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The Effect of Age and Microstructural White Matter Integrity on Lap Time Variation and Fast-Paced Walking Speed

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Abstract

Introduction—Macrostructural white matter damage (WMD) is associated with less uniform and slower walking in older adults. The effect of age and subclinical microstructural WM degeneration (a potentially earlier phase of WM ischemic damage) on walking patterns and speed is less clear. This study examines the effect of age on the associations of regional microstructural WM integrity with walking variability and speed, independent of macrostructural WMD.

Methods—This study involved 493 participants (n=51 young; n=209 young-old; n=233 old-old) from the Baltimore Longitudinal Study of Aging. All completed a 400-meter walk test and underwent a concurrent brain MRI with diffusion tensor imaging. Microstructural WM integrity was measured as fractional anisotropy (FA). Walking variability was measured as trend-adjusted variation in time over ten 40-meter laps (lap time variation, LTV). Fast-paced walking speed was assessed as mean lap time (MLT). Multiple linear regression models of FA predicting LTV and MLT were adjusted for age, sex, height, weight, and WM hyperintensities.

Results—Independent of WM hyperintensities, lower FA in the body of the corpus callosum was associated with higher LTV and longer MLT only in the young-old. Lower FA in superior longitudinal, inferior fronto-occipital, and uncinate fasciculi, the anterior limb of the internal capsule, and the anterior corona radiate was associated with longer MLT only in the young-old.

Conclusion—While macrostructural WMD is known to predict more variable and slower walking in older adults, microstructural WM disruption is independently associated with more variable and slower fast-paced walking only in the young-old. Disrupted regional WM integrity may be a subclinical contributor to abnormal walking at an earlier phase of aging.

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Conflict of interest

The authors declare no conflict of interest

Keywords

Diffusion tensor imaging; white matter integrity; lap time variation; fast-paced walking speed

Introduction

Variable and slow walking contribute to disability and are common consequences of aging (Brach et al., 2007) (for review, see (Vermeulen et al., 2011). Macrostructural white matter damage (WMD) is consistently shown to be associated with variable and slow walking in older adults (Starr et al., 2003, Rosano et al., 2007, Bolandzadeh et al., 2014). However, less is known about the effect of age and subclinical WM changes on walking patterns and speed. Subclinical WM changes reflecting the subtle emergence of ischemic WM damage can be detected using fractional anisotropy (FA) based on diffusion tensor imaging (DTI) (Werring et al., 1999, Gallo et al., 2005). Higher FA indicates greater integrity of WM microstructural components, whereas lower FA may reflect demyelination or axonal damage of the WM (Sen and Basser, 2005). Microstructural WM integrity is known to generally decline with age (Westlye et al., 2010, Sexton et al., 2014). These subclinical brain changes may reflect the impact of early ischemic changes on walking at an earlier phase of life, thus offering a potential opportunity for early intervention.

While initial DTI studies show that the disruption of WM microstructure is associated with variable and slow walking in patients with Parkinson's disease, small vessel disease, and leukoaraiosis (Della Nave et al., 2007, de Laat et al., 2011a, de Laat et al., 2011b, Vercruysse et al., 2015), less is known about normal aging. Since subclinical age-related ischemic changes may contribute to the development of variable and slow walking, this issue is important to the field. To date, only two studies sought to examine microstructural WM integrity and gait disturbance in community-dwelling older adults (Bhadelia et al., 2009, Bruijn et al., 2014). However, these studies have either focused on one specific WM tract or have not considered important covariates, such as age and macrostructural WMD.

Since macrostructural WMD, compared to microstructural WM integrity, might be considered a more advanced manifestation of ischemic small vessel disease of the brain, the stage of macrostructural WMD might be more advanced in the old-old than the young-old, Thus, the effect of microstructural WM integrity on walking variability and speed may be overridden by more advanced macrostructural WMD in the old-old. One prior DTI study that accounted for macroscopic WMD focused on relatively young older adults in their early seventies and found that a lower WM integrity in the genu of the corpus callosum was related to lower gait scores. (Bhadelia et al., 2009). Since younger adults would be expected to have healthier WM, and less abnormal walking performance than older adults, prior DTI studies have confirmed that among younger persons there is little association between WM integrity and gait (Van Impe et al., 2012, Bruijn et al., 2014).

The spatial distribution of microstructural WM integrity in relation to walking variability and speed remains to be defined among community-dwelling older adults. Pioneer DTI studies have identified specific regions of WM microstructure that are associated with variable and slow walking, particularly in patient populations (Della Nave et al., 2007,

Bhadelia et al., 2009, de Laat et al., 2011a, de Laat et al., 2011b, Bruijn et al., 2014, Vercruysse et al., 2015). Regions of interest that can potentially affect walking extend beyond those directly linking the motor cortex. For example, the cortico-cortical WM tracts connecting the frontal, temporal, and occipital lobes, are involved in processing motor and sensory information. The corpus callosum, the largest WM structure in the central nervous system, plays an essential role in integrating functions between left and right hemispheres (Kochunov et al., 2005). The anterior portion of the corpus callosum (genu, rostrum, and body) connects bilateral prefrontal areas which support executive function. The prefrontal cortex is known to be related to gait planning (Miller and Cohen, 2001). The splenium (posterior portion) of the corpus callosum connecting bilateral temporal, parietal, and occipital lobes, is important for processing the visuospatial information (Raybaud, 2010). The subcortical WM tracts, such as the anterior limb of the internal capsule and the anterior corona radiata, carry fibers important for motor functions (Hendelman, 2006).

One limitation in studying variable walking is the lack of a clinically accessible measure of gait variability. Prior studies primarily relied on motion analysis or force plate systems to assess gait variability from one step to the next (Bruijn et al., 2014) (Koo et al., 2012). An alternative is to assess variability in walking time across multiple “laps” of a longer walk. Variability in walk time or walking pace across repeated measures or laps offers an easily accessible way to assess gait variability. It is known to be related to functional decline (Li et al., 2001) and mortality (Vestergaard et al., 2009).

