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A prospective study of focal brain atrophy, mobility, and fitness

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Abstract

Background: The parallel decline of mobility and cognition with aging is explained in part by shared brain structural changes that are related to fitness. However, the temporal sequence between fitness, brain structural changes, and mobility loss has not been fully evaluated.

Methods: Participants were from the Baltimore Longitudinal Study of Aging, aged 60 or older, initially free of cognitive and mobility impairments, with repeated measures of fitness(400m time), mobility(6m gait speed), and neuroimaging markers over 4 years(n=332). Neuroimaging markers included volumes of total brain, ventricles, frontal, parietal, temporal, and subcortical motor areas, and corpus callosum. Autoregressive models were used to examine the temporal sequence of each brain volume with mobility and fitness, adjusted for age, sex, race, body mass index, height, education, intracranial volume, and *APOE* ϵ 4 status.

Results: After adjustment, greater volumes of total brain and selected frontal, parietal, and temporal areas, and corpus callosum were unidirectionally associated with future faster gait speed over and beyond cross-sectional and autoregressive associations. There were trends toward faster gait speed being associated with future greater hippocampus and precuneus. Higher fitness was unidirectionally associated with future greater parahippocampal gyrus, and not with volumes in other areas. Smaller ventricle predicted future higher fitness.

Conclusion: Specific regional brain volumes predict future mobility impairment. Impaired mobility is a risk factor for future atrophy of hippocampus and precuneus. Maintaining fitness preserves parahippocampal gyrus volume. Findings provide new insight into the complex and bidirectional relationship between the parallel decline of mobility and cognition often observed in older persons.

Graphical Abstract

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Keywords

temporal sequence; gait; fitness; brain atrophy; spatial distribution

Introduction:

Gait is a powerful predictor of vital health outcomes, including disability, hospitalization, dementia, and mortality [1, 2]. The central control of walking is a critical component of mobility maintenance in older adults, and neuropathology is a major cause of mobility limitation with aging. It is well established that slower gait is cross-sectionally associated with poorer cognition and neuroimaging abnormalities, suggesting the existence of age-related shared neuropathology underlying cognitive and mobility impairments [3, 4].

Brain structural changes underlying mobility loss are not well understood. In part, this is because current neuroimaging studies focusing on mobility and brain structure are mostly cross-sectional or rely on global neuroimaging markers or one or a few regions of interest (ROIs). For example, recent cross-sectional studies demonstrate that gray matter areas, such as cortical areas of precuneus, motor, prefrontal regions and subcortical areas of hippocampus, thalamus and caudate, are associated with mobility in older adults, but the temporal sequence of this association remains unknown [5–7]. A few longitudinal studies show brain structural changes, such as changes in total brain volume and white matter hyperintensities, predict gait decline, but the spatial distribution is undetermined [8–10]. Recent longitudinal studies have shown prior mobility performance is associated with future volumes of hippocampus and superior parietal lobe [11, 12], which are involved with spatial navigation. However, the temporal sequence is not established because prior brain volumes at the time of gait assessment were not measured and not accounted for in the analyses.

Although the brain structure deteriorates in aging with the prefrontal and medial temporal lobes being the most vulnerable areas [13], there is some evidence that maintaining fitness

help counteract the functional effect of brain aging. Potential mechanisms for this association are supported by animal studies and include exercise-induced neurogenesis, endothelial cell proliferation, vascularization, neurotransmitters, and neurotrophic factors [14, 15]. Whether maintaining fitness counteracts brain aging in community-dwelling older adults remain unclear because of the limited availability of longitudinal studies adequate to test this hypothesis. The specific cortical and subcortical structure implicated in the protection has not been identified [10, 16]. Only a few cross-sectional neuroimaging studies show higher fitness is associated with neuroimaging markers mostly localized in prefrontal and medial temporal lobes [17–19]. In the absence of robust longitudinal analyses, whether this association is causal or, rather, individuals with higher education are more likely to have greater brain volume and cognitive reserve and more likely to engage in physical activity and thus have higher fitness level remain questionable. Additionally, recent studies have shown that fitness and physical activity levels modify the influence of the genetic risk factor on white matter integrity and biomarkers of AD in older adults without cognitive impairment, dementia or overt neurological disease [20, 21]. Whether the longitudinal relationship persists despite the presence of the genetic risk factor, such as *APOE ε4*, is unknown.

Collectively, the temporal sequence between brain volumetric changes, gait deterioration or fitness, as well as the specific cortical and subcortical structures in this causal pathway, have not been examined. Understanding the directionality and main areas of interest provides new insight into the complex mechanisms that explain the parallel decline of cognitive and mobility function in specific older individuals.

In this present study, we aimed to determine temporal sequences between changes in brain volumes, mobility and fitness in an “inception” aging cohort of well-characterized community-dwelling older adults with initially unimpaired cognition and mobility. Based on prior findings, we hypothesize that volumes of frontal, prefrontal, and temporal areas and subcortical areas would be associated with future gait speed, over and beyond cross-sectional and autoregressive associations; and gait speed would also predict future volumes of hippocampus and superior parietal lobe. We hypothesize that there would be a bi-directional relationship between fitness and brain structure, especially in the medial temporal lobe.

Materials and Methods:

Study population:

Because of the focus on temporal sequences, an “inception” cohort aged 60 or older was drawn from the Baltimore Longitudinal Study of Aging (BLSA). A total of 332 participants met the following criteria and were included in this study, (1) initially free of cognitive impairment, dementia, Parkinson’s disease, stroke, congestive heart failure, peripheral artery disease, and dismobility (defined as gait speed < 0.6 m/sec) [22], (2) initial MMSE greater than or equal to 24, (3) with repeated measures of fitness, mobility, and brain volumes by MRI at 2- and/or 4-year follow-up within a ± 0.5 year time window (Figure 1).

Visits at and after certain health-related conditions that substantially affect neuroimaging, such as closed head injury, emergence of ataxic gait, chemotherapy, and a fractured skull were excluded from the analysis (Figure 1, n=31).

