White matter abnormalities in mobility-impaired older persons

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Abstract

Objective: To investigate the relationship between white matter abnormalities and impairment of gait and balance in older persons.

Methods: We used quantitative MRI to evaluate the brain tissue compartments of 28 older individuals separated into normal and impaired groups on the basis of mobility performance testing using the Short Physical Performance Battery (SPPB). In addition, individuals were tested on six indices of gait and balance. For imaging data, segmentation of intracranial volume into four tissue classes was performed using a semi-automated approach-template-driven segmentation (TDS, ). In which the initial signal-intensity based
statistical tissue classifier classification was provided by a reviewer and results of the classifier is refined using an a digital brain atlas as anatomical template.

Results: Both decreased white matter volume, which was age-related, and increased white matter signal abnormalities (WMSA), which were not age-related, were observed in the mobility impaired group compared with the controls. Average WMSA for impaired individuals were nearly double those of controls. We also observed suggestive correlation trends between four of the six indices of gait/balance and WMSA.

Conclusions: This cross-sectional study suggests that decreased white matter volume is age-related, while increased WMSA are most likely to occur as a result of disease. Both of these changes are independently associated with impaired mobility in older persons and therefore likely to be additive factors of motor disability.

Introduction

Gait dysfunction is uncommon in persons under 65 years but the prevalence increases to 14% in the next decade and affects almost 50% of persons over 85 years\(^1\). These patients typically demonstrate a characteristic clinical picture, which includes small steps, shuffling, hesitation, poor balance and unstable turns. The disease mechanisms responsible for mobility disorders include deconditioning, arthritis, neuromuscular disease and central nervous system (CNS) diseases. Well-defined CNS diseases that cause gait and balance dysfunction (e.g., Parkinson's disease, Progressive Supranuclear Palsy) are present only in a fraction of older persons with failing mobility\(^2\). We hypothesize that accumulation of randomly distributed lesions in the white matter (e.g. with cardiovascular or neurodegenerative etiology) coincides with the accumulation of damage to specific fiber connections involved in the control of gait. The effects of these lesions may explain, at least in part, a significant portion of mobility disorders of the elderly. White matter signal abnormalities (WMSA) on MRI in older persons do in large part represent focal lesions, which are often assumed to be of ischemic origin, although a specific histologic diagnosis cannot be established by MRI alone\(^3,4\). We undertook this study in order to better define the role of WMSA in gait and balance disorders commonly occurring in older persons.

Methods

Subjects and Recruitment. Eighty-nine people responded to recruitment efforts and were interested in participating. Seventy-eight respondents who met the inclusion criteria of age > 70 years were further screened by telephone to determine eligibility based on the following exclusion criteria: non-English speaking, cognitive impairment (Mini-Mental Status Exam (MMSE) <24), distance vision >20/70, terminal illness or incapacitating treatment, unstable cardiovascular disease (e.g., myocardial infarction within 6 months, unstable angina), pulmonary disease requiring oxygen, Parkinson's disease (or other CNS disorder known to directly affect balance), epilepsy, peripheral nerve disorder, lower extremity amputation, weight >250 lbs, claustrophobia, pacemaker or other metallic
devices or implants, arthritis compromising mobility, stroke with neurological deficit, and medications compromising motor function (e.g. phenothiazines, butyrophenones). As a result of the phone screen, 4 individuals were not eligible while an additional 20 did not wish to participate further. The remaining 54 individuals signed consent forms and performed the Short Physical Performance Battery (SPPB). Twenty individuals were excluded on the basis of SPPB criteria (SPPB = 9 or 10; see below), and one other because the maximum number in that group assignment had already been reached. The remaining 33 individuals underwent an exam by a study physician which included a medical history, vital signs, and a neurological assessment to determine final eligibility.

