiany region definition implemented in FreeSurfer.²⁴ Volumetric measures calculated for ROIs of limbic system structures included the hippocampus, amygdala, thalamus, anterior cingulate (rostral + caudal segments), and posterior cingulate were calculated. Volumetric measures calculated for ROIs of basal ganglia structures included the caudate, putamen, globus pallidus, and nucleus accumbens. To control for differences in head size across participants, volumetric estimates were adjusted by dividing an ROI volume by the ICV estimate.²⁵ This approach is supported for single structure volumes for both subcortical and cortical structures.²⁵ The ICV-adjusted volumes of each left and right ROI were combined.

Quantitative Gait Analysis

A Qualisys Motion Capture System (Qualisys, Gothenburg, Sweden) recorded the position of 34 markers placed bilaterally on the feet, legs, hips, trunk, and arms during walking. The walking tests were completed on the same day as the MRI scanning session. Participants walked on a level surface along an 8.8-m pathway (data captured in middle 4 m of pathway) under two conditions (1) usual-paced walking and (2) fast-paced walking. Participants walked without an assistive device and performed two 30-sec trials for each condition. Instructions for usual-paced walking were “walk at your comfortable speed.” Instructions for fast-paced walking were “walk as quickly as you safely can.” Excellent test-retest reliability intraclass correlation coefficient (ICC) for gait speed ($ICC > 0.90$) and cadence ($ICC = 0.93$) has been reported in nondemented older adults.²⁶

Executive Function Performance Measure

Executive function was measured with the Trail Making Test part A (TMT-A) and part B (TMT-B) representing cognitive functions of complex visual scanning, processing speed, attention, and the ability to shift sets.²⁷

Statistical Analysis

Data analysis was conducted using SPSS Version 19 statistical software (SPSS, Inc, Chicago, IL). Data were evaluated for distribution and outliers using histograms and scatter plots. Fisher’s exact test was used to examine differences in categorical variables between aMCI and NC groups. Independent *t* tests were conducted to identify differences between aMCI versus NC older adults in demographics, health conditions, cognitive function, spatiotemporal gait parameters, and MRI brain structure volumetric measures normalized for ICV. Levene’s test for equality of variances was applied to ensure that variability in the *t* test comparison groups was approximately equal.

Incorporating measures that differed significantly between the aMCI and NC groups, we examined neural correlates of stride length and executive function as a single group. The aMCI and NC groups were merged because there was no significant difference in MRI brain structure volume between them. Bivariate Pearson correlations were conducted to identify highly correlated variables and potential confounders. Pearson partial correlations were used to examine neural correlates. To adjust for potential confounding of motor function, we used TMT-B minus TMT-A (TMT-B – TMT-A) for the executive function variable. To adjust for potential confounding of height on stride length, we divided stride length (meter) by height (meter). We adjusted for age in all models. Pearson’s partial correlation analyses were conducted between (1) stride length (meter)/height (meter) and MRI brain region volumes of limbic and basal ganglia structures and (2) TMT-B – TMT-A and MRI brain region volumes of limbic and basal ganglia structures. The strength of Pearson correlation coefficients was interpreted as follows: weak if less than 0.10–0.29, moderate if 0.30–0.49, and strong if 0.50 or greater.²⁸

RESULTS

Demographic and Baseline Characteristics

Descriptive statistics of the 46 participants (23 aMCI, 23 NC) are presented in Table 1. There were no statistically significant differences between the aMCI and NC groups in age, education level, health conditions, height, lower-limb impairments, or use of an assistive device for walking. Most participants were white (93.5%). Fifteen participants had mild impairment of lower-limb protective or vibration sensation (eight aMCI, seven NC), but there was no significant difference between the groups and no participants demonstrated moderate or severe sensory impairment. Three participants reported using an assistive device for walking in the home or in the community.

As expected, function on global cognition (MMSE), memory (Logical Memory I and II), attention, and executive function (TMT-A and TMT-B) was significantly reduced (all P values < 0.05) in the older adults with aMCI compared with those with NC. In addition, as expected, because we excluded people with dementia, there was no significant difference on the AD Assessment Scale-Cognitive Subscale ($P = 0.25$) between the groups.

