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Neuroimaging correlates of lateral postural control in older ambulatory adults

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Abstract

Background—In older adults, impaired postural control contributes to falls, a major source of morbidity. Understanding central mechanisms may help identify individuals at risk for impaired postural control.

Aims—To determine the relationship between gray matter volume (GMV), white matter hyperintensities (WMH), mean dif-fusivity (MD), and fractional anisotropy (FA) with lateral postural control.

Methods—Neuroimaging and postural control were assessed in 193 community-dwelling older adults (mean age 82, 55.4% female, 44.6% black). GMV, WMH, and diffusion tensor-derived markers of microstructure (MD and FA) were quantified for total brain and regions of interest. Lateral postural control was defined as the root mean square error (RMSE) of lateral sway during a visual feedback test. Associations were assessed with linear regression, adjusted for total brain atrophy and risk factors for impaired postural control.

Results—RMSE was higher for women than men ($p < 0.001$) and inversely correlated with gait speed ($r = -0.20$, $p = 0.01$), modified mini-mental state ($r = -0.27$, $p < 0.001$), digit symbol substitution test ($r = -0.20$, $p = 0.01$) and quadriceps strength ($r = -0.18$, $p = 0.01$). RMSE was inversely associated with GMV of bilateral precuneus ($r = -0.26$, $p = 0.01$) and FA of corpus callosum and selected tracts in the right hemisphere (anterior thalamic radiation, cingulum,

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

inferior longitudinal and fronto-occipital fasciculi), independent of covariates ($r = -0.34$ to -0.18 , $p < 0.04$).

Discussion—Lower GMV and microstructural white matter integrity in selected networks can explain worse lateral postural control in older ambulatory adults without neurologic diseases.

Conclusion—Neuroimaging markers of poor postural control in healthy aging may help identify increased fall risk and design preventative fall strategies.

Keywords

Postural control; Balance; Neuroimaging; Diffusion tensor imaging; Aging

Introduction

Falls are a major source of morbidity in the elderly resulting in impaired quality of life [1] and rising mortality [2]. Balance abnormalities occur with aging and predict falls [3]; however, we do not have a clear understanding of the neurobiological drivers of age-related balance impairment. To develop strategies to reduce balance impairment, it is important to identify early balance changes and the underlying neurologic contributors. One important risk factor for falling is impaired postural control, especially in the medio-lateral direction [3]. Standing balance relies on afferent inputs from visual, vestibular, and proprioceptive systems as well as lower extremity strength, that decline with normal aging [4]. While there is an association between cognition and specifically executive function with standing balance [5], the relationship between central nervous system structural integrity and balance remains unclear.

Neuroimaging studies in patients with Parkinson's disease support a link between the postural instability/gait difficulty subtype and gray matter atrophy in motor, cognitive, limbic, and association areas [6], as well as microstructural changes in the substantia nigra, globus pallidus [7] and body of the corpus callosum [8]. However, neuroimaging studies of postural control in older individuals without neurological diseases are sparse and results are conflicting. Some but not all studies find poorer standing balance is associated with cerebral atrophy and white matter disease [9–11]. Higher microstructural white matter integrity is associated with better gait characteristics [12], however, there is limited data analyzing brain microstructure in relationship to balance. One small study using diffusion tensor imaging (DTI) showed microstructural integrity of frontal and fronto-occipital white matter tracts was associated with balance [13], but these results were not replicated in another similarly sized study of balance and whole brain measurements [14]. However, this second study found whole brain gray matter density was significantly related to balance instability [14].

The purpose of this study is to examine macro- and microstructural characteristics that are associated with postural control in a sample of community-dwelling older adults. Postural control was assessed via traditional sensory integration balance tests and by a lateral weight shifting test guided by visual feedback. This task engages cognitive resources to maintain appropriate frequency of lateral weight shifting and has been previously associated with executive function [15]. We hypothesize that regions and tracts involved in sensory

integration, motor output, balance, and executive function will be associated with lower integrity of gray and white matter and poorer lateral postural control. Understanding these early changes may lead to identifying individuals at risk for impaired postural control and a mechanism for fall prevention.

