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White Matter Hyperintensities Predict Functional Decline in Voiding, Mobility and Cognition in Older Persons

Dorothy B. Wakefield, MS[1], **Nicola Moscufo, PhD**[3], **Charles R. Guttmann, MD**[3], **George A. Kuchel, MD**[4], **Richard F. Kaplan, PhD**[2], **Godfrey Pearlson, MD**[5], and **Leslie Wolfson, MD**[1]

[1] Department of Neurology, University of Connecticut Health Center, Farmington, CT and Hartford Hospital, Hartford CT

[2] Department of Psychiatry, University of Connecticut Health Center, Farmington, CT

[3]Department of Radiology, Brigham & Women's Hospital, Boston, MA

[4] Center on Aging, University of Connecticut, Farmington, CT

[5] Department of Psychiatry, Yale University, New Haven, CT and Institute of Living, Hartford, CT

Abstract

Objective—To compare MRI data to functional assessments of mobility, urinary control, and cognition to determine common or distinctive features in the distribution of brain white matter hyperintensities (WMHs) associated with functional decline/impairment.

Design—Baseline data from subjects 75-89 years enrolled in a longitudinal study. Assessors and subjects were blinded to group assignment.

Participants—99 subjects were enrolled using a balanced 3×3 matrix stratified by age and mobility performance. Exclusion criteria included: medication, systemic conditions, and neurologic diseases which can compromise mobility.

Setting—Healthy community-dwelling volunteers.

Measurements—WMHs were identified using semi-automated segmentation method and regional burdens were assessed utilizing a WM parcellation atlas. Quantitative measures of mobility, urinary incontinence (UI) severity and executive function/processing speed were obtained.

Results—WMHs occur predictably in predominantly periventricular areas. There were powerful correlations between global (tWMH) and regional WMH (rWMH) with r values of 0.5-0.9 for eight of ten structures analyzed. The tWMH predicted functional measures of UI, mobility and executive function/processing speed nearly as well as the best regional measures. The total volume

*Correspondence and Requests for Reprints should be addressed to: Leslie Wolfson, MD Department of Neurology, University of Connecticut Health Center 263 Farmington Avenue Farmington, CT 06030-1840 Telephone #: (860) 679-3186 Fax #: (860) 679-4446 **wolfson@nso.uchc.edu**.

Author Contributions:
Dorothy Wakefield-Data management, analysis, draft of manuscript
Nicola Moscufo-Image analysis, produced imaging data/figure, manuscript revision
Charles Guttmann- Supervision and quality control of imaging data, manuscript revision
George Kuchel-Urinary incontinence, responsible for test selection, data analysis, manuscript revision
Richard Kaplan-Cognitive function, responsible for test selection, testing and data analysis, manuscript revision
Godfrey Pearlson-Supervision and quality control of MRI scanning and transmission of data
Leslie Wolfson-Draft of manuscript, examined/selected subjects, Grant PI

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of WMH independently explains 5-11% of the variability for mobility, UI severity and executive function/processing speed and is a sensitive (0.7-0.8) predictor of functional decline. The odds of decline in each of the three functional domains increased by 1.5 to 2.4 times with each 1% increase in tWMH.

Conclusion—This work establishes the importance of brain WMH burden in three major geriatric syndromes. Our findings support the inclusion of total WMH burden as a risk factor in the predictive/diagnostic criteria.

