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The Motor Signature of Mild Cognitive Impairment: Results From the Gait and Brain Study

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Background. Early motor changes associated with aging predict cognitive decline, which suggests that a "motor signature" can be detected in predementia states. In line with previous research, we aim to demonstrate that individuals with mild cognitive impairment (MCI) have a distinct motor signature, and specifically, that dual-task gait can be a tool to distinguish amnestic (a-MCI) from nonamnestic MCI.

Methods. Older adults with MCI and controls from the "Gait and Brain Study" were assessed with neurocognitive tests to assess cognitive performance and with an electronic gait mat to record temporal and spatial gait parameters. Mean gait velocity and stride time variability were evaluated under simple and three separate dual-task conditions. The relationship between cognitive groups (a-MCI vs nonamnestic MCI) and gait parameters was evaluated with linear regression models and adjusted for confounders.

Results. Ninety-nine older participants, 64 MCI (mean age 76.3±7.1 years; 50% female), and 35 controls (mean age 70.4±3.9 years; 82.9% female) were included. Forty-two participants were a-MCI and 22 were nonamnestic MCI. Multivariable linear regression (adjusted for age, sex, physical activity level, comorbidities, and executive function) showed that a-MCI was significantly associated with slower gait and higher dual-task cost under dual-task conditions.

Conclusion. Participants with a-MCI, specifically with episodic memory impairment, had poor gait performance, particularly under dual tasking. Our findings suggest that dual-task assessment can help to differentiate MCI subtyping, revealing a motor signature in MCI.

Key Words: Gait speed—Dual-task—Mild cognitive impairment—Gait variability—Cognition-motor decline.

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MILD cognitive impairment (MCI) is considered a predementia state. Although older adults with MCI are at a higher risk of conversion to dementia, almost one third of individuals with MCI will remain clinically stable or even revert to normal. This fact highlights the potential hazard of treating MCI patients as a homogeneous group. This heterogeneity is a challenge for clinicians; as it is difficult to accurately predict conversion to dementia, particularly Alzheimer's disease, once MCI is identified. To overcome this challenge, the search for useful biomarkers in MCI, including motor markers, is an emerging area of research (1–5).

Although the main clinical hallmark of MCI is memory impairment (6), motor dysfunction has been previously described, including gait disorders (6–8). Over the past decade, large cohort studies have shown that impairments of brain control of gait are not only evident early in Alzheimer and non-Alzheimer dementias but also predicts conversion to dementia in general populations (8–10). However, only few studies have focused on MCI populations, and it has been suggested that gait analysis, particularly while dual tasking, may be a new window for the evaluation of brain function in MCI (11,12). Dual-task gait helps to isolate the cognitive control component of locomotion and provides insights into the mechanisms of motor control (13). It is a motor-divided attention task that requires individuals to walk while doing a cognitively demanding task (reciting words or calculations) and unmasks latent gait disturbances only evident under cognitive stress. It can be expressed as a dual-task cost that adjusts for baseline gait characteristics of the individual (13). In line with previous work, we aimed to examine whether individuals with MCI had a different

"motor signature," with the main goal of assessing the ability of dual-task gait to distinguish between amnestic MCI (a-MCI) and non-amnestic MCI (na-MCI) subtypes. To date, the role of dual-task gait to reveal distinct motor signatures by MCI subtype has not been described.

Methods

Study Participants

We included MCI participants and controls recruited from the "Gait and Brain Study," which is an ongoing longitudinal prospective cohort study designed to determine whether early gait disorders can predict cognitive and mobility decline, progression to dementia, and frailty status among older adults (14). General inclusion criteria were 65 years and older and the ability to walk independently without a gait aid (eg, cane or walker). Exclusion criteria included lack of English proficiency, Parkinsonism, or any neurologic disorder with residual motor deficits (eg, stroke), musculoskeletal disorders (eg, severe osteoarthritis of lower limbs) or history of knee/hip replacement affecting gait performance at clinical examination, use of psychotropics (eg, neuroleptics or benzodiazepines), and major depression. The University of Western Ontario's Research Ethics Board approved this project, and signed informed consent was obtained.

