THE ROLE OF CENTRAL NERVOUS SYSTEM IN COMPLEX WALKING AMONG OLDER ADULTS

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ABSTRACT

Gait is a complex process which requires dynamic interactions between musculoskeletal, cardiopulmonary, and nervous systems. Previous studies identified brain regions correlated with simple walking, suggesting importance of central nervous system (CNS) in maintaining walking performance. Most of the previous evidence focused on speed and length of gait, and finding of brain regions with gait characteristics from other important domains was limited. Compared to simple walking, community walking is accompanied with greater environment challenges, and likely involves additional neural inputs of the brain. Thus, studying usual walking speed may not reveal the whole picture of neural correlates of community walking in daily life.

This dissertation aims to identify brain regions related to performance of different walking tasks to provide evidence of the role of brain in community walking in older adults.

In the first and second paper, I included over 200 participants from the Health, Aging, and Body Composition study in which gray matter volume and gray matter density were measured using magnetic resonance imaging. In the third paper, I included 117 participants from three independent samples with prefrontal cortex (PFC) activation measured using functional near infrared spectroscopy. Frontal, anterior cingulate, superior parietal, cerebellar, and subregions from basal ganglia related to executive and motor function are associated with aspects of walking performance, including spacing and timing control. Middle and superior frontal gyrus, postcentral gyrus, and superior temporal gyrus, related to executive function,

somatosensory, and vestibular function, respectively, are involved during fast paced walking but not simple walking. I observed increased PFC activation during dual-task walking compared to simple walking, and heterogeneous PFC activation patterns that differ in walking performance. Brain is important for spacing and timing control during walking, and is increasingly engaged as the challenges of community walking increase, shown by the results of structural and functional correlates of complex walking compared with simple walking.

The public health significance of this work includes evidence for 1) identifying early subclinical brain impairment using walking performance; 2) interventions to improve the performance of community walking; and 3) goal-oriented exercise and training that restores efficiency in PFC control to improve community walking.

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1.0 Introduction

About two-thirds of people over 70 suffer from gait impairment. This prevalence increases with age.[1] Gait impairment impacts independent living in older adults. This greatly reduces the quality of late life, and shortens life expectancy.[1] Gait performance is also related to risk of falling, which is a major cause of mobility decline in older adults.[2]

Gait is a complex process which involves speed and direction control, spatial orientation, attention, information processing, executive function, and memory.[3,4] To achieve successful gait performance, dynamic interactions are required between musculoskeletal, cardiopulmonary, and nervous systems.[5] The central nervous system (CNS) is important for maintenance of stable walking among older adults. Automatic control of movement is responsible for controlling postural muscle tone and locomotor movements, which involves cerebral motor cortex, limbic system, basal ganglia, and brainstem tegmentum.[6] Purposeful locomotion requires integration of sensory information, planning and execution, which involves frontal cortex, parietal cortex, basal ganglia, and cerebellum.[4,7] In previous reviews, gray matter volumes in the cerebellum, basal ganglia, frontal, and hippocampal regions were associated with gait.[4,7]

To capture the multidimensional feature of gait, a framework of gait domains has been developed and validated.[8-10] Independent gait domains comprised of quantitative gait measures include pace, rhythm, and variability.[8] Gait domains reflect the subtle and selective gait alterations, predict adverse health conditions and outcomes, and reflect different underlying cognitive pathologies.[10,11] Previous studies observed associations of multiple quantitative gait measures with fall risk and life-space assessment score, indicating that gait domains are also closely related to community walking ability.[12,13] From a previous review, changes in brain

structures during aging, including gray matter atrophy and loss of gray matter integrity, were related to poor performance in gait pace, rhythm, and variability.[7] A large number of studies have established the associations of brain structural measures with gait characteristics in older ages, with the focus on gait speed or step length only.[7] Regional findings of gait characteristics from domains other than pace was limited.[7]

Compared to simple walking studied in the lab, community walking is often accompanied with greater environmental challenges, and likely involves more networks of the brain.[14,15] Complex walking tasks, such as fast walking and dual-task walking, are often used to mimic community walking in the lab, as they challenge walking capacity and require additional neural inputs compared to simple walking.[3,16] Compared to simple walking, complex walking likely reflects more subtle changes of brain and better reveal the neural correlates of community walking in older adults.

Prefrontal cortex is a key area of information processing and executive functions needed during community walking, such as the integration of sensory-motor cycle of interactions that links individual with environment, and planning of locomotion and goal attainment. [16-20] Prefrontal cortex is also one of the regions most susceptible to age-related atrophy.[21] Previous evidence suggests older adults experience changes in prefrontal cortex activation during complex walking compared with younger adults. [22,23] When studying older adults alone, mixed results of prefrontal cortex activation with walking performance and functional status have been observed, and may indicate heterogeneity in underlying PFC activation patterns.[18]

In order to further our understanding of neural control of community walking, this dissertation project aims to 1) identify regional brain structures represented by gray matter volume that are related to each independent gait domain; 2) assess structural and functional

neural correlates of complex walking, such as fast-paced walking and dual task walking; and 3) assess the association between prefrontal cortex activation and complex walking performance with and without accounting for heterogeneity in PFC activation patterns in an older population. Our results address the gaps in understanding the mechanisms of CNS control during community walking in older adults, and could provide evidence to improve mobility in older adults by targeting cognitive function and PFC control to improve higher-order coordination.

2.0 Neural correlates of gait characteristics represented by pace, rhythm, and variability domains in older adults

This paper evaluated regional gray matter volumes related to independent gait domains of simple walking, including pace, rhythm, spatial variability and temporal variability, derived from quantitative gait measures. A dimension reduction method identified regions that were important for each gait domain by selecting important regional gray matter volumes.

2.1 Introduction

The central nervous system (CNS) is critical for maintenance of stable walking among older adults.[3] Global and regional gray matter atrophy has been shown to be related to slower gait speed.[7]

A framework of the central control of gait has been developed and validated in previous literature.[8-10] Based on this previous work, three major independent gait domains comprised of quantitative gait measures including pace, rhythm, and variability were identified, and accounted for the majority of variance in gait.[8] Previous evidence suggests that the three gait domains are discrete and are associated with selected cognitive and motor characteristics.[10] Pace, representing velocity and length of gait, were related to attention and executive function.[5] Pace was also related to risk of non-amnestic mild cognitive impairment and vascular dementia.[8,10,11,24] Poor rhythm, representing time control of gait, was associated with memory decline.[8] Conclusions of

cognitive function with gait variability, representing fluctuations of steps, are relatively scarce and inconsistent from current literature.

While a large number of studies have established the associations of brain structural measures with gait characteristics in older ages, much of the research has focused on gait speed or step length only. Compared to the evidence on pace domain, the understanding of brain regions that regulate gait rhythm and variability, is limited. Because selected gait domains may reflect underlying cognitive characteristics, the assessment of neural correlates helps to explain underlying mechanisms of gait with cognitive characteristics. If the model of gait with cognition is proven robust through the underlying neural correlates assessment, it could provide evidence for future studies to identify gait characteristics in cognitive aging, and to assess the effect of cognitive interventions.[10]

In this study, we used composite scores combined of multiple gait metrics from each gait domain to have a comprehensive representation of gait. Previous evidence suggests that gait metrics from spatial and temporal variability are associated with different brain areas, so we evaluated the associations of regional grey matter volume (GMV) with pace, rhythm, spatial variability, and temporal variability domains.[25] In addition, we evaluated the association of GMV with gait change with age to identify their temporal relationship. We hypothesize that pace domain, which was associated with attention and executive function, would be related to GMV prefronto-parietal and subcortical networks (in particular the basal ganglia) and cerebellar (in particular the lateral part).[4,7] We hypothesize similar associations for spatial variability, because it represents fluctuations of spacing of steps. We hypothesize that rhythm domain, which was associated with memory decline from previous work would both be associated with GMV of the

hippocampus;[8] we hypothesize similar patterns for temporal variability representing fluctuations of timing of steps.

2.2 Methods

2.2.1 Study population

The Health, Aging, and Body Composition (Health ABC) is a prospective cohort study of community-dwelling older adults aged 70 years and over that began in 1997.[26] We used the data from Healthy Brain Project, an ancillary study of Health ABC. Community-dwelling black and white older adults were enrolled in the study began in 1997 in Memphis, TN, and Pittsburgh, PA. A total of 314 participants at the Pittsburgh study site who were eligible and had MRI of brain and the 20-meter walking task at year 10 participated in the ancillary study. Eligibility included absence of neurologic or psychologic diagnoses. Participants were seen annually for up to five years and quantitative gait measures at year 10, year 14, and year 15 were available. One participant who was missing date of gait measures was excluded. A total of 73 (23%) participants were missing for MRI measures, baseline walking measures, or covariates. After implementing a non-parametric missing data imputation on baseline values, we obtained an imputed dataset with 313 subjects.[27] (Appendix A-1) Last, we excluded 22 (7%) outliers defined as 3.4 times of standard deviation below or above the average of any gait domain measures before the analyses.[28] The baseline characteristics of covariates were similar before and after excluding the outliers (data not shown). Out of the 291 participants in our final study sample, 105 (36%) had only baseline gait measures; 64 (22%) had 2 repeated gait measures; 122 (42%)

had three repeated gait measures. Participants who were younger, without APOE allele 4, without stroke or hypertension, with knee pain, and had higher baseline pace scores and lower variability scores were more likely to have repeated gait measures (Appendix A-3).

2.2.2 MRI measures

GMV, white matter, and cerebrospinal fluid were calculated by segmenting the skull-stripped T1-weighted image in native anatomical space.[29] The details for MRI acquisition and image processing are provided in Rosano et al. 2012.[29] Gray matter regions selected were frequently identified in previous studies on neural correlates of walking characteristics, including regions related to: 1) sensorimotor (precentral gyrus, putamen, caudate, thalamus, supplementary motor, precuneus, postcentral gyrus, inferior parietal, globus pallidum, cerebellar); 2) executive function (anterior cingulate, prefrontal cortex, superior parietal, insula); and 3) memory (hippocampus, entorhinal cortex, parahippocampus, amygdala, posterior cingulate).[7] GMVs were computed in AAL2 atlas regions for regions of interest to represent gray matter atrophy. Participants' regional GMVs were adjusted for total intracranial volume (ICV).

2.2.3 Gait measures

Participants walked on an 8-m long computerized GaitMat II walkway at usual pace. The first 2 and last 2 meters were not instrumented to allow for acceleration and deceleration, so that gait measurements were conducted for 4 meters of steady-state walking. Quantitative gait measures were processed and computed by GaitMat II computer system. Measures were obtained at baseline of our study (Health ABC year 10 or year 11) as well as at follow-up visits

(Health ABC years 14 and 15), including: step velocity and step length from the pace domain; swing time, stance time, and step time from the rhythm domain; step length variability, stride length variability from the spatial variability domain; and step time variability, swing time variability, and stance time variability from the temporal variability domain (Appendix A-2). Step length is the distance between the first switch closure of one foot to the first switch closure of the other foot, and step time is the time corresponding to completing one step length. Stride length is the distance between the first switch closure of one foot to the first switch closure of the previous foot on the ipsilateral side. Swing time is the time when the foot is off the ground. Stance time is the time when the foot is in contact with the ground. The gait measures were described in previous literature.[30] Variabilities of gait measures were calculated as the coefficient of variation using the formula (standard deviation/mean)*100.[31] We required a minimum of 4 steps for each pass and minimum of 4 passes for calculating variability to exclude any unstable values.

We combined the quantitative gait measures into a composite z-score for each domain. These include gait velocity and step length combined into pace domain; swing time, stance time, and step time combined into rhythm domain; step length variability, and stride length variability combined into spatial variability domain; step time variability, swing time variability, and stance time variability combined into temporal variability domain.[9] Gait measures were centered by baseline mean and scaled by baseline standard deviation. The sum of the standardized measures in each domain were calculated as the composite z score. The baseline quantitative gait measures within the same domain were positively correlated with each other (range ρ: 0.42-0.96). After computing the composite z-scores of quantitative gait measures, there were no strong correlations across gait domains. (Appendix B-1)

2.2.4 Covariates

Covariates were selected if they were considered as important risk factor of gait decline or GMV change. Age, sex, race, and the presence of at least one APOE e4 allele were assessed at the beginning of the Health ABC study (1997-1998). Other clinical or health-related variables were assessed at year 10 or year 11 baseline, including body mass index (BMI) calculated from weight/(height)^2, hypertension if participants self-reported a hypertension diagnosis or antihypertension medication use, stroke if self-reported ever having a stroke, knee pain, and quadriceps strength measured using an isokinetic Kin-Com dynamometer.[32,33]

2.2.5 Statistical analysis

We used missForest {R package version 1.4} to impute the missing data at baseline.[27] We set the number of trees in each model as 100. The estimated out of bag normalized root mean squared error was 0.08 for the set of continuous variables and proportion of falsely classified was 0.13 for the set of categorical variables.

We summarized characteristics at baseline as number (percentage) in each category for categorical variables and mean (standard deviation) for continuous variables. We assessed unadjusted bivariate associations between baseline characteristics and z-scores of gait domains using two-sample t-tests for categorical variables and Spearman correlation coefficient for continuous variables. For two-sample t-tests, we reported group mean difference of composite z-scores of each domain and test p values. For Spearman correlation coefficient tests, we reported the Spearman correlation coefficient and p values using asymptotic t distribution. (Table 2-1)

We used sparse partial least squares (SPLS) {R package version 2.2-3} to select from regional GMVs that are important for gait domains prediction.[34] Instead of modeling the association of gait measures with regions of interest (ROIs) using ordinary least squares regression, we applied the SPLS to select variables based on both covariance between response and predictors and variation of predictors by solving latent decomposition of the response and predictor matrix.[35] SPLS model addresses the problem of large numbers of predictors and multicollinearity, and has consistent performance when modeling a large number of irrelevant variables.[35] To adjust for common risk factors between brain structure and repeated gait measures, we first used linear mixed models to model gait domains, including centered age as repeated measures, and sex, race, BMI, APOE alleles, hypertension, stroke, knee pain, and quadriceps strength as single measures. We tested the random effect of age on gait measures using likelihood ratio test. If the test result is significant, we kept the complex model including random effect of both intercept and age, and output their values for each subject as gait domain measures for SPLS modeling. If test result was insignificant, we reduced model with random effect of intercept only, and output intercept values of each subject for SPLS modeling. We applied a 10-fold cross validation (CV) for parameter tuning of hidden components κ and thresholding parameter $\lambda 1$. Because the CV curve was flat, we selected the smallest hidden components κ and the largest thresholding parameter when mean squared error was less than 1.1 times the minimum mean squared error to avoid local solution issues.[35] Brain measures were standardized with mean and standard deviation in all the statistical analyses. All the analyses were conducted in R.

2.3 Results

2.3.1 Baseline characteristics and gait measures

The average age of the participants at baseline was 83 (standard deviation=2.8). Among the 291 participants, 172 (59%) were female; 127 (41%) were Black. The average BMI was 27 (standard deviation=4.5). A total of 71 (24%) participants had at least one APOE e4. The number of participants with hypertension was 205 (70%), 23 (8%) had stroke, and 129 (44%) reported having knee pain. The average quadriceps strength at baseline was 81 N*m (standard deviation=29). (Table 2-1) There was an overall trend of decreasing pace with age (annual change rate=-0.37), and increasing rhythm (annual change rate=0.25), spatial variability (annual change rate=0.43), and temporal variability (annual change rate=0.48) with age. (Table 2-1, Appendix B-2)

Table 2-1. Baseline demographic and health characteristics and differences or correlations with gait domains in older adults (n=291).

Characteristics	**Overall (n=291)**	**Mean Differences or Correlations with Walking [a]**			
		Pace	**Spatial Variability**	**Rhythm**	**Temporal Variability**
Demographics					
Age, mean (SD)	83 (2.8)	-0.18 (0.002)	0.17 (0.004)	0.02 (0.68)	0.18 (0.002)
Female, n (%)	172 (59%)	-1.07 (<0.0001)	0.22 (0.26)	-0.95 (0.0006)	0.46 (0.20)
Black, n (%)	120 (41%)	-0.92 (<0.0001)	0.19 (0.26)	0.78 (0.004)	-0.12 (0.62)
BMI, mean (SD)	27 (4.5)	-0.18 (0.002)	0.03 (0.59)	0.01 (0.91)	0.01 (0.82)
APOE allele 4	71 (24%)	-0.34 (0.18)	-0.10 (0.86)	0.40 (0.19)	0.10 (0.30)
Morbidities					
Hypertension	205 (70%)	-0.84 (0.0006)	0.15 (0.58)	0.49 (0.09)	0.31 (0.29)
Stroke, n (%)	23 (8%)	-1.01 (0.03)	0.56 (0.25)	-0.13 (0.82)	0.56 (0.17)

Motor function					
Knee Pain, n (%)	129 (44%)	-0.79 (0.0004)	0.26 (0.24)	0.63 (0.02)	0.11 (0.41)
Quadriceps Strength, mean (SD)	81 (29)	0.36 (<0.0001)	-0.16 (0.01)	0.01 (0.88)	-0.15 (0.01)
Annual change in gait, mean (SD) ($m*s^{-1}*year^{-1}$)[b]					
Pace	-0.37 (0.38)	-0.11 (0.14)	-0.01 (0.94)	0.18 (0.01)	0.08 (0.30)
Spatial variability	0.43 (0.51)	-0.10 (0.15)	-0.41 (<0.0001)	0.04 (0.60)	-0.09 (0.22)
Rhythm	0.25 (0.65)	0.08 (0.27)	-0.01 (0.91)	-0.20 (0.01)	-0.02 (0.78)
Temporal variability	0.48 (0.78)	-0.05 (0.52)	-0.07 (0.37)	-0.09 (0.18)	-0.41 (<0.0001)

a. T test for categorical variables and spearman correlation for continuous variables. P values are presented in parentheses;

b. Annual changes in gait were calculated in the subgroup of participants (186, 64%) with quantitative gait measures at more than one time point.

Of the gait measures, pace was correlated with the most number of baseline characteristics. Pace was negatively correlated with age (rho=-0.18) and positively correlated with quadriceps strength (rho=0.34). Participants who were female, black, had higher BMI, had hypertension or stroke, and having knee pain were more likely to have a lower pace score at baseline. Females were more likely to have a lower rhythm score (female: -0.47 vs male: 0.48, diff=-0.95), while black participants (black: 0.37 vs white: -0.40, diff=0.78) and participants having knee pain (with knee pain: 0.27 vs without: -0.36, diff=0.63) were more likely to have a higher rhythm score at baseline. Both spatial variability and temporal variability were positively correlated with age (rho=0.15 and 0.18), and negatively correlated with quadriceps strength (rho=-0.16 and =-0.15). For rhythm, spatial variability, and temporal variability, baseline scores

were negatively correlated with annual change (rho is -0.20, -0.41, and -0.41, respectively), such that those with lower values at baseline experienced greater changes over time (Table 2-1).

2.3.2 Pace, spatial variability, rhythm, and temporal variability at average age (83 years) with GMV

After adjusting for sex, race, BMI, APOE alleles, hypertension, stroke, knee pain, and quadriceps strength, SPLS model selected right cerebellar 4-5 ($\beta = 0.12, 95\%CI: 0.04, 0.21$) and left inferior orbitofrontal ($\beta = 0.12, 95\%CI: 0.03, 0.22$) positively related to pace score at 83 years of age; left anterior cingulate cortex ($\beta = -0.12, 95\%CI: -0.22, -0.03$) and left superior parietal ($\beta = -0.13, 95\%CI: -0.24, -0.03$) negatively related to spatial variability; right putamen negatively related to rhythm ($\beta = -0.10, 95\%CI: -0.21, 0.01$) and right posterior cingulate cortex positively related to rhythm ($\beta = 0.09, 95\%CI: -0.03, 0.20$); and right cerebellar 4-5 negatively related to temporal variability ($\beta = -0.12, 95\%CI: -0.24, -0.03$) while left cerebellar 9 positively related to temporal variability ($\beta = 0.12, 95\%CI: -0.003, 0.24$) (Figure 2-1, Appendix A-4)

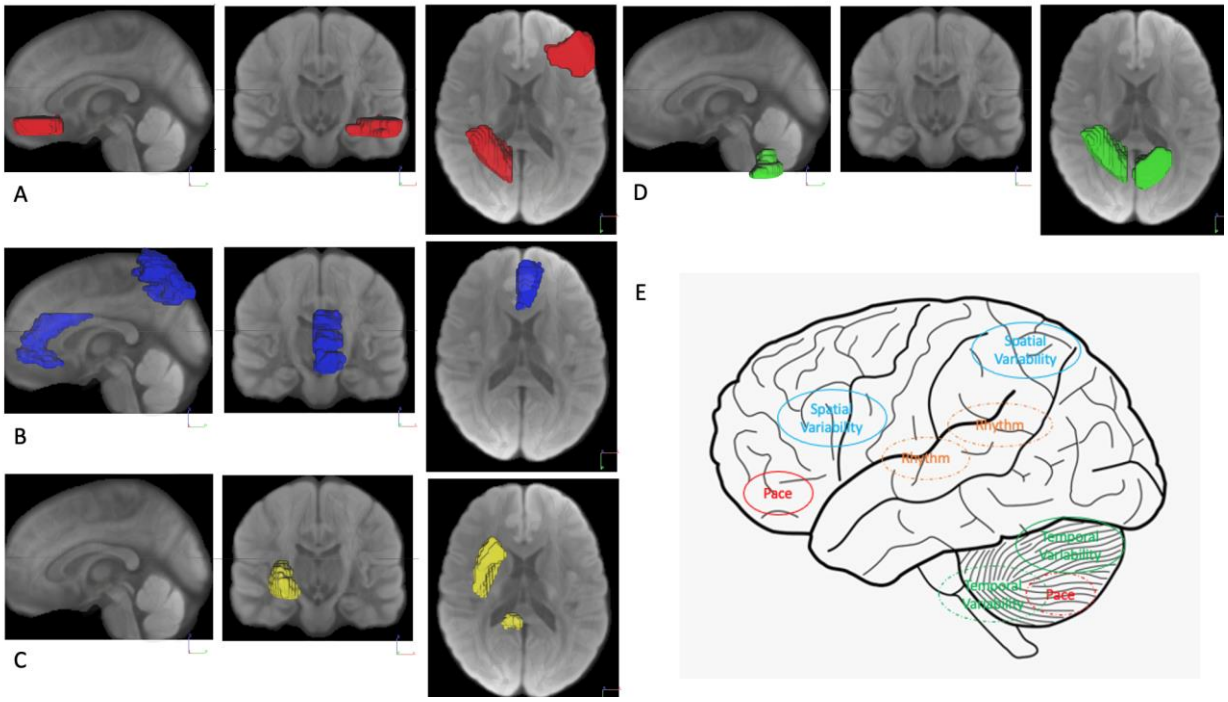

Figure 2-1. Gray matter volumes (GMVs) associated with gait domains of pace (A), spatial variability (B), rhythm (C), and temporal variability (D). Regions of interest (ROIs) are presented from sagittal, coronal, and axial view. Selected regions are shown together, with different colors for each gait domain, and solid outline indicating left regions and dashed outline indicating right regions (E).

