The association between white matter hyperintensities and executive decline in mild cognitive impairment is network dependent

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Abstract

White matter hyperintensities (WMH) in Mild Cognitive Impairment (MCI) have been associated with impaired executive functioning, although contradictory findings have been reported. The aim of this study was to examine whether WMH location influenced the relation between WMH and executive functioning in MCI participants (55–90 years) in the European multicenter memory-clinic-based DESCRIPA study, who underwent MRI scanning at baseline (N = 337). Linear mixed model analysis was performed to test the association between WMH damage in three networks (frontal-parietal, frontal-subcortical and frontal-parietal-subcortical network) and change in executive functioning over a 3-year period. WMH in the frontal-parietal and in the frontal-parietal-subcortical network were associated with decline in executive functioning. However, the frontal-subcortical network was not associated with change in executive functioning.

Our results suggest that parietal WMH are a significant contributor to executive decline in MCI and that investigation of WMH in the cerebral networks supporting cognitive functions provide a new way to differentiate stable from cognitive declining MCI individuals.

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Keywords: Mild cognitive impairment; White matter hyperintensities; Executive function; Frontoparietal circuit

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1. Introduction

White matter hyperintensities (WMH) are a common MRI finding in older brains (Schneider et al., 2003). WMH prevalence and severity increases with age (Galluzzi et al., 2008) and their presence has been associated with cognitive dysfunction and an increased risk of Alzheimer’s disease (AD) (Frisoni et al., 2007; Schneider et al., 2003). WMH are also common in individuals with mild cognitive impairment (MCI) (Bombois et al., 2007; de Mendonca et al., 2005; Debette et al., 2007; Tullberg et al., 2004). Although not all MCI individuals progress to AD, MCI is considered a transitional phase between normal aging and dementia, and shares cognitive and pathological features with AD (Portet et al., 2006; Visser et al., 2009). The effect of WMH on cognition is related to disconnection of functionally related cortical and subcortical structures through fiber tract demyelination and gliosis (de Groot et al., 1998; Inzitari, 2000), as shown by Diffusion Tensor Imaging (DTI) (Taylor et al., 2001). Previous studies into the influence of WMH on cognition in MCI individuals are conflicting. Several studies have shown that WMH presence was associated with executive dysfunctioning (Bombois et al., 2007; Burns et al., 2005; Debette et al., 2007; Tullberg et al., 2004), but others (de Mendonca et al., 2005; Smith et al., 2000) could not confirm these findings. These discrepancies between studies may be the result of a focus on WMH load instead of on location of WMH. The aim of this study was therefore to investigate the relationship between executive functioning and WMH location, instead of WMH frequency or load. We particularly focused on executive functions because the strongest effects in the above-mentioned positive WMH studies have been found in this cognitive domain. Only few studies have investigated the relation between cognition and specific WMH location (de Groot et al., 1998; Gold et al., 2005; Sheline et al., 2008) and only one study has addressed directly the effect of WMH on cognition-mediating networks (Babiloni et al., 2008), despite the suggested underlying notion of disconnection in many studies (Debette et al., 2007; Smith et al., 2008; Swartz et al., 2008; Tullberg et al., 2004).

A multitude of networks throughout the brain are involved in cognitive processes. Information-processing, integration and executive control are mediated by the frontostriatal (Goldman-Rakic, 1987; Heyder et al., 2004) and fronto-cerebellar network (Heyder et al., 2004; Schmahmann and Pandya, 1997). These two circuits partly have similar projection paths (Schmahmann and Pandya, 1997). The cerebellum and basal ganglia both project to the prefrontal cortex via the thalamus. Furthermore, the parietal lobe plays a role in executive control, especially within the frontoparietal (Jung and Haier, 2007; Stevens et al., 2007) and parietal—basal ganglia—cerebellum circuit (Middleton and Strick, 2000). It has been suggested that disruption of these networks may explain executive dysfunctioning in MCI (Heyder et al., 2004) or dementia (Goldman-Rakic, 1987). It is of particular interest to test this hypothesis in MCI individuals since they have subtle cognitive deficits in the executive domain (Ribeiro et al., 2006) and their WMH load lies between normal aging and AD (Yoshita et al., 2006). We investigated whether WMHs on multiple locations within a predefined network can predict reduced executive performance over time in MCI individuals.