Group Comparisons of Gait and Brain Volumetric Measures

During fast-paced walking, older adults with aMCI demonstrated significantly slower gait speed ($P = 0.004$) and shorter stride length ($P = 0.01$) compared with the NC; however, there were no significant group differences in measures of gait rhythm (cadence and single-limb support time) (Table 2). Gait parameters during usual-paced walking did not significantly differ between older adults with aMCI compared with the NC. Brain volumetric measures of the limbic or basal ganglia structures did not differ significantly between the aMCI and NC groups (Table 2).

Neural Correlates of Stride Length in Limbic and Basal Ganglia ROIs

After adjusting for age, correlations of moderate strength were identified between stride length/height and hippocampal volume ($r = 0.33$, $P = 0.02$) and stride length/height and anterior cingulate volume ($r = 0.43$, $P = 0.003$). However, correlations between stride length/height and other limbic structures were weak and lacked statistical significance (Table 3). After adjusting for age, correlations of weak to moderate strength approached significance between stride length/height and the putamen volume ($r = 0.29$, $P = 0.05$) and reached statistical significance between stride length/height and the nucleus accumbens volume ($r = 0.36$, $P = 0.01$). However, correlations between stride length/height and other basal ganglia structures were weak and lacked statistical significance (Table 3).

Neural Correlates of Executive Function in Limbic and Basal Ganglia ROI

Better performance on the TMT-B – TMT-A was moderately correlated with greater hippocampal volume ($r = -0.37$, $P = 0.01$), anterior cingulate volume ($r = -0.32$, $P = 0.003$), and posterior cingulate volume ($r = -0.38$, $P = 0.01$), after adjusting for age. Correlations between TMT-B – TMT-A and other limbic structures (amygdala and thalamus) were weak and were not statistically significant (Table 3). Correlations between TMT-B – TMT-A and basal ganglia structures were also weak and not statistically significant.

DISCUSSION

In this study, reduced pace (stride length and gait speed) was demonstrated in older adults with aMCI compared with NC during fast-paced walking. Furthermore, in an effort to identify neural correlates of gait, larger hippocampal and anterior cingulate volumes were correlated with longer stride length and better executive function across older adults with aMCI and NC, suggesting a shared neural basis for fast-paced walking and executive function in older adults without dementia. Early identification of impairments and underlying neural mechanisms may lead to more effective and timely efforts to minimize loss of mobility in older adults, especially those at risk for AD.

Our findings of reduced pace in aMCI compared with NC older adults concur with previous studies,^{8,29} but significant differences were observed only during fast walking in our study. Differences in usual gait speed approached significance, but our relatively small sample size likely contributed to the lack of statistically significant differences than have been previously reported. For example, Verghese et al.⁸ examined gait speed and stride length in 349 older adults with aMCI and NC and reported significantly slower gait speed and shorter stride length during a usual-paced walking task in people with aMCI.

Correlations between reduced mobility and medial temporal lobe atrophy in older adults have been reported^{4,30}; however, the results of the current study extend this body of research by demonstrating shared limbic, especially cingulate and hippocampal, neural correlates of gait and executive function. It is also interesting to note that the basal ganglia structures, known for their role in motor control, had weaker correlations with gait and executive function compared with the limbic system structures. Within the basal ganglia structures, although nearly significant and significant correlations were detected between the putamen and nucleus accumbens volumes and stride length, there were no statistically significant correlations with executive function. The weaker and fewer neural correlates of gait parameters found within basal ganglia structures was possibly due the low challenge of our walking task (straight path and steady state), requiring less basal ganglia specific function for control or recalibration of the gait pattern.

Potential Neural Mechanisms

Age and age-related co-morbid conditions are known to play a role in aspects of brain health that impact gait performance and executive function. Declining gait performance in older adults with cognitive impairment may occur via alterations in memory, spatial processing, attention, and executive functions resulting in reduced influence on planning, navigation, and course correction.^{11,31} In addition, brainstem areas that receive excitatory input from the cerebral cortex, limbic system, and cerebellum as well as inhibitory input from the basal ganglia influence gait performance.¹³

Neuronal loss occurring in the medial temporal lobe, including the hippocampus, during prodromal or early clinical stages of AD causes axonal loss, resulting in deafferentation of brain regions to which these axons project, possibly having an indirect effect on gait speed. Degenerative processes have also been reported in the posterior and anterior cingulate cortex during early stages of AD and, therefore, may play a role in declining gait performance via

loss of structural integrity and reduced connectivity between functionally connected regions of the brain.³²

