White matter hyperintensities and within-person variability in community-dwelling adults aged 60 to 64 years

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Abstract

Estimates of white matter hyperintensities (WMH) derived from T2-weighted MRI were investigated in relation to cognitive performance in 469 healthy community-dwelling adults aged 60 to 64 years. Frontal lobe WMH but not WMH from other brain regions (temporal, parietal, and occipital lobes, anterior and posterior horn, periventricular body) were associated with elevated within-person reaction time (RT) variability (trial to trial fluctuations in RT performance) but not performance on several other cognitive tasks including psychomotor speed, memory, and global cognition. The findings are consistent with the view that elevated within-person variability is related to neurobiological disturbance, and that attentional mechanisms supported by the frontal cortex play a key role in this type of variability.

Key words: White matter hyperintensities; MRI; cognitive function; Within-person variability; Intraindividual variability.

Within-person cognitive variability refers to within-session, or session-to-session, variability in cognitive performance. Here, we focus on the trial-to-trial response variability of reaction times (RT) as the measure has recently received considerable research interest due to its potential as a neuropsychological diagnostic and assessment tool in clinical contexts, and possible ability to provide valuable theoretical insights into cognitive processes in aging and clinical populations. A major reason for this research interest is the suggestion that increased within-person variability reflects neurobiological disturbance leading to some compromise of central nervous system integrity (Hendrickson, 1982; Hultsch & MacDonald, 2004; Li & Lindenberger, 1999). Consistent with this possibility, behavioral studies show within-person variability to be greater with older age (e.g., Anstey, 1999; Bunce, MacDonald & Hultsch, 2004; Hultsch, MacDonald, & Dixon, 2002; MacDonald, Hultsch, & Bunce, 2006; Nessleroade & Salthouse, 2004; West, Murphy, Armilio, Craik, & Stuss, 2002; Wegesin & Stern, 2004), mild cognitive impairment or mild dementia (Christensen, Dear, Anstey, Parslow, Sachdev, & Jorm, 2005; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Knotek, Bayles, & Kaszniak, 1990), traumatic brain injury (e.g., Bleiberg, Garmoe, Halpern, Reeves, & Nadler, 1997; Stuss, Murphy, Binns, & Alexander, 2003; Stuss, Pogue, Buckle, & Bondar, 1994), Parkinson's disease (Burton, Strauss, Hultsch, Moll, & Hunter, 2006), and epilepsy (Bruhn & Parsons, 1977). Moreover, these effects have been found in several cognitive domains including psychomotor performance (e.g., Anstey, 1999; Bunce et al., 2004), executive function (e.g., West et al., 2002), sustained attention (MacDonald et al., 2006), and memory (e.g., Hultsch et al., 2000). Although this research provides considerable support for the suggestion that within-person variability reflects neurobiological integrity, a major limitation is that virtually all of the evidence is behavioral. Two our knowledge, only two brain-imaging studies have investigated within-person variability. The first (Bellgrove, Hester, & Garavan, 2004), found a significant association between within-person variability in a go/no-go response paradigm and task-related frontal activations as measured by functional magnetic resonance imaging (MRI). This study, however, was conducted in young persons only. The second study, from the present group (Anstey, Mack, Christensen et al., in press), found that intraindividual variability was associated with corpus collosum size in individuals with mild cognitive disorders, but not in a normative sample.

It is this paucity of research that motivates the present study. Specifically, we investigate the association between white matter hyperintensities (WMH) and within-person variability in a psychomotor task among healthy community-dwelling adults aged 60 to 64 years. WMH

refer to the white matter lesions that manifest as high signal intensities on T2-weighted MRI. White matter is of particular interest here as the nerve structures therein consist mainly of myelinated axons that form connective pathways to and from the brain, and also between different brain structures. The myelin around the axons provides an insulating sheath that increases the speed and efficiency of conduction (Kivipelto, Soininen, & Tuomilehto, 2002). Therefore, damage to these structures, as indicated by the presence of WMHs, is likely to affect the efficiency of information transfer within, and to and from, the brain. As the level of WMH increases, subtle changes in cognitive function are likely to occur, such as slowed RTs and greater within-person variability. Within the context of cognitive aging, this is of interest as it is suggested that the neurobiological basis for age-related slowing and associated higher-order cognitive deficits, is the degeneration of neural pathways and synaptic connectivity with increasing age (e.g., Salthouse, 1992). An important question is how far such degeneration reflects healthy aging, and how much is pathological.

