White Matter Hyperintensities and Cognitive Impairment in Healthy and Pathological Aging

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Title: White matter hyperintensities and cognitive impairment in healthy and pathological aging – A Quantified Brain MRI Study

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Running title: WMH and cognitive impairment in healthy and pathological aging

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Abstract

Background**:** Brain changes involving white matter (WM), often an indication of cerebrovascular pathology, are frequently seen in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Few studies have examined possible cognitive domain- or group-specific cognitive effects of WM pathology in old age, MCI and AD.

Objective: Our purpose was to examine the relationship between white matter hyperintensities (WMH), a typical marker for WM pathology, and cognitive functioning in healthy old age and pathological aging using quantified MRI data.

Methods: We utilized multi-domain neuropsychological data and quantified MRI imaging data from a sample of 42 cognitively healthy older adults and 44 patients with MCI/AD (total n = 86).

Results: After controlling for age and education, in the whole sample, WMH in the temporal and parieto-occipital lobes was associated with impairments in processing speed, and parieto-occipital pathology with verbal memory impairment. Additionally, temporal WMH was associated with impaired processing speed in the patient group specifically.

Conclusions: White matter pathology is strongly associated with impaired processing speed, and our results indicate that these impairments arise from WMH in the temporal and parieto-occipital regions. In MCI and AD patients with temporal WMH, processing speed impairments are especially prominent. The results of the study increase our knowledge of cognitive repercussions stemming from temporal and/or parieto-occipital WM pathology in healthy and pathological aging.

1. INTRODUCTION

Pathological developments in white matter (WM) pathways can disrupt cerebral networks associated with cognitive processes [1]. These brain changes are typically seen in structural magnetic resonance imaging (MRI) as white matter hyperintensities (WMH), often reflecting the distribution of cerebral small vessel disease [2]. White matter lesions have been associated with impairments in processing speed, executive functions, working memory, visual episodic memory and verbal episodic memory [3–12].

Significant comorbidity and overlap exists between Alzheimer's disease (AD) and cerebrovascular pathology [13]. Both share a number of risk factors such as smoking, diabetes, obesity, and hypertension [14], and elevated WMH as well as vascular diseases such as atherosclerosis increase the risk for AD [15,16]. Also, AD patients show degeneration in several WM tracts [17] and heightened levels of WM pathology in posterior cerebral regions [18]. Therefore, it is of importance to study how WM pathology *per* se can affect cognition in mild cognitive impairment (MCI; often an early stage of AD) and AD.

Many studies have focused on the associations between gray matter volume and cognition in MCI and AD [19], but studies on the cognitive repercussions of WM pathology in MCI and AD are fewer. The existing studies have shown that WM lesion load predicts cognitive decline [20] and WM lesions in the fornices and corpus callosum correlate with cognitive decline in AD patients [21]. Furthermore, WM lesions affect global cognition and memory through global cortical thickness and medial temporal lobe thickness, similarly for cognitively healthy and impaired groups (MCI/AD) [22]. We recently found indications of visually rated frontal WMH having a trend-level effect on general cognition specifically in AD patients [23], and later reported a similar association between left frontal WMH and processing speed specifically in AD patients [24].

The current study aimed to continue our previous line of research by using quantitative MRI analysis methods, while utilizing a portion of the same patient sample as used before. We examined the possible effects of WMH on multiple cognitive domains in cognitively healthy and a mixed group of MCI and AD patients, with an interest in seeing: (1) if there would be differences in the effects between the two groups; (2) would the differences be similar to what has been reported with visual rating methods.

2. METHODS

2.1. Participants

Data was originally collected in the DEMPET and TWINPIB research projects over several years at the National PET-Centre in Turku, Finland [25–27]. Both studies were carried out in accordance with relevant guidelines and regulations and were approved by the Joint Ethical Committee of the University of Turku and Turku University City Hospital. Oral and written information about the study was given to the participants, who gave informed consent for participation. The diagnosis of MCI was carried out according to the Petersen criteria [28], whereas AD patients fulfilled the DSM-IV criteria for dementia as well as the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association) criteria for probable AD [29]. The MCI patients were of the amnestic-type, characterized by episodic memory impairment, and traditionally seen as the typical prodromal state to AD [30].

