Functional Impact of White Matter Hyperintensities in Cognitively Normal Elderly Subjects

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Objective: To investigate the impact white matter hyperintensities (WMH) detected on magnetic resonance imaging have on motor dysfunction and cognitive impairment in elderly subjects without dementia.

Design: Cross-sectional study.

Setting: Population-based study on the incidence and prevalence of cognitive impairment in Olmsted County, Minnesota.

Participants: A total of 148 elderly subjects (65 men) without dementia ranging in age from 73 to 91 years.

Main Outcome Measures: We measured the percentage of the total white matter volume classified as WMH in a priori-defined brain regions (ie, frontal, temporal, parietal, occipital, periventricular, or subcortical). Motor impairment was evaluated qualitatively using the Unified Parkinson's Disease Rating Scale summary measures of motor skills and quantitatively using a digitized portable walkway system. Four cognitive domains were evaluated using z scores of memory, language, executive function, and visuospatial reasoning.

Results: A higher WMH proportion in all regions except the occipital lobe was associated with lower executive function z score (P value <.01). A higher WMH proportion in all regions, but most strongly for the parietal lobe, correlated with higher Unified Parkinson's Disease Rating Scale gait, posture, and postural stability sum (P value <.01). A higher WMH proportion, whether periventricular, subcortical, or parietal, correlated with reduced velocity (P value <.001).

Conclusions: We conclude that executive function is the primary cognitive domain affected by WMH burden. The data suggest that WMH in the parietal lobe are chiefly responsible for reduced balance and postural support compared with the other 3 lobes and may alter integration of sensory information via parietal lobe dysfunction in the aging brain. Parietal white matter changes were not the predominant correlate with motor speed, lending evidence to a global involvement of neural networks in gait velocity.

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WHITE MATTER HYPERINTENSITIES (WMH) ON T2-WEIGHTED MAGNETIC RESONANCE IMAGING (MRI) AND T2-WEIGHTED FLUID-ATTENUATED INVERSION RECOVERY MRI HAVE BEEN ASSOCIATED WITH COGNITIVE DYSFUNCTION, PARTICULARLY MEMORY AND EXECUTIVE DYSFUNCTION, IN ELDERLY INDIVIDUALS. In addition to age-associated cognitive deficits, WMH may also contribute to age-associated impairments in gait and balance. In 1 recent study, WMH were correlated with both motor and cognitive functions in the same individuals. While there has been interest in the relative contribution of periventricular vs subcortical WMH to gait disorders and cognitive impairment, there has been less attention focused on the lobar distribution of WMH. The goals of the current study were to determine (1) the association between WMH and motor and cognitive deficits in a group of elderly subjects without dementia who were derived from a population-based cohort, (2) how the radial location (periventricular vs subcortical) of the WMH influenced these associations, and (3) how the lobar location of the WMH influenced these associations. We hypothesized that WMH in certain regions (eg, frontal lobe) would have greater impact than WMH in other regions (eg, occipital lobe). Moreover, we hypothesized that periventricular WMH would correlate with motor dysfunction and subcortical WMH would correlate with cognitive dysfunction based on the assumption that periventricular WMH may disrupt action potential propagation in long descending fiber tracts, while subcortical WMH would disrupt propagation in corticocortical fibers.

METHODS

SAMPLE CHARACTERISTICS

Subjects were participants in the Mayo Clinic Study of Aging (MCSA), a population-based