**Mobility performance testing with the Short Physical Performance Battery (SPPB).** Physical performance was assessed with a clinical test of lower-extremity function, the SPPB. Originally devised in conjunction with the Established Populations for Epidemiologic Studies of the Elderly, this test has known inter-observer and test-retest reliability, and has been used to predict subsequent disability in elderly people. The SPPB uses ratings of performance on three timed tasks: standing balance, chair rise, and walking speed. Based on the total score, individuals were separated into two mobility groups: normal (i.e., SPPB = 11 or 12), and impaired mobility, (i.e., SPPB < 9). Individuals with intermediate performance scores (i.e., SPPB = 9 or 10) were excluded from the study.

**Gait and Balance Testing.** In order to assess gait and balance, we measured six indices of function which characterize different but complementary aspects of mobility: four measures of balance requiring measurement with a force platform (EquiTest System, NeuroCom International, Clackamas, OR) (Stabilogram Diffusion Analysis (SDA), Altered Sensory Input (ASI), Post-Translation Stability Test (PTST), and Functional Base of Support (FBOS)), and two low-tech measures (Gait Velocity (GV) and Single-Leg Stance Time (SLST)).

**SDA** - The individual stood on the force platform while gazing at an eye-level target one meter away. Five trials (30 seconds each) were recorded. Trials contaminated by inadvertent movements or deliberate shifts of balance were aborted and repeated. During analysis a stabilogram-diffusion plot of mean square displacement (centrifugal drift of the center of force (COF)) vs. time interval between measurements was generated.

**ASI** - Individuals were exposed to nine 20-second trials of standing on an unstable surface (Sensory Organization Test, EquiTest, Neurocom, Clackamas, OR) created by making the motorized platform surface tilt at an angle equivalent to the angle of sway of the body at any given time (sway-referenced platform) with and without modification of visual input (closed eyes or sway-referenced vision). Standing time before the occurrence of a loss of balance was measured for each trial. The outcome measure is cumulative standing time over 9 trials. Maximum possible score is 180 (9 trials x 20 seconds/trial).

**PTST** - The balance stimuli used in the PTST are 36 forward translations of the support surface. Strain gauge transducers in the platform measure vertical and shear forces applied by the individual. The vertical force-time product was calculated for each of the
36 trials then the mean of the 36 trials was determined and reported in Newton seconds (Nsec)\textsuperscript{8}.

**FBOS** - With the platform stationary, individuals were asked to lean maximally forward and then backward without bending their hips or knees, and without losing their balance. The mean anterior and posterior center of force (COF) positions in the sagittal plane were calculated and reported as the ratio of A-P distance between the mean forward and backward COF positions, divided by foot length. The better FBOS of the 2 trials is reported\textsuperscript{9}.

**GV** - Individuals walked at usual pace on an 8-meter course. The time for walking 8 meters was measured by a photoelectric timing device. The faster of two trials was used in the analysis.

**SLST** - Wearing comfortable shoes (excepting narrowed heels), with hands on hips, the individual balanced as long as possible on one leg. Two trials for each leg were performed. The best time of the four trials was used for analysis.

**Quantitative MRI.** Twenty-eight individuals were successfully imaged, including 16 mobility-impaired and 12 normally mobile individuals. Imaging was performed on a Siemens Vision Magnetom 1.5 Tesla MRI (Siemens Medical Systems, Erlangen, Germany) located in the John Dempsey Hospital at the University of Connecticut Health Center.

**Image acquisition** - The head was imaged from foramen magnum to superior convexity with contiguous 3mm-thick sections. Nominal in-plane resolution was 0.9375x0.9375 mm\textsuperscript{2} (field of view (FOV) = 24cm x 24cm, acquisition matrix = 256 x 192). Two types of image contrast, PD-weighted (PDw) and T2-weighted (T2w) were obtained with two interleaved, long repetition time (TR = 3000ms) dual-echo (TE1=30ms, TE2=80ms) conventional spin-echo sequences. The total imaging time for this sequence was kept at 11 minutes and 37 seconds by applying the half-Fourier method. The digital image data was transferred to the Brigham and Women's Hospital for further processing.