2.3.3 Annual changes in rhythm with GMV

After adjusting for sex, race, BMI, APOE alleles, hypertension, stroke, knee pain, and quadriceps strength, SPLS model selected right putamen and right pallidum, where greater GMV is associated with smaller rhythm annual increasing ($\beta = -0.07, 95\%CI: -0.13, 0.02;\ and\ \beta = -0.07, 95\%CI:\ -0.14, 0.02, respectively$), and left superior orbitofrontal, where greater GMV is related to faster annual rhythm increasing ($\beta = 0.07, 95\%CI: 0.001, 0.18$). (Figure 2-2, Appendix A-5) We did not assess the association of GMV with change in pace, spatial

variability, and temporal variability, as the likelihood ratio test results did not show significant inter-subject variation in the effect of age on these gait domains.

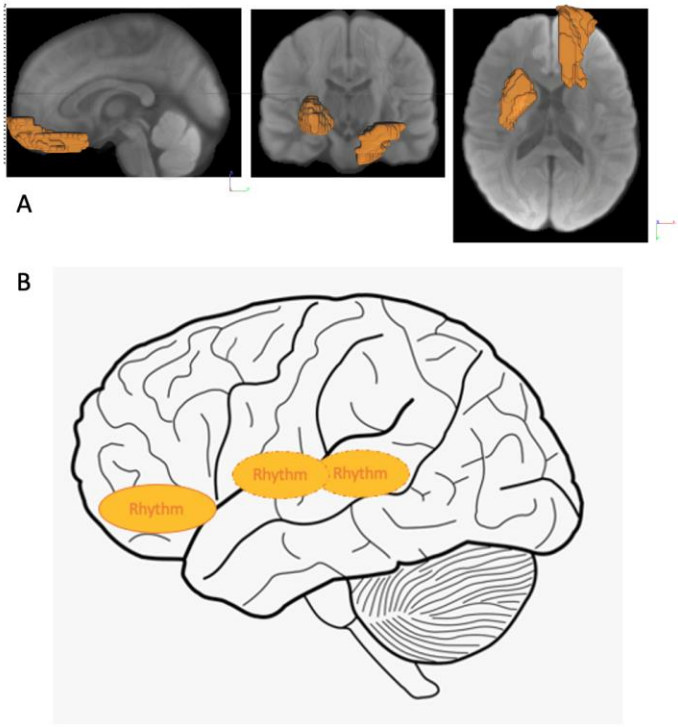

Figure 2-2. Gray matter volumes (GMVs) associated with annual rhythm change (A). Regions of interest (ROIs) are presented from sagittal, coronal, and axial view. Selected regions for annual rhythm change are shown with solid outline indicating left regions and dashed outline indicating right regions (E).

2.4 Discussion

In this study, we represented gait with domains of pace, rhythm, spatial variability and temporal variability and selected ROIs where regional GMVs were related to the gait domains. Several important regions for gait were identified. These include right cerebellar 4-5 and left inferior orbitofrontal cortex related to pace score; left anterior cingulate cortex and left superior parietal cortex related to spatial variability score; right putamen and right posterior cingulate

cortex related to rhythm score; and cerebellar 4-5 and cerebellar 9 related to temporal variability score. In addition, we observed right putamen, right pallidum, and left superior orbitofrontal cortex related to rhythm annual change.

Different motor-related regions were identified for gait domains. Pace score, which represents velocity and length of gait (Appendix A-2), was positively associated with GMV in orbitofrontal region. We also observed that spatial variability score, which represents fluctuations of spacing of steps (Appendix A-2), is negatively related to GMV in left anterior cingulate and left superior parietal.[10] In a previous study, GM integrity in left anterior cingulate has also been related to step length variability.[25] Anterior cingulate projects to prefrontal cortex that serves executive function in motor-related function, and our results are consistent with previous work where both pace and spatial variability domains are related to the fronto-parietal networks involved in executive function, attention, decision making, performance monitoring, and proprioception in motor control.[10,25]

We observed that right putamen was related to both cross-sectional rhythm and annual rhythm change, which reflects time control of gait. Putamen receives information from motor and premotor cortex, and has been thought to play a central role in motor control.[36] In previous studies, damage to putamen was related to gait asymmetry in stroke patients and functional impairment of movement in Parkinson's disease.[37,38] We also observed GMV in right posterior cingulate related to cross-sectional rhythm, and GMV in right pallidum, and left superior orbitofrontal cortex related to annual rhythm change. Posterior cingulate is a key node in the default mode network, and is commonly affected in neurodegenerative disease such as Alzheimer's disease.[39] Pallidum was related to step width, but the association was not robust after covariates adjustment.[40] Loss of white matter integrity in orbitofrontal cortex was related to

freezing of gait, which is a common symptom of parkinsonism.[41] Our results are in line with the conclusion from previous research that impairment in gait rhythm is associated with freezing of gait in parkinsonism.[42]

We observed cerebellar regions for motor and balance control associated with temporal variability, which represents fluctuations of timing of steps.[25] Similar association has been identified in a previous study led by Manor, et al., where higher temporal variability was associated with a smaller cerebellum.[43] Our results are consistent with previous evidence that temporal variability was associated with brain regions important for motor and balance control.[25]

Mixed directions were observed for GMVs with rhythm and temporal variability. The reason for this could be negative correlations between the identified regions with regions that were not identified from the model. Regional GMVs were measured cross-sectionally in our study, so may not be the most accurate way of capturing the GMV profile. Our results may also suggest that rhythm and temporal variability are not related to gait performance in a linear association, and both increased and reduced rhythm score reflects compromised gait. For example, increased step time was associated with higher score of physical fatigue, while reduced swing time was observed in older adults with Parkinson's disease.[44] Increased temporal variability could result from decreased motor skill during aging, while reduced variability could be related to a greater fall risk.[45,46] Consistent with this hypothesis, in a previous study, reduced temporal variability was associated with smaller hippocampal volumes.[25] Future studies should assess nonlinear associations of neural correlates with quantitative gait measures of rhythm and temporal variability.

Our results support our hypothesis that pace is positively associated with GMV in selected subregions in frontal and cerebellar lobes. We also found that spatial variability relates

to left anterior cingulate cortex and superior parietal, which are part of the fronto-parietal network that is involved in executive function in motor control.[25] We did not observe any association of basal ganglia with pace nor spatial variability domains. We observed annual rhythm change and temporal variability related to motor control regions, including subregions from basal ganglia and cerebellum. In addition, spatial and temporal variability likely relates to neural correlates of different function of gait control, which is consistent with our hypothesis. Last, we did not observe any association of memory-related regions with rhythm and temporal variability. This is inconsistent with previous findings where worse performance on rhythm was related to risk of amnestic MCI and memory decline.[8,9] Instead, rhythm and temporal variability may be rudimentary features of gait.[10]

There are several limitations in this study. Only 64% of the participants had repeated assessment of gait, and only 42% of the participants had more than two measures. Our results of gait annual changes need to be interpreted with caution, as the within-subject covariance matrices were derived from data of the 42% of participants with more than two repeated measures.[47] The composite scores derived from z-scores of individual gait metrics may not fully capture the complex performance of each domain. However, the results are expected to be robust as the gait measurements we included in each domain were correlated with each other. The SPLS model tends to randomly select one of the multiple highly correlated GMVs. This could cause problem if GMV in important regions were highly correlated with GMV in other regions. Last, other age-related neural pathologies, such as amyloid and tau aggregation, could potentially affect the gait performance.[48] However, they were not available in our study.

By using composite scores derived from comprehensive quantitative gait assessments, we are able to capture gait performance in multiple domains and obtain more robust associations

with greater inter-reliability,[8] minimize the number of gait outcomes, and reduce correlations of gait outcomes. This could mitigate the problems of multicollinearity and multiple comparisons. Our study sample was representative of community-dwelling older adults. We used non-parametric missing data imputation to reduce selection bias. Further, we excluded the participants who were considered as outliers in terms of gait measures to reduce the impact of outliers on our results. Participants were followed up to 5 years and had repeated quantitative gait measures. Use of the study sample allowed us to take account of repeated measures and evaluate longitudinal associations of brain structure with gait measures in a community-based setting. Last, SPLS models were used to select GMVs of important regions from the large number of gray matter ROIs.[49]

We selected GMVs in frontal and cerebellar regions from modeling of pace at baseline; superior parietal and anterior cingulate cortex from modeling of spatial variability at baseline; putamen and posterior cingulate cortex from modeling of rhythm at baseline; and cerebellar regions from modeling of temporal variability at baseline. Our results also suggest that subregions in basal ganglia and frontal regions were important for rhythm change with age. Our results suggest that independent gait domains were related to GMVs of different brain regions, and could provide evidence for studies on gait measures with cognitive characteristics.

3.0 Regional Gray Matter Density Associated with Fast-paced Walking in older adults: a voxel-Based Morphometry Study

This paper evaluated gray matter density related to both fast-paced walking and usual-paced walking using voxel-wise analyses to identify additional neural resources correlated with community walking due to greater locomotor adaptation challenges and faster processing and integration requirement than simple walking.

3.1 Introduction

Slower walking speed is associated with risk of adverse outcomes, including mobility disability, cognitive decline, mortality, falls, and institutionalization, as well as worse brain integrity in older adults.[50-53] To date, most studies on walking in older adults have focused on walking speed under usual conditions.

It has recently been shown that walking speed during tasks asking participants to walk as fast as possible may also be important for detecting clinical outcomes in older adults. Evidence suggests that fast-paced walking speed is associated with aging-related adverse events.[54] Fast-paced walking challenges locomotor adaption and requires faster processing and integration of multiple inputs and motor response. Fast-paced walking speed also requires more active neural control than usual-paced walking.[55] Previous studies suggest that fast-paced walking speed was associated with cognitive function and can predict changes in cognitive function during follow-up in older adults.[56-59]

Previous evidence suggests that usual walking speed was associated with brain structure and integrity in older adults. Slower usual walking speed in older adults without any diagnosed neurological diseases was associated with lower gray matter (GM) and white matter (WM) volume, increased white matter hyperintensity (WMH) burden, lower fractional anisotropy (FA) and increased mean diffusivity (MD) of both sensory or motor related regions and higher-order regions (see review[7]). Fewer studies have assessed the neural correlates of fast-paced walking speed. A previous study suggests that fast-paced walking speed was associated with total cerebral volume and not associated with hippocampal volume in healthy older adults.[50] Fast-paced walking speed was also correlated with GM volume in right caudate nucleus, bilateral thalamus, and left putamen among older adults with memory problems.[60]

In this study, we investigated the association of gray matter density, – a measure related to both volume and cortical thickness, with fast-paced walking speed and usual-paced walking speed. We conducted voxel-wise regression to identify regions of the brain where gray matter density was associated with fast-paced walking speed among older adults using the Health, Aging, and Body composition (Health ABC) study.[61] We hypothesized that gray matter density of regions associated with executive function and memory would be associated with fast-paced walking speed but not to usual-paced walking speed.

3.2 Methods

3.2.1 Study population

The Health ABC study is a longitudinal cohort study that investigated physical and cognitive functional change among the elderly who were physically and cognitively healthy at baseline. Participants aged 70-79 were recruited in community-based settings from Pittsburgh, PA (n=1,501) and Memphis, TN (n=1,574) from 1997-1998.[62] Demographic information was obtained at baseline. Participants were followed annually and completed questionnaires and performance tests for the evaluation of body composition, health status, and adverse health outcomes.[63]

A subset (n=325) of the Pittsburgh site who participated in the clinical visit at Year 10 or Year 11 (2006-2008) completed MRI scanning if they met the inclusion criteria: 1) no assistive devices for walking; 2) eligible for a 3T magnetic resonance imaging (MRI) scan; 3) had a mobility measure at the previous visit; 4) no medical history of neurological or psychological illnesses.[31,64] Participants with valid MR measures were included in our analysis (n=312). Participants who did not complete the fast-paced walking speed task were excluded (n=20, 6%). Participants with missing covariates including education, body mass index (BMI), depression severity score (Center for Epidemiologic Studies Depression Scale, CESD), or digit symbol substitution task (DSST) score were excluded from the analyses (n=8, 2%). Our final dataset included 284 (87%) participants from the Health ABC MRI subset. Distribution of the demographics and clinical variables were similar between the original subset and our final dataset (not shown).

3.2.2 MRI measures

MRI scans were obtained at the MR Research Center of the University of Pittsburgh using a 3 T Siemens Tim Trio MR Scanner and a Siemens 12-channel head coil. An axial, whole-brain T1-weighted magnetization prepared rapid gradient echo (MPRAGE) was collected with repetition time (TR)=2300ms, echo time (TE)=3.43ms, flip angle (FA)=9deg, field of view (FOV)=224x256, $1mm^3$ isotropic resolution, no gap, and no acceleration. An axial, whole-brain fluid attenuated inversion recovery (FLAIR) sequence to appropriately identify white/gray matter were also collected. This sequence had TR=9160ms, TE=90ms, FA=150deg, FOV=212x156, 1x1x3mm resolution, 3mm gap, and no acceleration.

All processing steps were conducted in SPM12.[65] All image space interpolation was performed using 4th degree B-spline method and similarity metric for registrations was mutual information (for motion correction) or normalized mutual information (coregistration between different image types). FLAIR images were coregistered to the MPRAGE (12 degree of freedom transformations) then a multi-spectral segmentation was conducted of both the MPRAGE and coregistered FLAIR into 6 tissues: gray matter, white matter, cerebrospinal fluid (CSF), skull, soft-tissue, and air. Default values were used for the segmentations in SPM. Native space segmentations of the gray matter were input into the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) algorithm using the standard pipeline for generating a study-specific template and normalizing each segmentation to that template.[66] This generates a study-specific gray matter template through iterative co-registrations and averages, then co-registers each map to the final template. This outputs a gray matter density map, which is highly associated with volume and cortical thickness, and is considered to reflect the amount of gray matter locally.[67] This is because when a single participant's gray matter is coregistered to a

standard space (like MNI), the gray matter has to be compressed or expanded depending on whether the MNI space gray matter is smaller or larger, respectively. When it is compressed the density goes up and when it is expanded the density goes down – thus a greater volume and cortical thickness results in a greater density.

3.2.3 Walking speed measures

Walking tests were performed within 6 months of the MRI scan. Participants were asked to walk along a 20m corridor from a standing start during both the usual-paced walking task and the fast-paced walking task. Participants were instructed to walk "as you normally would" and "as fast as you can," respectively.[62] Time to finish the tasks was recorded by stop watch and converted to speed in m/s. Walking speed of fast-paced walking and usual-paced walking was treated as the outcome.

3.2.4 Covariates

Demographics, clinical information, and cognitive function were obtained at baseline of the Health ABC Study or the time of MRI. Demographic characteristics included age at the time of MRI measurement, as well as sex, race, education, and body mass index (BMI) obtained at baseline. BMI (kg/m^2) was calculated from self-reported height and weight values at the time of MRI. Clinical information included cardiovascular disease (CVD), stroke or TIA (transient ischemic attack), hypertension, diabetes, and depression. History of CVD and stroke or TIA was identified from the questionnaire as ever having the event at baseline and was updated by self-report annually. Participants were defined as having hypertension if they had a systolic blood

pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or self-reported a hypertension diagnosis or antihypertension medication use at the time of MRI measurement. Participants were defined as having diabetes if their fasting plasma glucose was >126 mg/dL or 2-hour post-challenge >200 Hg/dL, or self-reported a diabetes diagnosis or diabetes medication use.[68] Depressive symptoms were described at the time of MRI based on the 20-item Center for Epidemiologic Studies-Depression (CES-D) scale.[69] The Modified Mini—Mental State Examination (3MSE) was used to assess general cognitive function at the time of MRI.[70] The Digit Symbol Substitution Test (DSST) was also administered at the same time to assess processing speed.[71]

3.2.5 Statistical analysis

The characteristics of the study population are presented as mean (standard deviation) for continuous variables and count (percentage) for categorical variables. Unadjusted associations between the sample's characteristics and fast-paced walking speed are reported as Spearman correlation coefficients for continuous variables and mean difference from independent t-test for categorical variables.

Voxel-wise analyses tested the associations between fast-paced walking speed and gray matter density from the entire brain using SnPM.[72] SnPM computed non-parametric p-values corrected using a cluster-wise inference method (cluster forming threshold of $p<0.001$) that controlled the family wise error rate (FWE) at $\alpha=0.05$. This analysis was done in the whole brain and did not exclude any regions. Next, we extracted the average gray matter density of clusters significantly associated with fast-paced walking speed by utilizing the automated anatomical labeling atlas.[73]

For each region, the association between gray matter density and fast-paced walking speed was modeled using nested linear models with adjustment for 1) demographics (age, sex, race, education, and BMI), 2) plus clinical variables (cardiovascular disease, stroke or TIA, hypertension, diabetes, and depression), and 3) plus cognitive function (3MSE and DSST scores). Demographics and clinical variables were adjusted in the models as potential confounders. 3MSE and DSST scores were included in the fully adjusted model in order to test whether this association was independent of cognitive function. Lastly, a cut-off point of 0.3 m/s was chosen for the point estimate of fast-paced walking speed change per SD change of gray matter density to suggest a meaningful association between the regional gray matter density and fast-paced walking speed after the full adjustment. This cut-off was selected to represent a medium effect, which approximates the average effect of 14-year change of age on the change of fast-paced walking speed in our study sample. Regression analyses were conducted in SAS 9.4. The same analyses were repeated for usual-paced walking speed and gray matter density.

3.3 Results

Participants were on average 83 years old (SD=2.8), 58% women and 41% black. Average walking speed was 1.0 m/s (SD=0.21) for usual-paced walking and 1.4 m/s (SD=0.34) for fast-paced walking. Greater usual-paced walking speed was correlated with greater fast-paced walking speeds ($r=0.58$, $p<0.0001$). Participants who were female, black, had a lower level of education, or had a history of knee pain were more likely to have a slower fast-paced walking speed. In addition, those who were older, had greater BMI, greater depressive symptoms

(CESD), worse cognitive function (3MSE or DSST score), had hypertension, or had diabetes also were more likely to have a slower fast-paced walking speed (Table 3-1).

Table 3-1. Characteristics of the study population and association with fast-paced walking speed (n=284): Health, Aging, and Body Composition Study, 2010-2011.

	Mean (SD) or n (%)	**Association with fast pace walking speed (m/s)** [a]	**p-value**
Age (year)	83 (2.8)	-0.15	0.01
Female	164 (58%)	-0.23 (0.04)	<0.0001
Black	116 (41%)	-0.16 (0.04)	<0.0001
Education >high school	146 (51%)	0.16 (0.04)	<0.0001
BMI	27 (4.4)	-0.27	<0.0001
CVD	80 (28%)	-0.02 (0.05)	0.59
Stroke or TIA	21 (7.4%)	-0.09 (0.08)	0.24
Hypertension	256 (90%)	-0.16 (0.05)	<0.0001
Diabetes	73 (26%)	-0.09 (0.05)	0.05
CES-D	6.6 (5.9)	-0.17	0.004
Knee pain [b]	122 (43%)	-0.19 (0.11)	<0.0001
3MSE score	93 (6.7)	0.23	<0.0001
DSST	37 (13)	0.25	<0.0001
Usual-paced walking speed (m/s) [c]	1.0 (0.21)	0.58	<0.0001

Fast-paced walking speed (m/s)	1.4 (0.34)

Note: BMI - body mass index; CVD - cardiovascular disease; TIA - transient ischemic attack; CESD - Center for Epidemiologic Studies-Depression; 3MSE - Modified Mini-Mental State Examination; DSST - Digit Symbol Substitution Test

a. Spearman correlation coefficient for continuous variable and group mean difference (SD) from t-test for categorical variable;

b. Knee pain (in the past month) was evaluated during the visit at Year 10;

c. For usual-paced walking speed, n=269 participants.

In the unadjusted voxel-wise analyses, greater fast-paced walking speed was positively correlated with greater gray matter density in clusters from: the frontal and temporal lobe, pre- and post-central gyrus, inferior parietal lobule, precuneus gyrus, lingual, parahippocampal and fusiform gyrus, calcarine cortex, middle occipital gyrus, supramarginal and angular gyrus, Rolandic operculum, insular cortex, cingulum, hippocampus, amygdala, and cerebellum (figure 3-1 Appendix A-6, and Appendix B-3). Regions correlated with usual-paced walking speed are shown in figure 3-1, Appendix A-7, and Appendix B-5. Clusters from insula, cerebellum, parahippocampus, calcarine, middle and inferior frontal, temporal, middle occipital, amygdala, fusiform gyrus, lingual gyrus, and precuneus, were correlated with both fast-paced and usual-paced walking speed. Fast-paced walking speed but not usual-paced walking was correlated with gray matter density in clusters from pre-central gyrus and inferior parietal lobule. In addition, usual-paced walking speed but not fast-paced walking speed was associated with gray matter

density in clusters from cuneus, caudate, putamen, gyrus rectus, and superior occipital gyrus. (Appendix B-7)

Regions that were significantly associated with fast-paced walking speed after adjustment for demographic variables, clinical morbidities, and cognitive function, are shown in Table 3-2, figure 3-1, and Appendix B-4. After further adjusting for covariates, fast-paced walking speed was positively correlated at coefficient ≥ 0.3 m/s with gray matter density of clusters in: right middle and superior frontal gyrus, right postcentral gyrus, and left superior temporal gyrus. Adjustment for cognitive function had little impact on the findings. We found no association between fast-paced walking speed with gray matter density of hippocampal regions or with basal ganglia. (Figure 3-1 and Table 3-2) Regions that are significantly associated with usual-paced walking after covariates adjustment are shown in Appendix A-8, figure 3-1, and Appendix B-6. Usual paced walking speed was positively correlated with gray matter density of left caudate region at coefficient ≥ 0.3 m/s after adjustment of demographics and morbidities, but not after further adjusting for cognition. In addition, no regions were associated with both usual and fast-paced walking speed after adjustment (Appendix B-8). In general, the effect size of gray matter density of each region on usual-paced walking was smaller than fast-paced walking speed.

Table 3-2. Association between fast-paced walking speed and gray matter density. Corresponding coefficients (β) and p-values are shown across three nested models.