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Table 1. Demographics, Health History, and Cognitive and Motor Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Interquartile Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>148</td>
</tr>
<tr>
<td>No. of diabetic subjects (%)</td>
<td>29 (19.6)</td>
</tr>
<tr>
<td>No. with hypertension (%)</td>
<td>103 (66.8)</td>
</tr>
<tr>
<td>No. with high cholesterol or lipid level (%)</td>
<td>93 (62.8)</td>
</tr>
<tr>
<td>No. of women (%)</td>
<td>83 (56.1)</td>
</tr>
<tr>
<td>Age, y</td>
<td>79 (76 to 83) [73 to 91]</td>
</tr>
<tr>
<td>Education, y</td>
<td>13 (12 to 16) [6 to 20]</td>
</tr>
<tr>
<td>Estimated MMSE score</td>
<td>28 (28 to 29) [24 to 30]</td>
</tr>
<tr>
<td>Global z score</td>
<td>0.7 (0.1 to 1.1) [-1.6 to 2.2]</td>
</tr>
<tr>
<td>Memory measures</td>
<td></td>
</tr>
<tr>
<td>z Score</td>
<td>0.7 (0.2 to 1.4) [-1.7 to 2.6]</td>
</tr>
<tr>
<td>WMS-R logical memory II score</td>
<td>18.0 (14.0 to 23.5) [2.0 to 37.0]</td>
</tr>
<tr>
<td>WMS-R visual reproduction II score</td>
<td>24.0 (18.0 to 29.2) [0.0 to 41.0]</td>
</tr>
<tr>
<td>AVLT delayed recall score</td>
<td>8.0 (6.0 to 10.0) [0.0 to 15.0]</td>
</tr>
<tr>
<td>Language measures</td>
<td></td>
</tr>
<tr>
<td>z Score</td>
<td>0.3 (-0.1 to 0.8) [-1.9 to 2.4]</td>
</tr>
<tr>
<td>Boston Naming Test score</td>
<td>56.0 (52.2 to 58.0) [39.0 to 60.0]</td>
</tr>
<tr>
<td>Category fluency total score</td>
<td>41.0 (36.0 to 47.0) [27.0 to 69.0]</td>
</tr>
<tr>
<td>Executive function measures</td>
<td></td>
</tr>
<tr>
<td>z Score</td>
<td>0.5 (-0.0 to 1.0) [-1.8 to 2.5]</td>
</tr>
<tr>
<td>WAIS-R digit symbol score</td>
<td>43.0 (35.0 to 50.0) [23.0 to 75.0]</td>
</tr>
<tr>
<td>Trail Making Test Part B score</td>
<td>90.0 (74.0 to 121.0) [40.0 to 300.0]</td>
</tr>
<tr>
<td>Visuospatial measures</td>
<td></td>
</tr>
<tr>
<td>z Score</td>
<td>0.4 (-0.1 to 1.0) [-2.2 to 2.8]</td>
</tr>
<tr>
<td>WAIS-R picture completion score</td>
<td>14.0 (12.0 to 16.0) [3.0 to 20.0]</td>
</tr>
<tr>
<td>WAIS-R block design score</td>
<td>24.0 (20.0 to 29.0) [6.0 to 43.0]</td>
</tr>
<tr>
<td>UPDRS, median (% &gt; 0) [range]</td>
<td></td>
</tr>
<tr>
<td>Upper sum</td>
<td>0 (13.5) [0 to 6]</td>
</tr>
<tr>
<td>Lower sum</td>
<td>1 (1.4) [0 to 2]</td>
</tr>
<tr>
<td>Gait and postural stability sum</td>
<td>0 (25.4) [0 to 4]</td>
</tr>
<tr>
<td>Gait, posture, and postural stability sum</td>
<td>0 (35.9) [0 to 4]</td>
</tr>
<tr>
<td>Velocity, cm/s</td>
<td>108 (92 to 119) [40 to 156]</td>
</tr>
<tr>
<td>Ambulation time, s</td>
<td>6.7 (6.0 to 8.7) [2.6 to 18.5]</td>
</tr>
<tr>
<td>Stride length, cm</td>
<td>118 (106 to 130) [41 to 162]</td>
</tr>
</tbody>
</table>

Abbreviations: AVLT, Auditory Verbal Learning Test; MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson’s Disease Rating Scale; WAIS-R, Wechsler Adult Intelligence Scale–Revised; WMS-R, Wechsler Memory Scale–Revised.

a Health history information was identified through self-report and medications.
b Converted to MMSE score from the Short Test of Mental Status score to assist in interpretability.

study on the incidence and prevalence of cognitive impairment in Olmsted County, Minnesota. The institutional review boards at Mayo Clinic and Olmsted Medical Center approved all MCSA procedures. The MCSA participants were randomly selected and invited to undergo subsequent in-person evaluations, as well as neurological and neuropsychological testing. Magnetic resonance imaging has been incorporated into the MCSA since its inception in 2005. A detailed report of design and sampling has been previously published.10 From the total population of 1434 MCSA controls, 436 MCSA participants underwent both quantitative gait testing and MRI as of May 2008. Of these, only subjects who received a consensus committee diagnosis of neurologically normal,10 had a sum of boxes Clinical Dementia Rating score of zero, and had neuropsychological, neurological, and motor examinations performed within 120 days of MRI acquisition were included in the present study. Subjects were excluded if they had potentially confounding diagnoses such as tumor, alcohol, single stroke, or Parkinson disease. The MRIs of subjects were evaluated for artifacts and removed if the quality interfered with image analysis. The final cohort included 148 elderly subjects (65 men) without dementia ranging in age from 73 to 91 years, with a median of 79 years. Their median estimated Mini-Mental State Examination score was 28, with a range from 24 to 30 (Table 1). All subjects gave written informed consent to participate.

