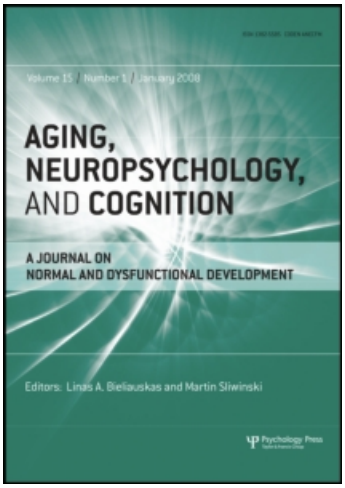

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White Matter Hyperintensities and Working Memory: An Explorative Study

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White Matter Hyperintensities and Working Memory: An Explorative Study

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ABSTRACT

White matter hyperintensities (WMH) are commonly observed in elderly people and may have the most profound effect on executive functions, including working memory. Surprisingly, the Digit Span backward, a frequently employed working memory task, reveals no association with WMH. In the present study, it was investigated whether more detailed analyses of WMH variables and study sample selection are important when establishing a possible relationship between the Digit Span backward and WMH. To accomplish this, the Digit Span backward and additional working memory tests, WMH subscores, and cardiovascular risk factors were examined. The results revealed that performance on the Digit Span backward test is unrelated to WMH, whereas a relationship between other working memory tests and WMH was confirmed. Furthermore, a division between several white matter regions seems important; hyperintensities in the frontal deep white matter regions were the strongest predictor of working memory performance.

Keywords: Working memory; White matter; Aging; Executive functions; Cardiovascular risk factors.

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INTRODUCTION

Changes in brain structures are characteristic for aging, and include lesions in the white matter (De Leeuw et al., 2001). As white matter lesions are observed as hyperintensities on T2 and fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) they are often referred to as white matter hyperintensities (WMH). The white matter forms the cortico-cortical and cortico-subcortical connections and is important for functioning of the prefrontal cortex (PFC), a brain area that contains extensive connections with both cortical and subcortical areas (Pandya & Yeterian, 1996). This functional connectivity of the PFC implies a central role for the PFC in the integration of various cognitive functions, which is necessary for executive function (Royall et al., 2002). As WMH reduce the functional connectivity of the PFC with other (sub-)cortical regions, they have been found to induce deficits in executive function (O'Brien et al., 2002; O'Sullivan et al., 2001).

Working memory is considered one of the executive functions that is related to PFC functioning (Funahashi, 2006). A specific frontal involvement in working memory performance has furthermore been suggested by both functional neuroimaging (Narayanan et al., 2005; Wager & Smith, 2003) and lesion studies (Bor, Duncan, Lee, Parr, & Owen, 2006; Ferreira et al., 1998). However, previous studies examining the association between WMH and working memory performance report varying results. One of the most frequently encountered tests of working memory includes the Digit Span backward test, which surprisingly appears unaffected by WMH (e.g., Oosterman, Sergeant, Weinstein, & Scherder, 2004; Sachdev, Wen, Christensen, & Jorm, 2005; Schmidt et al., 1993; Skoog, Berg, Johansson, Palmertz, & Andraesson, 1996; Ylikoski et al., 1993). Other tests of working memory, such as the Letter–Number sequencing test, do reveal associations with WMH (Deary et al., 2006; Nordahl et al., 2006). Whether this indicates that specifically Digit Span backward performance is unrelated to WMH remains unspecified. Several explanations for this observation can be optioned.

First of all, Digit Span backward performance might be unrelated to WMH.

Secondly, it could be argued that examining more detailed WMH data might reveal some associated Digit Span backward impairment. Most studies to date have either focused on total WMH score or made a division between periventricular (PVH) and deep white matter hyperintensities (DWMH). We argue that a further differentiation within the PVH and DWMH regions, such as frontal and parietal DWMH, might be useful in detecting a relationship with Digit Span backward performance. Conform a previous study in which WMH in specifically the dorsal PFC was found to relate to working memory functioning (Nordahl et al., 2006), we propose that the frontal white matter might be most important for working memory.