The BLSA protocol was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences. Participants provided written informed consent at each BLSA visit.

Mobility:

Mobility was measured as gait speed over a 6-meter course at the usual pace. Two trials were performed, and the faster trial was used for analyses.

Fitness:

Fitness was measured by time to complete the long-distance corridor walk (LDCW) [23]. Time to complete LDCW has been previously validated against peak VO_{2max} obtained from the maximal treadmill test. It provides a valid measure of aerobic capacity in older adults aged 60 or older [23]. Detailed instructions of the LDCW were previously published [23, 24]. In brief, participants were instructed to walk on a 20-meter course continuously for ten laps as fast as possible immediately after a 2-minute warm-up walk. During the test, participants were not allowed to run. At each lap, standard verbal encouragement was given by the examiner. Time to complete each lap in seconds was recorded using a stopwatch. The test could be stopped if the heart rate of the participant was greater than 170 bpm, or the participant reported chest pain, leg pain, dyspnea, or other significant symptoms.

Cognitive status and other health conditions:

At each visit, participants were screened using the Blessed Information Memory Concentration (BIMC) Test [25]. If the BIMC score was 4 or higher, participants were evaluated using the Clinical Dementia Rating Scale (CDR) [26] or the dementia questionnaire. Additionally, participants in some sub-studies were evaluated using the CDR at each visit. If the BIMC was 4 or higher, the CDR score was 0.5 or higher, or the dementia questionnaire was abnormal, participants were reviewed at a consensus diagnostic conference. Mild cognitive impairment was determined using the Petersen criteria [27]. Diagnoses of dementia and Alzheimer's disease were determined by the Diagnostic and Statistical Manual (DSM)-III-R [28] and the National Institute of Neurological and Communication Disorders and Stroke – Alzheimer's Disease and Related Disorders Association criteria [29], respectively.

The presence of other health conditions, including Parkinson's disease, congestive heart failure, peripheral artery disease, and stroke, were assessed during the follow-up visits by nurse practitioners who used information on medical history, treatment, and diagnostic tests.

Global and regional brain volumes:

Data acquisition: Magnetization-prepared rapid gradient echo (MPRAGE) images were acquired on a 3-T scanner (Philips Achieva). The acquisition parameters were as follows:

repetition time = 6.8 ms, echo time = 3.2 ms, flip angle = 8°, image matrix = 256 × 256, 170 slices, pixel size = 1 × 1 mm, slice thickness = 1.2 mm.

Calculation of regional brain volumes

A semi-automated quality control (QC) protocol was applied to all scans to identify and exclude segmentation errors. The first step of the QC protocol involved ranking all scans by a QC score calculated based on the statistics of ROI volumes for the complete sample. This procedure was used to identify scans that showed important deviations from sample distributions of individual ROIs, as well as outliers of the multivariate distribution of all ROIs (i.e. using Mahalanobis distance from the sample mean). ROI segmentations of the top-ranked 100 scans were visually verified using an in-house viewer specifically designed to streamline such QC procedures. Scans with important segmentation errors were excluded.

Regional brain volumes were identified using a multi-atlas label fusion method, called MUSE, which was the top-ranking method in an extensive ROI segmentation challenge [30, 31]. In this framework, multiple atlases with semi-automatically extracted ground-truth ROI labels are first warped individually to the target image using a non-linear registration method and the ensemble is fused into a final consensus segmentation. This workflow for segmenting the brain into a set of anatomical ROIs has been previously validated extensively in the BLSA MRI dataset [32]. Importantly, the proposed multi-atlas segmentation approach has been shown to be robust and accurate, owing to its use of multiple atlases and multiple registration methods. This ensemble approach has consistently outperformed segmentations using individual warping methods alone and has achieved a high accuracy in several benchmark datasets [30]. The MUSE methodology has been used for processing thousands of scans from various datasets, producing robust and consistent results, eliminating the requirement of QC for each individual ROI beyond the semi-automated QC described above. MUSE is available through the image processing portal: <https://ipp.cbica.upenn.edu/>

Global neuroimaging markers included total brain and ventricular volumes. Based on prior knowledge [3, 5, 6, 33], we identified brain areas of interest important for gait and fitness, including sub-regions in frontal (middle frontal, medial frontal, inferior frontal, and superior frontal gyri, supplementary and primary motor areas), parietal (primary sensory cortex (i.e. postcentral gyrus), precuneus, angular gyrus), medial temporal (hippocampus, parahippocampal gyrus, entorhinal cortex), subcortical motor (basal ganglia, thalamus), corpus callosum, and white matter volumes for frontal, parietal, temporal, and occipital lobes.

Covariates:

Covariates that were related to brain health, mobility, and fitness included age, sex, race, body mass index, height, education, intracranial volume, and *APOE* $\epsilon 4$ status (any $\epsilon 4$ versus non-carrier).

Statistical analyses:

The correlation between usual gait speed and 400m time at each visit was examined using partial correlation analysis, controlling for age, sex, height, and body mass index.

To compare our data with those reported in prior cross-sectional studies, we first examined the cross-sectional association of brain volume in each ROI with gait speed or 400m time at each visit using linear regression, adjusting for age, sex, race, years of education, height, body mass index, intracranial volume, and *APOE* status.

We then examined the temporal sequence between each volumetric measure of interest and gait speed using bivariate autoregressive cross-lagged models from structural equation modeling [34]. Both the autoregressive and cross-lagged associations were simultaneously assessed. Specifically, the autoregressive analyses assessed the relationship between each brain volume at time t and time $t+1$, as well as the relationship between gait speed at time t and time $t+1$. The cross-lagged analyses assessed the relationship between each regional brain volume at time t and gait speed at time $t+1$, while adjusting for gait speed at time t . The cross-lagged analyses also assessed the relationship between gait speed at time t and each regional brain volume at time $t+1$, while adjusting for the brain volume at time t . Associations between each pair of sequential time periods (i.e. baseline to 2-year, and 2-year to 4-year follow-up) were set to be equal in both autoregressive and cross-lagged analyses (Figure 2A).