Medical and Cognitive Assessments

Participants were interviewed on relevant sociodemographic and clinical variables (Table 1). Basic and instrumental activities of daily living were evaluated using the Lawton–Brody scale (15). Global cognition was assessed using the Montreal Cognitive Assessment and the Mini-Mental State Examination. Controls were selected based on scores of at least 28 out of 30 on the Montreal Cognitive Assessment and

Table 1. Demographics and Clinical Characteristics According to Cognitive Status

	Study Groups			*p* Value*		
Characteristic	Controls (*n* = 35)	na-MCI (*n* = 22)	a-MCI (*n* = 42)	na-MCI/a-MCI	na-MCI/ Controls	a-MCI/ Controls
Age, mean (±*SD*)	70.37 (±3.93)	74.18 (±6.54)	77.33 (±7.26)	.03	.26	<.01
Females, *n* (%)	29 (82.86%)	14 (63.64%)	18 (42.86%)	.11	.10	<.01
No. of medications, mean(±*SD*)	4.46 (±2.84)	8.09 (±3.79)	9.24 (±3.89)	.56	<.01	<.01
No. of comorbidities, mean (±*SD*)	3.49 (±2)	6.89 (±3)	6.86 (±3)	.74	<.01	<.01
HTN, *n* (%)	14 (40.00%)	13 (59.09%)	28 (66.67%)	.55	.16	.02
DBT, *n* (%)	3 (8.57%)	4 (18.18%)	9 (21.43%)	.76	.28	.12
OA, *n* (%)	10 (28.57%)	8 (36.36%)	11 (26.19%)	.40	.54	.82
CA, *n* (%)	9 (25.71%)	9 (40.91%)	18 (42.86%)	.88	.23	.12
MI, *n* (%)	0 (0%)	1 (4.55%)	8 (19.05%)	.15	.39	.01
STK, *n* (%)	0 (0%)	0 (0%)	0 (0%)	—	—	—
Previous fall (y/n) *n*, (%)	11 (24%)	10 (42%)	13 (30%)	.34	.04	.19
Fear of falling (y/n) *n*, (%)	2 (5.71%)	3 (13.64%)	5 (11.90%)	.84	.30	.35
Physical activity, *n* (%)	26 (74.29%)	15 (68.18%)	22 (52.38%)	.31	.31	.12
Vigorous	7 (20.00%)	3 (13.64%)	13 (30.95%)	.22	.62	.05
Moderate	2 (5.71%)	4 (18.18%)	7 (16.67%)	.13	.54	.28
Sedentary				.88	.14	.14
Simple-gait velocity (cm/s), mean (±*SD*)	123.72 (±20.59)	108.90 (±19.17)	99.52 (±21.45)	.20	.03	<.01
MMSE, mean (±*SD*)†	29.31 (±1.02)	29.14 (±0.83)	27.24 (±2.07)	<.01	.91	<.01
MoCA, mean (±*SD*)†	28.06 (±1.78)	25.67 (±2.03)	22.76 (±2.88)	<.01	<.01	<.01
Trail making A, mean (±*SD*)‡	—	43.31 (±14.97)	51.03 (±15.28)	.06	—	—
Trail making B, mean (±*SD*)‡	—	107.70 (±39.72)	141.91(±67.81)	.03	—	—
Digit Span–forward, mean (±*SD*)§	—	11.41 (±2.04)	10.81 (±1.82)	.24	—	—
Digit Span–backward, mean (±*SD*)§	—	7.95 (±2.10)	6.36 (±2.13)	.01	—	—
Letter number sequence, mean (±*SD*)‖	—	8.55 (±2.32)	7.24 (±2.85)	.07	—	—
Rey auditory verbal learning (/15), mean (±*SD*)¶	—	7.95 (±2.17)	2.93 (±1.83)	<.01	—	—
Rey auditory verbal learning (/45), mean (±*SD*)#	—	18.95 (±4.18)	14.05 (±4.06)	<.01	—	—
Boston naming, mean (±*SD*)**	—	13.89 (±1.10)	13.20 (±1.57)	.09	—	—

Notes: **p* value obtained by analysis of variance among na-MCI, a-MCI, and control groups; aMCI = amnestic MCI; CA = cancer; DBT = diabetes mellitus; HTN = hypertension; MCI = mild cognitive impairment; MI = myocardial infarct; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; na-MCI, nonamnestic MCI; OA = osteoarthritis; *SD* = standard deviation; STK = stroke.

†Scores range from 0 to 30, higher scores representing better function.

‡Final score is total time in seconds to complete task.

§Final score is the sum of points from each correct trial. Maximum score is 16.

‖Final score is the sum of points from each correct trial. Maximum score is 21.

