Mediating Role of Cerebellar Subregion Volume in the Relationship Between Gait Speed and Working Memory

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Abstract

Introduction: The relationship between gait speed and working memory is well-understood in older adults. However, it remains to be determined whether this relationship also exists in younger adults; and there is little known regarding the possible neural mechanism underlying the association between gait speed and working memory. The aims of this study are to determine if there is: 1) an association between gait speed and working memory performance; and 2) a mediating role of cerebellar subregion volume in the correlation between gait speed and working memory in healthy younger adults.

Methods: 1054 younger adults (28.7 ± 3.6 years) from the Human Connectome Project were included in the analyses. A four-meter gait test was used to assess gait speed. The N-back task was conducted to measure working memory performance [accuracy and response time(RT)]. T1-weighted structural MRI data (obtained using Siemens 3T MRI scanner) was used to assess cerebellar subregion volumes. Linear regression and mediation analysis were used to examine the relationships between the variables after controlling for age, sex, and education.

Results: Faster gait speed was associated with faster working memory RT in younger adults. Greater cerebellar subregion volumes were associated with faster gait speed and better working memory performance. Faster gait speed was correlated with faster working memory RT through greater volume of cerebellar region VIIIa.

Conclusions: The present study suggests faster gait speed is associated with faster RT during working memory tasks in younger individuals. The specific subregion of the cerebellum (VIIIa) may serve as an important neural basis linking gait speed and working memory.

Introduction

Gait refers to the cyclic nature of an individual's walking behavior and their unique movement pattern, and gait speed reflects an integration of the musculoskeletal, visual, and peripheral nervous systems¹. Because gait is a higher-order locomotor capacity, assessing gait speed is a simple and reliable way of estimating functional capacity and motor function². Beyond musculoskeletal mechanisms, gait control involves complex brain processes such as the integration of motor, perceptual, and cognitive functions (e.g., memory, attention, and executive function)^{3,4}. Thus, it has been postulated that slowing gait may be a predictor for cognitive decline. Indeed, a body of longitudinal and cross-sectional evidence in older adults suggests an association between slower gait speed and lower global cognition^{5,6}, attention and psychomotor speed⁷, verbal memory⁸, executive function^{8,9}, working memory¹⁰, processing speed¹¹, and greater risk of developing dementia¹². However, since the relationship between gait speed and cognitive function has been primarily focused in geriatric and dementia studies, the evidence regarding gait speed, cognitive function, and cerebellum in younger adults is scarce. Characterizing this relationship in younger adults will provide a complementary and foundational understanding about the relationship between gait speed and working memory.

Since a report depicting impaired gait in World War I victims with gunshot-induced cerebellum damage¹³, it has been increasingly recognized that the cerebellum is an essential brain region for control and integration of motor activity¹⁴. Through feedforward and feedback loops, the cerebellum receives inputs from cerebral cortex and pontine nuclei and sends outputs to the thalamus and red nuclei¹⁵. The cerebellum integrates the inputs to fine-tune motor activity and regulates voluntary movements (e.g., posture and balance), visually guided movements, and balanced muscular activity. The cerebellum also identifies and regulates mismatch between actual and intended bodily movements (i.e., error correction)^{16,17}. Cerebellum lesions are associated with gait dysfunction¹⁸ and greater cerebellar gray matter volume is related to faster gait speed^{19,20}.

The cerebellum also engages in a broad range of cognitive processes, well-beyond its historical association with motor control and motor coordination. Cerebellar lesion studies reveal impaired executive function, spatial attention, planning, language processes, and learning and memory^{21–23}. An anatomical foundation for the cerebellar contribution to cognition is the connection between the cerebellum and prefrontal and parietal cortices^{24,25}. Through this fronto-parietal-cerebellar network, the cerebellum plays an important role in cognitive function²⁶. Particularly, evidence regarding a cerebellar contribution to working memory in humans has been established based on human functional imaging studies. For example, there is a strong positive correlation between cerebellar gray matter volume and working memory performance²⁷. In addition, greater cerebellar subregion gray matter volumes (e.g., lobules VI, right VIIIa, and Crus I) predicts better working memory performance^{28,29}. Moreover, functional magnetic resonance imaging (fMRI) activation within the bilateral regions lobules VI, Crus I, and VIIIa were observed during the n-back working memory task^{30,31}.