Region	MNI coordinates (x, y, z)	Model 1 [a]	Model 2 [b]	Model 3 [c]
		β (p-value) [d]		
Right Angular Gyrus	62, -50, 36	0.23 (0.01)	0.22 (0.01)	0.21 (0.02)
Right Cerebellum 4-5	24, -50, -20	0.14 (0.04)	0.13 (0.06)	0.12 (0.08)

Right Cerebellum 6	26, -56, -18	0.13 (0.03)	0.12 (0.05)	0.11 (0.08)
Left Cerebellum Crus 2	-38, -66, -38	0.11 (0.04)	0.10 (0.06)	0.09 (0.10)
Right Cerebellum Crus 2	44, -68, -40	0.13 (0.04)	0.11 (0.07)	0.10 (0.09)
Left Middle Orbital Frontal Gyrus	-8, 38, -12	0.13 (0.03)	0.11 (0.07)	0.09 (0.14)
Right Middle Orbital Frontal Gyrus	10, 42, -6	0.14 (0.03)	0.13 (0.06)	0.10 (0.12)
Right Middle Frontal Gyrus	28, 54, 2	0.35 (0.001)	0.35 (0.001)	0.31 (0.01)
Right Superior Frontal Gyrus	14, 68, 24	0.37 (0.01)	0.36 (0.01)	0.31 (0.04)
Right Fusiform Gyrus	26, -52, -16	0.17 (0.04)	0.15 (0.07)	0.13 (0.14)
Left Lingual Gyrus	-16, -66, 2	0.11 (0.05)	0.11 (0.06)	0.10 (0.08)
Right Lingual Gyrus	16, -48, 4	0.20 (0.03)	0.19 (0.03)	0.18 (0.04)
Right Insula	38, 10, 10	0.24 (0.05)	0.20 (0.11)	0.14 (0.30)
Right Paracentral Lobule	8, -36, 60	0.24 (0.05)	0.22 (0.08)	0.21 (0.09)
Right Inferior Parietal Gyrus	60, -40, 46	0.25 (0.01)	0.23 (0.01)	0.23 (0.01)
Right Postcentral Gyrus	64, 0, 18	0.38 (0.04)	0.36 (0.05)	0.35 (0.05)
Right Precuneus	14, -40, 58	0.21 (0.03)	0.20 (0.05)	0.19 (0.05)
Right Rolandic Operculum	44, -14, 16	0.15 (0.04)	0.13 (0.09)	0.11 (0.14)
Left Supramarginal Gyrus	-44, -34, 26	0.23 (0.005)	0.22 (0.01)	0.19 (0.02)
Right Supramarginal Gyrus	66, -36, 38	0.17 (0.03)	0.14 (0.07)	0.11 (0.16)
Left Middle Temporal Gyrus	-58, -38, 12	0.21 (0.03)	0.19 (0.06)	0.16 (0.10)
Right Middle Temporal Gyrus	70, -18, -6	0.22 (0.04)	0.20 (0.06)	0.15 (0.19)
Right Superior Temporal Pole	34, 10, -24	0.31 (0.01)	0.30 (0.02)	0.26 (0.04)

Left Superior Temporal Gyrus	-54, -38, 14	0.37 (0.001)	0.34 (0.004)	0.31 (0.01)
Right Superior Temporal Gyrus	68, -18, -4	0.31 (0.02)	0.27 (0.04)	0.24 (0.06)

Note: BMI - body mass index; TIA - transient ischemic attack; CESD - Center for Epidemiologic Studies-Depression; 3MSE - Modified Mini-Mental State Examination; DSST - Digit Symbol Substitution Test

a. Model 1: general linear model adjusting for demographics (age, sex, race, education, and BMI);

b. Model 2: based on model 1, further adjusting for morbidities (cardiovascular disease, stroke or TIA, hypertension, diabetes, and CESD score);

c. Model 3: based on model 2, further adjusting for cognition (3MSE and DSST scores).

d. The coefficient of 1 SD change of regional gray matter density on fast-paced walking speed and the corresponding p value

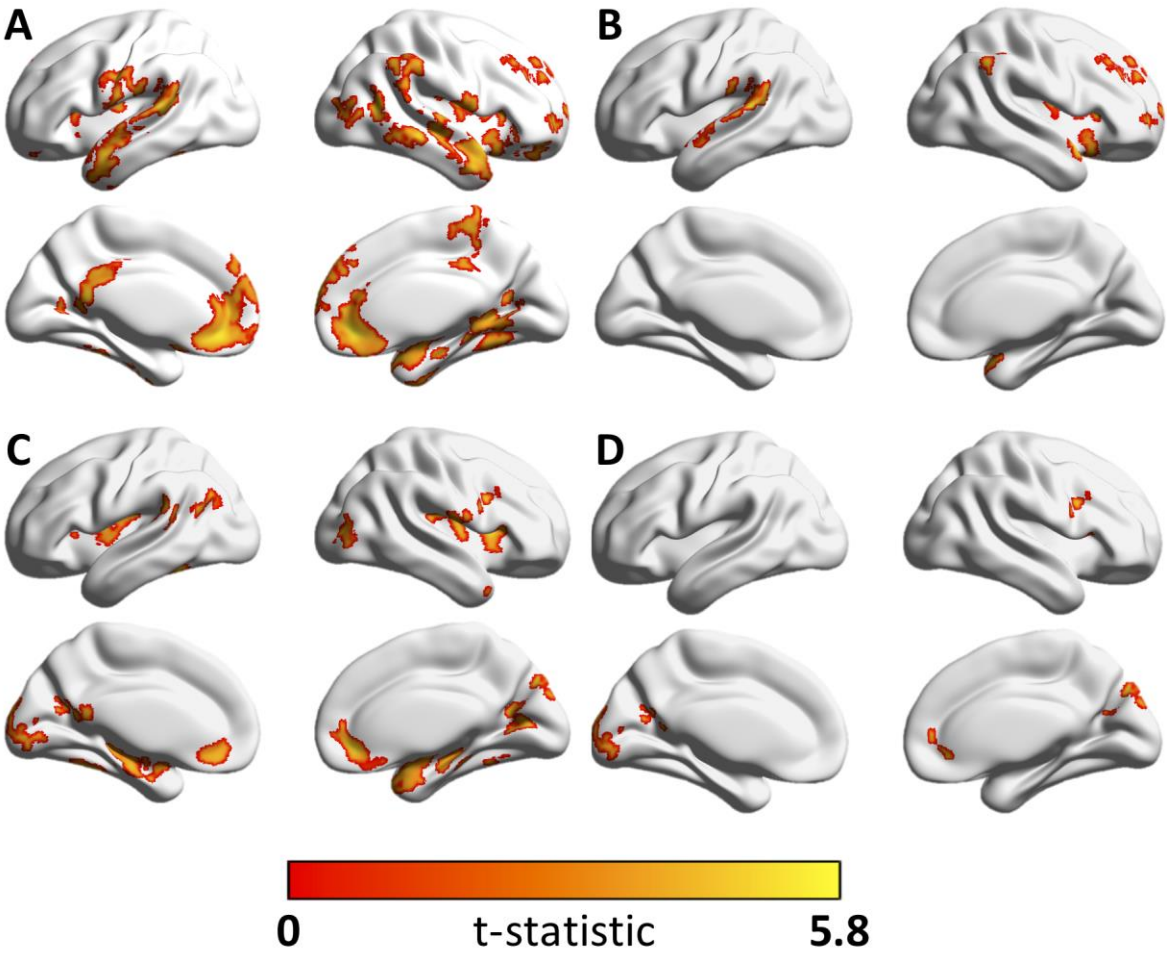

Figure 3-1. (A) Association between gray matter density and fast-paced walking speed unadjusted and (B) regions that remained significant after adjusting for demographic variables, clinical morbidities, and cognitive function – including those with smaller effect sizes, i.e. <0.3 m/s. (C) Association between gray matter density and usual-paced walking speed unadjusted and (D) regions that remained significant after adjusting for demographic variables, clinical morbidities, and cognitive function – including those with smaller effect sizes, i.e. <0.3 m/s. Color bar indicates value of the t-statistic testing the association between gray matter density and fast- (A and B) or usual-paced (C and D) walking speed.

3.4 Discussion

We found that fast-paced walking speed was positively associated with gray matter density in cortical regions including right middle and superior frontal gyrus, right postcentral gyrus, and left superior temporal gyrus. Associations were robust to adjustment for demographic factors, clinical factors, and cognitive function. Our hypothesis was accurate, as fast-paced walking speed but not usual-paced walking speed, was associated with clusters related to executive function.[74] However, no memory-related clusters were associated with fast-paced or usual-paced walking speed.

In this study, we examined the whole brain to capture a wide network or regions related to fast-paced walking speed in older adults without neurological and psychological diseases. The brain regions from cortical, subcortical, and cerebellum identified from the unadjusted analyses where gray matter density was correlated with either fast-paced or usual-paced walking speed may reflect the functions of brain related to mobility.[4] Clusters from cortical, subcortical, and cerebellar regions were correlated with both fast-paced and usual-paced walking speed. This could reflect the correlation between two walking measures, which was measured as 0.58 in our sample. On the other hand, these two measures were not perfectly correlated, and each was correlated with specific regions. Fast-paced walking speed was correlated with parietal regions, and usual-paced walking speed was correlated with regions of basal ganglia and occipital. This may indicate that different mechanisms of neuronal control were involved in fast-paced walking than usual-paced walking. It was suggested that fast-paced walking involves a higher conscious control than usual-paced walking.[59]

Previous studies have been limited. One study focused on associations of fast-paced walking speed with total brain volume and hippocampal volume[50] and only adjusted for age.

Another study assessed regional gray matter volume associated with faster fast-paced walking speed[60], but only participants having memory complaints were recruited – limiting its generalizability to older populations without impairment of cognitive function.

After adjustment for demographic variables, clinical factors, and cognitive function, we observed that faster fast-paced walking speed was associated with gray matter density in right middle and superior frontal gyrus, right postcentral gyrus, and left superior temporal gyrus. These regions are specifically related to executive, somatosensory, and vestibular function.[74-76] In a previous study of resting-state functional connectivity and walking, greater resting-state functional connectivity between the midbrain locomotor region and right superior frontal gyrus was associated with greater walking capacity, indicating that superior frontal gyrus was a relevant locomotor area.[77] This is consistent with our finding, where fast-paced walking was a measure of walking capacity and was related to the structure of superior frontal gyrus. Right postcentral gyrus is a somatosensory region that facilitates the automatic process of walking,[78] and has been identified to be related to walking in studies investigating brain activation.[19,79] Previous studies using functional near-infrared spectroscopy observed increased activation in superior temporal gyrus during postural control and balance, indicating that this area is involved in dynamic balance.[80,81] Our study suggests that superior temporal gyrus could play a role in fast-paced walking through balance control. However, future studies are needed to verify the results by analyzing functional associations with the brain.

Associations tended to be lateralized to the right hemisphere for fast-paced walking. Right hemisphere dominance for vestibular and ocular motor structures in right-handed volunteers has been previously reported in a positron emission tomography study.[82] Another study using electroencephalography also observed increased right hemispheric engagement

related to ventral attention.[83] A previous review suggested a lateralized model for motor control: the left cortex is specialized for predictive control while the right cortex is specialized for impedance control specifying velocity and position based impedance.[84] Our results are consistent with previous evidence suggesting the increased engagement of the right hemisphere during the fast walking process that may be associated with increased engagement of vestibular function and impedance control.

Adjustment for covariates including demographics, morbidities, and cognitive function did not attenuate the associations of gray matter density of middle and superior frontal gyrus, right postcentral gyrus, and left superior temporal gyrus, with fast-paced walking speed. The association of usual-paced walking speed with regional gray matter density was not as robust to the adjustment of covariates. In addition, no regions were associated with both usual and fast-paced walking speed after adjustment. This may indicate: 1) the association of fast-paced walking but not usual-paced walking was independent of age, sex, race, education, BMI, and morbidities, CVD, stroke or TIA, hypertension, diabetes, and depression. 2) Cognitive function represented by 3MSE and DSST scores is not likely to be a mediator between gray matter density and fast-paced walking speed. This may not hold true for usual-paced walking speed. 3) Although there's overlap of brain regions related to usual- and fast-paced walking speed in consistent with the correlation between the two walking measures, this overlap could be largely explained by covariates that may be common causes of the brain aging and mobility loss.

Fast-paced walking speed but not usual-paced walking speed was correlated with gray matter density of superior frontal gyrus. Compared with usual-paced walking, fast-paced walking was more strongly correlated with gray matter density of clusters in general. Our results are consistent with previous hypotheses that: 1) Fast-paced walking, but not usual-paced walking,

was associated with cognitive function in older adults[56-59] and may be related to cognitive execution;[74] 2) complex walking like fast-paced walking provides greater levels of variability and allows difference in fitness to be identified, which would not be identified in usual-paced walking;[58] and 3) fast-paced walking necessitates a higher level of conscious control and thus is more closely correlated with cortical structure than usual-paced walking.[59]

Negative findings also merit attention. We did not find a significant association of fast-paced walking speed with memory-related areas (e.g., hippocampus) after adjustment with cognitive function. This is surprising given the association of fast-paced walking with dementia.[4,85] Associations were also not significant with basal ganglia, which is involved in the automatic control of voluntary movements.[6] Basal ganglia was observed to be associated with usual walking speed among older adults in previous studies, where a combined effect of the neurodegenerative process may be involved.[60,86] Only the caudate was associated with usual-paced walking, while many studies have found the association of walking speed with gray matter volume in motor-related regions such as precentral gyrus, frontal, hippocampal, and cerebellar regions. The negative findings could be explained by several reasons. As a more demanding task, it is possible that a different mechanism is involved in fast-paced walking that is different from usual-paced walking or complex walking tasks.[59] We only studied gray matter density, which may not sufficiently describe the age-related changes in brain correlated with fast-paced walking. For example, there could be changes in other brain imaging parameters, including white matter volume and integrity, brain activity, subclinical manifestations (e.g., micro bleeding, β-Amyloid), and functional connectivity, before the changes of gray matter density could be detected. A previous study identified associations of slower walking speed with lower white matter microstructure in thalamic radiations.[87] The associations of slower walking speed with

greater white matter hyperintensities were observed in basal ganglia and thalamic radiation.[88-91] A previous study using florbetapir PET observed significant association between β-Amyloid in putamen and slow gait speed.[92] It is also important to put the results of gray matter density in the context of other modalities because of compensatory mechanisms and functional reserve of the brain. Our voxel-wise multiple comparisons correction reflects the latest in the field,[93] which may also influence the results we have observed. We used a cut-off of 0.3 m/s to select the regions in multivariate-adjusted linear regressions, thus we focused on the effect size instead of hypothesis testing results (p values). Inconsistencies may also result from different sample of participants. Specifically, if those who were unable to complete fast-paced walking had different gray matter density profiles than our study sample.

There is the need to find simple markers to detect early dementia risk in older adults. Traditional methods like MRI and cognitive assessments are either invasive or require lots of time and specialist input. Gait measures are relatively simple yet important measures in the older population. Usual walking speed is a simple measure, but its association with brain integrity might not be strong enough at the individual level. More complex motor tasks, such as dual task walking, are promising because of their potential to reflect changes in the central nervous system to a greater extent compared to usual walking speed.[57] However, dual task walking is complicated to administer and difficult to standardize. Fast gait may be a good compromise, as previous evidence suggest that it reveals cognitive characteristics, and it requires relatively simple and consistent protocol compared to other complex walking tasks.[57-59] Our study indicates that fast gait does reflect integrity in certain brain regions, but not those that are memory-related. This may suggest that fast-paced gait speed alone is not helpful for detecting risk of memory-

related dementia. However, it could be helpful to detect other general signs of advanced brain aging or problems with executive function.

There are several limitations in our study. We used a selective population: only participants who survived and completed MRI scanning in Year 10 or Year 11 and had complete data profile were included from the Health ABC study. In addition, the age range of our study sample is narrow with the average age of 83 (SD=2.8), preventing generalization to the younger elderly. Our study is cross-sectional and so any associations are non-temporal and non-causal. Longitudinal studies may help explain the causal relationships amongst these variables. Last, we only investigated the association with gray matter density. Other brain imaging parameters should be assessed to further understand the neural correlates associated with fast-paced walking speed. As a result, it's important to interpret our results with caution, as they need to be put in the context of other neural modalities.

In this study, we conducted voxel-wise analyses between fast-paced walking speed and gray matter density, which allows for the comparisons across the entire brain with a high regional specificity and without prior region-specific assumptions. Our study sample is relatively large in size with sufficient sampling of male and black participants. Our study adds to the current evidence of the neural correlates of fast-paced walking speed. We identified several clusters in the brain including right middle and superior frontal gyrus, right postcentral gyrus, and left superior temporal gyrus independent of demographic variables, clinical factors, and cognitive function among older adults. The association of frontal and temporal gyri with fast-paced but not usual-paced walking speed may explain previously observed associations between fast-paced walking speed and cognitive function.[57-59]

4.0 Assessment of Prefrontal Cortex Activation and Performance during Walking with Different Dual Tasks in Older Adults: A Functional Near Infra-red Spectroscopy Study

This paper evaluated the real-time activation of prefrontal cortex, a key region of cognitive control and higher order processing, during dual task walking, to test the importance of prefrontal cortex in community walking in older adults.

4.1 Introduction

Poor mobility in older adults is related to physical and cognitive impairment, institutionalization, and risk of falls, which is a major cause of injury and morbidity in older adults.[2,18,32] Community walking is often accompanied by environmental challenges which require additional cognitive networks of the brain that are not involved during unchallenged walking as typically studied in the lab.[14,15] Dual-task walking involves a simultaneous physical or cognitive task. It is used to mimic community walking in mobility studies.[94]

The prefrontal cortex subserves higher order information processing and executive functions.[95] PFC likely plays an important role in dual-task walking. Previous evidence suggests that dual-task walking is associated with increasing activation in prefrontal regions in older adults.[96] However, dual-tasks of different types and difficulty levels have been used in the current literature, making the results less comparable across studies. Few studies have evaluated PFC activation across walking with different types of dual-task in older adults to provide evidence of task-specific effect on PFC activation.[16] Increased PFC activation level was observed in walking

while talking compared with simple walking, and obstacle walking compared with simple walking.[97,98] No studies has assessed the effect of physical and cognitive dual task interaction on PFC activation.

The PFC may provide functional compensation when direct locomotor networks of primary motor cortex, basal ganglia, and cerebellar locomotor regions are insufficient to support dual-task walking.[99] PFC is also one of the regions that are most susceptible to age-related atrophy.[23] Older adults with cognitive impairment, high stress or fatigue, high risk of falling, and ataxic gait showed greater PFC activation than healthy older adults during dual-task walking.[22] The results suggest that greater prefrontal activation during dual-task walking is related to decreased functional status of older adults. Dual-task performance capabilities may also be an indicator of functional status in older adults.[100]

Mixed directions of the association between PFC activation and performance of dual-task walking were observed from previous studies. This may suggest that PFC is activated at different walking tasks in older adults, and older adults with different PFC activation patterns have different walking performance. The PFC activation pattern reflects older adults' ability to respond to environmental challenges, and may be related to neurocognitive changes with aging.[21] No study has tested the association of PFC activation pattern with task performance and functional status in older adults.

With real-time functional near infrared spectroscopy (fNIRS) measures of both simple walking and walking with different dual-tasks, we aim to address the evidence gaps of task-specific and function-related effect on PFC activation in older adults. First, we aim to evaluate changes in PFC activation after adding physical and cognitive dual-tasks in walking. We hypothesize that PFC activation is increased in dual-task walking compared with even walking. We also

hypothesize that PFC activation during the task with combined physical and cognitive dual-tasks is lower than expected from the sum of the individual dual-tasks. Second, we aim to assess the association of walking and cognitive performance during walking tasks with PFC activation. We hypothesize that walking performance is negatively associated with PFC activation. Third, we applied clustering on PFC activation across walking tasks in an exploratory analysis and described the cognitive and physical functions of older adults with different PFC activation patterns across walking tasks.

4.2 Methods

4.2.1 Study Population

We used three independent studies, including Neural Mechanisms of Community Mobility (NMCM), Program to Improve Mobility in Aging, Near-Infrared Spectroscopy sub study (PRIMA-NIRS), and Move Monongahela-Youghiogheny Healthy Aging Team (Move MYHAT).

The NMCM study aims to study brain function with relation to navigating challenges experienced while walking in the community. Twenty-nine participants were recruited from a previous study through a convenience sample from both newspaper advertisements and from other studies.[101]

The PRIMA-NIRS study is an ancillary (n=43) to a randomized clinical trial (parent study NCT02663778) which aimed to assess the effects of motor skill training on central motor control in older adults with walking difficulties. Participants were contacted from the Pittsburgh

Pepper Center Community Research Registry.[102] One participant was excluded because the participant was unable to complete the walking tasks, generating a final sample size of 42. We included the baseline data for the 42 participants.

The Move MYHAT study aims to study nigrostriatal dopamine on mobility resilience in older adults. Participants were recruited from a parent study, where samples were drawn randomly from the voter registration lists of continuous small-town communities in Southwestern Pennsylvania.[103] We included the baseline data from 46 participants who have completed baseline assessment by the time we started the analyses.

Participants included from the three studies were 1) older than 65; 2) without presence of major neurological or psychiatric diseases, including dementia; 3) able to walk without assistance. Participants were additionally required to have a gait speed between 0.6 and 1.2 m/s in PRIMA-NIRS. In addition, participants from PRIMA-NIRS were excluded if they had medical conditions that cause safety concern for participating in an exercise program. Details of medical conditions were reported in a previous paper. [25]

4.2.2 Walking task assessment

Participants walked on a track with 15 meter straight-ways on either side. One side is a standard, level-surface track and the other is an uneven surface track. Participants made full circles of the track while doing either simple walking or walking with a simultaneous cognitive task, reciting every other letter of the alphabet. Details of walking task assessment has been reported in a previous paper.[104] In total, there are four task conditions: 1) walking on the even surface (even walking), 2) walking on the uneven surface (uneven walking), 3) walking on the even surface with the alphabet task (even ABC), 4) walking on the uneven surface with the

alphabet task (uneven ABC). Each task was completed 4 times by each participant. Task order was pseudo-randomized for each participant, such that even and uneven walking always alternated. Participants stood quietly for 20 seconds before each task to serve as a baseline condition. Walking speed was calculated as 15/ (time from the beginning of walking until both feet are off track) in m/s. The rate of correct letters was calculated in number/s, where number of correctly specified letters during task was divided by time to complete tasks.

4.2.3 Functional Near Infrared Spectroscopy (fNIRS)

For fNIRS measurement and analyses we followed the recommendations from consensus guidelines for fNIRS.[105] Participants were asked to wear an eight-channel continuous wave fNIRS headband (Octa-Mon; Artinis Medical Systems, Elst, Netherlands) during walking. The fNIRS instrument used near infrared light transmitted at two wavelength of 850 and 760 nm. The device has two detectors and eight light emitting diodes sources. Optical data was sampled at a frequency of 50 Hz.

Figure 4-1 shows the placement of fNIRS optodes on subject's forehead. Four sources and one detector cover the PFC of each hemisphere. Each channel consists of one detector and one source on the same side.

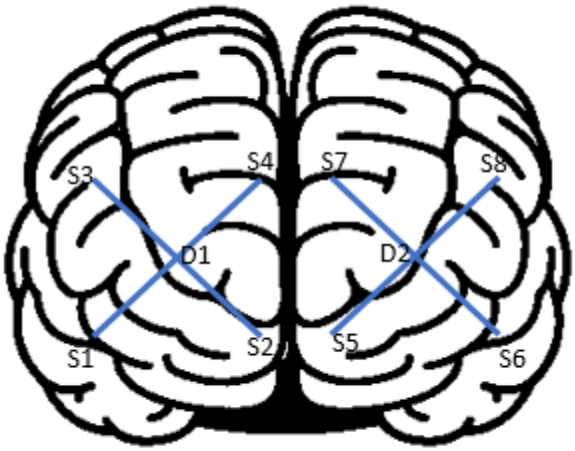

Figure 4-1. Placement of the functional near-infrared spectroscopy (fNIRS) optodes on brain. The fNIRS cap consisted of 8 sources and 2 detectors.