Nine missing data points for neuropsychological measures were imputed by EM missing data analysis in SPSS. From the original sample of 148 participants, 62 participants were excluded due to insufficient MRI data quality for quantification. The final sample consisted of 42 cognitively healthy adults, 14 patients with MCI and 30 patients with AD, 86 participants in all. This sample is a portion

of the one that has been utilized before [23,24]. Since the individual group sizes of the MCI and AD groups were relatively small, they were pooled together.

No differences were found between the groups regarding age (t(84) = -.463, p = .645), education (U = 855.500, z = -.653, p = .514) or gender (χ^2 (2) = .385, p = .535). However, since age and education have typically strong connections with cognitive performance, they were set as covariates to control against possible confounding effects.

(Table 1 here)

2.2. Neuropsychological measures

A number of neuropsychological tests were used to compute four cognitive composite variables (see Table 2). The composite variables were calculated by first converting the individual test scores into z-scores by using the means and standard deviations of the whole sample, after which the mean of the individual tests for each domain was calculated. See Kaskikallio et al. [23] for further details.

(Table 2 here)

In group-wise analyses (see Table 3) cognitively healthy controls performed significantly better than patients with MCI or AD in every cognitive domain as would be expected (p < .01).

(Table 3 here)

2.3. Magnetic resonance imaging

Magnetic resonance imaging was performed with 1.5T Philips Intera (Best, the Netherlands). White matter hyperintensities were analyzed using three dimensional (3D) T1 FFE transaxial (TR/TE 25/5, 58 ms, slice thickness 2 mm, matrix 512 x 512) and 2D FLAIR coronal (fluid attenuated inversion recovery, TR/TE: 11000/140 ms, slice thickness 5 mm, matrix 512 x 512) images. The same sequence was applied to the whole sample.

The T1 image was first segmented into 133 regions using an automated multi-atlas segmentation method [31,32]. First, 28 best-matching atlases were selected from the original 79 manually segmented atlases (http://www.neuromorphometrics.com/), and the selected atlases were non-rigidly registered with the T1 image. The brain segmentation was generated from the 28 atlas segmentations using the Expectation-Maximization (EM) algorithm. Then, the T1 image was registered with the FLAIR image, and the segmentation result was propagated to the FLAIR image to provide spatial information for the segmentation of WM hyperintensities and to compute regional WM hyperintensity measures (See Fig 1).

(Fig 1 here)

The method for the segmentation of WM hyperintensities is based on the method presented in Wang et al. [33], and is presented in detail in Koikkalainen et al. [34]. The WM hyperintensities are segmented using the EM algorithm in a stepwise way:

(1) Segment WM in two classes from T1 image representing hypointense WM regions in T1 image and normal bright WM regions.
(2) Using the results of the previous step as an initialization, segment the FLAIR image to three classes: cerebrospinal fluid (CSF), normal brain tissue, and hyperintense voxels.
(3) Using the results of the previous step as an initialization, segment the WM and subcortical regions from the FLAIR image in two classes. The class with higher intensities was then regarded as the segmentation of WM hyperintensities.

Means and standard deviations of WM hyperintensity volumes in different brain areas and sample groups can be found in Table 4. The mean values in the patient groups were systematically higher than those of the controls, with the AD patients having the highest values. However, no statistically significant differences in WM hyperintensity volumes were found between the MCI group and AD group ($p > .05$), nor between the control group and the whole patient group (i.e. MCI+AD, $p > .05$), though the difference in the left parieto-occipital area was on the threshold of being significant ($p = .052$, $d = 0.424$).

(Table 4 here)

2.4. Statistical analysis

Several multiple linear regression analyses were conducted for testing the main research questions. For each regression model, age and level of education were entered as control variables in step 1. Following this, the measure for WMH in each anatomical region of interest was added as a dependent variable in step 2. One of the four cognitive composites (processing speed, verbal memory, visual memory, verbal functions) was set as the independent variable. Separate analyses were conducted for the eight anatomical regions of interest (left frontal, right frontal, left parieto-occipital, right parieto-occipital, left temporal, right temporal, bilateral frontal, bilateral parieto-occipital), and for each of the four cognitive composites.

Analyses including the whole sample (Controls, MCI & AD) were run first. For those regression models that achieved significance, further subgroup analyses were performed, i.e., the models were re-run separately for the controls group and the patient group (MCI+AD). Data analysis was done with the IBM SPSS statistics software v. 24.

