

# A Regions-of-Interest Volumetric Analysis of Mobility Limitations in Community-Dwelling Older Adults

Caterina Rosano,<sup>1</sup> Howard J. Aizenstein,<sup>2</sup> Stephanie Studenski,<sup>3,4</sup> and Anne B. Newman<sup>1,3</sup>

<sup>1</sup>School of Public Health, Department of Epidemiology, <sup>2</sup>Department of Psychiatry, Western Psychiatric Institute and Clinic, and <sup>3</sup>Division of Geriatric Medicine, Department of Medicine, University of Pittsburgh, Pennsylvania.

<sup>4</sup>Department of Medicine, Division of Geriatric Medicine, University of Pittsburgh School of Medicine, and GRECC, VA Pittsburgh Healthcare System, Pennsylvania.

**Background.** In community-dwelling older adults, greater mobility impairment is associated with greater burden of diffuse brain structural abnormalities, such as higher white matter hyperintensities. This study examined the association between gray matter volumes of regions related to motor control, gait, and balance and whether this association is independent of burden of white matter hyperintensities.

**Methods.** A random sample of 327 participants of the Cardiovascular Health Study (78.3 ± 4.1 years old, 57% women) contributed brain magnetic resonance imaging (MRI) and mobility data. A brain imaging automated method measured gray matter volume in cerebellum, basal ganglia, and prefrontal and parietal cortex in both hemispheres. Gait speed was measured while walking 15 feet at usual pace. Standing balance was assessed by timing tandem stance. Associations between each region's volume and gait speed or balance were measured before and after adjustment for demographics, head size, cardiovascular risk factors, and 0–9 grading scores of white matter hyperintensities.

**Results.** Smaller left cerebellum and left prefrontal regions were associated with slower gait, independently of covariates and of white matter hyperintensities. Smaller right putamen, right posterior superior parietal cortex, and both left and right cerebellum were associated with balance difficulty, independently of covariates and white matter hyperintensities.

**Conclusions.** Smaller gray matter volumes in regions crucial for motor control are associated with slower gait and poorer balance, and the association appears to be independent of other diffuse brain abnormalities such as white matter hyperintensities.

COMMUNITY-DWELLING older adults often experience mobility limitations in the absence of neurological conditions or acute clinical events, but rather as a consequence of multifactorial changes in multiple systems, including musculoskeletal, cardiopulmonary, and central nervous systems (1). This type of mobility impairment is common among older adults, and it dramatically increases the risk for hospitalization and death (2). Understanding the mechanisms underlying these age-related mobility impairments is an increasingly urgent public health issue because the number of older adults at risk for physical disability is rapidly increasing.

There is strong emergent evidence that age-related lower-extremity mobility limitations are associated (3–16) with diffuse brain magnetic resonance imaging (MRI) abnormalities, such as white matter hyperintensities independently of other health-related factors that may affect mobility. However, it is not clear how such diffuse abnormalities could selectively affect mobility control. It is possible that focal abnormalities of the neurons and/or of the white matter localized in specific brain regions linked to mobility control would cause slower gait or difficulty with balance, without necessarily causing other clinically evident neurological deficits, such as dementia.

We are aware of only three small sample studies (9,17) addressing the problem of the localization of brain

abnormalities in association with mobility in older adults. However, none of these studies has quantified the severity and the localization of gray matter volumetric loss in association with mobility limitations in a large sample of community-dwelling older adults.

This study used a fully automated volumetric method to quantify the gray matter volumes of regions related to mobility control (Figure 1) and used a regions-of-interest approach. We hypothesized that gray matter volumes in these mobility-related regions would be associated with slower gait speed and difficulty with balance independently of other health-related conditions and of diffuse age-related brain MRI abnormalities, such as white matter hyperintensities, ventricular enlargement, smaller total brain volume, and subclinical brain infarcts.

## METHODS

### Study Population

The Cardiovascular Health Study (CHS) is a population-based, ongoing study of coronary heart disease and stroke risk in community-dwelling adults 65 years old and older. A sample of 5201 adults aged 65+ were recruited from Medicare Part A lists starting from 1989 in four clinical centers (Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA). In 1992–1993,