There have been several studies investigating WMH and cognitive function, and a meta-analysis of this work (Gunning-Dixon & Raz, 2000) suggests negative associations between WMH and processing speed, immediate and delayed recall, executive function, and global cognition. Additionally, a recent review (Christensen, Anstey, Leach, & Mackinnon, in press) did not identify strong associations between WMH and verbal and performance IQ. Although this body of work provides valuable insights into WMH-cognition relations, most studies that investigated information processing rate, examined mean differences in processing speed rather than measures of intraindividual differences in processing speed.

To address this gap in the literature, we investigated WMH in relation to within-person variability and information processing speed in two psychomotor tasks, simple-RT and choice-RT. We also considered performance on several higher-order cognitive tasks tapping working and episodic memory, vocabulary, and global cognition. As it is important to establish if associations vary according to brain region, our analyses also take into account several major brain structures (frontal, temporal, parietal and occipital lobes). This is of particular interest as although processing speed is likely to be affected by white matter lesions throughout the brain, theoretical accounts of within-person variability propose that fluctuations in executive control (Bunce et al., 2004; West et al., 2002), or relatedly, attentional lapses (Bunce, Warr, & Cochrane, 1993), may underlie increasing variability in older persons. Although this latter position has been questioned (Salthouse, 1993), functional brain imaging work implicates the frontal cortex in executive control (see Cabezza & Nyberg,

2000), and the functional MRI work (Bellgrove et al., 2004) and neuropsychological work in traumatic brain injured patients (Stuss at al., 2003) cited earlier suggests an association between frontal structures and intraindividual variability. Together, this work leads to the expectation that WMH in frontal regions in particular will be associated with elevated within-person variability.

In this paper, we build upon earlier work in this population that identified associations between WMH and motor function (Sachdev, Wen, Christensen, & Jorm, 2005). We also consider the periventricular region (anterior and posterior horns, and periventricular body) as earlier work (Wen & Sachdev, 2004) indicates this area to be particularly prone to WMH. As the periventricular region is susceptible to ischemia due to reduced blood flow arising from cardiovascular diseases such as arteriosclerosis (Spangler, Challa, Moody, & Bell, 1994), valuable insights may result as to the mechanisms by which cardiovascular disease may affect cognitive function in the elderly.

METHOD

Participants

Participants were sampled randomly from the electoral rolls for Canberra, ACT, and Queanbeyan, NSW, Australia, as part of the PATH Through Life Project which involves approximately 2500 persons in each of three age groups, 20-24, 40-44, and 60-64 years (for further details, see Anstey, Dear, Christensen, & Jorm, 2005). They were asked to complete a questionnaire under the supervision of a professional interviewer. In addition to the cognitive measures described below, data relating to mental health and lifestyle were also collected. Some basic physical tests were also carried out (e.g., blood pressure, grip strength, visual acuity) and the participants were asked to provide a cheek swab from which DNA could be extracted. In the 60-64 years old age group, 622 participants were randomly selected and invited to undergo brain MRI scanning, with 478 agreeing to the MRI scan. For the present study, one participant was removed due to an MRI data logging problem, and a further eight persons eliminated following screening for mild cognitive impairment. The resulting sample of 469 individuals had a mean age of 62.61 years (SD = 1.41), was 48 percent female, and reported a mean of 14.15 years (SD = 2.54) of education.