4.2.4 Signal Processing

Raw signals detected by the fNIRS device were exported to Matlab (MATLAB and Statistics Toolbox Release 2017b, The MathWorks, Inc., Natick, MA) using the NIRS Brain AnalyzIR Toolbox. Out of the total 468 measurements for the 117 participants, 9 measures had unusable fNIRS data (1.9%), and 6 measures were missing for time records of walking tasks (1.1%). Further, we excluded about 1% of our data where participants were not following the protocol during walking tasks. Modified Beer-Lambert law was applied to calculate changes of HbO2 and HHb concentrations across time, assuming the partial pathlength factor (DPF) as 0.1.[106] We applied a bandpass filter before modeling to reduce non-evoked noises. In first-level modeling, we applied a canonical model with autoregressive pre-whitening approach using iteratively reweighted least-squares (AR-IRLS) to model O_2Hb for each task.[107] Using standing

period before each task as the baseline reference, we conducted channel-wise student's t tests for changes of O_2Hb of each test by comparing the level of O_2Hb of walking tasks with baseline. Mixed-effects model with fixed effect of tasks using robust weighted least-square was applied to combine the results of the 4 tests for each individual. We exported single t-statistics for each channel and task per subject.

4.2.5 Covariates

We included covariates that were identified to be associated with PFC activation during mobility tasks, including age, sex, obesity, cardiovascular disease, diabetes, and physical and mental fatigability.[22,96] We additionally adjusted for height, weight, and joint pain when modeling walking speed, and adjusted for education when modeling alphabet rate. In addition, we assessed participants' cognitive functions with a neuropsychological assessment. We calculated participants' life space assessment (LSA) score, which documents their usual patterns of mobility during the 4 weeks prior to the assessment.[108]

Height and weight were self-reported by participants. Obesity was defined as BMI >30. Participants were defined as having cardiovascular disease if they self-reported any of angina, congestive heart failure, or heart attack. Diabetes was also self-reported. Fatigability was measured using the Pittsburgh Fatigability Scale.[109] Participants were asked about the level of physical and mental fatigue they experienced during different proposed tasks, with 0 being no fatigue and 5 being extreme fatigue. One participant from PRIMA-NIRS was missing for fatigue measures, and we replaced missing value with fatigue measures from the following visit of PRIMA-NIRS study. Four observations from Move MYHAT with missing value were replaced with the sample mean. Joint pain was assessed by asking participants if they had joint pain in

their knees, hips, and ankles in the past lasting at least one month. One participant from PRIMA-NIRS and four participants from Move MYHAT were missing for joint pain, and were replaced with no joint pain, which is the majority among our participants. Education was categorized as four levels: high school/ equivalent (9-12 years), college (13-16 years), post graduate (≥17), and other (<9 years). The neuropsychological assessment included Mini Mental State Exam (MMSE), Trails Making Part A, and Trails Making Part B.[110,111] MMSE scores were created from the Modified Mini Mental State Exam in PRIMA using the appropriate item scores. Because of the ceiling effect of MMSE assessment, the MMSE scores were left skewed, and we categorized the scores with a cut-off point of the sample mean. Trails Making Part A and Trails Making Part B test scores are recorded as time to finish the tests in second. The maximum times allowed for conducting the Trails Making Part A and Trails Making Part B test are 90 s and 240 s, respectively. No observation from the three studies exceeded the maximum times allowed. Two participants from the PRIMA-NIRS study are missing for the Trails Making test scores thus were excluded when comparing the scores. Total LSA score was calculated as the sum of scores of each of the 5 life-space levels, which was obtained by multiplying the level number by value of independence times value of frequency of movement.[108]

4.2.6 Statistical analysis

We applied linear mixed models to compare the channel-wise PFC activation t statistics across tasks in each study. We assessed whether there are effects of 1) physical dual-task (uneven walking) by including an indicator of uneven walking, 2) cognitive dual-task (alphabet task) by including an indicator of alphabet task, and 3) the interaction of having both physical and cognitive dual-tasks by including the interaction term of uneven walking and alphabet task in

the model. Random effects of subject and tasks within subjects were included in the model. Age, sex, cardiovascular diseases, diabetes, obesity, and physical and mental fatigability scores were adjusted in the models. We meta-analyzed the results of three studies using the fixed-effect model.[112]

We applied linear mixed models to assess the effect of PFC activation at each channel on walking speed and alphabet rate. Models include fixed effects of PFC activation t statistics, walking task, and the interaction term of activation and task, and random effect of subject. When modeling walking speed, we adjusted for age, sex, height, weight, cardiovascular diseases, diabetes, physical and mental fatigability scores, and joint pain. When modeling alphabet rate, we adjusted for age, sex, education, obesity, cardiovascular diseases, diabetes, and physical and mental fatigability scores. We meta-analyzed the results of three studies using the fixed-effect model.

We applied k means clustering on channel-wise PFC activation t statistics across all the tasks.[113] Because a different fNIRS device was used in Move MYHAT and to reduce the systematic errors of fNIRS measurement across studies, we standardized PFC activation t statistics for move MYHAT as well as the t statistics for NMCM and PRIMA-NIRS together, by subtracting the mean from data and dividing by standard deviation. Number of clusters was determined by gap statistics. The maximized value of gap statistics was selected using the global maximum criterion.[114] Participants were clustered into 5 classes of different PFC activation patterns across channels and walking tasks. Walking task performance including walking speed and rate of correct letters, cognitive functions including MMSE, trails making A, and trails making B scores, and physical functions including LSA score, and physical and mental fatigability scores, were summarized for each class, and compared across classes using chi-

square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables.

4.3 Results

Demographics, clinical features, cognitive and physical functions, and walking task performance are displayed in table 1. The average age of each study is 76 (standard deviation: 5.8, NMCM), 76 (standard deviation: 6.6, PRIMA-NIRS), and 73 (standard deviation: 5.6, Move MYHAT). Around 60% of participants are female. Participants from NMCM have a lower prevalence of obesity and joint pain, and better performance in Trails Making A test and Trails Making B test. Participants from PRIMA-NIRS have higher prevalence of diabetes, higher average physical and mental fatigability scores, and lower LSA scores. Participants from Move MYHAT are more likely to be female and have lower education levels. (Table 4-1)

Average walking speed was lower for dual-task conditions compared to even walking. Average rate of correct letters was lower during uneven ABC walking compared to even ABC walking. The average walking speed was comparable in NMCM (0.79-0.97 m/s) and PRIMA-NIRS (0.78-0.94 m/s), and higher in Move MYHAT (0.88-1.05 m/s). The average rate of correct letters for even and uneven walking was lower in Move MYHAT. (Table 4-1)

Table 4-1. Baseline characteristics of three studies: Neural Mechanisms of Community Mobility (NMCM); Program to Improve Mobility in Aging, Near-Infrared Spectroscopy sub study (PRIMA-NIRS); and Move Monongahela-Youghiogheny Healthy Aging Team (Move MYHAT).

Study	**NMCM**	**PRIMA-NIRS**	**Move MYHAT**
n	29	42	46
Demographics			
Age, mean (SD)	76 (5.8)	76 (6.6)	73 (5.6)

Female, n (%)	15 (51.7)	25 (59.5)	30 (65.2)
Education level, n (%)			
High School/ Equivalent (9-12 years)	4 (13.8)	9 (21.4)	14 (30.4)
College (13-16 years)	15 (51.7)	16 (38.1)	22 (47.8)
Post Graduate (≥17)	10 (34.5)	17 (40.5)	10 (21.7)
Height, mean (SD), m	1.7 (0.11)	1.7 (0.09)	1.6 (0.11)
Weight, mean (SD), kg	75 (14.7)	83 (15.3)	79 (18.4)
Clinical Features			
Obesity, n (%)	3 (10.3)	13 (31.0)	19 (41.3)
Cardiovascular Disease, n (%)	3 (10.3)	4 (9.5)	2 (4.3)
Diabetes, n (%)	6 (20.7)	13 (31)	11 (23.9)
Joint Pain, n (%)	5 (17.2)	16 (38.1)	16 (34.8)
Cognitive function			
MMSE	29 (1.5)	29 (0.9)	28 (2.1)
Trails making Part A	27 (7.6)	32 (10)	33 (12)
Trails making Part B	74 (27)	78 (40)	84 (33)
Physical function			
Physical Fatiguability Score, mean (SD)	15 (7.5)	19 (8.1)	17 (7.6)
Mental Fatiguability Score, mean (SD)	9 (8.2)	10 (9.1)	11 (7.8)
Life Space Assessment	87 (19)	74 (17)	92 (20)
Walking task Performance, mean (SD), m/s			
Even	0.97 (0.14)	0.94 (0.16)	1.05 (0.20)
Uneven	0.90 (0.15)	0.86 (0.15)	1.00 (0.23)
Even ABC	0.83 (0.17)	0.83 (0.15)	0.93 (0.22)
Uneven ABC	0.79 (0.16)	0.78 (0.13)	0.88 (0.22)
Rate of correctly specifying alphabet, mean (SD), s^{-1}			
Even ABC	0.66 (0.23)	0.62 (0.18)	0.57 (0.14)

Uneven ABC	0.64 (0.21)	0.59 (0.17)	0.56 (0.15)

Walking on the uneven surface was associated with increased PFC activation averaged across all channels compared with even walking (beta coefficient: 0.50, 95%CI: 0.21, 0.80). Adding the alphabet dual-task is associated with a similar increase in PFC activation (beta coefficient: 0.59, 95%CI: 0.29, 0.87). The PFC activation t statistics of walking on the uneven surface with the alphabet task is 0.47 less than the sum of PFC activation in each individual dual-task condition (95%CI: -0.89, -0.05). (Table 4-2)

Table 4-2. Meta-analyzed beta coefficients and confidence intervals of the effects of dual tasks and interaction between dual tasks on the t statistics of prefrontal cortex activation. Models adjusted for age, sex, cardiovascular diseases, diabetes, obesity, and physical and mental fatigability scores.

Effect	**Beta (95% confidence interval)**
Uneven surface walking	0.50 (0.21, 0.80)
Alphabet task	0.59 (0.29, 0.87)
Interaction of uneven surface walking and alphabet task	-0.47 (-0.89, -0.05)

Walking speed was negatively associated with PFC activation t statistics across tasks (point estimate of coefficient range: -0.011, -0.003) (figure 4-2, Appendix A-9). We observed significant interactions of walking tasks and PFC activation on walking speed (all p values<0.0001), suggesting the associations of walking speed with PFC activation differ by walking task. However, the directions of interaction of task and PFC activation t statistics were not consistent across studies. (Appendix B-9)

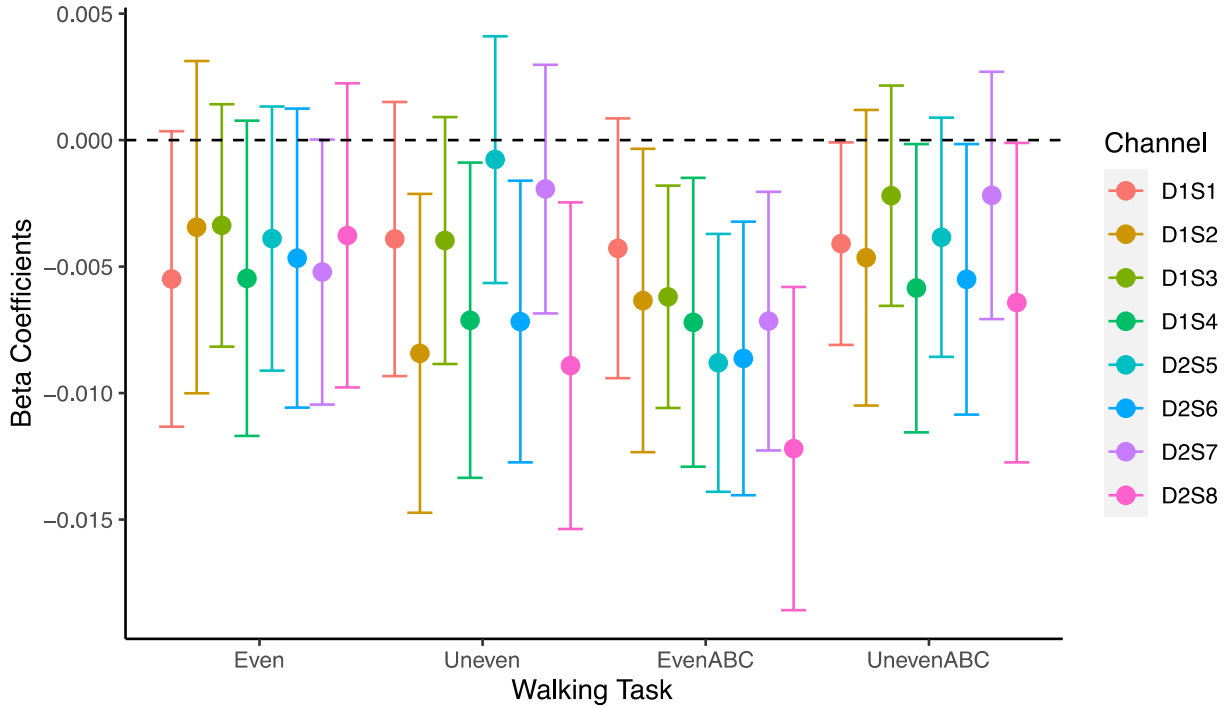

Figure 4-2. The meta-analyzed associations of walking speed (m/s) with t statistics of prefrontal cortex activation. Models conducted separately for each channel, and adjusted for age, sex, height, weight, cardiovascular diseases, diabetes, physical and mental fatiguability scores, and joint pain.

We observed a negative association of rate of correct alphabet with activation at left PFC (point estimate of coefficient range: -0.012, -0.002), but not with right PFC (figure 4-3, Appendix A-10). P values of interactions of walking tasks and PFC activation on alphabet rate range between 0.002 and 0.04, suggesting the associations of correct letter rate with PFC activation differ by walking tasks. The directions of interaction of task and PFC activation t statistics were not consistent across studies. (Appendix B-10)

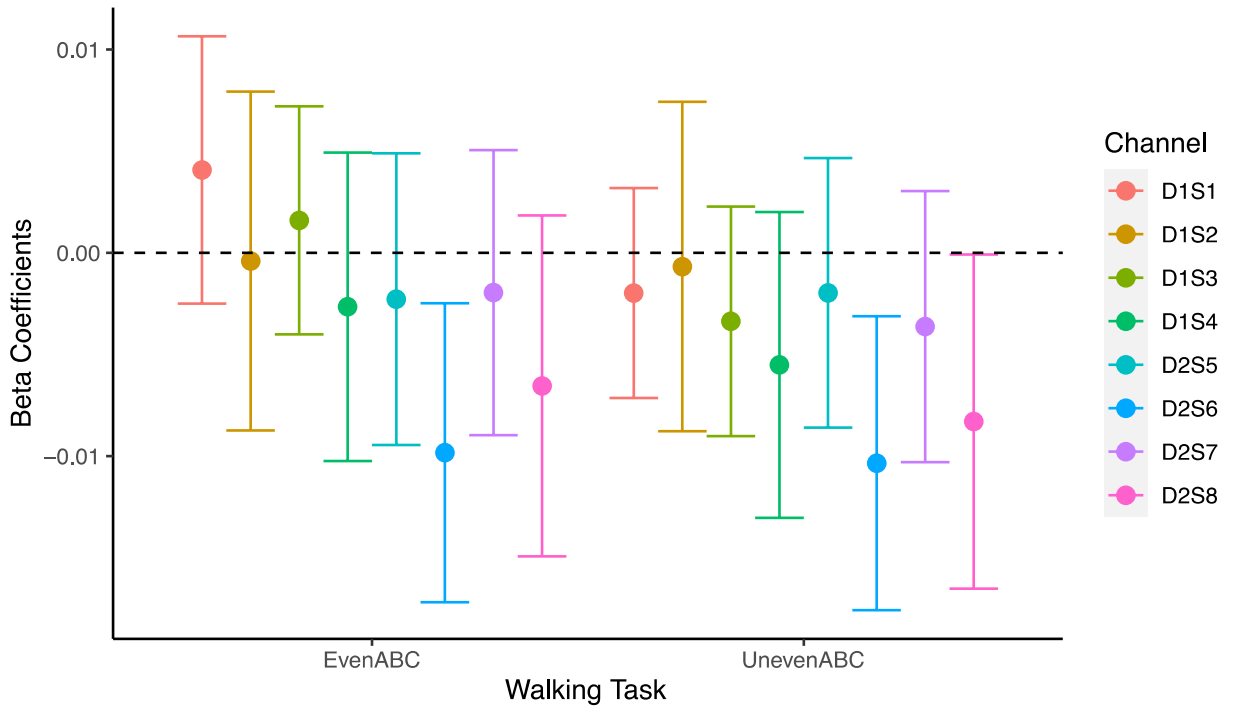

Figure 4-3. The meta-analyzed associations of correct alphabet rate (number/s) with t statistics of prefrontal cortex activation. Models conducted separately for each channel, and adjusted for age, sex, education, obesity, cardiovascular diseases, diabetes, and physical and mental fatiguability scores.

Five classes were identified after clustering based on t statistics of PFC activation: class 1 (n=15) if participants have negative PFC activation t statistics across tasks and channels; class 2 (n=46) if participants have low level of negative PFC activation t statistics at most but not all tasks and channels; class 3 (n=18) if participants have negative PFC activation t statistics during walking without alphabet task and positive PFC activation t statistics during walking with alphabet task; class 4 (n=27) if participants have positive PFC activation t statistics at certain tasks (more often at even and uneven) and channels; and class 5 (n=11) if participants have positive PFC activation t statistics across all tasks and channels. (Figure 4-4) According to the box plots of task performance stratified by classes, class 3 has slightly slower rate of correct letters than the other classes. Class 4 has slightly slower walking speed than the other four classes. Class 5 performs the best in both cognitive and physical tasks. (Figure 4-4) We did not

observe any difference in neuropsychological test scores, LSA scores, or physical and mental fatiguability scores by PFC activation class. (Appendix A-11)

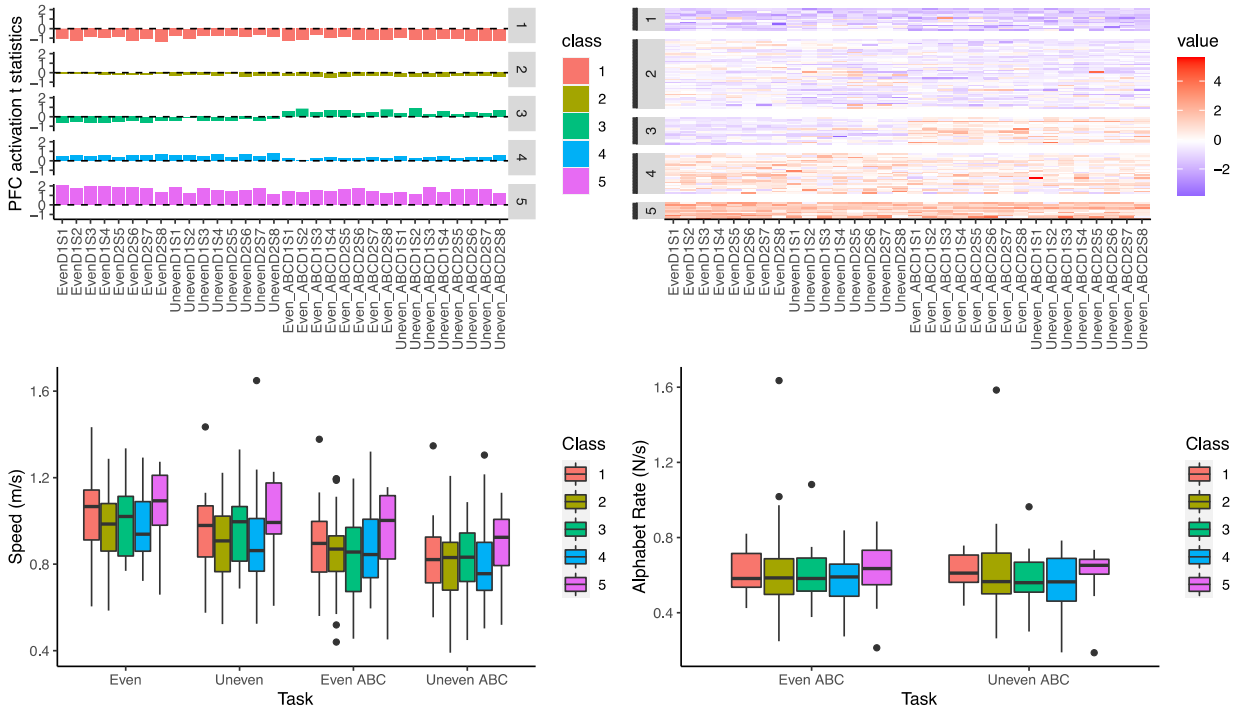

Figure 4-4. Group average (A) and individual-level (B) t statistics of prefrontal cortex activation across tasks and channels. Average walking speed (m/s) (C) and average correct alphabet rate (number/s) (D) by classes of each walking tasks.

4.4 Discussion

We observed increased PFC activation during both uneven walking and walking with an alphabet task compared with even walking in older adults. There is a negative interaction effect of walking with the combined uneven and alphabet task on PFC activation, such that activation during the combined task is lower than expected from the sum of the two individual dual-tasks. Task performance, including both walking speed and alphabet rate, were negatively related to PFC

activation. Five classes of PFC activation patterns during walking were identified. No differences in cognitive and physical functions are observed across classes, though some of the classes have small numbers of individuals.

PFC, which subserves executive function and attention, is engaged during gait in older adults, and is increasingly engaged as the walking tasks become more challenging.[115] In our results, physical and cognitive dual-tasks increased PFC activation to a similar extent. The finding is consistent with the results published in a previous review, where researchers found that obstacle walking and letter generation tasks while walking result in significant increases in PFC activation relative to unchallenged walking.[94] Our study found a smaller brain activation for the combined physical and cognitive challenges compared to the expected from the sum of individual conditions. Only one previous study assessed the interaction of physical and cognitive dual-tasks with fNIRS, and observed a similar dual-task interference.[80] Our results, along with previous findings, consistently suggest capacity limitation in neural resources among older adults. This theory was previously explained in the dual-task context by Boisgontier et al., where the information processing and throughput capacity in a brain circuit is reduced because of neuropathology on brain function in older adults.[100] This results in a plateau of brain activation and worse walking performance when the task difficulty level reached neural resource limit among older adults.[100]

Over-activation in PFC in older adults has been observed.[21] However, whether over-activation is related to declined or maintained performance is under debate. In a systematic review of fNIRS on cortical activity in posture and walking tasks, PFC activation during dual-task walking was associated with performance on motor tasks and cognitive tasks.[96] However, the direction of the associations were not consistent across those studies and the underlying mechanism is not clear.[97,116,117] Our results of negative associations of walking task performance with greater PFC

activation suggest that neural inefficiency theory may play a role underlying PFC over-activation among older adults. According to the neural inefficiency theory, over-activation in PFC among older adults results from not being able to efficiently allocate resources to support tasks, and is related to declined task performance.[21]

Current literature hypothesized that overactivation is likely to stem from multiple causes.[21] Our clustering analyses identified three classes of overactivation: class 3 with higher PFC activation during walking with greater cognitive demand; class 4 with higher PFC activation during even and uneven walking than walking with greater cognitive demand; and class 5 with higher PFC activation than the other classes across all walking tasks. In addition, we observed slightly slower alphabet rate in class 3, slightly slower walking speed in class 4, and greater alphabet rate and walking speed in class 5. Over-activation in PFC is likely related to inefficiency in cognitive-related and motor-related neural resources for class 3 and class 4, respectively, while over-activation is likely related to compensatory theory for class 5. Evidence supporting the compensatory theory has been observed in previous studies.[118] According to the compensatory theory, additional neural resources are recruited in older adults for maintaining successful walking and cognitive performance. Unlike younger adults who activate PFC only at higher demand, older adults increasingly activated PFC at all tasks, including tasks of lower demand.[21] Our results also indicate that not all of older adults exhibited overactivation, consistent with previous findings.[18] We observed two classes of older adults with low PFC activations (class 1 and class 2). Although they perform slightly better than the inefficiency groups, they do not perform as well as the compensatory group.