Finally, subject selection might affect outcomes. Several studies selected participants with cardiovascular risk factors, risks that are known to relate to cognitive performance and WMH. For example, hypertension, diabetes, and atrial fibrillation have all been related to executive dysfunctioning (Kilander et al., 1998; Kuo et al., 2005). The Framingham Stroke Risk Profile (D'Agostino, Wolf, Belanger, & Kannel, 1994; Wolf, D'Agostino, Belanger, & Kannel, 1991) is composed of many of these risk factors. With this profile score, a total risk score (sex dependent) is calculated based on the following risks: age, untreated or treated systolic blood pressure, diabetes, smoking behaviour, cardiovascular disease (history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, congestive heart failure), atrial fibrillation, and left ventricle hypertrophy. As the Framingham Stroke Risk Profile has been shown to relate to both WMH (Jeerakathil et al., 2004) and cognitive deterioration (Elias et al., 2004), it is important to determine how the Framingham Stroke Risk Profile contributes to working memory. These associations should furthermore be controlled for when establishing unique WMH effects.

Based on the three explanations mentioned above, the objective of the present paper is to examine the association between the Digit Span backward and WMH. We were interested in examining a possible relationship between Digit Span backward performance and WMH by means of a further differentiation within the PVH and DWMH regions. Additional working memory tests were selected to confirm previous observations of WMH-related impairments in working memory performance. As working memory contains both a verbal and a visuospatial store (Baddeley, 1986), one test examining verbal and one examining spatial processes were selected. The Paced Auditory Serial Addition Task, a task of verbal working memory (Audoin et al., 2005) revealing age-related decrement in task performance (Diehr et al., 2003), was chosen as representative of verbal working memory processes. The Spatial Working Memory test of the Cambridge Neuropsychological Test Automated Battery (CANTAB), a task sensitive to age-related cognitive decline (Robbins et al., 1998), was chosen to examine visuospatial working memory. For all working memory tests, total WMH score as well as several subscores (e.g., frontal DWMH) in relation to performance were examined. Finally, possible contributions of the Framingham Stroke Risk Profile were taken into account.

METHODS

Subjects

The recruitment of participants for this study was accomplished in cooperation with the Sint Lucas Andreas Hospital in Amsterdam, the

Netherlands. To increase the probability of WMH, the selection procedure of the subjects was as follows. First of all, age, the major risk factor for WMH (Ylikoski et al., 1995), was taken into account: age was restricted to a minimum of 65 years old for inclusion. The Framingham Stroke Risk Profile was considered as a risk for WMH with the exception of age, which was not included in the Framingham Stroke Risk Profile score but examined as a separate variable. Medical records from independently living elderly visiting the outpatient clinic (e.g., of cardiology or internal medicine) were screened to select those subjects suffering from one or more of the risk factors included in the Framingham Stroke Risk Profile. To furthermore include participants with low Framingham Stroke Risk Profile scores, subjects who were spouses or friends from subjects under treatment or neurological outpatients, visiting the hospital for low back pain or a peripheral nerve problem, participated; all fulfilled at least the age criteria. Blood pressure was measured in upright sitting position, after at least 10 min of rest, using an aneroid Sphygmomanometer. Exclusion criteria were the presence of neurodegenerative disease (e.g., dementia, Parkinson's disease), a history of stroke, hydrocephalus, transient ischemic attack, alcohol or other substance abuse, thyroid disease, and psychiatric disorders. All subjects had normal or corrected-to-normal vision and hearing. Furthermore, the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) was used as a screening instrument to exclude possible dementia: a score of ≥24 was required for participation, which provides a fairly accurate indication of the absence of dementia (Grut, Fratiglioni, Viitanen, & Winblad, 1993). Education was assessed with an ordinal scale ranging from 1 (incomplete primary school) to 7 (university; Heslinga, van den Burg, & Saan, 1983). Depressive symptoms were rated with the subscale depressive symptoms of the Symptom Checklist-90 (SCL-90) (Arrindell & Ettema, 1986).

Fifty-four subjects participated; subject details are presented in Table 1. Approval for this study was obtained from the medical ethics committee. All subjects signed an informed consent.

TABLE 1. Subject characteristics

	N = 54
Age (yrs)	72.5 (5.5)
Sex (% male)	42.6
Education	4.0 (1.48)
MMSE	27.7 (1.7)
FSRP	9.8 (4.5)

Data regarding age, education, MMSE and FSRP represent means (*SD*). A score of 4 for education represents approximately 10 years of education. FSRP, Framingham Stroke Risk Profile; MMSE, Mini Mental State Examination.