¶Final score is the number of words remembered out of a list of 15 in trial 6 (delayed recall).

#Final score is the total number of words remembered for trials 1–3.

**Final score is the number of pictures correctly identified out of 15.

the Mini-Mental State Examination. MCI participants scored .5 on the global rating of Clinical Dementia Rating scale and fulfilled the following four criteria (16,17):

1. Presence of spontaneous cognitive complaints.
2. Objective cognitive impairment in the following four cognitive domains: memory, executive function, attention, and language.
3. Preserved activities of daily living on the disability scale (15) confirmed by clinician's interviews.
4. Absence of dementia using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

An extensive neuropsychologic test battery was administered to the MCI group evaluating the following cognitive domains: executive function—Trail Making Tests A and B (18); verbal episodic memory—Rey Auditory Verbal Learning Test (RAVLT) (19); naming—Boston Naming Test (20); pure attention—Digit Span Test (forward and backward), and attention/working memory—Letter–Number Sequencing tests (21). Consistent with current procedures and previous studies, we used a cutoff of 1.5 *SD* below the age-adjusted means to identify impaired cognitive domains (12,22,23). Participants were classified as a-MCI if they had impairment in verbal episodic memory (recall trials 1–3 and delayed recall-trial 6 of RAVLT), while participants subtyped as na-MCI had impairment in one or more nonmemory tests of the neuropsychologic battery but not in verbal episodic memory (12,22,23).

Quantitative Gait Assessment

Gait performance under simple and dual tasks was assessed using an electronic walkway (GAITRite System, 600 cm long), which provides data for both spatial and temporal gait parameters. Start and end points were marked on the floor 1 m from either mat end to avoid recording acceleration/deceleration phases. Each participant performed one practice trial walking on the mat. Gait variability under each testing condition was calculated as the coefficient of variation for stride time: CV = (standard deviation of stride time/mean stride time) × 100.

$$\mathrm{CV}_{st} = \left(\sqrt{\frac{SD_{st}}{\mathrm{mean}_{st}}} \right) \times 100,$$

where SD_{st} is the standard deviation of stride time; and mean_{st} is the mean stride time. Gait velocity (cm/s) and stride time variability (CV_{st}, %) were measured during the simple and dual-task trials. The simple-task trial consisted of walking the length of the mat at participant's usual pace. For the dual-task trials, participants walked at their usual pace with no instruction to prioritize the gait or cognitive task; while doing the following cognitive tasks aloud, (i) counting backwards from one hundred by ones (ii) subtracting serial sevens from one hundred, and (iii) naming animals; rationale for dual-task condition selection has been described elsewhere (14). Allowing both gait and cognitive tasks to vary provides a better representation of daily living activities. To balance and minimize the effects of learning and fatigue, the order of the simple and dual tasks was randomized. Reliability has been previously established for this protocol in people with MCI (14).

Dual-task gait cost (%) was calculated as ([simple-task gait value − dual-task gait value]/simple-task gait value) × 100 (22).

Data Analysis

Demographics and clinical characteristics were summarized using either means and standard deviations, or frequencies and percentages, as appropriate. Comparisons between groups were made on both raw scores (simple and dual-task gait) and dual-task cost scores with ANOVA or Student's *t* tests, and multiple comparisons were accounted for with Tukey–Kramer adjustments. Chi-square tests were used for categorical measures and, where expected cell sizes were less than 5, Fisher's Exact test. Stride time data was transformed with log 10 to improve equality of variances. Multivariate linear regression modeling was used to evaluate the association between group status (a-MCI vs na-MCI) and the outcomes of gait velocity and stride time variability under each of the four walking conditions, for a total of eight regression models adjusting for age, sex, physical activity level, comorbidities, and executive function. These five potential confounding variables were selected based on clinical significance and the literature, as potential factors affecting the relationship between gait and cognition. Specifically, adjustments for executive function were made to explore gait responses in dual-tasking driven by episodic memory deficits, which is the hallmark of a-MCI, and not by executive dysfunction. A similar linear regression test was done to evaluate the association between dual-task cost in the MCI population and performance in episodic memory assessed by delayed recall in the RAVLT. Statistical significance was set at $p < .05$ (two-sided). Statistical analyses were conducted using SPPS (v21.0, IBM Corporation, Chicago, IL).

Results

Ninety-nine participants, 64 with MCI (mean age 76.3 ± 7.1 years; 50% female) and 35 controls (mean age 70.4 ± 3.9 years; 82.9% female) were included in the analysis. In the MCI group, 42 were a-MCI and 22 were na-MCI.