Collectively, the literature provides evidence for the cerebellum's involvement in both gait speed and working memory. Both gait speed and working memory also depend on information-processing ability and attention, which are primarily prefrontal-cortex dependent functions³². It is speculated that signals from the prefrontal regions may communicate via the fronto-cerebellar network and reach cerebellum to induce motor and cognitive outputs^{19,33}. This anatomical pathway of the cerebellum gives rise to the plausible link between motor and cognition. What remains unknown is whether subregions of the cerebellum are involved in both gait speed and working memory. A mediating role of the cerebellum would add important insights into our understanding of the shared neural mechanism underlying any potential associations between gait speed and working memory. To test this research question, we selected cerebellar subregions of interest that are linked to working memory. Working memory paradigms have been shown to elicit fMRI activity in the Crus I²⁷, bilateral VIIb and right VIIIa^{30,34}. Therefore, we selected the cerebellar Crus I, VIIb, and right VIIIa as volumetric regions of interest for the present study. We also quantified bilateral cerebellum volume to test whether the hypothesized mechanism are driven by total cerebellar volume rather than specific subregion volumes.

The aims of this study were to investigate the associations between (1) gait speed and cerebellar subregion volumes; (2) gait speed and working memory performance; (3) cerebellar subregion volumes

and working memory performance; and (4) the mediating role of cerebellar subregions in the relationship between gait speed and working memory performance. We hypothesized that (1) faster gait speed would be associated with greater cerebellar subregion volumes; (2) faster gait speed would be associated with better working memory performance; (3) greater cerebellar subregion volumes would be associated with better working memory performance; and (4) greater cerebellum subregion volume would mediate the relationship between faster gait speed and better working memory performance. To test these hypotheses, we leveraged the publicly available cross-sectional dataset of healthy younger adults from the Human Connectome Project³⁵. In a sizable and well-characterized younger sample, available data from Human Connectome Project including gait speed, working memory performance, and high-resolution MRI data were analyzed. As an index of working memory performance, we used n-back task performance. In addition to working memory performance, we also tested the fluid cognition composite score to test the specificity of the relationship between gait speed, cerebellar subregion volumes, and working memory.

Methods

Participants

The publicly available younger adults data from University of Minnesota (Wu-Min) Human Connectome Project (<https://www.humanconnectome.org/study/hcp-young-adult/document/1200-subjects-data-release>) were used for the present study³⁵. Healthy younger adults (19–35 years) were recruited from Missouri, using the recruiting strategy that reflected the population distribution of the US. Participants were excluded from the study if they had a history of psychiatric disorder, substance abuse, neurological, or cardiovascular disease, two or more seizures after age five or a diagnosis of epilepsy, any genetic disorder (e.g., cystic fibrosis or sickle cell disease), multiple sclerosis, cerebral palsy, brain tumor or stroke, premature birth, currently on chemotherapy or immunomodulatory agents, or history of radiation or chemotherapy that could affect the brain, thyroid hormone treatment in the past month, treatment for diabetes in the past month (other than gestational or diet-controlled diabetes), use of daily prescription medications for migraines in the past month, < 25 on the Mini Mental State Exam³⁶ on the Day 1 visit, pregnancy, MR contraindications (e.g., unsafe metal in the body, moderate or severe claustrophobia). All experimental procedures and data sharing were performed according to relevant guidelines and regulations³⁷. Participants visited Washington University two different days for magnetic resonance imaging (MRI) scanning and cognitive assessments.

Gait Speed Assessment

The four-meter gait test, an established and valid measurement of gait speed, was performed. The test was administered as a part of the motor assessment in the NIH toolbox³⁸ which was adapted from the Short Physical Performance Battery³⁹. During the gait speed test, participants were instructed to walk four meters at their usual pace. Participants completed one practice session before performing two-timed walks. Scores were recorded in seconds and the faster performance among the two walks was used as

the reported score. Scores were computed in meters per second (m/sec). Higher computed scores indicate better gait speed (i.e., fewer seconds to walk four meters).

