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Cerebral Amyloid Deposition is Associated with Gait Parameters in the Mayo Clinic Study of Aging

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Abstract

BACKGROUND/OBJECTIVES—To determine the cross-sectional association between cerebral amyloid-beta (Aβ) deposition and gait.

DESIGN—Cross-sectional.

SETTING—Population-based cohort study in Olmsted County, MN.

PARTICIPANTS—Cognitively normal individuals (n=611), aged 50-69 years, enrolled in the Mayo Clinic Study of Aging with concurrent PiB-PET imaging and gait assessment. Participants with a history of stroke, alcoholism, Parkinson's disease, subdural hematoma, traumatic brain injury, or normal pressure hydrocephalus were excluded.

MEASUREMENTS—PiB-PET SUVR was measured in prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, posterior cingulate, and motor-specific regions of interest (ROIs). Gait parameters (speed, cadence, stride length, double support time, and intra-individual stance time variability) were measured using GAITRite® instrumentation. Linear regression models were adjusted for age, sex, body mass index, education, APOE ε4 allele, Charlson comorbidity index, and depression. In secondary analyses, we additionally adjusted for neurodegeneration (hippocampal volume, FDG PET SUVR, and cortical thickness) in AD-associated regions.

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Author Contributions: Drs. Wennberg and Mielke had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in data acquisition, analysis and/or interpretation of the data and critical revision of the manuscript. Drs. Wennberg and Mielke and Mr. Hagen conducted statistical analyses. Drs. Petersen, Jack, Knopman, and Mielke were obtained funding and provided study supervision.

Conflict of Interest Disclosures: Drs Wennberg, Savica, and Hollman, and Mr Hagen report no disclosures.

RESULTS—In fully adjusted models including neuroimaging measures of neurodegeneration, higher PiB-PET SUVR across all ROIs was associated with slower gait speed ($P < .05$ except for the parietal ROI), lower cadence and longer double support time ($P \leq .05$ except for the motor ROI), and greater stance time variability ($P < .05$). In sex-stratified analyses, the association between higher PiB-PET SUVR across all ROIs and measures of gait was only present among women.

CONCLUSION—PiB-PET SUVR across ROIs, independent of general measures of AD-associated neurodegeneration, is associated with poorer performance on multiple gait parameters among cognitively normal women, aged 50-69 years. Longitudinal studies are needed to determine whether Aβ predicts gait decline in both women and men.

Keywords

amyloid-beta; gait; neuroimaging; epidemiology; cohort

INTRODUCTION

Over a third of adults aged 70 and older have clinically significant gait abnormalities,[1] which predict disability, dementia, and death.[2] Neurodegenerative disorders are often associated with disrupted mobility, suggesting a robust connection between the central nervous system (CNS) and gait.[3] However, there is a paucity of research linking subclinical neuropathology and gait.[3]

Animal models suggest that amyloid-beta (Aβ) deposition is associated with sensorimotor deficits. For example, Aβ plaques have been associated with decreased sensorimotor function in APP-PS1 mouse models.[4] Another study reported that Aβ plaques preceded motor deficits,[5] suggesting that Aβ pathology could potentially cause gait disturbances.

While the association between cerebrovascular pathologies and gait has been widely reported by others,[6, 7] few human studies have examined the association between Aβ and gait. A recent study among cognitively normal (CN) and cognitively impaired adults aged 70 and older reported that Aβ deposition was associated with slower gait speed.[8] These findings did not adjust for either neurodegeneration or cerebrovascular pathologies. However, because gait abnormalities can be influenced by other brain pathologies (e.g., neurodegeneration), and are common in older adults, it is difficult to isolate the effects of Aβ on gait. In an attempt to overcome this obstacle, we investigated the association between Aβ and multiple gait parameters in a younger cohort of CN individuals aged 50-69 year olds. Further, to better understand the distinct contribution of Aβ on gait, we adjusted for Alzheimer's disease (AD)-associated neurodegeneration. Lastly, because women have a trend for greater PiB-PET SUVR,[9] we also determined whether there were sex differences in the associations between Aβ and gait.