The same analytical approach was applied to examine the temporal sequence between each volumetric measure of interest and fitness (i.e. 400m time) (Figure 2B). Because we previously reported the temporal sequence between gait speed and 400m time [35], in this study we also examined this temporal sequence to confirm prior findings. All autoregressive cross-lagged models were assessed using model fit statistics, including the root mean square error of approximation (RMSEA), Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI). Values of RMSEA less than 0.05 indicate good fit and less than 0.08 indicate acceptable fit. Values of CFI and TLI greater than 0.90 indicate good fit and greater than 0.95 indicate excellent fit.

All analyses were adjusted for demographics (age, sex, race), and additionally adjusted for education and intracranial volume related to brain volume, and for height and body mass index related to mobility performance and fitness. *APOE* $\epsilon 4$ status was further adjusted to test the strength of these relationships.

To test whether these relationships were affected by a potential informative censoring, we repeated the analyses by excluding those who did not have data at the 4-year visit due to death ($n=3$) and potential health conditions ($n=67$).

Due to the 20 brain areas examined in this study, the False Discovery Rate (FDR) approach was used to correct for multiple testing in cross-lagged associations. A trend with an FDR-adjusted $p<0.10$ was also reported. Statistical analyses were performed using SAS statistical software (v 9.4, SAS Institute Inc., Cary, NC), and MPlus 7.11 (Muthen & Muthen).

Results:

Sample characteristics at baseline and follow-up are presented in Table 1. Most participants had data at 2-year ($n=293$) and 4-year follow-up ($n=185$). 39 had data at 4-year follow-up but did not have data at 2-year follow-up. Those with and without 2-year follow-up data did

not differ in age, sex, race, body mass index, *APOE* ε4 status, MMSE scores, usual gait speed, 400m time, or global and regional brain volumes (Supplementary Table 1).

At each visit, faster gait speed was associated with faster 400m time ($r=-0.5$, $p<0.001$). Cross-sectional associations between gait speed and brain volume in each ROI after adjustment are presented in Supplementary Table 2. At baseline, there were trends of faster gait speed being associated with greater volumes of supplementary motor and primary motor cortices. At 2-year follow-up, there were trends of faster gait speed being associated with greater volumes of superior frontal gyrus, primary motor cortex, and parietal white matter. At 4-year follow-up, faster gait speed was associated with greater volume of superior frontal gyrus. There were trends of faster gait speed being associated with greater volumes of primary motor cortex and parietal white matter. No other cross-sectional associations or trends were found.

Cross-sectional associations between 400m time and brain volume in each ROI are presented in Supplementary Table 2. At baseline, faster 400m time was associated with greater volumes of superior frontal gyrus and primary sensory cortex. At 2-year and 4-year follow-ups, faster 400m time was associated with greater volume of superior frontal gyrus.

Autoregressive cross-lagged models indicated that prior faster 400m time was unidirectionally associated with future faster gait speed, over and beyond autoregressive and cross-lagged associations ($p<0.01$).

Cross-lagged model fit statistics showed acceptable to excellent fit (Supplementary Table 3). The temporal sequence between each brain volume and gait speed is presented in Table 2. There were unidirectional associations of greater volumes of total brain and selected cortical brain volumes- including corpus callosum, frontal, temporal, and parietal white matter- and subcortical areas of hippocampus and thalamus with future faster gait speed, independent of cross-sectional and autoregressive associations (Table 2; FDR-adjusted $p<0.05$). Selected cortical brain volumes that predicted future gait speed included areas in frontal (middle frontal, medial frontal, inferior frontal, superior frontal, supplementary motor, primary motor cortices, white matter), parietal (precuneus, postcentral, angular gyrus, white matter), and medial temporal lobes (hippocampus, entorhinal cortex) (Table 2; FDR-adjusted $p<0.05$). There were trends towards greater volumes of parahippocampal gyrus and occipital white matter being associated with future faster gait speed (Table 2; FDR-adjusted $p<0.10$). There were trends toward faster gait speed being associated with future greater volumes of precuneus, hippocampus, and temporal white matter, over and beyond cross-sectional and autoregressive associations (Table 2; FDR-adjusted $p<0.10$). No other associations or trends were observed in other areas (Table 2).

The temporal sequence between each brain volume and fitness is presented in Table 3. There were unidirectional associations of higher fitness (i.e. faster 400m time) with future greater volume of parahippocampal gyrus, over and beyond cross-sectional and autoregressive associations (Table 3; FDR-adjusted $p<0.05$). There were trends toward faster 400m time being associated with future greater volumes of hippocampus, entorhinal cortex, and with smaller volumes of caudate and putamen. Smaller ventricular volume was unidirectionally

associated with future faster 400m time. There were trends of greater volumes of superior frontal gyrus, angular gyrus and hippocampus being associated with future faster 400m time (Table 3). No other associations or trends were observed in other areas (Table 3).

Results remained similar after excluding those who did not have data at the 4-year visit due to death and potential health conditions, except that associations between prior gait speed and subsequent volumes of precuneus and hippocampus were slightly attenuated (data not shown).

Discussion:

This study demonstrates for the first time that among initially cognitively and mobility unimpaired older adults, structural changes in selected brain areas precede the decline of mobility performance while, on the contrary, lower physical fitness precedes volumetric reduction of specific brain areas. Our findings depict complex and bidirectional relationships between age-associated changes in brain structure and mobility performance. Selected brain areas, widespread from frontal, parietal, and temporal areas, and including cortical gray matter and white matter as well as corpus callosum, unidirectionally predict future gait speed. Prior gait speed **may indicate** future volumes of precuneus and hippocampus, both important for spatial navigation [36, 37]. By contrast, a prior higher fitness level unidirectionally predicts future brain structure localized in the medial temporal lobe. Ventricular volume, a sensitive but not specific marker of brain health, predicts future fitness levels.