Assessment of Working Memory

Three tests of working memory were employed: the Digit Span backward, the Paced Auditory Serial Addition Task (PASAT) and the Spatial Working Memory test (CANTAB). The Digit Span backward test was chosen to examine whether previous findings could be replicated and if more controlled analyses could prove that significant associations between WMH and performance on this test do exist. Additionally, verbal working memory, as measured with the PASAT, and spatial working memory, as assessed with the Spatial Working Memory test, were examined.

Digit Span Backward (Wechsler, 1987)

In the Digit Span backward test, an order of digits was orally presented. The participants were requested to repeat the digits in the reversed order. For each number of digits, two sequences were presented and set size increased with one digit in case at least one sequence was successfully reproduced. The task always started with practice trials containing two or three digits. The total number of correct reproductions was of interest.

PASAT (Gronwall, 1977)

In this task digits, ranging from 1 to 9, were serially presented and subjects were instructed to sum each digit to its preceding digit. This means that subjects must be able to keep the first digit in mind, add the second digit and, while adding, the second digit must be actively stored in order to add the third digit to. The task always started with a practice trial, which was employed as long as necessary to establish full comprehension. Both the 3.2- and the 2.4-s versions were administered. With the 3.2-s version, the time interval between the digits was 3.2 s, with performance expressed as the number of correct responses. Since speed of processing may strongly attenuate working memory performance as assessed with the PASAT, the 2.4-s version was adjusted. This version was read aloud by the examiner (conform subjects processing speed) and the time necessary to complete this version was noted.

Spatial Working Memory (CANTAB)

In this test several boxes are displayed, in one of which a blue token is hidden. Subjects have to search for this token and, once found, collect them in an empty space on the right side of the screen. After a token has been located, a new token is hidden. Subjects were instructed that once a token was found, that particular box would never be used again to hide a token. Every box in the display was used once to hide a token in. The number

of boxes and, hence, the number of tokens in a single trial varied from 3 to 8. The condition with three boxes represented practice trials. We focus here on the number of 'between errors', which represents the number of times subjects re-opened a box where a blue token had already been discovered in.

MRI Procedure

A 1.5-Tesla scan was used to obtain brain MRIs (General Electric, Millwaukee, USA). Whole brain axial and coronal FLAIR (repetition time [TR] = 10000 ms, echo-time [TE] = 150 ms, inversion time [TI] = 2200 ms, slice thickness 5 mm, interslice gap 0 mm, 24 slices) and axial T2-weighted fast spin echo (TR = 6500 ms, TE = 102 ms, echo train 24, slice thickness 5 mm, interslice gap 1 mm, 22 slices) were acquired to allow detailed visualization of WMH. A highly experienced rater (PhS), blinded to the clinical assessments, rated the degree of white matter hyperintensities using a semi-quantitative visual rating scale (Scheltens et al., 1993). Total WMH, PVH and DWMH were rated. With this scale, PVH are examined in three regions, frontal and occipital caps and periventricular bands, and rated on a three-point scale: none (score 0); 5 mm or less (score 1); 6 mm or greater (score 2). DWMH are examined in four regions of the brain, the temporal, frontal, parietal, and occipital lobes, which were rated as follows: none (score 0); 3 mm or less and five or less lesions (score 1); 3 mm or less and six or more lesions (score 2); 4–10 mm and five or less lesions (score 3); 4–10 mm and six or more lesions (score 4); 11 mm or greater and one or more lesions (score 5); and large confluent lesions (score 6). Total scores and subscores were used for the analyses.

Statistical Analyses

All statistical analyses were performed using SPSS version 11.5. Normality of all variables was assessed with skewness and kurtosis. Natural logarithmic, square root, or Blom transformation was applied to normalize scores.

Firstly, Spearman rank correlations between the working memory variables were calculated to examine the compatibility between the tests. Spearman rank correlations between the Framingham Stroke Risk Profile and both white matter variables and working memory tests were calculated. Since better performance on one test is highly likely to relate to better performance on another task, and a higher Framingham Stroke Risk Profile score is likely to be associated with lower cognitive performance and higher WMH scores, testing was performed one-sided.