METHODS

The Mayo Clinic Study on Aging (MCSA) is a prospective population-based cohort study designed to assess the incidence and prevalence of mild cognitive impairment (MCI) in

Olmsted County, MN. In 2004, Olmsted County residents between the ages of 70 and 89 were identified using the medical records-linkage system of the Rochester Epidemiology Project (REP); an age- and sex-stratified random sampling design was used to ensure that men and women were equally represented in each 5-year age strata.[10, 11] In 2012, participant recruitment was extended to include those aged 50 years and older. Participants completed an in-clinic visit that included a physician examination, an interview by a study coordinator, and neuropsychological testing. The present study included 611 CN participants, aged 50-69 years, with complete concurrent neuroimaging and gait measures. Participants with a history of stroke, alcoholism, Parkinson's disease (PD), subdural hematoma (SDH), traumatic brain injury (TBI), or normal pressure hydrocephalus (NPH) were excluded from the analysis.

The study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. All participants provided written informed consent.

Gait Assessment

GAITRite® instrumentation (CIR systems Inc., Havertown, PA) was used to assess gait parameters.[12] GAITRite® is an electronic walkway 5.6 m in length and 0.9 m wide. Participants were instructed to walk at their normal pace without gait aids on the walkway, initiating and terminating their walk 1 m before and after the walkway. In the present study, we focused on examining spatio-temporal, spatial, and temporal gait parameters, including participant gait speed (m/s); cadence (steps per minute); stride length, defined as the distance (cm) between successive heel contact points on the same foot; double support time, defined as the amount of time (sec) that both feet are on the walkway; and intra-individual variation in stance time (coefficient of variation (CoV)). Stride length and double support time were measured on each side (i.e., left and right) for each step. We created a single average value across both sides and all steps. Nurse-timed gait speed (m/s) was also assessed. The time taken to walk 25 feet (7.62 m) at a self-selected pace was recorded from the first footfall at the starting point to the last footfall at the finish line. The use of a cane or walker was allowed if this was normally used.

Imaging

Aβ positron emission tomography (PET) images were performed using C11 Pittsburgh Compound B (PiB),[13] and were obtained 40 to 60 minutes after injection. The present study used standardized uptake value ratios (SUVR) from the usual MCSA AD-associated regions of interest (ROIs): prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate. We also included a motor-specific ROI, which consisted of the precentral gyrus, postcentral gyrus, Rolandic operculum, and supplementary motor area. All ROIs were normalized to uptake in cerebellar grey matter.[14, 15]

Participants completed magnetic resonance imaging (MRI) and PET scans on the same day; CT was obtained for attenuation correction. Fludeoxyglucose (FDG)-PET SUVR was formed from the angular gyrus, posterior cingulate, inferior temporal ROIs normalized to the pons and vermis;[16] images were obtained 30-40 minutes after injection. The PiB-PET images were partially volume corrected, while the FDG PET images were not partially volume correct, as evidence has shown that these methods improve diagnostic

performance.[17-19] All MRI scans were completed on one of three 3T machines, and cortical surface was parcellated using FreeSurfer version 5.3.0 (https://surfer.nmr.mgh.harvard.edu/). Hippocampal volume (HVa) was adjusted for total intracranial volume, using our in-house fully automated imaging processing pipeline.[20] An AD-signature cortical thickness measure was formed from the entorhinal, inferior temporal, middle temporal, and fusiform ROIs.[21, 22]

Covariates

Participant demographics including age, sex, and education were ascertained at the in-clinic examination. Body mass index (BMI) was calculated using participant height (cm) and weight (kg), which were also measured in-clinic. Participants also completed the Beck Depression Inventory (BDI); a score of ≥13 was used as the cut-point for depression.[23] Apolipoprotein E (APOE) genotype was obtained from DNA collected at a blood draw. Medical conditions and the Charlson comorbidity index[24] were determined for each participant by medical record abstraction using the medical records-linkage system of the REP.[10, 25]