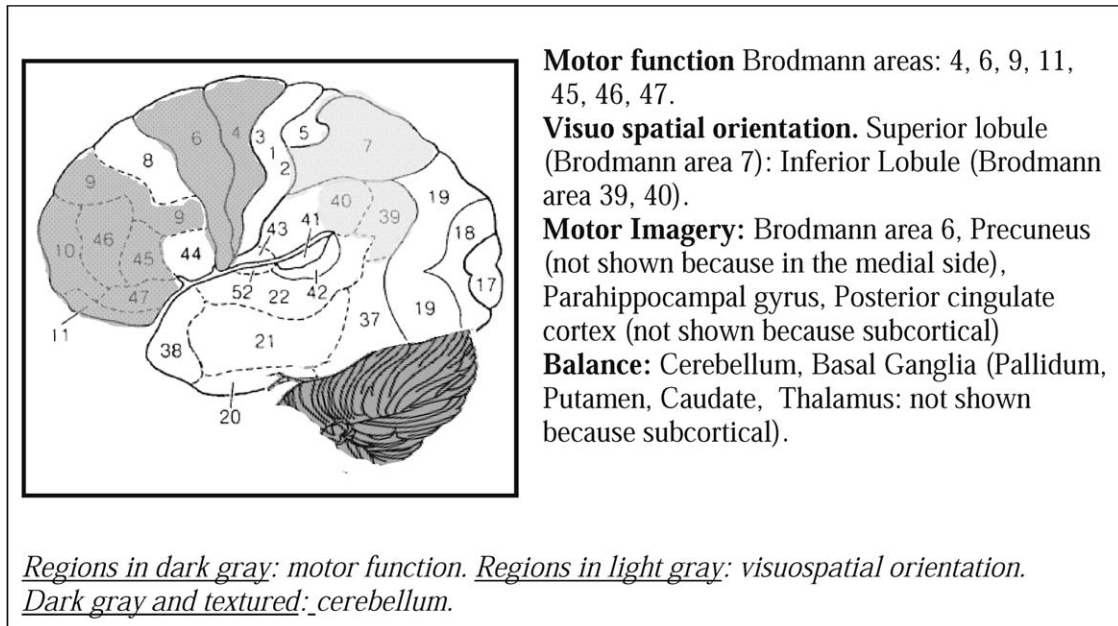


Figure 1. Brain regions known to be associated with mobility.

687 African Americans were added to the original cohort. Demographics, information on all hospitalizations, review of medical records, selected laboratory and clinical evaluations, neurological examination, and assessment of health-related factors were characterized (18). Brain MRIs were originally acquired in 523 participants in Pittsburgh as part of the CHS in 1997–1999 (19). As part of an ongoing National Institute on Aging (NIA)-funded research project, these images are being retrieved from the optical disks and are being reread using the automated labeling pathway (ALP). The order in which the brain MRIs are being retrieved from the optical disk is essentially random as it follows the identification number of the participants. For this study, we used the first 327 brain MRIs from participants for whom we had mobility data in concurrent years. No significant difference was observed between the two samples with regard to demographics or health-related factors.

### Measurements

**Brain MRI measures.**—Brain MRI assessments included volumetric measures of gray matter of individual regions (Figure 1) and of total brain, and semiquantitative visual ratings of diffuse brain MRI abnormalities (white matter hyperintensities, ventricular enlargement, and subclinical brain infarcts).

**Brain MRI protocol.**—The CHS MRI cerebral protocol has been previously published (20). MR images were collected in 1997–1999 at the University of Pittsburgh Medical Center MR Research Center using a 1.5 T Signa scanner (GE Medical Systems, University of Pittsburgh, PA) with high performance gradients (4 G/cm and 150 T/m-s) (21). A three-dimensional Spoiled Gradient Recalled

(SPGR) image and a brief scout T1-weighted image were obtained, followed by standardized sagittal T1-weighted spin-echo images, spin density/T2-weighted and axial T1-weighted images.

**Semiquantitative brain MRI measures.**—Severity of white matter hyperintensities and of ventricular enlargement was visually rated by radiologists on a 10-point scale from 0 to 9, according to an atlas of predefined visual standards (20). Severity of white matter hyperintensities was considered high if grade was  $\geq 3$  and low if grade was  $< 3$ . This cut point was chosen based on previous studies conducted on the CHS cohort. (22) The largest right–left diameter from the inner table of the skull was computed (in cm) on the brain MRI and was used as a measure of head size. Subclinical brain infarcts  $> 3$  mm were defined as masses that lacked a vascular distribution and were hyperintense on both spin-density and T2-weighted sequences.

**Automated Labeling Pathway.**—Quantitative brain volumetric measures were obtained for all Brodmann areas using a procedure previously described (23–27). For this study, volumetric measures of regions known to be associated with mobility from previous studies were used (Figure 1). The ALP closely emulates the hand-tracing method in that regions of interest, including all Brodmann areas and subcortical structures, have been previously drawn on the MNI colin27 template brain according to the automated anatomical labeling (AAL) neuroanatomical atlas (24,28). After skull and scalp stripping (29), and after segmentation of gray matter, white matter, and cerebrospinal fluid, the brain atlas and the brain of the individual are aligned, and intensity normalization is done on each individual's SPGR image as well as on the colin27 template to give each

individual the same orientation and image-intensity distribution as the template and to improve the registration accuracy. The registration procedure uses a fully deformable automatic algorithm (30) that does not warp or stretch the individual brain and thus minimizes measurement inaccuracies; it also allows for a high degree of spatial deformation compared to other standard registration packages (e.g., Automated Image Registration [AIR] or Statistical Parametric Mapping [SPM]). Voxel counts of the gray matter of each region of interest and of the gray matter of the whole brain were obtained for each individual. Total brain volume was also calculated as the sum of voxel counts from the gray matter, the white matter, and the cerebrospinal fluid of the whole brain.

**Mobility measures.**—Gait speed and ability to hold balance stance are very simple measures that strongly correlate to a variety of important aging outcomes, such as falls, development of functional disability, and risk for mortality and nursing home placement (31,32). For this study, we chose two mobility measures: gait speed and difficulty holding the tandem stance for more than 10 seconds. (33). The participants of this study were all able to walk. Gait speed was assessed by measuring the time to walk a 15-foot course at usual pace. Gait speed was used both as continuous and as dichotomous (<1.0 m/s vs ≥ 1.0 m/s). This cutoff was chosen because a gait speed < 1.0 m/s appears to identify persons who are at high risk of developing health-related adverse events (34,35) and also older adults who are more likely to have underlying brain MRI abnormalities.

