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The association of brain structure with gait velocity in older adults: a quantitative volumetric analysis of brain MRI

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Abstract

Introduction—While cortical processes play an important role in controlling locomotion, the underlying structural brain changes associated with slowing of gait in aging are not yet fully established. Our study aimed to examine the relationship between cortical gray matter volume (GM), white matter volume (WM), ventricular volume (VV), hippocampal and hippocampal subfield volumes, and gait velocity in older adults free of dementia.

Methods—Gait and cognitive performance was tested in 112 community-residing adults, age 70 years and over, participating in the Einstein Aging Study. Gait velocity (cm/s) was obtained using an instrumented walkway. Volumetric MRI measures were estimated using a FreeSurfer software. We examined the cross-sectional relationship of GM, WM, VV, and hippocampal total and subfield volumes and gait velocity using linear regression models. In complementary models, the effect of memory performance on the relationship between gait velocity and regional volumes was evaluated.

Results—Slower gait velocity was associated with smaller cortical GM and total hippocampal volumes. There was no association between gait velocity and WM or VV. Among hippocampal

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Ethical standards and patient consent We declare that all human studies have been approved by the Albert Einstein College of Medicine Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all participants gave informed consent prior to inclusion in this study.

Conflict of interest We declare that we have no conflict of interest.

subfields, only smaller presubiculum volume was significantly associated with decrease in gait velocity. Addition of the memory performance to the models attenuated the association between gait velocity and all volumetric measures.

Conclusions—Our findings indicate that total GM and hippocampal volumes as well as specific hippocampal subfield volumes are inversely associated with locomotor function. These associations are probably affected by cognitive status of study population.

Keywords

Volumetric MRI; Gait velocity; Cortical volume; Hippocampal subfields; Memory

Introduction

Aging is associated with a decline in locomotor function as measured by gait velocity. Slow gait velocity is associated with increased risk of multiple adverse outcomes such as falls, dementia, and mortality [1–3]. Aging is also associated with structural alterations in the brain regions involved in locomotor function, including the cerebellum, frontal and prefrontal cortices, and hippocampus [4, 5]. Global brain atrophy, as well as regional gray matter (GM) volume loss [6, 7], and decreased white matter (WM) integrity [8] has been described parallel to a decline in locomotor function in older adults leading to the assumption that neurodegeneration in these regions are responsible for the foreseen decline in gait dynamic stability.

The hippocampus is a key brain region involved in a variety of physiological processes including cognitive and locomotor functions [9, 10]. Previous neuroimaging studies suggest that hippocampal atrophy is also associated with slower gait velocity and stride length [7, 11]. The hippocampal formation consists of multiple subfields (subregions) including the cornu ammonis area 1 (CA1), CA2, CA3, CA4, dentate gyrus (DG), presubiculum, subiculum, and fimbria. These subfields differ in their histology, connectivity, and function [12]. Recent studies suggest that hippocampal subfields are differentially vulnerable to aging, and are implicated in different pathologic conditions such as dementia, chronic pain, post-traumatic stress disorder, and mood disorders [13–16]. Animal studies demonstrate involvement of ventral hippocampal subfields in locomotor function [17, 18]; however, the subfield volumetric changes associated with locomotor function in humans have not been studied.

Regional brain atrophy in older adults is associated with changes in several other functional domains besides mobility including cognitive function [9]. Therefore, to better understand the relationship between regional brain volume, locomotor function, and cognitive function, the associations between these variables should be evaluated within the same models and in the same sample. The purpose of this study was to identify the spatial distribution of region-specific neuronal loss underlying the slowing of gait among older community dwellers. We hypothesized that, among older adults, atrophy of cortical GM, WM, hippocampus, as well as increase in ventricular volume, may be responsible for decline in locomotor function as measured by gait velocity. In addition, we tested whether memory performance affects the relationship between volumetric measures and locomotor function. We hypothesized that

associations between gait velocity and regional volumetric measures, specifically in hippocampus, would be attenuated when examined jointly with memory performance. In order to further explore the latter hypothesis, we separately looked at the cognitively healthy subset of participants.