Hierarchical multiple regression analyses were performed to analyse the influence of WMH on working memory. The working memory variables were analysed separately as dependent variables with the predictors being

examined in three steps (models). The first step always consisted of forcing confounders (age, education, depressive symptoms) into the analysis. Secondly, the Framingham Stroke Risk Profile score was entered. Finally, using a stepwise selection procedure, white matter variables were examined to find out whether white matter additionally explained some of the variance in working memory performance. Three analyses were performed for each working memory variable. Total WMH was examined first. Secondly, possible contributions of total PVH and DWMH were considered. In the final analysis, the PVH and DWMH subscores (e.g., frontal and occipital PVH) were examined. All tests were analysed in this way. Due to the relative small sample size, only adjusted R^2 (R^2_{adj}) values are reported. Significance for entry was set at $p < .05$.

RESULTS

Of the 54 participants who were initially enrolled in the study, MRI scans were unavailable for three subjects (due to claustrophobia). Additionally, one subject did not complete the SCL-90 and two did not *fully* complete the SCL-90, although they completed the majority of the questions (11/16 and 12/16). To prevent excluding these two subjects from the analysis because of partial missing data, we decided to use the completed questions to estimate their total score on this scale. This may provide a more accurate reflection of their depressive symptoms score as opposed to replacing their missing data with the mean or median of the total study sample. MRI scans, educational achievement and SCL-90 scores were available for 50 participants.

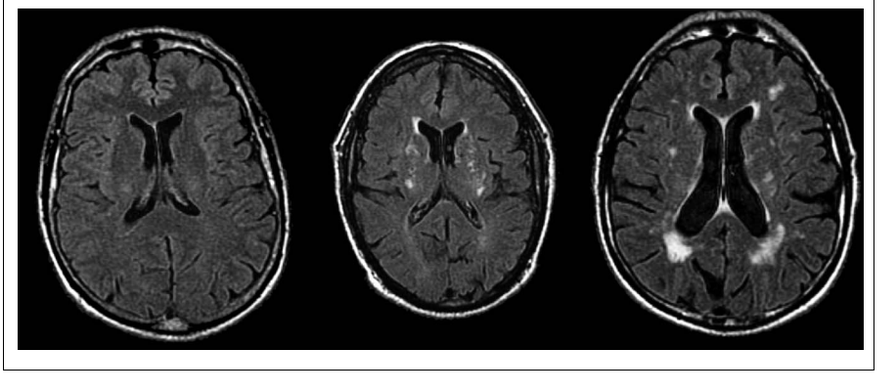
The Digit Span backward test was completed by 49 subjects, 42 subjects completed the PASAT 2.4-s version, whereas 47 subjects completed the Spatial Working Memory test. A large number of subjects ($n = 15$) were unable to perform the PASAT 3.2-s version, which was therefore not included in the analyses.

The prevalence of WMH was quite high in our study sample: 90% of the participants had some WMH. PVH were present in 84% and DWMH in 74% of the participants. PVH were most prevalent in the frontal regions (74%), followed by lateral (62%) and occipital (44%) PVH. The highest prevalence of DWMH was observed in the frontal lobes (74%) with a sharp decrease in the parietal lobe (34%). Occipital DWMH were not observed in any subject and temporal DWMH were present in one subject only (2%). We did not include these latter two regions in the analyses of the various white matter subscores (the final analysis). Examples of WMH are presented in Figure 1.

Spearman Rank Correlations

The PASAT revealed a significant correlation with the Digit Span backward test ($\rho = -.42$, $p < .01$) and Spatial Working Memory errors ($\rho = .55$,

FIGURE 1. Axial FLAIR images of WMH. The image on the left represents a normal brain, whereas the other two images show increasing WMH loads. FLAIR, fluid-attenuated inversion recovery; WMH, white matter hyperintensities.



$p < .001$). The correlation between the Digit Span backward test and the Spatial Working Memory errors was nonsignificant ($\rho = -.12$, $p = .21$).