3. RESULTS

Results of the analyses including the whole sample are presented in Tables 5-7. Age and education were controlled for in every analysis. Analyses involving the whole sample (Controls, MCI & AD) were performed first, here two main findings emerged:

(1) White matter hyperintensities in the left and right parieto-occipital areas, as well as in the left temporal lobe was associated with impairments in processing speed;
(2) White matter hyperintensities in the left parieto-occipital areas was associated with impaired performance in verbal memory.

Following this, further subgroup analysis was performed.

(1) Regression analyses concerning the areas that were significantly associated with processing speed impairments in the whole group (the left and right parieto-occipital areas, left temporal lobe) were run separately for the healthy control and patient subgroups. In these analysis, WMH in the left or right parieto-occipital areas, or the temporal lobe was not associated with processing speed in the healthy controls group. However, in the patient group a significant regression concerning left temporal WMH and impaired processing speed was found (Step 2: $F(3,40) = 5.451$, $p = .003$, $R^2 = .290$, $f^2 = .130$). In this case, the level of left temporal WMH was significantly associated with impaired processing speed for patients with MCI or AD ($\beta = -.316$, $p = .027$, 95 % CI [-.622, -.010]). No significant associations were found between left or right parieto-occipital WMH and processing speed for the patient group.

(2) Regression analyses concerning WMH in the left parieto-occipital area and verbal memory were run separately for the healthy control and patient group. Here, left parieto-occipital WMH was not significantly associated with verbal memory specifically in either of the subgroups.

(Tables 5-7 here)

4. DISCUSSION

Previously we have reported indications of a cumulative effect of AD pathology and WM pathology: Alzheimer's disease patients with prominent visually rated left frontal WMH had the most significant decreases in processing speed, notably larger than in patients with milder WMH [24]. This effect was not replicated in the current study (that utilized a portion of the same patient sample) using quantified MRI, as no significant associations between frontal WM and cognitive impairment were found. The most likely reason for differing findings is the decrease in sample size, which inevitably weakened the power to detect smaller effects. Furthermore, the MCI and AD group were pooled into one group, which eliminates the possibility to detect group-specific effects in MCI and AD patients. Additionally, there were slight differences between the excluded and included participants regarding age and cognition. Finally, as moving from categorical to continuous data requires the usage of different data analysis methods (i.e., from analysis of covariance to multiple regression), this change may have affected the results.

A replicated finding was the association between parieto-occipital WMH and impaired processing speed. This effect seems quite robust and is in line with previous studies that have reported similar associations [35]. A novel finding is the association between left parieto-occipital WMH and verbal memory. This finding is also consistent with previous studies, as the posterior parietal cortex (PPC) is often activated in memory retrieval tasks, and has several contributions to episodic memory by itself [36], and parietal lesions can cause impairments to attention during memory retrieval processes [37]. The PPC is connected to the middle temporal lobe by several WM tracts [36], the degradation of which has been correlated with impairments in episodic memory in cognitively healthy [38] and traumatic brain injury patients [39]. Similar associations regarding posterior WM lesions have also been reported for patients with schizophrenia [40] and MCI [41,42].

Previously we have examined only frontal and parietal structures, as the reliability of visually rated WM changes in the temporal lobe is considerably lower [43]. In the current study using quantified analysis, the temporal areas were included as well. Though it should be considered preliminary in nature, the data seems to point to a significant association between WMH in the left temporal lobe and processing speed specifically in the patient group, while no such effect was seen for the cognitively healthy group. To our knowledge these associations have not been reported before for MCI or AD patients, but they are in line with previous findings in stroke patients [44] and temporal

epilepsy patients [45]. The association is also consistent with previous literature regarding cumulative effects of WM pathology on cognitive functions in AD patients (for example: [20–24,46,47]). This finding most likely reflects the concomitant repercussions related to the accumulation of primary AD pathology and WM pathology. As AD is characterized by a number of neurodegenerative changes that gradually lead to global cognitive impairment, when concurrent major WM pathology develop, the cognitive impairments following from these two pathologies appear to be cumulative in some respects. The fact that we did not see the same association in the control group is somewhat surprising (see: [44,48]), but could be due to e.g. differences in group size, age of participants or magnitude of WMH.

A number of explanations can be formulated about these connections and overlap between the pathologies (18): (1) White matter pathology can represent an independent pathology of ischemic origin, adding its own contribution to the overall symptomology; (2) White matter pathology might have a heterogeneous etiology that can interact with or represent primary AD pathology; (3) Alzheimer's disease and WM pathology can be related through other factors, such as mutual risk factors. These scenarios are mutually non-exclusive, and there might be variation between individual cases, with some perhaps reflecting a mix of all three explanations. Some of the scenarios might be more relevant when discussing certain cerebral regions (see for example [49]).