Working Memory Task

An n-back task with 2- and 0-back load levels were used to examine working memory, which was performed within MRI scanner⁴⁰. Blocks of trials consisted of pictures of places, tools, faces and body parts were presented during the test. The four different stimulus types were presented in separate blocks within each run. Within each run, half of the blocks used a 2-back working memory task and half used a 0-back working memory task as a working memory comparison. A 2.5 second cue indicated the task type and target for 0-back at the start of the block. Each of the two runs comprised of eight task blocks (10 trials of 2.5 seconds each, 25 seconds in total) and four fixation blocks (15 seconds each). On each trial, the stimulus was presented for two seconds, followed by a 500 ms inter-task interval³⁵. Accuracy across all conditions in the working memory task (%) and median response time for all conditions (RT; ms) were used as variables of interest in the present study.

Fluid Cognition Composite Score

A comprehensive battery of neuropsychological tests was administered to evaluate cognitive function, including Picture Sequence Memory, Dimensional Change Card Sort, Flanker task, Oral Reading Recognition, Picture Vocabulary, Pattern Comparison, and List Sorting. Specific descriptions regarding the administration and scoring methods of these tests are further detailed in previous studies^{41,42}. The subtest scores were averaged to generate composite scores using the NIH Toolbox Cognition Battery. One of the composite scores was the fluid cognition composite score in which executive function test scores (e.g., Flanker, Dimensional Change Card Sort, Picture Sequence Memory, and List Sorting) were normalized. The fluid cognition composite score was standardized using a mean of 100 and standard deviation of 15.

MRI Data Acquisition

Whole-brain MRI scan was conducted using a customized Siemens (Munich, Germany) 3.0 Tesla Skyra MR scanner at Washington University. A 32-channel head coil (SC72) was used for radio frequency transmission and reception. A high-resolution T1-weighted anatomical image was acquired with gradient echo sequence: field of view = 224 mm, voxel size = $0.7 \times 0.7 \times 0.7$ mm, slice thickness = 0.9 mm, repetition time = 2400 ms, echo time = 2.14 ms, inversion time = 1000 ms, flip angle = 8° , and duration = 7:40 min³⁵.

Cerebellar Subregion Analysis

The Statistical Parametric Mapping version 12 (Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk>) software package's Spatially Unbiased Infratentorial Template (SUIT) toolbox, running on MATLAB (MathWorks, Natick, MA, version 2018a), was used for cerebellar subregion

volume analyses. First, from the T1-weighted high-resolution anatomical images, infratentorial structures (e.g., cerebellum and brainstem) were isolated from the surrounding cortical tissue^{43,44}. Using the unified segmentation procedure, gray matter, white matter, and cerebrospinal fluid were segmented as part of the isolation procedure⁴⁵. Next, gray matter volume segmentations were normalized into the probabilistic SUI template using the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) registration approach⁴⁶. Subsequently, cerebellar subregion gray matter volumes (mm³) were generated across participants.

Whole Cerebellar Volume Analysis

T1-weighted high-resolution anatomical images were processed using the FreeSurfer (version 5.3.0) automatic cortical reconstruction process for cortical parcellation and subcortical segmentation (recon-all)⁴⁷. Bilateral cerebellar volume (mm³) was calculated from this automated segmentation process.

Statistical Analysis

We used the Shapiro-Wilk test to determine normality of demographic, gait speed, working memory performance, whole cerebellar volume, and cerebellar subregion volumes. First, we investigated the relationship between gait speed and working memory performance. To accomplish this, we used linear regression models where gait speed was set as an independent variable and working memory performance was included as a dependent variable after controlling for age, sex, and years of education. Second, we investigated the link between gait speed and cerebellar volumes (bilateral cerebellum and cerebellar subregions). In the linear regression model, gait speed was set as an independent variable and cerebellar subregion volumes were included as dependent variables after controlling for age, sex, years of education, and total intracranial volume (ICV). ICV, estimated by FreeSurfer⁴⁷, was included as a covariate to adjust cerebellar volumes based on previous investigations that identified significant sex-related differences in ICV^{48,49}. Third, the relationship between cerebellar subregion volume and working memory performance was individually explored. Cerebellar volumes were set as independent variables and working memory performance was included as a dependent variable after adjusting for age, sex, years of education, and ICV. All variables were coded as continuous variables.