Although the interactions of PFC activation with task on performance are significant, they are not consistent across included study samples. We did not observe increases in strength of

associations between PFC activation and task performance as the task demand increased. These may be due to heterogeneity in PFC activation across tasks within the population, as shown by the clustering results and explained above. Alphabet performance is only associated with activation in left PFC, which signifies the semantic working memory process.[119] Unlike what we observed for alphabet rate, for walking speed, we did not observe any lateralized effect of left and right PFC activation. Activation in both left and right PFC regions were related to walking performance. This may be explained by hemispheric asymmetry reduction in older adults (HAROLD), where a more bilateral PFC activation pattern was reported in older adults than younger adults due to aging-related reorganization of neural circuits.[120] We did not identify any class with different PFC activations during walking on the uneven surface than during walking on the even surface. This may suggest that reciting the alternate alphabet as the dual-task is better for challenging PFC resources and identifying heterogeneities within populations than walking on an uneven surface. Last, there were no significant differences in cognitive and physical functions across classes. Our interpretations of clustering results are subjective without proof of cognitive and physical status differences. However, this might suggest that PFC activation along with walking performance could reflect subtle changes that would not be reflected by these clinical measures. Our results of clustering analyses need to be interpreted with caution, as some classes have small numbers of participants and the study is underpowered to detect the differences across classes.

Our study is subject to several limitations. First, the study power is limited by small sample sizes of each study. This could limit our study power to assess the associations between task performance and PFC activation, and to detect differences in cognitive and physical functions across classes identified from clustering analyses. Participants were recruited using different sampling methods across studies, so the differences in the underlying populations is a concern.

However, the Cochran's Q statistics of meta-analysis suggest no evidence of heterogeneity in results across studies. The signal-to-noise ratio of fNIRS measurement for some observations is low, which reduces the data quality. We applied conservative statistical modeling to filter the noise and mitigate its impact on our results. Correlations across channels may have an impact on the results of associations between walking task performance and PFC activation, but we were not able to address that in our analyses. The approach of identifying heterogeneous classes of PFC is exploratory, and the interpretations of clustering results are subjective. Also, by standardizing the t statistics of PFC activation, we could eliminate the true differences in activation patterns among participants between different studies. However, these results do support the hypothesis that there are different activation patterns within a population. More evidence is needed to test the heterogeneous groups of PFC activation patterns during walking tasks. Assessment of aging-related brain structural and neurochemical changes, such as gray matter volume in PFC, decline in white matter volume, cholinergic reduction, and dopaminergic denervation, could help to interpret neural models of age-related changes in the context of dual-task condition.[18,23] Finally, we only assessed activation in the PFC region, with limited understanding of activations in other important regions such as pre-motor cortex, supplementary motor area, and sensorimotor cortex. Future functional imaging studies on multiple regions including both PFC and other locomotor and cognition related regions are desired to create a complete profile of brain activation for the interpretation of aging-related brain activity changes.

Our study has some notable strengths. We applied the fNIRS processing pipeline with a high sensitivity and specificity in assessing brain activity, and used the t statistics comparing between tasks with baselines to obtain robust measures of task activation.[107] The comprehensive assessment of PFC activation and performance during walking with both physical and cognitive

dual-tasks allow us to compare across PFC activation during simple walking and walking with different concurrent task difficulty. We used reciting the alternate letters of the alphabet as the cognitive dual-task, as the associations of alphabet dual-task performance with cognitive functions were stronger than other cognitive dual-tasks.[121] Community walking as a daily activity involves motor and cognitive challenges. Successfully navigating the challenges requires attentional resources from PFC in older adults. Thus, we included both cognitive and physical challenges to walking. We applied the clustering analysis and identified heterogeneous groups of PFC activation patterns during walking tasks. Our results suggest that both neural inefficiency and compensatory theories may exist in older adults, and it is important to consider the heterogeneity in PFC activation when studying the association. This might also partially explain the inconsistencies of association between PFC and walking performance from current literature. Last, both theories demonstrate the wide agreement on age-related shift from automatic movement control to attentional movement control.[18] Interventions that could help to improve efficiency and capacity of brain activation in older adults, and shift back to automatic movement control during walking are desired.

5.0 Summary and Conclusions

Gait is a complex process which requires dynamic interactions between musculoskeletal, cardiopulmonary, and nervous systems.[5] Previous studies and scientific reviews have identified gray matter volumes in frontal, basal ganglia, hippocampal, and cerebellar regions correlated with simple walking, suggesting the important role of CNS in maintaining walking performance.[4,7] Based on a framework of gait domains that has been developed and validated previously, quantitative gait measures from pace, rhythm, and variability domains were used to capture the complexities of movement.[8-10] The quantitative measures are related to gray matter atrophy and loss of gray matter integrity, and reflect different underlying cognitive pathologies.[10,11] Prefrontal cortex, identified from previous literature of neural correlates of walking, is a key area of information processing and executive functions during community walking. [16-20] It is also one of the regions that are most susceptible to age-related atrophy.[21]

My dissertation work aims to address the evidence gaps of current literature, including 1) most of the previous evidence focused on speed and length of gait, and relations of specific brain regions with gait characteristics from other important domains was limited;[7] 2) compared to simple walking, community walking is often accompanied by greater environment challenges, and likely involves additional neural inputs of the brain.[14,15] Thus, studying usual walking speed alone may not reflect the subtle changes of brain and reveal the whole picture of neural correlates that are important for maintaining community walking in daily life; 3) mixed results of prefrontal cortex activation with walking performance and functional status have been observed, which makes it difficult to interpret age-related differences in PFC activation during walking.[18]

The overarching goal of my dissertation work is to identify brain regions related to the performance of walking tasks to provide evidence of the role of brain in community walking in older adults.

Because walking performance not only includes velocity and length of gait, but also timing and fluctuations across steps, we assessed these independent domains of usual walking and their neural correlates in older adults in the first paper. We used data from the Health, Aging, and Body Composition study. After missing data imputation and outlier exclusion, 291 participants had baseline gait measures at year 10, with 186 of them having repeated gait. GMVs were computed in AAL2 atlas regions for selected regions of interest (ROIs). We calculated domain scores of pace, spatial variability, rhythm, and temporal variability, representing velocity and length, fluctuations of spacing, time control of gait, and fluctuations of timing, respectively. We used sparse partial least squares to select important ROIs.[34] Our results suggest that pace is positively associated with GMV in selected subregions in frontal and cerebellar lobes. We also found that spatial variability relates to left anterior cingulate cortex and superior parietal lobe. The frontal, anterior cingulate, and superior parietal regions are part of the fronto-parietal network that is involved in executive function.[10,25] We observed annual rhythm change and temporal variability related to motor control regions, including subregions from basal ganglia and cerebellum, suggesting timing control of gait may be more rudimentary feature of gait. In addition, only rhythm showed significant inter-subject variation in age related effect.

In the second paper, we used fast paced walking to mimic the challenges of quickly processing and integrating multiple inputs and motor response and adapting locomotion during community walking, and assessed its neural correlates in older adults. We collected data from 284 older adults from the Health, Aging, and Body composition study. We examined the whole

brain using voxel-wise analyses on magnetic resonance imaging data to capture a wide network or regions related to fast-paced walking speed.[72] We then extracted gray matter density for all identified regions and modeled the association with fast-paced walking speed after adjusting for demographic factors, clinical factors, and cognitive function. We repeated the analyses for usual-paced walking. In general, the effect size of gray matter density of each region on usual-paced walking was smaller than fast-paced walking speed. We found that fast-paced walking speed, but not usual paced walking speed, was positively associated with gray matter density in cortical regions including right middle and superior frontal gyrus, right postcentral gyrus, and left superior temporal gyrus, related to executive function, somatosensory, and vestibular function, respectively.[74-76] Associations were lateralized to the right hemisphere, and robust to adjustment for demographic factors, clinical factors, and cognitive function. The results suggest that right cortex is specialized for vestibular control and impedance control, which are increasingly engaged in fast walking, and fast paced walking involved a higher conscious control than usual-paced walking.[84]

The third paper aims to evaluate PFC activation during community walking. We used the cross-sectional design with data from three independent samples (n=29, 42, and 46). We assessed PFC activation using functional near infrared spectroscopy during simple walking and dual task walking with cognitive and/or physical challenges. We compared PFC activation across tasks and its relation with walking performance after adjusting for multiple covariates. Finally, we clustered on PFC activation and summarized dual-task performance and physical functions by classes of PFC activation. Challenged walking is associated with greater PFC activation than even walking in older adults. We also found a smaller brain activation for the combined physical and cognitive challenges compared to the expected from the sum of individual conditions.

Walking task performance is negatively associated with greater PFC activation. The clustering analyses identified five classes of PFC activation. Our results suggest that PFC is increasingly engaged as the walking tasks with more physical and cognitive challenges. Capacity limitation in neural resources is likely to occur among older adults, impairing walking performance when environmental challenges increase. Older adults who are not able to efficiently allocate resources to support tasks have declined walking task performance.[21] PFC activation across tasks is heterogeneous within the population: low PFC activation for class 1 and class 2; cognitive-related and motor-related over-activation for class 3 and class 4, respectively; and over-activation at all tasks, including tasks of lower demand for class 5. In class 5, additional neural resources are likely to be recruited in older adults for maintaining successful walking and cognitive performance.[118]

Our analyses identified several brain regions related to executive and motor function that are important for maintaining walking performance from the aspects of velocity and length, timing control, and fluctuations of spacing and timing. These regions include frontal, anterior cingulate, superior parietal, cerebellar, and subregions from basal ganglia. In addition, we found that right middle and superior frontal gyrus, right postcentral gyrus, and left superior temporal gyrus, related to executive function, somatosensory, and vestibular function, respectively, are additionally involved during challenged walking compared with simple walking.[74-76] Last, we observed the importance of PFC in motor control during dual-task walking through assessment of its increased activation. We observed an overall negative association of PFC activation with walking performance, and heterogeneous PFC activation patterns that define groups which differ in walking performance. Our results suggest the important role of CNS in achieving successful walking performance among older adults. Early subclinical brain pathology could be identified

based on performance of walking, such as reduced gait velocity and length, increased variability of spacing, and reduced fast paced walking speed. Community walking is an important part of daily life that is accompanied by greater environmental challenges, requires additional neural resources related to executive function and other functions specific to the environmental challenges compared to simple walking. Our results also provide evidence that interventions on executive function, as well as on somatosensory and vestibular function, may help to improve the performance of community walking. Last, our results suggest that age-related PFC over-activation that indicates inefficiency in allocating resources and compensatory mechanisms for maintaining successful performance of community walking may both exist in the same population. This provides evidence to support future interventions of goal-oriented exercise and training to restore efficiency in PFC control during walking so that the performance of community walking can be improved.[5]

6.0 Appendix Tables

Table 6-1. Missing data to impute for the 313 participants.*

NDIX AVariables	N missing	N total sample size
Gray matter volumes	2	
Intracranial volume	8	
Hypertension	1	
Quadriceps strength	18	
APOE e4 allele	15	
Gait measures	21	
Total	54	259

*One participant from the original study sample was excluded because of missing date of gait measures.

Table 6-2. Quantitative gait measures at baseline (year 10) from each domain.

Gait measures	Mean (SD)
Pace domain	0.08 (1.92)
Gait speed (m/s)	0.91 (0.19)
Step length (m)	0.53 (0.09)
Rhythm domain (s)	-0.08 (2.30)
Swing time	0.39 (0.04)
Stance time	0.78 (0.10)
Step time	0.59 (0.06)
Spatial variability domain (m)	-0.09 (1.79)
Step length variability	2.07 (0.39)
Stride length variability	1.64 (0.36)
Temporal variability domain (s)	-0.23 (1.92)
Step time variability	1.85 (0.31)
Swing time variability	2.00 (0.34)
Stance time variability	1.93 (0.29)

Table 6-3. Baseline characteristics by number of repeated gait measures.

Characteristics	Number of repeated gait measures=0 (n=105)	Number of repeated measures ≥ 1 (n=186)
Age, mean (SD)	84 (3.0)	83 (2.6)
Female, n (%)	61 (58%)	111 (60%)
Black, n (%)	45 (43%)	75 (40%)
BMI, mean (SD)	27 (4.4)	27 (4.5)
APOE allele 4	28 (27%)	43 (23%)
Hypertension	79 (75%)	126 (68%)
Stroke, n (%)	10 (10%)	13 (7%)
Knee Pain, n (%)	42 (40%)	87 (47%)
Quadriceps Strength, mean (SD)	80 (31)	81 (28)
Pace, mean (SD)	-0.43 (2.1)	0.37 (1.7)
Rhythm, mean (SD)	-0.01 (2.2)	-0.12 (2.3)
Spatial variability, mean (SD)	0.45 (1.9)	-0.39 (1.6)
Temporal variability, mean (SD)	0.14 (2.0)	-0.43 (1.9)

Table 6-4. Gray matter volumes (GMVs) associated with gait at average age. Regions of interest (ROIs) selected from sparse partial least square model. Results were adjusted for age, sex, race, BMI, APOE alleles, hypertension, stroke, knee pain, and quadriceps strength.

Gait domains	**Gray matter regions**	**β coefficients (95% confidence interval)**
Pace	right cerebellum 4-5	$0.12\ (0.04, 0.21)$
	left inferior orbitofrontal	$0.12\ (0.03, 0.22)$
Rhythm	right putamen	$-0.10\ (-0.21, 0.01)$
	right posterior cingulum	$0.09\ (-0.03, 0.20)$
Spatial variability	left anterior cingulum	$-0.12\ (-0.22, -0.03)$
	left superior parietal	$-0.13\ (-0.24, -0.03)$
Temporal variability	right cerebellum 4-5	$-0.12\ (-0.24, -0.03)$
	left cerebellum 9	$0.12\ (-0.003, 0.24)$

Table 6-5. Gray matter volumes (GMVs) associated with gait annual change. Regions of interest (ROIs) selected from sparse partial least square model. Results were adjusted for age, sex, race, BMI, APOE alleles, hypertension, stroke, knee pain, and quadriceps strength.

Gait domains	**Gray matter regions**	**β coefficients (95% confidence interval)**
Rhythm	right putamen	$-0.07\ (-0.13, 0.02)$
	right pallidum	$-0.07\ (-0.14, 0.02)$
	left superior orbitofrontal	$0.07\ (0.001, 0.18)$

Table 6-6. Gray matter density of regions associated with fast-paced walking speed without adjustment.

Hemisphere	ROI	Cluster Size (Voxels)	t-statistic (max)	X	Y	Z
Right	Middle Temporal Gyrus	1091	5.4	70	-18	-6
	Cerebellum 6	792	5	26	-56	-18
	Superior Temporal Gyrus	737	5.6	68	-18	-4
	Cerebellum Crus 1	595	4.9	36	-74	-32
	Insula	398	5.3	38	10	10
	Middle Frontal Gyrus	335	4.8	28	54	2
	Superior Medial Frontal Gyrus	298	5	14	68	22
	Cerebellum 4-5	296	5	24	-50	-20
	Superior Temporal Pole	292	4.9	34	10	-24
	Middle Orbital Frontal Gyrus	273	5.4	10	42	-6
	Anterior Cingulate	269	5.2	8	38	-8
	Fusiform Gyrus	256	4.5	26	-52	-16
	Cerebellum Crus 2	255	5.1	44	-68	-40
	Inferior Temporal Gyrus	242	4.6	60	-62	-4
	Supramarginal Gyrus	228	4.5	66	-36	38
	Rolandic Operculum	225	4.6	44	-14	16
	Lingual Gyrus	216	4.4	16	-48	4
	Middle Temporal Pole	209	5	54	4	-16
	Middle Occipital Gyrus	192	4.2	46	-82	6
	Parahippocampus	190	4.6	30	8	-26
	Superior Frontal Gyrus	159	5.1	14	68	24
	Paracentral Lobule	144	4.3	8	-36	60
	Cerebellum 8: Vermis	136	4.7	0	-72	-40
	Middle Cingulate	129	4.5	4	-36	40
	Amygdala	121	4.8	32	4	-26
	Lateral Orbital Frontal Gyrus	113	4.1	36	58	-2
	Hippocampus	95	4.1	32	-4	-20
	Inferior Orbital Frontal Gyrus	94	4.1	38	32	-2
	Gyrus Rectus	89	4.1	4	38	-16
	Inferior Parietal Gyrus	87	4.2	60	-40	46
	Calcarine Sulcus	79	4.1	18	-50	4
	Superior Orbital Frontal Gyrus	77	4.4	22	46	-14
	Angular Gyrus	70	4.2	62	-50	36
	Precuneus	59	4.3	14	-40	58

	Postcentral Gyrus	50	4.5	64	0	18
	Inferior Frontal Operculum	36	4.9	42	10	8
	Cerebellum 3	32	3.8	10	-44	-22
	Inferior Triangular Frontal Gyrus	26	4.3	36	22	10
	Cerebellum 8	15	3.8	6	-64	-32
Left	Cerebellum Crus 1	780	5	-30	-72	-30
	Cerebellum 6	703	4.4	-22	-50	-22
	Middle Temporal Gyrus	655	5.3	-58	-38	12
	Cerebellum Crus 2	648	5.1	-38	-66	-38
	Superior Temporal Gyrus	495	5.6	-54	-38	14
	Cerebellum 8	392	4.4	-30	-64	-46
	Insula	339	4.6	-26	26	0
	Middle Orbital Frontal Gyrus	321	5.3	-8	38	-12
	Cerebellum 4-5	320	4.3	-22	-50	-20
	Anterior Cingulate	262	5	-8	42	-4
	Inferior Temporal Gyrus	249	4.3	-40	-28	-24
	Postcentral Gyrus	233	5.1	-54	-10	26
	Superior Medial Frontal Gyrus	218	4.7	-12	52	4
	Middle Cingulate	203	4.9	-2	-28	44
	Fusiform Gyrus	153	4.3	-34	-40	-24
	Cerebellum 7b	144	4.8	-32	-64	-46
	Posterior Cingulate	120	4.7	-6	-46	18
	Gyrus Rectus	107	4.4	-10	34	-14
	Supramarginal Gyrus	96	4.3	-44	-34	26
	Superior Temporal Pole	91	3.9	-50	18	-12
	Calcarine Sulcus	88	3.9	-16	-64	8
	Precentral Gyrus	77	4.7	-56	-8	32
	Cerebellum 9	76	4.2	-18	-52	-52
	Precuneus	59	5.3	-8	-48	16
	Rolandic Operculum	51	4	-36	-8	16
	Superior Orbital Frontal Gyrus	47	3.9	-10	14	-22
	Inferior Orbital Frontal Gyrus	37	4.1	-16	10	-18
	Olfactory Gyrus	36	3.9	-16	12	-18
	Middle Temporal Pole	26	3.9	-56	4	-34
	Lingual Gyrus	18	3.8	-16	-66	2

Table 6-7. Gray matter density of regions associated with usual-paced walking speed without adjustment.

Hemisphere	ROI	Cluster Size (Voxels)	t-statistic (max)	X	Y	Z
Right	Cerebellum Crus 1	594	4.5	38	-62	-32
	Cerebellum 6	491	4.3	24	-50	-22
	Cerebellum Crus 2	346	4.3	44	-66	-40
	Insula	328	5.5	34	14	8
	Cerebellum 4-5	290	4.4	22	-48	-22
	Parahippocampus	221	4.2	32	-20	-20
	Calcarine Sulcus	200	4.6	12	-72	8
	Inferior Frontal Operculum	188	4.7	38	18	32
	Cerebellum 8: Vermis	183	4.5	6	-68	-36
	Middle Temporal Pole	177	4.4	36	10	-30
	Middle Orbital Frontal Gyrus	147	5.0	8	40	-8
	Cuneus	141	4.9	8	-80	36
	Rolandic Operculum	136	4.7	38	-18	18
	Middle Occipital Gyrus	123	4.3	38	-84	6
	Hippocampus	113	3.9	32	-18	-18
	Caudate	112	4.3	20	-4	24
	Cerebellum 8	103	4.4	8	-68	-34
	Amygdala	98	4.2	28	2	-20
	Fusiform Gyrus	89	4.0	26	-32	-20
	Superior Temporal Pole	71	4.6	34	10	-30
	Inferior Triangular Frontal Gyrus	63	4.3	38	18	30
	Anterior Cingulate	49	4.7	8	38	-8
	Cerebellum 7b	46	3.5	26	-80	-50
	Lingual Gyrus	29	4.2	14	-62	8
	Cerebellum 7: Vermis	27	4.0	2	-70	-32
	Cerebellum 9: Vermis	27	3.7	0	-62	-40
	Putamen	25	4.7	32	14	8
	Postcentral Gyrus	24	3.7	64	-2	16
	Middle Temporal Gyrus	22	3.9	50	-74	0
	Gyrus Rectus	7	3.4	2	22	-16
Left	Cerebellum Crus 2	668	5.7	-40	-64	-44
	Cerebellum Crus 1	651	5.1	-32	-68	-30
	Cerebellum 8	632	5.4	-32	-62	-46
	Cerebellum 6	625	4.7	-26	-54	-20
	Insula	259	4.5	-34	10	10

	Cerebellum 4-5	246	4.3	-24	-46	-22
	Fusiform Gyrus	246	4.4	-32	-20	-22
	Calcarine Sulcus	201	4.2	-4	-86	-8
	Hippocampus	185	4.4	-30	-20	-20
	Caudate	181	4.3	-18	-12	22
	Cerebellum 7b	160	5.0	-34	-62	-46
	Superior Temporal Gyrus	140	5.9	-56	-40	22
	Middle Orbital Frontal Gyrus	118	4.4	-8	38	-14
	Superior Occipital Gyrus	118	4.8	-10	-98	20
	Middle Temporal Gyrus	105	5.3	-46	-58	20
	Parahippocampus	97	4.5	-30	-20	-22
	Precuneus	84	4.5	-8	-46	14
	Angular Gyrus	67	4.0	-46	-74	28
	Cuneus	62	4.2	-6	-100	14
	Lingual Gyrus	50	3.8	-16	-52	-10
	Cerebellum 9	36	3.7	-18	-50	-56
	Gyrus Rectus	36	4.0	-6	36	-16
	Amygdala	29	3.5	-28	2	-20
	Rolandic Operculum	25	4.0	-38	-20	16
	Inferior Temporal Gyrus	25	3.7	-44	-50	-16
	Supramarginal Gyrus	20	4.1	-52	-40	26

Table 6-8. Association between usual-paced walking speed and gray matter density. Corresponding coefficients (β) and p-values are shown across three nested models.