Participants also completed cognitive testing. The neuropsychological battery was administered by a psychometrist and included nine tests covering four domains: 1) **memory** (Auditory Verbal Learning Test Delayed Recall Trial;[26] Wechsler Memory Scale-Revised Logical Memory II & Visual Reproduction II);[27] 2) **language** (Boston Naming Test[28] and Category Fluency;[29] 3) **executive function** (Trail Making Test B[30] and WAIS-R Digit Symbol subtest;[31] and 4) **visuospatial skills** (WAIS-R Picture Completion and Block Design subtests).[31]

For each participant, determination of cognitive status (i.e., CN, MCI, or dementia) was based on consensus agreement between the study coordinator, examining physician, and neuropsychologist who evaluated the participant, taking into account education, prior occupation, visual or hearing deficits, and reviewing all other participant clinical information.[11] Cognitive test performance in the four domains (memory, executive function, language, and visual-spatial) was compared with the age-adjusted scores of CN individuals previously obtained using Mayo's Older American Normative Studies.[32] This approach relies on prior normative work and extensive experience with the measurement of cognitive abilities in an independent sample of subjects from the same population. Participants with scores ≥1.5 SD below the age-specific mean in the general population were considered for a diagnosis of possible MCI. Individuals who performed in the normal range and did not meet criteria for MCI or dementia, which was diagnosed using DSM-IV criteria,[33] were deemed CN.

Statistical Analyses

We used Wilcoxon-Mann-Whitney tests and chi-square analyses to compare participant characteristics by sex. We created z-scores for all of the gait parameters, except stance time variability, so that the coefficients were comparable. Stance time variability was log-transformed to create a more normal distribution. Linear regression analyses were used to determine the cross-sectional association between PiB-PET SUVR, as a continuous variable,

and gait parameters. All models were adjusted for age, sex, BMI, education, APOE ε4 allele, Charlson comorbidity index, and depression. In additional analyses, we also adjusted for AD-associated neurodegeneration (HVa, FDG PET SUVR, and cortical thickness) in order to better isolate the effects of Aβ on gait. Finally, we examined the interaction between sex and Aβ and APOE ε4 allele and Aβ. The interactions terms for sex were significant at the $P < .10$ level, so we subsequently stratified the analyses by sex. Interaction terms between APOE ε4 allele and Aβ were not significant. All analyses were completed using Stata version 12.0 (Stata Corp, College Station, TX).

RESULTS

The participant characteristics, by sex, are presented in Table 1. Men had completed more years of education than women. Men were more frequently hypertensive, but there were no other sex differences in medical conditions or number of comorbidities. Considering measures of neurodegeneration, men had lower median FDG PET SUVR and HVa. Men performed better than women in the visual-spatial domain. However, women performed better in all other cognitive domains (memory, language, attention, and global). Among the gait parameters, men had faster gait speed and longer stride length, whereas women had higher cadence and greater intra-individual stance time variability. In analyses that compared gait speed measured by GAITRite® instrumentation to that measured by a nurse using a stopwatch, we found that these two measurements were highly correlated for the whole sample (spearman rho=0.69, $p<0.001$), men (spearman rho=0.67, $p<0.001$), and women (spearman rho=0.70, $p<0.001$).

In multivariable adjusted linear regression models, higher PiB-PET SUVR in the orbitofrontal and temporal ROIs were associated with significantly slower gait speed (Table 2). Higher PiB-PET SUVR in all ROIs was associated with lower cadence. Greater PiB-PET SUVR in all ROIs except the parietal ROI was associated with greater stance time variability. Lastly, greater PiB-PET SUVR in all ROIs, except the motor ROI, was also associated with longer double support time. PiB-PET SUVR was not associated with stride length. Next, we repeated the analyses additionally adjusting for AD-associated neurodegeneration, as measured by cerebral glucose uptake, HVa, and cortical thickness (Table 3). After adjusting for these covariates, the results remained and many of the associations between PiB-PET SUVR and gait were stronger. For example, greater PiB-PET SUVR in all ROIs, except the parietal ROI, was now associated with slower gait speed. Higher PiB-PET SUVR in all ROIs was still associated with lower cadence and longer double support time, except in the motor ROI. Greater PiB-PET SUVR in the temporal lobe was associated with shorter stride length. Finally, PiB-PET SUVR in all regions was associated with greater stance time variability. Comparing the ROIs, the strongest associations were observed between PiB-PET SUVR in the temporal lobe and poorer performance across all measures of gait. Comparing gait parameters, we found gait speed, cadence, and double support time were most strongly influenced by Aβ burden.