Methods

Study population

Community-dwelling white and black older adults were enrolled in the ongoing Health, Aging, and Body Composition Study (Health ABC study), a prospective cohort study which began in 1997 to examine contributors to physical functioning. At study entry, adults ranged in age from 70 to 79 years, and lived in Memphis, TN or Pittsburgh, PA. Participants were recruited from a random sample of Medicare eligible adults living within designated zip codes, and were eligible if they reported no difficulties performing activities of daily living, walking a quarter mile, or climbing 10 steps without resting. They were also free of life-threatening cancers and planned to remain within the study area for at least 3 years. This study was approved by the institutional review boards of the University of Pittsburgh, the University of Tennessee, Memphis, and the Coordinating Center, the University of California San Francisco. All participants signed a written informed consent.

In 2006–2007 (Year 10 of the parent Health ABC cohort), 819 of the initial sample of 1527 participants at the Pittsburgh study site, who were alive and living in the area, were asked to participate in the Healthy Brain Project (HBP), a neuroimaging substudy of cognition and mobility. Of the 819, 727 completed the clinic visit and 325 were eligible (no contraindications to brain magnetic resonance imaging [MRI], had completed mobility performance measures, and had no major hospitalizations in the preceding 3 months) and 315 received MRI at 3 T in 2006–2007. Of these, 193 participants also completed the instrumented balance examination 2 years later. A subset of 173 participants had complete data on DTI with fractional anisotropy (FA) and mean diffusivity (MD).

Image acquisition, processing, and selection of tracts

A 3T Siemens Tim Trio MR scanner with a Siemens 12-channel head coil was used for obtaining MRI scans in 2006–2007. Image acquisition and analyses for this study has been previously described [16]. Magnetization-prepared rapid gradient echo (MPRAGE) images were acquired to obtain gray matter volume (GMV), volume of white matter hyperintensities (WMH), and used in the processing of DTI data. Diffusion tensor images were acquired using single-short spin-echo sequence with 12 directions and preprocessed using the FMRIB's Diffusion Toolbox [17] to remove unwanted distortions (voxel size = 2 mm × 2 mm; slice thickness = 3 mm). Using the segmentation of gray matter from the MPRAGE, the MD was restricted to gray matter of the hippocampus, as defined in the Automated Anatomical Labeling Atlas [18]. Gray matter atrophy of total brain was computed as the ratio of GMV by intracranial volume. Volume of WMH was quantified using a previously published algorithm [19]. Regions and tracts of interest were selected from the Automated Anatomical Labeling Atlas [18] and the Johns Hopkins University White Matter Atlas [20]. FA is a measure of directionality of diffusion in the white matter, with higher values

indicating greater white matter integrity. Higher values of MD indicate free diffusion and, therefore, less dense gray matter tissue [21].

Assessment of standing balance

The test of standing balance was based on the original Clinical Test of Sensory Interaction on Balance [22, 23]. The test assesses use of vision, somatosensation and peripheral vestibular sensation in 4 test conditions: eyes open and eyes closed on a stable surface and on a compliant surface (a 7.5 cm thick medium-density foam pad). At the second HBP follow-up, participants stood upright with feet together, for as long as they could up to 30 s or until they lost their balance. Assessments were conducted on a force platform and participants wore a safety harness and were guarded by a research technician. Ground reaction forces were recorded from the force platform (Bertec Corp) using Labview software (National Instruments, Inc.), and the root mean square (RMS) of the center of pressure (COP) in the anteroposterior (AP) and mediolateral (ML) directions was computed for trials that lasted at least 15 s. The RMS of the COP is a measure of the variability of displacements of the COP. The condition of eyes open on foam was included in this analysis because of prior results [15].

Assessment of lateral postural control

Participants performed a postural control test in which they controlled the movement of their mediolateral center of pressure (ML COP) using visual feedback [15]. Subjects stood on the force platform with their feet 16 cm apart. On a computer monitor approximately 1.5 m in front of the subjects, an open circle moved across the screen along a horizontal line. In addition, an “X” that represented the subject’s ML COP was displayed on the same horizontal line. Subjects were instructed to keep the “X” inside the open circle. The tracking task at 0.25 Hz was selected for analyses because it had the strongest relationship with cognitive function in this cohort [15]. The target’s movement was scaled to a range of 16 cm, so that during slow movements, participants would be shifting their weight from one foot to the other while keeping both feet in contact with the platform. The root mean square error (RMSE) between the position of the target and ML COP was computed.