Methods

Participants

We studied 112 non-demented older adults drawn from the Einstein Aging Study (EAS). The study design and methods of the EAS have been described in detail previously [19]. Briefly, potential participants were recruited through systematic sampling from Medicare and voter registration lists for Bronx County, New York. Eligible participants were aged 70 and older, Bronx residents, non-institutionalized, and English-speaking. Exclusion criteria included severe visual or auditory impairments that precluded neuropsychological testing, active psychiatric symptomatology that interfered with the ability to complete assessments, and non-ambulatory status. At the time of this study, none of the participants were diagnosed with Parkinson's disease or had severe orthopedic disease that could potentially limit their gait function. In addition, the participants were all free of hydrocephalus based on both neurological evaluation (triad of obvious gait disturbances, cognitive dysfunction, and urinary incontinence) and imaging criteria (Evans' index: average=0.27, SD=0.04, range=0.23–0.30). The participants who were diagnosed with dementia or did not meet standard MRI eligibility criteria—metallic implants that obscure or interfere with MRI—were also excluded from this MRI study. The participants received in-person assessments including medical history, neuropsychological testing, and general and neurologic examinations.

Ethical approval for all parts of this study was obtained from the Institutional Review Board of the Albert Einstein College of Medicine.

Gait evaluation

Quantitative gait studies were performed on a computerized walkway mat (457.2×90.2×0.6 cm) with embedded pressure sensors (GAITRite, CIR systems, USA) [20]. Subjects were asked to walk on the mat at their “normal pace” for two trials in a well-lit hallway wearing comfortable footwear. Start and stop points were marked by white lines on the floor placed 3 ft from the mat edge to account for initial acceleration and terminal deceleration. Based on footfalls recorded on the walkway, the computer software automatically computes gait parameters as the mean of the two trials. The participants were not using any walking aid while walking on the walkway mat.

While the software generates information on several gait parameters, we focused on velocity (cm/s) in this analysis, given its role as a universal screening measure of health and function in older patients as well as its role as a robust predictor of multiple adverse geriatric outcomes [21]. High reliability of the GAITRite system, and gait velocity measurements in particular, has been reported in our center [20], and the system is widely used in both clinical and research settings.

Assessment of memory function

Verbal memory was assessed using the free recall score (range 0–48) from the Free and Cued Selective Reminding Test–Immediate Recall (FCSRT-IR) [22]. The verbal memory performance was used as a proxy for cognitive function localized to the hippocampus in our analysis. Details of the EAS neuropsychological test battery has been previously described [19].

Criteria for classification of subjects as mild cognitive impairment (MCI) is described in detail previously [19]. Briefly MCI participants included both amnesic MCI (aMCI) and non-amnesic MCI (naMCI) elderly. The participants were classified as aMCI if the memory domain was impaired or naMCI if there was impairment in one or more domains other than memory as defined below. Amnesic MCI diagnosis required objective memory impairment, subjective memory impairment indicated by responses to self-reports or informant reports, and absence of functional decline and that they are not classified as clinically demented. Non-amnesic MCI was diagnosed in non-demented participants without functional impairment who did not meet the memory criterion for aMCI but had impairment (1.5SD below the age adjusted mean) in at least one non-memory cognitive domain of attention, executive function, visuospatial ability, or language.

Dementia diagnosis was based on the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) [23] and was assigned at consensus case conferences attended by the study clinicians and licensed neuropsychologist, and included a comprehensive review of cognitive test results, relevant neurological signs and symptoms, and functional status [19].

MRI acquisition and processing

Imaging was performed using a 3.0 T MRI scanner (Achieva Quasar TX; Philips Medical Systems, Best, the Netherlands) and 32-channel head coil (Sense Head Coil; Philips Medical Systems, Best, the Netherlands). T1-weighted whole-head structural imaging was performed using sagittal three-dimensional magnetization-prepared rapid acquisition gradient echo (MP-RAGE) with TR/TE 9.9/4.6 ms; 240 mm² FOV; 240×240 matrix; partition thickness, 1 mm; and parallel acceleration factor 2.0. In addition, a 3D T2-weighted fluid-attenuated inversion recovery (T2W-FLAIR) acquisition was obtained with the following pulse sequence parameters: TR/TE/TI 11000/120/2800 ms; 240×240 mm FOV; 240×240 matrix; 1 mm partition thickness and parallel acceleration factor 2.0.