Keywords

White matter hyperintensities; Impaired function; Impaired Urinary function; Functional decline in cognitive function; Impaired mobility

INTRODUCTION

Magnetic resonance imaging (MRI) has advanced understanding of diseases of the nervous system, particularly those involving brain white matter (WM). The detail seen on T2-weighted and FLAIR sequences has allowed localization and quantification of the underlying disseminated focal WM abnormalities. White matter hyperintensities (WMHs), commonly present in the MRIs of older persons were initially ignored but have subsequently been linked to hypertension and other vascular disease risk factors.[1] An increasing body of knowledge has associated these abnormalities to functional deterioration of mobility, [23] urinary control [4]and cognition. [5] In three earlier reports we performed hypothesis-driven evaluations of WMH presence within brain regions known to be critical to mobility, cognition or voiding.[678] Essentially these studies confirmed the association between the functions and some of the proposed pathways. While the three studies utilized different rWMHs, the current study combines the subsets of rWMHs from each of the three. This cross-sectional study compares tWMH and rWMH to each other, as well as examining the relationship to functional assessments of the three geriatric syndromes. Our goal is to define common or distinctive features in the distribution or volume of brain WMHs responsible for deterioration of these functions which lead to predictive or diagnostic criteria.

METHODS

Subjects

Ninety-nine subjects, 75-89 years, were recruited from the community for a four-year longitudinal study defining the relationship between WMH accrual and mobility impairment. From 312 individuals screened by phone there were 164 eligible, consenting individuals from which 117 came for a physical exam performed by the senior investigator (LW) who also administered the exclusion criteria. Exclusion criteria included: medication, systemic conditions (e.g., arthritis), and neurologic diseases (e.g., Parkinson's disease) which can compromise mobility. Additional exclusions included cognitive impairment (Mini-Mental State Exam < 24), corrected distance vision > 20/70, unstable cardiovascular disease (e.g., unstable angina), pulmonary disease requiring oxygen, inability to walk 10 meters independently in < 50 seconds, lower extremity amputation, weight > 113.5 kg (250 lbs), claustrophobia, presence of a pacemaker or other metallic devices/implants, excessive alcohol intake and expected lifespan < 4 years. Seventeen subjects were excluded due to arthritis, Parkinson's disease and claustrophobia, and one due to a clinically silent tentorial meningioma. Subjects were enrolled using a balanced 3×3 matrix which stratified age (75-79; 80-84 and > 85) and mobility performance in terms of Short Physical Performance Battery (SPPB) scores (11-12; 9-10 and < 9). Subjects provided informed consent and then underwent physical, neurological and cognitive assessment, plus brain MRI. Participants and

assessors were blinded to clinical, mobility and imaging outcomes. The protocol was approved by the Institutional Review Board.

Assessment Tools

UI severity was measured using the Urinary Incontinence Severity Index [9] a validated self-reported instrument in which leakage is characterized as none, slight, moderate, or severe. This particular incontinence-related instrument was chosen since white matter hyperintensities appear to be much more closely related to incontinence severity than to the presence of incontinence, category of incontinence, bother or ultimate impact on function [8]. Mobility was assessed using the SPPB score [10], Tinetti Total score, as well as Tinetti Gait score[11]. Laboratory testing of mobility performance included timed stair descent and self-paced maximum velocity. Measures of executive functioning included the Trail Making Test (Trails Part B) [12], the Stroop Color and Word Test [13], and the California Computerized Assessment Package (CalCAP) sequential reaction time (SQ1). [14]

Brain MR Imaging and total WMH (tWMH)