In this study, we quantified the associations of FA in regional WM tracts with lap time variation (LTV) and mean lap time (MLT) in the young, the young-old, and the old-old without overt neurological disease or mobility limitation. We hypothesize that FA in selected WM tracts would be associated with higher LTV and longer MLT in older adults, and not in the young adults. We also hypothesize that the relationship in the old-old would be attenuated by advanced macrostructrual WMD.

Methods

Study Population

This study used data from the ongoing Baltimore Longitudinal Study of Aging (BLSA) (Shock, 1984). 545 participants underwent their brain MRI from 2009 to 2013. Participants were excluded if they were diagnosed with mild cognitive impairment, Alzheimer’s disease, dementia, Parkinson’s disease or had history of stroke. Mild cognitive impairment was determined by Petersen criteria for mild cognitive impairment (Zonderman et al., 1995). Dementia and Alzheimer’s disease were determined by the Diagnostic and Statistical Manual (DSM)-III-R and the National Institute of Neurological and Communication Disorders—Alzheimer’s Disease and Related Disorders Association criteria (McKhann et al., 1984). Parkinson’s disease and stroke were based on self-reported diagnosis by physicians. Among the 545, 493 men and women completed the 400-meter walk test without a walking aid during the same visit as the brain MRI. The 493 participants were grouped into three age categories; the young (aged<50), the young-old (aged 50-70), and the old-old (aged>70). The study protocol was approved by the institutional review board of record at the time of data collection. All participants provided written informed consent.

Image acquisition

Data were acquired on a 3 Tesla Philips Achieva scanner at the National Institute on Aging. Each participant underwent a T1-weighted magnetization-prepared rapid gradient-recalled echo (MPRAGE) scan, an interleaved proton density (PD) and T2-weighted dual-echo scan, a fluid-attenuated inversion recovery (FLAIR) scan, and two DTI scans at each visit.

The MPRAGE protocol was as follows: number of slices = 170, voxel size = $1\times1\times1.2mm^3$, reconstruction matrix = 256×256, flip angle = 8° and TR/TE = 6.5/3.1 msec. The interleaved PD/T2 dual-echo scan was acquired axially with a total of 100 slices (50 slices each), reconstruction matrix = 256×256, voxel size = $0.94\times0.94\times3mm^3$, TR = 3000 msec, TE = 8ms/100ms. The FLAIR sequence was acquired axially with number of slices = 35, voxel size = $0.83\times0.83\times4.4mm^3$, reconstruction matrix = 320×320, TR/TE/TI = 11000/68/2800 msec.

The DTI protocol was as follows: number of gradients = 32, max b-factor = 700 s/mm^2, TR/TE = 7454/75 msec, number of slices = 70, voxel size = $0.81\times0.81\times2.2mm^3$, reconstruction matrix = 320×320, acquisition matrix = 116×115, field of view = 260×260 mm, flip angle = 90°. Each DTI acquisition had two b0 images, which were averaged in k-space. Two separate DTI acquisitions each with NSA = 1 were obtained and then combined offline (as explained in Image processing) for an effective NSA = 2 to improve signal-to-noise ratio.

Image processing

The DTI processing followed standard practice for tensor fitting and quality assessment and is explained in detail in earlier publications (Lauzon et al., 2013). Briefly, the individual diffusion weighted volumes were affine co-registered to a minimally weighted (b0) target to compensate for eddy current effects and physiological motion. The gradient tables were corrected for the identified rotational component using finite strain (Alexander et al., 2001). To combine two DTI sessions with different intensity normalization constants that were unknown, each diffusion weighted image was normalized by its own reference image prior to tensor fitting.

To segment the WM, the Eve White Matter atlas (Lim et al., 2013) was combined with corresponding WM labels from multi-atlas segmentation using 35 manually labeled atlases from NeuroMorphometrics with the BrainCOLOR protocol (Klein et al., 2010), and an FA mapped MRI. The WM labels were then intersected with WM segmentation and the resulting labels are iteratively grown to fill the remaining WM space from the multi-atlas labels. The WM regions of interest labels obtained from the T1 image for each visit were affine registered to the FA image and used to extract region-specific average FA measures. After reviewing the distributions of quality control summary statistics generated by our pipeline (Lauzon et al., 2013), eighteen scans were excluded due to either excessive motion or images that had globally high diffusion measure bias.

The tissue segmentation was done using a validated automated approach (Davatzikos et al., 2001) and intracranial volume (ICV) was obtained. The volume of WMH was quantified using MPRAGE, T2 and FLAIR images based on validated support vector machine

classifier approach (Lao et al., 2008, Zacharaki et al., 2008). Macrostructural WMD was measured as a ratio of total volume of WMH by ICV.

The FA in each individual tract was computed as the average from left and right hemispheres. In this study, WM tracts were selected *a priori* based on their known associations with mobility. The selected tracts included the cortico-cortical (superior longitudinal, inferior fronto-occipital, and uncinate fasciculi) (Dunsky et al., 2006, Scherder et al., 2011, Vercruysse et al., 2015), the interhemispheric (the corpus callosum) (Della Nave et al., 2007, Bhadelia et al., 2009, de Laat et al., 2011a), and the subcortical tracts (the anterior limb of the internal capsule, and the anterior corona radiata) (Vercruysse et al., 2015).

Mobility measures

LTV was obtained from the 400-meter Long Distance Corridor Walk (LDCW). As administered in the BLSA, the LDCW consists of a 2.5-minute walk at a normal pace followed immediately by a 400-meter walk as quickly as possible. The course is 20 meters long in an uncarpeted corridor marked by orange traffic cones at either end. Participants are instructed to walk to the far cone and back for ten laps of 40 meters as quickly as possible. Participants receive encouragement and feedback on laps remaining after completing each lap (Simonsick et al., 2001). Participants were not permitted to jog and all participants in this study completed the 400-m walk without a walking aid.