Mediation analysis was conducted for the second aim of the study; to examine if cerebellar subregion volume mediated (or partially mediated) the relationship between gait speed and working memory performance. Based on the significant associations that meet the assumption of mediation from the prior linear regression analyses, we conducted a bootstrapped mediation analysis to determine the effect of gait speed (IV; independent variable), indirectly through cerebellar subregion volume (M; mediator), on working memory performance (DV; dependent variable). The mediation analysis package⁵⁰ within SPSS (v. 26.0, IBM, Armonk, NY) was used for mediation analyses. We used the 95% confidence interval obtained from 5000 bootstrap resamples⁵¹ to explore the indirect mediation effect of cerebellar subregion volume on the relationship between gait speed and working memory performance. Age, sex, years of education, and ICV were included as covariates.

Results

Participants

Among a total of 1206 participants who completed the study protocol, 152 individuals were excluded due to missing data (cerebellar volume $n = 114$, data processing error $n = 1$, and working memory performance $n = 37$). Thus, 1054 participants' data were included for the current study. Overall, the participants had an average age of 28.7 years and 14.9 years of education. 54.4% of the participants were women and 74.8% of the sample was white. The average gait speed score of the participants was 1.3 meter/sec (Table 1).

Table 1
Demographics data of the participants.

		Total Sample (n = 1054)
		Mean $\pm$ SD
Demographics		
	Age (years)	28.7 $\pm$ 3.6
	Female (n,%)	573 (54.4%)
	White (n,%)	788 (74.8%)
	Education (years)	14.9 $\pm$ 1.7
	Gait Speed (m/sec)	1.3 $\pm$ 0.1
ICV & Cerebellum Subregion Volume (mm³)		
	ICV	1581794.7 $\pm$ 188453.0
	Bilateral Cerebellum	115822.8 $\pm$ 12283.4
	Bilateral Crus I	38473.1 $\pm$ 938.6
	Bilateral VIIb	25199.7 $\pm$ 663.8
	Right VIIIa	6970.7 $\pm$ 187.8
Cognitive Tests		
	Working Memory Accuracy (%)	86.9 $\pm$ 8.8
	Working Memory Median RT (ms)	862.9 $\pm$ 123.7
	Fluid Cognition Composite Score	115.3 $\pm$ 11.5

Notes: SD, standard deviation; ICV, total intracranial volume; RT, response time.

Association between Gait Speed and Working Memory/Fluid Cognition Composite Performance

While there was a significantly negative association between gait speed and working memory RT ($B = -41.519$, $p = 0.031$, 95% CI $-79.31, -3.72$), no association between gait speed and working memory accuracy was detected ($B = -0.799$, $p = 0.535$, 95% CI $-3.33, 1.73$). There was no significant correlation between gait speed and fluid cognition composite score was found ($B = 3.141$, $p = 0.071$, 95% CI $-0.28, 6.56$).

Association between Cerebellar Subregion Volumes and Working Memory/Fluid Cognition Composite Performance