Image processing

We processed all MRIs automatically using the FreeSurfer software package (version 5.2, available at <http://surfer.nmr.mgh.harvard.edu/>). Image processing methods in the EAS have been previously described in detail [13]. Briefly, the processing stream starts with a hybrid watershed algorithm, which removes non-brain tissue, automated transformation to the Talairach reference space and segmentation of the subcortical white matter and deep gray matter. FLAIR images were used for pial surface refinement. All volumes including cortical GM volume, total cerebral WM volume, ventricular volume, and total hippocampal volume (HV) were segmented using FreeSurfer's standard segmentation procedure using a probabilistic brain atlas [24]. Additionally, for each subject, the estimated intracranial

volume (TICV) was calculated by the procedure described by Buckner et al. [25]. Subsequently, we performed automated subfield segmentation of the hippocampus using a recently added procedure within the FreeSurfer suite. This procedure uses Bayesian inference and a probabilistic atlas of the hippocampal formation, which is based on manual delineations of subfields in T1-weighted MRI scans from a number of different subjects [26]. Using this method, seven subfield volumes were calculated for each side of the hippocampus: CA1, CA2-3, CA4-DG, presubiculum, subiculum, fimbria, and hippocampal fissure. The larger subfields are shown to correlate well with manual volume estimates, with an average dice coefficient of around 0.7 for CA2-3, CA4-DG, presubiculum, and subiculum [26]. Thus, for the purpose of this study, we chose larger subfields of CA1, CA2-3, CA4-DG, presubiculum, and subiculum. Automated volume estimates of these subfields are shown to correlate well between different MRI scanners [27]. Segmentation results were also visually inspected for errors in all datasets, but no manual edits were needed.

Statistical analyses

All statistical analyses were conducted using SPSS, version 20 (SPSS Inc., Chicago, IL). We examined the associations of gait velocity with demographic variables using Spearman rank correlation coefficients (r_s) or independent sample t tests. A series of linear regression analyses were performed to examine the association between gait velocity and MR-derived volumetric measures accounting for the influence of covariates. The main potential confounders for gait speed (age and gender) and the other potential confounders for brain volumes (education and TICV) were included as covariates. A Sidak correction factor [28] with an adjusted p value of 0.0125 for total volumetric analysis—and separately for each hemisphere—($\alpha=0.05$, four comparisons for each region of interest: hippocampus, total ventricle, cortical GM, and WM) and p value of 0.01 for hippocampal subfields ($\alpha=0.05$, five hippocampal subfields) was used to correct for type I error. Only the regions that were significantly associated with gait measures in the unadjusted preliminary models were entered in more complex models, initially adjusted for covariates including age, gender, education, and TICV (basic adjusted model), and then further adjusted for free recall scores to account for structural changes common to cognitive and gait function in aging (fully adjusted model). Furthermore, in order to evaluate whether inclusion of MCI participants significantly affected the outcomes, we repeated all previous models, with similar criteria, after exclusion of MCI participants.

Results

Demographic characteristics

Sample characteristics are summarized in Table 1. Total sample had a mean age of 79.3 years and was 59.8 % women and 54.4 % white, with a mean of 14.2 years (SD=3.5) of education. The mean gait velocity was 95.0 cm/s (SD=21.6). Gait velocity was inversely correlated with age ($r_s=-0.31$, $p=0.001$) and positively correlated with education ($r_s=0.27$, $p=0.004$). Gait velocity was not significantly different between men and women. The FCSRT-IR free recall scores did not show an association with age, gender, or education in this subsample; however, it was positively correlated with gait velocity ($r_s=0.22$, $p=0.022$).

As expected, older participants had smaller total brain volume (TBV) ($r_s = -0.31, p = 0.001$) and total HV ($r_s = -0.41, p < 0.001$). Women had smaller TBV ($t = -6.3, p < 0.001$) and total HV ($t = -3.1, p = 0.003$) than men. There was no significant correlation between TBV and total HV and education level.