A 3-Tesla Siemens Allegra (Erlangen, Germany) MRI system was used to acquire the following MR brain scans: T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE, 176 contiguous 1 mm-thick axial slices, TR/TE=2500/2.74 ms, TI=900 ms, matrix size=256×208), T2-weighted 3D Fast Spin Echo (T2, 176 contiguous 1 mm-thick sagittal slices, TR/TE=2500/353 ms, matrix size=256×220), and T2-weighted Fluid Attenuated Inversion Recovery (FLAIR, 128 contiguous 1.3 mm-thick sagittal slices, TR/TE=6000/353 ms, TI=2200 ms, matrix size=256×208). Image pre-processing included magnetic field-related signal inhomogeneities[15] and linear affine registration of FLAIR and T2 series to the MPRAGE series.[16] The skull-stripped intracranial cavity (ICC) was obtained from the T2 series using an in-house program implemented in Matlab (Mathworks Inc., Natick, Massachusetts) and included the brain parenchyma, and ventricle as well as cortical cerebrospinal fluid. The MPRAGE and FLAIR series were used for automated identification of the WMH using two applications, i.e. FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) and Slicer (www.slicer.org). Specifically, the MPRAGE series was used as input in FreeSurfer[17] and both MPRAGE and FLAIR series were used as inputs in the EM segmentation module of Slicer.[18] The WMH maps were combined into one using Matlab (WMH spatial overlap between the maps had to be more than 10% and WMH three voxels or smaller were excluded). Final WMH maps were produced after review, which included manual correction of remaining false positive and false negative WMHs if present. Volumes of WMH and ICC for each subject were determined in Matlab and expressed as milliliters (number of voxels × voxel volume/1000). To correct for head size difference, for each subject the total WMH volume was expressed as percent (%) of the intracranial cavity volume.

Regional WMH (rWMH)

For regional analysis we used a WM parcellation atlas[19], which provides a functional map of approximately 32% of total brain WM. This atlas was first aligned to each subject brain and then overlaid onto the tWMH map obtained with the segmentation method described above to identify WM regions of interest (ROIs) [7]. The ROIs we selected contain the following fiber tracts: Anterior, superior and posterior corona radiata (ACR, SCR, PCR), cingulate gyrus (CGC), genu, body and splenium of corpus callosum (GCC, BCC, SCC), anterior and posterior limb of internal capsule (ALIC, PLIC), superior longitudinal fasciculus (SLF). For those ROIs with hemispheric distribution the volumes were expressed as total after adding the left and right volumes together. We expressed the rWMH as fraction (%) of the ROI by dividing the rWMH total volume (mL) by the total volume (mL) of the ROI.

Statistical Analysis

SAS version 9.1 (SAS Institute, Inc., Cary, NC) was used for the statistical analysis. Spearman correlations were calculated to measure the relationship between tWMH and regional WMHs. Regression models were used to examine the amount of variation explained by tWMH compared to the best of the regionals. Dependent variables were 5 mobility measures (Tinetti total score, Tinetti Gait Score, SPPB Score, time (seconds) to descend three stairs, self-paced maximum velocity (m/sec)), UI severity, and 3 cognitive measures (TrailsB, CalCAPSQ1, Stroop-color-word). Multivariate cumulative logit regression analysis was performed to evaluate MRI variables that significantly contributed to prediction of the categorical UI Severity. Linear regression analysis was used for all other dependent variables. Each model had one MRI variable, as well as age, gender, and BMI. BMI was replaced by education level (high school grad vs. not a grad) in models for cognitive measures. To examine how well tWMH predicts functional decline, we conducted a sensitivity analysis and produced Receiver Operating Characteristic (ROC) curves for each of the dependent variables. ROC curves plot sensitivity along the Y-axis vs. 1-specificity on the X-axis. Area under the ROC curve (AUC) was calculated and used to compare models. Maximum possible area under a curve is 1, so models with area closest to 1 were considered best. Possible confounders were age, gender, BMI, and education level (HS graduate or Not). Final models for SPPB, Tinetti total score and Tinetti gait score controlled for age. Models for Incontinence, self-paced maximum velocity, and time downstairs controlled for gender, and cognitive models controlled for age and level of education. Functional decline was indicated by a Tinetti total score ≤ 24, Tinetti gait score ≤ 10, and SPPB ≤ 9. Moderate and severe incontinence indicated impairment. Because most individuals performed in the normal range on the cognitive measures, and there was no normative data for the CalCAP RT measure for people in this age range, we used relative rather than normative based impairment. This was also done for self-paced maximum velocity and time to descend three stairs. We compared several cut-off points as the markers for functional decline using percentiles from our sample. Logistic regression models were then fitted and odds ratios were calculated. A two-tailed level of $\alpha \leq 0.05$ was the threshold for statistical significance.