Bilateral Crus I ($B = 0.0008$, $p = 0.002$, 95% CI $0.0002, 0.001$), Right VIIIa ($B = 0.0039$, $p = 0.004$, 95% CI $0.001, 0.006$), and bilateral cerebellar ($B = 0.0007$, $p = 0.009$, 95% CI $0.00001, 0.0001$) volumes predicted significantly greater working memory performance accuracy. While greater right VIIIa volume also predicted shorter working memory RT ($B = -0.047$, $p = 0.020$, 95% CI $-0.08, -0.007$), the relationship between bilateral Crus I volume and working memory RT was at the borderline significance ($B = 0.007$, $p = 0.054$, 95% CI $-0.15, 0.0001$). There was also no significant relationship between whole cerebellar volume and working memory RT ($B = -0.0003$, $p = 0.431$, 95% CI $-0.001, 0.0005$). Bilateral VIIb volume did not significantly predict any of the working memory performance indices including accuracy ($B = 0.001$, $p = 0.118$, 95% CI $-0.0002, 0.002$) and RT ($B = -0.012$, $p = 0.211$, 95% CI $-0.03, 0.007$). Next, while greater bilateral Crus I ($B = 0.001$, $p = 0.0008$, 95% CI $0.0005, 0.001$) and right VIIIa ($B = 0.003$, $p = 0.034$, 95% CI $0.0003, 0.007$) volumes were associated with higher fluid cognition composite score, there were no associations between bilateral VIIb ($B = 0.001$, $p = 0.215$, 95% CI $-0.0006, 0.002$) and whole cerebellum volumes ($B = 0.00005$, $p = 0.156$, 95% CI $-0.00002, 0.0001$) and fluid cognition composite score (see Table 2).

Table 2

Association between cerebellar subregion volumes/Gait Speed and working memory performance.

		B Coefficient	t	p- value	95% CI for B
Gait Speed					
	Working Memory Acc	-0.799	-0.620	0.535	-3.33, 1.73
	Working Memory RT	-41.519	-2.155	0.031	-79.31, -3.72
	Fluid Cognition Composite Score	3.141	1.801	0.071	-0.28, 6.56
Bilateral Crus I					
	Working Memory Acc	0.0008	2.977	0.002	0.0002, 0.001
	Working Memory RT	-0.007	-1.925	0.054	-0.01, 0.0001
	Fluid Cognition Composite Score	0.001	3.329	0.0008	0.0005, 0.001
Bilateral VIIb					
	Working Memory Acc	0.001	1.560	0.118	-0.0002, 0.002
	Working Memory RT	-0.012	-1.250	0.211	-0.03, 0.007
	Fluid Cognition Composite Score	0.001	1.239	0.215	-0.0006, 0.002
Right VIIIa					
	Working Memory Acc	0.003	2.851	0.004	0.001, 0.006
	Working Memory RT	-0.046	-2.243	0.025	-0.08, -0.005
	Fluid Cognition Composite Score	0.003	2.123	0.034	0.0003, 0.007
Bilateral Cerebellum					
	Working Memory Acc	0.00007	2.582	0.009	0.00001, 0.0001
	Working Memory RT	-0.0003	-0.786	0.431	-0.001, 0.0005
	Fluid Cognition Composite Score	0.00005	1.418	0.156	-0.00002, 0.0001

Notes: 95% CI, 95% confidence interval, PSQI used as a continuous variable; regression analyses were adjusted for age, sex, education year, and ICV for cerebellar subregions; regression analyses were

adjusted for age, sex, and education year for gait speed; ACC, accuracy; RT, response time.

Association between Gait Speed and Cerebellar Subregion Volumes

Results showed that faster gait speed predicted greater right VIIIa ($B = 76.710$, $p = 0.007$, 95% CI 20.35, 133.07) and bilateral VIIb ($B = 116.207$, $p = 0.045$, 95% CI 2.56, 229.84) volumes. However, there was no significant association between gait speed and bilateral Crus I volume ($B = 39.713$, $p = 0.783$, 95% CI -244.27, 323.70) and whole cerebellar volume ($B = 382.186$, $p = 0.766$, 95% CI -2147.78, 2912.15) (see Table 3).

Table 3
Association between gait speed and cerebellar subregion volumes.

	B Coefficient	t	p-value	95% CI for B
Bilateral Crus I	39.7138	0.274	0.783	-244.27, 323.70
Bilateral VIIb	116.2071	2.006	0.045	2.56, 229.84
Right VIIIa	67.470	2.340	0.019	10.91, 124.03
Bilateral Cerebellum	382.186	0.296	0.766	-2147.78, 2912.15

Notes: 95% CI, 95% confidence interval; regression analyses were adjusted for age, sex, education year, and total intracranial volume; Bold indicates $p < 0.05$.

