Domain-specific cognitive effects of white matter pathology in old age, mild cognitive impairment and Alzheimer’s disease

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Domain-specific cognitive effects of white matter pathology in old age, mild cognitive impairment and Alzheimer’s disease

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ABSTRACT
Concomitant white matter (WM) brain pathology is often present in patients with mild cognitive impairment (MCI) and Alzheimer’s disease (AD). Cognitive effects of WM pathology on cognition in normal and pathological aging have been studied, but very little is known about possible group-specific effects in old age, MCI and AD. The purpose of the current study was to examine the relationship between WM pathology and cognitive functioning in four cognitive domains in old age, MCI and AD. The study utilized multi-domain neuropsychological data and visually rated MRI imaging data from a sample of 56 healthy older adults, 40 patients with MCI and 52 patients with AD (n = 148). After controlling for age and education, main effects of frontal WM pathology (especially in the left hemisphere) were found for cognitive performances in two domains, whereas a main effect of parieto-occipital WM pathology was only found for processing speed. In addition, with regard to processing speed, an interaction between group and WM changes was found: Patients with AD that had moderate or severe left frontal WM pathology were considerably slower than patients with AD that had milder cerebrovascular pathology. Frontal WM pathology, especially in the left hemisphere, seems to affect cognitive functions in many domains in all three groups. The results of the study increase our knowledge of cognitive repercussions stemming from frontal and/or parieto-occipital WM pathology in AD. Clinicians should be aware that patients with AD with prominent frontal cerebrovascular pathology can have considerably slowed cognitive processing.

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KEYWORDS
White matter; Alzheimer’s disease; mild cognitive impairment; cognition; memory

Introduction
Cerebrovascular contributions to cognitive impairment are common in older adults: the risk for developing vascular white matter (WM) pathology increases clearly with age (Feigin, Lawes, Bennett, Anderson, & West, 2003), and prevalence estimates of WM lesions can exceed 80% in very old populations (Stephan et al., 2012). These vascular brain changes are often seen in T2-weighted structural magnetic resonance imaging (MRI) as areas of...
increased signal, or hyperintensities, that reflect the distribution and severity of cerebral small vessel disease (Pantoni, Poggesi, & Inzitari, 2007). Cerebral small vessel disease is the most common cause of vascular cognitive impairment (VCI). VCI encompasses the full spectrum of cerebrovascular symptomatology from vascular mild cognitive impairment (MCI) to vascular dementia (Dichgans & Leys, 2017). Changes in WM may have direct effects on cognition by disrupting brain networks subserving cognitive processes (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2008), the cognitive repercussions being dependent on the volume and severity of the lesions (Brickman et al., 2011). Furthermore, there are indications that degradation in specific tracts, especially frontal-subcortical and frontotemporal, can have critical implications on cognitive functioning (e.g. Brickman et al., 2011; Metzler-Baddeley, Jones, Belaroussi, Aggleton, & O’Sullivan, 2011).

Regarding cognitive impairment, WM pathology has most strongly been associated with slowed processing speed and impairment in executive functioning (Au et al., 2006; de Groot et al., 2000; Gunning-Dixon & Raz, 2000; Prins et al., 2005). However, deficits in other cognitive domains, such as episodic memory (Au et al., 2006; Gunning-Dixon & Raz, 2000; Maillard et al., 2012; Nordahl et al., 2006, 2005; Schmidt et al., 2005) and working memory (Jokinen et al., 2012; Nordahl et al., 2006, 2005) have been described as well. Indeed, the results of a fairly recent meta-analysis on VCI indicate that the consequences of WM lesions are not limited to just typical frontal lobe impairments (e.g. attention, executive functions), but can lead to multi-domain cognitive deterioration (Vasquez & Zakzanis, 2015).

Considerable comorbidity and overlap between vascular and AD pathology has been demonstrated (Toledo et al., 2013). A recent cohort study of 2000 elderly patients showed that severe WM lesions could be found in a third of patients with AD (Claus et al., 2016), and there are indications that patients with AD may suffer from elevated WM pathology especially in posterior cerebral regions (Brickman, 2013; Yoshita et al., 2006). Moreover, several distinct WM pathways have been implicated to show microstructural and macrostructural degeneration in AD (Mito et al., 2018). Furthermore, older adults with a high level of WM pathology have an increased risk of developing AD (Prins, van Dijk, & Den Heijer, 2004; Wolf, Ecke, Bettin, Dietrich, & Gertz, 2000). Cerebrovascular risk factors such as hypertension, smoking and diabetes are also risk factors for AD (Duron & Hanon, 2008), and vascular diseases such as atherosclerosis increase the risk for AD as well (Breteler, 2000).