COGNITIVE MEASURES

Neurological and neuropsychological tests performed by the MCSA10 have been described previously. For this study, 4 cognitive domains were defined using a neuropsychological battery, including Wechsler Adult Intelligence Scale–Revised subtests. The composite standardized z scores were calculated for each subtest and included the subtest score subtracted by the mean and standard deviation from the overall MCSA cohort for that test. The domains included memory (logical memory II and visual reproduction II subtests from the Wechsler Memory Scale–Revised), delayed recall subtest from the Auditory Verbal Learning Test; language (Boston Naming Test, Semantic Fluency Test); visuospatial (picture completion and block design subtests from the Wechsler Adult Intelligence Scale–Revised); and executive function (Trail Making Test Part B and digit symbol subtest from the Wechsler Adult Intelligence Scale–Revised). A global z score was calculated from the average z score of the 10 tests that form the 4 cognitive domains. A regression method was used to derive an estimated Mini-Mental State Examination score from the 38-item Short Test of Mental Status.

GAIT MEASURES

Qualitative gait assessment was determined with the modified Unified Parkinson’s Disease Rating Scale.11 The motor examination portion of the test was broken into 4 measures: upper sum (speech volume, facial expression, hand tremor at rest, rigidity of neck and arms); lower sum (leg tremor at rest and leg rigidity); gait and postural stability sum with posture; and gait and postural stability sum without posture. A higher postural stability score can be interpreted as impairment in balance, whereas a higher posture score indicates the shoulders are leaning forward in a stooped manner. The possible number of points for the upper sum, lower sum, and gait and postural stability measure with and without posture were 28, 16, 12, and 8 points, respectively (Table 1).

Quantitative gait assessment was measured using a 4.88-m digitized walkway system with embedded pressure sensors (GAIT-Rite: CIR Systems, Havertown, Pennsylvania).13 Gait velocity was measured from the first footfall to the last, in units of centimeters per second. Ambulation time was recorded as the amount of time it took to walk the length of the walkway from initial step to last. The stride length was measured as the average distance between consecutive steps of the left foot while walking the length of the walkway.

MRI PROCEDURES

Scan Protocol

All scans were performed at 3 T (GE Signa, Milwaukee, Wisconsin) at the Mayo Clinic, Rochester, Minnesota. The standardized MRI protocol included a sagittal, T1-weighted, 3-dimensional volume magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence. Scan parameters include a section thickness of 1.2 mm in the 170 contiguous partitions with a field of view of

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26.0 cm × 26.0 cm, 256 × 256 matrix, bandwidth = 31.3 kHz, 8°
flip angle, repetition time = 6.6 milliseconds, and echo time = 2.8
milliseconds. An axial, T2-weighted fluid-attenuated inversion re-
covery scan was acquired with 48 contiguous slices, each 3.0 mm
in thickness, field of view = 22 cm × 22 cm, repetition time = 11 000
seconds, inversion time = 2250 milliseconds, echo time = 147 mil-
liseconds, bandwidth = 31.3 kHz, and matrix = 256 × 192.

White Matter Atlas

A white matter (WM) parcellation atlas was manually traced
onto a custom T1 template using the program Analyze (Bio-
medical Imaging Resource, Rochester, Minnesota) by a trained
neuroanatomist. A detailed description of the custom tem-
plate design can be found in Venuri et al.14 Radial WM par-
cellation within the 4 lobes of the brain (frontal, temporal, pa-
rietal, and occipital) was based on standardized anatomical
criteria (Figure 1). The periventricular zone was defined as
the region within a boundary drawn midway between the ven-
tricular lining and the depth of the deepest penetrating sulcus
at any point along the circumference of the lateral ventricle.
The WM outside of this boundary, which included the WM in
the cortical gyri, defined the subcortical zone.