<u>Health and physical variables</u>

Self-reported health histories were recorded, and included details of heart and blood pressure problems, stroke, and diabetes (coded 1 = Yes, 2 = No). Grip Strength was taken using the Smedley hand dynamometer (Model No PE7, Stoelting Co., Wood Dale, Illinois), which measures the force exerted in kilograms. The average of two trials from the dominant hand was the measure used here. Corrected Visual Acuity was measured using a 3 m Snellen Chart that contained seven lines that subtend 1 min of arc at distances of 60, 36, 24, 16, 9, 6 and 5 m. A participant's score was the total number of letters readable, and scores ranged from 0 to 28. Depressive symptoms in the past month were assessed by the Goldberg depression scale (Goldberg, Bridges, Duncan-Jones & Grayson, 1988), which give scores of 0 to 9 for number of symptoms of depression.

<u>Psychomotor tasks</u>

<u>RT Mean level</u>: RT was tested using a small box held with both hands, with left and right buttons at the top to be depressed by the index fingers. The front of the box had three lights: two red stimulus lights under the left and right buttons respectively and a green get-ready light in the middle beneath these. There were four blocks of 20 trials measuring simple reaction time (SRT), followed by two blocks of 20 trials measuring choice reaction time (CRT). For SRT everyone used their right hand regardless of dominance. The interval between the 'get-ready' light and the first light of the trial was 2.3 secs for both SRT and CRT.

Means were calculated after removing outliers. This was done by firstly eliminating any values over 6000 ms. Next, means and standard deviations were calculated for each individual for each block and values were eliminated which lay outside three standard deviations for each individual. A number of very slow individuals still retained RT scores greater than 1000 ms. In a final step, these values were dropped before the final means per block were calculated for each participant. Here we present the grand mean across blocks for the respective tasks.

<u>Calculation of RT within-person variability</u>: Following procedures reported elsewhere (Anstey et al., 2005; Christensen et al., 2005), mean absolute residuals (in ms) (MAR) were calculated for each individual by averaging the deviations from regression models of RT against trial number and block number in each of the simple and choice RT series (Blocks 1-4 inclusive were simple RT and blocks 5-6 were choice RT blocks). A quadratic function of trial number was used because the decline in RT with practice is not linear. Block number

was treated as categorical. These models were designed to remove both intra-block practice effects and the effect of the short rest periods between blocks, leaving residuals that measure only random variation. In contrast, simply using each person's standard deviation of RT would inflate the apparent variability for participants who showed substantial improvement over the course of their trials.

As expected, the between-subject variance of absolute residuals for the sample was found to increase as participants' mean reaction time increased, reflecting an association between within-person variability and reaction time. Therefore, a measure of within-person variability that was independent of mean RT was computed. Graphical explorations revealed that the log of MAR decreases approximately linearly with the reciprocal of RT (i.e., with reaction speed). Therefore, the strength of the associations between the mean absolute residuals (MAR) and RT was estimated through a regression of log(MAR) against speed. The linear slope of this function was calculated for simple ($b = -0.55$) and choice times ($b = -0.35$) using the 40 choice RTs and 80 simple RTs. The slopes b indicates the degree of association between log MAR and speed. To adjust for speed, deviations from the line of best fit were calculated using the formula $\log \text{MIV} = \log \text{MAR} - b(1/\text{mean RT})$, where MIV is the individual mean independent variability (i.e., the mean absolute residual adjusted for speed). Two scores of intra-individual variability adjusted for speed were computed for each individual. These were the individual mean-independent variation for simple reaction times (MIVS) and the mean-independent variation for choice reaction times (MIVC). For example, for the simple reaction times the corrected variation was given by:

$$\text{MIVS} = \text{MAR}.\exp\{0.55/\text{MeanRT}\}$$

Here, 'MeanRT' is an individual's mean reaction time in seconds, and the coefficient '0.55' is the regression slope described above (the regression intercept is ignored). The effect of this is that the variance is adjusted upwards more in participants with fast reaction times, to achieve a measure of variation independent of speed. Scatterplots of MIV against mean RT confirmed that these two measures are approximately uncorrelated, so that by using MIV the association of WMH with RT variability can be assessed independently of any association of WMH with mean RT.