The limbic system is instrumental in modulating various goal-directed behaviors, and it may be instrumental in maintaining gait performance with advancing age, because walking is a goal-directed behavior that encompasses functions supported by the limbic system, including volitional, emotional, and automatic processes.¹³ Of particular relevance to the current discussion is that descending limbic connectivity on reticulospinal tracts has been shown in animals to drive cognitive or emotional references for the initiation of locomotor behavioral patterns; it is also well established that the reticulospinal system is important for generating locomotor pattern responses.¹³ Because these neural populations are interconnected with the limbic system, walking pace may be negatively impacted by limbic system influences in people without known neurological impairment.

Cognitive and emotional influences on the motor system occur via functional connectivity from the anterior cingulate gyrus.³³ The posterior cingulate is proposed to be involved in memory retrieval and evaluation of information, whereas the anterior cingulate is more involved in executive functions.³³ The synergistic and overlapping functions of brain structures identified in this study provide potential therapeutic targets for preserving locomotion as well as executive function via strategies promoting neuroplasticity and neuroprotection for older adults. It is plausible that interventions targeting neuroplastic effects will promote gains in both cognitive and physical domains of function.

Clinical Implications

Walking quickly and changing speed are important for maintaining independent community ambulation. Both self-selected and maximal walking speed have been reported to discriminate between community-dwelling older adult fallers and non-fallers, suggesting that assessment of both usual pace and fast walking are informative in predicting risk for fall-related injury.³⁴ Callisaya et al.³⁵ reported that worsening cognitive impairment was associated with reduced ability to increase speed and walk quickly. Faster gait speed is important to community mobility, for example, during activities such as crossing a busy street or catching a bus. Given the functional relationship between executive processes and gait control, dual-task clinical tests that increase cognitive load and environmental challenge are also important in the assessment of older adults with cognitive impairment. Dual-task gait tests improve sensitivity for detecting gait impairments, executive impairments, and increased risk for dementia.³⁶

Our findings suggest that gait speed and stride length during fast-paced walking are associated with cognitive function and limbic system brain region volume, and this has potential clinical implications. In a 30-yr longitudinal analysis, a more rapid rate of physical function decline has been reported in individuals with nonamnestic causes of dementia; however, physical function in those with AD-type dementia also declined at a faster rate than cognitively healthy older adults. In people with all types of dementia, during the transition from a cognitively normal state to a dementia diagnosis, the rate of physical performance decline was significantly greater compared with those who maintained normal cognitive

function.³⁷ This suggests a critical window for early detection and implementation of prevention and rehabilitative strategies.

There is increasing evidence that physical exercise interventions improve physical performance as well as executive function in older adults at risk for dementia. A 6-mo, twice-weekly multicomponent exercise trial demonstrated protective effects on cortical gray matter and cognitive function in older adults with aMCI.³⁸ Resistance exercise programs also seem to positively influence neural mechanisms that contribute to cognitive function. Participation in a 6-mo, twice-weekly resistance training program significantly improved performance on a test of response inhibition and associative memory in older women with MCI, suggesting that resistance exercise contributes to functional plasticity in brain regions associated with executive function.³⁹

Early identification of individuals at risk for AD and related dementia is important to allow for the development of targeted preventive and rehabilitation strategies. Clinically, a combination of measures to examine cognitive, physical, and complex daily activities (e.g., scheduling, transportation) may be the most predictive of brain health and functional decline. Future research is needed to investigate rehabilitation assessment and early intervention strategies to mitigate loss of independence in older adults at risk for dementia.

This study has many strengths, but limitations must be considered. We are unable to infer causation due to the cross-sectional design of this study. This study provides a foundation for larger and longitudinal investigations by identifying a shared neural basis of gait and executive function in brain regions that are vulnerable to age and neurodegenerative changes. Additional neuroimaging modalities will be beneficial for future studies to understand mechanisms underlying gait and executive function.