The balance stand test consisted of the ability to hold the semitandem position (one foot in front of the other) for at least 10 seconds. Participants who could not hold this stance were classified as having difficulty with tandem stance. For this analysis, we recoded this variable as “difficulty holding balance no (= 0)/yes (= 1).”

### Covariates

Covariates for this study were those health-related measures that can contribute to motor performance or that can be associated with brain MRI abnormalities: demographics (age, race, gender, education), prevalent cardiovascular diseases (5,36) (physician diagnosis of myocardial infarction, angina, coronary artery bypass surgery or percutaneous transluminal coronary angioplasty, congestive heart failure, stroke or transient ischemic attack, or intermittent claudication), osteoarthritis (at knee and/or hip), visual acuity, deep venous thrombosis, hypertension, Modified Mini-Mental Status Examination score, dementia status, and dementia type. All measures were assessed close to the time of the MRI, except demographics, which were collected at the beginning of the study. Dementia status and type (Alzheimer’s disease, vascular dementia, Parkinson’s disease, and others) were classified according to published criteria. None of the participant had Parkinson’s disease. The interval of time between brain MRI and mobility tests was also added to the model as a covariate.

Potential modifiers of the association between focal gray matter volumes and mobility were those diffuse brain MRI

Table 1. Population Characteristics,  $N = 327$

Characteristics	Participants Included in This Study ( $N = 327$ )
Age at MRI, mean years ( $SD$ )	78.2 (3.9)
Gender, $n$ (%) women	186 (56.5)
Education, mean years ( $SD$ )	13.9 (2.6)
Race, $n$ (%) white	236 (71.7)
Modified Mini-Mental State Examination score, mean ( $SD$ )	93.5 (5.7)
Dementia, $n$ (%)*	31 (9.4)
Mild cognitive impairment, $n$ (%)	64 (19.5)
TIA or stroke, $n$ (%)	13 (6.2)
Prevalent cardiovascular disease, $n$ (%)	89 (27.1)
Medication intake for Parkinson-related symptoms, $n$ (%)	6 (1.9)
Former smoker, $n$ (%)	156 (47.4)
Hypertension, $n$ (%)	103 (31.3)
Diabetes, $n$ (%)	39 (11.9)
Gait speed in m/s, mean ( $SD$ )	0.9 (0.2)
Prevalence of those with speed < 1.0 m/s, $n$ (%)	199 (60.9)
Prevalence of those with balance difficulty, $n$ (%)	93 (29.1)
Prevalence of ventricular grade ≥ 4, $n$ (%) <sup>†</sup>	151 (47.9)
Prevalence of white matter grade ≥ 3, $n$ (%) <sup>‡</sup>	116 (35.6)

Notes: \*Of these, 28 cases were Alzheimer’s disease, 3 were vascular dementia, and 0 were Parkinson’s dementia.

<sup>†</sup>Severity of ventricular grade was scored on a 0–9 scale

<sup>‡</sup>Severity of white matter hyperintensities was scored on a 0–9 scale.

MRI = magnetic resonance imaging; TIA = transient ischemic attack;  $SD$  = standard deviation.

abnormalities described earlier: white matter hyperintensities, subclinical brain infarcts, ventricular enlargement, gray matter volume of the whole brain, and total brain volume.

### Statistical Analysis

Analyses were cross-sectional, although the actual dates of the MRI and gait measures span a 2-year time period (from 1997 through 1999), with a mean (standard deviation [ $SD$ ]) interval of time of 2.5 (3.6) months. Focal gray matter volume of each region of interest was modeled as independent variable and the mobility measure (either gait or balance) was the dependent variable.

Statistical modeling was applied separately for each region. The bivariate association between regions-of-interest gray matter volumes and mobility measures was tested using nonparametric Spearman correlation coefficients and Mann–Whitney  $U$  test, a nonparametric equivalent of the  $t$  test. To control for false positives and overall significance of the cross-sectional association between individual regions and dependent variables, a Sidak correction for multiple comparisons  $p$  value < .002 was used (from the 36 regions from both hemispheres, Figure 1). Regions significantly associated after Sidak correction from bivariate analysis were selected for multivariate cross-sectional analysis of the gray matter–mobility association.

In regression models, the regression coefficients associated to each of the regions’ volumetric measures were examined in separate models because regions’ volumetric measures of the brain are highly correlated with each other ( $0.5 < r < 0.8$ ,  $p < .001$ ) and the simultaneous presence in the same model would exceed the threshold for collinearity.