Other cognitive measures

A brief battery of cognitive tests including RT was administered to participants within 6 months of the MRI scan). This included the Mini-Mental State Examination (Folstein,

Robins, & Helzer, 1983), the Symbol Digit Modalities Test (Smith, 1982), a test of immediate and delayed recall (the first trial of the California Verbal Learning Test and a Delayed Recall Trial: Delis, Kramer, Kaplan, & Ober, 1987), and a test of word knowledge (Spot-the-Word: Baddeley, Emslie, & Nimmo-Smith, 1992).

MRI Procedure

Imaging was conducted with a 1.5 Tesla Gyroscan (ACS-NT, Philips Medical Systems, Best, Netherlands) for T1-weighted 3D structural and T2-weighted FLAIR sequence MRI. A 2D scout mid-sagittal cut for AC-PC plane alignment was first acquired. Then 3D structural MRI was acquired in coronal orientation using a T1-weighted FFE sequence (TR/TE/NEX = 28.05/2.64/2; flip angle = 30°; matrix size = 256 × 256; FOV = 260 × 260 mm; slice thickness = 2.0 mm, inter-slice distance = 1.0 mm), yielding over-contiguous coronal slices with an in-plane spatial resolution of 1.016 × 1.016 mm/pixel. The FLAIR sequence was acquired in coronal orientation (TR/TE/TI/NEX = 11000/140/2600/2; matrix size = 256 × 256; FOV= 230 × 230 mm; slice thickness = 4.0 mm with no gap between slices) with in-plane spatial resolution of 0.898 × 0.898 mm/pixel. The total time of each subject's scanning session was approximately 20 minutes. MRI scans were transferred to an independent Windows NT workstation and analyzed using the software packages ANALYZE (Mayo Foundation, Rochester MI, USA) and SPM99 (Cognitive Neurology Group, National Hospital for Nervous Diseases, London, UK).

Quantification of White Matter Hyperintensities

WMHs were identified on FLAIR sequences and co-registered with a T1 image of the same subject. They were normalized spatially in Talairach space so that WMH could be identified and then localized. Falsely classified WMH were identified through visual inspection of WMH maps and removed. Using a standard atlas (Duvernoy, 1999), we traced anatomical regions (deep white matter - frontal, parietal, temporal and occipital; periventricular white matter - anterior cap, posterior cap and periventricular body) on the standard single brain included in SPM99 software. Using these brain region of interest masks, the WMH volumes, number, location and size were calculated automatically by implementing FSL (Image Analysis Group, FMRIB, Oxford University, UK: http://www.fmrib.ox.ac.uk/fsl/) in the script language PERL. Since both linear and nonlinear transforms were applied onto each individual MRI, the WMH thus measured did not equate exactly to absolute volume. The relative value, or "density" (ratio of WMH against white

matter, expressed as a percentage), of the WMH of each individual was used. Here, abnormal signal intensities greater than 6 SDs above the mean white matter intensity were classified as WMH. The details of the method, which has excellent reliability and good validity, are described elsewhere (Wen & Sachdev, 2004).

<u>Missing data</u>

For missing data on a minority of variables, values were imputed with the EM algorithm in SPSS using all of the variables in the present study (see Shafer & Graham, 2002). Missing data frequencies before imputation were less than 2% for most variables, and less than 5% for all variables except for age (5.2%), years' education, and visual acuity (both 5.7%).

RESULTS

Descriptive data and bivariate correlations between WMH and the other major variables in this study, are presented in Table 1. The percentages in the extreme left column (beside the variable name) indicate the proportion of participants who exhibited WMH in that brain region, with ranges from approximately 50 percent of the sample for frontal and temporal lobes, to 100 percent for parietal and occipital lobes, and anterior horn. (For more detailed information of the distribution of WMH by brain region in this sample, see Wen and Sachdev, 2004.) As immediate and delayed recall measures were highly intercorrelated (.82, P<.001), and findings did not vary for the two variables, in the interest of space, the mean of the two measures is reported in statistics below.