CONCLUSIONS

Compared with older adults with intact cognition, older adults with aMCI demonstrated reduced gait speed and stride length during fast-paced walking and lower performance on a test of executive function. Shared limbic system correlates of gait pace (gait speed and stride length) and executive function were identified in older adults with aMCI and NC. These findings suggest a neural basis for the relationship between declining gait pace and executive function in older adults without dementia. The findings of this study improve our understanding of potential mechanisms associated with gait changes in older adults. Taken together, identifying a neural basis for declining gait speed and executive function has implications for rehabilitation professionals in efforts to provide targeted, effective, and timely strategies to mitigate loss of mobility due to age-related and neurodegenerative changes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors thank Katie Askren, PhD, for MRI data processing, Rebecca Archer, BS, for quantitative gait data processing, and June van Leynseele, MA, for study coordination.

The study was supported by National Institute of Aging at the NIH (2R01 AG14777-06A2, PI: LT), Biobehavioral Nursing Research Training Program, University of Washington (T32 NR007106), Integrated Brain Imaging Center, University of Washington (1RCA NS073008 01, PI: TJG), and Alzheimer's Association International New Investigators Award (PI: ELM).

Previous presentations of this research (some results presented): APTA IV STEP Conference Presentation July 2016, Columbus Ohio Science in Medicine Lecture, October 2016, University of Washington.

REFERENCES

1. Albers MW, Gilmore GC, Kaye J, et al.: At the interface of sensory and motor dysfunctions and Alzheimer's disease. *Alzheimers Dement* 2015;11:70–98 [PubMed: 25022540]
2. Brookmeyer R, Johnson E, Ziegler-Graham K, et al.: Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement* 2007;3:186–91 [PubMed: 19595937]
3. Smith AD, Yaffe K: Dementia (including Alzheimer's disease) can be prevented: statement supported by international experts. *J Alzheimers Dis* 2014;38:699–703 [PubMed: 24326609]
4. Makizako H, Shimada H, Doi T, et al.: The association between decline in physical functioning and atrophy of medial temporal areas in community-dwelling older adults with amnesic and nonamnesic mild cognitive impairment. *Arch Phys Med Rehabil A* 2011;92:1992–9
5. Holtzer R, Epstein N, Mahoney JR, et al.: Neuroimaging of mobility in aging: a targeted review. *J Gerontol A Biol Sci Med Sci* 2014;69:1375–88 [PubMed: 24739495]
6. Aggarwal NT, Wilson RS, Beck TL, et al.: Motor dysfunction in mild cognitive impairment and the risk of incident Alzheimer disease. *Arch Neurol* 2006;63:1763–9 [PubMed: 17172617]
7. Mielke MM, Roberts RO, Savica R, et al.: Assessing the temporal relationship between cognition and gait: slow gait predicts cognitive decline in the Mayo Clinic Study of Aging. *J Gerontol A Biol Sci Med Sci* 2013;68:929–37 [PubMed: 23250002]
8. Verghese J, Robbins M, Holtzer R, et al.: Gait dysfunction in mild cognitive impairment syndromes. *J Am Geriatr Soc* 2008;56:1244–51 [PubMed: 18482293]
9. Fritz NE, Kegelmeyer DA, Kloos AD, et al.: Motor performance differentiates individuals with Lewy body dementia, Parkinson's and Alzheimer's disease. *Gait Posture* 2016;50:1–7 [PubMed: 27544062]
10. Buchman AS, Bennett DA: Loss of motor function in preclinical Alzheimer's disease. *Expert Rev Neurother* 2011;11:665–76 [PubMed: 21539487]
11. Bird CM, Burgess N: The hippocampus and memory: insights from spatial processing. *Nat Rev Neurosci* 2008;9:182–94 [PubMed: 18270514]
12. Jack CR, Jr, Vemuri P, Wiste HJ, et al.: Evidence for ordering of Alzheimer disease biomarkers. *Arch Neurol* 2011;68:1526–35 [PubMed: 21825215]
13. Takakusaki K: Neurophysiology of gait: from the spinal cord to the frontal lobe. *Mov Disord* 2013;28:1483–91 [PubMed: 24132836]
14. Verghese J, Wang C, Lipton RB, et al.: Motoric cognitive risk syndrome and the risk of dementia. *J Gerontol A Biol Sci Med Sci* 2013;68:412–8 [PubMed: 22987797]
15. Hughes CP, Berg L, Danziger WL, et al.: A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;140:566–72 [PubMed: 7104545]
16. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98 [PubMed: 1202204]
17. Petersen RC, Smith GE, Waring SC, et al.: Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8 [PubMed: 10190820]
18. Rosen WG, Mohs RC, Davis KL: A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984;141:1356–64 [PubMed: 6496779]
19. Weschler D: *Weschler Memory Scale*, 3rd ed. San Antonio, Corporation TP, 1997