Gait velocity and brain volumetric measures

Initially, we evaluated the association between gait velocity and volumetric measures in the whole sample. In unadjusted models and after correction for multiple comparisons, only the association between ventricular volume and gait velocity was not significant and therefore, it was not entered in further adjusted models. The participants with faster gait velocity had larger cortical GM volume (i.e., less GM atrophy) in the basic adjusted models. This association remained significant but was attenuated after adjusting for memory scores in the fully adjusted model. Although faster gait velocity was associated with larger WM volumes in the unadjusted model, this association did not remain significant after correction for other covariates. There was a positive correlation between gait velocity and total HV in the unadjusted and basic models; however, this association did not remain significant in the fully adjusted models (Table 2; Figs. 1 and 2).

Subsequently, we examined the association between gait velocity and hemispheric volumetric measures. Both right and left cortical GM volumes were significantly correlated with gait velocity in basic (left: $\beta = 0.38, p = 0.015$; right: $\beta = 0.41, p = 0.010$) and fully (left: $\beta = 0.34, p = 0.031$; right: $\beta = 0.38, p = 0.017$) adjusted models. There was no correlation between gait velocity and unilateral WM or ventricular volume in the adjusted models. Although both left and right HV were associated with gait velocity in the unadjusted models, after basic adjustment, only smaller right HV was associated with decrease in gait velocity ($\beta = 0.29, p = 0.004$). This association was attenuated but remained significant in the fully adjusted model ($\beta = 0.25, p = 0.012$) (Table 3).

Among the hippocampal subfields, only lower presubiculum region volumes showed an association with gait performance in the basic models ($\beta = 0.21, p = 0.042$). Association between subiculum volume and gait velocity was marginally significant in basic models ($\beta = 0.19, p = 0.058$). In the fully adjusted model, addition of memory scores to the model considerably attenuated the association between hippocampal subfields and gait velocity (Table 4).

Gait velocity and brain volumetric measures in cognitively healthy participants

Of the 112 participants, 20 met criteria for MCI who were excluded from analysis for the purpose of this part of study. Similar to models for the whole sample, GM volume was positively correlated with gait velocity in basic and fully adjusted models (Table 5). WM volume was not associated with gait velocity after adjustment for other covariates. There was no correlation between ventricular volume and gait velocity. Contrary with the results for the whole sample, total HV was only significantly associated with gait velocity in unadjusted models and this association did not remain significant in neither of basic or fully adjusted models (Table 5).

Further, we investigated the association between gait velocity and hemispheric volumetric measures in the cognitively healthy subsample. Again, both right and left cortical GM volumes were significantly correlated with gait velocity in the basic (left: $\beta=0.41$, $p=0.024$; right: $\beta=0.44$, $p=0.016$) and fully (left: $\beta=0.39$, $p=0.029$; right: $\beta=0.43$, $p=0.017$) adjusted models. There was no correlation between gait velocity and unilateral WM or ventricular volume in any of the adjusted models. Although both left and right HV were associated with gait velocity in unadjusted models, neither associations remained significant in basic or fully adjusted models (Table 3).

Discussion

In this cross-sectional study of community-residing older adults, we identified a number of structural correlates of gait velocity. In models adjusting for age, gender, education, and TICV, slower gait velocity was associated with smaller volume in the cortical GM and in the hippocampus, predominantly on the right side. Similar models showed that among hippocampal subfields, presubiculum volume is associated with gait velocity.

Our finding of the association between cortical GM volume and slowing of gait is in accordance with other studies that have reported cross-sectional associations between smaller GM volumes and several gait measures including gait velocity [29], step length, and step width [6, 30]. The mechanism linking reduced GM volume to slow gait velocity are uncertain. Perhaps, neuronal or synaptic loss leading to reduced GM volume account for slowed gait velocity. Alternatively, GM volume loss and slowing of gait velocity may be associated with common risk factors such as vascular disease that are connected to either normal aging or subclinical dementia pathology.

When free recall, a measure of hippocampus-dependent memory, was added to the models, the association between cortical GM volume and gait velocity was attenuated. This result remained consistent even after exclusion of MCI participants. This observed attenuation suggests that gait velocity and memory may share brain substrates reflected by cortical GM volume. It is not clear if this association is related to normal brain aging processes or the influence of pre-clinical dementia. Prior studies have shown that both gait velocity [1] and lower free recall memory performance [31] are associated with an increased incidence of dementia in older adults. We suggest that neurodegenerative or other pathological changes in brain volume may contribute to both decline in gait velocity and memory before the onset of dementia.