Alzheimer’s disease has an insidious symptom progression: typically the early stages are characterized by episodic memory impairment (amnestic MCI) before the disease develops into the full-blown dementia syndrome (Petersen, 2016). These memory impairments reflect cortical atrophy in the entorhinal cortex. Gradually the loss of neurons and synapses in more wide-spread cortical and subcortical regions lead to atrophy in the affected areas, and global cognitive impairment as the disease progresses (Förstl & Kurz, 1999). White matter lesions can sometimes be found also in patients with MCI (DeCarli et al., 2001).

The effects of vascular brain changes on cognitive function in MCI and AD have been examined in a few studies. For example, Bilello et al. (2015) reported that WM lesions in the fornices and corpus callosum correlated with cognitive decline in patients with AD, while no significant associations were found for the control or MCI groups, whereas Brickman et al. (2008) showed that WM lesion load predicts the rate of cognitive decline in AD. Furthermore, we recently found a trend-level effect of frontal WM pathology on cognition concerning AD specifically: Patients with AD who had severe frontal WM pathology performed notably worse on a measure of general cognitive functioning
than patients with milder pathology, whereas no such effects were observed for cognitively healthy adults or patients with MCI (Kaskikallio et al., 2019). It should be noted that the abovementioned studies utilized general-level measures for cognitive functioning that did not account for changes in specific cognitive domains. Finally, Rizvi et al. (2017) reported that global and medial temporal lobe thickness mediate the effects of WM hyperintensity volumes on global cognition and memory functioning, for both cognitively healthy and cognitively impaired (MCI/AD).

White matter hyperintensities have most commonly been measured by validated rating scales such as the Scheltens (Scheltens et al., 1993) and Fazekas (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987) scales. In addition to this, a number of sophisticated quantitative methods for analyzing these changes have been developed as well (Brickman, 2013). However, these quantitative methods have not been integrated into clinical work and visual rating scales still remain the primary methods for obtaining diagnostic information in a clinical context (Harper, Barkhof, Fox, & Schott, 2015; Harper et al., 2016). Furthermore, strong linkages between visual-rating based assessment and clinical cognitive measures have been established in the literature (Harper et al., 2015). Research also indicates that visual rating scales have a high reliability in assessing WM pathology (Gouw et al., 2006) and that they are in fact often comparable to quantitative methods (e.g. see Quinque et al., 2012). The Fazekas scale has been utilized extensively in WM research (Wahlund et al., 2017), and Wahlund et al. (2001) have developed a modified version of the scale (also called the Age-Related White Matter Changes Scale, ARWMCS), which includes more detailed rating of WM changes in different brain regions.

Previous literature indicates that WM changes often lead to multi-domain cognitive impairments (e.g. Gunning-Dixon & Raz, 2000; Vasquez & Zakzanis, 2015). The effects of WM pathology in healthy adults, MCI and AD have been examined before, but comparing the differences of the effects between groups has typically not been a main focus. This is regrettable, since increasing the knowledge of vascular cognitive effects in each of these three groups would be especially relevant for clinicians. Previously we have examined the effects of WM pathology on cognition in these three groups using a general-level cognitive measure (Kaskikallio et al., 2019). In the current study we utilize the same patient sample and examine more specifically the possible effects of WM pathology on multiple cognitive domains in older adults, patients with MCI and patients with AD. The main interest was to see whether there would be differences in the effects between the groups.