20. Steinberg BA, Bieliauskas LA, Smith GE, et al.: Mayo's Older Americans Normative Studies: Age- and IQ-Adjusted Norms for the Wechsler Memory Scale-Revised. *Clin Neuropsychol* 2005;19:378–463 [PubMed: 16120536]
21. Yesavage JA, Brink TL, Rose TL, et al.: Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982;17:37–49 [PubMed: 7183759]
22. Smieja M, Hunt DL, Edelman D, et al.: Clinical examination for the detection of protective sensation in the feet of diabetic patients. International Cooperative Group for Clinical Examination Research. *J Gen Intern Med* 1999;14:418–24 [PubMed: 10417599]
23. Fischl B, Liu A, Dale AM: Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans Med Imaging* 2001;20:70–80 [PubMed: 11293693]
24. Desikan RS, Segonne F, Fischl B, et al.: An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 2006;31:968–80 [PubMed: 16530430]
25. Westman E, Aguilar C, Muehlboeck JS, et al.: Regional magnetic resonance imaging measures for multivariate analysis in Alzheimer's disease and mild cognitive impairment. *Brain Topogr* 2013;26:9–23 [PubMed: 22890700]
26. Steffen TM, Hacker TA, Mollinger L: Age- and gender-related test performance in community-dwelling elderly people: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. *Phys Ther* 2002;82:128–37 [PubMed: 11856064]
27. Greenlief CL, Margolis RB, Erker GJ: Application of the Trail Making Test in differentiating neuropsychological impairment of elderly persons. *Percept Mot Skills* 1985;61:1283–9 [PubMed: 4094872]
28. Cohen J: *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed. Hillsdale, NJ, Lawrence Erlbaum, 1988
29. Holtzer R, Verghese J, Xue X, et al.: Cognitive processes related to gait velocity: results from the Einstein Aging Study. *Neuropsychology* 2006;20:215–23 [PubMed: 16594782]
30. Zimmerman ME, Lipton RB, Pan JW, et al.: MRI- and MRS- derived hippocampal correlates of quantitative locomotor function in older adults. *Brain Res* 2009;1291:73–81 [PubMed: 19631621]
31. Buckner RL: Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron* 2004;44:195–208 [PubMed: 15450170]
32. Bozzali M, Giulietti G, Basile B, et al.: Damage to the cingulum contributes to Alzheimer's disease pathophysiology by deafferentation mechanism. *Hum Brain Mapp* 2012;33:1295–308 [PubMed: 21520352]
33. Bush G, Luu P, Posner MI: Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 2000;4:215–22 [PubMed: 10827444]
34. Middleton A, Fulk GD, Herter TM, et al.: Self-selected and maximal walking speeds provide greater insight into fall status than walking speed reserve among community-dwelling older adults. *Am J Phys Med Rehabil* 2016;95:475–82 [PubMed: 27003205]
35. Callisaya ML, Launay CP, Srikanth VK, et al.: Cognitive status, fast walking speed and walking speed reserve-the Gait and Alzheimer Interactions Tracking (GAIT) study. *Geroscience* 2017;39:231–9 [PubMed: 28374167]
36. MacAulay RK, Wagner MT, Szeles D, et al.: Improving sensitivity to detect mild cognitive impairment: cognitive load dual-task gait speed assessment. *J Int Neuropsychol Soc* 2017;23:493–1 [PubMed: 28413999]
37. Tolea MI, Morris JC, Galvin JE: Trajectory of mobility decline by type of dementia. *Alzheimer Dis Assoc Disord* 2016;30:60–6 [PubMed: 25886717]
38. Suzuki T, Shimada H, Makizako H, et al.: A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. *PLoS One* 2013;8:e61483 [PubMed: 23585901]
39. Liu-Ambrose T, Nagamatsu LS, Voss MW, et al.: Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. *Neurobiol Aging* 2012;33:1690–8 [PubMed: 21741129]

TABLE 1.