Although WM volume was not associated with gait velocity in our sample, previous studies in older adults have shown that reduced white matter integrity measured by fractional anisotropy [8] and higher WM lesion volumes [7] are associated with slower gait. In this study, we did not evaluate WM lesion volume or white matter integrity. Taken in aggregate, these findings suggest that microstructural integrity may be important in the earlier stages of motoric decline in aging, before frank volume changes are detected.

Lateral ventricle volume is an indirect measure of atrophy because CSF is under pressure and any parenchymal loss results in passive ventricle expansion [32]. Larger ventricular

volumes have been associated with slower gait velocity among individuals with dementia [33], but the association is not consistent in healthy older adults [34–37]. In our sample, ventricular volume was not associated with slower gait velocity. The different results could be explained by the use of qualitative visual scales to assess the ventricle volume in some of these studies [35, 36], limited adjustments for covariates, and differences in the baseline cognitive and functional status of participants. Since our sample comprises relatively healthy older adults, we speculate that the ventricular volume may be associated with slower gait velocity in persons at more advanced stages of locomotor decline. Testing this hypothesis will require larger samples and longitudinal MRI and gait data.

In the current study, we showed that smaller HV is associated with slower gait velocity. However, this association did not remain significant after exclusion of MCI subjects. Hippocampal involvement in cognitive and locomotor function is supported by animal models of hippocampal lesions that produce impairments in learning and memory as well as impairments in motor coordination, balance, and spontaneous perseverative turning [17, 18]. Some of the previous studies have linked hippocampal atrophy to decline in gait function in non-demented elderly [7, 11, 38]. In a cross-sectional study, Zimmerman et al. [11] showed that decreased stride length (but not stride length variability) is associated with smaller HV. Rosso et al. [38] reported a negative correlation between gray matter integrity and step length variability. In a longitudinal study, Callisaya et al. [7] found that hippocampal atrophy was associated with a decline in gait speed and step length. In contrast with these studies, one group [37, 39] reported a positive association between HV and a greater (i.e., worse performance) stride time variability only in cognitively healthy adults. One explanation for these inconsistencies may be the differences between studied populations, using different measures of gait to assess locomotor function, and differences in the baseline cognitive and functional status of participants (e.g., inclusion or exclusion of MCI population).

Association of HV with memory performance has been established in older adults [10, 40]. In the current study, we showed that the association between gait velocity and HV is attenuated by the addition of a memory measure to the models. We also showed that in the cognitively healthy participants, HV is not associated with gait velocity. There are a few possible explanations for these findings. The hippocampal and parahippocampal formations may play important roles in spatial navigation during walking [41], which is an important cognitive function to maintain a normal gait. Hippocampus is also involved in the corticocerebellar network, which is critical for establishing the cognitive strategies and motor routines involved in executing different movements of the foot [42], and therefore memory disorders arising from atrophy of hippocampus may account for uncoordinated gait and locomotor functional decline. Alternatively, this attenuation could simply mean that similar neuronal structures are involved in processing and executing of both memory and gait functions.

We also found an asymmetric—right more than left—association between HV loss and gait velocity in the whole sample. This might be explained by the critical role of right hippocampus in navigation [43]. It has been suggested that this role may be more prominent

when cognitive impairment is present [44]. Alternatively, the right-sided findings may be due to asymmetric neurodegeneration and reorganization of neuronal motor pathways.

We found an association between slower gait velocity and presubiculum volume, while the association between gait velocity and subiculum volume was marginal. Studies in animal models [45, 46] and humans have shown differential roles for each of the hippocampal subfields in specific processes including memory (subiculum and CA2-3) [15] and pain (CA2-3 and CA4-DG) [13]. The CA2-3, CA4-DG, and subiculum subfields were significantly smaller in PD patients who have slow gait [47]. The subfield-specific association between HV and gait velocity might be explained by anatomical differences among regions. Complex networks of afferent and efferent pathways connect the hippocampus to other parts of the motor pathway. The entorhinal cortex is the major source of afferent stimuli to the hippocampus that terminate on the dendrites of the CA1, CA3, DG, and subiculum [48]. The fornix fibers comprise the efferent output from the hippocampus originating in the CA1 region and projecting to the anterior thalamus, the mammillary region, and limbic midbrain [49]. The other efferent fibers include fimbria fibers that originate in presubiculum, subiculum, and CA2-4 and project to the anterior thalamus, the preoptic area, and the hypothalamus [50]. Our subfield findings indicate a change in the volume of regions from which the fimbria fibers originate. Further studies on both animals and humans are required to fully define the role of each subfield in the context of locomotor function.