Table 2. Bivariate Association Between Gait Speed and Gray Matter Volume

Brain Region	Left Hemisphere		Right Hemisphere	
	Mean Gray Matter Volume Difference, cm <sup>3</sup> (95% CI)	Percent Gray Matter Volume Difference, %	Mean Gray Matter Volume Difference, cm <sup>3</sup> (95% CI)	Percent Gray Matter Volume Difference, %
<b>Motor Function</b>				
Prefrontal regions				
BA 4	0.26 (−0.006, 0.53)	5.6	0.17 (−0.11, 0.44)	3.4
BA 6	0.78 (0.22, 1.33)*	6.5*	0.70 (0.14, 1.26)	5.9
BA 9	0.41 (0.15, 0.70)*	6.4*	0.18 (−0.08, 0.44)	3.3
BA 11	0.58 (0.15, 1.00)*	4.7*	0.89 (0.42, 1.37)*	6.6*
BA 45	0.31 (0.08, 0.50)*	5.9*	0.15 (−0.10, 0.39)	3.0
BA 46	0.21 (−0.03, 0.44)	3.9	0.11 (−0.07, 0.38)	2.2
BA 47	0.16 (−0.07, 0.38)	2.7	0.19 (−0.02, 0.40)	3.3
<b>Visuospatial Orientation</b>				
Posterior parietal regions				
BA 7	0.53 (0.09, 0.97)	6.4	0.42 (−0.04, 0.87)	4.7
BA 39	0.32 (0.008, 0.62)	5.3	0.09 (−0.22, 0.41)	1.6
BA 40	0.19 (−0.07, 0.46)	3.6	0.14 (−0.12, 0.39)	2.6
<b>Motor Imagery</b>				
Para-hippocampus	0.22 (0.02, 0.42)	4.5	0.25 (0.03, 0.46)	4.4
Precuneus	0.60 (0.14, 1.06)*	6.2*	0.47 (0.08, 0.86)*	4.9*
<b>Balance</b>				
Basal ganglia				
Putamen	0.07 (−0.14, 0.28)	7.0	0.11 (−0.10, 0.32)	9.3
Caudate	0.14 (−0.07, 0.36)	3.7	0.11 (−0.13, 0.34)	2.8
Thalamus	−0.03 (−0.13, 0.06)	−4.1	−0.05 (−0.15, 0.04)	−6.0
Cerebellum	4.83 (1.78, 7.87)*	13.5*	3.46 (0.33, 6.60)	9.2

Notes: Comparison of participants with gait speed  $\geq 1$  m/s versus those with gait speed  $< 1.0$  m/s.

\*Associations that were significant at  $p < .002$  from nonparametric test.

CI = confidence interval; BA = Brodmann area.

Linear regression models were used when the dependent variable was continuous (gait speed), and logistic models were used for dichotomous variables (gait speed  $< 1.0$  vs  $\geq 1.0$  m/s or difficulty holding balance yes/no). Because brain regions vary greatly in volume, the strength of associations was compared across regions and across models by reporting standardized regression coefficients.

Analyses were adjusted for head size, and the other covariates were added subsequently. The presence of effect modifiers was tested by adding the interaction terms between focal gray matter volume from mobility-related regions and measures of diffuse brain MRI abnormalities (that is, white matter hyperintensities, subclinical brain infarcts, ventricular enlargement, and total brain volume). Interaction terms by gender were also tested for significance.

Collinearity diagnostic tests were used to detect associations between focal gray matter volume and other variables that could weaken the power of the model (e.g., total brain gray matter volume). SPSS for Windows (version 14.0; SPSS, Inc., Chicago, IL) was used.

## RESULTS

Participants in this study were  $78.3 \pm 4.1$  years old, 57% women, 72% white (Table 1). About 60% of the sample had a gait speed  $< 1.0$  m/s, and 30% had balance difficulty. As expected, slower gait speed and balance difficulty were significantly correlated ( $r = -0.25$ ,  $p < .0001$ ). Consistent with other studies (37–39), smaller gray matter volumes in the prefrontal regions were associated with severity of

Table 3. Gait Speed, Multivariate Regression Models

Brain Region	Mean cm <sup>3</sup> (SD)	Standardized OR (95% CI)*			
		Model 1	Model 2	Model 3	Model 4
BA 9 L	6.2 (1.1)	0.69 (0.5, 0.9)	0.70 (0.5, 0.9)	0.71 (0.6, 0.9)	0.72 (0.6, 0.9)
BA 45 L	5.1 (1.0)	0.76 (0.6, 0.9)	0.78 (0.6, 1.0)	0.79 (0.6, 1.0)	0.82 (0.6, 1.0)
Cerebellum L	32.7 (12.9)	0.67 (0.5, 0.9)	0.67 (0.5, 0.9)	0.68 (0.5, 0.9)	0.69 (0.5, 0.9)
BA 11 L	12.0 (1.8)	0.78 (0.6, 0.9)	0.80 (0.6, 1.0)	0.80 (0.6, 1.0)	0.80 (0.6, 1.1)
BA 11 R	13.1 (2.0)	0.658 (0.5, 0.9)	0.69 (0.5, 0.9)	0.70 (0.5, 0.9)	0.71 (0.5, 0.9)

Notes: Model 1 was adjusted for head size. Model 2 was adjusted for head size, age, and prevalent cardiovascular diseases. Model 3 = Model 2 + dementia status. Model 4 = Model 3 plus white matter hyperintensities greater or equal than grade 3.

\*Decrease in the risk to have gait speed  $< 1.0$  m/s for 1 SD increase in regional volume.

SD = standard deviation; OR = odds ratio; CI = confidence interval; BA = Brodmann area; R = right; L = left.