2. Methods

2.1. Participants

Participants were recruited from the DESCRIPA study, a multicenter prospective cohort study by the European Alzheimer’s Disease Consortium (EADC) aimed at developing clinical criteria and screening guidelines for predementia AD (Visser et al., 2008). Nondemented individuals with cognitive complaints were followed for at least 2 years. Inclusion criteria were age 55 years or older, new referral to a memory clinic because of cognitive complaints and no dementia diagnosis. Exclusion criteria were any somatic, psychiatric, or neurological disorder that could have caused the cognitive impairment, such as stroke, other neurodegenerative diseases, such as Parkinson’s disease, severe head trauma, brain tumor, alcohol abuse, or severe depression (Visser et al., 2008). For this study participants were selected from 10 participating centers where MRI scanning was done as part of clinical practice or a research protocol. MRI was available for 375 (86%) out of 435 participants (van de Pol et al., 2009). Reasons for MRI exclusion were medical contraindication, patient refusal, poor MRI scan quality or avoidance of a waiting list for MRI assessment (then a CT scan was made). Participants with and without MRI did not differ on demographic characteristics, Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score, or prevalence of vascular risk factors (results not shown). Another 17 participants were excluded because of a transient ischemic attack or cerebral infarction, to exclude participants with diseases know to be associated with vascular dementia. Participants were invited annually for follow-up assessment during 2 or 3 years, including questionnaire, MMSE and cognitive tests. AD at follow-up was diagnosed according the NINCDS-ADRDA criteria by the local diagnostic team that was blinded from baseline assessment results (McKhann et al., 1984). At baseline, neuropsychological tests were available for 337 individuals (94%). Follow-up data on neuropsychological function was available for 244 participants (72%) after 1 year, for 177 (53%) after 2 years, and for 81 participants (24%) after 3 years. Reasons for dropout were refusal (n = 77), death (n = 17), inability to contact (n = 28), no neuropsychological assessment had been performed at follow-up (n = 41), no follow-up measurements were available, due to baseline assessment being less than 3 years earlier (n = 70), or other reasons (N = 23). Patients who did not fulfill the three
follow-up sessions did not differ from the patients that completed the study in terms of the basic characteristics or cardiovascular risk factors. Patients who dropped out earlier did have a significant higher amount of signal hyperintensities in the basal ganglia, than those that completed the study ($p = 0.025$). The study was approved by the Medical Ethics Committee of each participating center.

2.2. Tests

2.2.1. Baseline clinical assessment

All participants underwent a standard diagnostic workup, including clinical history taking, medical and neurological examination, clinical chemistry, functional evaluation using the Clinical Dementia Rating scale (CDR) (Morris, 1993), rating scales for depression and neuropsychiatric symptoms, a neuropsychological test battery and neuroimaging. Depression severity was determined according to a cut-off based on the Hamilton Depression Rating Scale (HDRS, five centers) (Hamilton, 1960), the Montgomery Åsberg Rating Scale (MADRS, four centers) (Montgomery and Asberg, 1979), the 15-item Geriatric Depression Scale (GDS-15, seven centers) (Sheikh and Yesavage, 1986), the Cornell Scale for Depression in Dementia (Cornell, four centers) (Alexopoulos et al., 1988) or the Centre of Epidemiological Studies depression scale (CES-D, one center) (Radloff, 1977). To pool data from different depression scales, we dichotomized scores for clinically significant depressive symptomatology on each scale (Visser et al., 2008). These cut-offs were a score $> 13$ on the HDRS (Leentjens et al., 2000), a score $> 14$ on the MADRS (Leentjens et al., 2000), a score $> 7$ on the GDS-15 (Malakouti et al., 2006), a score $> 10$ on the Cornell (Alexopoulos et al., 1988) and a score $> 24$ on the CES-D (Haringsma et al., 2004). The MMSE (Folstein et al., 1975) was administered as a general cognitive screening.

2.2.2. Neuropsychological examination

In each center a neuropsychological battery was performed to evaluate performance in several cognitive domains. A composite score for executive functions for each measurement in time was constructed by calculating the mean of the $z$-scores of the Trail Making Test (TMT) part B and the Stroop Color-Word Task (SCWT) card three $z$-score (de Groot et al., 2000). At baseline, 167 (46.6%) participants had completed the TMT-B and the SCWT-3, 10 participants (2.8%) only had data on the TMT-B, 160 participants (44.7%) had only completed the TMT-B. This is because the SCWT was administered in only a subset of centers (6 out of 10 centers), based on the local protocol. When available, both tests were included to achieve a more precise measure of executive functioning. When only one measurement was available, this score was used. The correlation between both cognitive tests was $r = 0.41$ ($p < 0.001$). However, both tests have been shown to load on the same construct and can be considered as valid measures of executive functioning (Van der Elst et al., 2008). We tested the number of available executive tests as a covariate in the analyses.