**Methods**

**Participants**

The data used in the current study has been collected over several years as part of the DEMPET and TWINPIB research projects (Kemppainen et al., 2006; Koivunen et al., 2011; Scheinin et al., 2011) conducted at the National PET-Centre in Turku, Finland. 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. The participants received oral and written information about the study and gave informed consent. The Petersen et al. (2001) criteria were used for the diagnosis of MCI, whereas patients with AD fulfilled the DSM-IV criteria for dementia as well as the NINCDS-ADRDA
An extensive neuropsychological assessment was performed on all the participants. In this study inclusion in the healthy adult control group required a minimum score of 25 in the Mini-Mental State Examination. Two 24-point exceptions were admitted in light of their otherwise adequate level of cognitive performance. Furthermore, one participant in the healthy adults group who had severe frontal and parieto-occipital WM changes and also exceptionally high level of cognitive performance was excluded as an outlier. The final sample consisted of 56 healthy adults, 40 patients with MCI and 52 patients with AD. Finally, nine missing data points for neuropsychological measures were imputed by EM missing data analysis in SPSS. The patient sample in this study has been utilized before in our previous study (Kaskikallio et al., 2019).

Clinical characteristics and demographical data of the participants are presented in Table 1. Group-wise differences regarding gender were analyzed by Pearson’s chi-square, age by independent samples t-test and education by Mann-Whitney’s U-test. The control group was younger than the MCI group, t(95) = −2.27, p < .05, d = .05, and the AD group, t(107) = −2.08, p < .05, d = .04, and also more educated than the AD group, U = 1070.50, z = −2.78, p = .005, η² = .06. Gender distributions were equal in all three groups, χ² (2) = .59, p = .745. Due to group-wise differences, age and education were set as covariates in the main analyses.

**Cognitive measures**

Nine neuropsychological tests (see Table 2), were originally used to form the four composite variables (processing speed, verbal memory, visual memory, verbal functions). These tests are adequately validated and have been frequently utilized in the literature (e.g. see Au et al., 2006; Bilello et al., 2015; Gunning-Dixon & Raz, 2000; Nordahl et al., 2005; Vasquez &

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**Table 1. Demographic and clinical characteristics of study participants.**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>148</td>
<td>56</td>
<td>40</td>
</tr>
<tr>
<td>Women %</td>
<td>47.3%</td>
<td>44.6%</td>
<td>45%</td>
</tr>
<tr>
<td>Age M (SD), years</td>
<td>72.83 (5.23)</td>
<td>71.38 (5.44)</td>
<td>74.00 (5.40)</td>
</tr>
<tr>
<td>Right-handed</td>
<td>137</td>
<td>51</td>
<td>38</td>
</tr>
<tr>
<td>Left-handed</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ambidextrous</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>73</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Vocational school</td>
<td>57</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Upper secondary</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Academic degree</td>
<td>16</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>WM Pathology: Frontal a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none/focal</td>
<td>98</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>b.confuent</td>
<td>39</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>diffuse</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>WM Pathology: Parieto-occipital a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none/focal</td>
<td>100</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>b.confuent</td>
<td>37</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>diffuse</td>
<td>11</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

---

a Frontal MRI data is missing for one participant, and parieto-occipital data for another.
b. confluent = beginning confluent; WM = white matter.
In order to ensure the internal consistency of the composites, a maximum likelihood factor analysis with oblique rotation was performed on the nine cognitive tests (see Supplement 1 for a more in-depth description). In the resulting model eight of the tests loaded on four factors as expected. The exception was the CERAD Semantic fluency test, which loaded as a sole item to a separate fifth factor. Since these results indicated that semantic fluency should be omitted from the verbal composite, the test was removed from the model and the factor analysis was re-run with the remaining eight tests. This resulted in a four-factor model, which supported the formation of the four composite cognitive variables, These were utilized in the study.

It should be noted, that the test data of the CERAD Naming test has been utilized in our previous study (Kaskikallio et al., 2019), as one of the seven tests that were used to calculate The CERAD Total Score. The data for this test has not been utilized in any other way before, i.e. the test data has not been analyzed separately. For obtaining the composite variables, all individual tests scores were first converted 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 cognitive domain was calculated.

The processing speed composite was computed by calculating the mean of the reversed performance time (maximum score of 300 – performance) of the Trail Making Test A (Poutiainen, Kalska, Laasonen, Närhi, & Räsänen, 2010) and the raw score of the Digit Symbol Coding subtest from the Finnish WAIS-R (Wechsler, 1992). The time limit of Trail Making Test B, i.e. 300 seconds was used in calculating the reverse score, since the performance of several participants exceeded the original 150 second time limit of Trail Making Test A. In the Trail Making Test A the participant is required to consecutively connect 25 encircled numbers on a sheet of paper by drawing lines. The score represents the amount of time that is required for completion. In the Digit Symbol Coding the participant is supplied with nine digit-symbol pairs, followed by a list of digits. The participant is required to write down the corresponding symbol as fast as possible under each digit during a time-limit of 120 seconds, the score representing the number of correct symbols written.