The Framingham Stroke Risk Profile score significantly correlated with several white matter variables: a higher Framingham Stroke Risk Profile score related to higher total WMH ($\rho = .31$, $p < .05$), DWMH ($\rho = .28$, $p < .05$), lateral PVH ($\rho = .28$, $p < .05$), and parietal DWMH ($\rho = .35$, $p < .01$) scores, and marginally to PVH ($\rho = .23$, $p = .055$) and frontal DWMH ($\rho = .22$, $p = .06$).

Finally, a higher Framingham Stroke Risk Profile score was related to worse performance on the PASAT ($\rho = .31$, $p < .05$) and, marginally, to the Spatial Working Memory errors ($\rho = .23$, $p = .06$).

Digit Span backward (Table 2)

Performance on the Digit Span backward test was entered as the dependent variable in the regression analysis. The first model, consisting of the confounders, explained 8.5% ($p = .07$) of the observed variance, after which the Framingham Stroke Risk Profile score did not make a significant contribution ($R^2_{adj} = .082$, $p = .37$). None of the white matter variables (total WMH, PVH or DWMH, WMH subscores) was a significant predictor of task performance.

PASAT (Table 2)

PASAT completion time was entered as dependent variable. Age, education and depressive symptoms together explained 21.7% ($p < .01$) of the observed variance. The Framingham Stroke Risk Profile produced a non-significant increment of 2.2% ($p = .15$). Despite that neither total WMH,

TABLE 2. Working memory performance in relation to white matter hyperintensities

	Digit Span backward (# correct)		PASAT completion time		Spatial working memory	
Predictors	R^2_{adj}	β	R^2_{adj}	β	R^2_{adj}	β
Confounders	.085		.217**		.269**	
Age		–.043		.288		–.054
Depressive symptoms		–.112		.092		.325*
Education		.310*		–.342*		–.406**
FSRP	.082	–.132	.239	.219	.279	.169
Total WMH	–	–	–	–	–	–
PVH and DWMH	–		–		.381**	
PVH		–		–		–
DMWH		–		–		.356**
WMH subscores	–		.303*		.391**	
Fontal PVH		–		–		–
Lateral PVH		–		–		–
Occipital PVH		–		–		–
Frontal DWMH		–		.285*		.366**
Parietal DWMH		–		–		–

Hierarchical multiple regression analysis were performed. The confounders and the Stroke Risk Profile score were forced to enter, whereas the white matter scores were subjected to a stepwise selection procedure. β coefficients are only reported if the predictor entered the analysis. Significance levels of the stroke risk profile and the white matter data represent significance of the *increase* in R^2_{adj}. DWMH, Deep White Matter Hyperintensities; FSRP, Framingham Stroke Risk Profile; PVH, Periventricular Hyperintensities; WMH, White Matter Hyperintensities.
*$p < .05$; ** $p < .01$.

nor PVH and DWMH were significant predictors of performance, frontal DWMH (R^2_{adj} = 30.3%, $p < .05$) was. Since completion time may negatively correlate with number of errors (a faster completion time may increase inaccuracy), the analyses were repeated with the 2.4-s version number correct as a covariate. This did not attenuate the observed effects of frontal DWMH (data not shown).

Spatial Working Memory (Table 2)

The number of 'between errors' was analysed as the dependent variable. Age, education and depressive symptoms together explained 26.9% of the observed variance ($p < .01$), after which the Framingham Stroke Risk Profile score added a non-significant 1% ($p = .21$). Total WMH turned out not to be a significant predictor of task performance. With regard to PVH and DWMH data, DWMH significantly predicted Spatial Working Memory performance (R^2_{adj} = .381, $p < .01$), with frontal DWMH as the strongest predictor (R^2_{adj} = .391, $p < .01$).

A Unique Contribution of Frontal DWMH?

Task performance of the participants in relation to severity of frontal DWMH, as well as the presence or absence of hyperintensities in the other white matter regions, is presented in Table 3. It can be deduced from this table that the majority of the subjects presented with diffuse WMH, that is hyperintensities in the white matter were not restricted to a single location. In order to explore the unique contribution of frontal DWMH to task performance, analyses were repeated while controlling for the other WMH subregions. To reduce the number of covariates, only the confounders that significantly related to performance in the previous analyses were included. The results were partly comparable to previous observations; frontal DWMH still significantly predicted Spatial Working Memory performance ($\beta = .371$, $p < .05$). However, the association between PASAT performance and frontal DWMH was diminished ($\beta = .248$, $p = .16$).