2.3. MRI acquisition and image analysis

All participants underwent MRI scanning within 2 months of baseline clinical assessment, according to a standard local MRI protocol. All scanning was performed at 1.0 or 1.5 T and included 3D T1-weighted gradient-echo and fast fluid attenuated inversion recovery (FLAIR) sequences. MRI data were analyzed centrally by a single experienced rater who was blinded to clinical information. Degree of WMH severity and location was rated on axial FLAIR images using the Age-Related White Matter Changes (ARWMC) semiquantitative visual rating scale (Wahlund et al., 2001). The intrarater agreement was determined on a test set of 20 scans scored twice (weighted kappa = 0.95). WMH were measured in frontal, temporal and parieto-occipital lobes (combined parietal and occipital WMH), signal hyperintensities in the basal ganglia and WMH in the infratentorial region, left and right separately (Wahlund et al., 2001). For readability, the parieto-occipital WMH will be referred to as the parietal WMH. WMH for each region were calculated by summing left and right WMH load. For our analyzes the number of networks specified in our hypotheses was limited to those networks where sufficient participants were present. We created three main networks: (1) the frontal-parietal network, consisting of all participants with frontal and/or parietal WMH; (2) the frontal-subcortical network, consisting of all participants with frontal and/or parietal WMH and/or cerebellar WMH; (3) the frontal-parietal-subcortical network, consisting of participants with frontal and/or parietal and/or cerebellum WMH.

2.4. Statistical analysis

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS, Inc, Chicago), version 15.0. The association between WMH location and executive functioning over time was examined using linear mixed model (LMM) analysis. LMM analysis offers several advantages over more traditional analysis of variance models, e.g. individuals with missing observations are retained in the analysis and mixed models estimates the parameters more precise (Verbeke and, 2000). Model assumptions were assessed by inspection of the residuals. Time of testing was entered as repeated factor, executive functioning as dependent variable and WMH load/location and follow-up moment as fixed factor. We first analyzed the data for WMH load to investigate the association with executive decline, and then we ran the same models for WMH location. For the three main networks (frontal-parietal, frontal-subcortical, frontal-parietal-subcortical), three separate models were tested to deal with the overlap between groups, because participants can be present in more than one network. Combining the three networks in one model, would have made it necessary to test second and third order interactions, which...
would have created power issues. Covariates included in the model were age (continuous), education level (low = primary school or less; intermediate = secondary school; high = more than secondary school), sex, history of hypertension, hyperlipidemia, hypercholesterolemia or atherosclerosis, depression (actual or past), total WMH load and number of executive tests. In the models examining WMH load, we excluded the covariate WMH load and used the summed WMH load for each network as predictor variable. The covariate number of executive tests was excluded since it added no significant explained variance to the model. Study center was included as an extra level. The location analyses were repeated without cardiovascular risk factors and depression. We chose to present to analyses with the covariates in the table, because earlier studies showed their relevance in studying their relationship to cognitive functioning (Anson and Paran, 2005; Duron and Hanon, 2008).

The best fitting covariance mode, the homogenous Toeplitz structure, was determined on the −2 restricted log likelihood (−2LL) difference, the parameters difference and the Schwarz’s Bayesian Information Criteria (BIC). p-values below 0.05 were considered statistically significant. Thirteen outliers were detected, but were retained in the model as removal of these did not change the estimation of the fixed effects significantly.

3. Results

3.1. Group characteristics

Table 1 shows the characteristics of the selected group. The mean age of the study group was 69.4 years (SD = 7.9, range 55–90 years). There were more women than men in the group and most of the participants were low educated. Common cardiovascular risk factors were hypertension (44.5%) and hypercholesterolemia or hyperlipidaemia (36.9%). Depression was present in 11.3% of the participants. Table 2 shows the WMH distribution for each location within the investigated networks.

### Table 1
Characteristics of the study population at baseline measurement (n = 337) that underwent scanning. Continuous variables are represented as mean (SD) and categorical variables as number (%)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.4 (7.9)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>9.9 (4.0)</td>
</tr>
<tr>
<td>Educational level (%) (n = 335)</td>
<td></td>
</tr>
<tr>
<td>Primary school or less</td>
<td>140 (41.5%)</td>
</tr>
<tr>
<td>Secondary School</td>
<td>124 (36.8%)</td>
</tr>
<tr>
<td>More than secondary school</td>
<td>71 (21.1%)</td>
</tr>
<tr>
<td>MMSE score (n = 334)</td>
<td>27.6 (2.1)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>191 (56.7%)</td>
</tr>
<tr>
<td>History or treatment of hypertension (%)</td>
<td>150 (44.5%)</td>
</tr>
<tr>
<td>History of hypercholesterolemia/hyperlipidemia (%)</td>
<td>121 (35.9%)</td>
</tr>
<tr>
<td>History of artherosclerosis (any kind) (%)</td>
<td>60 (17.8%)</td>
</tr>
<tr>
<td>Presence of depression (%) (n = 330)</td>
<td>38 (11.3%)</td>
</tr>
</tbody>
</table>

Note. MMSE = Mini-Mental State Examination; WMH: White Matter hyperintensities.