The verbal memory composite was computed by calculating the mean of the test scores of Logical memory 1 (immediate recall) and Logical memory 2 (delayed recall) from the Finnish WMS-R (Wechsler, 1996). In Logical memory 1 the participant is presented two short stories and has to verbally recount each story immediately after hearing it. In Logical memory 2 the participant is asked to retell both stories from memory after a delay of 35–45 minutes.

The visual memory composite was computed by calculating the mean of the test scores of Visual reproduction 1 (immediate recall) and Visual reproduction 2 (delayed recall) from the Finnish WMS-R (Wechsler, 1996). In Visual reproduction 1 the participant is presented nine digit-symbol pairs and has to draw the corresponding symbol as fast as possible under each digit during a time-limit of 90 seconds, the score representing the number of correct symbols written.
recall) from the Finnish WMS-R. In Visual reproduction 1 the participant is shown four different visual designs one by one for a limited time, and asked to draw each design from memory immediately afterwards. In Visual reproduction 2 the participant is asked to reproduce the designs from memory after a delay of 35–45 minutes.

Finally, the verbal function composite was computed by calculating the mean of the test scores of the Similarities subtest from the Finnish WAIS-R, as well as the subtest from the Finnish CERAD neuropsychological battery (Pulliainen, Hokkanen, Salo, & Hänninen, 1999). In the Similarities subtest the participant is shown a series of word-pairs and has to describe their commonality, requiring verbal concept formation and reasoning (Weiss, Saklofske, Coalson, & Raiford, 2010). The Naming subtest is a shortened version of the original Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), and includes 15 pictures of different objects or animals that the participant has to name.

**Brain imaging measures**

Magnetic resonance imaging of the subjects was performed with 1.5T Philips Intera (Best, the Netherlands). White matter pathology was analyzed using two-dimensional (2D) T2 TSE transaxial (TR/TE 4850/100 ms, slice thickness 5 mm, matrix 512 × 512) and 2D FLAIR coronal (fluid attenuated inversion recovery, TR/TE: 11,000/140 ms, slice thickness 5 mm, matrix 512 × 512) images. The same sequence was applied to the whole sample. Our focus was on WM pathology in the frontal and parieto-occipital lobes, since visual ratings of these regions have the highest interrater reliability (Wahlund et al., 2001). Two radiologists analyzed the MRI sequences independently on a personal computer, by utilizing the Wahlund/ARWMCS scale (Wahlund et al., 2001) that ranges from 0 (no lesions) to 3 (confluent lesions). Cohen’s weighted Kappa was used to calculate the inter-rater reliability. There was moderate agreement (Altman, 1999) between the two raters for the left frontal (κ = .501, p < .001), right frontal (κ = .527, p < .001) and left parieto-occipital (κ = .538, p < .001) areas and good agreement for the right parieto-occipital area (κ = .650, p < .001). A mean of the two ratings was calculated and rounded up to whole numbers. This means, that in cases of disagreement between the raters, the higher one of the two scores was assigned as the hemispheric WM score. These hemispheric scores, assigned to the frontal and parieto-occipital lobes in the left and right hemispheres respectively, were stratified into three groups: none/focal changes (0–1 points), beginning confluent changes (2 points) and diffuse changes (3 points). Additionally, summary scores for the frontal and occipito-parietal regions were computed by combining the hemispheric scores, which were then stratified similarly into three groups: none/focal changes (0–2 points in the hemispheric summary score), beginning confluent changes (3–4 points) and diffuse changes (5–6 points).