While our findings are promising, a few limitations should be noted. First, locomotor and cognitive control processes are dependent on complex neural networks, not simply isolated brain regions. The coordinated involvement of other cortical and subcortical regions as well as their interconnecting white matter tracts needs to be clarified. Although the size of our sample is large in terms of imaging studies, it may not be sufficient for detecting small associations between brain MRI measures and gait velocity, especially after controlling for multiple covariates in the models. As this is a cross-sectional study, we cannot determine causality. Our study also has notable strengths. The EAS is a longitudinal study of a systematically recruited, ethnically and educationally diverse elderly cohort residing in Bronx, New York. The gait assessment and imaging procedures and processing were done using standardized and reliable protocols.

In summary, we report that cortical GM volume and total HV as well as specific hippocampal subfield volumes are associated with slow gait velocity in older individuals free of dementia. These associations probably vary in different samples based on their cognitive function. Further longitudinal studies are required to investigate the role of specific cortical regions and hippocampal subfields in locomotor function of the elderly population and the temporal relationship between these measures.

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Fig 1. Partial regression plot of the relationship between MRI markers and gait velocity controlling for age, gender, education, and TICV

Fig 2. Simple scatter plots of the associations between MRI volumetric measures and gait velocity

Table 1
Sample demographics, memory performance, and imaging findings in relation to gait velocity

	Total sample	Gait velocity	
	(N= 112)	<i>r/t^b</i>	<i>p value</i>
Men/women	45/67	1.45	0.147
% White	54.5	2.17	0.032
Age (years)	79.3 (5.0)	-0.31	0.001
Education (years)	14.2 (3.4)	0.27	0.004
Gait velocity (cm/s)	95.0 (21.6)	–	–
FCSRT-IR free recall	32.2 (6.6)	0.21	0.022
FCSRT-IR total recall	47.4 (1.8)	0.15	0.112
Total HV ^a	6.5 (0.8)	0.35	<0.001
Total cortical GM volume	352 (45.2)	0.42	<0.001
Total cortical WM volume	246 (47.2)	0.35	<0.001
Total ventricular volume	106 (19.5)	0.31	0.313
TBV	986 (105.8)	0.38	<0.001
TICV	1360 (205.4)	0.22	0.019

A *p* value of less than 0.05 was considered statistically significant and the corresponding results are shown in *italics*

FCSRT-IR Buschke and Grober Free and Cued Selective Reminding Test–Immediate Recall, *HV* hippocampal volume, *TBV* total brain volume, *TICV* total intracranial volume

^a MRI volumetric data are given in cubic centimeters

^b Using Spearman correlation (*r_s*) for continuous variables and *t*-test for categorical variables

Table 2
Association between gait velocity and brain volumetric measures in all subjects

ROI in the model	Models with gait velocity as outcome	β	t	p
Total HV	Unadjusted	0.35	3.95	<0.001
	Basic adjusted ^a	0.24	2.50	0.014
	Fully adjusted ^b	0.20	1.95	0.053
Cortical GMV	Unadjusted	0.35	4.03	<0.001
	Basic adjusted	0.40	2.57	0.011
	Fully adjusted	0.36	2.34	0.021
WMV	Unadjusted	0.32	3.55	0.001
	Basic adjusted	0.21	1.60	0.112
	Fully adjusted	0.14	1.05	0.296
VV	Unadjusted	-0.02	-0.29	0.767

A p value of less than 0.05 was considered statistically significant and the corresponding results are shown in *italics*

ROI region of interest, HV hippocampal volume, GMV gray matter volume, WMV white matter volume, VV ventricular volume

^aBasic adjusted model was adjusted for age, gender (female as reference), education, and total intracranial volume

^bFully adjusted model was adjusted for the same variables in basic adjusted model, as well as memory performance