**Image Analysis** - Template driven segmentation (TDS) of the head MR images yielded estimated volumes of normal appearing white matter (WM), white matter signal abnormalities (WMSA), gray matter (GM), and cerebro-spinal fluid (CSF) (Figure 1)\textsuperscript{10,11}. Tissue class labeling consisted of an initial segmentation to isolate the intracranial contents from skull and extracranial soft-tissues using only minimal operator-interaction\textsuperscript{12-14}. An initial signal intensity-based tissue classification of the intracranial contents was subsequently refined by imposing a priori anatomical information derived from a reference atlas\textsuperscript{10,15}. In order to minimize the confounding effect of gain field inhomogeneity on the initial signal intensity-based classification, a radiologist manually prepared a separate k-nearest neighbor (kNN) classifier\textsuperscript{16} for every contiguous group of five slices (total of 52 slices; scalp-containing top two slices received separate classifier) of each individual's data. In TDS, the digital reference atlas\textsuperscript{15}, which is subdivided into over 120 anatomical labels, is matched to a given individual's images using a
combination of automated linear and nonlinear registration algorithms. The method improves the identification of WMSA within the anatomically defined white matter by correctly identifying areas of mild abnormality, which would be classified as gray matter by kNN classification\textsuperscript{10,11}

Statistical Analyses. The tissue volume estimates, normalized to intracranial cavity volume ($100 \times$ tissue volume/intracranial cavity volume), of mobility impaired individuals were compared to control individuals using the Mann-Whitney Test. Similarly, we compared WMSA normalized to total WM ($100 \times$ WMSA/(WM+WMSA)) between the two groups of individuals.

To examine the association of poor mobility with brain tissue volumes or age, we performed multiple linear regression, with SPPB as the dependent variable, and age, and tissue class estimates as the independent variables. Only tissue class estimates found to differ significantly between the groups ($p<0.05$) were entered into the regression models. Since SPPB is categorically scaled and not normally distributed, an iteratively reweighted least squares analysis assuming SPPB variance proportional to a binomial variance was performed as the primary multivariate analysis. We also performed linear regression analysis with the same predictors but MMSE as the outcome variable in one statistical model, as well as by including MMSE as a potential confounder (independent variable) in a separate model maintaining SPPB as the dependent variable. The six functional indices of mobility were related to age and tissue class estimates (with and without MMSE as an additional predictor) using ordinary least squares analysis and a Bonferroni correction for multiple comparisons. The relationship between MMSE and age, or tissue class estimates was also evaluated with Spearman rank correlation coefficients. A two-tailed alpha level of 0.05 was used for significance.

Results

Thirty-three individuals were enrolled in the study after screening. Four individuals’ MRI studies were incomplete and could not be further processed and one individual’s MR images demonstrated severe artifacts and were excluded from the study. Image processing to estimate tissue volumes was performed on the MR images of the remaining 28 individuals. The demographic characteristics of the study sample are presented in Table 1. Of note is a four years difference in average age of the two groups ($p < 0.02$, Mann-Whitney U), a small difference in MMSE scores between groups ($p < 0.0402$, Mann-Whitney U), and the absence of a significant difference in the presence of hypertension in the two groups. We also compared age, gender, ethnicity, education and the presence of hypertension between the excluded individuals and the two groups of normal and mobility-impaired individuals. There were no significant differences noted in these demographic variables, suggesting that the individuals actually studied were comparable to those who volunteered.

Table 2 presents group results of the six tests of gait and balance used in this study. Five of the six measures showed significantly better performance by the group with SPPB scores of 11 or 12 compared with the group with SPPB below 9.
Table 3 presents the group results of normalized tissue class volumes using automated template-driven segmentation (TDS) applied to the kNN signal-intensity based segmentation. Average WMSA volume for the mobility-impaired group was nearly double that of controls \((p=0.01)\), while WM volume was less for the mobility-impaired group \((p=0.03)\). CSF and GM volumes did not differ significantly. On average, WMSA constituted 1.76% of total WM (ie, WM+WMSA) in normal controls as compared to 3.49% in the gait-impaired individuals \((p=0.02)\).