Consideration of the bivariate correlations reveals several noteworthy associations between WMH and cognitive performance. First, no statistically reliable associations were found between WMH and the higher-order cognitive variables (recall, MMSE, digit backwards, and Spot the word), or the simple psychomotor task. Importantly though, both of the within-person variability measures for the choice-RT task (MARC, MIVC) correlated significantly with frontal WMH, but not with WMH in other brain regions. Also, posterior horn and periventricular body WMHs were significantly associated with slower mean responding in the choice-RT task.

Tables 1 and 2 about here

These associations were explored further in a series of hierarchical multiple regressions that examined linear and quadratic terms (the quadratic term estimates how far a curvilinear

relationship exists between independent and dependent variables). In these analyses, we adjusted for several potential confounding variables. As gender and years' education were found to correlate significantly with several of the cognitive variables (female gender and more years' education were associated with higher performance), those variables were entered into each model. In addition, as an association between depression and WMH was found in an earlier study in this population (Jorm, Anstey, Christensen et al., 2005), depression was taken into account in the analyses. In order to minimize the possibility of Type I errors, alpha was set at .01 in these analyses.

In the interest of space, only significant statistics from the regression analyses relating to WMH are presented in Table 2. After adjusting for gender, education, and depression, only frontal and posterior horn WMH selectively predicted cognitive performance. Consistent with bivariate analyses, WMH was not associated with performance on any of the higher-order cognitive tasks. However, it is important to note that of the four lobes (frontal, temporal, parietal, occipital), only frontal WMH was significantly associated with within-person variability on both measures, but not slowing in the choice RT task. Indeed, the significant quadratic term for MIVC (that term for MARC approached significance, p = .011) suggests that the greater the severity of frontal WMH, the greater the degree of within-person variability. This curvilinear trend is demonstrated in Figure 1. All other associations involving the four lobes were statistically unreliable.

Figure 1 about here

The other significant association evident in Table 2 is that between posterior horn WMH and mean choice responding; slower responding was associated with greater white matter lesioning. As this brain region is particularly prone to ischemia due to cardiovascular disease, we repeated the regressions adjusting for cardiovascular risk factors (hypertension, heart disease, stroke, diabetes). This made no difference to the original results.

Finally, in order to eliminate the possibility that perceptual and motor processes were responsible for the findings relating to within-person variability in the choice RT task, we controlled for visual acuity to assess perceptual processes, and grip strength to control for motor functioning. Again, taking these variables into account made little difference to our initial findings.

DISCUSSION

Although there have been numerous studies showing increased within-person variability in aging and clinical populations using behavioral measures, this is the first study to demonstrate an association between within-person variability in RT performance and WMH in a large community-based sample of older adults. A highly reliable automated procedure (Wen & Sachdev, 2004) was used to estimate lesioning in specific brain areas (frontal, temporal, parietal and occipital lobes, anterior and posterior horns, and periventricular body), thereby avoiding the need for the quantification of lesions through rating scales. The findings extend our earlier work demonstrating associations between WMH and motor functioning (Sachdev et al., 2005), and identify an important dissociation. Specifically, WMHs in the frontal cortex were significantly associated with greater variability, but not slowing of information processing or performance on several other higher-order cognitive tasks. Moreover, with one exception, WMH in other brain regions failed to predict either variability or performance on any of the other cognitive tasks. The exception was the association between posterior horn WMH and choice-RT suggesting greater lesioning in this brain region was associated with slower responding. These findings were evident after having adjusted for gender, years of education, depression, and perceptual and motor functions, and remained when cerebrovascular disease history had been taken into account.

The results are important theoretically as they build upon functional MRI (Bellgrove et al., 2004) and neuropsychological work (Stuss et al., 2003), and clearly suggest that deterioration of neural pathways in the frontal cortex make a major contribution to the increased RT variability commonly observed in older adults as well as clinical groups. Moreover, the findings are consistent with the view that increased within-person variability reflects frontally moderated attentional lapses or relatedly, fluctuations in executive function (Bunce et al., 1993, 2004; West et al., 2002). This possibility is further supported by the absence of significant associations between WMH in other brain regions and within-person variability.