In subsequent analyses, we found significant interactions between sex and PiB-PET SUVR in predicting gait measures. Therefore, we stratified the above analyses by sex and repeated the analyses, including adjustment for AD-associated neurodegeneration. Among men, we

did not find significant associations between PiB-PET SUVR in any ROI and any gait measure (Table 4). Among women, higher PiB-PET SUVR in all ROIs was significantly associated with reduced gait speed and cadence, longer double support time, and greater stance time variability (Table 5). The strongest associations were again found between PiB-PET SUVR in the temporal lobe and all gait parameters, with cadence as the most strongly affected parameter.

Finally, in sensitivity analyses we examined whether additionally adjusting for diabetes or hypertension affected the association between PiB-PET SUVR and gait. Adjusting for these comorbidities did not attenuate the association in the whole group or in sex-stratified analyses. We also examined whether there was an interaction between PiB-PET SUVR and the APOE ε4 allele, but did not find evidence for an interaction that affected the association between PiB-PET SUVR and gait.

DISCUSSION

In this study we examined the cross-sectional association between PiB-PET SUVR in AD-associated ROIs and a motor ROI and gait parameters in 611 CN MCSA participants aged 50 to 69 years. We found that greater PiB-PET SUVR across multiple ROIs was significantly associated with slower gait speed, lower cadence, longer double support time, and greater stance time variability. PiB-PET SUVR in the temporal lobe was the region most strongly associated with all gait parameters. Importantly, these results remained, and became stronger, after adjusting for AD-associated neurodegeneration. This finding suggests that Aβ pathology may be associated with gait, independent of general measures of AD-associated neurodegeneration. In analyses stratified by sex, we found robust associations between PiB-PET SUVR and gait in women, but did not observe any associations among men.

Our results are supported by evidence from studies in both animal models and humans. In APP-PS1 mouse models, Aβ plaques are associated with sensorimotor function,[4, 5] and have even been found to precede sensorimotor decline.[5] However, studies in another murine model did not replicate this finding.[34] Notably, few studies have translated these findings to human studies. One autopsy study reported that AD pathology was associated with declining gait speed over an average follow-up time of 6.4 years prior to death. AD pathology was defined as Aβ plaques and neurofibrillary tangles so the effect of Aβ on gait could not be isolated.[35] A second study recently found that greater Aβ deposition in multiple ROIs was associated with slower gait speed among both CN and cognitively impaired individuals aged 70 and older.[8] Their association was particularly strong in the putamen, suggesting that Aβ in these regions disrupts motor circuitry thereby impacting gait. However, this study did not control for either cerebrovascular pathology or other markers of neurodegeneration (e.g., glucose uptake, hippocampal atrophy, cortical thickness). Because other types of brain pathologies that impact gait, including neurodegeneration, are common in older adults, it is difficult to isolate the impact of Aβ from other brain pathologies on gait from these earlier findings.

Our findings in a younger cohort, ages 50-69, replicate and extend these findings. We found that higher PiB-PET SUVR across both AD-associated and motor ROIs was not only

associated with slower gait speed, but was also associated with worse performance across other gait parameters including lower cadence, longer double support time, and greater stance time variability. Importantly, after adjusting for AD-related neurodegeneration, the association between Aβ and gait was stronger. These results further suggest that higher brain Aβ levels could directly impact gait.

We observed the strongest association between PiB-PET SUVR in the temporal lobe and gait. Similarly, studies have shown ventricular enlargement in the temporal horn is associated with worse gait parameters, including stride time variability and gait speed.[36, 37] Thus, it is not unexpected that Aβ in the temporal regions might be most associated with gait parameters.