Mediation Analysis

The presence of significant relationship between gait speed (IV; independent variable) and right VIIIa volume (M; mediator), and right VIIIa volume (M) and working memory RT (DV; dependent variable) suggest that only right VIIIa met the assumption for a mediation analysis. The mediation analysis was conducted using the bootstrapped method with a bias-corrected confidence estimates and included age, sex, years of education, and ICV as covariates in the regression model. Mediation analyses indicated the relationship between gait speed and working memory RT was mediated by right cerebellar VIIIa volume ($B = -3.103$, $p = 0.023$, 95% CI -8.60, -0.02). Moreover, the indirect effects of gait speed (IV) on working memory RT (DV) became no longer significant ($B = -35.605$, $p = 0.064$, 95% CI -73.40, 2.19) when controlling for right VIIIa volume, suggesting a partial mediation effect (Fig. 1; Panel A).

As there was a significant mediation effect of right VIIIa, we further tested the possible mediating role of left VIIIa (M) in the relationship between gait speed (IV) and working memory RT (DV). Working memory accuracy was not tested because there was no significant association between gait speed (IV) and working memory RT (DV). Greater left VIIIa volume (M) predicted shorter working memory RT (DV) ($B = -0.048$, $p = 0.014$, 95% CI -0.08, -0.009). There was no significant association between gait speed (IV) and left VIIIa (M) ($B = 50.564$, $p = 0.093$, 95% CI -8.48, 109.61); thus, left VIIIa volume did not meet the assumption of mediation. We also evaluated the possible mediating role of the bilateral VIIIa volume in the relationship between gait speed and working memory performance. Greater bilateral VIIIa volume (M)

predicted shorter working memory RT (DV) ($B = -0.029$, $p = 0.008$, 95% CI -0.05, -0.007). In addition, faster gait speed (IV) significantly predicted greater bilateral VIIIa volume (M) ($B = 118.034$, $p = 0.024$, 95% CI 14.93, 221.13), meeting the assumption of the mediation. Mediation analyses revealed that a mediating role of right VIIIa volume in the relationship between gait speed and working memory RT ($B = -3.422$, $p = 0.007$, 95% CI -8.58, -0.02). Moreover, the indirect effects of gait speed (IV) on working memory RT (DV) became no longer significant ($B = -35.202$, $p = 0.067$, 95% CI -72.95, 2.55) when controlling for right VIIIa volume, suggesting a partial mediation effect (Fig. 1; Panel B).

Discussion

We found a mediating role of the cerebellar subregion volume on the association between gait speed and working memory performance. Furthermore, we show that faster gait speed was associated with shorter working memory RT. In addition, faster gait speed was linked to greater right VIIIa and bilateral VIIIa volumes. The right VIIIa and bilateral VIIIa volumes were related to shorter working memory RT. Lastly, the association between faster gait speed and shorter working memory RT was mediated by greater VIIIa volume. We also tested fluid cognition composite score as a control and found that greater right VIIIa and Crus I volumes were associated with better fluid cognition composite score. However, since there was no significant link between gait speed and fluid cognition composite score, this suggests that the mediation was specific to the working memory task and not general fluid cognition.

In the present study, there was a relationship between greater cerebellar subregion volumes (bilateral Crus I and right VIIIa) and better n-back task performance. Prior work investigating the link between working memory and the cerebellum has primarily used verbal working memory⁵², but other modalities employing object and spatial stimuli also elicited cerebellar activations⁵³, suggesting cerebellar engagement in non-verbal n-back tasks. The Crus I and right VIIIa have been well-recognized as contributors to working memory. For example, working memory-related functional MRI activation during the n-back task was found in the bilateral regions of Crus I and VIIIa³⁰. Further, greater cerebellar subregion gray matter volumes (e.g., lobules VI, right VIIIa, and Crus I) predict better working memory performance^{28,29}. In support, greater VIIIa gray matter volume is associated with better working memory tasks (e.g., the Backward Digit Span task and the Letter/Number Sequencing task)²⁸. Moreover, lesion studies reported that cerebellar stroke involving the VIII is a risk factor for increased error during a working memory task (i.e., Wisconsin Card Sorting Test)⁵⁴. Overall, the present results of the positive correlation between cerebellar subregion volumes and n-back task performance align well with the existing body of literature and suggest that the VIIIa and Crus I represent an important component of working memory.