Region	MNI coordinates (x, y, z)	Model 1 [a]	Model 2 [b]	Model 3 [c]
		β (p-value) [d]		
Left Angular Gyrus	(-46, -74, 28)	0.08 (0.003)	0.06 (0.01)	0.04 (0.12)
Left Calcarine Sulcus	(-4, -86, -8)	0.12 (0.002)	0.10 (0.005)	0.08 (0.03)
Right Calcarine Sulcus	(12, -72, 8)	0.06 (0.008)	0.05 (0.03)	0.03 (0.11)
Left Caudate	(-18, -12, 22)	0.41 (<0.001)	0.34 (0.002)	0.28 (0.01)
Right Caudate	(20, -4, 24)	0.20 (<0.001)	0.16 (0.004)	0.13 (0.02)
Right Cerebellum 4-5	(22, -48, -22)	0.06 (0.03)	0.05 (0.08)	0.04 (0.11)
Left Cerebellum 6	(-26, -54, -20)	0.05 (0.04)	0.03 (0.22)	0.01 (0.56)
Right Cerebellum 6	(24, -50, -22)	0.06 (0.02)	0.04 (0.09)	0.03 (0.17)
Left Cerebellum Crus 1	(-32, -68, -30)	0.06 (0.01)	0.05 (0.04)	0.03 (0.13)
Right Cerebellum Crus 1	(38, -62, -32)	0.06 (0.03)	0.05 (0.06)	0.04 (0.08)
Left Cerebelum Crus 2	(-40, -64, -44)	0.05 (0.03)	0.04 (0.08)	0.03 (0.19)
Right Anterior Cingulate	(8, 38, -8)	0.10 (0.001)	0.08 (0.006)	0.06 (0.05)
Left Cuneus	(-6, -100, 14)	0.21 (<0.001)	0.18 (0.004)	0.15 (0.01)
Right Cuneus	(8, -80, 36)	0.12 (0.001)	0.11 (0.003)	0.09 (0.01)
Right Inferior Frontal Operculum	(38, 18, 32)	0.16 (<0.001)	0.13 (0.003)	0.10 (0.04)
Right Inferior Triangular Frontal Gyrus	(38, 18, 30)	0.06 (0.01)	0.05 (0.06)	0.03 (0.17)
Left Middle Orbital Frontal Gyrus	(-8, 38, -14)	0.05 (0.02)	0.03 (0.15)	0.01 (0.53)

Right Middle Orbital Frontal Gyrus	(8, 40, -8)	0.08 (0.002)	0.07 (0.01)	0.05 (0.08)
Right Fusiform Gyrus	(26, -32, -20)	0.08 (0.03)	0.06 (0.10)	0.04 (0.26)
Left Insula	(-34, 10, 10)	0.13 (0.02)	0.09 (0.10)	0.04 (0.51)
Right Insula	(34, 14, 8)	0.15 (0.004)	0.10 (0.06)	0.05 (0.38)
Left Lingual Gyrus	(-16, -52, -10)	0.07 (0.02)	0.06 (0.04)	0.04 (0.18)
Right Lingual Gyrus	(14, -62, 8)	0.06 (0.02)	0.05 (0.05)	0.03 (0.25)
Right Middle Occipital Gyrus	(38, -84, 6)	0.05 (0.01)	0.04 (0.05)	0.03 (0.11)
Left Superior Occipital Gyrus	(-10, -98, 20)	0.12 (0.002)	0.11 (0.007)	0.09 (0.02)
Left Precuneus	(-8, -46, 14)	0.07 (0.05)	0.05 (0.13)	0.03 (0.43)
Right Putamen	(32, 14, 8)	0.22 (0.03)	0.15 (0.14)	0.04 (0.70)
Left Rolandic Operculum	(-38, -20, 16)	0.14 (0.008)	0.10 (0.05)	0.06 (0.27)
Right Rolandic Operculum	(38, -18, 18)	0.07 (0.04)	0.05 (0.21)	0.03 (0.36)
Left Supramarginal Gyrus	(-52, -40, 26)	0.04 (0.02)	0.04 (0.03)	0.02 (0.16)
Left Middle Temporal Gyrus	(-46, -58, 20)	0.07 (0.01)	0.05 (0.05)	0.03 (0.25)
Right Superior Temporal Pole	(34, 10, -30)	0.15 (0.04)	0.11 (0.12)	0.04 (0.57)
Left Superior Temporal Gyrus	(-56, -40, 22)	0.10 (0.005)	0.08 (0.02)	0.05 (0.11)

Notes: BMI - body mass index; TIA - transient ischemic attack; CESD - Center for Epidemiologic Studies-Depression; 3MSE - Modified Mini-Mental State Examination; DSST - Digit Symbol Substitution Test

a. Model 1: general linear model adjusting for demographics (age, sex, race, education, and BMI);

b. Model 2: based on model 1, further adjusting for morbidities (cardiovascular disease, stroke or TIA, hypertension, diabetes, and CESD score);

c. Model 3: based on model 2, further adjusting for cognition (3MSE and DSST scores).

d. The coefficient of 1 SD change of regional gray matter density on usual-paced walking speed and the corresponding p value

Table 6-9. Association of walking speed (m/s) with t statistics of prefrontal cortex activation, adjusted for age, sex, height, weight, cardiovascular diseases, diabetes, physical and mental fatiguability scores, and joint pain.

Task	Channel	Point Estimate	95% Confidence Interval
Even	**D1S1**	-0.005	(-0.011, 0.000)
	D1S2	-0.003	(-0.010, 0.003)
	D1S3	-0.003	(-0.008, 0.001)
	D1S4	-0.005	(-0.012, 0.001)
	D2S5	-0.004	(-0.009, 0.001)
	D2S6	-0.005	(-0.011, 0.001)
	D2S7	-0.005	(-0.010, 0.000)
	D2S8	-0.004	(-0.010, 0.000)
Uneven	**D1S1**	-0.004	(-0.009, 0.002)
	D1S2	-0.008	(-0.015, -0.002)
	D1S3	-0.004	(-0.009, 0.001)
	D1S4	-0.007	(-0.013, -0.001)
	D2S5	-0.001	(-0.006, 0.004)
	D2S6	-0.007	(-0.013, -0.002)
	D2S7	-0.002	(-0.007, 0.003)
	D2S8	-0.009	(-0.015, -0.002)
Even ABC	**D1S1**	-0.004	(-0.009, 0.001)
	D1S2	-0.006	(-0.012, 0.000)
	D1S3	-0.007	(-0.011, -0.002)
	D1S4	-0.007	(-0.013, -0.001)
	D2S5	-0.009	(-0.014, -0.004)
	D2S6	-0.009	(-0.014, -0.003)
	D2S7	-0.007	(-0.012, -0.002)
	D2S8	-0.012	(-0.019, -0.006)
Uneven ABC	**D1S1**	-0.004	(-0.008, 0.000)
	D1S2	-0.005	(-0.010, 0.001)
	D1S3	-0.002	(-0.007, 0.002)
	D1S4	-0.006	(-0.012, 0.000)
	D2S5	-0.004	(-0.009, 0.001)
	D2S6	-0.006	(-0.011, 0.000)
	D2S7	-0.002	(-0.007, 0.003)
	D2S8	-0.006	(-0.013, 0.000)

Table 6-10. Association of rate of correctly specifying alphabet (number/s) with t statistics of prefrontal cortex activation, adjusting for age, sex, education, obesity, cardiovascular diseases, diabetes, obesity, and physical and mental fatiguability scores.

Task	Channel	Point Estimate	95% Confidence Interval
Even ABC	**D1S1**	0.004	(-0.002, 0.011)
	D1S2	0.000	(-0.009, 0.008)
	D1S3	0.002	(-0.004, 0.007)
	D1S4	-0.003	(-0.010, 0.005)
	D2S5	-0.002	(-0.009, 0.005)
	D2S6	-0.010	(-0.017, -0.002)
	D2S7	-0.002	(-0.009, 0.005)
	D2S8	-0.007	(-0.015, 0.002)
Uneven ABC	**D1S1**	-0.002	(-0.007, 0.003)
	D1S2	-0.001	(-0.009, 0.007)
	D1S3	-0.003	(-0.009, 0.002)
	D1S4	-0.006	(-0.013, 0.002)
	D2S5	-0.002	(-0.009, 0.005)
	D2S6	-0.010	(-0.018, -0.003)
	D2S7	-0.004	(-0.010, 0.003)
	D2S8	-0.008	(-0.017, 0.000)

Table 6-11. Average cognitive and physical functions by classes. Continuous variables compared across classes using analysis of variance and categorical variables compared across classes using chi-square test.

Cognitive functions	**Average by classes**	**Test statistics (p values)**
Mini Mental State Exam, ≥mean, n (%)	11 (73) (Class 1) 35 (76) (Class 2) 10 (56) (Class 3) 17 (63) (Class 4) 5 (45) (Class 5)	5.5 (0.24)
Trails Making Part A, mean (standard deviation)	32 (14) (Class 1) 29 (7.9) (Class 2) 33 (13) (Class 3) 32 (9.9) (Class 4) 34 (15) (Class 5)	0.89 (0.47)
Trails Making Part B, mean (standard deviation)	73 (29) (Class 1) 80 (36) (Class 2) 84 (32) (Class 3) 83 (39) (Class 4) 76 (26) (Class 5)	0.31 (0.87)
Physical functions	**Average by classes**	**Test statistics (p values)**
Life Space Assessment, mean (standard deviation)	81 (23) (Class 1) 85 (20) (Class 2) 86 (20) (Class 3) 80 (21) (Class 4) 93 (16) (Class 5)	1.13 (0.35)
Physical Fatiguability, mean (standard deviation)	18 (7.5) (Class 1) 18 (7.0) (Class 2) 14 (9.8) (Class 3) 17 (7.3) (Class 4) 16 (9.7) (Class 5)	0.81 (0.52)
Mental Fatiguability, mean (standard deviation)	12 (9.1) (Class 1) 11 (8.7) (Class 2) 5.9 (5.7) (Class 3) 11 (8.6) (Class 4) 9.7 (7.9) (Class 5)	1.44 (0.23)

7.0 Appendix Figures

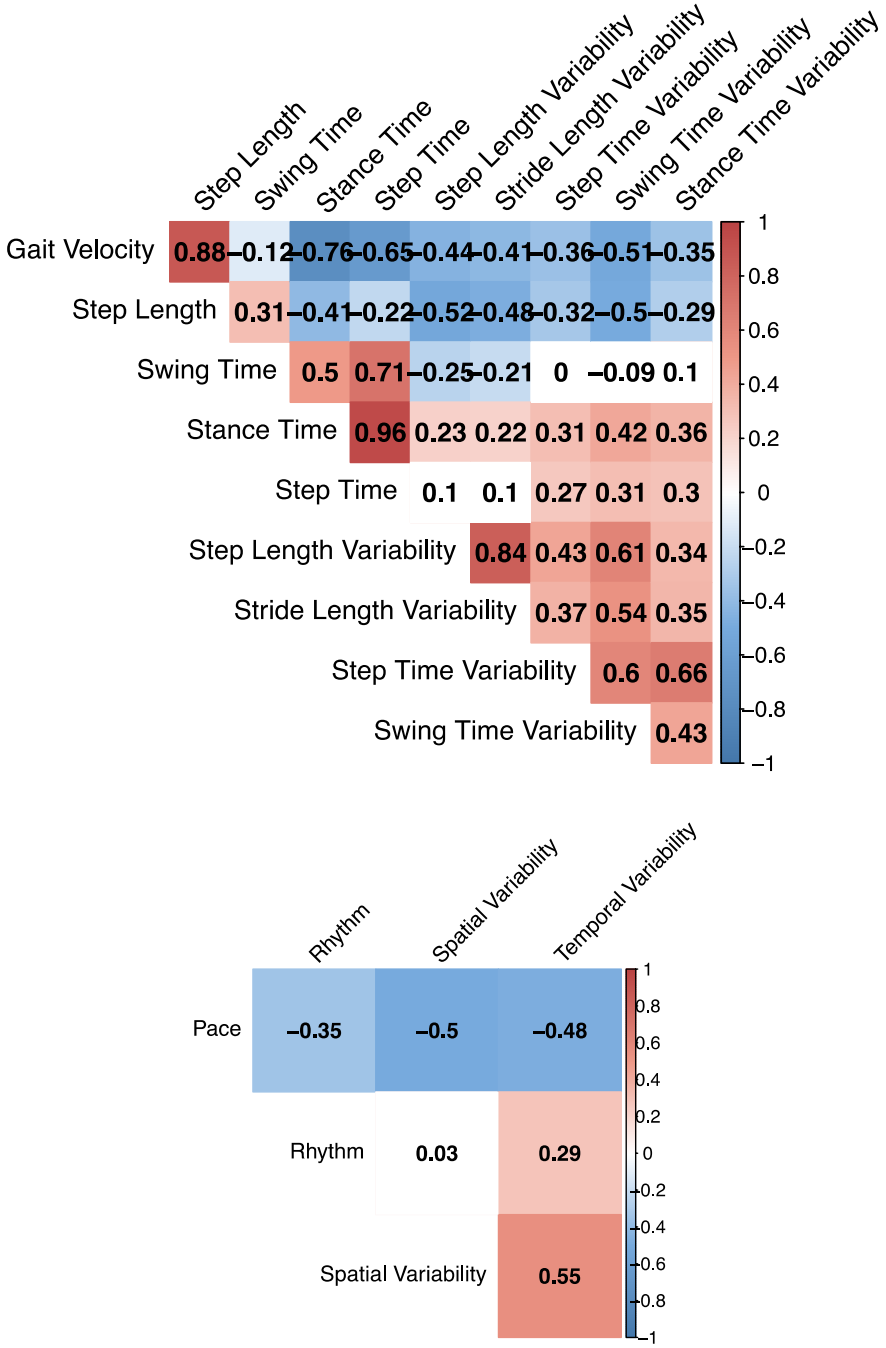

Figure 7-1. Distributions and correlations of gait measures.

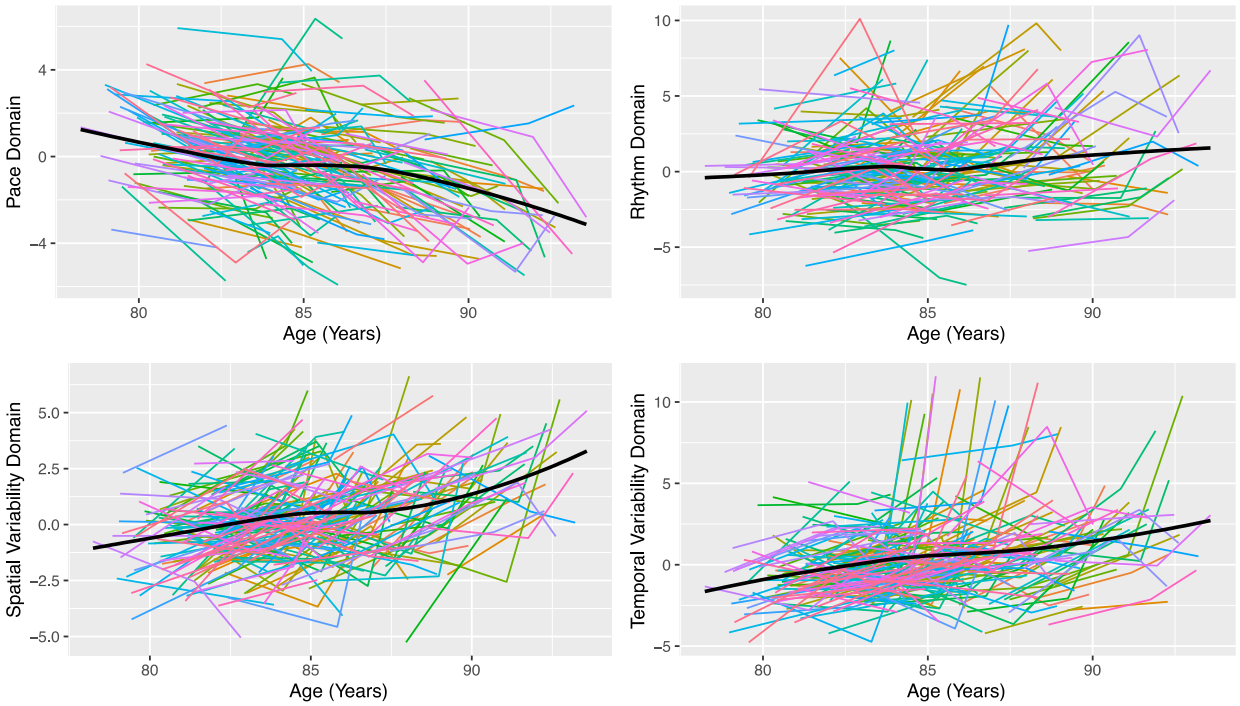

Figure 7-2. Average changes in characteristics of each walking domain (pace, rhythm, spatial variability, and temporal variability) with age.

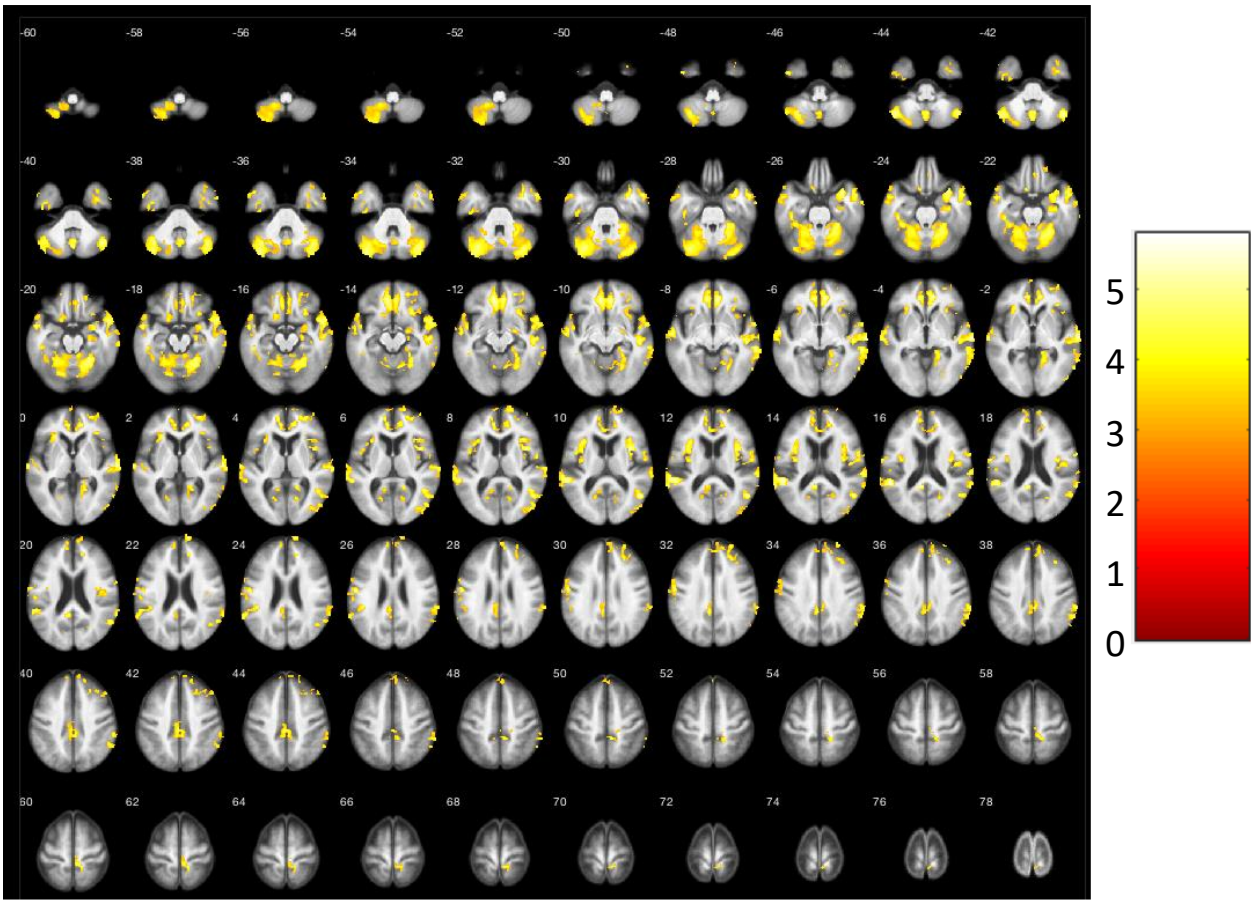

Figure 7-3. Association between gray matter density and fast-paced walking speed without adjusting for any covariates. Color bar indicates value of the t-statistic testing the association between gray matter density and fast-paced walking speed.

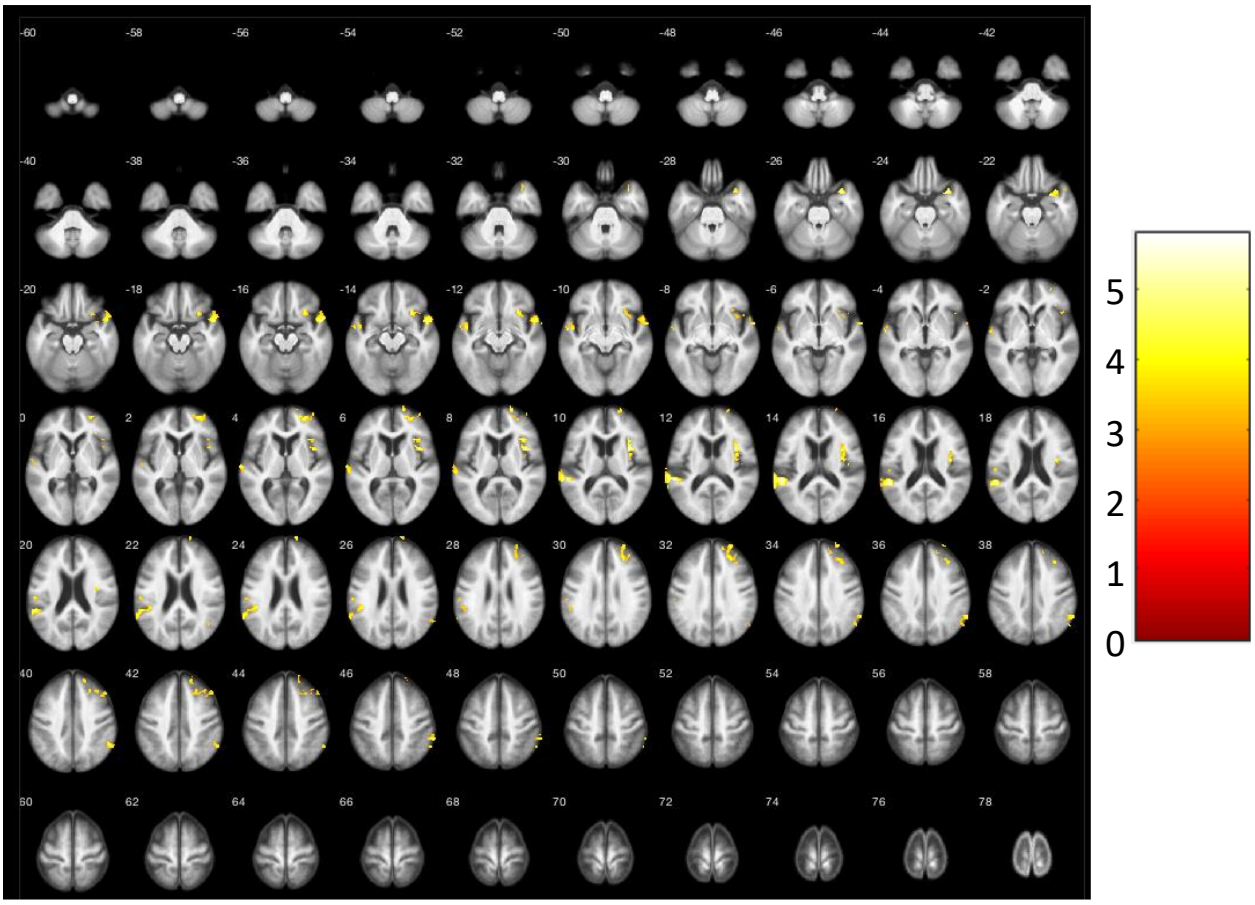

Figure 7-4. Association between gray matter density and fast-paced walking speed that remained significant after adjusting for demographic variables, clinical morbidities, and cognitive function – including those with smaller effect sizes, i.e. <0.3 m/s.. Color bar indicates value of the t-statistic testing the association between gray matter density and fast-paced walking speed.