For each participant, MLT (in seconds) was computed as the arithmetic mean of the time to complete each of the ten 40-meter laps. Lap time may increase as the lap number increases due to fatigability and those with chronic medical conditions could be more fatigued than those without. Thus, LTV was measured as the residual standard deviation (SD) of the lap time. It captures the variability in residual lap time across ten laps, not from stride-to-stride. First, the individual trajectory was computed from a participant-specific regression of lap time on lap number using linear random-effects models with random intercepts and slopes. The residual was computed as the difference between the lap time from each lap and the predicted lap time based on participant-specific regression of lap time on lap number. Finally, the SD of the residuals from ten laps was obtained and used in the analysis. This detrended SD is considered a more accurate measure of variability than the SD of MLT as it controls for the effect of fatigue-related slowing on variability (Simonsick et al., 2014, Tian et al., 2015).

Health-related conditions

Self-report of osteoarthritis of the knees, leg pain when walking, and difficult walking 1/4 mile were obtained through an interviewer-administered interview. Smoking history was categorized as current or recent smoker vs never or former smoker. Obesity was assessed as body mass index in kg/m^2. Physical activity was assessed using a standardized physical activity questionnaire (Taylor et al., 1978). Based on self-report of the degree of difficulty walking under various conditions, walking ability was scored from 0 to 9 (0=unable to walk one-quarter of a mile, 9=walking a mile is very easy) (Simonsick et al., 2009).

Statistical analysis

Sample characteristics, mobility measures, and neuroimaging markers of interest were compared among three age groups using Chi-square and one-way ANOVA as appropriate. Pairwise comparisons were examined using Turkey test or chi-square test as appropriate.

The associations of FA predicting LTV and MLT were analyzed using multivariate linear regression in separate age groups. As outcomes in the model, values of LTV and MLT were log transformed due to their skewed distributions. Models were all adjusted for age, sex, height, and weight. Covariates were chosen based on their known associations with WM health, walking variability, and walking speed. The association between FA and LTV was additionally adjusted for MLT because higher gait variability may be affected by slower walking speed (Beauchet et al., 2009). In this exploratory analysis, associations were reported as significant at $p \leq 0.05$.

To examine the contribution of macrostructural WMD to the relationship between FA and mobility measures, models were further adjusted for WMH for all age groups.

To examine the strength of the associations, models were additionally adjusted for smoking status, obesity, and walking ability. These covariates were included in a prior study examining fatigability during the 400-m walk (Simonsick et al. 2014).

Results

Table 1 describes sample characteristics, mobility measures, and neuroimaging markers among three age groups. As expected, compared to the young group, the young-old and the old-old had fewer smokers, higher prevalence of osteoarthritis of knees, and lower walking activity scores (Table 1). The old-old had higher LTV and longer MLT than the young-old and the young ($p<0.001$ for both). The young-old had longer MLT than the young, while there was no significant difference in LTV between the young-old and the young ($p>0.05$). The old-old had lower FA in all tracts of interest except the uncinate fasciculus and had higher WMH than the young-old and the young (Table 1). Compared to the young, the young-old had lower FA in the superior longitudinal fasciculus, the inferior fronto-occipital fasciculus, the genu of the corpus callosum, and the anterior corona radiata. The young and the young-old did not significantly differ in FA in other tracts or in WMH (all $p>0.05$). After adjustment for age, sex, height, and weight, lower FA in the body of the corpus callosum was associated with higher LTV only in the young-old, not in the young or the old-old (Table 2, Model 1). The significant association in the young-old persisted after further adjustment for WMH or MLT (Table 2, Model 2 and 3). The association between FA in other tracts of interest and LTV was not significant in all age groups (Table 2).

After adjustment for age, sex, height, and weight, lower FA in the superior longitudinal, inferior fronto-occipital, and uncinate fasciculi, the anterior limb of the internal capsule, and the anterior corona radiata was associated with longer MLT only in the young-old, not in the young or in the old-old (Table 3, Model 1). FA in the genu and the splenium of the corpus callosum was not associated with MLT in the young-old (Table 3, Model 1). Lower FA in the body of the corpus callosum was associated with longer MLT in both the young-old and

the old-old (Table 3, Model 1). The significant associations in the young-old persisted after further adjustment for WMH (Table 3, Model 2). The association between FA in the body of the corpus callosum and MLT in the old-old was attenuated after further adjustment for WMH (Table 3, Model 2). FA in other tracts of interest was not associated with MLT in the old-old (Table 2). The significant associations in the young-old persisted after further adjustment for smoking status, obesity, and walking activity scores (data not shown).

Discussion

Disrupted regional microstructural WM integrity is associated with more variable and slower fast-paced walking only among the young-old. Microstructural WM integrity may be an important, early neuroimaging marker of subtle development of abnormal walking. Adjustment for macrostructural WMD did not substantially affect the results in the young-old.

This study is the first to demonstrate the localization of microstructural WM integrity in relation to walking variability and speed in a sample of community-dwelling adults without overt neurological diseases. We quantified the relationship in the young, the young-old, and the old-old to understand the effect of age and microstructural WM integrity on variability and the mean performance of fast-paced walking. Our key finding is that disruption of WM microstructure is associated with more variable and slower fast-paced walking only in the young-old, even after adjusting for macrostructural WMD. Findings suggest that in the young-old, the presence and the amount of macrostructural WMD did not substantially contribute to the relationship between WM microstructure and abnormal walking. Interestingly, there was a marginal association between FA in the body of the corpus callosum and fast-paced walking speed in the old-old. Further adjustment for macrostructural WMD attenuated this association. We suspect that the impact of WM microstructure on mobility performance may be overridden by advanced WM neurodegeneration in the old-old, because the evolution of WM degeneration is much stronger in the old-old than in the young-old. We observed little associations in the old-old may be due to the fact that abnormal gait tends to be more multifactorial in advancing age. There may be other non-neural components contributing to abnormal gait in the old-old. As expected, we did not find any associations in young adults. These findings suggest that subtle alterations in WM microstructure may be a subclinical indicator of emerging motor deficits at an earlier and younger point in the lifespan.