**Statistical analysis**

A series of separate univariate ANCOVAs were conducted for testing the main research questions. Separate analyses were conducted for each of the six anatomical regions of interest (left frontal, right frontal, left parieto-occipital, right parieto-occipital, bilateral frontal, bilateral parieto-occipital), and for each of the four cognitive composites (processing speed, verbal memory, visual memory, verbal functions).
White matter pathology (in each anatomical region of interest) and group (Control, MCI, AD) were set as independents, age and level of education as covariates and the cognitive composite score as the dependent variable (WM pathology x group x cognitive composite). Two sets of analyses were run: One set containing both left and right hemispheric scores in the same model as independent variables, and another set containing the regional summary score as the independent. One participant was excluded from the frontal analysis and another from the parieto-occipital analysis due to missing MRI data. IBM SPSS statistics software v. 24 was used for data analysis.

**Results**

First, as expected, there were significant differences between cognitively healthy older adults, patients with MCI and patients with AD in almost all of the composite cognitive measures (see Table 3 for results). White matter pathology seemed to have the most robust effects on processing speed: Main effect of WM changes on processing speed was found for both the bilateral frontal (Figure 1; $\eta^2 = .044$) and bilateral parieto-occipital (Figure 2; $\eta^2 = .050$) areas. Furthermore, a significant interaction between group and left frontal WM pathology on processing speed was discovered as well (Figure 3), with a nearly moderate-level effect size ($\eta^2 = .054$). The interaction was due to the fact that patients with AD that had moderate or severe WM lesions in the left frontal lobe had considerably slower processing speed than patients with AD that had milder lesions in the corresponding area.

As for the other cognitive domains, main effect of left frontal WM pathology on visual memory was found (Figure 4; $\eta^2 = .047$). However, no significant effects between WM pathology and verbal-logical memory or verbal functions were observed.

**Discussion**

The aim of this study was to examine possible group-specific associations between WM pathology and cognitive functions in cognitively healthy older adults, patients with MCI and patients with AD. The same patient sample was utilized as in our previous study (Kaskikallio et al., 2019), which utilized a rough general level measure for cognitive functioning, the CERAD Total Score. The current study follows this line of research, but takes a more comprehensive approach and examines the effects in several specific cognitive domains, targeting specific cognitive functions.

In general, without focusing on group-specific effects, we found that frontal WM pathology (especially in the left hemisphere) was associated with cognitive impairment in processing speed and visual memory, whereas parieto-occipital pathology was associated solely with slowed processing speed. In addition to this, we found a specific interaction effect between group and level of left frontal WM changes on processing speed, due to WM changes having a larger effect on the performance of patients with AD. However, no associations between WM pathology and verbal memory or verbal functions were observed.

The general (not group-specific) associations between left frontal WM pathology and impairments in visual memory seen in the current study build on previous research linking WM pathology to impairments in immediate and delayed memory (Vasquez & Zakzanis, 2015). A majority of studies on memory functions have focused on verbal memory, but detriments in visuospatial memory have been reported as well (e.g. Chin et al., 2012;
Table 3. Univariate ANCOVA results of the study variables.