Demographic and clinical characteristics are presented in Table 1. Participants with MCI were older than controls; and there was a statistical difference in age between MCI subtypes ($p = .03$). Comorbidities that may affect the relationship between gait and cognition (ie, hypertension, diabetes mellitus, osteoarthritis, cancer, myocardial infarction, and stroke) did not differ between MCI groups, nor the number of medications, physical activity, fear of falling, and history of falls. Global cognition (Montreal Cognitive Assessment and Mini-Mental State Examination) differed

between controls and MCI groups, as expected. For specific cognitive domains, we found statistical significant differences between the MCI groups. In brief, na-MCI group showed normal episodic memory performance and low; but not severely, executive function and attention. The a-MCI showed lower episodic memory performance (RAVLT, $p < .01$) as expected, and lower executive function (Trail Making Test B, $p = .03$) revealing the multidomain characteristic of our a-MCI group. Amnestic MCI participants walked slower than na-MCI. After adjusting for potential confounders, multivariable linear regression showed that the gait velocities were statistically different only under dual-task walking ($p < .05$, Table 2). Similarly, a-MCI participants showed higher stride time variability than na-MCI in all walking test conditions with a statistically significant difference for simple and dual-task counting gait ($p < .05$, Table 2). Amnestic MCI, suffered the highest dual-task cost, with significant differences in all three velocity dual task conditions ($p < .05$, Table 3). Table 4 shows that dual-task gait cost predicts performance in delayed recall, a measure of episodic memory, in MCI participants. Differences in dual-task gait cost velocity between controls and MCI subtypes are shown in Figure 1.

Discussion

This study demonstrated that a-MCI participants have greater deficits in gait velocity and stride time variability than na-MCI individuals and, specifically, that dual-task walking conditions can differentiate these cognitive subtypes. In line with previous gait research, our findings suggest that both a-MCI and na-MCI demonstrate a motor signature during dual-task gait that differs from controls.

It has been shown that there is a transition period whereby gait slowing occurs concurrently or predicts cognitive loss and progression to MCI (8,23–25). Previous studies have confirmed gait and cognitive associations in MCI; however, the effect of dual-task gait on cognitive subtyping has not been explored (1,2,12,14,22,26–29). We argued that the cognitive stress applied while dual-tasking unmasks motor characteristics related to specific cognitive deficits and may help cognitive subtype differentiation (11). In line with our hypothesis, dual-task gait differed by MCI subtyping in this study. With a complex dual task such as serial sevens gait, a-MCI participants showed a 23% gait velocity reduction versus 14% for na-MCI. This higher cost was also seen for gait variability, although it lacked statistical significance, likely due to the large standard deviations of our sample (Table 3).

The inverse association between dual-task cost and episodic memory performance (Table 4) confirms that other cognitive domains beyond executive function are involved in controlling and maintaining a safe gait in MCI, an association that remained significant even after adjusting for the executive dysfunction present in the a-MCI group. This result agrees with two recent cohort studies which showed that slow gait predicted decline in episodic memory (30) and that good performance in both executive function and episodic memory were protective against further gait decline (31).

Simple gait velocity testing is easy to perform and provides an excellent general measure of overall function (32–35); however, dual-task gait can provide additional valuable clinical information, particularly in the absence of impaired physical function, about the role of cognitive reserve on gait (13). Dual-task costs were higher in a-MCI, particularly with complex cognitive task and were also associated with lower episodic memory. Thus, dual-task gait has the potential to enhance diagnostic capabilities in MCI differentiating cognitive subtypes.

Mechanistically, our results may raise the possibility of a shared pathogenesis in memory and gait decline. Episodic memory relies on brain networks including the hippocampus and frontal–hippocampal circuits that are important in spatial orientation and navigation. They are central for gait control in addition to prefrontal cortex and striatal networks

Table 2. Association Between Cognitive Status as a Predictor Variable and Gait Performance as an Outcome Variable in the MCI Groups