Our approach to measure gait variability using lap time variation (LTV) is novel. We derived LTV from records of lap time (40 meters per lap) from the 400-meter walk test. Compared to the conventional gait variability which is measured from step to step, LTV may be a more global measure of walking variation across time. With this approach, we observed that lower microstructural WM integrity in the body of the corpus callosum was associated with higher LTV in the young-old. This finding was in line with prior findings that WM degeneration in the corpus callosum was strongly associated with gait dysfunction (Bhadelia et al., 2009), balance (de Laat et al., 2011a), and fall risk (Koo et al., 2012). This association was robust even with further adjustment for MLT or macrostructural WMD. It suggests that FA in WM

may be an independent neuroimaging marker of LTV and this relationship was not affect by slower fast-paced walking.

We also observed a strong association of microstructural WM integrity in the body of the corpus callosum with fast-paced walking speed only in the young-old. There was also a trend for lower FA in the splenium of the corpus callosum to be associated with slower fast-paced walking speed after adjustment for covariates. The role of the corpus callosum in mobility has been consistently reported (Bhadelia et al., 2009, de Laat et al., 2011a). Disruption in the corpus callosum affects the interconnection between two hemispheres which may influence gait control. We did not find the association in the genu of the corpus callosum reported in prior DTI studies (Bhadelia et al. 2009; de Laat et al. 2011). This discrepancy might be due to differing age effects on the three segments of the corpus callosum because they differ in myelin formation. The genu of the corpus callosum primarily contains thinly myelinated or unmyelinated fibers, with smaller diameters and densely packaged associative fibers connecting prefrontal cortices from bilateral hemispheres; in contrast, the body of the corpus callosum contains heavily myelinated fibers responsible for motor, somatosensory, and auditory cortices; while the splenium of corpus callosum contains more heavily myelinated fibers and also thinly myelinated fibers connecting the temporal, parietal, and occipital lobes from bilateral hemispheres (Lamantia and Rakic, 1990, Kochunov et al., 2005). FA in the body and splenium of the corpus callosum, which are composed of heavily myelinated fibers, declines more slowly across the lifespan compared to FA in the genu (Kochunov et al., 2005, Kochunov et al., 2007). Our study is consistent in that FA in the body and splenium of the corpus callosum is less strongly associated with age compared to the genu. The genu's densely packaged associative fibers are myelinated by oligodendrocytes that are the most metabolic active cells in the central nervous system (McTigue and Tripathi, 2008), and are vulnerable to metabolic damage (Thorburne and Juurlink, 1996, Juurlink, 1997). Findings from prior studies suggest that the body and splenium of the corpus callosum are less vulnerable to aging processes and metabolic damage compared to the genu. The fact that we did not observe a significant association with FA in the genu of the corpus callosum may be due to a stronger collinearity between age and FA in the genu of the corpus callosum. It may also be due to the use of a fast walking pace in the present study.

In addition to the corpus callosum, this study also examines cortico-cortical association fiber tracts that are involved in information processing and visual perception (Makris et al., 2005, Charlton et al., 2006, Dunsky et al., 2006) and play an important role in mobility (Penke et al., 2010, Zheng et al., 2012). Dysfunction in the uncinate fasciculus may contribute to gait disturbances through worsened movement imagery (Dunsky et al., 2006, Scherder et al., 2011). We found that lower FA in all these tracts was associated with slower fast-paced walking speed, which is in line with previous DTI findings (Iseki et al. 2010; Vercruysse et al. 2015). We also observed a significant association between FA in the subcortical tracts (the anterior limb of the internal capsule and the anterior corona radiate) and fast-paced walking speed, in line with prior findings (Vercruysse et al. 2015). These subcortical tracts are in the motor control pathway, connecting the motor area of the cortex to subcortical WM (Hendelman, 2006).

Prior studies have shown that variability in speed-related behaviors is predictive of functional decline and overall slowing (MacDonald et al., 2003, Bielak et al., 2010). Increased gait variability may be more likely to be the result of neural or musculoskeletal deterioration compared to slow walking (Kang and Dingwell, 2008). Accumulating evidence from longitudinal studies suggests that being variable may be an early stage of becoming slow. In this study, disrupted WM microstructural integrity in the body of the corpus callosum is associated with both LTV and MLT only in the young-old. One possible explanation for our findings is that variable walking mediates the relationship between FA in the body of the corpus callosum and slower fast-paced walking. Longitudinal studies are needed to test this hypothesis.

This study has limitations. We used the EVE White Matter atlas which was generated using a quantitative susceptibility mapping approach. This approach addresses the issue of crossing fibers, but the selection of WM tracts is restricted to the accuracy of the brain atlas employed. We are aware that prior studies have reported that the corticospinal tract plays an important role in mobility performance in older persons (Bolandzadeh et al., 2014, Bruijn et al., 2014). Using the EVE White Matter atlas, we were unable to test the relationship in the corticospinal tract. This cross-sectional analysis does not indicate any causation between WM microstructural disruption and abnormal walking. In addition, our study sample may be healthier than the general population due to their voluntary participation in the BLSA and requirements for MRI eligibility.

In conclusion, disrupted regional WM microstructural integrity may independently affect variability and speed of fast-paced walking only in the young-old. DTI measures of WM microstructure may be useful as early indicators of motor deficits for the young-old who have not yet developed advanced WM damage.

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References

Alexander DC, Pierpaoli C, Basser PJ, Gee JC. Spatial transformations of diffusion tensor magnetic resonance images. IEEE transactions on medical imaging. 2001; 20:1131–1139. [PubMed: 11700739]

Beauchet O, Annweiler C, Lecordroch Y, Allali G, Dubost V, Herrmann FR, Kressig RW. Walking speed-related changes in stride time variability: effects of decreased speed. Journal of neuroengineering and rehabilitation. 2009; 6:32. [PubMed: 19656364]

Bhadelia RA, Price LL, Tedesco KL, Scott T, Qiu WQ, Patz S, Folstein M, Rosenberg I, Caplan LR, Bergethon P. Diffusion tensor imaging, white matter lesions, the corpus callosum, and gait in the elderly. Stroke; a journal of cerebral circulation. 2009; 40:3816–3820.