Covariates

At HBP baseline, demographic data including self-reported participant age, race, and sex were recorded. Body mass index was calculated from height and weight measurements at baseline. Factors that may contribute to balance were considered as covariates. Global cognitive function was tested by the Modified Mini-Mental State Exam (3MS). The 3MS ranges from 0 to 100 and a score of 80 or below indicates poor cognitive function [24]. The digit symbol substitution test (DSST) was obtained as a measure of executive function and visuospatial attention. The number correct in 90 s was recorded. Six-m gait speed was measured as usual gait speed over a 6-m course. The average of two trials was used. Peak knee extensor strength was measured concentrically at 60° per second using an isokinetic dynamometer (Kin-Com 125 AP Dynamometer, Harrison, TN). Ankle position was measured via goniometer at - 10°, - 20°, and - 30° from the neutral position. Abnormal sense of position was considered if the contralateral ankle was placed 5° outside from the measured ankle. In the Romberg test, participants stood with their feet together, eyes open

and then closed. The test was abnormal if a participant could not complete it for at least 30 s. Mild parkinsonian signs (MPS) was measured using the Unified Parkinson's Disease Rating Scale part III (motor), which identifies bradykinesia, tremor, rigidity, and gait disturbances. MPS was considered present per the protocol by Louis et al [25]: two or more items with a score of 1, one item with a score of 2, or rest tremor score of 1, and did not meet diagnostic criteria for Parkinson's disease. Ankle-arm index < 0.9 was used as a surrogate measure of peripheral arterial disease [26]. History of stroke, vision problems, and joint pain were self-reported.

Statistical analysis

Associations between participants' characteristics and postural measures were tested with Pearson's correlations for continuous variables and *t* tests for categorical variables. Associations between RMSE and neuroimaging markers of total brain were first tested with partial Pearson's correlations adjusted for total atrophy. Regional analysis of a given modality was further tested if the partial correlations *p* value for the total brain measure was $p < 0.05$. Linear regression models assessed associations between regions of interest thus identified and RMSE, adjusted for variables that were univariately associated with RMSE as described above. Analyses were adjusted for false discovery rate (FDR) < 0.05 to account for multiple comparisons.

Results

Compared to the larger cohort, participants included in this analysis were not substantially healthier (Table 1). Higher RMSE, indicating poorer postural control, was associated with female sex, slower six-meter gait speed, poorer score on the 3MS and DSST, and weaker quadriceps strength ($p < 0.05$ for all, Table 2). Associations between RMSE and other measures of standing balance were not significant (Table 2). Higher sway during the standing task on foam with eyes open was associated with male sex, lower DSST score, and weaker quadriceps strength, but not with other variables (Table 2).

Lower total brain GMV ($r = -0.24$, $p = 0.001$) and lower FA of total brain white matter ($r = -0.22$, $p = 0.01$) significantly associated with greater RMSE. WMH volume ($p = 0.08$) and MD of total GMV ($p = 0.07$) were not associated with RMSE at $p < 0.05$. Neuroimaging measures of total brain were not significantly associated with standing balance with eyes open on foam, measured as mediolateral sway ($p > 0.3$ for all).

Gray matter volume

In analyses conducted for regions of interest adjusted for total brain gray matter atrophy, lower GMV of the bilateral precuneus and right supplementary motor area were associated with greater RMSE (FDR adjusted p all < 0.05 , Table 3). Associations with total brain GMV and GMV of bilateral precuneus, but not with other gray matter regions of interest, remained significant after further adjustment for sex, peak knee extensor strength, or DSST score (Table 4; Fig. 1).

White matter fractional anisotropy

Associations between lower FA of individual tracts and higher RMSE were significant for the anterior thalamic radiation, cingulum (lower and upper), inferior longitudinal and fronto-occipital fasciculi in the right hemisphere, and for the body of the corpus callosum (FDR adjusted p all < 0.05 , Table 3). Associations with FA of individual white matter tracts of interest remained significant after adjustment for sex, peak knee extensor strength, and DSST score, however, associations with total brain FA were attenuated by sex (Table 4; Fig. 1).

Discussion

In this cohort of ambulatory older adults, poorer lateral postural control appears related to a selective spatial distribution of gray and white matter characteristics; specifically, associations were stronger for lower total GMV and localized in the precuneus bilaterally, and for lower microstructural integrity localized in the corpus callosum and frontotemporo-occipital areas in the right hemisphere.