DISCUSSION

This study confirms previous observations of a lack of an association between Digit Span backward performance and WMH. Despite that total WMH, DWMH and PVH as well as detailed white matter subscores were examined, not a single significant association between any of these variables and Digit Span backward performance was observed. However, decreased performance on the PASAT and Spatial Working Memory tests was related to hyperintensities in the white matter. The effect of frontal DWMH on task performance was more pronounced than the effect of either total WMH or DWMH. These effects were present even though we controlled for several important confounders, which included age, education, depressive symptoms and the Framingham Stroke Risk Profile. The results highlight the importance of test selection as well as differentiating between the various white matter locations when examining working memory performance in aging.

The notion that the Digit Span backward test was unrelated to any WMH variable might imply that this test differs functionally from the other working memory tests included in the present study. A previous meta-analytic review differentiated between reordering tasks (i.e., Digit Span backward) and tests that require concurrent manipulation *and* storage of information, and observed stronger age effects on the latter tests compared to the Digit Span backward (Bopp & Verhaeghen, 2005). Although the Digit Span backward is considered more demanding compared to short-term memory tests (e.g., Digit Span forward), storage precedes manipulation and thereby the demands that are placed on working memory are relatively small. Both the PASAT and Spatial Working Memory tests do require

TABLE 3. Working memory performance based on severity of frontal DWMH

No. subjects	Age	WMH	Digit Span backward (# correct)	Spatial working memory errors	PASAT completion time (s)
5	75.2 (9.5)	–	4.4 (1.7)	44.75 (8.3) (*n* = 4)	300.2 (60.5) (*n* = 4)
1	68	PVH frontal	5	52	–
1	78	PVH lateral	10	12	192
1	66	PVH frontal and lateral	7	20	122
1	71	PVH frontal and occipital	5	1	137
4	73 (8.7)	PVH frontal, lateral and occipital	6.75 (1.7)	36.25 (17.2)	185.8 (5.9) (*n* = 3)
2	74.5 (0.7)	DWMH frontal (1)	3.5 (0.7)	48.5 (37.5)	189.16 (*n* = 1)
1	66	DWM frontal (1), PVH lateral	9	8	147
4	69.75 (4.1)	DWMH frontal (1), PVH frontal	8.3 (1.5) (*n* = 3)	45.3 (8.4) (*n* = 3)	195.25 (29.8)
1	70	DWMH frontal (1) and parietal	9	57	183
1	78	DWMH frontal (1) and parietal, PVH lateral	7	31	221
1	68	DWMH frontal (1) and parietal, PVH occipital	6	47	206
7	69 (4.8)	DWMH frontal (1), PVH frontal and lateral	7 (1.2)	38.3 (21.4)	231 (54.5)
1	75	DWMH frontal (1) and parietal, PVH frontal and occipital	5	25	225
2	73.5 (6.4)	DWMH frontal (1), PVH frontal, lateral and occipital	4.5 (2.1)	26.5 (13.4)	229 (89.1)
1	75	DWMH frontal (1) and parietal, PVH frontal, lateral and occipital	3	–	–
1	75	DWMH frontal (2), PVH frontal and lateral	4	42	215
1	68	DWMH frontal (2), PVH frontal and occipital	4	36	267
1	81	DWMH frontal (2) and parietal, PVH frontal and lateral	5	72	–
1	74	DWMH frontal (2) and parietal, PVH frontal, lateral and occipital	5	49	276
1	70	DWMH frontal (3), PVH frontal, lateral and occipital	6	54	213
2	71.5 (6.4)	DWMH frontal (4) and parietal, PVH frontal	6 (0)	53 (21.2)	266.5 (169)
1	78	DWMH frontal (4), PVH frontal, lateral and occipital	6	75	274
5	72 (3.7)	DWMH frontal (4) and parietal, PVH frontal, lateral and occipital	5.4 (1.1)	64.2 (22.8)	292.75 (110.2) (*n* = 4)
1	71	DWMH frontal (5) and parietal, PVH lateral and occipital	7	44	266
2	75 (2.8)	DWMH frontal (6) and parietal, PVH frontal, lateral and occipital	6 (0)	61.5 (0.7)	315 (*n* = 1)

Performance of the participants based on WMH. The severity of frontal DWMH (Scheltens et al., 1993) was considered and is displayed in parentheses; other WMH regions were dichotomized into presence/absence scores and denoted in case hyperintensities were present in those regions. Scores with regard to age and working memory performance represent mean (SD).