Bielak AA, Hultsch DF, Strauss E, Macdonald SW, Hunter MA. Intraindividual variability in reaction time predicts cognitive outcomes 5 years later. Neuropsychology. 2010; 24:731–741. [PubMed: 20853957]

Bolandzadeh N, Liu-Ambrose T, Aizenstein H, Harris T, Launer L, Yaffe K, Kritchevsky SB, Newman A, Rosano C. Pathways linking regional hyperintensities in the brain and slower gait. NeuroImage. 2014; 99:7–13. [PubMed: 24841418]

Brach JS, Studenski SA, Perera S, VanSwearingen JM, Newman AB. Gait variability and the risk of incident mobility disability in community-dwelling older adults. J Gerontol A Biol Sci Med Sci. 2007; 62:983–988. [PubMed: 17895436]

Bruijn SM, Van Impe A, Duysens J, Swinnen SP. White matter microstructural organization and gait stability in older adults. Frontiers in aging neuroscience. 2014; 6:104. [PubMed: 24959139]

Charlton RA, Barrick TR, McIntyre DJ, Shen Y, O'Sullivan M, Howe FA, Clark CA, Morris RG, Markus HS. White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. Neurology. 2006; 66:217–222. [PubMed: 16434657]

Davatzikos C, Genc A, Xu D, Resnick SM. Voxel-based morphometry using the RAVENS maps: methods and validation using simulated longitudinal atrophy. NeuroImage. 2001; 14:1361–1369. [PubMed: 11707092]

de Laat KF, Tuladhar AM, van Norden AG, Norris DG, Zwiers MP, de Leeuw FE. Loss of white matter integrity is associated with gait disorders in cerebral small vessel disease. Brain: a journal of neurology. 2011a; 134:73–83. [PubMed: 21156660]

de Laat KF, van Norden AG, Gons RA, van Oudheusden LJ, van Uden IW, Norris DG, Zwiers MP, de Leeuw FE. Diffusion tensor imaging and gait in elderly persons with cerebral small vessel disease. Stroke; a journal of cerebral circulation. 2011b; 42:373–379.

Della Nave R, Foresti S, Pratesi A, Ginestroni A, Inzitari M, Salvadori E, Giannelli M, Diciotti S, Inzitari D, Mascalchi M. Whole-brain histogram and voxel-based analyses of diffusion tensor imaging in patients with leukoaraiosis: correlation with motor and cognitive impairment. AJNR American journal of neuroradiology. 2007; 28:1313–1319. [PubMed: 17698534]

Dunsky A, Dickstein R, Ariav C, Deutsch J, Marcovitz E. Motor imagery practice in gait rehabilitation of chronic post-stroke hemiparesis: four case studies. International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation. 2006; 29:351–356. [PubMed: 17106356]

Gallo A, Rovaris M, Riva R, Ghezzi A, Benedetti B, Martinelli V, Falini A, Comi G, Filippi M. Diffusion-tensor magnetic resonance imaging detects normal-appearing white matter damage unrelated to short-term disease activity in patients at the earliest clinical stage of multiple sclerosis. Archives of neurology. 2005; 62:803–808. [PubMed: 15883269]

Hendelman, W. Atlas of Functional Neuroanatomy. CRC Press; 2006.

Juurlink BH. Response of glial cells to ischemia: roles of reactive oxygen species and glutathione. Neuroscience and biobehavioral reviews. 1997; 21:151–166. [PubMed: 9062938]

Kang HG, Dingwell JB. Separating the effects of age and walking speed on gait variability. Gait & posture. 2008; 27:572–577. [PubMed: 17768055]

Klein, A.; Dal Canton, T.; Ghosh, SS.; Landman, B.; Lee, J.; Worth, A. Open labels: online feedback for a public resource of manually labeled brain images; 16th Annual Meeting for the Organization of Human Brain Mapping; 2010.

Kochunov P, Lancaster J, Hardies J, Thompson PM, Woods RP, Cody JD, Hale DE, Laird A, Fox PT. Mapping structural differences of the corpus callosum in individuals with 18q deletions using targetless regional spatial normalization. Hum Brain Mapp. 2005; 24:325–331. [PubMed: 15704090]

Kochunov P, Thompson PM, Lancaster JL, Bartzokis G, Smith S, Coyle T, Royall DR, Laird A, Fox PT. Relationship between white matter fractional anisotropy and other indices of cerebral health in normal aging: tract-based spatial statistics study of aging. Neuroimage. 2007; 35:478–487. [PubMed: 17292629]

Koo BB, Bergethon P, Qiu WQ, Scott T, Hussain M, Rosenberg I, Caplan LR, Bhadelia RA. Clinical prediction of fall risk and white matter abnormalities: a diffusion tensor imaging study. Archives of neurology. 2012; 69:733–738. [PubMed: 22332181]

Lamantia AS, Rakic P. Cytological and quantitative characteristics of four cerebral commissures in the rhesus monkey. J Comp Neurol. 1990; 291:520–537. [PubMed: 2329189]

Lao Z, Shen D, Liu D, Jawad AF, Melhem ER, Launer LJ, Bryan RN, Davatzikos C. Computer-assisted segmentation of white matter lesions in 3D MR images using support vector machine. Academic radiology. 2008; 15:300–313. [PubMed: 18280928]

Lauzon CB, Asman AJ, Esparza ML, Burns SS, Fan Q, Gao Y, Anderson AW, Davis N, Cutting LE, Landman BA. Simultaneous analysis and quality assurance for diffusion tensor imaging. PloS one. 2013; 8:e61737. [PubMed: 23637895]

Li S, Aggen SH, Nesselroade JR, Baltes PB. Short-term fluctuations in elderly people's sensorimotor functioning predict text and spatial memory performance: The Macarthur Successful Aging Studies. Gerontology. 2001; 47:100–116. [PubMed: 11287736]

Lim IA, Faria AV, Li X, Hsu JT, Airan RD, Mori S, van Zijl PC. Human brain atlas for automated region of interest selection in quantitative susceptibility mapping: application to determine iron content in deep gray matter structures. NeuroImage. 2013; 82:449–469. [PubMed: 23769915]

MacDonald SW, Hultsch DF, Dixon RA. Performance variability is related to change in cognition: evidence from the Victoria Longitudinal Study. Psychology and aging. 2003; 18:510–523. [PubMed: 14518812]

Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr. Pandya DN. Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cereb Cortex. 2005; 15:854–869. [PubMed: 15590909]

McTigue DM, Tripathi RB. The life, death, and replacement of oligodendrocytes in the adult CNS. Journal of neurochemistry. 2008; 107:1–19. [PubMed: 18643793]

Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annual review of neuroscience. 2001; 24:167–202.