Descriptive characteristics of participants

Characteristics	All Participants (N = 46)	NC (n = 23)	aMCI (n = 23)	P
Age, mean (SD)	83.7 (4.9)	82.5 (4.4)	85.0 (4.8)	0.07
Sex, female, n (%)	34 (73.9)	18 (78.3)	16 (69.6)	0.78
Education, n (%)				0.87
High school degree	20 (43.5)	11 (47.8)	9 (39.1)	—
College graduate	15 (32.6)	7 (30.4)	8 (34.8)	—
Graduate degree	11 (23.9)	5 (21.7)	6 (26.1)	—
Geriatric Depression Scale (0–15)	2.02 (1.94)	1.52 (1.65)	2.52 (2.11)	0.08
Health conditions, n (%)				
Heart disease	20 (43.5)	10 (43.5)	10 (43.5)	1.0
Hypertension	27 (58.7)	15 (65.2)	12 (52.2)	0.55
Diabetes	5 (10.9)	4 (17.4)	1 (4.3)	0.35
Osteoarthritis	8 (17.4)	5 (21.7)	3 (13)	0.70
Rheumatoid arthritis	3 (6.5)	2 (8.7)	1 (4.3)	0.60
Cognitive function, mean (SD)				
MMSE (0–30)	27.9 (2.3)	29.2 (1.0)	26.5 (2.7)	<0.001
ADAS-Cog	15.3 (7.1)	14.1 (6.6)	16.5 (7.5)	0.25
Logical Memory I (0–50)	24.0 (8.2)	29.1 (5.1)	18.8 (7.5)	0.001
Logical Memory II (0–50)	19.0 (9.3)	24.6 (7.3)	13.5 (7.7)	0.001
TMT-A, sec	48.2 (18.4)	41.4 (14.6)	55.0 (19.5)	0.01
TMT-B, sec	117.0 (51.1)	100.8 (35.9)	133.3 (59.1)	0.03

ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive.

TABLE 2.

Gait performance: Spatiotemporal gait parameters

Spatiotemporal Gait Parameters		All Participants (N = 46), Mean (SD)	NC (n = 23), Mean (SD)	aMCI (n = 23), Mean (SD)	P
Usual-paced walking					
Pace	Gait speed, m/sec	1.03 (0.27)	1.09 (0.24)	0.99 (0.18)	0.14
Rhythm	Stride length, m	1.11 (0.20)	1.17 (0.18)	1.08 (0.17)	0.09
	Cadence, steps/min	110.4 (10.4)	112.8 (12.3)	110.0 (9.6)	0.48
	Single-limb support, %	63.7 (4.9)	67.15 (4.9)	66.8 (4.6)	0.78
Fast-paced walking					
Pace	Gait speed, m/sec	1.34 (0.30)	1.47 (0.28)	1.24 (0.22)	0.004
Rhythm	Stride length, m	1.25 (0.23)	1.34 (0.19)	1.20 (0.19)	0.01
	Cadence, steps/min	127.6 (13.8)	130.9 (14.1)	124.1 (13.2)	0.10
	Single-limb support, %	66.7 (4.9)	72.7 (4.2)	70.1 (5.0)	0.11

TABLE 3.

Neural correlates of gait and executive function ($N = 46$)

	Limbic volume/ICV ^a	Hippocampus	Amygdala	Thalamus	Anterior cingulate	Posterior cingulate
Stride length (m)/height (m)		$r = 0.33$ $P = 0.02$	$r = 0.30$ $P = 0.50$	$r = 0.17$ $P = 0.28$	$r = 0.43$ $P = 0.003$	$r = 0.23$ $P = 0.12$
TMT-B – TMT-A		$r = -0.37$ $P = 0.01$	$r = -0.27$ $P = 0.07$	$r = -0.25$ $P = 0.10$	$r = -0.32$ $P = 0.003$	$r = -0.38$ $P = 0.01$
Basal ganglia volume/ICV ^a		Caudate	Putamen	Globus pallidus	Nucleus accumbens	—
Stride length (m)/height (m)		$r = 0.18$ $P = 0.24$	$r = 0.29$ $P = 0.05$	$r = 0.07$ $P = 0.64$	$r = 0.36$ $P = 0.01$	—
TMT-B – TMT-A		$r = -0.01$ $P = 0.93$	$r = -0.23$ $P = 0.13$	$r = -0.15$ $P = 0.31$	$r = -0.26$ $P = 0.08$	—

^aCombined right- and left-side brain volumes, adjusted for ICV.

Partial correlations adjusted for age.