Strengths of the present study include using several validated neuropsychological tests for cognitive measurements and utilizing quantified measures for MRI analysis, although it should be stated that higher resolution magnetic imaging have been utilized in a number of previous studies, (for example: [8,48,50](8,48,50)). Furthermore, the sample size is not ideal due to many participants being excluded. Other limitations include the cross-sectional design and most importantly an increased risk for family-wise errors. As several hierarchical regression models have been run, the risk for family-wise Type I (detecting a false positive) errors is heightened. At the same time, the utilization of e.g. Bonferroni adjustments would nullify any significant findings and increase the risk of Type II errors (detecting a false negative [51]). A further factor that argues for the importance of trying to avoid a Type II error is the small sample size that entails lower statistical power to detect smaller effects, which could increase the risk for Type II errors as well.

In conclusion, first, the linkages between WM pathology and cognitive processing speed that have been reported in previous studies, including our own, seem quite robust. These can be replicated in the current study for parieto-occipital areas. Second, the utilization of more accurate quantified MRI data has allowed us to include the temporal lobes into the analyses. Regarding this area, the data indicates preliminary associations between left temporal WMH and processing speed in patients with MCI or AD. However, due to the increased risk for family-wise errors, and small effect sizes, caution should be used before drawing clinical inferences from the results, especially those regarding the temporal lobe. Overall, it would be recommended to validate the results with larger samples in the future.

STATEMENTS

Statement of Ethics: The work has followed internationally accepted standards for research practice and reporting. Data collection was carried out in accordance with relevant guidelines and regulations and was approved by the Joint Ethical Committee of the University of Turku and Turku University City Hospital. Oral and written information about the study was given to the participants, who gave informed consent for participation.

Disclosure statement: Juha Koikkalainen and Jyrki Lötjönen are shareholders of Combinostics Ltd.

Author Contributions: All authors listed have made substantial and direct contributions to the work, have approved the final version of the work and agree to be accountable for all aspects of the work. More specifically, AK performed the statistical analyses and wrote the initial draft. PG and MK helped in data analysis, interpretation and manuscript drafting. JR organized the data collection, and together with MK and PG contributed to the conception of the study. TT and RP performed the original visual MR analyses, whereas JL and JK performed the quantitative MR imaging analyses. JR, TT, RP, JL and JK critically reviewed the manuscript.

Figure legends: Fig 1. *An overview of the segmentation process.*

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Table 1

Demographic and Clinical Characteristics of Study Participants

	All	Cognitively healthy	Patient group (MCI+AD)	MCI	AD
n	86	42	44	14	30
Women %	41.9 %	45.2 %	38.6 %	40 %	43.3 %
Age M (SD), years	71.76 (4.73)	71.52 (5.20)	71.00 (4.40)	71.64 (4.74)	72.16 (4.15)
Right-handed	79	38	41	13	28
Left-handed	3	1	2	1	1
Ambidextreous	4	3	1	0	1
Education level					
Primary school	43	20	23	6	17
Vocational school	32	15	17	5	12
Upper secondary	2	2	0	0	0
Academic degree	9	5	4	3	1

Note. MCI = Mild cognitive impairment, AD = Alzheimer's disease.

Table 2.

Neuropsychological composites, tests and cognitive domains

Composites/Domains	Tests
Processing speed	Trail Making Test A Digit Symbol Coding (WAIS-R)
Verbal-logical memory	Logical memory 1 (WMS-R) Logical memory 2 (WMS-R)
Visual-spatial memory	Visual reproduction 1 (WMS-R) Visual reproduction 2 (WMS-R)
Verbal functions	Similarities (WAIS-R) Naming (CERAD)

Table 3.

Neuropsychological Composite Score Performances in Whole Sample and Subgroups

Cognitive composite score	All	Cognitively healthy	Patient group (MCI+AD)	Group difference [1]	MCI	AD	Group difference [1]
Processing speed	0 (0,91)	0.33 (0.67)	-0.31 (1.00)	$p < .001$	-0.03 (0.85)	-0.44 (1.05)	$p > .05$
Verbal-logical memory	0 (0.98)	0.47 (0.76)	-0.45 (0.96)	$p < .001$	-0.08 (0.96)	-0.61 (0.93)	$p > .05$
Visual-spatial memory	0 (0.93)	0.29 (0.84)	-0.28 (0.95)	$p = .005$	-0.55 (0.89)	-0.38 (0.97)	$p > .05$
Verbal functions	0 (0.80)	0.21 (0.52)	-0.20 (0.97)	$p = .015$	0.14 (0.64)	-0.36 (1.06)	$p > .05$

Note. MCI = Mild cognitive impairment, AD = Alzheimer's disease. The composite variables were calculated by first converting individual test scores into z-scores by utilizing the means and standard deviations of the whole sample, after which the mean of the relevant individual tests for each domain was calculated. Means are reported first, followed by standard deviations in brackets.