Region of Interest–Based Quantification
of WMH in Each Subject

White matter hyperintensities were segmented from normal brain
tissue on fluid-attenuated inversion recovery images using an in-
house semiautomated image analysis software tool named Histo-
seg, which produces a binary mask.15 Next, we used tools in the
Statistical Parametric Mapping 5 suite,16 as well as custom-built
software to assign the identified WMH to specific lobar and radial
regions of interest. For each subject, we first coregistered the fluid-
attenuated inversion recovery image and its associated binary WMH
mask to the MPRAGE image, using a 6-df affine registration. Next,
using the unified segmentation17 algorithm in Statistical Paramet-
ric Mapping 5, we simultaneously segmented the MPRAGE im-
age into gray matter, WM, and cerebrospinal fluid and computed
the discrete cosine transform parameters to spatially normalize the
subject images into the space of the custom template. We then
applied these inverse discrete cosine transform parameters to the
WM atlas, thereby obtaining a set of anatomical atlas labels cor-
responding to the subject’s MPRAGE image. Finally, we used these
subject space labels to parcellate the binary WMH masks into the
aforementioned segments. We used a hard classification scheme
to binarize the segmentation maps produced by Statistical Para-
metric Mapping 5, whereby each voxel was labeled as gray mat-
ner, WM, or cerebrospinal fluid, depending on which of the 3 tis-
sue classes had a higher probability for that voxel. To determine
WM volume in each region of interest, the resulting binary WM
masks were parcellated into the same regions of interest as the WMH
masks. To adjust for intersubject differences in the volume of the
WM in each lobe, a derived value WMH proportion (WMHp) was
also created to represent the percentage of WM in each lobe that
was “at risk.” The WMHp was defined for a given region (x) as the
volume of the WMH in a given region of interest (WMHx) divided
by the volume of WM in that region of interest (WMx), and mul-
tiplied by 100 [ie, WMHp(x) = (WMHx/WMx) × 100]. Using WMHp
to evaluate functional impairment controls for variations in brain
size across different subjects, eliminating the need to normalize
WMH data by total intracranial volume.

STATISTICAL ANALYSIS

Data were analyzed with nonparametric methods when they were
not normally distributed. Log transforms were applied for graphic

Results

Subjects’ frontal lobe WM volume (Table 2) tended to be more than double their temporal WM volume (P < .001), about 60% greater than their parietal WM volume (P < .001), and more than triple their occipital WM volume (P < .001). In terms of the percentage of WM tis-
sue at risk, WMHp of the occipital lobe was far greater than that of the other 3 lobes (P < .001). Still, on aver-
age a typical subject’s parietal WMHp was greater than their temporal or frontal WMHp (P < .01). The WMHp
was far greater in the periventricular zone compared with subcortical WMHp (P < .001).

Relationship Between WMHp
And Cognitive Test Scores

We analyzed the effect of laterality for periventricular vs subcortical regions and for lobar measures. There were
do no differences between right and left; therefore, we com-
bia the right and left hemisphere data for all subsequent
analyses. Where no significant association was
found between regional WMHp and cognitive data, the
total WMHp correlation and significance value are re-
Table 3. Correlative Relationship Between the WMHp and Cognitive Measures

<table>
<thead>
<tr>
<th>Region WMHp</th>
<th>MMSEb</th>
<th>Visuospatial Composite Score</th>
<th>Executive Function Composite Score</th>
<th>Trail Making Test B</th>
<th>WAIS-R Digit Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>-0.02 (.83)</td>
<td>-0.16 (.06)</td>
<td>-0.22 (.007)c</td>
<td>0.29 (&lt;.001)</td>
<td>-0.15 (.07)</td>
</tr>
<tr>
<td>Periventricular</td>
<td>-0.02 (.81)</td>
<td>-0.15 (.07)</td>
<td>-0.23 (.005)</td>
<td>0.30 (&lt;.001)</td>
<td>-0.16 (.05)</td>
</tr>
<tr>
<td>Subcortical</td>
<td>-0.02 (.80)</td>
<td>-0.16 (.06)</td>
<td>-0.22 (.009)</td>
<td>0.28 (&lt;.001)</td>
<td>-0.14 (.09)</td>
</tr>
<tr>
<td>Frontal</td>
<td>-0.02 (.80)</td>
<td>-0.14 (.09)</td>
<td>-0.20 (.01)</td>
<td>0.31 (&lt;.001)</td>
<td>-0.12 (.14)</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.02 (.78)</td>
<td>-0.15 (.08)</td>
<td>-0.25 (.002)</td>
<td>0.30 (&lt;.001)</td>
<td>-0.19 (.03)</td>
</tr>
<tr>
<td>Parietal</td>
<td>-0.03 (.73)</td>
<td>-0.16 (.06)</td>
<td>-0.22 (.009)</td>
<td>0.27 (&lt;.001)</td>
<td>-0.14 (.08)</td>
</tr>
<tr>
<td>Occipital</td>
<td>-0.07 (.41)</td>
<td>-0.06 (.45)</td>
<td>-0.17 (.05)</td>
<td>0.14 (.10)</td>
<td>-0.17 (.05)</td>
</tr>
</tbody>
</table>