		Sample Stratified by Amnestic and Nonamnestic Status		*p* Value*	
Walking Test Condition [Mean (±*SD*)]	Full MCI Sample (*n* = 64)	na-MCI (*n* = 22)	a-MCI (*n* = 42)	Unadjusted	Adjusted
Velocity (cm/s)					
Simple gait	102.74 (±21.03)	108.90 (±19.17)	99.52 (±21.45)	.09	.10
Counting gait	95.42 (±25.21)	105.16 (±21.75)	90.32 (±25.63)	.02	**.03**
Naming animals gait	85.00 (±27.72)	95.93 (±25.63)	79.27 (±27.32)	.02	**.03**
Serial sevens gait	83.32 (±28.92)	93.69 (±26.32)	77.90 (±29.03)	.04	.05
Stride time variability (CV, %)					
Simple gait	3.01 (±2.29)	2.40 (±1.38)	3.33 (±2.60)	.05	.04
Counting gait	4.15 (±3.20)	2.90 (±0.98)	4.81 (±3.73)	.01	**.01**
Naming animals gait	5.00 (±4.31)	3.82 (±2.10)	5.63 (±5.00)	.27	.08
Serial sevens gait	5.90 (±5.10)	4.83 (±3.53)	6.47 (±5.71)	.15	.27

Notes: a-MCI = amnestic MCI; CV = coefficient of variation; MCI = mild cognitive impairment; na-MCI = nonamnestic MCI; *SD* = standard deviation.
*Linear regression modeling adjusted for age, sex, Trail Making Test B, physical activity, and comorbidities between MCI subtypes; significant values after adjusting are in bold.

Table 3. Dual-Task Gait Cost (%) Differences in a-MCI and na-MCI

Walking Test Condition [Mean (±*SD*)]	Full MCI Sample (*n* = 64)	na-MCI (*n* = 22)	a-MCI (*n* = 42)	*p* Value*
Velocity dual-task cost (%)				
Counting gait	7.60 (±11.63)	3.44 (±9.28)	9.79 (±12.24)	**.04**
Naming animals gait	18.34 (15.43)	12.32 (±13.39)	21.50 (±15.63)	**.03**
Serial sevens gait	20.10 (±16.52)	14.15 (±15.59)	23.21 (±16.31)	**.03**
Stride time variability dual-task cost (%)				
Counting gait	59.91 (±92.03)	47.36 (±77.98)	66.49 (±98.84)	.43
Naming animals gait	61.09 (±82.60)	72.11 (±74.89)	54.88 (±86.98)	.63
Serial sevens gait	63.46 (±88.08)	59.03 (±73.22)	65.74 (±95.68)	.89

Notes: CI = confidence intervals; MCI = mild cognitive impairment; *SD* = standard deviation.
*Linear regression modeling adjusted for age, sex, Trail Making Test B, physical activity level, and comorbidities; significant values are in bold.

Table 4. Association Between Dual-Task Gait Cost (%) and Episodic Memory and Learning Performance (RAVLT) in the MCI Group

Dual-Task Cost (%) (Predictor)	Change in RAVLT (Unadjusted β Coefficient)	*t* Statistic	*p* Value*	95% Confidence Interval	
Velocity					
Counting gait	.079	2.556	**.013**	.017	.140
Naming animals gait	.058	2.437	**.018**	.010	.105
Serial sevens gait	.053	2.422	**.019**	.009	.096
Stride time variability					
Counting gait	.003	.779	.439	−.005	.012
Naming animals gait	.001	.795	.430	−.002	.005
Serial sevens gait	−.005	−1.014	.316	−.015	.005

Notes: MCI = mild cognitive impairment; RAVLT = Rey Auditory Verbal Learning Test; changes shown above represent 1% increase in dual-task cost.
*Linear regression adjusted for age, sex, Trail Making Test B, physical activity level, and comorbidities; significant values are in bold.