Multivariate analysis was performed using SPPB as the outcome measure and age, WM volume, and WMSA volume estimates obtained with TDS as the predictors. Age was considered as a potential confounder since the mobility-impaired group was older than the control group (see Table 1). Stepwise regression found WMSA \((p=0.008)\) age \((p=0.047)\) and WMSA \((p=0.015)\) age \((p=0.052)\) to be the strongest predictors of SPPB score. with aAge adjusted white matter volume \((p=0.7852)\) adding little did not add to predictive ability value (see Table 4). The addition of MMSE as a potential confounder (predictor) didn't significantly impact these findings (see Table 4). Furthermore, age did not act as a confounder of WMSA volume since the regression coefficient for WMSA volume did not change regardless of whether or not age was included in the regression model. Despite age and WMSA accounting for nearly equivalent proportions (R-squared values of 0.17 and 0.18, respectively) of the variance, WMSA volume was a stronger predictor, as indicated above by the \(p\)-values. For a 1% change in normalized WMSA volume the model predicts a change in SPPB score of nearly two points \((1.86 \text{ points})\) (1.43 points when including MMSE as an independent variable). A similar result was obtained when the analysis was repeated using only the mobility impaired \((\text{SPPB}<9)\) individuals.

In an effort to relate these predictors to more specific aspects of balance and gait, age and WMSA were related to the six functional indices of mobility used in this study \((\text{GV, SDA, FBOS, PTST, ASI, SLST})\). After correcting for multiple comparisons, neither age nor WMSA volume reached significance as a predictor for any of the six indices; however, 4 of the 6 indices \((\text{GV, SLST, ASI, and PTST})\) showed strong trends for both age and WMSA volume (see Table 5).

Despite the use of an MMSE criterion of 24 to exclude cognitively impaired individuals, the groups demonstrated a slight difference in MMSE scores \((29.3 \text{ vs } 28.2; \ p=0.0402, \text{ Mann-Whitney test})\). Variability in MMSE scores was also greater for the mobility-impaired group compared with controls \((p<0.002; \text{ F-test, df}=26)\). Age and WMSA were not significantly correlated with MMSE scores, although a trend was seen for both \((r=-0.35, \ p=0.07, \text{ Spearman, and } r=-0.36, \ p=0.06, \text{ Spearman, respectively})\). In a linear regression model that included WMSA, WM, and age as possible predictors of MMSE, WMSA showed the strongest association, albeit without demonstrating statistical significance. The regression coefficients for these tissues were -0.56 \((p=0.09)\) for WMSA, 0.10 \((p=0.17)\) for WM, and -0.04 \((p=0.29)\) for age. CSF volume fraction was significantly correlated with MMSE \((r=-0.39, \ p=0.04, \text{ Spearman})\). WM and GM fractions were not significantly correlated with MMSE (for both \(r=0.28, \ p=0.15, \text{ Spearman})\).
Discussion

Stratification of motor performance using the SPPB created two groups of individuals that demonstrated significant differences in their levels of mobility, as quantified using standardized measures of gait and balance. By comparison with published cross-sectional studies of normal aging using these same indices, the group differences in the current study for SLST and FBOS are greater than the declines in these scores reported for the eighth decade8,9,17, while for GV the group difference is greater than the decline reported for the seventh and eighth decades18,19.

Among the tissue categories identified by TDS, only the normal and abnormal white matter (WM and WMSA) clearly discriminated the two groups that were defined on the basis of mobility. This supports our hypothesis that white matter changes are related to the gait and balance disorder under study.

Multivariate analysis suggested that mobility status was most closely related to WMSA and aging, while the normalized WM volume was not a significant predictor after adjusting for age differences between the groups. The effect of WMSA on mobility was stronger than the effect of age as measured either by R-squared or by the regression coefficients. While the association between WMSA and mobility was statistically significant, that between WM and mobility (p=0.052) narrowly missed the targeted level of significance in the relatively small group under study. These results can be explained by a model that includes two mechanisms that result in decreasing mobility and balance. First, aging is associated with mobility decline. Age-related white matter volume loss may be mediating some of the effect of aging on mobility. The second postulated mechanism is focal disruption of white matter, e.g., on the basis of microangiopathic small vessel pathology, i.e. disease related. These independent mechanisms, one associated with normal aging and the other disease-related, would lead to impaired mobility in an additive fashion. Such a model involving normal and pathologic processes is supported by recent reports associating WMSA and cardiovascular risk factors20-23, which thus add to the age-related risk of impaired mobility.