Table 4. Bivariate Association Between Balance Difficulty and Gray Matter Volume

Brain Region	Left Hemisphere		Right Hemisphere	
	Mean Gray Matter Volume Difference, cm <sup>3</sup> (95% CI)	Percent Gray Matter Volume Difference, %	Mean Gray Matter Volume Difference, cm <sup>3</sup> (95% CI)	Percent Gray Matter Volume Difference, %
<b>Motor Function</b>				
Prefrontal regions				
BA 4	-0.06 (-0.34, 0.22)	-1.3	0.11 (-0.18, 0.22)	2.2
BA 6*	0.21 (-0.38, 0.80)	1.8	0.29 (-0.30, 0.89)	2.5
BA 9*	0.38 (0.10, 0.67)	6.0	0.23 (-0.05, 0.51)	4.1
BA 11*	0.35 (-0.10, 0.81)	2.9	0.46 (-0.06, 0.98)	3.5
BA 45*	0.25 (-0.06, 0.50)	4.7	0.16 (-0.10, 0.42)	3.2
BA 46	0.25 (0.003, 0.50)	4.8	0.23 (0.002, 0.45)	4.5
BA 47	0.28 (0.04, 0.52)	4.9	0.14 (-0.08, 0.37)	2.5
<b>Visuospatial Orientation</b>				
Posterior parietal regions				
BA 7	0.28 (-0.19, 0.75)	3.5	0.75* (0.27, 1.23)*	8.5*
BA 39	0.31 (-0.01, 0.64)	5.3	0.29 (-0.04, 0.63)	4.9
BA 40	0.24 (-0.03, 0.51)	4.5	0.14 (-0.08, 0.37)	2.5
<b>Motor Imagery</b>				
Para-hippocampus	0.23 (0.02, 0.44)	4.8	0.22 (-0.01, 0.45)	3.9
Precuneus*	0.10 (-0.39, 0.59)	1.1	0.50 (0.07, 0.89)	5.1
<b>Balance</b>				
Basal ganglia				
Putamen	0.26 (0.05, 0.48)*	24.6*	0.25 (0.04, 0.47)*	21.4*
Caudate	0.23 (0.004, 0.46)	5.9	0.18 (-0.07, 0.43)	4.6
Thalamus	-0.10 (-0.19, -0.003)	-11.4	-0.07 (-0.18, 0.03)	-8.3
Cerebellum*	6.29 (3.10, 9.49)*	18.2*	5.41* (2.12, 8.70)*	14.5*

Notes: Comparison of participants with gait speed  $\geq$  1m/s versus those with gait speed  $<$  1.0 m/s.

\*Associations that were significant at  $p < .002$  from nonparametric test.

BA = Brodmann area; CI = confidence interval.

white matter hyperintensities, independent of age and total brain volume (range of correlation coefficients: -0.19, -0.14;  $p < .007$ ).

Bivariate associations were in the expected direction for all 34 regions, with smaller gray matter volumes associated with slower gait (Tables 2 and 4). However, after correction for multiple comparisons, a selective spatial distribution of focal gray matter volumes significantly associated with slower gait versus balance difficulty was observed.

#### Associations With Speed

The regions associated with slower gait speed at  $p < .0002$  included left prefrontal regions, left cerebellum, and right Brodmann area 11 (Table 2). The same topographic distribution was found when speed was coded as continuous. There was a significant although modest (5%–6%) mean volumetric difference in the prefrontal regions between the two groups, and a more substantial volumetric difference of 13.8% in the cerebellum.

In multivariate regression models, smaller left cerebellum and several left prefrontal regions were significantly associated with slower gait speed (Table 3). The associations were independent of head size, age, prevalent cardiovascular disease, dementia status, and burden of white matter hyperintensities (Table 3, Models 1–5). Further adjustment for gender, education, high body mass index, osteoarthritis, or peripheral arterial disease changed the regression coeffi-

cients by 1%–3%. Interactions of focal gray matter volumes by gender were not significant ( $p > .05$ ).

Adjustment for other markers of diffuse brain MRI abnormalities (subclinical brain infarcts, smaller total gray matter volume, smaller total brain volume, and ventricular enlargement) did not substantially change the regression coefficients (average change 2%–3%). Interestingly, the association between burden of white matter hyperintensities grade 3 and slower speed was not significant in these multivariate models ( $p > .05$ ). Indeed, none of the markers of diffuse brain MRI abnormalities was significantly associated with slower gait speed in the multivariate models. Interaction terms between gray matter volume in these regions and white matter hyperintensities or other markers of diffuse brain MRI abnormalities were also not significant ( $p > .05$ ).

#### Associations With Balance Difficulty

The regions of interest associated with balance difficulty at  $p < .0002$  were cerebellum and putamen in the right and left hemisphere, and the right superior posterior parietal lobe (Table 4). There were substantial mean differences between participants with and without balance difficulty—in particular for putamen, for which we found a 25% difference.