Table 3
Association between gait velocity and hemispheric hippocampal volumes

ROI in the model	Models with gait velocity as outcome	β	t	p
All participants ($N=112$)				
Left HV	Unadjusted	<i>0.24</i>	<i>2.69</i>	<i>0.008</i>
	Basic adjusted ^a	0.15	1.59	0.114
	Fully adjusted ^b	0.09	0.96	0.336
Right HV	Unadjusted	<i>0.40</i>	<i>4.58</i>	<i><0.001</i>
	Basic adjusted	<i>0.29</i>	<i>2.96</i>	<i>0.004</i>
	Fully adjusted	<i>0.25</i>	<i>2.56</i>	<i>0.012</i>
Cognitively healthy adults ($N=92$)				
Left HV	Unadjusted	<i>0.24</i>	<i>2.38</i>	<i>0.019</i>
	Basic adjusted	0.10	0.96	0.336
	Fully adjusted	0.02	0.22	0.823
Right HV	Unadjusted	<i>0.36</i>	<i>3.76</i>	<i><0.001</i>
	Basic adjusted	0.20	1.88	0.063
	Fully adjusted	0.17	1.55	0.123

A p value of less than 0.05 was considered statistically significant and the corresponding results are shown in *italics*

ROI region of interest, CHI cognitively healthy adults, HV hippocampal volume

^a Basic adjusted model was adjusted for age, gender (female as reference), education, and total intracranial volume

^b Fully adjusted model was adjusted for the same variables in basic adjusted model, as well as memory performance

Table 4
Association between gait velocity and hippocampal subfield volumes in total sample

ROI in the model (hippocampal subfield)	Models with gait velocity as outcome	β	t	p
Presubiculum	Unadjusted	<i>0.32</i>	<i>3.55</i>	<i>0.001</i>
	Basic adjusted ^a	<i>0.21</i>	<i>2.06</i>	<i>0.042</i>
	Fully adjusted ^b	0.15	1.51	0.134
Subiculum	Unadjusted	<i>0.31</i>	<i>3.52</i>	<i>0.001</i>
	Basic adjusted	0.19	1.91	0.058
	Fully adjusted	0.13	1.23	0.221
CA1	Unadjusted	<i>0.24</i>	<i>2.65</i>	<i>0.009</i>
	Basic adjusted	0.17	1.59	0.114
	Fully adjusted	0.12	1.07	0.283
CA2/CA3	Unadjusted	<i>0.27</i>	<i>3.02</i>	<i>0.003</i>
	Basic adjusted	0.16	1.60	0.111
	Fully adjusted	0.12	1.23	0.219
CA4/DG	Unadjusted	<i>0.29</i>	<i>3.18</i>	<i>0.002</i>
	Basic adjusted	0.18	1.82	0.071
	Fully adjusted	0.14	1.43	0.154

A p value of less than 0.05 was considered statistically significant and the corresponding results are shown in *italics*

^a Basic adjusted model was adjusted for age, gender (female as reference), education, and total intracranial volume

^b Fully adjusted model was adjusted for the same variables in basic adjusted model, as well as memory performance

Table 5
Association between gait velocity and brain volumetric measures in cognitively healthy individuals

ROI in the model	Models with gait velocity as outcome	β	t	p
Total HV	Unadjusted	0.32	3.31	0.001
	Basic adjusted ^a	0.17	1.56	0.120
	Fully adjusted ^b	0.11	1.02	0.310
Cortical GMV	Unadjusted	0.39	4.10	0.000
	Basic adjusted	0.43	2.41	0.018
	Fully adjusted	0.42	2.36	0.020
WMV	Unadjusted	0.34	3.45	0.001
	Basic adjusted	0.20	1.32	0.187
	Fully adjusted	0.16	1.04	0.300
VV	Unadjusted	0.01	0.01	0.988

A p value of less than 0.05 was considered statistically significant and the corresponding results are shown in *italics*

ROI region of interest, HV hippocampal volume, GMV gray matter volume, WMV white matter volume, VV ventricular volume

^aBasic adjusted model was adjusted for age, gender (female as reference), education, and total intracranial volume

^bFully adjusted model was adjusted for the same variables in basic adjusted model, as well as memory performance