Our findings suggest that control of posture involves a widespread network of brain areas and tracks and are consistent with the previously shown importance of fronto and fronto-occipital white matter tract integrity [13] and total gray matter [14] in balance. The role of the precuneus has largely been assigned to visuospatial processing [27] and the association may be accounted for by the visual targeting in the task.

It is unclear why there was significance of association with GMV but not MD. These results may reflect that more severe gray matter changes are needed before they become evident as impairment on the postural tracking task. We found no association between total WMH and impaired postural control in both the tracking task and the task of standing balance. This is inconsistent with a prior study in a healthy aging cohort where white matter disease was associated with poor balance [9]. WMH volume is a conventional MRI method for analyzing white matter disease; however, our study suggests there is involvement of subcortical white matter as indicated by microstructural integrity, which may be an early indicator of white matter damage.

The primary posturography variable in this study was a visual feedback center of pressure tracking task which engages cognitive resources in addition to relatively automatic postural responses. We recently showed this complex task is associated with executive function in this cohort [15] and it underscores the involvement of this cognitive domain in maintaining optimal standing balance in everyday functioning in older age. Dual task paradigms have previously demonstrated the importance of attention in dynamic postural control [28].

While postural instability is commonly seen in healthy aging, it can be a feature of Parkinson's disease, a neurodegenerative disorder that may have a younger age of onset. We found that MPS was present in 31.1% of our cohort, consistent with prevalence estimates of 15–40% in older community-dwelling individuals [25]. A previous study showed impairments in postural sway along the mediolateral axis in Parkinson's disease patients before the onset of clinical balance dysfunction symptoms [29]. We did not find MPS to be

associated with posturography tasks in our study and presence of MPS did not attenuate the associations of regions of interest in the linear regression model (data not shown). Brain regions important in postural control may be similar in Parkinson's disease compared to healthy aging, however, the underlying etiology and pathology of MPS remains unknown [25]. Our findings of lower GMV and microstructural changes in the body of the corpus callosum are consistent with findings from Parkinson's disease patients with primarily postural instability and gait difficulty [6, 8]. In our study of healthy participants, we did not find any associations with poor postural control and the basal ganglia unlike in patients with Parkinson's disease [7].

There are several limitations of this study. This was a cross-sectional study and did not analyze longitudinal associations of brain changes over time. Additionally, our cohort included healthy older individuals and we could not directly compare cerebral changes between healthy older individuals and those with poor postural control due to overt neurologic disease.

In summary, lower GMV and impaired microstructural integrity of widely spread white matter may explain otherwise unexplained poor postural control in ambulatory older adults free from clinically overt neurologic disease. The etiology of these changes is unknown and should be investigated in future studies so potential intervention may be initiated. Despite exercise programs for age-related balance problems [30, 31], by the time balance problems become clinically overt, the underlying neurologic changes have unfolded and potential treatment may be less effective. Once identified, early MRI markers of impaired postural control in both healthy aging and neurodegenerative disorders may aid the clinician in identifying the increased risk for falling to institute early preventative fall strategies. Future studies should also investigate longitudinal change in neuroimaging markers as a predictor of impaired postural control.

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Fig. 1.

Axial and sagittal magnetic resonance imaging displaying regions and tracts of significance.

a Associations for gray matter volume (GMV) were stronger for cortical regions with only total GMV and bilateral precuneus (red) independent of covariates. **b** Associations with fractional anisotropy appeared localized to the right hemisphere [anterior thalamic radiation (red), lower cingulum (green), upper cingulum (blue), inferior longitudinal fasciculus (teal) and inferior fronto-occipital fasciculus (yellow)] and body of corpus callosum (purple), independent of covariates

Baseline characteristics among those subjects who were included in the Health, Aging, and Body Composition Study (Health ABC study) visit in year 10, those eligible for enrollment in the Healthy Brain Project (HBP), and those included in our analytic cohort