In the present study, the associations between Aβ and gait were only found among women. Women tend to have thinner cortices than men, and greater cortical thinning is associated with poorer performance on measures of gait.[38] Additionally, studies have shown ventricular enlargement in the temporal horn is associated with worse performance on gait parameters, including stride time variability and gait speed.[36, 37] Notable, across the lifespan women experience faster perikaryon volumetic decline in the temporal lobe than men.[39] It also appears that women are more susceptible to the effects of neuropathology than men.[40] Together, this may explain why we observed this association in women but not men. We also found that women perform significantly better on cognitive tests in all domains, except visual-spatial. Given that past studies have shown that poorer cognitive test performance is associated with poorer performance on gait parameters,[41] the fact that women have better cognitive test performance gives further credence to our finding that greater PiB-PET SUVR is associated with poorer gait. Longitudinal research is warranted to determine whether this sex difference persists when examining Aβ as a predictor of declines in gait.

Gait control involves complex brain functioning, and requires the coordination and integration of motor, perceptual, and cognitive processes. Changes in spatio-temporal and temporal parameters have been linked with changes in the CNS. Conversely, changes in spatial measures are more closely associated with musculoskeletal decline.[42] In this study, we found associations between PiB-PET SUVR and spatio-temporal (cadence), temporal (double support time), and intra-individual variance (stance time SD) measures of gait, but not spatial (stride length) measures. Therefore, our results are congruent with, and more strongly related to CNS (i.e., PiB-PET SUVR), but not musculoskeletal, control.

It is possible that other mechanisms may also be responsible for the observed association between Aβ and gait. PiB-PET SUVR and mobility decline may be co-occurring events due to a shared systemic aging process (e.g., inflammation, senescence).[43] It is also possible that other pathologies not measured in the present study are responsible for the observed association. We adjusted for AD-associated neurodegeneration. However, more subtle neurodegeneration or neurodegeneration in other brain regions could still affect the observed association between Aβ and gait.[44] Additionally, vascular pathologies, TAR DNA-binding protein 43 (TDP43), and/or tauopathies may also affect gait but could not be measured.

This study has several strengths, including the well characterized population-based sample, use of multiple gait parameters objectively measured with GAITRite®, and extensive imaging of several indices (i.e., HVa, glucose uptake, cortical thickness, and PiB-PET SUVR). Despite these strengths, the study also had limitations. First, as previously mentioned, we were unable to account for additional pathologies that might affect gait parameters including vascular pathologies, tauopathies, or TDP43 deposition. However, animal studies have shown that Aβ affects neuronal function independently of tau,[45] and we were able to adjust for AD-associated neurodegeneration, as measured by MRI and FDG PET. Second, multiple gait parameters are strongly associated with lean body mass;[46] however, because lean body mass is not available in the MCSA, we were unable to control for this potential confounder. Instead, we included BMI as a covariate in our regression models to account for the confounding effect of body composition. Third, Olmsted County residents are primarily of Northern European descent, so our findings may not be directly generalizable to all populations. Finally, this study is cross-sectional, so directionality cannot be inferred. As more data become available in this cohort, we will investigate the longitudinal association between PiB-PET SUVR and gait.

Our findings suggest that Aβ deposition, measured by PiB-PET SUVR, may affect gait independent of general measures of AD-associated neurodegeneration and medical conditions associated with disrupted mobility (i.e., dementia, MCI, stroke, alcoholism, PD, SDH, TBI, or NPH). Gait has long been considered a predictor of declining physical function; recent evidence also supports its efficacy for capturing changes in the CNS.[3] Because gait predicts cognitive decline, dementia, disability, and death [2, 41] and is reflective of neuropathologies, it may be a useful clinical tool to help identify those at risk for cognitive decline and dementia.[47]

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Table 1

Participant Characteristics, Median (IQR) or N (%)