In multivariate models, smaller right cerebellum, right putamen, and right Brodmann area 7 were associated with a greater risk for balance difficulty, independent of covariates and of burden of white matter hyperintensities

Table 5. Difficulty With Balance, Multivariate Regression Models

Region	Mean cm <sup>3</sup> (SD)	Standardized OR (95% CI)*			
		Model 1	Model 2	Model 3	Model 4
BA7 R	8.5 (1.9)	0.68 (0.5, 0.9)	0.75 (0.6, 1.0)	0.77 (0.6, 1.0)	0.78 (0.6, 1.0)
Putamen R	1.2 (0.9)	0.67 (0.5, 0.9)	0.72 (0.5, 0.9)	0.73 (0.6, 1.0)	0.72 (0.6, 1.0)
Cerebellum R	35.8 (13.3)	0.68 (0.5, 0.9)	0.74 (0.6, 0.9)	0.76 (0.6, 1.0)	0.78 (0.6, 1.0)
Cerebellum L	32.7 (12.9)	0.63 (0.5, 0.8)	0.65 (0.5, 0.9)	0.66 (0.5, 0.9)	0.67 (0.5, 0.9)

Notes: Model 1 was adjusted for head size. Model 2 was adjusted for age, head size, and prevalent cardiovascular diseases. Model 3 = Model 2 + dementia status. Model 4 = Model 3 plus white matter grade > 3.

\*Decrease in the risk to have difficulty with balance for 1 SD increase in regional volume.

SD = standard deviation; OR = odds ratio; CI = confidence interval; BA = Brodmann area; R = right; L = left.

(Table 5, Models 1–5). Associations remained significant, and regression coefficient changed modestly (< 4%) after adjustment for gender, education, high body mass index, osteoarthritis, or peripheral arterial disease. Interactions of focal gray matter volumes by gender were not significant.

Further adjustment for other markers of diffuse brain MRI abnormalities (subclinical brain infarcts, smaller total gray matter volume, smaller total brain volume, and ventricular enlargement) did not change the results. In fully adjusted models, neither burden of white matter hyperintensities nor

any of the other markers of diffuse brain MRI abnormalities was significantly associated with balance difficulty. Interaction terms between gray matter volume in these regions and white matter hyperintensities or other markers of diffuse brain MRI abnormalities were all not significant. Adding the interval of time between brain MRI and mobility tests to the models yielded similar results for both speed and balance.

## DISCUSSION

In this group of community-dwelling older adults, gray matter volumes of brain regions relevant to motor control were associated with poorer lower-extremity mobility measures, independently of cognitive function or of other health-related factors that may influence mobility and also independently of underlying diffuse brain MRI abnormalities. Importantly, specific aspects of performance seemed to involve a selective spatial distribution of atrophy (Figure 2). Smaller cerebellum and dorsolateral prefrontal regions, predominantly in the left hemisphere, were associated with slower gait speed (Figure 2A), whereas smaller basal ganglia, superior posterior parietal cortex, and cerebellum, predominantly in the right hemisphere, were associated with balance difficulty (Figure 2B).

The spatial localization and the hemispheric predominance of gray matter atrophy may be due to impairment of the underlying circuits controlling speed and balance. For example, it has been shown that selective atrophy of the dorsolateral prefrontal regions in the left hemisphere is associated with poorer performance on executive control functions (40). Several studies (41–43) have shown that poorer executive control functions are associated with slower gait speed. A possible pathway may lead from shrinkage of the executive control–related regions in the left hemisphere to impaired executive control function and ultimately poorer gait control and slower gait speed. Likewise, because we rely on the posterior parietal cortex in the right hemisphere to regulate our visuospatial attention and orientation (44,45), atrophy of these regions in conjunction with putamen atrophy, may lead to poorer balance control and difficulty holding the tandem stance. Longitudinal studies examining the temporal sequence of these events, with data on executive control and visuospatial attention performance, are needed to test the presence of such central mechanisms of gait and balance control.

In fully adjusted models, gray matter volumes (but not white matter hyperintensities or total brain volumes) were

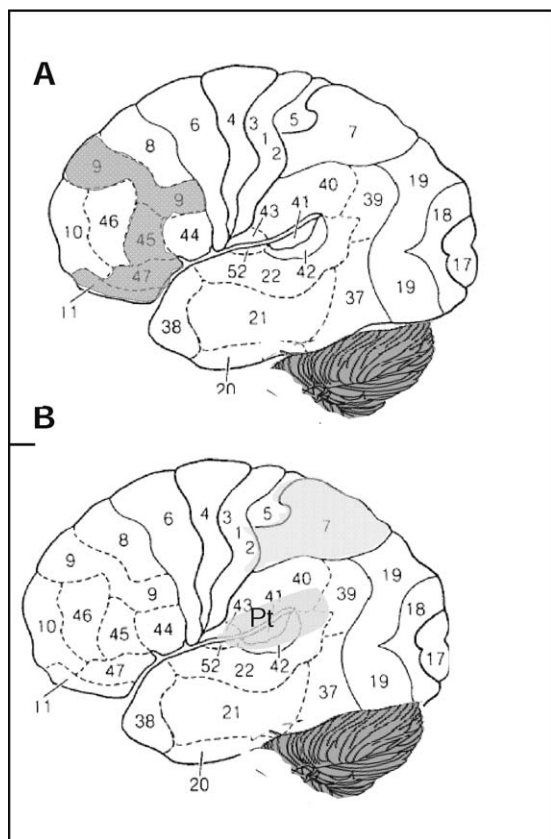


Figure 2. **A**, Brain regions for which smaller gray matter volumes were associated with slower gait included prefrontal regions and cerebellum (dark gray). **B**, Brain regions for which smaller gray matter volumes were associated with balance difficulty included putamen (Pt), superior posterior parietal lobule, or Brodmann area 7 (light gray) and cerebellum (dark gray).

independently associated with mobility measures. This finding suggests that focal neuronal loss is of greater relevance to poorer mobility than is total brain shrinkage or diffuse white matter hyperintensity burden. Total brain atrophy and ventricular enlargement are considered hallmarks of the aging process and may reflect nonspecific, age-dependent brain changes. Perhaps focal gray matter volumetric changes represent a distinct age-independent phenomenon and one that may cause limitations of a specific aspect of mobility, depending on the localization.