[1] Student's T-test was used to study differences between groups.

Table 4.

White Matter Hyperintensity Volumes According to Anatomical Areas

Anatomical area	All	Cognitively healthy	Patient group (MCI+AD)	Group difference[1]	MCI	AD	Group difference[1]
Total WMH Burden[2]	6.87 (8.80)	5.29 (5.06)	8.39 (11.13)	$p > .05$	6.91 (9.02)	9.09 (12.07)	$p > .05$
Frontal Left WMH	1.45 (1.51)	1.18 (0.97)	1.71 (1.86)	$p > .05$	1.39 (1.54)	1.87 (2.00)	$p > .05$
Frontal Right WMH	1.72 (2.12)	1.39 (1.15)	2.04 (2.73)	$p > .05$	1.84 (2.36)	2.13 (2.92)	$p > .05$
Frontal Bilat. WMH	3.17 (3.57)	2.56 (1.99)	3.75 (4.55)	$p > .05$	3.23 (3.88)	4.00 (4.87)	$p > .05$
Temporal Left WMH	0.45 (0.75)	0.34 (0.58)	0.55 (0.88)	$p > .05$	0.45 (0.91)	0.59 (0.89)	$p > .05$
Temporal Right WMH	0.51 (0.88)	0.45 (0.71)	0.57 (1.03)	$p > .05$	0.43 (0.68)	0.64 (1.16)	$p > .05$
Temporal Bilat. WMH	0.96 (1.54)	0.79 (1.17)	1.12 (1.83)	$p > .05$	0.88 (1.56)	1.23 (1.96)	$p > .05$
Parieto-occipital Left WMH	1.26 (1.95)	0.85 (0.95)	1.65 (2.52)	$p > .05$	1.38 (2.25)	1.78 (2.66)	$p > .05$
Parieto-occipital Right WMH	1.49 (2.38)	1.09 (1.71)	1.87 (2.85)	$p > .05$	1.42 (2.14)	2.08 (3.14)	$p > .05$
Parieto-occipital Bilat. WMH	2.75 (4.22)	1.93 (2.43)	3.53 (5.32)	$p > .05$	2.80 (4.37)	3.87 (5.75)	$p > .05$

Note. MCI = Mild cognitive impairment, AD = Alzheimer's disease, Bilat = Bilateral, WMH = White Matter Hyperintensity. Means of segmented WMH volumes are reported, details can be found in section 2.3. of Method. WMH values are in millilitres.

[1] Student's T-test was used to study differences between groups.

[2] The summed value of WMH volumes in frontal, temporal and parieto-occipital areas.

Table 5.

Hierarchical Multiple Regression Analyses of Associations Between Frontal White Matter Hyperintensities and Cognitive Functions

	Processing speed				Verbal memory				Visual memory				Verbal functions			
	ΔR^2	f^2	β	95% CI	ΔR^2	f^2	β	95% CI	ΔR^2	f^2	β	95% CI	ΔR^2	f^2	β	95% CI
Step 1: Covariates	.131*	.151			.143*	.167			.064†	.068			.160*	.191		
Education			.231*	[.037, .425]			.375*	[.167, .583]			.162	[-.050, .370]			.387***	[.218, .556]
Age			-.290*	[-.033, -.025]			-.073	[-.011, -.030]			-.204†	[-.062, .208]			-.124	[-.160, -.090]
Step 2: Frontal left	.015	.018			.006	.007			.026	.029			.028	.034		
WMH volume			-.126	[-.250, .000]			-.118	[-.250, .011]			-.160	[-.290, -.030]			-.135	[-.240, -.030]
Step 2: Frontal right	.014	.016			.031†	.038			.031	.034			.017	.021		
WMH volume			-.120	[-.210, -.030]			-.174†	[-.260, -.080]			-.176†	[-.270, -.090]			-.129	[-.200, -.050]
Step 2: Frontal bilat. WMH volume	.014	.016			.024	.029			.030	.033			.018	.022		
			-.125	[-.018, -.070]			-.154	[-.210, -.100]			-.173	[-.230, -.120]			-.134	[-.180, .090]

Note. WMH = White Matter Hyperintensity, Bilat = Bilateral, CI = Confidence interval. Confidence intervals have been calculated on standardized coefficients (β). Separate models were run for each ROI and cognitive variable. In every model education and age were first entered as control variables in step 1, and then WHM volumes were added to the model in step 2.