Abbreviations: MMSE, Mini-Mental State Examination; WAIS-R, Wechsler Adult Intelligence Scale–Revised; WM, white matter; WMHp, percentage of white matter at risk.

a Percentages were calculated in the 4 main lobes and radial location.
b Converted to MMSE score from the Short Test of Mental Status score to assist in interpretability.
c Significant.

Table 2. Volumes Used to Determine the WMHp

<table>
<thead>
<tr>
<th>Region</th>
<th>WMH volume, cm³ Median (Interquartile Range)</th>
<th>WM volume, cm³ Median (Interquartile Range)</th>
<th>WMHp³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8.8 (5.3 to 15.5) [1.3 to 62.1]</td>
<td>333 (301 to 370) [228 to 449]</td>
<td>3 (2 to 5) [0 to 14]</td>
</tr>
<tr>
<td>Periventricular</td>
<td>5.6 (3.4 to 9.2) [1.0 to 25.7]</td>
<td>44 (40 to 48) [30 to 57]</td>
<td>12 (8 to 22) [2 to 48]</td>
</tr>
<tr>
<td>Subcortical</td>
<td>3.1 (1.6 to 6.3) [0.2 to 36.3]</td>
<td>290 (258 to 321) [196 to 394]</td>
<td>1 (1 to 2) [0 to 10]</td>
</tr>
<tr>
<td>Frontal</td>
<td>2.4 (1.3 to 5.1) [0.2 to 27.8]</td>
<td>141 (127 to 155) [98 to 202]</td>
<td>2 (1 to 4) [0 to 17]</td>
</tr>
<tr>
<td>Temporal</td>
<td>1.4 (0.9 to 2.1) [0.1 to 6.5]</td>
<td>62 (56 to 69) [27 to 87]</td>
<td>2 (2 to 4) [0 to 10]</td>
</tr>
<tr>
<td>Parietal</td>
<td>1.9 (0.8 to 4.4) [0.1 to 20.4]</td>
<td>86 (76 to 96) [55 to 116]</td>
<td>2 (1 to 6) [0 to 20]</td>
</tr>
<tr>
<td>Occipital</td>
<td>2.6 (1.6 to 3.7) [0.4 to 7.4]</td>
<td>44 (39 to 48) [26 to 65]</td>
<td>6 (4 to 8) [1 to 17]</td>
</tr>
</tbody>
</table>

Abbreviations: WM, white matter; WMH, white matter hyperintensity; WMHp, percentage of white matter at risk.

Greater WMHp correlated with worse performance in the executive function domain, with no independent effect of periventricular or subcortical WMHp. Lobar distribution of WMH showed correlations with the executive function domain z score for frontal, temporal, and parietal lobes, but not for the occipital lobe (Figure 2). There was no correlation between digit symbol scores and overall WMH. In contrast, significant correlations were found with Trail Making Test Part B scores and periventricular, subcortical, and total WMH. Trail Making Test Part B scores correlated best with frontal (Figure 2), temporal, and parietal lobe WMHp, but not occipital WMHp. Plots of the Spearman rank order correlations between z scores of cognition and regional WMHp (Figure 2) demonstrate a similar pattern of strength. There was no relationship between WMHp and the z scores for memory (R = -0.05; P = .52) or language (R = -0.10; P = .22), but the visuospatial domain showed a trend toward worse performance with greater WMHp (R = -0.16; P = .06).