	All Participants (N=611)	Men (N=310)	Women (N=301)	*P*
Age	62.7 (57.3, 66.5)	63.1 (58.1, 66.7)	62.4 (57.0, 66.0)	.26
Years of Education	16 (13, 17)	16 (14, 17)	15 (13, 16)	**.007**
Body mass index (kg/m^2)	28.8 (26.0, 32.4)	29.1 (26.8, 32.0)	28.2 (24.9, 33.1)	.08
APOE ε4	179 (29)	87 (28)	92 (31)	.50
Charlson comorbidity index	3 (2, 5)	3 (2, 5)	3 (2, 5)	.98
Diabetes	51 (8)	31 (10)	20 (6)	.13
Hypertension	198 (32)	112 (36)	86 (29)	**.046**
Depression, N (%)	41 (7)	19 (6)	22 (7)	.56
PiB-PET SUVR average	1.30 (1.25, 1.36)	1.29 (1.25, 1.34)	1.31 (1.25, 1.37)	.10
PiB-PET SUVR ≥1.4	92 (15)	39 (13)	53 (18)	.08
FDG PET SUVR	1.54 (1.44, 1.63)	1.52 (1.44, 1.61)	1.55 (1.47, 1.64)	**.004**
HVa (cm^3)	-0.32 (-0.87, 0.09)	-0.47 (-1.02, 0.04)	-0.21 (-0.69, 0.22)	**<.001**
Cortical thickness (mm)	2.96 (2.87, 3.05)	2.96 (2.86, 3.03)	2.97 (2.88, 3.05)	.18
Memory, z-scored	1.38 (0.80, 1.94)	1.19 (0.48, 1.68)	1.60 (0.96, 2.12)	**<.001**
Language, z-scored	1.04 (0.55, 1.51)	0.95 (0.45, 1.43)	1.12 (0.72, 1.63)	**<.001**
Attention, z-scored	1.33 (0.83, 1.80)	1.16 (0.72, 1.61)	1.51 (1.05, 1.96)	**<.001**
Visual-spatial, z-scored	1.15 (0.54, 1.65)	1.26 (0.70, 1.79)	0.96 (0.38, 1.46)	**<.001**
Global, z-scored	1.50 (1.02, 1.97)	1.36 (0.93, 1.88)	1.65 (1.11, 2.06)	**<.001**
Gait speed (m/s)	1.22 (1.10, 1.32)	1.24 (1.13, 1.34)	1.18 (1.07, 1.31)	**<.001**
Cadence (steps/min)	108.7 (101.7, 113.9)	105.8 (99.6, 110.4)	112.3 (106.3, 117.9)	**<.001**
Stride length (cm)	135.3 (123.3, 145.8)	142.6 (132.6, 150.5)	128.0 (117.3, 136.6)	**<.001**
Log Stance time CoV	1.23 (0.90, 1.51)	1.21 (0.87, 1.46)	1.27 (0.94, 1.55)	**.007**

IQR = interquartile range; APOE = Apolipoprotein E; HVa = hippocampal volume; CoV = coefficient of variation; ROIs = regions of interest. Depression was determined by a score of ≥13 on the Beck Depression Inventory. FDG PET SUVR was formed from the angular gyrus, posterior cingulate, and inferior temporal ROIs. HVa was adjusted for total intracranial volume. Cortical thickness was formed from the entorhinal, inferior temporal, middle temporal, and fusiform ROIs. Bolded text represents significant p-values at the 0.05 level.

Table 2

Cross-sectional Association Between PiB-PET SUVR and Gait Parameters

PiB-PET ROIs	Gait Speed (N=611) B (95% CI)	Cadence (N=611) B (95% CI)	Stride Length (N=611) B (95% CI)	Double Support Time (N=611) B (95% CI)	Stance Time CoV (N=610) B (95% CI)
Prefrontal	-0.38 (-0.80, 0.04)	-0.82 (-1.26, -0.39)**	0.07 (-0.30, 0.44)	0.59 (0.17, 1.00)**	0.12 (0.02, 0.24)*
Orbitofrontal	-0.41 (-0.81, -0.02)*	-0.79 (-1.20, -0.38)**	0.01 (-0.34, 0.36)	0.58 (0.19, 0.97)**	0.25 (0.04, 0.47)*
Parietal	-0.34 (-0.77, 0.08)	-0.77 (-1.22, -0.32)**	0.08 (-0.31, 0.46)	0.54 (0.11, 0.96)*	0.11 (-0.004, 0.22)
Temporal	-1.41 (-2.49, -0.34)**	-1.90 (-3.03, -0.77)**	-0.54 (-1.50, 0.43)	1.60 (0.53, 2.67)**	0.35 (0.07, 0.64)*
Anterior cingulate	-0.39 (-0.82, 0.04)	-0.82 (-1.27, -0.38)**	0.05 (-0.34, 0.43)	0.61 (0.19, 1.04)**	0.29 (0.07, 0.52)*
Posterior cingulate/precuneus	-0.36 (-0.76, 0.04)	-0.74 (-1.16, -0.33)**	0.03 (-0.32, 0.39)	0.55 (0.15, 0.94)**	0.25 (0.04, 0.46)*
Motor ROI	-0.43 (-1.09, 0.24)	-1.01 (-1.71, -0.32)**	0.14 (-0.46, 0.73)	0.65 (-0.01, 1.31)	0.05 (0.009, 0.10)*