RESULTS

Participant Characteristics

At baseline we enrolled 99 older subjects (mean = 82.1, SD = 4.1 years, range 75 to 89 years) of whom 60% were female. Subjects were well educated non-Hispanic whites with only 7 non-high school graduates. Moderate/severe incontinence was present in 38%. Mean IADL (23.5 ± 1.1%), CESD (8.2 ± 6.7) and MMSE (28.4 ± 1.3) scores indicated that most were independent with normal affective and cognitive function. The average Tinetti total score was 25.8 (SD=2.56). The mean tWMH was 1.00% (SD=0.91, min-max: 0.02-4.23%). Sixty-four of these were in the 0 to 1% range, 23 in the 1-2% range, 6 in the 2-3% range and 6 were above 3%. The outcome variables and the WMHs are described in Table 1.

Predictably, WMHs occur more frequently in the periventricular regions with detectable presence in subcortical areas as well (Figure 1). The observed distribution suggests a progression of WMH in an outward direction. We reasoned that the amount of WM damage at the regional level is probably highly related to the total quantity of WMH, which implies that an association observed between different functional impairments, i.e., cognitive, mobility, voiding, and regional WM lesion burden could be reflected also in the association with total WMH burden. To test this hypothesis we measured and compared the association between tWMH and rWMH burdens previously analyzed and relevant for aspects of cognitive, urinary or mobility function. We found strong correlations ($r = 0.5 - 0.9$) between

tWMH and 8 of the 10 structures analyzed; the other two structures had correlations of 0.20 and 0.30. This observation provides strong support to our hypothesis above.

All regression models were significant, with 4 degrees of freedom and with p-values between 0.04 and <0.0001. Our main focus was comparing the amount of variation explained by tWMH and rWMH over and above age, gender, and BMI or education. UI severity had its strongest relationship to the rWMH in the SCR although other structures were also significantly related (Table 2). The tWMH was associated with UI severity almost as strongly as the best of the regional burdens. The strongest association with mobility, as measured by both Tinetti Total and Gait Scores, was shown by the rWMH in SCC, although the tWMH had almost the same strength (Table 2). The tWMH also showed a strong association to executive function/processing speed (Table 2). Thus each of the three functional domains mobility, cognition and UI, were almost as strongly related to the tWMH as to the individual rWMHs.

Since the rWMHs were strongly correlated with tWMH, and tWMH had almost as strong a relationship with the 3 functional domains as the rWMH, we next examined the sensitivity of the dependent variables to changes in tWMH. Logistic regression models were fitted with tWMH predicting varying levels of decline/impairment for each of the dependent variables, and sensitivity and specificity were calculated. We selected different cut-off points for each of the measures so that we could compare the sensitivity and specificity for different levels of function. Sensitivity varies with specificity, so Table 3 shows the highest sensitivity achieved at levels of specificity greater than 0.50, as well as the area under the ROC curve for each model. Models with tWMH, age, and education level predicted a Trails B score of 148 or more with sensitivity 0.84 at specificity 0.54 and AUC of .83. Education was not a significant predictor in these models most likely because 93% of subjects were high school graduates. Two other cut-offs for Trails B score (slowest 10% and 30%) were also examined, but neither was as sensitive or specific. An SPPB score <11 was predicted with 0.79 sensitivity at specificity 0.56 and AUC of 0.66 (not shown). However, an SPPB score ≤ 9, which is more indicative of impairment, had lower sensitivity, specificity, and AUC (.71, . 51, and .63). Moderate/severe incontinence was predicted with 0.81 sensitivity and 0.67 specificity with an AUC of 0.77.