We also found that WMHs in the periventricular body, and particularly the posterior horn, were strongly associated with slowing. As lesioning in this brain region is a likely consequence of restricted blood flow stemming from cerebrovascular disease (Spangler et al., 1994), this finding suggests a possible mechanism by which cerebrovascular disease may influence speeded mental processing. Although this interpretation is plausible, contrary to

expectations, adjusting statistically for cerebrovascular disease history did not attenuate this association. Therefore, this finding should be treated with caution.

The results provide intriguing insights into the possible neurobiological mechanisms underlying within-person variability. Although there are other contributing factors, as WMH largely reflect lesioning to the myelinated axons that form connective pathways in the brain, the findings suggest that one of the major contributors to increased variability is damage to these pathways, particularly in the frontal cortex. This is consistent with the view that increased variability is one of the behavioral manifestations of neurobiological disturbance and central nervous system integrity (Hendrickson, 1982; Hultsch & MacDonald, 2004; Li & Lindenberger, 1999). However, it is unlikely that damage to white matter structures alone is the factor responsible for increased within-person variability. Indeed, neural network models (e.g., Li, Aggen, Nesselroade, & Baltes, 2001) implicate the neurotransmitter dopamine in variability of cognitive performance, and there is work suggesting the cholinergic neurotransmitter system is associated with the efficiency of inhibitory control (Edgington & Rusted, 2003). As increased variability and attentional lapses may be associated with impaired inhibitory control (Bunce et al., 1993), it is plausible that the cholinergic system also influences within-person variability. Together, it is likely that a combination of factors, including disruption to the dopaminergic and cholinergic neurotransmitter systems, and the presence of WMH, contribute to increased variability. The implications of the present research are twofold. First, the degree of white matter lesioning in the frontal cortex in particular is associated with within-person variability. Second, that neurobiological disturbance is characterized by more erratic responding that is captured by measures of within-person variability, but not mean RT.

There are some limitations in the present research that we should acknowledge. First, the data were cross-sectional, and therefore we are unable to make inferences as to causality. Additionally, although all of the participants in this study were screened for dementia, and MCI cases removed, it is possible that those persons exhibiting increased variability and greater frontal WMH, were in the preclinical phase of an, as yet, undiagnosed neurological condition. Planned investigation of this population in the future will shed light on how far our findings were related to incipient neurological disorders. Third, although not a limitation, it is worth commenting on the possibility that the paucity of significant associations between WMH and cognitive variables generally, may have been related to the relatively young age of the present sample (60 to 64 years). It is possible that the degree of white matter lesioning in

this age group was not such that it impacted on cognitive function. Relatedly, our definition of WMH (>6 SDs above the mean white matter intensity) may only include more intense hyperintense signals. Mild changes in signal (seen as fuzziness) were excluded, as it is not customary to include this as WMH in visual inspection procedures. Therefore, the estimation of pathology was possibly conservative. This may also have contributed to the relatively small effect sizes. A final possibility is that the cognitive measures themselves were not sensitive to white matter lesioning at levels in the present study. Future investigation of this population will help provide insights into these issues. However, the present findings clearly suggest that measures of within-person variability relative to other cognitive measures may provide particularly useful measures for the early identification of neurobiological disturbance. It is important that further work replicates and confirms these findings.

To conclude, this study suggests that damage to the neural pathways of the frontal cortex is strongly associated with increased within-person variability in adults aged 60 to 64 years. It is of note that associations between WMH and other cognitive variables were virtually absent. Although at present it is unclear as to whether persons with greater frontal WMH and intraindividual variability were in the preclinical phase of a neurological disorder, the findings suggest that measures of within-person variability may provide particularly sensitive diagnostic tools in clinical contexts for the identification of individuals suffering neurobiological disturbance and decline. This possibility is particularly exciting given the relatively young age of our sample, as it highlights the potential of these measures for early identification of persons requiring clinical intervention. It is our intention to explore this potential in future assessments of this community-based sample.