Penke L, Munoz Maniega S, Murray C, Gow AJ, Hernandez MC, Clayden JD, Starr JM, Wardlaw JM, Bastin ME, Deary IJ. A general factor of brain white matter integrity predicts information processing speed in healthy older people. J Neurosci. 2010; 30:7569–7574. [PubMed: 20519531]

Raybaud C. The corpus callosum, the other great forebrain commissures, and the septum pellucidum: anatomy, development, and malformation. Neuroradiology. 2010; 52:447–477. [PubMed: 20422408]

Rosano C, Brach J, Studenski S, Longstreth WT Jr. Newman AB. Gait variability is associated with subclinical brain vascular abnormalities in high-functioning older adults. Neuroepidemiology. 2007; 29:193–200. [PubMed: 18043004]

Scherder E, Eggermont L, Visscher C, Scheltens P, Swaab D. Understanding higher level gait disturbances in mild dementia in order to improve rehabilitation: 'last in-first out'. Neuroscience and biobehavioral reviews. 2011; 35:699–714. [PubMed: 20833200]

Sen PN, Basser PJ. A model for diffusion in white matter in the brain. Biophys J. 2005; 89:2927–2938. [PubMed: 16100258]

Sexton CE, Walhovd KB, Storsve AB, Tamnes CK, Westlye LT, Johansen-Berg H, Fjell AM. Accelerated changes in white matter microstructure during aging: a longitudinal diffusion tensor imaging study. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2014; 34:15425–15436. [PubMed: 25392509]

Shock N, Greulich R, Andres R, Arenberg D, Costa P, Lakatta E, Tobin J. Normal human aging: The Baltimore longitudinal study of aging. 1984 NIH Publ No. 84-245.

Simonsick EM, Montgomery PS, Newman AB, Bauer DC, Harris T. Measuring fitness in healthy older adults: the Health ABC Long Distance Corridor Walk. Journal of the American Geriatrics Society. 2001; 49:1544–1548. [PubMed: 11890597]

Simonsick EM, Newman AB, Ferrucci L, Satterfield S, Harris TB, Rodondi N, Bauer DC, Health ABCS. Subclinical hypothyroidism and functional mobility in older adults. Archives of internal medicine. 2009; 169:2011–2017. [PubMed: 19933964]

Simonsick EM, Schrack JA, Glynn NW, Ferrucci L. Assessing fatigability in mobility-intact older adults. Journal of the American Geriatrics Society. 2014; 62:347–351. [PubMed: 24417536]

Starr JM, Leaper SA, Murray AD, Lemmon HA, Staff RT, Deary IJ, Whalley LJ. Brain white matter lesions detected by magnetic resonance [correction of resosnance] imaging are associated with balance and gait speed. Journal of neurology, neurosurgery, and psychiatry. 2003; 74:94–98.

Taylor HL, Jacobs DR Jr. Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. Journal of chronic diseases. 1978; 31:741–755. [PubMed: 748370]

Thorburne SK, Juurlink BH. Low glutathione and high iron govern the susceptibility of oligodendroglial precursors to oxidative stress. Journal of neurochemistry. 1996; 67:1014–1022. [PubMed: 8752107]

Tian Q, Simonsick SM, Resnick SM, Shardell MD, Ferrucci L, Studenski SA. Lap Time Variation and Executive Function in Older Adults: The Baltimore Longitudinal Study of Aging. Age and Ageing. 2015

Van Impe A, Coxon JP, Goble DJ, Doumas M, Swinnen SP. White matter fractional anisotropy predicts balance performance in older adults. Neurobiology of aging. 2012; 33:1900–1912. [PubMed: 21872363]

Vercruysse S, Leunissen I, Vervoort G, Vandenberghe W, Swinnen S, Nieuwboer A. Microstructural changes in white matter associated with freezing of gait in Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society. 2015; 30:567–576. [PubMed: 25640958]

Vermeulen J, Neyens JC, van Rossum E, Spreeuwenberg MD, de Witte LP. Predicting ADL disability in community-dwelling elderly people using physical frailty indicators: a systematic review. BMC geriatrics. 2011; 11:33. [PubMed: 21722355]

Vestergaard S, Patel KV, Bandinelli S, Ferrucci L, Guralnik JM. Characteristics of 400-meter walk test performance and subsequent mortality in older adults. Rejuvenation research. 2009; 12:177–184. [PubMed: 19594326]

Werring DJ, Clark CA, Barker GJ, Thompson AJ, Miller DH. Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. Neurology. 1999; 52:1626–1632. [PubMed: 10331689]

Westlye LT, Walhovd KB, Dale AM, Bjornerud A, Due-Tonnessen P, Engvig A, Grydeland H, Tamnes CK, Ostby Y, Fjell AM. Life-span changes of the human brain white matter: diffusion tensor imaging (DTI) and volumetry. Cerebral cortex. 2010; 20:2055–2068. [PubMed: 20032062]

Zacharaki, EI.; Kanterakis, S.; Bryan, RN.; Davatzikos, C. Measuring brain lesion progression with a supervised tissue classification system; Medical image computing and computer-assisted intervention: MICCAI International Conference on Medical Image Computing and Computer-Assisted Intervention; 2008. p. 620-627.