Our study is consistent with previous literature and provides important additional information. First, this study highlights the importance of central control of gait and the neuroprotective effect of cardiorespiratory fitness by examining the temporal sequence of brain volumes with mobility and fitness. Further, this study determines the spatial distribution of brain areas associated with mobility and fitness by examining both cortical and subcortical gray matter and white matter in multiple areas of interest. Third, we account for potential effects of *APOE* $\epsilon 4$ status, the main Alzheimer's disease genetic risk factor, on observed associations.

Almost surprisingly, brain areas associated with future mobility do not overlap with areas associated with prior fitness levels, suggesting different underlying mechanisms. Areas predicting future gait speed are important for execution, sensorimotor integration, and movement coordination, while areas that are associated with prior fitness fall in watershed areas, suggesting that the protective effect of fitness may be vascular in nature.

We found that selected cortical gray matter and white matter unidirectionally predict future gait speed, and these associations are localized in frontal, parietal, and temporal lobes as well as corpus callosum, suggesting specific regions where brain structural changes occur earlier than mobility and predict future mobility. The entorhinal cortex in the medial temporal lobe predicts future gait speed, which is in line with one recent study showing that entorhinal cortex, not other subregions of the medial temporal lobe, is associated with dual-task cost in older individuals with MCI [38]. The entorhinal cortex is one of the early

affected regions in AD pathology [39]. This may further support the mechanism underlying poor gait predicting future AD risk.

We also observe gait tended to predict future precuneus and hippocampus volumes, which are important areas for spatial navigation and are previously identified areas associated with mobility performance [11, 12]. Our study extended prior research by examining autoregressive and cross-lagged associations simultaneously to demonstrate a specific temporal sequence. Our work reinforces the notion that mobility performance is an early predictor of future brain structure localized in spatial navigation-related areas of the hippocampus and precuneus. Both hippocampus and precuneus support the allocentric processing of spatial relations [36, 37], which declines with aging [40]. In addition, the strength of hippocampal-precuneus functional connectivity has been suggested as an early sign of AD [41]. Because both hippocampal and precuneus volumes predict subsequent gait speed, there may be a bidirectional relationship between precuneus volume and gait speed. These findings may suggest that **gait decline and atrophy of hippocampus and precuneus co-occur**.

It is interesting to note that the temporal sequence between fitness and brain volumes is in the opposite direction of the sequence between brain and mobility. We observe higher prior fitness unidirectionally predicts future brain volumes localized in the medial temporal lobe, including the significant association in the parahippocampal gyrus and trends in the hippocampus and entorhinal cortex. One previous study shows higher fitness is specifically associated with the microstructural integrity localized in the medial temporal lobe, and not in other areas, in another aging cohort [17]. Our results are in line with prior findings and advance our understanding of the temporal sequence and the specific cortical and subcortical structure distribution [33]. This study provides new insight into the potential mechanisms whereby maintaining fitness protects against age-related memory decline and reduces future risk of MCI/AD.

Notably, we observe trends of higher fitness predicting future smaller subcortical motor areas of putamen and caudate, which appears counterintuitive. The unexpected trend with caudate volume may be explained by a slight J or U shape of caudate volume with advancing age reported in other cohorts [42–44]. Although it is unclear why caudate volume shows a slightly increasing trend with age, it is possible that the apparent volumetric increase is due to increasing iron deposition with age [45]. Future longitudinal studies are needed to better understand how subcortical motor areas change with age and their relationships with mobility and fitness.

This study has novel aspects. First, the study population is well characterized by the assessment in cognition, mobility, and health conditions, which allows us to examine the temporal sequence in a well-defined “inception” cohort. Second, the spatial distribution of cortical and subcortical gray matter as well as white matter, is well defined using the MUSE template, which allows us to understand the specificity of brain volumetric structure in relation to mobility and fitness. Third, information on APOE $\epsilon 4$ status allows us to examine the robustness of the relationships to the $\epsilon 4$ AD risk allele.

Several limitations should be noted. First, participants in the BLSA are volunteers from the community, and thus tend to be healthier than the general population. In addition, our findings may only be generalizable to a relatively healthy population due to initial exclusion criteria of cognitive impairment, dementia, disability, congested heart failure, stroke, Parkinson's disease, peripheral artery disease, and health conditions substantially affecting neuroimaging data. Second, examining multiple areas of interest may introduce false positive associations. Third, our sample size is modest and not all participants had data at 4-year follow-up. Of note, after excluding those who did not have data at the 4-year visit due to death and potential health conditions, associations between prior gait speed and subsequent volumes of precuneus and hippocampus were slightly attenuated. It is possible that this attenuation is due to a smaller sample. It is also possible that death and potential health conditions contribute to these observed associations. We may have missed some significant associations due to insufficient statistical power. Fourth, we used the performance measure during the long-distance corridor walk as the alternative and valid measure of fitness in older adults [23]. Using the graded maximal exercise testing to assess aerobic capacity in individuals aged 80 or older may not be possible due to their health conditions and physical limitations.

Although this study established several important findings, future directions are needed to deepen our understanding of the brain, mobility, and fitness. First, this study only focused on brain volumetric measures. Applying a multimodality approach may further our understanding of underlying biological mechanisms, such as devascularization of gray matter, demyelination and axonal loss of white matter. Second, future studies are warranted to understand how longitudinal changes of brain structure are associated with concurrent declines in mobility and fitness. Further, future fMRI studies are needed to better understand the functional connectivity of brain regions underlying mobility and fitness.