An interesting question that future studies should answer to unravel the pathogenesis of age-related mobility impairment is the link between focal gray matter/neuronal loss and white matter abnormalities/myelin degeneration. White matter abnormalities may either be a surrogate marker of neurodegenerative processes starting in the gray matter (46), or they may trigger the events that cause mobility impairment through disruption of neuronal connectivity and retrograde neuronal degeneration. Although it cannot be excluded, the first mechanism is unlikely, as signs of Wallerian degeneration have not been found (47). Longitudinal studies of the temporal and spatial distribution of gray and white matter changes are needed to test the hypothesis that white matter abnormalities mediate the association between gray matter volume and mobility impairment or vice versa. The use of more quantitative measures of white matter abnormalities, such as diffusion tensor imaging markers, could also help to address another interesting question, that is, whether white matter abnormalities localized in specific connectivity tracts are linked with specific aspects of mobility control. Because this was a cross-sectional study that used crude 0–9 measures of diffuse white matter hyperintensities, it could not address these important issues.

We are aware of only one other study analyzing the relative contribution of focal volumetric measures versus diffuse white matter hyperintensities in association with mobility. This study also found that the association between focal shrinkage and mobility is independent of white matter hyperintensities and therefore supports our findings. However, Guo and colleagues (17) measured only one set of regions localized within the temporal lobe, whereas we measured many regions of the brain. Two other substantial differences that limit a direct comparison with the work of Guo and colleagues is that it analyzed a selected population (women only) rather than community-dwelling older adults, and that it used the Timed Pick Up and Go task, which is a more laboratory-controlled measure than are our mobility measures.

Geriatric research has focused on the contribution of muscle strength, osteoarthritis, peripheral neuropathy, and other peripheral components to mobility impairment. To our knowledge, this is the first regions-of-interest study to document an association between spatial distribution of gray matter volumes and gait and balance in community-dwelling older adults. Our findings will need to be replicated to be validated, and until then can be only suggestive of a selective spatial distribution of gray matter atrophy that can cause mobility limitations. Future studies of brain imaging biomarkers of mobility control should measure the distri-

bution and the burden of both gray matter atrophy and white matter abnormalities.

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#### CORRESPONDENCE

Address correspondence to Caterina Rosano, MD, MPH, 130 N Bellefield, Room 519, Pittsburgh, PA, 15213. E-mail: [rosanoc@edc.pitt.edu](mailto:rosanoc@edc.pitt.edu)

#### REFERENCES

- Alexander NB. Gait disorders in older adults. *J Am Geriatr Soc*. 1996;44:434–451.
- Perera S, Studenski S, Chandler JM, Guralnik JM. Magnitude and patterns of decline in health and function in 1 year affect subsequent 5-year survival. *J Gerontol A Biol Sci Med Sci*. 2005;60A:894–900.
- Baloh RW, Yue Q, Socotch TM, Jacobson KM. White matter lesions and disequilibrium in older people. I. Case-control comparison. *Arch Neurol*. 1995;52:970–974.
- Longstreth WT Jr, Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke*. 1996;27:1274–1282.
- Camicoli R, Moore MM, Sexton G, Howieson DB, Kaye JA. Age-related brain changes associated with motor function in healthy older people. *J Am Geriatr Soc*. 1999;47:330–334.
- Longstreth WT Jr, Arnold AM, Beauchamp NJ, et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke*. 2005;36:56–61.
- Tell GS, Lefkowitz DS, Diehr P, Elster AD. Relationship between balance and abnormalities in cerebral magnetic resonance imaging in older adults. *Arch Neurol*. 1998;55:73–79.
- Starr JM, Leaper SA, Murray AD, et al. Brain white matter lesions detected by magnetic resonance [correction of resonance] imaging are associated with balance and gait speed. *J Neurol Neurosurg Psychiatry*. 2003;74:94–98.
- Benson RR, Guttmann CR, Wei X, et al. Older people with impaired mobility have specific loci of periventricular abnormality on MRI. *Neurology*. 2002;58:48–55.
- Carmelli D, DeCarli C, Swan GE, et al. The joint effect of apolipoprotein E epsilon4 and MRI findings on lower-extremity function and decline in cognitive function. *J Gerontol Med Sci*. 2000;55A:M103–M109.
- Sachdev PS, Wen W, Christensen H, Jorm AF. White matter hyperintensities are related to physical disability and poor motor function. *J Neurol Neurosurg Psychiatry*. 2005;76:362–367.
- Rosano C, Branch J, Longstreth WT, Newman AB. Quantitative measures of gait characteristics indicate prevalence of underlying subclinical structural brain abnormalities in higher-functioning older adults. *Neuroepidemiology*. 2006;26:52–60.
- Baloh RW, Ying SH, Jacobson KM. A longitudinal study of gait and balance dysfunction in normal older people. *Arch Neurol*. 2003;60:835–839.
- Whitman GT, Tang Y, Lin A, Baloh RW. A prospective study of cerebral white matter abnormalities in older people with gait dysfunction. *Neurology*. 2001;57:990–994.
- Wolfson L, Wei X, Hall CB, et al. Accrual of MRI white matter abnormalities in elderly with normal and impaired mobility. *J Neurol Sci*. 2005;232:23–27.

16. Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT, Newman AB. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc*. 2005;53:649–654.
17. Guo X, Steen B, Matousek M, et al. A population-based study on brain atrophy and motor performance in elderly women. *J Gerontol Med Sci*. 2001;56A:M633–M637.
18. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol*. 1991;1:263–276.
19. Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluation of dementia in the cardiovascular health cognition study. *Neuroepidemiology*. 2003;22:1–12.
20. Yue NC, Arnold A, Longstreth WT, et al. Sulcal, ventricular, and white matter changes at MR imaging in the aging brain: data from the Cardiovascular Health Study. *Radiology*. 1997;202:33–39.
21. Manolio TA, Kronmal RA, Burke GL, et al. Magnetic resonance abnormalities and cardiovascular disease in older adults. The Cardiovascular Health Study. *Stroke*. 1994;25:318–327.
22. Kuller LH, Shemanski L, Manolio T, et al. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. *Stroke*. 1998;29:388–398.
23. Rosano C, Becker J, Lopez O, et al. Morphometric analysis of gray matter volume in demented older adults: exploratory analysis of the Cardiovascular Health Study brain MRI database. *Neuroepidemiology*. 2005;24:221–229. Epub 2005 Apr 12.
24. 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;15:273–289.
25. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation maximization algorithm. *IEEE Trans Med Imaging*. 2001;20:45–57.
26. Wu M, Rosano C, Lopez-Garcia P, Carter C, Aizenstein H. Optimum template selection for Atlas-based segmentation. *Neuroimage*. 2007;34:1612–1618.
27. Wu M, Carmichael O, Lopez-Garcia P, Carter CS, Aizenstein HJ. Quantitative comparison of neuroimage registration by air, spm, and a fully deformable model. *Hum Brain Mapp*. 2005;27:747–54.
28. Woods RP, Grafton ST, Watson JD, Sicotte NL, Mazziotta JC. Automated image registration: II. *J Comput Assist Tomogr*. 1998;22:153–165.
29. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp*. 2002;17:143–155.
30. Thirion JP. Image matching as a diffusion process: an analogy with Maxwell's demons. *Med Image Anal*. 1998;2:243–260.
31. Guralnick JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332:556–561.
32. Guralnick JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol Med Sci*. 2000;55A:M221–M231.
33. Hirsch CH, Fried LP, Harris T, Fitzpatrick A, Enright P, Schulz R. Correlates of performance-based measures of muscle function in the elderly: the Cardiovascular Health Study. *J Gerontol Med Sci*. 1997;52A:M192–M200.
34. Cesari M, Kritchevsky SB, Penninx BW, et al. Prognostic value of usual gait speed in well-functioning older people—results from the Health, Aging and Body Composition Study. *J Am Geriatr Soc*. 2005;53:1675–1680.
35. Montero-Odasso M, Schapira M, Soriano ER, et al. Gait velocity as a single predictor of adverse events in healthy seniors aged 75 years and older. *J Gerontol A Biol Sci Med Sci*. 2005;60:1304–1309.
36. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Ann Epidemiol*. 1995;5:278–285.
37. DeCarli C, Murphy DG, Tranh M, et al. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. *Neurology*. 1995;45:2077–2084.
38. Tullberg M, Fletcher E, DeCarli C, et al. White matter lesions impair frontal lobe function regardless of their location. *Neurology*. 2004;63:246–253.
39. Wen W, Sachdev P, Shnier R, Brodaty H. Effect of white matter hyperintensities on cortical cerebral blood volume using perfusion MRI. *Neuroimage*. 2004;21:1350–1356.
40. Royall DR, Rauch R, Roman GC, Cordes JA, Polk MJ. Frontal MRI findings associated with impairment on the Executive Interview (EXIT25). *Exp Aging Res*. 2001;27:293–308.
41. Kuo HK, Leveille SG, Yu YH, Milberg WP. Cognitive function, habitual gait speed, and late-life disability in the National Health and Nutrition Examination Survey (NHANES) 1999–2002. *Gerontology*. 2006;53:102–110.
42. Carlson MC, Fried LP, Xue QL, Bandeen-Roche K, Zeger SL, Brandt J. Association between executive attention and physical functional performance in community-dwelling older women. *J Gerontol Psychol Sci Soc Sci*. 1999;54B:S262–S270.
43. Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT, Newman AB. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc*. 2005;53:649–654.
44. Gerhardstein P, Peterson MA, Rapsack SZ. Age-related hemispheric asymmetry in object discrimination. *J Clin Exp Neuropsychol*. 1998;20:174–185.
45. Goldstein G, Shelly CJ. Does the right hemisphere age more rapidly than the left? *Clin Neuropsychol*. 1981;3:65–78.
46. Nedergaard M, Ransom B, Goldman SA. New roles for astrocytes: redefining the functional architecture of the brain. *Trends Neurosci*. 2003;26:523–530.
47. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. *Stroke*. 1997;28:652–659.

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