Table 1

Variable	Year 10 Health ABC cohort (Pitts- burgh site, <i>n</i> = 727)	HBP cohort (<i>n</i> = 325)	Analytic cohort (<i>n</i> = 193)
Age (years)	83.31 (2.78)	82.98 (2.81)	82.43 (2.53)
Female sex	378 (51.99%)	181 (55.69%)	107 (55.44%)
Body mass index (kg/m ²)	27.65 (4.62)	27.45 (4.44)	27.78 (4.38)
History of stroke	33 (4.54%)	29 (8.92%)	13 (6.74%)
History of diabetes	172 (23.66%)	87 (26.77%)	42 (21.76%)
History of hypertension	629 (86.52%)	277 (85.23%)	167 (86.53%)
Total cholesterol (mg/dL)	194.72 (41.90)	191.57 (42.89)	191.76 (40.81)
Smoking status			
Never	353 (48.56%)	165 (50.77%)	103 (53.37%)
Current	21 (2.89%)	6 (1.85%)	5 (2.59%)
Former	352 (48.42%)	143 (44.00%)	85 (44.04%)
Minutes Walking Per Week	74.77 (133.60)	83.46 (124.54)	77.83 (115.98)

Demographic characteristics and contributors of balance among 193 participants in relation to the lateral tracking task and standing balance on foam with eyes open

Table 2

Variable Mean (SD) or N (%)	Entire sample (n= 193)	ML RMSE of the Postural Tracking Task r (p value) [†] or t statistic (p value) [*]	Standing balance with eyes open on foam (ML sway) r (p value) [†] or t statistic (p value) [*]
Age (y)	82.43 (2.53)	0.06 (0.38)	0.09 (0.24)
Female sex	107 (55.44%)	- 5.46 (< 0.001)	3.17 (0.002)
Body mass index (kg/m ²)	27.78 (4.38)	0.10 (0.15)	0.19 (0.07)
Stroke history	13 (6.74%)	1.08 (0.28)	0.20 (0.84)
Six-meter Gait Speed (m/s)	1.08 (0.20)	- 0.20 (0.01)	- 0.01 (0.94)
Modified mini-mental state (median, IQR)	96.0 (7.0)	- 0.27 (< 0.001)	- 0.07 (0.40)
Digit symbol substitution test (# correct in 90 s)	39.08 (12.23)	- 0.20 (0.01)	- 0.18 (0.02)
Peak knee extension strength (Nm)	85.45 (30.05)	- 0.18 (0.01)	- 0.23 (0.004)
Abnormal sense of Ankle Position	18 (9.33%)	- 1.03 (0.31)	- 1.00 (0.33)
Romberg test (held balance < 30 s)	23 (11.92%)	0.67 (0.50)	- 0.08 (0.94)
Mild parkinsonian signs (yes)	60 (31.08%)	0.31 (0.75)	1.63 (0.11)
Poor or very poor eyesight	7 (3.63%)	0.18 (0.86)	- 1.59 (0.11)
Peripheral arterial disease	34 (17.61%)	- 0.34(0.73)	0.43 (0.67)
Joint pain	1 (0.52%)	- 0.13 (0.90)	1.12 (0.26)
Standing on firm surface, eyes open (ML Sway)	0.18 (0.12)	0.09 (0.21)	0.34 (< 0.001)
Standing on firm surface, eyes closed (ML Sway)	0.18 (0.14)	0.03 (0.66)	0.21 (0.001)
Standing on foam, eyes open (ML Sway)	0.93 (0.51)	0.03 (0.73)	N/A
Standing on foam, eyes closed (ML Sway)	1.33 (0.72)	- 0.14(0.14)	0.51 (< 0.001)

ML mediolateral, RMSE root mean square error

[†] P-values calculated with Pearson's correlations for continuous variables

^{*} t tests for categorical variables

Table 3

Correlations (r , p value) of the lateral tracking task (ML RMSE) with brain regions of interest ($n = 193$)

Brain Regions	Adjusted ^a r (p value)	False discovery rate-adjusted p value
GMV regions		
Left pallidum	– 0.001 (0.99)	0.99
Right pallidum	0.01 (0.92)	0.96
Left putamen	0.10 (0.89)	0.96
Right putamen	0.01 (0.91)	0.96
Left caudate	0.01 (0.88)	0.96
Right caudate	– 0.04 (0.57)	0.84
Left thalamus	– 0.09 (0.23)	0.42
Right thalamus	– 0.08 (0.28)	0.47
Left cerebellum	– 0.17 (0.02)	0.07
Right cerebellum	– 0.10(0.19)	0.38
Left superior frontal gyri	– 0.03 (0.70)	0.96
Right superior frontal gyri	– 0.11 (0.14)	0.31
Left middle frontal gyri	– 0.10(0.90)	0.96
Right middle frontal gyri	– 0.16 (0.04)	0.11
Left superior parietal lobe	– 0.20 (0.01)	0.07
Right superior parietal lobe	– 0.14(0.05)	0.12
Left precentral gyrus	– 0.18 (0.02)	0.08
Right precentral gyrus	– 0.17 (0.02)	0.07
Left paracentral lobule	– 0.07 (0.32)	0.50
Right paracentral lobule	– 0.15 (0.04)	0.11
Left precuneus	– 0.26 (< 0.001)	0.01
Right precuneus	– 0.26 (< 0.001)	0.01
Left supplementary motor area	– 0.17 (0.03)	0.12
Right supplementary motor area	– 0.19 (0.01)	0.01
FA of white matter tracts		
Left anterior thalamic radiation	– 0.17 (0.05)	0.06