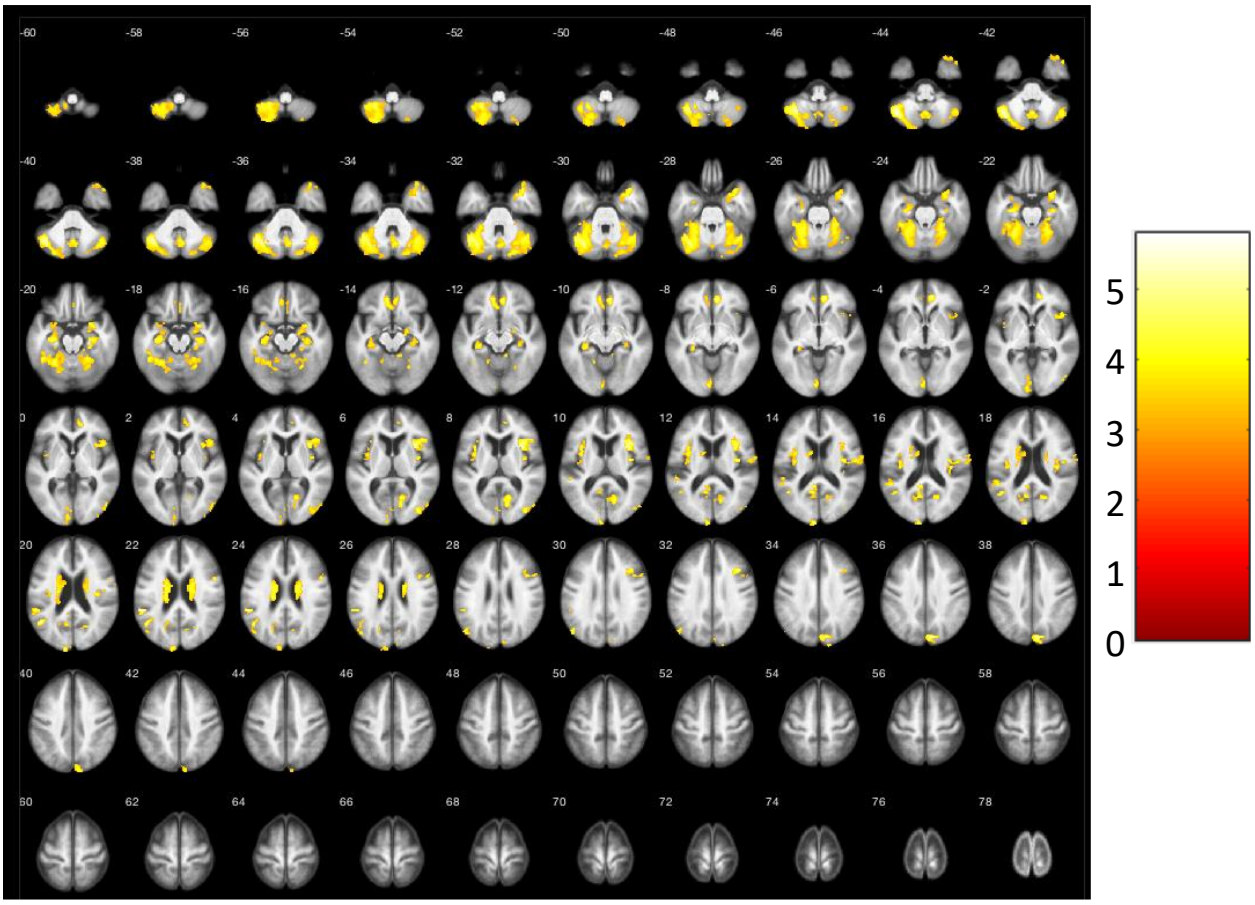

Figure 7-5. Association between gray matter density and usual-paced walking speed without adjusting for any covariates. Color bar indicates value of the t-statistic testing the association between gray matter density and fast-paced walking speed.

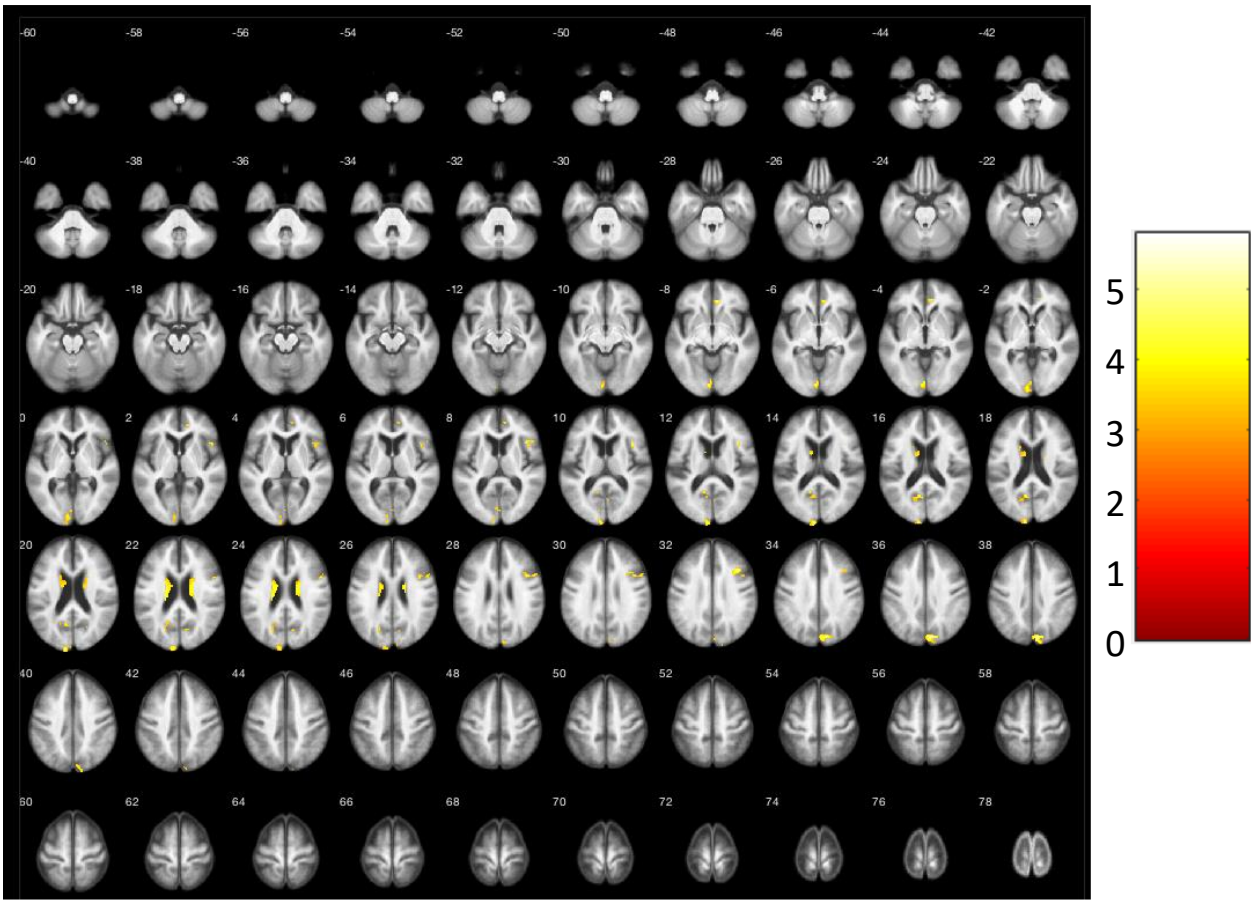

Figure 7-6. Association between gray matter density and usual-paced walking speed that remained significant after adjusting for demographic variables, clinical morbidities, and cognitive function – including those with smaller effect sizes, i.e. <0.3 m/s.. Color bar indicates value of the t-statistic testing the association between gray matter density and fast-paced walking speed.

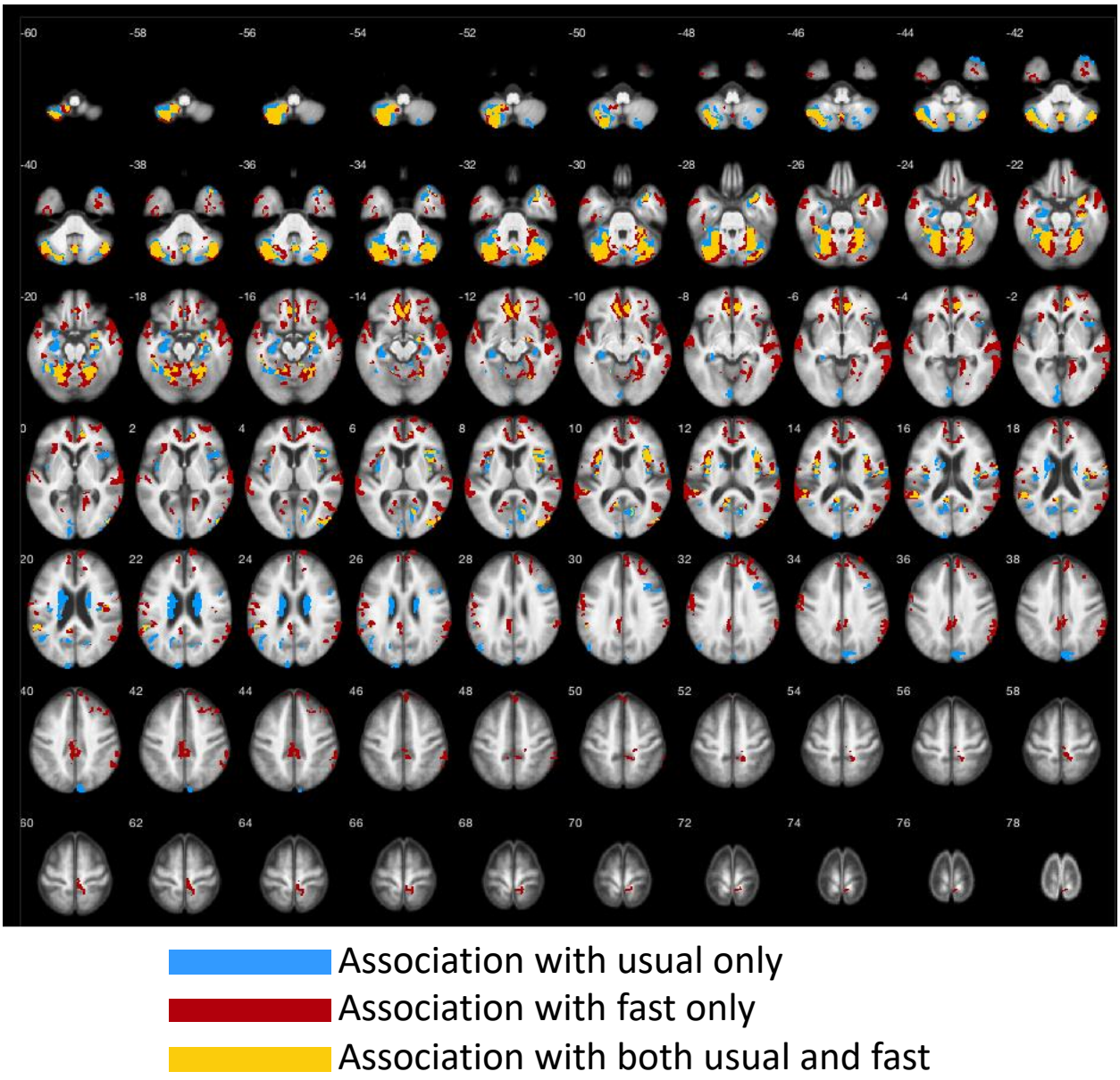

Figure 7-7. Association between gray matter density and walking speed without adjusting for covariates. Colors indicate whether association was with usual-paced walking speed only (blue), fast-paced walking speed only (red), or both usual- and fast-paced walking speed (yellow).

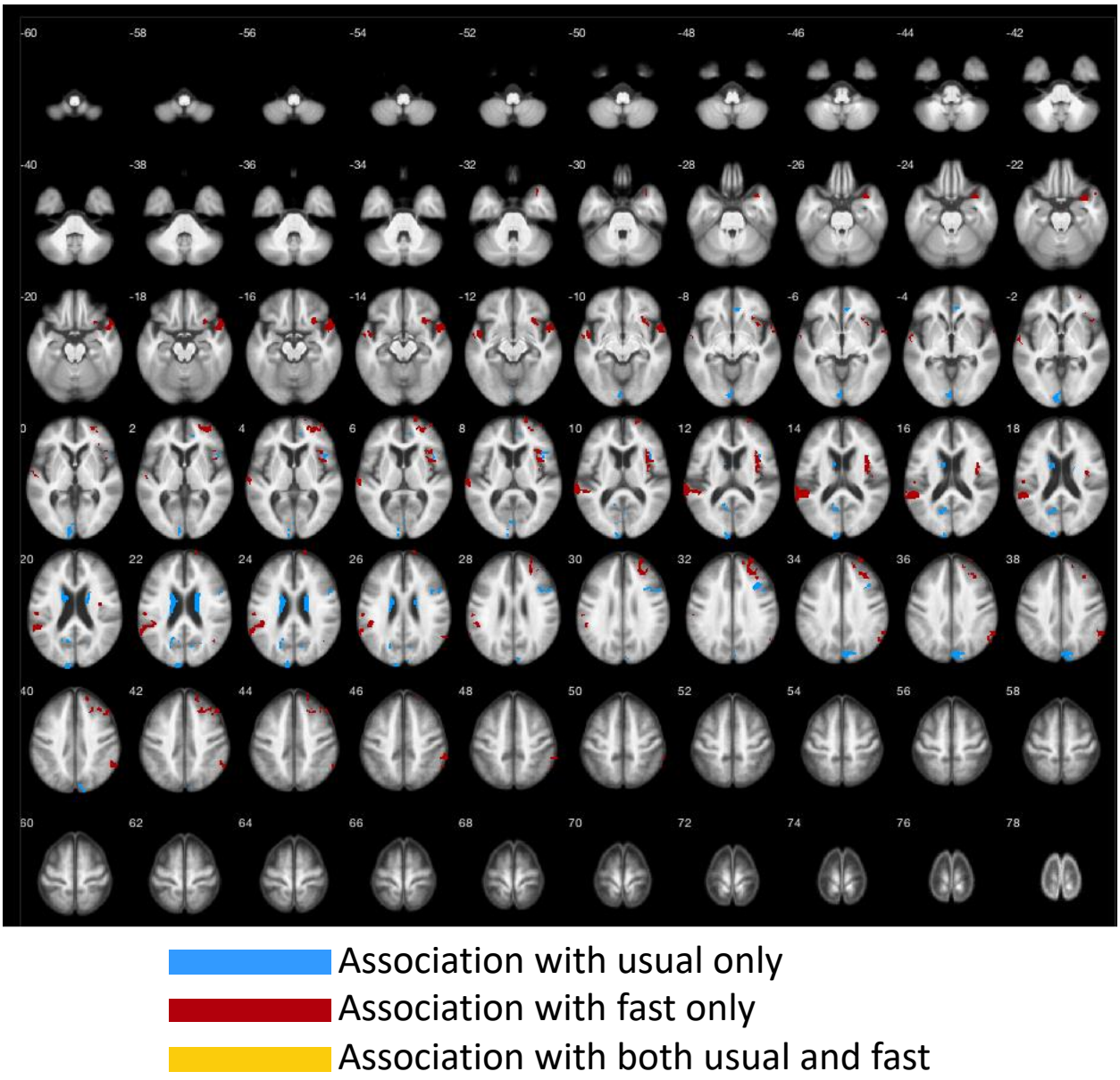

Figure 7-8. Association between gray matter density and walking speed after adjusting for covariates. Colors indicate whether association was with usual-paced walking speed only (blue), fast-paced walking speed only (red), or both usual- and fast-paced walking speed (yellow). No regions showed association with both usual- and fast-paced walking speed after adjustment.

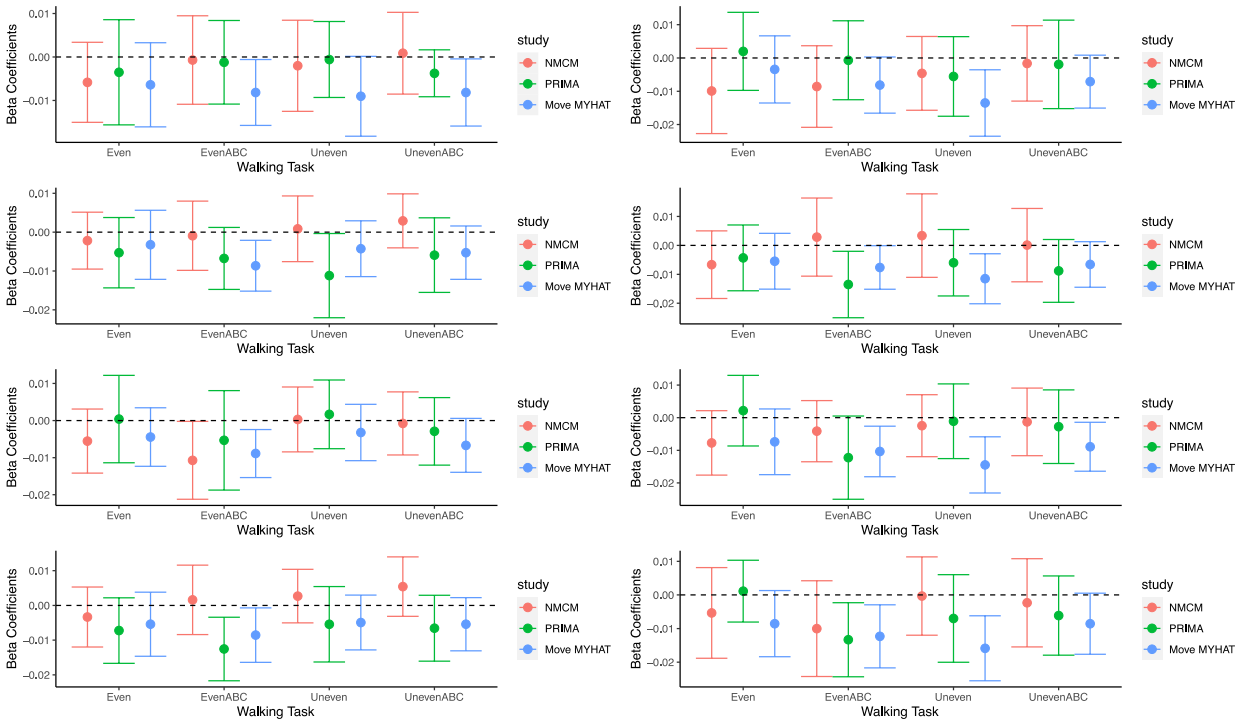

Figure 7-9. The associations of walking speed (m/s) with t statistics of prefrontal cortex activation for each channel (Channel 1-Channel 8) in Neural Mechanisms of Community Mobility (NMCM), Program to Improve Mobility in Aging, Near-Infrared Spectroscopy sub study (PRIMA-NIRS), and Move Monongahela-Youghiogheny Healthy Aging Team (Move MYHAT). Modeling adjusted for age, sex, height, weight, cardiovascular diseases, diabetes, physical and mental fatiguability scores, and joint pain.

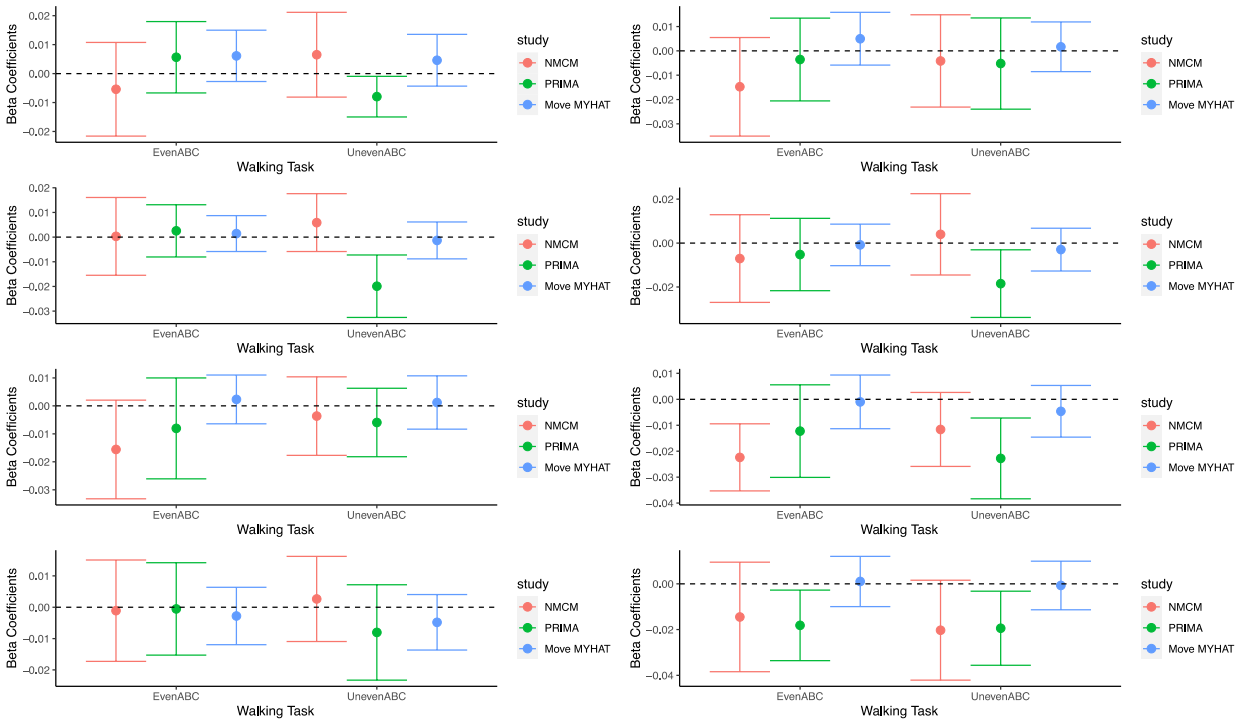

Figure 7-10. The associations of correct alphabet rate (number/s) with t statistics of prefrontal cortex activation for each channel (Channel 1-Channel 8) in Neural Mechanisms of Community Mobility (NMCM), Program to Improve Mobility in Aging, Near-Infrared Spectroscopy sub study (PRIMA-NIRS), and Move Monongahela-Youghiogheny Healthy Aging Team (Move MYHAT). Modeling adjusted for age, sex, education, obesity, cardiovascular diseases, diabetes, and physical and mental fatiguability scores.