The crucial functions for successfully accomplishing the n-back task encompass encoding, continuous updating of upcoming stimuli, temporary maintenance of stimuli, inhibiting irrelevant stimuli, and directing attention to relevant information⁵⁵. Evidence has been generated concerning a cerebellar role in monitoring expected and observed outcomes and encoding the sequence of stimuli⁵⁶ as well as maintenance of information over temporal delays (i.e., coordination of temporal information)⁵⁷, which are

essential components to accomplish working memory tasks⁵⁸. These cerebellar functions may corroborate the link between greater bilateral cerebellar volume and better working memory performance we observed. In addition, the relationship between greater cerebellar subregion volumes and better n-back task performance may suggest the cerebellum as a supportive system interacting with the prefrontal and parietal regions to facilitate successful task accomplishment. Specifically, the highly-organized circuits between the Crus I and VIIIa and the frontal and parietal cortex constitute a neural network underpinning the central executive mechanism^{59,60}. Moreover, the contribution of cerebello-parietal loop (VIIIa and the inferior parietal lobule) to the maintenance and storage of information has been reported⁵². Given that greater gray matter volume is associated with greater dendrites and synapses⁶¹, greater Crus I and right VIIIa gray matter volumes may be associated with greater number of synapses or dendrite arborization possibly increasing the integrity within the frontal-parietal-cerebello cognitive network formation, which may be related to better n-back task performance. This hypothesis, however, remains speculative and further studies should investigate the mechanistic and translational evidence to robustly test this hypothesis.

A previous investigation found the relationship between lower cerebellar gray matter volume and slower gait speed in older adults¹⁹. Conversely, we failed to observe a significant association between whole cerebellar gray matter volume and gait speed in younger individuals. However, there were positive associations between cerebellar subregions including the VIIb and VIIIa volumes, and gait speed. Theories detailing how these cerebellar subregions contribute to motor control have been documented. Human neuroimaging findings suggest the presence of sensorimotor homunculi in the lobules VII and VIII⁶². Further, resting-state functional connectivity evidence has reported that activity in sensorimotor regions correlates with the cerebellar anterior lobe and lobule VIII⁶³. This evidence suggests that output from cerebellar lobule VII and VIII targets the premotor cortex⁶⁴, which is involved in motor learning and movement sequences (i.e., gait control) as well as generating signals to the motor cortex (M1) to initiate voluntary movements of walking¹⁹. Collectively, these results provide evidence that the relationship between the cerebellar volume and gait speed may be specific to the cerebellar subregions of VII and VIIIa in younger individuals.

One line of evidence suggests gait speed and stability as predictors for cognitive processes such as attention and executive function⁶⁵. In community-dwelling older adults, slower baseline gait speed predicts a decline in attention and psychomotor speed over five years⁷. Prospective studies indicated the relationship between a decline in gait speed and lower attention and executive function performance in older individuals⁶⁶. In support, Montero-Odasso et al. (2012) suggested that gait speed in older adults with cognitive impairment is linked to impaired working memory ability⁶⁵. The literature concerning the relationship between gait speed and working memory has primarily focused on older adults, but the present study extends the existing literature by suggesting the predictive role of gait speed on working memory performance in a large sample of healthy younger adults. There was also a marginally significant association between gait speed and fluid cognition composite score ($p = 0.071$), indicating

that gait speed may predict broader range of cognitive tasks, beyond working memory. Our results further elucidate that the relationship between gait speed and working memory performance may be mediated by the VIIIa volume. However, the present results should be viewed as support for a partial, not full, mediation effect since, with the addition of the mediator to the model, the p -value for the indirect effects became slightly above the threshold for statistical significance ($p \geq 0.064$).