**RELATIONSHIP BETWEEN WMHp AND AMBULATION**

Gait and postural stability sum scores were significantly correlated with total WMHp, periventricular WMHp, and subcortical WMHp (Table 4). Unified Parkinson’s Disease Rating Scale scores of tremor and rigidity split into upper and lower extremity sums were not associated with any of the WMHp variables (R = 0.05; P = .54). In contrast, the total WMHp, periventricular WMHp, and subcortical WMHp correlated significantly with gait and postural stability sum scores (Table 4). There was a correlation between parietal WMHp and gait/postural stability that may account for this finding since there were no significant relationships with other lobar WMHp scores. The addition of the posture score strengthened the correlation globally (Figure 2). Reduced gait velocity (Table 4) correlated with periventricular and subcortical WMHp (P < .001), and velocity was associated with lobar WMHp (P < .001). Shorter stride length correlated with a greater periventricular and subcortical WMHp (P < .001), as did frontal, temporal, and parietal WMHp. The relationship between velocity and stride length with occipital WMHp was not as strong but was significant (P < .005).

**COMMENT**

In a cohort of 148 community-dwelling elderly individuals without dementia, we investigated whether a relationship exists between WMH load and motor or cognitive impairment. Few studies have investigated the differential impact of lobar, periventricular, and subcor-
tical WMH on functional impairment in neurologically normal individuals. Of those, only one to our knowledge has evaluated the relationships between WMH volume and both motor and cognitive dysfunction in normal elderly subjects. We found that decreases in executive function correlated with a greater WMHp, with the effect driven by a global increase in WMHp, though occipital WMHp correlates did not reach significance. In addition to a role in executive function, WMHp also correlated significantly with gait and posture measures. The strongest relationship we found was between quantitative measures of gait velocity and WMHp. We acknowledge that the sensitivity of cognition and gait assessments may differ; however, the strength of the correlations was consistently greater with gait than cognition. This observation may suggest that the deleterious effects of WMH could impact motor function to a greater extent than cognition. On a note of caution, our reported correlations were statistically significant, but our imaging observations accounted for a small portion of the observed variance in cognitive and gait abnormalities related to WMH.

Increasing WMH volumes have been hypothesized to have an impact on ambulation in older adults, but the mechanism remains to be determined. Our elderly cohort was neurologically normal, and none were diagnosed with Parkinson disease. To our knowledge, our study is the first to examine associations of Unified Parkinson’s Disease Rating Scale items with burden of WMH. The strongest relationship we observed with the Unified Parkinson’s Disease Rating Scale was between the WMHp in the parietal lobe with gait and postural control with or without posture added. Gait and postural control are important factors for successful aging, with balance disturbances and falls being hypothesized to result from the interruption of frontal lobe connections and descending motor fibers. A recent study evaluating qualitatively graded WMH and posturographic measures of

Figure 2. The plots along the top row depict the strength of the correlation that total, periventricular (PV), and subcortical (SC) white matter hyperintensity proportion have with clinical measures of cognition and motor skills. The bottom 4 plots are between the white matter hyperintensity proportion of the 4 main lobes of the brain and the clinical measures of cognition and motor skills. G/PS indicates gait and postural stability; G/P/PS, gait, posture, and postural stability; MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson’s Disease Rating Scale.
measures of mobility\textsuperscript{7,20,23} have been used to support the quantitative measure of speed. Walking speed\textsuperscript{19} or subjective information via parietal lobe dysfunction in the aging brain. That the WM changes alter integration of sensory information compared with the other 3 lobes. We hypothesize that the WM changes alter integration of sensory information via parietal lobe dysfunction in the aging brain.

The relationship between WMHp and motor disturbances was further strengthened by examining a quantitative measure of speed. Walking speed\textsuperscript{19} or subjective measures of mobility\textsuperscript{7,20,23} have been used to support the hypothesis that increases in WMH are related to impaired mobility. Regardless of regional involvement, a greater WMHp was strongly associated with reduced gait velocity. Somewhat surprising was the degree to which gait velocity correlated with WMH. It is a widely held view that speed of cognition undergoes the greatest decline with “normal” aging. The relationship between WMHp and gait velocity suggests that age-related abnormalities of WM may have the greatest impact on motor speed. Parietal WM changes were not the predominant correlate with motor speed, lending evidence to a global involvement of neural networks in gait velocity, whereas balance may require less cognitive input and rely more on the somatosensory input into the parietal lobe. 