Conclusion:

In conclusion, volumes of selected cortical gray matter and white matter, localized in frontal, medial, and temporal lobes, as well as corpus callosum, unidirectionally predict future mobility. Mobility performance may also predict future precuneus and hippocampal volumes, both important for allocentric processing of space. Prior higher fitness unidirectionally predicts future medial temporal lobe, particularly in the parahippocampal gyrus. These findings are scientifically important and provide new insights into the complex mechanisms that explain the parallel decline of cognitive and mobility function in specific older individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reference:

1. Beauchet O, Annweiler C, Callisaya ML, De Cock AM, Helbostad JL, Kressig RW, Srikanth V, Steinmetz JP, Blumen HM, Verghese J, and Allali G, Poor Gait Performance and Prediction of Dementia: Results From a Meta-Analysis. *J Am Med Dir Assoc*, 2016 17(6): p. 482–90.10.1016/j.jamda.2015.12.092 [PubMed: 26852960]
2. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, Brach J, Chandler J, Cawthon P, Connor EB, Nevitt M, Visser M, Kritchevsky S, Badinelli S, Harris T, Newman AB, Cauley J, Ferrucci L, and Guralnik J, Gait speed and survival in older adults. *JAMA*, 2011 305(1): p. 50–8.10.1001/jama.2010.1923 [PubMed: 21205966]
3. Holtzer R, Epstein N, Mahoney JR, Izzetoglu M, and Blumen HM, Neuroimaging of mobility in aging: a targeted review. *J Gerontol A Biol Sci Med Sci*, 2014 69(11): p. 1375–88.10.1093/gerona/glu052 [PubMed: 24739495]
4. Morris R, Lord S, Bunce J, Burn D, and Rochester L, Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease. *Neurosci Biobehav Rev*, 2016 64: p. 326–45.10.1016/j.neubiorev.2016.02.012 [PubMed: 26915926]
5. Allali G, Montembeault M, Brambati SM, Bherer L, Blumen HM, Launay CP, Liu-Ambrose T, Helbostad JL, Verghese J, and Beauchet O, Brain Structure Covariance Associated with Gait Control in Aging. *J Gerontol A Biol Sci Med Sci*, 201810.1093/gerona/gly123
6. Blumen HM, Brown LL, Habeck C, Allali G, Ayers E, Beauchet O, Callisaya M, Lipton RB, Mathuranath PS, Phan TG, Pradeep Kumar VG, Srikanth V, and Verghese J, Gray matter volume covariance patterns associated with gait speed in older adults: a multi-cohort MRI study. *Brain Imaging Behav*, 201810.1007/s11682-018-9871-7
7. Callisaya ML, Beare R, Phan TG, Chen J, and Srikanth VK, Global and regional associations of smaller cerebral gray and white matter volumes with gait in older people. *PLoS One*, 2014 9(1): p. e8490910.1371/journal.pone.0084909 [PubMed: 24416309]
8. Callisaya ML, Beare R, Phan TG, Blizzard L, Thrift AG, Chen J, and Srikanth VK, Brain structural change and gait decline: a longitudinal population-based study. *J Am Geriatr Soc*, 2013 61(7): p. 1074–9.10.1111/jgs.12331 [PubMed: 23796055]
9. Moscufo N, Wakefield DB, Meier DS, Cavallari M, Guttmann CRG, White WB, and Wolfson L, Longitudinal microstructural changes of cerebral white matter and their association with mobility performance in older persons. *PLoS One*, 2018 13(3): p. e019405110.1371/journal.pone.0194051 [PubMed: 29554115]
10. Pinter D, Ritchie SJ, Gatringer T, Bastin ME, Hernandez M, Corley J, Maniega SM, Pattie A, Dickie DA, Gow AJ, Starr JM, Deary IJ, Enzinger C, Fazekas F, and Wardlaw J, Predictors of gait speed and its change over three years in community-dwelling older people. *Aging (Albany NY)*, 2018 10(1): p. 144–153.10.18632/aging.101365 [PubMed: 29356686]
11. Demnitz N, Zsoldos E, Mahmood A, Mackay CE, Kivimaki M, Singh-Manoux A, Dawes H, Johansen-Berg H, Ebmeier KP, and Sexton CE, Associations between Mobility, Cognition, and Brain Structure in Healthy Older Adults. *Front Aging Neurosci*, 2017 9: p. 15510.3389/fnagi.2017.00155 [PubMed: 28588477]
12. Rosso AL, Verghese J, Metti AL, Boudreau RM, Aizenstein HJ, Kritchevsky S, Harris T, Yaffe K, Satterfield S, Studenski S, and Rosano C, Slowing gait and risk for cognitive impairment: The hippocampus as a shared neural substrate. *Neurology*, 2017 89(4): p. 336–342.10.1212/WNL.0000000000004153 [PubMed: 28659421]
13. Storsve AB, Fjell AM, Tamnes CK, Westlye LT, Overbye K, Aasland HW, and Walhovd KB, Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: regions of accelerating and decelerating change. *J Neurosci*, 2014 34(25): p. 8488–98.10.1523/JNEUROSCI.0391-14.2014 [PubMed: 24948804]
14. Vivar C, Potter MC and van Praag H, All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis, in *Neurogenesis and Neural Plasticity*. 2012, Springer: Berlin, Heidelberg p. 189–210.
15. Stimpson NJ, Davison G and Javadi AH, Joggin' the Noggin: Towards a Physiological Understanding of Exercise-Induced Cognitive Benefits. *Neurosci Biobehav Rev*, 2018 88: p. 177–186.10.1016/j.neubiorev.2018.03.018 [PubMed: 29572187]