Models adjusted for age, sex, BMI education, APOE ε4, Charlson comorbidity index, and depression

*$P < .05$.

**$P \leq .01$.

CoV = coefficient of variation; ROIs = regions of interest.

Table 3

Cross-sectional Association Between PiB-PET SUVR and Gait Parameters after adjusting for Alzheimer's disease-associated neurodegeneration

PiB-PET ROIs	Gait Speed (N=581) B (95% CI)	Cadence (N=581) B (95% CI)	Stride Length (N=581) B (95% CI)	Double Support Time (N=581) B (95% CI)	Stance Time CoV (N=580) B (95% CI)
Prefrontal	-0.24 (-0.45, -0.03) *	-0.26 (-0.49, -0.03) *	-0.14 (-0.35, 0.06)	0.26 (0.05, 0.47) *	0.13 (0.02, 0.24) *
Orbitofrontal	-0.45 (-0.84, -0.05) *	-0.58 (-1.01, -0.14) **	-0.20 (-0.59, 0.19)	0.52 (0.12, 0.92) **	0.27 (0.05, 0.48) *
Parietal	-0.19 (-0.41, 0.02)	-0.27 (-0.51, -0.03) *	-0.08 (-0.29, 0.13)	0.24 (0.02, 0.45) *	0.12 (0.005, 0.23) *
Temporal	-0.80 (-1.34, -0.26) **	-0.63 (-1.23, -0.03) *	-0.65 (-1.18, -0.12) *	0.73 (0.19, 1.28) **	0.12 (0.10, 0.67) **
Anterior cingulate	-0.50 (-0.93, -0.08) *	-0.51 (-0.98, -0.03) *	-0.35 (-0.76, 0.07)	0.54 (0.12, 0.97) *	0.31 (0.08, 0.53) **
Posterior cingulate/precuneus	-0.44 (-0.84, -0.04) *	-0.45 (-0.89, -0.003) *	-0.30 (-0.69, 0.09)	0.47 (0.07, 0.87) *	0.26 (0.05, 0.47) *
Motor ROI	-0.09 (-0.17, -0.002) *	-0.06 (-0.15, 0.03)	-0.08 (-0.16, 0.01)	0.07 (-0.01, 0.15)	0.05 (0.005, 0.09) *

Models adjusted for age, sex, BMI education, APOE ε4, Charlson comorbidity index, depression and AD-signature neurodegeneration (FDG PET SUVR, HVa, and cortical thickness).

* $P < .05$.

** $P \leq .01$.

CoV = coefficient of variation; ROIs = regions of interest.

Table 4

Cross-sectional Association Between PiB-PET SUVR and Gait Parameters in Men After Adjusting for AD-associated Neurodegeneration