<table>
<thead>
<tr>
<th>Region of analysis</th>
<th>IV</th>
<th>Processing speed</th>
<th>Verbal memory</th>
<th>Visual memory</th>
<th>Verbal functions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F(df)</td>
<td>p</td>
<td>F(df)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td></td>
<td>η²</td>
<td></td>
<td>η²</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>Group</td>
<td>4.69(2, 129)</td>
<td>.011</td>
<td>.068</td>
<td>8.99(2, 129)</td>
</tr>
<tr>
<td></td>
<td>WM Score</td>
<td>1.32(2, 129)</td>
<td>.272</td>
<td>.020</td>
<td>2.38(2, 129)</td>
</tr>
<tr>
<td></td>
<td>Group*WM</td>
<td>3.67(2, 129)</td>
<td>.028</td>
<td>.054</td>
<td>2.69(2, 129)</td>
</tr>
<tr>
<td></td>
<td>WM Score</td>
<td>0.24(2, 129)</td>
<td>.976</td>
<td>.000</td>
<td>0.68(2, 129)</td>
</tr>
<tr>
<td></td>
<td>Group*WM</td>
<td>2.63(2, 129)</td>
<td>.076</td>
<td>.039</td>
<td>2.75(2, 129)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>Group</td>
<td>10.31(2, 137)</td>
<td>.000</td>
<td>.131</td>
<td>21.59(2, 137)</td>
</tr>
<tr>
<td></td>
<td>WM Score</td>
<td>3.16(2, 137)</td>
<td>.046</td>
<td>.044</td>
<td>0.88(2, 137)</td>
</tr>
<tr>
<td></td>
<td>Group*WM</td>
<td>1.45(3, 137)</td>
<td>.231</td>
<td>.031</td>
<td>0.23(3, 137)</td>
</tr>
<tr>
<td>Parieto-occipital</td>
<td>Group</td>
<td>5.93(2, 131)</td>
<td>.003</td>
<td>.083</td>
<td>9.66(2, 131)</td>
</tr>
<tr>
<td></td>
<td>WM Score</td>
<td>.17(2, 131)</td>
<td>.840</td>
<td>.003</td>
<td>0.31(2, 131)</td>
</tr>
<tr>
<td></td>
<td>Group*WM</td>
<td>2.48(2, 131)</td>
<td>.118</td>
<td>.019</td>
<td>0.01(1, 131)</td>
</tr>
<tr>
<td></td>
<td>WM Score</td>
<td>.94(2, 131)</td>
<td>.394</td>
<td>.014</td>
<td>0.40(2, 131)</td>
</tr>
<tr>
<td></td>
<td>Group*WM</td>
<td>.63(1, 131)</td>
<td>.430</td>
<td>.005</td>
<td>0.76(1, 131)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>Group</td>
<td>9.10(2, 136)</td>
<td>.000</td>
<td>.118</td>
<td>11.98(2, 136)</td>
</tr>
<tr>
<td></td>
<td>WM Score</td>
<td>3.56(2, 136)</td>
<td>.031</td>
<td>.050</td>
<td>0.72(2, 136)</td>
</tr>
<tr>
<td></td>
<td>Group*WM</td>
<td>1.99(4, 136)</td>
<td>.099</td>
<td>.055</td>
<td>1.43(4, 136)</td>
</tr>
</tbody>
</table>

The left and right hemispheric scores were entered simultaneously into the same model, whereas analyses containing the summary score for both hemispheres were run in a separate model. All results have been adjusted for education and age. WM = white matter.
Villeneuve, Massoud, Bocti, Gauthier, & Belleville, 2011). In the current study, the three groups differed in verbal-logical memory scores, but performance was not associated with the level of WM pathology. It is most likely that these group differences were associated with other neuropathological processes, such as medial temporal lobe atrophy (MTA), which has been linked to verbal memory impairment in AD (Laakso et al., 1995).

The overall associations between frontal and parieto-occipital WM pathology and processing speed are in line with previous research. Slowed processing speed has been characterized as a cardinal symptom of WM pathology (Gunning-Dixon & Raz, 2000; Vasquez & Zakzanis, 2015), and many studies have suggested that frontal-subcortical WM tracts have critical associations with processing speed (Alexander, Stuss, Picton, Shallice, &
Furthermore, the association between parieto-occipital WM changes and processing speed is consistent with previous studies focusing on parietal structures (Peers et al., 2005; Quinque et al., 2012; Turken et al., 2008), and gives support to the view that disruption of frontal-parietal tracts is associated with impairments of processing speed as well.

Of relevance to the discussion of parietal WM pathology is a recent study by McAleese et al. (2017), that included the post-mortem examination of 27 AD and 28 non-AD brains. The authors reported that posterior cerebral WM changes in AD may not have a vascular origin, but might instead be associated with Wallerian degeneration, triggered by cortical degeneration related to AD. As there exists a considerable amount
of overlap between vascular and AD pathology (Toledo et al., 2013), and posterior cerebral regions in particular may contain elevated WM pathology (Brickman, 2013; Yoshita et al., 2006), the parieto-occipital WM changes of the AD group in our study may have a mixed etiology and we cannot rule out that some of it may be caused by Wallerian degeneration.

Finally, the interaction effect concerning processing speed was due to the fact that patients with AD with severe or moderate left frontal WM lesions had the slowest cognitive processing performances. Patients with AD that had moderate or severe lesions seemed to differ from patients with AD that had milder lesions, suggesting that concomitant WM pathology in AD leads to additive slowing of cognitive processing.