† *p* < .10. * *p* < .05. *** *p* < .001.

Table 6.

Hierarchical Multiple Regression Analyses of Associations Between Temporal White Matter Hyperintensities and Cognitive Functions

	Processing speed				Verbal memory				Visual memory				Verbal functions			
	ΔR^2	f^2	β	95% CI	ΔR^2	f^2	β	95% CI	ΔR^2	f^2	β	95% CI	ΔR^2	f^2	β	95% CI
Step 1: Covariates	.131*	.151			.143*	.167			.064†	.068			.160*	.191		
Education			.231*	[.037, .425]			.375*	[.167, .583]			.162	[-.050, .370]			.387***	[.218, .556]
Age			-.290*	[-.329, -.251]			-.073	[-.011, -.030]			-.204†	[-.062, .208]			-.124	[-.160, -.090]
Step 2: Temporal left	.049*	.059			.004	.005			.022	.024			.006	.007		
WMH volume			-.228*	[-.471, -.015]			-.062	[-.327, .203]			-.150	[-.413, .113]			-.075	[-.291, .141]
Step 2: Temporal right WMH volume	.018	.021			.004	.005			.005	.005			.004	.005		
			-.134	[-.340, .072]			-.058	[-.280, .164]			-.070	[-.292, .152]			-.064	[-.244, .116]
Step 2: Temporal bilat. WMH volume	.034†	.041			.004	.005			.013†	.014			.015	.018		
			-.187†	[-.305, .069]			-.064	[-.191, .063]			-.112	[-.239, .015]			-.073	[-.177, .031]

Note. WMH = White Matter Hyperintensity, Bilat = Bilateral, CI = Confidence interval. Confidence intervals have been calculated on standardized coefficients (β).

Separate models were run for each ROI and cognitive variable. In every model education and age were first entered as control variables in step 1, and then WHM volumes were added to the model in step 2.

† *p* < .10. * *p* < .05. *** *p* < .001.

Table 7.

Hierarchical Multiple Regression Analyses of Associations Between Parieto-Occipital White Matter Hyperintensities and Cognitive Functions

	Processing speed				Verbal memory				Visual memory				Verbal functions			
	ΔR^2	f^2	β	95% CI	ΔR^2	f^2	β	95% CI	ΔR^2	f^2	β	95% CI	ΔR^2	f^2	β	95% CI
Step 1: Covariates	.131*	.151			.143*	.167			.064†	.068			.160*	.191		
Education			.231*	[.037, .425]			.375*	[.167, .583]			.162	[-.050, .370]			.387*	[.218, .556]
Age			-.290*	[-.329, -.251]			-.073	[-.011, -.030]			-.204†	[-.062, .208]			-.124	[-.160, -.090]
Step 2: ParOcc left	**.045***	.055			**.042***	.052			.027	.030			.017	.021		
WMH volume			-.216*	[-.308, -.124]			-.207*	[-.305, -.109]			-.164	[-.263, -.064]			-.130	[-.212, -.048]
Step 2: ParOcc right	**.040***	.048			.034	.041			.008	.009			.024	.029		
WMH volume			-.201*	[-.277, -.125]			-.154	[-.234, -.073]			-.086	[-.168, -.004]			-.153	[-.220, -.086]
Step 2: ParOcc bilat	**.044***	.053			.033†	.040			.015	.016			.022	.029		
WMH volume			-.213*	[-.256, -.170]			-.182†	[-.227, -.137]			-.124	[-.171, .077]			-.147	[-.184, -.110]

Note. WMH = White Matter Hyperintensity, Bilat = Bilateral, CI = Confidence interval. Confidence intervals have been calculated on standardized coefficients (β).

Separate models were run for each ROI and cognitive variable. In every model education and age were first entered as control variables in step 1, and then WHM volumes were added to the model in step 2.

† $p < .10$. * $p < .05$. *** $p < .001$.