	Men				
	Gait Speed (N=296)	**Men Cadence (N=296)**	**Stride Length (N=296)**	**Double Support Time (N=296)**	**Stance Time CoV (N=296)**
PiB-PET ROIs	**B (95% CI)**	**B (95% CI)**	**B (95% CI)**	**B (95% CI)**	**B (95% CI)**
Prefrontal	0.04 (-0.23, 0.37)	-0.22 (-0.53, 0.09)	0.23 (-0.09, 0.55)	0.03 (-0.24, 0.29)	-0.06 (-0.24, 0.11)
Orbitofrontal	-0.05 (-0.66, 0.57)	-0.41 (-0.98, 0.16)	0.28 (-0.31, 0.87)	0.07 (-0.42, 0.56)	-0.07 (-0.39, 0.26)
Parietal	0.08 (-0.26, 0.41)	-0.18 (-0.49, 0.13)	0.25 (-0.07, 0.57)	-0.06 (-0.33, 0.20)	-0.08 (-0.26, 0.10)
Temporal	-0.32 (-1.08, 0.45)	-0.43 (-1.13, 0.28)	-0.07 (-0.81, 0.67)	0.27 (-0.34, 0.88)	0.02 (-0.39, 0.42)
Anterior cingulate	0.15 (-0.51, 0.81)	-0.31 (-0.92, 0.30)	0.46 (-0.17, 1.09)	-0.08 (-0.60, 0.45)	-0.05 (-0.40, 0.30)
Posterior cingulate/precuneus	0.14 (-0.49, 0.77)	-0.35 (-0.93, 0.23)	0.48 (-0.13, 1.08)	-0.12 (-0.63, 0.38)	-0.15 (-0.48, 0.18)
Motor ROI	0.03 (-0.10, 0.15)	-0.05 (-0.16, 0.07)	0.08 (-0.04, 0.20)	-0.03 (-0.12, 0.07)	-0.009 (-0.08, 0.06)

Models adjusted for age, sex, BMI education, APOE ε4, Charlson comorbidity index, depression, and AD-signature neurodegeneration (FDG PET SUVR, HVa, and cortical thickness).

*$P < .05$.

**$P \leq 01$.

AD = Alzheimer's disease; ROIs = regions of interest; CoV = coefficient of variation

Table 5

Cross-sectional Association Between PiB-PET SUVR and Gait Parameters in Women After Adjusting for AD-associated Neurodegeneration

PiB-PET ROIs	Gait Speed (N=285) B (95% CI)	Cadence (N=285) B (95% CI)	Stride Length (N=285) B (95% CI)	Double Support Time (N=285) B (95% CI)	Stance Time CoV (N=284) B (95% CI)
Prefrontal	-0.34 (-0.61, -0.07)*	-0.52 (-0.84, -0.21)**	-0.11 (-0.33, 0.12)	0.47 (0.14, 0.79)**	0.19 (0.05, 0.34)**
Orbitofrontal	-0.64 (-1.17, -0.11)*	-0.96 (-1.57, -0.35)**	-0.22 (-0.65, 0.21)	0.89 (0.27, 1.5)**	0.40 (0.12, 0.69)**
Parietal	-0.33 (-0.61, -0.04)*	-0.50 (-0.83, -0.17)**	-0.11 (-0.34, 0.13)	0.47 (0.14, 0.81)**	0.21 (0.06, 0.36)**
Temporal	-1.06 (-1.83, -0.28)**	-1.45 (-2.34, -0.55)**	-0.45 (-1.08, 0.17)	1.33 (0.42, 2.23)**	0.59 (0.17, 1.01)**
Anterior cingulate	-0.77 (-1.35, -0.19)**	-1.16 (-1.82, -0.49)**	-0.28 (-0.75, 0.19)	1.08 (0.41, 1.75)**	0.43 (0.12, 0.75)**
Posterior cingulate/precuneus	-0.65 (-1.19, -0.12)*	-0.96 (-1.57, -0.35)**	-0.25 (-0.68, 0.18)	0.95 (0.33, 1.57)**	0.42 (0.14, 0.71)**
Motor ROI	-0.13 (-0.25, -0.02)*	-0.20 (-0.34, -0.07)**	-0.05 (-0.14, 0.05)	0.18 (0.05, 0.32)**	0.07 (0.008, 0.13)*

Models adjusted for age, sex, BMI education, APOE ε4, Charlson comorbidity index, depression, and AD-signature neurodegeneration (FDG PET SUVR, HVa, and cortical thickness).

*$P < .05$.

**$P \leq 01$.

AD = Alzheimer's disease; ROIs = regions of interest; CoV = coefficient of variation