That only a few percent of total white matter were classified as abnormal and were, nevertheless, associated with clinical deficits is not surprising. Since neural networks depend on white matter fiber tracts for communication between neuronal units, relatively small, strategically located white matter lesions can have severe functional consequences. Our findings, however, are insufficient to demonstrate a causal relationship between WMSA and mobility. Changes in gray matter, which are not specifically identified by our image analysis method, may be concurrent to the detected WMSA and could provide an alternate or complementary explanation for the mobility deficits studied.

While individuals with overt dementia were excluded from the study using the MMSE cutoff of 24, individuals with mild cognitive changes could not be excluded with this instrument24. A small but significant group difference in MMSE scores was found. However, MMSE was not a significant predictor of SPPB and didn't significantly alter
the predictive power of WMSA and age on SPPB according to linear regression analysis. Both SPPB and MMSE were somewhat related to age and brain tissue changes. MMSE scores were negatively correlated with the intracranial CSF fraction (an indicator of brain atrophy), and demonstrated a non-significant negative correlation trend with WMSA and age. The results of linear regression analysis showed a relatively strong regression coefficient between WMSA and MMSE. However this trend did not reach statistical significance. This is not at all surprising, as MMSE was used as an exclusion criterion, thus limiting the range of observed cognitive performance in the already small population under study. Taken together, These findings suggest some degree of overlap between the pathophysiologic mechanisms underlying cognitive changes and impairment of mobility in some these patients, while in other cases different etiologies are likely. For instance, it appears reasonable that randomly accumulating small ischemic insults in individuals with significant cardiovascular risk factors could lead both to problems of mobility and cognition, depending on the functional specificities of the affected brain regions. The severity of impairment in cognition or mobility depends most likely on the topographic distribution of lesions in the functionally heterogeneous network of white matter fibers.

A decrease in normal white matter volume with age has been demonstrated previously in primates and humans using quantitative histological methods. Several cross-sectional MRI and X-ray computed tomography (CT) studies of healthy volunteers also found a decline in normal appearing white matter and/or an increase in WMSA with age. These complementary observations from different modalities, post-mortem and in-vivo, suggested that aging is associated with white matter changes.

White matter abnormalities detected by MRI do not represent a specific histologic alteration. Several tissue abnormalities, e.g. edema, demyelination, infarction, cellular infiltration, dilated Virchow-Robin perivascular spaces, thickened ectatic arterioles, gliosis, etc. may generate hyperintense signal on T2-weighted MR images of white matter. In this study no effort was made to histopathologically differentiate the detected WMSA.

White matter abnormalities have been related to gait or balance disturbances in several previous imaging studies. This cross-sectional study underscores the importance of white matter changes in mobility/balance impairment in older people in whom an otherwise definable cause is lacking, and establishes the clinical importance of white matter lesions, independent of age. This finding is consistent with the relationship found by others between white matter abnormalities and cardiovascular risk factors. Nonetheless, other mechanisms leading to white matter alteration, e.g. transependymal fluid exudates caused by denudation of the ventricular ependyma, also merit consideration in the etiologic investigation of mobility disorders in otherwise healthy older persons. The lack of association between WMSA or age, and individual indices measuring specific aspects of mobility and balance is not surprising, given the lack of statistical power in our small sample. The correlation trend between functional measures of gait and balance and estimates of WM and WMSA volumes lends further evidence for the link between white matter abnormalities and mobility impairment. A larger, longitudinal study should help further delineate the role of white matter changes and their
risk factors in mobility/balance disorders of the elderly. The computerized, largely automated method that was used is well suited for large-scale studies, and potentially for the routine diagnostic evaluation of mobility disorders. Furthermore, this quantitative MRI approach can be used as the basis for regional analyses of white matter in the search for tracts critical to balance and gait, and might be extended to the study of signal abnormalities within gray matter structures.