3.2. Relation between location of WMH and executive functioning over time

Table 3 shows that WMH location was significantly associated with change in executive functioning over time. As can be seen in Figure 1 WMH in the frontal-parietal network (t = −2.838, p = 0.005), but not the presence of WMH in the frontal-parietal or frontal-subcortical network (t = −2.302, p = 0.12), was associated with executive dysfunctioning (t = −2.302, p = 0.012). For the longitudinal data, the results remained the same with a negative association between executive functioning and WMH in the frontal and parietal network (t = −2.00, p = 0.047) and in frontal-parietal-subcortical network (t = −2.782, p = 0.005) and no significant association between executive functioning and WMH in the frontal-subcortical network (p > 0.05).

Adding medial temporal lobe atrophy as a proxy for brain atrophy to the model did not change our results substantially: WMH in the frontal-parietal network (t = −2.194, p = 0.029) and in the frontal-parietal-subcortical network (t = −3.056, p = 0.002) were associated with executive decline over time. This was not the case for the frontal-subcortical network (p > 0.05).

3.3. Relation between load of WMH and executive functioning over time

Table 4 shows the results for the association between executive functioning over time and load of WMH in the three dedicated networks. There was no significant association between WMH load in the frontal-parietal network,
the frontal-subcortical network or the frontal-parietal-subcortical network ($p > 0.05$).

4. Discussion

In this study we investigated WMH location, instead of load, in relation to anatomical circuits involved in executive functioning in participants with MCI. Based on our findings and the post-hoc analyses, it appeared that WMH in the fronto-parietal circuit predicted a reduction in executive functioning over time in individuals with MCI that was not yet evident at baseline. WMH in the frontal-parietal-subcortical circuit were also associated with executive decline, already evident from baseline, when the WMH were measured.

The significant associations between change in executive functioning over time on the one hand and WMH in the frontal-parietal network and in the frontal-parietal-basal ganglia network by contrast, could not be explained by cardiovascular risk factors or depression, as analyses with and without correction for these conditions yielded similar results. In older people, with no objective cognitive deficits, WMH are mainly found in frontal areas, whereas patients with AD show a higher load of WMH in posterior areas of the brain, including the parietal cortex (Yoshita et al., 2006). Our results suggest that some individuals with MCI have WMH in both frontal and posterior brain parts and that these participants are at risk for future decline in executive functioning. It is tempting to suggest a disconnection of neural pathways to and from the parietal lobe to explain the cognitive impairments in MCI patients. Based on our results, it can be suggested that the frontal-parietal network might play a key role in understanding the association with executive decline in MCI patients. The identification of these disconnections, i.e. the superior longitudinal fasciculus, may be considered as a biomarker, which can help to differentiate declining MCI patients from stable MCI patients. Furthermore, these results suggest that vascular and neurodegenerative pathological processes may have an additive effect in the etiology and development of these syndromes. Yoshita et al. (2006) already suggested that AD pathology could make posterior white matter tracts more vulnerable to vascular processes and thus thereby creating a regional specificity. There is also corroborating evidence from recent DTI studies, which have demonstrated significant group differences between AD patients, MCI patients and controls in the white matter integrity in posterior parts of the corpus callosum and the superior longitudinal fasciculus (Cho et al., 2008; Rose et al., 2000). It seems reasonable to link findings from DTI studies to our findings, since loss of white matter integrity can primarily be attributed to WMH formation (Vernooij et al., 2008). The importance of parietal lobe WMH as a location to induce executive decline over time, also corroborates findings from neuropathological studies, which have shown that late-developing areas are the first areas affected by AD related neuropathology. This is for posterior areas relative earlier than anterior areas (Braak and Braak, 1991, 1996).