16. Tian Q, Studenski SA, Resnick SM, Davatzikos C, and Ferrucci L, Midlife and Late-Life Cardiorespiratory Fitness and Brain Volume Changes in Late Adulthood: Results From the Baltimore Longitudinal Study of Aging. *J Gerontol A Biol Sci Med Sci*, 2016 71(1): p. 124–30.10.1093/gerona/glv041 [PubMed: 25896993]
17. Tian Q, Simonsick EM, Erickson KI, Aizenstein HJ, Glynn NW, Boudreau RM, Newman AB, Kritchevsky SB, Yaffe K, Harris T, Rosano C, and A.B.C.s. Health, Cardiorespiratory fitness and brain diffusion tensor imaging in adults over 80 years of age. *Brain Res*, 2014 1588: p. 63–72.10.1016/j.brainres.2014.09.003 [PubMed: 25204690]
18. Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, White SM, Wojcicki TR, McAuley E, and Kramer AF, Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*, 2009 19(10): p. 1030–9.10.1002/hipo.20547 [PubMed: 19123237]
19. Hayes SM, Salat DH, Forman DE, Sperling RA, and Verfaellie M, Cardiorespiratory fitness is associated with white matter integrity in aging. *Ann Clin Transl Neurol*, 2015 2(6): p. 688–98.10.1002/acn3.204 [PubMed: 26125043]
20. Schultz SA, Boots EA, Darst BF, Zetterberg H, Blennow K, Edwards DF, Kosciak RL, Carlsson CM, Gallagher CL, Bendlin BB, Asthana S, Sager MA, Hogan KJ, Hermann BP, Cook DB, Johnson SC, Engelman CD, and Okonkwo OC, Cardiorespiratory fitness alters the influence of a polygenic risk score on biomarkers of AD. *Neurology*, 2017 88(17): p. 1650–1658.10.1212/WNL.0000000000003862 [PubMed: 28341646]
21. Smith JC, Lancaster MA, Nielson KA, Woodard JL, Seidenberg M, Durgerian S, Sakaie K, and Rao SM, Interactive effects of physical activity and APOE-epsilon4 on white matter tract diffusivity in healthy elders. *Neuroimage*, 2016 131: p. 102–12.10.1016/j.neuroimage.2015.08.007 [PubMed: 26265157]
22. Cummings SR, Studenski S and Ferrucci L, A diagnosis of disability--giving mobility clinical visibility: a Mobility Working Group recommendation. *JAMA*, 2014 311(20): p. 2061–2.10.1001/jama.2014.3033 [PubMed: 24763978]
23. Simonsick EM, Fan E and Fleg JL, Estimating cardiorespiratory fitness in well-functioning older adults: treadmill validation of the long distance corridor walk. *J Am Geriatr Soc*, 2006 54(1): p. 127–32.10.1111/j.1532-5415.2005.00530.x [PubMed: 16420209]
24. Newman AB, Haggerty CL, Kritchevsky SB, Nevitt MC, Simonsick EM, and Health ABCRG, Walking performance and cardiovascular response: associations with age and morbidity--the Health, Aging and Body Composition Study. *J Gerontol A Biol Sci Med Sci*, 2003 58(8): p. 715–20 [PubMed: 12902529]
25. Fuld PA, Psychological testing in the differential diagnosis of the dementias. *Alzheimer's disease: senile dementia and related disorders*, 1978 7: p. 185–193
26. Morris JC, The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, 1993 43(11): p. 2412–4
27. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, and Kokmen E, Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*, 1999 56(3): p. 303–8 [PubMed: 10190820]
28. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. Fourth Edition ed. 1994, Washington, D.C.: American Psychiatric Association.
29. McKhann G, Drachman D, Folstein M, Katzman R, Price D, and Stadlan EM, Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 1984 34(7): p. 939–44 [PubMed: 6610841]
30. Doshi J, Erus G, Ou Y, Resnick SM, Gur RC, Gur RE, Satterthwaite TD, Furth S, Davatzikos C, and I. Alzheimer's Neuroimaging, MUSE: MULTI-atlas region Segmentation utilizing Ensembles of registration algorithms and parameters, and locally optimal atlas selection. *Neuroimage*, 2016 127: p. 186–195.10.1016/j.neuroimage.2015.11.073 [PubMed: 26679328]
31. Doshi JJ, Erus G, Ou Y, and Davatzikos C, Ensemble-based medical image labeling via sampling morphological appearance manifolds, in *In MICCAI Challenge Workshop on Segmentation: Algorithms, Theory and Applications*. 2013: Nagoya, Japan p. 1–4.

32. Erus G, Doshi J, An Y, Verganelakis D, Resnick SM, and Davatzikos C, Longitudinally and inter-site consistent multi-atlas based parcellation of brain anatomy using harmonized atlases. *Neuroimage*, 2018 166: p. 71–78.10.1016/j.neuroimage.2017.10.026 [PubMed: 29107121]
33. Hayes SM, Hayes JP, Cadden M, and Verfaellie M, A review of cardiorespiratory fitness-related neuroplasticity in the aging brain. *Front Aging Neurosci*, 2013 5: p. 3110.3389/fnagi.2013.00031 [PubMed: 23874299]
34. Bollen KA and Curran PJ, *Latent curve models: A structural equation perspective*. 2006, Hoboken, New Jersey: John Wiley & Sons.
35. Tian Q, An Y, Resnick SM, and Studenski S, The relative temporal sequence of decline in mobility and cognition among initially unimpaired older adults: Results from the Baltimore Longitudinal Study of Aging. *Age Ageing*, 2017 46(3): p. 445–451.10.1093/ageing/afw185 [PubMed: 27744302]
36. Burgess N, Maguire EA and O'Keefe J, The human hippocampus and spatial and episodic memory. *Neuron*, 2002 35(4): p. 625–41 [PubMed: 12194864]
37. Cavanna AE and Trimble MR, The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*, 2006 129(Pt 3): p. 564–83.10.1093/brain/awl004 [PubMed: 16399806]
38. Sakurai R, Barth A and Montero-Odasso M, Entorhinal Cortex Volume Is Associated With Dual-Task Gait Cost Among Older Adults With MCI: Results From the Gait and Brain Study. *J Gerontol A Biol Sci Med Sci*, 201810.1093/gerona/gly084
39. Braak H and Braak E, Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol*, 1991 82(4): p. 239–59 [PubMed: 1759558]
40. Colombo D, Serino S, Tuena C, Pedrolì E, Dakanalis A, Cipresso P, and Riva G, Egocentric and allocentric spatial reference frames in aging: A systematic review. *Neurosci Biobehav Rev*, 2017 80: p. 605–621.10.1016/j.neubiorev.2017.07.012 [PubMed: 28760627]
41. Kim J, Kim YH and Lee JH, Hippocampus-precuneus functional connectivity as an early sign of Alzheimer's disease: a preliminary study using structural and functional magnetic resonance imaging data. *Brain Res*, 2013 1495: p. 18–29.10.1016/j.brainres.2012.12.011 [PubMed: 23247063]
42. Fjell AM, Westlye LT, Grydeland H, Amlien I, Espeseth T, Reinvang I, Raz N, Holland D, Dale AM, Walhovd KB, and Alzheimer Disease Neuroimaging I, Critical ages in the life course of the adult brain: nonlinear subcortical aging. *Neurobiol Aging*, 2013 34(10): p. 2239–47.10.1016/j.neurobiolaging.2013.04.006 [PubMed: 23643484]
43. Long X, Liao W, Jiang C, Liang D, Qiu B, and Zhang L, Healthy aging: an automatic analysis of global and regional morphological alterations of human brain. *Acad Radiol*, 2012 19(7): p. 785–93.10.1016/j.acra.2012.03.006 [PubMed: 22503890]
44. Zheng F, Liu Y, Yuan Z, Gao X, He Y, Liu X, Cui D, Qi R, Chen T, and Qiu J, Age-related changes in cortical and subcortical structures of healthy adult brains: A surface-based morphometry study. *J Magn Reson Imaging*, 201810.1002/jmri.26037
45. Aquino D, Bizzi A, Grisoli M, Garavaglia B, Bruzzone MG, Nardocci N, Savoiardo M, and Chiapparini L, Age-related iron deposition in the basal ganglia: quantitative analysis in healthy subjects. *Radiology*, 2009 252(1): p. 165–72.10.1148/radiol.2522081399 [PubMed: 19561255]