DWMH, deep white matter hyperintensities; PVH, periventricular hyperintensities; WMH, white matter hyperintensities.

concurrent storage and manipulation ability, thereby increasing the load on working memory capacity.

Frontal DWMH was the strongest predictor of working memory performance as assessed with both the PASAT and Spatial Working Memory test. This observation is consistent with a previous study, which demonstrated WMH in the dorsal PFC to most strongly predict working memory-related brain activity (Nordahl et al., 2006). Presumably, WMH induces cortical disconnection with a resulting decrease in functional connectivity that underlies the age-related deficits in cognition (O'Sullivan et al., 2001). The assumption of frontal DWMH to be most important for working memory functioning as observed in the present study fits with the existing literature suggesting a central role of the frontal lobe in executive function. Frontal WMH may have the most profound deleterious effects for frontal lobe functioning, including working memory. One point that warrants caution in this line of argumentation is that, although the association between frontal DWMH and Spatial Working Memory performance remained significant after controlling for other WMH regions, the relationship with PASAT completion time was diminished. This indicates that part of the association between test performance and frontal DWMH might be due to hyperintensities in other white matter regions. An alternative explanation can be optioned, however. The high co-occurrence of hyperintensities in diverse white matter regions might imply that WMH in regions other than the frontal lobes are simply indicative of frontal DWMH. Furthermore, the consistent association between Spatial Working Memory performance and frontal DWMH does suggest a unique contribution of WMH in the frontal regions to working memory performance.

The Framingham Stroke Risk Profile was not a significant predictor of test performance in the present study. Part of this negative result might have been mediated by not including age in the total Framingham Stroke Risk Profile score. Furthermore, the small study population might account for this result. This is despite the observation that a significant correlation between several WMH variables and the Framingham Stroke Risk Profile score, as well as a significant correlation between Framingham Stroke Risk Profile and the PASAT and Spatial Working Memory variables was present.

One drawback of the present study might be that we did not control for perceptual or psychomotor speed, a cognitive function that is heavily affected in aging (Parkin & Java, 1999), which might have influenced executive function, including working memory performance (Salthouse & Meinz, 1995). As a consequence, we do not know how much of the variance was dependent upon processing speed instead of working memory processes. However, the Spatial Working Memory, a test which is free from a time constraint, was strongly associated with WMH. This

implies that reduced speed of processing could not have been a significant moderator of the WMH-working memory association. Furthermore, as age was controlled for in the first step of the analyses, not correcting for speed might not have profound implications for the interpretation of the present results.

One could argue that volumetric ratings may be more accurate than Scheltens' semiquantitative rating scale that was used in the present study (van Straaten et al., 2006). However, strong correlations between the Scheltens scale and volumetric measurements have been reported (Kappeller et al., 2003; van Straaten et al., 2006). As white matter ratings in the present study might deviate from volumetric ratings, the observed associations between WMH and working memory may underestimate the true relationship. These associations might only prove stronger when volumetric rating methods are applied.

This study has taken us one step further in answering the three proposed hypotheses. First of all, performance on the Digit Span backward was unrelated to WMH, whereas both the PASAT and Spatial Working Memory tests revealed significant associations with hyperintensities in the white matter. This confirms previous observations of working memory performance to relate to WMH (Deary et al., 2006; Nordahl et al., 2006). The lack of an association between Digit Span backward performance and WMH can be interpreted as an indication that this test differs from other measures of working memory in the aged population. Secondly, we partially showed that the examination of WMH subscores is promising, in that frontal DWMH was the strongest predictor of both PASAT and Spatial Working Memory performance. Finally, even though significant correlations between the Framingham Stroke Risk Profile score and various WMH and working memory variables were observed, this score did not significantly affect task performance in this study sample.

This study emphasizes the importance of task selection and examining detailed WMH scores, especially when the purpose is to assess possible deficits in working memory in aging. Considering tests that require concurrent storage and manipulation could be extremely valuable.

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