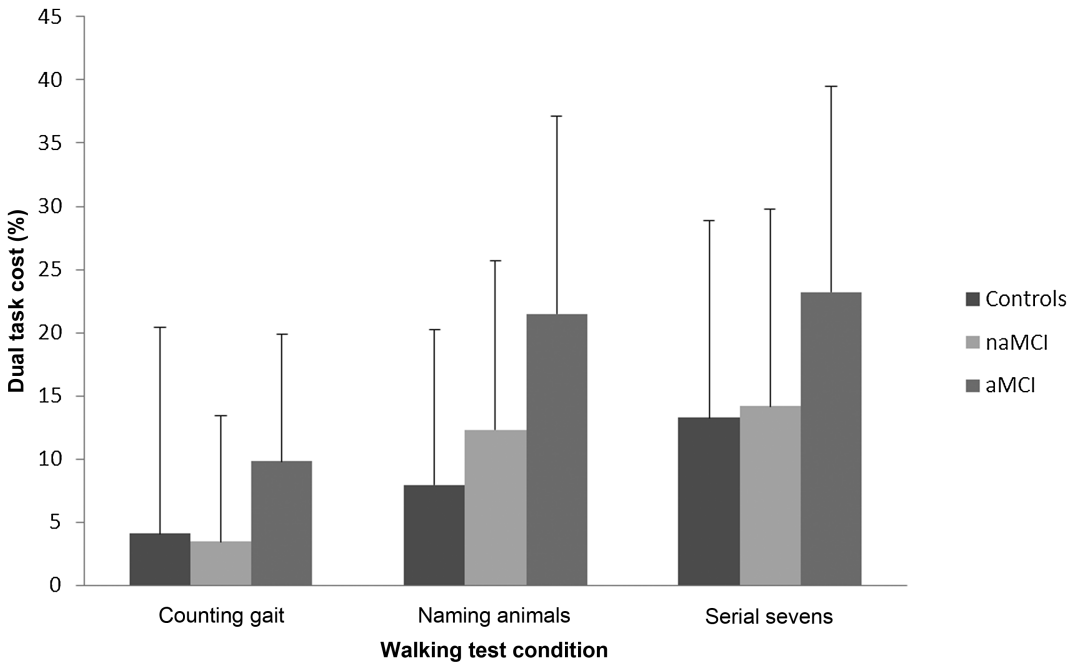

Figure 1. Dual-task cost for gait velocity during three dual-task conditions in controls and mild cognitive impairment subtypes.

involved in executive function and attention (24). Recent imaging studies using magnetic resonance spectroscopy in MCI revealed that higher dual-task gait cost is associated with altered neurochemistry and lower volume of the primary motor cortex, which is part of the executive network circuit of normal locomotion (36).

Similarly, stride variability correlated negatively with hippocampal neurochemistry in MCI (37), which could reflect the role of the hippocampus in the retrieval of complex foot movement sequences necessary for regular gait patterns (38). These shared circuits can be affected by both neurodegenerative and microvascular pathomechanims and may explain why dual-task gait unmasks latent mobility abnormalities in a-MCI and na-MCI (39). Following this line of reasoning, dual-task costs can reveal early changes in brain reserves when circuits involved in gait control and memory retrieval are needed to maintain a safe gait. Therefore, dual-task gait disturbances are a motor signature of MCI and could potentially be used as a biomarker of further cognitive decline. A recent prospective study with 3 years of follow-up found that older participants with objective cognitive complaints and slower gait, described as motoric cognitive risk syndrome, had a higher risk of developing dementia and vascular dementia with an adjusted hazard ratio of 3.27 and 12.81, respectively (5). Information on dual-task gait was not collected, so it is unknown if dual-task gait adds useful information to simple gait as a predictor of dementia in motoric cognitive risk syndrome. Interestingly, motoric cognitive risk syndrome participants were more likely to convert to vascular dementia. This may seem contradictory to our finding, of more gait disturbances in the a-MCI group that is expected to evolve toward Alzheimer's disease. However, motoric cognitive risk syndrome participants appeared to be actually frailer than our studied sample, with a slower mean gait velocity of 68 cm/s and more executive dysfunction, which may explain the higher risk to convert to vascular dementia.

Some limitations of this study need to be outlined. The cross-sectional design precludes a causal interpretation of the associations between changes in gait and cognitive subtyping. Variables likely to modify the association between gait and cognitive performance were controlled for; however, there is possibility of additional potential confounders. Cognitive performance during simple tasking (sitting) was not available in our participants, and therefore, the complementary role of the cost of dual-tasking on cognition was not assessed, which may further support our findings. Strengths include the comprehensive assessment of a highly functional MCI population with validated dual-task protocols on quantitative gait analysis designed to assess the role of cognition on gait.

Conclusion

Gait characteristics differ by MCI subtyping and higher dual-task gait cost was associated with a-MCI, revealing a distinct motor signature. Cognitive and motor dysfunctions in MCI are not causally interrelated and may instead reflect a burden in the brain networks shared by cognitive and motor control circuits (40,41). Adding markers of motor function, like dual-task gait, to the established biomarkers of cognitive decline in MCI may help to better identify cognitive subtyping and to predict conversion to Alzheimer's disease and other dementias in MCI. Prospective studies in MCI populations are needed to further confirm this hypothesis.

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