Figure 1.
Flowchart of participants selection

Figure 2. Cross-lagged models between each brain volume and mobility (A) or fitness (B). Paths with the same letter were set to be equal over time. Solid line indicates significant associations, and dashed line indicates non-significant associations, with exceptions of the relationship between prior gait speed and subsequent volumes of hippocampus and precuneus, and the relationship between prior ventricular volume and subsequent fitness. Please refer to Table 2 and Table 3 for statistical results.

Figure 3. Brain areas underlying gait decline and preserved by fitness

Brain areas on sagittal view (a), coronal view (b), and axial view (c) that are associated with gait speed, including frontal (light blue), parietal (light-to-medium blue), medial (medium-to-dark blue), and corpus callosum (dark blue), and parahippocampal gyrus (yellow) that is associated with fitness.

Table 1.

Sample characteristics

	Baseline (n=332)	2-year follow-up (n=293)	4-year follow-up (n=185)
	Mean [SD] or N (%)		
Demographics			
Age, years	73 [7.7]	75 [7.7]	77 [7.4]
Women	187 (56)	164 (56)	99 (54)
Blacks	83 (25)	68 (23)	49 (26)
Body mass index, kg/m ²	26.9 [4.3]	27.0 [4.5]	26.9 [4.3]
Mini-mental state exam	28.6 [1.3]	28.5 [1.4]	28.4 [1.4]
Cognitive impairment or dementia	0 (0)	2 (0.7)	7 (3.8)
Dismobility (gait speed 0.6 m/sec)	0 (0)	0 (0)	2 (1)
APOE ε4 carriers	80 (25)	73 (25)	43 (24)
Gait speed, m/s	1.18 [0.20]	1.17 [0.20]	1.15 [0.21]
Fitness (400m time), sec	268.4 [44.0]	281.8 [53.9]	291.3 [65.1]
Total brain volume, cm ³	1137.5 [115.7]	1125.9 [112.1]	1123.6 [111.9]
Ventricular volume, cm ³	37.0 [20.9]	40.6 [23.2]	40.1 [22.3]
Frontal lobe, cm ³			
Middle frontal gyrus	30.5 [4.1]	30.0 [4.0]	30.0 [4.0]
Medial frontal cortex	3.4 [0.6]	3.3 [0.6]	3.3 [0.6]
Inferior frontal gyrus	13.7 [2.0]	13.5 [2.0]	13.4 [2.0]
Superior frontal gyrus	23.8 [3.2]	23.4 [3.1]	23.2 [3.0]
Supplementary motor cortex	8.4 [1.3]	8.3 [1.2]	
Primary motor cortex	22.4 [2.7]	22.1 [2.7]	22.1 [2.6]
Parietal lobe, cm ³			
Primary sensory cortex	17.6 [2.2]	17.4 [2.2]	17.2 [2.0]
Precuneus	20.1 [3.1]	19.8 [3.0]	19.7 [3.0]
Angular gyrus	16.1 [2.3]	15.9 [2.3]	15.8 [2.1]
Medial temporal lobe, cm ³			
Hippocampus	7.4 [0.8]	7.3 [0.8]	7.3 [0.8]
Parahippocampal gyrus	7.1 [0.9]	7.0 [0.8]	6.9 [0.8]
Entorhinal cortex	4.4 [0.7]	4.3 [0.7]	4.2 [0.7]
Subcortical motor areas, cm ³			
Putamen	8.2 [1.0]	8.1 [1.0]	8.1 [1.0]
Caudate	6.3 [0.8]	6.3 [0.8]	6.3 [0.9]
Thalamus proper	14.4 [1.4]	14.2 [1.4]	14.2 [1.4]
White matter, cm ³			
Corpus callosum	11.6 [1.6]	11.5 [1.6]	11.4 [1.6]
Frontal white matter	174.0 [20.3]	171.9 [19.6]	172.1 [20.1]
Parietal white matter	87.1 [10.2]	86.2 [10.1]	86.7 [10.4]
Temporal white matter	103.0 [11.7]	102.1 [11.5]	102.2 [11.7]
Occipital white matter	42.9 [5.7]	42.6 [5.6]	42.6 [5.6]

Table 2.