Zheng JJ, Delbaere K, Close JC, Sachdev P, Wen W, Brodaty H, Lord SR. White matter hyperintensities are an independent predictor of physical decline in community-dwelling older people. Gerontology. 2012; 58:398–406. [PubMed: 22614074]

Zonderman AB, Giambra LM, Arenberg D, Resnick SM, Costa PT Jr. Kawas CH. Changes in immediate visual memory predict cognitive impairment. Arch Clin Neuropsychol. 1995; 10:111–123. [PubMed: 14589733]

Table 1

Sample characteristics, mobility measures, and neuroimaging markers for all three groups

	Young[1] (aged < 50) N=51	Young-old[2] (aged 50-70) N=209	Old-old[3] (aged 70-96) N=233	p-value	Pairwise comparison test
Characteristics					
Age, years	42.1±5.4	62.1±4.9	78.2±5.4	<.001	1<2, 2<3, 1<3
Female	24 (47.1)	136 (65.1)	114 (48.9)	0.001	1<2, 2>3
Education, years	17±2	17±3	17±3	0.391	-
Black	10 (19.6)	63 (30.1)	45 (19.3)	0.021	-
Height, m	1.72±0.10	1.68±0.09	1.67±0.10	0.001	1>2, 1>3
Weight, kg	79.6±18.5	78.8±16.4	74.3±13.6	0.005	2>3
Body mass index, kg/m^2	26.8±6.0	27.7±4.8	26.6±3.9	0.025	2<3
Health-related conditions					
Smoker	5 (10.2)	13 (6.3)	5 (2.2)	0.020	1>3, 2>3
Leg pain when walking	3 (6.0)	41 (19.6)	28 (12.0)	0.071	-
Difficulty walking ¼ mile	1 (2.1)	9 (4.3)	7 (3.0)	0.647	-
Osteoarthritis of knees	1 (2.0)	59 (28.2)	71 (30.5)	0.002	1<2
Walking ability score	8.7±1.2	8.3±1.7	8.1±1.6	0.031	1>3
Mobility measures					
Lap time variation, sec	0.64±0.26	0.71±0.30	0.87±0.42	<.001	2<3, 1<3
Mean lap time, sec	21.8±2.6	24.9±3.1	28.9±6.0	<.001	1<2, 2<3,1<3
Microstructural white matter integrity: Fractional anisotropy					
Uncinate fasciculus	0.3579±0.0407	0.3565±0.0402	0.3536±0.0431	0.692	-
Superior longitudinal fasciculus	0.4614±0.0206	0.4484±0.0238	0.4452±0.0337	0.001	1>2, 1>3
Inferior fronto-occipital fasciculus	0.3981±0.0249	0.3810±0.0242	0.3695±0.0299	<.001	1>2, 2>3, 1>3
Genu of corpus callosum	0.5584±0.0487	0.5196±0.0541	0.4661±0.0721	<.001	1>2, 2>3, 1>3
Body of corpus callosum	0.5446±0.0327	0.5304±0.0378	0.4995±0.0523	<.001	2>3, 1>3
Splenium of corpus callosum	0.6289±0.0292	0.6242±0.0299	0.6032±0.0565	<.001	2>3, 1>3
Anterior limb of the internal capsule	0.5333±0.0302	0.5259±0.0363	0.5091±0.0514	<.001	2>3, 1>3
Anterior corona radiate	0.4202±0.0280	0.3918±0.0299	0.3607±0.0356	<.001	1>2, 2>3, 1>3
Macrostructural white matter damage	0.0004±0.0017	0.0012±0.0026	0.0040±0.0057	<.001	2<3, 1<3

Note: Samples were free of Parkinson's and stroke and did not use a walking aid for the 400m walk. Values were mean ± SD or N (%) as noted. Macrostructural white matter damage was expressed as a ratio of total volume of white matter hyperintensities to the intracranial volume.

Table 2

Associations of fractional anisotropy in selected tracts with lap time variation for all three groups

	Young (aged 26 to 50) N=51	Young-old (aged 50-70) N=209	Old-old (aged 70-96) N=233
Model 1: adjusted for age, sex, height, and weight			
Cortico-cortical tracts			
Superior longitudinal fasciculus	−0.031 (−0.183, 0.121) 0.681	−0.019 (−0.086, 0.048) 0.576	0.036 (−0.010, 0.082) 0.125
Inferior fronto-occipital fasciculus	0.045 (−0.079, 0.168) 0.472	−0.036 (−0.103, 0.031) 0.291	−0.007 (−0.061, 0.047) 0.794
Uncinate fasciculus	−0.058 (−0.172, 0.056) 0.311	−0.029 (−0.086, 0.028) 0.314	0.012 (−0.040, 0.064) 0.650
Interhemispheric tract			
Genu of corpus callosum	0.091 (−0.075, 0.257) 0.276	0.004 (−0.070, 0.078) 0.908	−0.016 (−0.070, 0.038) 0.560
Body of corpus callosum	−0.024 (−0.188, 0.139) 0.765	−0.089 (−0.159, −0.019) 0.013	0.007 (−0.043, 0.057) 0.782
Splenium of corpus callosum	−0.016 (−0.200, 0.168) 0.862	−0.082 (−0.167, 0.002) 0.055	−0.009 (−0.052, 0.034) 0.669
Subcortical tracts			
Anterior limb of the internal capsule	0.011 (−0.156, 0.178) 0.894	0.017 (−0.053, 0.087) 0.637	0.008 (−0.042, 0.058) 0.757
Anterior corona radiata	0.047 (−0.108, 0.202) 0.545	−0.010 (−0.083, 0.064) 0.796	0.014 (−0.049, 0.077) 0.663
Model 2: model 1 + macrostructural white matter damage			
Cortico-cortical tracts			
Superior longitudinal fasciculus	−0.035 (−0.190, 0.120) 0.653	−0.013 (−0.083, 0.056) 0.706	0.036 (−0.014, 0.086) 0.162
Inferior fronto-occipital fasciculus	0.050 (−0.078, 0.178) 0.433	−0.032 (−0.101, 0.036) 0.352	−0.008 (−0.063, 0.047) 0.779
Uncinate fasciculus	−0.057 (−0.173, 0.059) 0.329	−0.027 (−0.085, 0.032) 0.369	0.009 (−0.044, 0.063) 0.732
Interhemispheric tract			
Genu of corpus callosum	0.090 (−0.082, 0.262) 0.296	0.014 (−0.063, 0.092) 0.713	−0.016 (−0.072, 0.040) 0.580
Body of corpus callosum	−0.031 (−0.202, 0.139) 0.711	−0.094 (−0.172, −0.016) 0.019	0.005 (−0.049, 0.059) 0.845
Splenium of corpus callosum	−0.032 (−0.237, 0.174) 0.755	−0.089 (−0.190, 0.012) 0.084	−0.014 (−0.061, 0.034) 0.571
Subcortical tracts			
Anterior limb of the internal capsule	0.015 (−0.156, 0.186) 0.860	0.020 (−0.051, 0.091) 0.581	0.006 (−0.047, 0.058) 0.837
Anterior corona radiata	0.045 (−0.114, 0.204) 0.574	0.000 (−0.083, 0.083) 0.996	0.010 (−0.063, 0.084) 0.783
Model 3: model 1 + mean lap time			
Cortico-cortical tracts			
Superior longitudinal fasciculus	−0.031 (−0.185, 0.123) 0.686	−0.002 (−0.070, 0.066) 0.957	0.041 (−0.001, 0.084) 0.058