Bibliography

1. Verghese J, LeValley A, Hall CB, Katz MJ, Ambrose AF, Lipton RB. Epidemiology of gait disorders in community-residing older adults. *J Am Geriatr Soc.* 2006;54(2):255-261.
2. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc.* 2012;60(11):2127-2136.
3. Rosso AL, Studenski SA, Chen WG, et al. Aging, the central nervous system, and mobility. *J Gerontol A Biol Sci Med Sci.* 2013;68(11):1379-1386.
4. Holtzer R, Epstein N, Mahoney JR, Izzetoglu M, Blumen HM. Neuroimaging of mobility in aging: a targeted review. *J Gerontol A Biol Sci Med Sci.* 2014;69(11):1375-1388.
5. Brach JS, Vanswearingen JM. Interventions to Improve Walking in Older Adults. *Curr Transl Geriatr Exp Gerontol Rep.* 2013;2(4).
6. Takakusaki K, Saitoh K, Harada H, Kashiwayanagi M. Role of basal ganglia-brainstem pathways in the control of motor behaviors. *Neuroscience research.* 2004;50(2):137-151.
7. Wilson J, Allcock L, Mc Ardle R, Taylor JP, Rochester L. The neural correlates of discrete gait characteristics in ageing: A structured review. *Neuroscience and biobehavioral reviews.* 2019;100:344-369.
8. Verghese J, Robbins M, Holtzer R, et al. Gait dysfunction in mild cognitive impairment syndromes. *J Am Geriatr Soc.* 2008;56(7):1244-1251.
9. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X. Quantitative gait dysfunction and risk of cognitive decline and dementia. *Journal of neurology, neurosurgery, and psychiatry.* 2007;78(9):929-935.
10. Lord S, Galna B, Verghese J, Coleman S, Burn D, Rochester L. Independent domains of gait in older adults and associated motor and nonmotor attributes: validation of a factor analysis approach. *J Gerontol A Biol Sci Med Sci.* 2013;68(7):820-827.
11. Mc Ardle R, Morris R, Wilson J, Galna B, Thomas AJ, Rochester L. What Can Quantitative Gait Analysis Tell Us about Dementia and Its Subtypes? A Structured Review. *J Alzheimers Dis.* 2017;60(4):1295-1312.
12. Verghese J, Holtzer R, Lipton RB, Wang C. Quantitative gait markers and incident fall risk in older adults. *J Gerontol A Biol Sci Med Sci.* 2009;64(8):896-901.
13. Suri A, Rosso AL, VanSwearingen J, et al. Mobility of Older Adults: Gait Quality Measures are associated with Life-Space Assessment Scores. *J Gerontol A Biol Sci Med Sci.* 2021.
14. Shumway-Cook A, Patla A, Stewart A, Ferrucci L, Ciol MA, Guralnik JM. Environmental components of mobility disability in community-living older persons. *Journal of the American Geriatrics Society.* 2003;51(3):393-398.
15. L. RA, L. MA, K. F, et al. Complex Walking Tasks and Risk for Cognitive Decline in High Functioning Older Adults. *Journal of Alzheimer's Disease.* In press.
16. Hamacher D, Herold F, Wiegel P, Hamacher D, Schega L. Brain activity during walking: A systematic review. *Neuroscience and biobehavioral reviews.* 2015;57:310-327.
17. Fuster JM. The prefrontal cortex—an update: time is of the essence. *Neuron.* 2001;30(2):319-333.

18. Seidler RD, Bernard JA, Burutolu TB, et al. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neuroscience and biobehavioral reviews.* 2010;34(5):721-733.
19. la Fougere C, Zwergal A, Rominger A, et al. Real versus imagined locomotion: a [18F]-FDG PET-fMRI comparison. *Neuroimage.* 2010;50(4):1589-1598.
20. Stuss DT, Levine B. Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annual review of psychology.* 2002;53(1):401-433.
21. Reuter-Lorenz PA, Cappell KA. Neurocognitive aging and the compensation hypothesis. *Current directions in psychological science.* 2008;17(3):177-182.
22. Udina C, Avtzi S, Durduran T, et al. Functional Near-Infrared Spectroscopy to Study Cerebral Hemodynamics in Older Adults During Cognitive and Motor Tasks: A Review. *Frontiers in aging neuroscience.* 2019;11:367.
23. Maillet D, Rajah MN. Association between prefrontal activity and volume change in prefrontal and medial temporal lobes in aging and dementia: a review. *Ageing research reviews.* 2013;12(2):479-489.
24. Morris R, Lord S, Bunce J, Burn D, Rochester L. Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease. *Neuroscience and biobehavioral reviews.* 2016;64:326-345.
25. Tian Q, Chastan N, Bair WN, Resnick SM, Ferrucci L, Studenski SA. The brain map of gait variability in aging, cognitive impairment and dementia-A systematic review. *Neuroscience and biobehavioral reviews.* 2017;74(Pt A):149-162.
26. Metti AL, Aizenstein H, Yaffe K, et al. Trajectories of peripheral interleukin-6, structure of the hippocampus, and cognitive impairment over 14 years in older adults. *Neurobiol Aging.* 2015;36(11):3038-3044.
27. Stekhoven DJ, Buhlmann P. MissForest--non-parametric missing value imputation for mixed-type data. *Bioinformatics.* 2012;28(1):112-118.
28. Shiffler RE. Maximum Z scores and outliers. *The American Statistician.* 1988;42(1):79-80.
29. Rosano C, Aizenstein HJ, Newman AB, et al. Neuroimaging differences between older adults with maintained versus declining cognition over a 10-year period. *Neuroimage.* 2012;62(1):307-313.
30. Brach JS, Perera S, Studenski S, Newman AB. The reliability and validity of measures of gait variability in community-dwelling older adults. *Arch Phys Med Rehabil.* 2008;89(12):2293-2296.
31. Rosso AL, Olson Hunt MJ, Yang M, et al. Higher step length variability indicates lower gray matter integrity of selected regions in older adults. *Gait Posture.* 2014;40(1):225-230.
32. Chen N, Rosano C, Karim HT, Studenski SA, Rosso AL. Regional Gray Matter Density Associated with Fast-Paced Walking in Older Adults: A Voxel-Based Morphometry Study. *J Gerontol A Biol Sci Med Sci.* 2020.
33. Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2006;61(1):72-77.
34. Zou H, Hastie T. Regularization and variable selection via the elastic net. *Journal of the royal statistical society: series B (statistical methodology).* 2005;67(2):301-320.

35. Chun H, Keleş S. Sparse partial least squares regression for simultaneous dimension reduction and variable selection. *Journal of the Royal Statistical Society: Series B (Statistical Methodology).* 2010;72(1):3-25.
36. Ouchi Y, Kanno T, Okada H, et al. Changes in dopamine availability in the nigrostriatal and mesocortical dopaminergic systems by gait in Parkinson's disease. *Brain.* 2001;124(4):784-792.
37. Alexander LD, Black SE, Patterson KK, Gao F, Danells CJ, McIlroy WE. Association between gait asymmetry and brain lesion location in stroke patients. *Stroke.* 2009;40(2):537-544.
38. Jones PS, Pomeroy VM, Wang J, et al. Does stroke location predict walk speed response to gait rehabilitation? *Hum Brain Mapp.* 2016;37(2):689-703.
39. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain.* 2014;137(Pt 1):12-32.
40. Rosano C, Aizenstein H, Brach J, Longenberger A, Studenski S, Newman AB. Gait measures indicate underlying focal gray matter atrophy in the brain of older adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2008;63(12):1380-1388.
41. Youn J, Cho JW, Lee WY, Kim GM, Kim ST, Kim HT. Diffusion tensor imaging of freezing of gait in patients with white matter changes. *Movement disorders : official journal of the Movement Disorder Society.* 2012;27(6):760-764.
42. Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N. Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. *Experimental brain research.* 2003;149(2):187-194.
43. Manor B, Newton E, Abduljalil A, Novak V. The relationship between brain volume and walking outcomes in older adults with and without diabetic peripheral neuropathy. *Diabetes care.* 2012;35(9):1907-1912.
44. Hausdorff JM, Levy BR, Wei JY. The power of ageism on physical function of older persons: Reversibility of age-related gait changes. *Journal of the American Geriatrics Society.* 1999;47(11):1346-1349.
45. Owings TM, Grabiner MD. Variability of step kinematics in young and older adults. *Gait & Posture.* 2004;20(1):26-29.
46. Hausdorff JM. Gait variability: methods, modeling and meaning. *Journal of neuroengineering and rehabilitation.* 2005;2(1):1-9.
47. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. *Statistics in medicine.* 1997;16(20):2349-2380.
48. Wennberg AM, Savica R, Mielke MM. Association between Various Brain Pathologies and Gait Disturbance. *Dement Geriatr Cogn Disord.* 2017;43(3-4):128-143.
49. Chung D, Keles S. Sparse partial least squares classification for high dimensional data. *Statistical applications in genetics and molecular biology.* 2010;9(1).
50. Camargo EC, Weinstein G, Beiser AS, et al. Association of Physical Function with Clinical and Subclinical Brain Disease: The Framingham Offspring Study. *J Alzheimers Dis.* 2016;53(4):1597-1608.
51. ABELLAN VAN KAN G, ROLLAND Y, ANDRIEU S, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people. *The Journal of Nutrition, Health & Aging.* 2009;13(10).

52. Buchman AS, Bennett DA. Loss of motor function in preclinical Alzheimer's disease. *Expert Rev Neurother.* 2011;11(5):665-676.
53. Callisaya ML, Blizzard L, Schmidt MD, et al. Gait, gait variability and the risk of multiple incident falls in older people: a population-based study. *Age and ageing.* 2011;40(4):481-487.
54. Callisaya M, Blizzard L, McGinley JL, Srikanth V. Risk of falls in older people during fast-walking–the TASCOG study. *Gait & posture.* 2012;36(3):510-515.
55. England SA, Granata KP. The influence of gait speed on local dynamic stability of walking. *Gait & posture.* 2007;25(2):172-178.
56. Shumway-Cook A, Guralnik JM, Phillips CL, et al. Age-associated declines in complex walking task performance: the Walking InCHIANTI toolkit. *J Am Geriatr Soc.* 2007;55(1):58-65.
57. Rosso AL, Metti AL, Faulkner K, et al. Complex Walking Tasks and Risk for Cognitive Decline in High Functioning Older Adults. *J Alzheimers Dis.* 2019.
58. Fitzpatrick AL, Buchanan CK, Nahin RL, et al. Associations of gait speed and other measures of physical function with cognition in a healthy cohort of elderly persons. *Journal of Gerontology: MEDICAL SCIENCES.* 2007;62A(11):1244–1251.
59. Deshpande N, Metter EJ, Bandinelli S, Guralnik J, Ferrucci L. Gait speed under varied challenges and cognitive decline in older persons: a prospective study. *Age Ageing.* 2009;38(5):509-514.
60. Allali G, Montembeault M, Brambati SM, et al. Brain Structure Covariance Associated with Gait Control in Aging. *J Gerontol A Biol Sci Med Sci.* 2018.
61. Newman AB, Simonsick EM, Naydeck BL, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *Jama.* 2006;295(17):2018-2026.
62. Simonsick EM, Newman AB, Nevitt MC, et al. Measuring higher level physical function in well-functioning older adults- expanding familiar approaches in the Health ABC study. *Journal of Gerontology: MEDICAL SCIENCES.* 2001;56A(10):M644-M649.
63. Houston DK, Nicklas BJ, Ding JZ, et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults- the Health, Aging, and Body Composition (Health ABC) Study. *Am J Clin Nutr.* 2008;87:150-155.
64. Nadkarni NK, Nunley KA, Aizenstein H, et al. Association between cerebellar gray matter volumes, gait speed, and information-processing ability in older adults enrolled in the Health ABC study. *J Gerontol A Biol Sci Med Sci.* 2014;69(8):996-1003.
65. Penny WD, Friston KJ, Ashburner JT, Kiebel SJ, Nichols TE. *Statistical parametric mapping: the analysis of functional brain images.* Elsevier; 2011.
66. Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage.* 2007;38(1):95-113.
67. Gennatas ED, Avants BB, Wolf DH, et al. Age-Related Effects and Sex Differences in Gray Matter Density, Volume, Mass, and Cortical Thickness from Childhood to Young Adulthood. *J Neurosci.* 2017;37(20):5065-5073.
68. Yaffe K, Fiocco AJ, Lindquist K, et al. Predictors of maintaining cognitive function in older adults- The Health ABC Study. *Neurology.* 2009;72:2029–2035.
69. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: Evaluation of a short form of the CES-D. *American journal of preventive medicine.* 1994;10(2):77-84.

70. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry.* 1987;48(8):314-318.
71. D. W. Manual for the Wechsler adult intelligence scale—third edition (WAIS-III). *San Antonio, TX: The Psychological Corporation.* 1997.
72. Holmes AP, Blair R, Watson J, Ford I. Nonparametric analysis of statistic images from functional mapping experiments. *Journal of Cerebral Blood Flow & Metabolism.* 1996;16(1):7-22.
73. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage.* 2002;15(1):273-289.
74. Li W, Qin W, Liu H, et al. Subregions of the human superior frontal gyrus and their connections. *Neuroimage.* 2013;78:46-58.
75. Ventre-Dominey J, Nighoghossian N, Denise P. Evidence for interacting cortical control of vestibular function and spatial representation in man. *Neuropsychologia.* 2003;41(14):1884-1898.
76. Corkin S, Milner B, Rasmussen T. Somatosensory thresholds: Contrasting effects of postcentral-gyrus and posterior parietal-lobe excisions. *Archives of Neurology.* 1970;23(1):41-58.
77. Boyne P, Maloney T, DiFrancesco M, et al. Resting-state functional connectivity of subcortical locomotor centers explains variance in walking capacity. *Hum Brain Mapp.* 2018;39(12):4831-4843.
78. Clark DJ, Christou EA, Ring SA, Williamson JB, Doty L. Enhanced somatosensory feedback reduces prefrontal cortical activity during walking in older adults. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences.* 2014;69(11):1422-1428.
79. Sacco K, Cauda F, Cerliani L, Mate D, Duca S, Geminiani GC. Motor imagery of walking following training in locomotor attention. The effect of "the tango lesson". *Neuroimage.* 2006;32(3):1441-1449.
80. Rosso AL, Cenciarini M, Sparto PJ, Loughlin PJ, Furman JM, Huppert TJ. Neuroimaging of an attention demanding dual-task during dynamic postural control. *Gait Posture.* 2017;57:193-198.
81. Karim H, Schmidt B, Dart D, Beluk N, Huppert T. Functional near-infrared spectroscopy (fNIRS) of brain function during active balancing using a video game system. *Gait Posture.* 2012;35(3):367-372.
82. Dieterich M, Bense S, Lutz S, et al. Dominance for vestibular cortical function in the non-dominant hemisphere. *Cerebral cortex.* 2003;13(9):994-1007.
83. Benwell CS, Harvey M, Thut G. On the neural origin of pseudoneglect: EEG-correlates of shifts in line bisection performance with manipulation of line length. *Neuroimage.* 2014;86:370-380.
84. Mutha PK, Haaland KY, Sainburg RL. The effects of brain lateralization on motor control and adaptation. *J Mot Behav.* 2012;44(6):455-469.
85. DiSalvio NL, Rosano C, Aizenstein HJ, et al. Gray Matter Regions Associated With Functional Mobility in Community-Dwelling Older Adults. *J Am Geriatr Soc.* 2019.
86. Dumurgier J, Crivello F, Mazoyer B, et al. MRI atrophy of the caudate nucleus and slower walking speed in the elderly. *Neuroimage.* 2012;60(2):871-878.

87. Verlinden VJ, de Groot M, Cremers LG, et al. Tract-specific white matter microstructure and gait in humans. *Neurobiol Aging.* 2016;43:164-173.
88. Bolandzadeh N, Liu-Ambrose T, Aizenstein H, et al. Pathways linking regional hyperintensities in the brain and slower gait. *Neuroimage.* 2014;99:7-13.
89. Nadkarni NK, McIlroy WE, Mawji E, Black SE. Gait and subcortical hyperintensities in mild Alzheimer's disease and aging. *Dement Geriatr Cogn Disord.* 2009;28(4):295-301.
90. Rosano C, Brach J, Longstreth WT, Jr., Newman AB. Quantitative measures of gait characteristics indicate prevalence of underlying subclinical structural brain abnormalities in high-functioning older adults. *Neuroepidemiology.* 2006;26(1):52-60.
91. Rosario BL, Rosso AL, Aizenstein HJ, et al. Cerebral White Matter and Slow Gait: Contribution of Hyperintensities and Normal-appearing Parenchyma. *J Gerontol A Biol Sci Med Sci.* 2016;71(7):968-973.
92. Del Campo N, Payoux P, Djilali A, et al. Relationship of regional brain β-amyloid to gait speed. *Neurology.* 2016;86(1):36-43.
93. Eklund A, Nichols TE, Knutsson H. Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences of the United States of America.* 2016;113(28):7900-7905.
94. Bishnoi A, Holtzer R, Hernandez ME. Brain Activation Changes While Walking in Adults with and without Neurological Disease: Systematic Review and Meta-Analysis of Functional Near-Infrared Spectroscopy Studies. *Brain Sci.* 2021;11(3).
95. Funahashi S, Andreau JM. Prefrontal cortex and neural mechanisms of executive function. *Journal of Physiology-Paris.* 2013;107(6):471-482.
96. Herold F, Wiegel P, Scholkmann F, Thiers A, Hamacher D, Schega L. Functional near-infrared spectroscopy in movement science: a systematic review on cortical activity in postural and walking tasks. *Neurophotonics.* 2017;4(4):041403.
97. Holtzer R, Verghese J, Allali G, Izzetoglu M, Wang C, Mahoney JR. Neurological Gait Abnormalities Moderate the Functional Brain Signature of the Posture First Hypothesis. *Brain topography.* 2016;29(2):334-343.
98. Chen M, Pillemer S, England S, Izzetoglu M, Mahoney JR, Holtzer R. Neural correlates of obstacle negotiation in older adults: An fNIRS study. *Gait Posture.* 2017;58:130-135.
99. Leff DR, Orihuela-Espina F, Elwell CE, et al. Assessment of the cerebral cortex during motor task behaviours in adults: a systematic review of functional near infrared spectroscopy (fNIRS) studies. *Neuroimage.* 2011;54(4):2922-2936.
100. Boisgontier MP, Beets IA, Duysens J, Nieuwboer A, Krampe RT, Swinnen SP. Age-related differences in attentional cost associated with postural dual tasks: increased recruitment of generic cognitive resources in older adults. *Neuroscience and biobehavioral reviews.* 2013;37(8):1824-1837.
101. Aizenstein HJ, Nebes RD, Saxton JA, et al. Frequent Amyloid Deposition Without Significant Cognitive Impairment Among the Elderly. *Archives of Neurology.* 2008;65(11):1509-1517.
102. Brach JS, VanSwearingen JM, Gil A, et al. Program to improve mobility in aging (PRIMA) study: Methods and rationale of a task-oriented motor learning exercise program. *Contemporary clinical trials.* 2020;89.
103. Ganguli M, Snitz BE, Saxton JA, et al. Outcomes of mild cognitive impairment by definition: a population study. 2011;68(6):761-767.

104. Hoppes CW, Huppert TJ, Whitney SL, et al. Changes in Cortical Activation During Dual-Task Walking in Individuals With and Without Visual Vertigo. *Journal of neurologic physical therapy : JNPT.* 2020;44(2):156-163.
105. Menant JC, Maidan I, Alcock L, et al. A consensus guide to using functional near-infrared spectroscopy in posture and gait research. *Gait Posture.* 2020;82:254-265.
106. Scholkmann F, Wolf M. General equation for the differential pathlength factor of the frontal human head depending on wavelength and age. *J Biomed Opt.* 2013;18(10):105004.
107. Huppert TJ. Commentary on the statistical properties of noise and its implication on general linear models in functional near-infrared spectroscopy. *Neurophotonics.* 2016;3(1):010401.
108. Peel C, Baker PS, Roth DL, Brown CJ, Bodner EV, Allman RM. Assessing mobility in older adults: the UAB Study of Aging Life-Space Assessment. *Physical therapy.* 2005;85(10):1008-1019.
109. Glynn NW, Santanasto AJ, Simonsick EM, et al. The Pittsburgh Fatigability scale for older adults: development and validation. *J Am Geriatr Soc.* 2015;63(1):130-135.
110. Folstein MF, Folstein SE, McHugh PRJJopr. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. 1975;12(3):189-198.
111. Bowie CR, Harvey PD. Administration and interpretation of the Trail Making Test. *Nat Protoc.* 2006;1(5):2277-2281.
112. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods.* 2010;1(2):97-111.
113. Hartigan JA, Wong MA. AK-means clustering algorithm. *Journal of the Royal Statistical Society: Series C (Applied Statistics).* 1979;28(1):100-108.
114. Tibshirani R, Walther G, Hastie T. Estimating the number of clusters in a data set via the gap statistic. *Journal of the Royal Statistical Society: Series B (Statistical Methodology).* 2001;63(2):411-423.
115. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Movement disorders : official journal of the Movement Disorder Society.* 2008;23(3):329-342; quiz 472.
116. Mirelman A, Maidan I, Bernad-Elazari H, et al. Increased frontal brain activation during walking while dual tasking: an fNIRS study in healthy young adults. *Journal of neuroengineering and rehabilitation.* 2014;11(1):1-7.
117. Takeuchi N, Mori T, Suzukamo Y, Tanaka N, Izumi S. Parallel processing of cognitive and physical demands in left and right prefrontal cortices during smartphone use while walking. *BMC neuroscience.* 2016;17:9.
118. Fettrow T, Hupfeld K, Tays G, Clark DJ, Reuter-Lorenz P, Seidler R. Brain activity during walking in older adults: Implications for compensatory versus dysfunctional accounts. 2020.
119. Gabrieli JD, Poldrack RA, Desmond JEJPotnAoS. The role of left prefrontal cortex in language and memory. 1998;95(3):906-913.
120. Zarahn E, Rakitin B, Abela D, Flynn J, Stern Y. Age-related changes in brain activation during a delayed item recognition task. *Neurobiol Aging.* 2007;28(5):784-798.
121. Jayakody O, Breslin M, Stuart K, Vickers JC, Callisaya ML. The associations between dual-task walking under three different interference conditions and cognitive function. *Gait Posture.* 2020;82:174-180.