Some studies have contested the role of WM pathology in cognitive decline in AD. Hirono, Kitagaki, Kazui, Hashimoto, and Mori (2000) reported that when global cortical atrophy was controlled for, WM hyperintensities did not correlate with global measures of cognition. More recently, Overdorp, Kessels, Claassen, and Oosterman (2014) found that after controlling for MTA and global cortical atrophy, WM hyperintensities were significantly associated with global cognition, but not with specific cognitive domains. It is important to note however, that the methodology of both studies contain limitations that may have influenced the outcome – perhaps the most important being that both utilize global measures for WM pathology, which may mask possible region-dependent effects. Furthermore, the first study contained minimal measures for memory functions and no constructs for specific domains and applied outdated cognitive constructs from WAIS-R (Verbal IQ, Performance IQ), which may confound possible domain-specific effects. On the other hand, the latter study included a wider range of specific cognitive constructs, but used minimal exclusion criteria and utilized a heavily mixed sample, containing patients with e.g. frontotemporal dementia, Parkinsonism disorders and Lewy body dementia.

Conversely, several studies have emphasized the cognitive repercussions that concomitant WM pathology in AD may lead to. For example, Bilello et al. (2015) reported that after controlling for total brain volume, WM lesion load in the corpus callosum and the fornices correlated with a global cognition measure in patients with AD. In a longitudinal study by Brickman et al. (2008), WM pathology interacted with total brain atrophy and predicted the rate of global cognitive decline in patients with AD; The greatest declines were seen in patients with high levels of baseline pathology in both white and grey matter. Rizvi et al. (2017) reported that WM hyperintensity volumes affect global cognition and memory functioning via global and medial temporal lobe thickness, similarly for controls and patients with MCI or AD. In a previous study, we found indications of frontal WM pathology having an effect on cognition on a general level specifically in patients with AD with severe frontal cerebrovascular pathology (Kaskikallio et al., 2019). Furthermore, cerebrovascular pathology has been associated with the incidence of dementia in elderly individuals as well (Mortimer, 2012).

Finally, some studies have taken another approach, and focused on the effects of amyloid pathology in subcortical vascular dementia (SIVD) patients (e.g. Kim et al., 2012, 2016; Lee et al., 2011; Park et al., 2014; Ye et al., 2015). The study by Park et al. (2014) suggests that amyloid might have a subtle effect on memory functioning in SIVD, as patients with extreme amyloidosis fared significantly worse in immediate and delayed memory tasks than those with lesser amyloid pathology. Overall, these studies have looked at the effects of cerebrovascular and AD pathologies independently. In line with
this, Marchant et al. (2013) reported that the measures for cerebrovascular and AD pathology were uncorrelated, supporting the independence of pathologies. On the other hand, Hughes et al. (2013) reported that vascular risk factors may increase the risk for amyloidosis, which suggests the possibility of independent processes as well as interactions between the pathologies (for a review on mixed pathologies see: Kapasi, DeCarli, & Schneider, 2017).

In the current study, patients with AD that had prominent left frontal WM lesions seem to have the greatest impairment in processing speed, which is most likely caused by the concomitant accumulation of primary AD pathology and cerebrovascular pathology. The neurodegenerative pathology of AD, i.e. the accumulation of amyloid plaques and neurofibrillary tangles as well as the accompanying neuronal loss, leads to gradual global cognitive impairment. When patients with AD also develop prominent cerebrovascular changes, the cognitive repercussions of these two pathologies seem to be cumulative in certain domains. As has been discussed before, manifold associations and overlap between WM pathology and AD have been observed, and several non-mutually exclusive explanations can be formulated about their connections (Brickman, 2013). First, WM pathology may represent a separate and independent pathological process of vascular origin that adds a cumulative contribution to the clinical symptomology, while not strictly promoting AD pathology. The second scenario is that the underlying etiology of WM pathology might be heterogeneous, and may interact with or also reflect the primary neurodegenerative processes of AD. As discussed before, several studies give support to this direction (e.g. Brickman et al., 2008; McAleese et al., 2017; Rizvi et al., 2017). A third possibility is that WM pathology and AD might be related through a shared association with a third set of factors, such as shared risk factors.