To determine how well tWMH predicted functional decline/impairment in each of the domains we calculated the odds ratios from the logistic regression models predicting functional decline/impairment. For dependent variables without established cut-offs for impairment (Self-paced maximum velocity, SQ1, Trails B, Stroop Color Word), we chose the cut-off from the model with the largest AUC. Table 4 shows the odds ratios. For each 1% increase in tWMH, subjects were 1.5 to 2.4 times as likely to have: moderate/severe incontinence, an SPPB score of 9 or less, a Tinetti total score of 24 or less, a Tinetti gait score of 10 or less, a Stroop Color Word score of 24 or less, an SQ1 greater than 633, and a walking velocity less than 0.69 m/sec.

DISCUSSION

White matter hyperintensities observed in MR images have clinical relevance because they are thought to represent tissue damage with potential effect on brain function. The type and extent of the impairment is, at least in part, linked to the specific pathways affected and the physiological effects of the diminished connectivity between various networks and neural structures. Since at present, the relationship between the total amount of brain WMH and that in sub-regions affecting specific tracts is unknown, the usefulness of global lesion burden as an indicator reflective of damage in areas containing relevant pathways remains to be defined. We took advantage of the availability of quantitative global and regional

measurements of WMH to assess this relationship. We sought to compare and produce a model for the rWMH contribution to each/all of the three functional domains of interest, i.e. executive functions, mobility, urinary continence. Unexpectedly, however, tWMH added almost as much to our regression models as did the best of the rWMHs. The stereotyped nature of the distribution of rWMH with the resulting high level of correlation between individual rWMHs and tWMH readily explains the extent to which tWMH predicts functional decline/impairment. Moreover, the measurement of rWMH is highly technical requiring the resources of an imaging research laboratory. By contrast, tWMH, can readily be determined using published scales, thus serving as a diagnostic surrogate for rWMH but not necessarily as a substitute in a model of that function.

Our findings show a strong association between tWMH to rWMH and demonstrate a significant predictive value of tWMH to functional deficit. These observations provide a basis for understanding the pattern and accrual of WMHs and helps in explaining the often reported relationship between the geriatric syndromes involving declines in cognitive domains, urinary function and mobility. [20-23] Comparable accrual of WMH in WM regions supporting these functional domains would explain these relationships although it also may be related to general brain connectivity. [7] Our findings offer potential insights into earlier reports in which seemingly distinct conditions such as upper and lower extremity impairment, decreased vision, sensory impairment and depression may represent shared risk factors for incontinence falling and functional dependence.[20]

Subjects with dementia were excluded from this study narrowing the range of cognitive function analyzed. Nevertheless, we still demonstrated a relationship between processing speed/executive function and tWMH. It is our clinical impression that by itself the volume of tWMH noted in our subjects is rarely associated with established dementia. By contrast, the relationship of mobility and UI to tWMH is not only robust but of clinical significance in these same subjects.

A predictable pattern of WMHs, in which tWMH relates to multiple functional domains, suggests the potential clinical value of methodologies capable of assessing tWMH. Three commonly used observational rating scales provide reliable cross-sectional assessment of hemispheric WMH burden although their ability to measure change over time is limited. A fourth scale has been developed to measure change. [24] Even with these limitations, visual assessment of WMH burden is realistic in the short-term, particularly if visual measures were validated against quantitative WMH [24]. This would allow clinicians to determine the importance of WMH in UI, mobility impairment or cognitive slowing, ultimately leading to predictive /diagnostic criteria based on the overall quantity of WMHs. The value and importance of the WMH is best illustrated by noting that it independently determines 5-11% (Table 2) of the variability for mobility, 5% of the variability for UI (Table 2) and 5-6% of the variability of executive function and processing speed (Table 2). These results are consistent with the recognized multi-factorial complexity of common geriatric syndromes in which no single risk factor is responsible for a large portion of the overall risk of developing the specific condition.[23]

The predictive value of WMH for cognitive, urinary and mobility function is supported by sensitivity in 0.7-0.8 range making this measurement a useful tool for forecasting function. Given that for each 1% increase in tWMH there is an increase of 1.5 to 2.4 times of the chance of diminished function in each of these domains indicates a major increase in risk across the 0-4.2% range. The mean tWMH of 1.0 in conjunction with median and 75th percentile tWMH values of 0.7 and 1.2 indicate a skewed distribution with only 35 subjects above the mean. We believe this suggests that the major burden of functional impairments

linked to WM damage lies in subjects in the skewed WMH tail above the 1% mean, i.e. about one-third of subjects.