Brain Regions	Adjusted ^a <i>r</i> (<i>p</i> value)	False discovery rate-adjusted <i>p</i> value
Right anterior thalamic radiation	− 0.26 (0.002)	0.002
Left superior longitudinal fasciculus	− 0.15 (0.08)	0.09
Right superior longitudinal fasciculus	− 0.17 (0.05)	0.06
Left lower cingulum	− 0.10(0.25)	0.25
Right lower cingulum	− 0.18 (0.01)	0.04
Left upper cingulum	− 0.17 (0.05)	0.06
Right upper cingulum	− 0.34 (< 0.001)	0.002
Left inferior longitudinal fasciculus	− 0.14(0.10)	0.11
Right inferior longitudinal fasciculus	− 0.24 (0.004)	0.002
Left inferior fronto-occipital fasciculus	− 0.17 (0.05)	0.06
Right inferior fronto-occipital fasciculus	− 0.20 (0.01)	0.04
Corpus callosum, genu	− 0.17 (0.04)	0.06
Corpus callosum, body	− 0.21 (0.01)	0.04
Corpus callosum, splenium	− 0.16 (0.05)	0.06

GMV gray matter volume, *FA* fractional anisotropy, *ML* mediolateral, *RMSE* root mean square error

^a Adjusted for atrophy which was calculated as the ratio of total *GMV* by intracranial volume

Table 4

Linear associations between GMV regions and FA tracts of interest, adjusted for covariates ($n = 193$)

Region/tract	Model 1	Model 2	Model 3	Model 4
GMV regions	Standardized β (p value)			
Total GMV ^b	-0.24 (<0.001)	-0.18 (0.01)	-0.25 (0.001)	-0.24 (0.001)
Left precuneus	-0.27 (0.001)	-0.19 (0.02)	-0.24 (0.003)	-0.23 (0.003)
Right precuneus	-0.30 (0.001)	-0.19 (0.03)	-0.26 (0.003)	-0.26 (0.002)
Right supplementary motor area	-0.19 (0.01)	-0.10(0.21)	-0.14(0.07)	-0.20 (0.01)
FA of white matter tracts				
Right anterior thalamic radiation	-0.24 (0.002)	-0.18 (0.02)	-0.21 (0.01)	-0.22 (0.004)
Right lower cingulum	-0.19 (0.01)	-0.15 (0.04)	-0.18 (0.02)	-0.16 (0.04)
Right upper cingulum	-0.28 (0.0003)	-0.21 (0.005)	-0.26 (0.001)	-0.25 (0.001)
Right inferior longitudinal fasciculus	-0.21 (0.007)	-0.19 (0.01)	-0.21 (0.01)	-0.18 (0.02)
Right inferior fronto-occipital fasciculus	-0.18 (0.01)	-0.16 (0.03)	-0.18 (0.02)	-0.16 (0.04)
Corpus callosum, body	-0.21 (0.009)	-0.17 (0.02)	-0.19 (0.02)	-0.17 (0.03)
FA all white matter	-0.19 (0.01)	-0.14(0.07)	-0.17 (0.03)	-0.16 (0.04)

Regions and tracts of interest chosen based on significant associations in Table 3. Model 1 is adjusted for gray matter atrophy of total brain. Model 2 is adjusted for atrophy and sex. Model 3 is adjusted for atrophy and peak knee extensor strength. Model 4 is adjusted for atrophy and digit symbol substitution test

^bTotal GMV was divided by ICV, and not adjusted for atrophy

GMV gray matter volume, FA fractional anisotropy, ICV intracranial volume