Table 1  Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Mobility Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>5:7</td>
<td>7:9</td>
</tr>
<tr>
<td>Age</td>
<td>79 ± 5 (70-85)</td>
<td>83 ± 6 (73-91)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>11 Cauc.:1 Af Am</td>
<td>16 Cauc:0 Af Am</td>
</tr>
<tr>
<td>Presence of Hypertension</td>
<td>6 [50%]</td>
<td>7 [44%]</td>
</tr>
<tr>
<td>Education [years]</td>
<td>15 ± 3 (11-20)</td>
<td>14 ± 4 (6-20)</td>
</tr>
<tr>
<td>SPPB score</td>
<td>11.3 ± 0.5 (11-12)</td>
<td>6.9 ± 1.3 (3-8)</td>
</tr>
<tr>
<td>MMSE score</td>
<td>29.3 ± 0.5 (29-30)</td>
<td>28.2 ± 1.3 (25-30)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.3±3.6(19.2-32.5)</td>
<td>27.3±4.3(20.3-35.2)</td>
</tr>
</tbody>
</table>

SPPB = Short Physical Performance Battery
MMSE = Mini-Mental State Examination
Cauc = Caucasian
Af Am = Afro-American
mean ± standard deviation (range) are presented where applicable
# - p= 0.02 (ANOVA)
Student's T-test
## - p= 0.02 (Mann-Whitney U)

Table 2  Gait and balance measures

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Mobility Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual gait velocity</td>
<td>1.2 ± 0.2</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>(m/s)</td>
<td>(0.2²) (12)</td>
<td>(16)</td>
</tr>
<tr>
<td>Single leg stance time</td>
<td>17.2 ± 4.1</td>
<td>4.0 ± 3.6</td>
</tr>
<tr>
<td>(sec)</td>
<td>(12)</td>
<td>(16)</td>
</tr>
<tr>
<td>Functional base of support (ratio)</td>
<td>0.43 ± 0.08² (12)</td>
<td>0.34 ± 0.10 (15)</td>
</tr>
<tr>
<td>Time to step during ASI (sec)</td>
<td>168 ± 15² (12)</td>
<td>130 ± 35 (13)</td>
</tr>
<tr>
<td>Short-term diffusion coefficient (mm²/s)</td>
<td>4.4± 2.1b (12)</td>
<td>8.6 ± 4.7 (16)</td>
</tr>
<tr>
<td>PTST Integrated vert. force (N/sec)</td>
<td>1.9 ± 1.4 (12)</td>
<td>2.4 ± 1.5 (12)</td>
</tr>
</tbody>
</table>
Values are mean ± standard deviation for (n) individuals. Not all measures were obtained in all Subjects
p <0.05\textsuperscript{a},
p<0.01\textsuperscript{b},
p < 0.001\textsuperscript{c} (Mann-Whitney U)
ASI = Altered sensory input
PTST= Post-translation stability test
vert. = vertical

\textbf{Table 3 Template-driven segmentation}

<table>
<thead>
<tr>
<th>Subjects</th>
<th>ICCV\textsuperscript{a}</th>
<th>WMSA\textsuperscript{b}</th>
<th>CSF\textsuperscript{c}</th>
<th>WM\textsuperscript{d}</th>
<th>GM\textsuperscript{e}</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (cc)</td>
<td>(% ICCV)</td>
<td>(% ICCV)</td>
<td>(% ICCV)</td>
<td>(% ICCV)</td>
<td>(% ICCV)</td>
</tr>
<tr>
<td>Controls</td>
<td>12 1447±141</td>
<td>0.6 ± 0.4</td>
<td>22.0 ± 3.6</td>
<td>32.6 ± 1.8</td>
<td>41.6 ± 2.8</td>
</tr>
<tr>
<td>Impaired</td>
<td>16 1416±136</td>
<td>1.1 ± 0.7</td>
<td>24.7 ± 4.5</td>
<td>30.0± 3.8</td>
<td>41.2 ± 2.8</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation for (n) individuals
ICCV = Intracranial Cavity Volume
WMSA = white matter signal abnormalities
CSF = Cerebrospinal Fluid
WM = normal appearing white matter
GM = gray matter
\textsuperscript{a} - Mann-Whitney U p = 0.64
\textsuperscript{b} - Mann-Whitney U p = 0.01
\textsuperscript{c} - Mann-Whitney U p = 0.16
\textsuperscript{d} - Mann-Whitney U p = 0.03
\textsuperscript{e} - Mann-Whitney U p = 0.77