The stereotyped anatomic distribution of WMHs in brain may be dictated by cerebral perfusion with the most poorly perfused areas demonstrating the greatest tendency to develop WMHs.[25] The presence and severity of WMHs is related to age with future accrual best predicted by current severity. [26] The distribution of WMHs, and the relationship of their severity to age and vascular disease risk factors, is consistent with the conclusion that abnormalities within brain microvascular may underlie WMHs. The pathophysiologic mechanism, although likely related to changes within blood vessel walls, remains unclear. The increasing clinical importance of WMHs, as reported in this work, raises the importance of defining causation as well as optimizing a risk factor abatement strategy, which minimizes the WMH accrual associated with functional deterioration.

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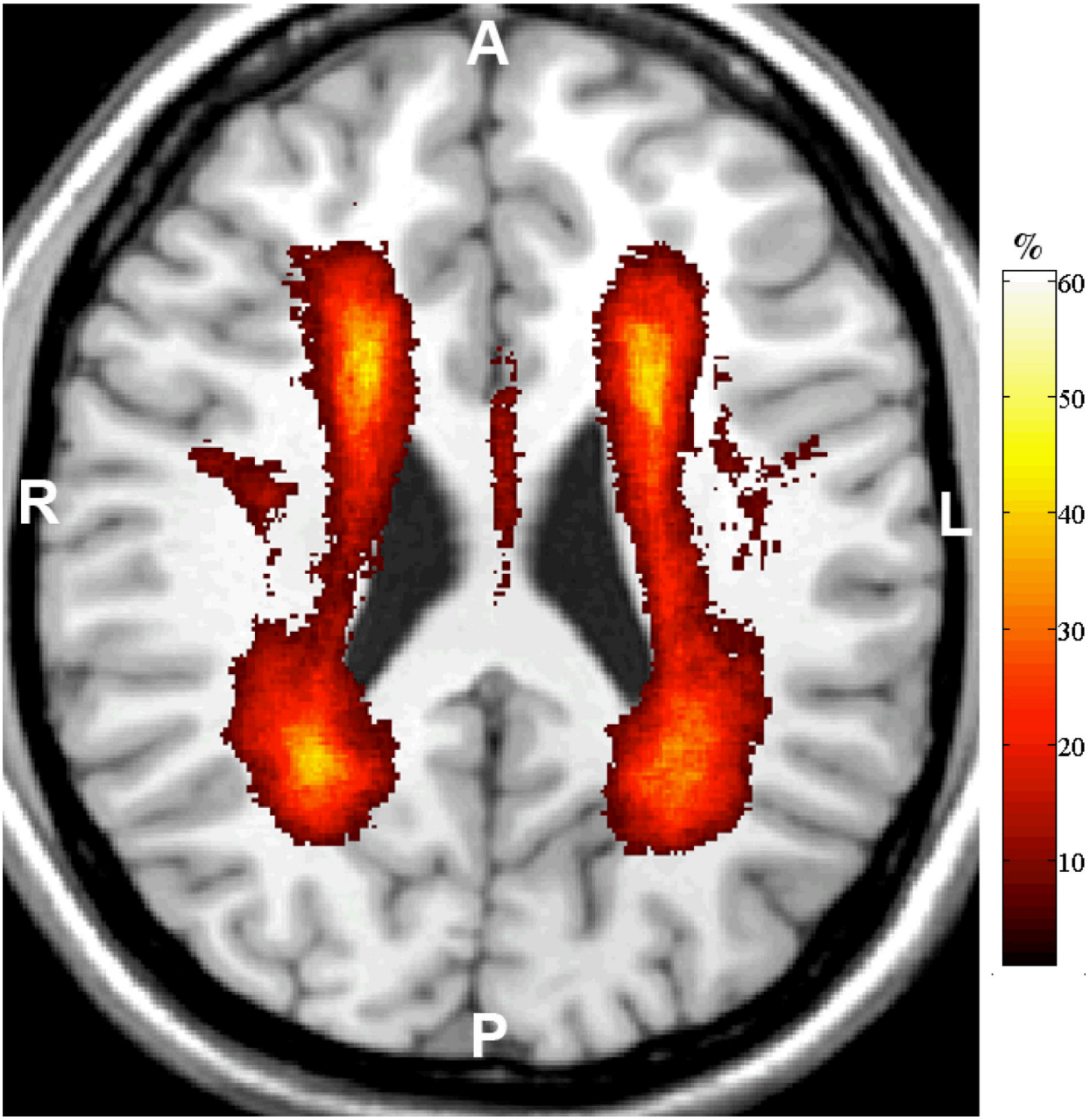