The current study has strengths and limitations. First, as cortical atrophy was not controlled for, we cannot rule out the possible effects of cortical atrophy on cognitive performance, such as for example cortical thickness mediating the effect of WM hyperintensity volumes on cognition as reported by Rizvi et al. (2017). Nonetheless, we also assume that brain atrophy is already to some degree intertwined in the group classification (C/MCI/AD), and that adding cortical atrophy in this analysis could in the worst case act as a “secondary control”, diminishing statistical power. Second, imaging techniques allowing for more specific analysis of brain pathology than visual rating scales have been used in some of the previous studies in the field. However, the current study still applied more specific topographical divisions based on visual rating than what is seen in many studies, which have either used global measures of WM pathology or examined larger areas of interest such as periventricular or subcortical regions (e.g. Debette et al., 2007; de Groot et al., 2000; Söderlund et al., 2006). Furthermore, visual rating scales have shown high reliability in assessing WM changes (Gouw et al., 2006), and the Fazekas/Wahlund scale has been used extensively in WM research (Wahlund et al., 2017). One strength of the current study is the utilization of multiple well-validated and established neuropsychological tests for each investigated domain. However, executive functions were not included in the analyses, since a significant portion of the AD group was not able to complete the measure intended for executive functions (Trail Making Test B). Future studies on the topic would benefit from recruiting patients with AD who are still in the early phase of disease progression, and able to perform more complex tasks. Other limitations include the cross-sectional design as well as unevenness in group sizes (see below). Moreover, group-wise differences, albeit of a small magnitude were found for education and age. Even though we controlled for these
variables, we cannot completely rule out the possibility of them having a confounding effect on the main results. Finally, as we have run multiple ANCOVAs, the risk for family-wise errors increases, but using e.g. Bonferroni corrections would nullify any significant findings. However, arguments against using Bonferroni adjustments have been made (see e.g. Perneger, 1998), as it cannot decrease Type I errors (false positives) without inflating the Type II error (false negatives), and in this case we would argue that the risk for Type II errors is greater than the risk for Type I errors. The two main reasons for this are: (1) the findings are novel; (2) The group sizes are uneven, since participants without WM pathology are over-represented whereas the sample sizes of the moderate/diffuse WM pathology groups are significantly smaller.

In order to check for family-wise error due to multiple comparisons, a series of alternate Multivariate ANCOVAs have been run as well (see Supplement 2 for in-depth description). The results here are for the most part similar as when running unilateral ANCOVAs, but differences can be found in the left frontal area. When the analysis was performed on the original nine test setup, left WM pathology had a significant main effect on all the cognitive variables ($p = .017, \eta^2 = .085$), whereas the interaction between group and left frontal WM had a trend-level effect on the cognitive variables ($p = .093, \eta^2 = .060$). When the analysis was conducted on the final eight test setup, the main effect of left frontal WM pathology on the cognitive variables became non-significant ($p = .118, \eta^2 = .056$), and the interaction between group and left frontal WM on the cognitive variables remained at a trend-level ($p = .094, \eta^2 = .060$). Though the effect of left WM pathology on all cognitive variables does not reach the level of statistical significance, we would argue that the result reflects a real phenomenon, since: (1) the effect sizes remain moderate, indicating that the interaction still explains a substantial amount of variation; (2) when separate univariate ANCOVAs are assessed, significant effects on processing speed ($p = .028, \eta^2 = .054$) and visual memory ($p = .046, \eta^2 = .047$) can still be seen. The change in significance seen when moving from the original nine test setup to the final eight test setup is due to the non-significance of the revised verbal function composite, which lowers the significance of left frontal WM pathology when its association to all the cognitive variables is assessed.

In conclusion, our study first of all builds on previous research detailing linkages between WM pathology and cognitive functioning. The most robust effects concern the association between WM pathology and processing speed: It seems that WM changes in both anterior and posterior cerebral areas lead to slowed processing speed in all groups. Additionally, our data indicates that WM pathology in the left frontal region seems to lead to impairments in visual memory. Secondly, the current study adds new knowledge by indicating that prominent left frontal WM pathology can lead to additive impairment of processing speed in AD.

Clinicians should be aware that prominent frontal cerebrovascular pathology can have effects on multiple cognitive domains in both healthy and pathological old age. Furthermore, patients with AD that have prominent left frontal WM pathology can show clearly increased cognitive slowing than would be expected in patients with AD that have milder cerebrovascular pathology in this cerebral region. Future studies should attempt to replicate the findings with larger samples, with preferably overall brain atrophy being controlled for.
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No potential conflict of interest was reported by the authors.

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