Although the precise neural mechanism underpinning the mediating role of the VIIIa in the association between gait speed and working memory remains unknown, cerebellar information processing ability can be a possible candidate. The cerebellum contributes to motor information processing by integrating sensory motor information such as the position of the limbs and the goal of the movement. To accomplish motor information processing, the cerebellum continuously corrects and updates the movement trajectory⁶⁷. Such motor function has striking similarity to executive function performance which requires continuously altering mental strategy to achieve a desired goal²⁸. Thus, the cerebellar contribution to motor control may be comparable to the cerebellar contribution to working memory. Indeed, the cerebellum and the prefrontal and parietal regions (i.e., regions involved in gait control and working memory) form circuits through the superior cerebellar peduncles and this anatomical connection may allow cerebellar linkage with sensorimotor and higher-order brain areas¹⁹, supporting the cerebellum's specialized role for information processing that can influence downstream motor control and cognitive function³². The cognitive region of the cerebellum which largely constitutes the lateral part of the cerebellum (including VIIIa) may be associated with gait speed possibly based on its reciprocal connections with the cerebral cortex. Therefore, the present study suggests that the specific subregion of the cerebellum (VIIIa) may be a key region serving as an important cerebellar interface linking mobility and working memory. Nevertheless, this hypothesis is speculative and further mechanistic and translational neuroimaging evidence are warranted to robustly test this hypothesis.

Lastly, our results also suggest that the mediation function of the VIIIa may not localize only in the right hemisphere, but the bilateral VIIIa may link the association between gait speed and working memory. Intriguingly, the mediation effect of the VIIIa was evident only in RT, not accuracy. There is a positive association between posterior cerebellum (including VIIIa) volume and cognitive processing that are associated with sensorimotor performance variability; thus, greater posterior cerebellum volume predicts faster choice RT²⁷. This evidence may support the correlation between gait speed (motor function) and motor aspects of working memory performance (RT) through the VIIIa.

Strengths and Limitations

An important strength of the present study was a large and well-characterized younger adult sample ($n = 1054$). Further, the Human Connectome Project's high-resolution neuroimaging data were used to elucidate the mediating role of cerebellar subregions in the relationship between gait speed and working memory performance. Nevertheless, our study is limited by its cross-sectional design, which warrants caution when interpreting the directionality of the current results. Future longitudinal and interventional studies will be necessary to clarify the role of the cerebellum in the link between gait speed and cognitive

function. A further potential limitation of the current study is that the n-back task used in the Human Connectome Project had a non-standard design in that it simultaneously examined category specific representations and working memory, using pictures of places, faces, tools, and body parts. Future studies using standardized n-back tasks need to clarify the relationship between gait speed, working memory, and cerebellar volume found in this study.

Conclusion

The present study suggests the positive correlation between gait speed and working memory RT in younger adults. This extends the body of literature focusing primarily on older adults, with evidence that the gait speed-cognitive function association may be present across adulthood. Our results suggest that faster gait speed is linked to faster RT during working memory tasks through greater Vllla volume. Extensive connections between the cerebellum, sensorimotor, and the cerebral cortex may provide the anatomical substrates for the cerebellar contributions to linking gait and working memory. Therefore, this finding may highlight the shared neural mechanism underlying the association between gait speed and working memory. Yet, due to moderately weak mediation effects, the present results should be interpreted with caution. Future work should explore the mediating role of the cerebellar subregion using older adult sample and longitudinal study design.

Declarations

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AUTHOR CONTRIBUTIONS

J.W. developed the study idea, analyzed the data, and drafted the paper. D.C., J.P., and J.C.S edited the paper. All authors reviewed, revised, and approved the final manuscript.

CONFLICT OF INTEREST

The authors declared no conflicts of interest with respect to the research, authorship, and publication of this article.

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Figures

A

B

Figure 1

Panel A represents the indirect mediating pathway between gait speed and working memory RT through the right Villa volume. Mediation analysis of the relationship between gait speed and working memory RT with the bilateral Villa volume as a mediator is illustrated in Panel B.