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White matter hyperintensities and variability

Table 1. Means, standard deviations, and bivariate correlations between WMH and other study variables

	M	SD	Age (yrs)	Gend	Educ (yrs)	Recall	MMSE	Digit back	Spot word	MARS	MARC	SRT (s)	CRT (s)	MIVS	MIVC
M	-	-	62.61	-	14.15	7.04	29.37	5.02	52.37	.038	.050	.249	.317	.258	.154
SD	-	-	1.42	-	2.54	2.06	1.00	2.13	5.78	.019	.014	.046	.040	.077	.039
Frontal (54.8%)	.107	.414	-.02	.07	-.05	-.01	.03	.01	-.02	.03	.16**	-.01	.08	.05	.14*
Temporal (48.8%)	.022	.056	-.08	-.08	-.04	.06	.08	.01	-.06	.06	.02	.00	.03	.08	.00
Parietal (100.0%)	.072	.223	-.03	-.03	-.05	-.03	-.02	-.03	-.02	.06	.07	.02	.07	.06	.05
Occipital (100.0%)	.115	.204	.12*	.03	.03	.01	-.03	.01	-.02	.09	.06	.04	.04	.08	.04
Ant horn (100.0%)	2.063	2.515	-.05	.11	-.09	.01	.07	-.03	-.04	-.01	.01	.02	.08	-.05	-.02
Post horn (78.5%)	.346	.745	-.06	.11	-.05	-.01	-.02	.04	-.05	.07	.05	.01	.16**	.06	-.01
Peri body (98.1%)	1.590	1.658	-.02	.14*	-.12*	-.01	.04	-.06	-.06	.03	-.01	.06	.12*	-.04	-.06

Notes
* p<.01; ** p<.001

Percentages adjacent to WMH variables represent percentage of sample that exhibited WMH in this brain region. All correlations computed on N = 469.
Gender: 1 = male, 2 = female
Gend = Gender; Educ = Years' education; MMSE = Mini Mental State Examination; MARS = Mean absolute residuals of the Simple-RT task; MARC = Mean absolute residuals of the Choice-RT task; SRT = Simple RT; CRT = Choice RT; MIVS = Mean independent variability of Simple-RT task; MIVC = Mean independent variability of Choice-RT task; Ant Horn = Anterior horn; Post Horn = Posterior horn; Peri Body = Periventricular body

Table 2. Polynomial regression analyses: Cognitive variable regressed on white matter hyperintensities

Predictor	Recall		MMSE		Backward Digit Span		Spot the Word		MARS		MARC		SRT		CRT		MIVS		MIVC	
	B	Beta	B	Beta	B	Beta	B	Beta	B	Beta	B	Beta	B	Beta	B	Beta	B	Beta	B	Beta
Frontal Lin[1]	-.01	.00	.10	.04	.19	.04	-.04	.00	.00	.02	.01	.15*	.00	-.02	.01	.08	.01	.04	.01	.13*
Quad[2]	.07	.07	-.06	-.12	.05	.05	-.50	-.16	.00	.02	.00	.26	.00	.02	.00	.00	.00	.06	.01	.29*
Post horn Lin[1]	-.07	-.03	-.02	-.02	.18	.06	-.25	-.03	.00	.06	.00	.05	.00	-.01	.01	.15*	.01	.07	.00	-.01
Quad[2]	.06	.08	.02	.06	.00	.01	.35	.18	.00	.04	.00	.20	.00	.10	.00	.28	.00	.02	.00	.17

Notes

*p<.01
1. df = 1, 464; 2. df = 1, 463; Adjusted for depression, gender, and years' education
Post horn = Posterior horn
MMSE = Mini Mental State Examination; MARS = Mean absolute residuals of the Simple-RT task; MARC = Mean absolute residuals of the Choice-RT task;
SRT = Simple RT; CRT = Choice RT; MIVS = Mean independent variability of Simple-RT task; MIVC = Mean independent variability of Choice-RT task

Figure caption

Figure 1. Choice RT variability (MIVC) as a function of white matter hyperintensity (WMH)