	Young (aged 26 to 50) N=51	Young-old (aged 50-70) N=209	Old-old (aged 70-96) N=233
Inferior fronto-occipital fasciculus	0.046 (−0.081, 0.172) 0.469	−0.022 (−0.090, 0.046) 0.523	0.008 (−0.042, 0.059) 0.740
Uncinate fasciculus	−0.060 (−0.177, 0.058) 0.311	−0.018 (−0.076, 0.039) 0.533	0.025 (−0.023, 0.073) 0.311
Interhemispheric tract			
Genu of corpus callosum	0.091 (−0.077, 0.259) 0.282	0.013 (−0.061, 0.086) 0.737	0.001 (−0.049, 0.052) 0.967
Body of corpus callosum	−0.024 (−0.191, 0.142) 0.769	−0.075 (−0.146, −0.003) 0.040	0.025 (−0.022, 0.071) 0.298
Splenium of corpus callosum	−0.016 (−0.204, 0.173) 0.867	−0.072 (−0.156, 0.013) 0.095	0.003 (−0.037, 0.043) 0.886
Subcortical tracts			
Anterior limb of the internal capsule	0.011 (−0.158, 0.180) 0.895	0.030 (−0.040, 0.100) 0.403	0.019 (−0.028, 0.065) 0.427
Anterior corona radiata	0.047 (−0.110, 0.205) 0.547	0.007 (−0.068, 0.081) 0.860	0.034 (−0.025, 0.092) 0.255

Note: Fractional anisotropy was in a standardized unit. Values of lap time variation was log transformed due to its skewed distribution.

Table 3

Associations of fractional anisotropy in selected tracts with mean lap time for all three groups

	Young (aged 26 to 50) N=51	Young-old (aged 50-70) N=209	Old-old (aged 70-96) N=233
Model 1: adjusted for age, sex, height, and weight			
Cortico-cortical tracts			
Superior longitudinal fasciculus	0.012 (−0.027, 0.050) 0.548	−0.028 (−0.044, −0.012) 0.001	−0.004 (−0.021, 0.012) 0.610
Inferior fronto-occipital fasciculus	0.014 (−0.017, 0.046) 0.370	−0.023 (−0.040, −0.007) 0.006	−0.016 (−0.035, 0.004) 0.110
Uncinate fasciculus	0.017 (−0.012, 0.047) 0.234	−0.018 (−0.032, −0.004) 0.012	−0.013 (−0.032, 0.005) 0.158
Interhemispheric tract			
Genu of corpus callosum	−0.001 (−0.044, 0.042) 0.963	−0.013 (−0.031, 0.005) 0.168	−0.014 (−0.033, 0.005) 0.154
Body of corpus callosum	0.021 (−0.021, 0.062) 0.319	−0.028 (−0.046, −0.011) 0.001	−0.018 (−0.036, −0.001) 0.043
Splenium of corpus callosum	0.026 (−0.021, 0.073) 0.269	−0.019 (−0.040, 0.002) 0.081	−0.013 (−0.028, 0.003) 0.102
Subcortical tracts			
Anterior limb of the internal capsule	−0.002 (−0.045, 0.040) 0.912	−0.020 (−0.037, −0.002) 0.025	−0.012 (−0.030, 0.006) 0.186
Anterior corona radiata	0.007 (−0.033, 0.047) 0.720	−0.026 (−0.044, −0.008) 0.004	−0.018 (−0.040, 0.005) 0.119
Model 2: model 1 + macrostructural white matter damage			
Cortico-cortical tracts			
Superior longitudinal fasciculus	0.015 (−0.023, 0.054) 0.428	−0.025 (−0.042, −0.008) 0.004	−0.001 (−0.019, 0.016) 0.881
Inferior fronto-occipital fasciculus	0.011 (−0.022, 0.043) 0.508	−0.021 (−0.038, −0.005) 0.012	−0.015 (−0.034, 0.005) 0.138
Uncinate fasciculus	0.015 (−0.014, 0.045) 0.297	−0.016 (−0.030, −0.001) 0.031	−0.012 (−0.031, 0.007) 0.206
Interhemispheric tract			
Genu of corpus callosum	0.005 (−0.039, 0.048) 0.837	−0.008 (−0.027, 0.011) 0.421	−0.011 (−0.031, 0.008) 0.259
Body of corpus callosum	0.028 (−0.014, 0.071) 0.181	−0.025 (−0.044, −0.006) 0.011	−0.016 (−0.035, 0.003) 0.092
Splenium of corpus callosum	0.046 (−0.004, 0.096) 0.070	−0.008 (−0.033, 0.017) 0.530	−0.009 (−0.026, 0.008) 0.292
Subcortical tracts			
Anterior limb of the internal capsule	−0.007 (−0.050, 0.036) 0.755	−0.017 (−0.035, 0.000) 0.049	−0.010 (−0.029, 0.009) 0.292
Anterior corona radiata	0.012 (−0.029, 0.052) 0.565	−0.023 (−0.043, −0.003) 0.026	−0.013 (−0.039, 0.013) 0.322

Note: Fractional anisotropy was in a standardized unit. Values of mean lap time were log transformed due to its skewed distribution.