The temporal sequence between gait speed and brain atrophy (n=332)

	Brain volume → future gait speed		Gait speed → future brain volume	
	β^* (SE), raw p-value	FDR-adjusted p-value	β^* (SE), raw p-value	FDR-adjusted p-value
Global	Total brain volume	0.104 (0.035), 0.003	-	0.011 (0.006), 0.089
	Ventricular volume	-0.062 (0.035), 0.077	-	-0.006 (0.004), 0.157
Frontal	Middle frontal	0.079 (0.035), 0.025	0.033	0.019 (0.011), 0.085
	Medial frontal	0.114 (0.035), 0.001	0.003	0.003 (0.015), 0.850
	Inferior frontal	0.137 (0.036), <0.001	0.003	0.015 (0.012), 0.234
	Superior frontal	0.160 (0.036), <0.001	0.003	0.004 (0.012), 0.750
Parietal	Supplementary motor	0.097 (0.036), 0.006	0.011	-0.012 (0.014), 0.413
	Primary motor	0.121 (0.036), 0.001	0.003	0.006 (0.011), 0.612
	Primary sensory	0.105 (0.035), 0.003	0.006	0.000 (0.012), 0.991
	Precuneus	0.105 (0.036), 0.003	0.006	0.026 (0.010), 0.007
	Angular gyrus	0.128 (0.035), <0.001	0.003	0.030 (0.017), 0.066
Medial temporal	Hippocampus	0.079 (0.035), 0.025	0.033	0.023 (0.008), 0.004
	Parahippocampal	0.072 (0.037), 0.051	0.058	0.025 (0.013), 0.054
	Entorhinal cortex	0.103 (0.038), 0.007	0.012	0.028 (0.016), 0.081
Subcortical motor	Putamen	-0.004 (0.035), 0.904	0.904	0.001 (0.007), 0.907
	Caudate	-0.014 (0.034), 0.681	0.717	-0.005 (0.009), 0.554
	Thalamus	0.074 (0.036), 0.038	0.048	0.003 (0.006), 0.661
White matter	Corpus callosum	0.112 (0.035), 0.002	0.006	0.000 (0.005), 0.983
	Frontal white matter	0.119 (0.035), 0.001	0.003	0.015 (0.007), 0.042
	Parietal white matter	0.102 (0.034), 0.003	0.006	0.015 (0.009), 0.086
	Temporal white matter	0.086 (0.035), 0.014	0.022	0.018 (0.007), 0.013
	Occipital white matter	0.068 (0.035), 0.052	0.058	0.018 (0.010), 0.069

Note. Models were adjusted for baseline age, sex, race (white, black, and others with white as the reference), body mass index, height, education, intracranial volume, and the presence of APOE $\epsilon 4$. Bold numbers reflect significant associations **with FDR-adjusted $p < 0.05$** .

Table 3.

The temporal sequence between 400m time and brain atrophy (n=332)

	Brain volume → future 400m time		400m time → future brain volume	
	β^* (SE), p-value	FDR-adjusted p-value	β^* (SE), p-value	FDR-adjusted p-value
Global				
Total brain volume	0.003 (0.025), 0.890	-	-0.008 (0.006), 0.232	-
Ventricular volume	0.086 (0.025), <0.001	-	-0.001 (0.004), 0.879	-
Frontal				
Middle frontal	0.020 (0.024), 0.415	0.675	-0.005 (0.011), 0.664	0.738
Medial frontal	-0.019 (0.025), 0.439	0.675	-0.013 (0.015), 0.387	0.553
Inferior frontal	-0.035 (0.025), 0.164	0.656	-0.017 (0.012), 0.160	0.267
Superior frontal	-0.056 (0.026), 0.028	0.267	-0.008 (0.012), 0.474	0.632
Supplementary motor	-0.019 (0.025), 0.439	0.675	0.004 (0.014), 0.755	0.795
Primary motor	-0.031 (0.025), 0.225	0.675	-0.002 (0.011), 0.884	0.884
Parietal				
Primary sensory	0.001 (0.025), 0.980	0.993	-0.006 (0.012), 0.622	0.732
Precuneus	-0.012 (0.025), 0.634	0.811	-0.015 (0.010), 0.127	0.231
Angular gyrus	-0.056 (0.025), 0.025	0.267	-0.026 (0.017), 0.116	0.231
Medial temporal				
Hippocampus	-0.051 (0.025), 0.040	0.267	-0.018 (0.008), 0.023	0.127
Parahippocampal	-0.017 (0.025), 0.495	0.707	-0.040 (0.012), 0.001	0.020
Entorhinal cortex	-0.023 (0.027), 0.397	0.675	-0.033 (0.016), 0.035	0.127
Subcortical motor				
Putamen	-0.026 (0.024), 0.276	0.675	0.015 (0.007), 0.032	0.127
Caudate	0.019 (0.023), 0.417	0.675	0.021 (0.008), 0.012	0.120
Thalamus	-0.024 (0.026), 0.348	0.675	-0.004 (0.006), 0.509	0.636
White matter				
Corpus callosum	-0.040 (0.025), 0.112	0.560	-0.010 (0.005), 0.058	0.158
Frontal white matter	-0.011 (0.025), 0.649	0.811	-0.012 (0.007), 0.114	0.231
Temporal white matter	0.005 (0.025), 0.825	0.917	-0.014 (0.007), 0.038	0.127
Parietal white matter	0.000 (0.024), 0.993	0.993	-0.009 (0.009), 0.284	0.437
Occipital white matter	0.006 (0.025), 0.798	0.917	-0.018 (0.010), 0.063	0.158

Note. Models were adjusted for baseline age, sex, race, body mass index, height, education, intracranial volume, and the presence of APOE ε4. For the 400m time, shorter time=faster speed. Bold numbers reflect significant associations with **FDR-adjusted p<0.05**.