No relationship between the WMHp was observed with z scores of memory or language but a trend was noted for the visuospatial domain, which might reflect an executive function component to visuospatial reasoning. Other studies have reported a relationship between memory and WMH, often in a cohort that included younger individuals and a wider range of cognitive functioning.\textsuperscript{2,3,6} We attempted to control for these factors by only selecting a neurologically normal elderly cohort with a narrow age range (73-91 years). The observed association between executive function and overall WMHp is consistent with the current literature.\textsuperscript{2,3,6} A lack of a correlation between executive function and the percentage of WM at risk in the occipital lobe supports the hypothesis that anterior brain regions may play a key role in the decline of executive function. These collective findings provide evidence that age-related decline in cognitive processing speed is in part related to increased prevalence of WM pathology with age. Correlations between WMH and timed measures of executive function, gait, and gait-postural scores support the conclusion that WMH contribute to functional impairment. The selective nature of the functional deficits associated with WMH suggests that the primary effect of WMH is to reduce the efficiency of neuronal signaling. This conclusion is strengthened by the fact that vastly different functional domains—cognition and gait—were affected, with the common theme being processing speed.

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Author Contributions: Study concept and design: Murray, Dickson, and Jack. Acquisition of data: Murray and Preboske. Analysis and interpretation of data: Murray, Senjem, Petersen, Hollman, Weigand, Knopman, Ferman, and Jack. Drafting of the manuscript: Murray, Preboske, and Jack. Critical revision of the manuscript for important intellectual content: Senjem, Petersen, Hollman, Weigand, Knopman, Ferman, Dickson, and Jack. Statistical analysis: Murray, Weigand, and Jack. Obtained funding: Petersen, Dickson, and Jack. Administrative, technical, and material support: Senjem and Jack. Study supervision: Ferman, Dickson, and Jack.

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Table 4. Correlative Relationship Between Qualitative and Quantitative Ambulation Measures and the WMHp

<table>
<thead>
<tr>
<th>Region WMHp</th>
<th>UPDRS: Gait and Postural Stability</th>
<th>UPDRS: Gait, Posture, and Postural Stability</th>
<th>Velocity</th>
<th>Stride Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.23 (0.006)\textsuperscript{b}</td>
<td>0.27 (0.01)\textsuperscript{b}</td>
<td>-0.42 (&lt;0.001)\textsuperscript{b}</td>
<td>-0.42 (&lt;0.001)\textsuperscript{b}</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0.22 (0.009)\textsuperscript{b}</td>
<td>0.26 (0.002)\textsuperscript{b}</td>
<td>-0.42 (&lt;0.001)\textsuperscript{b}</td>
<td>-0.40 (&lt;0.001)\textsuperscript{b}</td>
</tr>
<tr>
<td>Subcortical</td>
<td>0.23 (0.006)\textsuperscript{b}</td>
<td>0.24 (0.004)\textsuperscript{b}</td>
<td>-0.38 (&lt;0.001)\textsuperscript{b}</td>
<td>-0.39 (&lt;0.001)\textsuperscript{b}</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.20 (0.02)</td>
<td>0.23 (0.006)\textsuperscript{b}</td>
<td>-0.41 (&lt;0.001)\textsuperscript{b}</td>
<td>-0.44 (&lt;0.001)\textsuperscript{b}</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.18 (0.04)</td>
<td>0.21 (0.01)\textsuperscript{b}</td>
<td>-0.40 (&lt;0.001)\textsuperscript{b}</td>
<td>-0.39 (&lt;0.001)\textsuperscript{b}</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.28 (0.001)\textsuperscript{b}</td>
<td>0.30 (0.001)\textsuperscript{b}</td>
<td>-0.40 (&lt;0.001)\textsuperscript{b}</td>
<td>-0.39 (&lt;0.001)\textsuperscript{b}</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.14 (.09)</td>
<td>0.23 (0.006)\textsuperscript{b}</td>
<td>-0.29 (&lt;0.001)\textsuperscript{b}</td>
<td>-0.23 (0.005)\textsuperscript{b}</td>
</tr>
</tbody>
</table>

Abbreviations: UPDRS, Unified Parkinson’s Disease Rating Scale; WM, white matter; WMHp, percentage of white matter at risk.
\(^a^{Percentages were calculated in the 4 main lobes and radial location.}
\(^b^{Significant.}
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REFERENCES