Although previous studies have shown that basal ganglia signal hyperintensities influenced cognition in older persons by disrupting neural pathways in corticosubcortical circuits (Gold et al., 2005; Mori, 2002; Snowdon et al., 1997), we were not able to confirm the importance of basal ganglia lesions, since the frontal-subcortical network was not associated with executive functioning at baseline or follow-up. This suggests that isolated WMH in the basal ganglia are not sufficient to induce cognitive decline. However, since the combination of WMH in the frontal, basal ganglia and cerebellum showed the largest amount of dropout (21%) at follow-up, statistical power was lost and a possible selection bias cannot be ruled out. The use of LMM with using the Restricted Maximum Likelihood (REML) method, used in our analyses, already avoids small sample bias associated with fixed effects and also some selection bias.

The results demonstrate the importance of cognitive follow-up assessment, since both groups, with and without WMH in the networks did not differ strongly on baseline executive functioning, but differences became evident as a function of time. Participants without WMH at baseline, showed a small increase in executive functions over time, which may be attributed to a practice effect. Participants with WMH in the two associated networks did not show a benefit from repeated measurements, emphasizing the impact of WMH in these locations on the executive functions.

A strength of our study is the longitudinal design, which...
enabled the investigation of the deferred impact of the WMH distribution in persons with cognitive dysfunctions. Secondly, we investigated decline of executive functions instead of conversion to dementia (Smith et al., 2008; Wolf et al., 2000). Decline in cognitive performance may be a more sensitive indicator than conversion to MCI or dementia and reflects change earlier in the disease process. Thirdly, the investigation of WMH location, instead of load, in terms of underlying networks and its relation with cognition, is a new approach that does justice to the complexity of distributed white matter damage.

A limitation of the study was that no longitudinal MRI data were available. Secondly, the outcome on different rating scales for depressive symptoms were pooled after dichotomizing nondepressed individuals from mildly depressed or higher. Even though, all scales have been validated and great care was taken in selecting proper cut-off points, it might be that some inaccuracy was introduced by this procedure. Excluding depression form our model did not change our findings substantially. This suggests that despite the use of dichotomized variable, the presence of depression did not influence our results or conclusions. Thirdly, from a biological perspective, it is more plausible to expect a network disruption when at least one area of the network is affected. Unfortunately, for statistical reasons (most notably, collinearity and power issues) we were not able to test these associations in one single model. Fourthly, there were fewer participants with WMH in the frontal-subcortical network, compared with the other WMH networks. Even though we used the REML method to avoid small sample bias, it is possible that differences in power could have influenced the regional findings. Our findings should be validated in larger samples. Fifthly, we did not correct for brain atrophy. Several researchers (Smith et al., 2008; Swartz et al., 2008) showed that WMH and atrophy highly intercorrelate, and correction of WMH for atrophy would potentially lead to overcorrection of the effect on cognition. As a check, we corrected our analyses for medial temporal lobe atrophy, assessed by visual rating scales, which can be used as a proxy measure of brain atrophy (Appelman et al., 2009). Adding this variable to our model did not change our results.

Furthermore, the ARWMC scale used in this study to quantify WMH, was not designed to measure possible disruptions in white matter tracts caused by WMH. Therefore, our findings need to be confirmed by new tools (Sheline et al., 2008) to investigate the influence of WMH on actual neural networks.

In summary, circuits containing parietal WMH were predictive for decline in executive functioning in persons with MCI. Investigation of the underlying affected networks may reveal more about the mechanisms of why WMH may affect cognition and how individuals with

![Fig. 1. The location of WMH in relation to executive functioning (z-score) over the four yearly assessments: associations were analyzed using linear mixed models. The plots (A, B and C) show the significant relationships of executive functioning over time with presence of WMH in the three dedicated cortical networks. Error bars represent standard error from the mean. Abbreviations: WMH: White Matter hyperintensities; 0: baseline; 1: follow-up one; 2: follow-up two; 3: follow-up three.](image)

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**Table 4**

Association between WMH load in the dedicated cerebral networks and executive functioning over time

<table>
<thead>
<tr>
<th>Executive functioning over time</th>
<th>B</th>
<th>t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal – parietal network</td>
<td>0.001</td>
<td>0.066</td>
<td>0.947</td>
</tr>
<tr>
<td>Frontal – subcortical network</td>
<td>−0.02</td>
<td>−1.430</td>
<td>0.154</td>
</tr>
<tr>
<td>Frontal – parietal – subcortical network</td>
<td>−0.009</td>
<td>−0.927</td>
<td>0.355</td>
</tr>
</tbody>
</table>

WMH in left and right hemispheres were combined for each location. Linear Mixed Models were corrected for age, educational level, gender, history of hypertension, hypercholesterolemia/hyperlipidaemia or any arteriosclerosis and history or presence of depression. B = unstandardized beta coefficients.
stable MCI might be differentiated from those who show cognitive decline.

Disclosure statement

The authors declare to have no conflicts of interest.

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References