Figure 1.

The figure illustrates the distribution of WMHs and their frequency in one exemplary slice as observed in our study subjects. The frequency map is overlaid on the reference brain obtained from the International Consortium on Brain Mapping, UCLA. The color bar indicates the percent of subjects with WMH in that voxel. Symbols: A = anterior; P = posterior; L = left hemisphere; R = right hemisphere.

Table 1

Descriptive Statistics for Outcome Variables and Brain Regions

	Measure	N	Mean (SD)	Min - Max
Cognitive	TrailsB	98	125.3 (74.5)	43.7 - 419.1
	Stroop Color Word	98	26.6 (9)	5 - 50
	Sequential Process Time	96	610.8 (137.1)	298 - 854
Mobility	SPPB Score [*]	99	9.2 (2.2)	2 -12
	Tinetti Total Score [†]	99	25.8 (2.6)	14 - 28
	Tinetti Gait Score [‡]	99	11 (2)	3 - 12
	Gait Velocity	94	2.3 (0.5)	1 - 3.6
	Time down Stairs	87	5.1 (1.1)	2.5 - 7.7
WMH % [§]	tWMH [¶]	99	1.00 (0.91)	0.02 - 4.23
	ACR	99	8.37 (8.53)	0.00 - 53.20
	ALIC	99	1.29 (3.97)	0.00 – 34.63
	BCC	99	6.51 (6.18)	0.00 – 31.37
	CGC	99	0.09 (0.32)	0.00 - 2.34
	GCC	99	6.23 (5.15)	0.00 - 25.19
	PCR	99	23.41 (21.65)	0.00 - 84.00
	PLIC	99	0.83 (4.73)	0.00 - 44.72
	SCC	99	2 (2.85)	0.00 - 12.57
	SCR	99	8.76 (11.52)	0.00 - 60.78
	SLF	99	3.29 (6.19)	0.00 - 35.43

Abbreviation Description

tWMH Total White Matter Hyperintensity

ACR Region containing the Anterior corona radiata

ALIC Region containing the Anterior limb of internal capsule

BCC Region containing the Body of corpus callosum

CGC Region containing the Cingulum (cingulate gyrus)

GCC Region containing the Genu of corpus callosum

PCR Region containing the Posterior corona radiata

PLIC Region containing the Posterior limb of internal capsule

SCC Region containing the Splenium of corpus callosum

SCR Region containing the Superior corona radiata

SLF Region containing the Superior longitudinal fasciculus

[*] Short Physical Performance Battery. Scores have possible range from 0 to 12

[†] Scores have possible range from 0 to 28

[‡] Scores have possible range from 0 to 12

[§] tWMH is in % of ICC; regional burden is in % of the region volume

[¶] Abbreviations shown below:

Table 2

r^2 Added by Brain Regions to Regression Models over Age, Gender, and Body Mass Index

		Mobility Measures			Cognitive Measures			Incontinence
Brain Region	**Tinetti Total**	**Tinetti Gait**	**SPPB**	**Self-paced Maximum Velocity**	**Trails B**	**SQ1 (median)**	**Stroop Color Word**	**Severity**
tWMH	**0.09***	**0.16**	**0.11**	**0.08**	**0.05**	**0.10**	**0.08**	**0.06**
ACR	**0.03**	**0.08**	**0.08**	**0.04**	0.03	**0.09**	**0.04**	**0.06**
CGC	**0.05**	**0.13**	**0.06**	**0.05**	**0.04**	**0.07**	**0.04**	0.03
CGH	**0.06**	**0.13**	**0.09**	**0.06**	0.02	**0.07**	0.03	0.03
CST	**0.10**	**0.18**	**0.11**	**0.09**	**0.05**	**0.09**	**0.05**	**0.06**
GCC	**0.05**	**0.09**	**0.06**	**0.05**	0.02	**0.08**	**0.04**	0.01
PCR	**0.03**	**0.12**	0.03	**0.06**	**0.09**	**0.06**	**0.05**	0.02
PLIC	**0.06**	**0.10**	**0.05**	**0.04**	0.03	0.03	0.01	**0.07**
SCC	**0.10**	**0.16**	**0.11**	**0.09**	**0.04**	**0.17**	**0.06**	0.03
SCR	**0.08**	**0.13**	**0.07**	**0.09**	**0.05**	**0.07**	**0.03**	**0.07**
SFO	**0.03**	**0.08**	**0.04**	**0.05**	0.01	**0.04**	0.03	**0.04**
SLF	**0.02**	**0.06**	**0.04**	**0.06**	0.01	**0.05**	0.01	**0.04**

* Bold indicates $p < 0.05$

Table 3

Sensitivity/Specificity and Area Under Curve

	Sensitivity/Specificity	Area Under Curve
Moderate/Severe Incontinence	.81/.67	0.77
SPPB ≤ 9 (Lowest 43%)	.71/.51	0.63
Tinetti Total ≤ 24 (Lowest 24%)	.83/.63	0.79
Tinetti Gait ≤ 10 (Lowest 27%)	.73/.53	0.69
Velocity ≤ 0.69 m/sec (Slowest 50%)	.77/.54	0.71
Downstairs Time ≥ 6.2 sec (Slowest 50%)	.67/.60	0.65
Trails B ≥148 (Slowest 20%)	.84/.59	0.83
Stroop Color Word ≤ 24 (Lower 40%)	.83/.54	0.71
SQ1 ≥ 633 (Slowest 40%)	.76/.62	0.70

Table 4

Odds Ratios from Logistic Regressions with Total White Matter Hyperintensity Fraction Predicting Functional Decline

Outcome	Estimate	Standard Error	P-Value	OR (95% CI)
Moderate/Severe Incontinence	0.49	0.26	0.06	1.63 (0.98, 2.71)
SPPB ≤ 9	0.56	0.25	**0.03**	1.75 (1.07, 2.86)
Tinetti Total ≤ 24	0.69	0.27	**0.01**	1.98 (1.17, 3.38)
Tinetti Gait ≤ 10	0.58	0.25	**0.02**	1.79 (1.11, 2.9)
Velocity ≤ 0.69 m/sec	0.88	0.34	**0.01**	2.4 (1.23, 4.68)
Time down stairs ≥ 6.2 msec	0.52	0.33	0.11	1.68 (0.88, 3.21)
Trails B (≥148)	0.51	0.30	0.09	1.66 (0.93, 2.97)
Stroop Color Word (≤ 24)	0.61	0.27	**0.03**	1.85 (1.08, 3.16)
SQ1 (≥ 633)	0.51	0.25	**0.04**	1.67 (1.03, 2.7)