\textbf{Table 4 Multiple regression analysis for SPPB as outcome variable}

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Coefficient</th>
<th>S.E.</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.14 (-0.1916)</td>
<td>0.08 (0.0908)</td>
<td>-1.83 (-2.0905)</td>
<td>0.079 (0.047052)</td>
</tr>
<tr>
<td>White matter WM/ICC</td>
<td>0.04 (0.03909)</td>
<td>0.14 (0.1415)</td>
<td>0.24 (0.2965)</td>
<td>0.81 (0.778523)</td>
</tr>
<tr>
<td>WMSA/ICC</td>
<td>-1.43 (-1.85)</td>
<td>0.67 (0.64)</td>
<td>-2.15 (-2.89)</td>
<td>0.043 (0.008)</td>
</tr>
</tbody>
</table>
Tissue volume estimates obtained with template-driven segmentation (TDS)
SPPB = Short physical performance battery
WM = normal appearing white matter, ICC = intracranial cavity, WMSA = white matter signal abnormalities
S.E. = Standard Error of the estimate.
Values in parenthesis are results of regression analysis performed with only age, white matter, and WMSA as independent variables.
Multiple R-squared = 0.36.

**Table 5 Multiple regression for mobility indices**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Coefficient</th>
<th>p-value</th>
<th>Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GV</td>
<td>-0.018</td>
<td>0.051</td>
<td>-0.143</td>
<td>0.042</td>
</tr>
<tr>
<td>SLST</td>
<td>-0.688</td>
<td>0.013</td>
<td>-4.311</td>
<td>0.039</td>
</tr>
<tr>
<td>ASI</td>
<td>-3.060</td>
<td>0.023</td>
<td>-15.643</td>
<td>0.088</td>
</tr>
<tr>
<td>SDA</td>
<td>0.001</td>
<td>0.657</td>
<td>0.013</td>
<td>0.315</td>
</tr>
<tr>
<td>FBOS</td>
<td>-0.003</td>
<td>0.490</td>
<td>-0.049</td>
<td>0.111</td>
</tr>
<tr>
<td>PTST</td>
<td>0.136</td>
<td>0.020</td>
<td>0.840</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Tissue volume estimates obtained with template-driven segmentation (TDS)
WMSA = white matter signal abnormalities
GV = gait velocity
SLST = single leg stance time
ASI = time to step during altered sensory input
SDA = stabilogram diffusion analysis
FBOS = functional base of support
PTST = post-translation stability test
Figure 1: Segmentation of brain tissues. Brain images of two individuals, an 81-year-old man with no significant gait impairment and a short physical performance battery (SPPB) score of 11 (top row), and an 81-year-old gait-impaired man with an SPPB score of 8 (bottom row) are shown. The original proton-density-weighted (PDw) (left column) and T2-weighted (T2w) (second column) conventional spin-echo MR images of a representative section of the brain at the level of the lateral ventricles are presented adjacent to the results of template driven segmentation (TDS; third column). Tissue labels: gray matter (GM) = gray, normal appearing white matter (WM) = white, cerebrospinal fluid (CSF) = blue, white matter signal abnormalities (WMSA) = yellow. Tridimensional renderings of WMSA, identified by TDS are shown in yellow in the context of the individuals' ventricles (blue) in the fourth column. Periventricular abnormalities of these age-matched individuals are clearly more extensive in the individual with significant gait impairment (bottom), but are also present, to a lesser extent, in the individual with SPPB = 11 (top).

References


