Chapter 5

One step forward in unraveling the relationship between white matter and various executive functions

This chapter is based on:

One step forward in unraveling the relationship between white matter hyperintensities and various executive functions, submitted
Abstract

Various studies support an association between white matter hyperintensities (WMH) and deficits in executive function (EF) in nondemented aging. Studies examining EF and WMH have generally adopted EF as a phrase including various functions such as flexibility, inhibition, and working memory. However, these functions include distinctive cognitive processes and not all may be equally affected as a result of WMH. Furthermore, data concerning the precise involvement of diverse white matter regions in EF performance is lacking. Therefore, the goal of the present study was to examine how subregions of the white matter, such as frontal deep white matter, relate to a variety of EFs. The following EF domains were examined: Flexibility, Fluency, Inhibition, Planning, Set Shifting, and Working Memory. It was additionally assessed how age and cardiovascular risk factors contribute to WMH and the therewith related decline in EF. Analyses revealed that not all WMH subscores correlated with all EF domains, and that the white matter subscore most strongly predicting performance varied across the diverse EF domains. Age was the strongest predictor of both WMH and EF, while some additional effects of cardiovascular risk factors were noted. Despite that controlling for age and cardiovascular risk factors slightly attenuated some of the WMH-EF relationships, overall the associations between EF and WMH were quite robust. These results indicate that differentiating between EF domains is necessary when establishing an association with WMH, and that the precise involvement of WMH subregions may be attributed to the cognitive properties that comprise an EF domain.
Introduction

Normal aging is associated with a decline in cognitive functioning, including executive function (EF) (Keys & White, 2000; MacPherson, Phillips, & Della Sala, 2002). The white matter might be one of the brain structures that undergo degenerative changes in aging and mediate the decrement in EF (e.g. O'Sullivan et al., 2001). 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 crucial for EF (Royall et al., 2002). By reducing the functional connectivity of the PFC with other (sub-)cortical regions, WMH may relate to deficits in EF (Marshall, Hendrickson, Kaufer, Ivanco, & Bohnen, 2006; O'Brien et al., 2002; O'Sullivan et al., 2001).

Although an association between WMH and a decline in EF has been well established, several issues regarding this relationship require elucidation. The term EF has been used as a single construct including a variety of functions such as working memory, inhibition or flexibility. Previous studies mostly focused on a single or only a few tests as representative of the entire EF domain (e.g. Baum, Schulte, Girke, Reischies, & Felix, 1996; Gunning-Dixon & Raz, 2003; Marshall et al., 2006; Shenkin et al., 2005). Moreover, whether all EFs are affected by WMH remains indefinite. For example, WMH effects on flexibility, measured with the Trail Making Test part B (TMT-B), and fluency performance are inconsistent (Bartres-Faz et al., 2001; Baum et al., 1996; De Carli et al., 1995; Dufouil, Alperovitch, & Tzourio, 2003). Planning, another executive domain that is strongly affected by aging (Andres & Van der Linden, 2000; Phillips, Kliegel, & Martin, 2006; Robbins et al., 1998), has never been examined in relation to WMH in the aged population. Set shifting performance constitutes another EF domain where varying results with regard to WMH-related decline in task performance have been reported (Boone et al., 1992; Gunning-Dixon & Raz, 2003; Oosterman, Sergeant, Weinstein, & Scherder, 2004; Raz Rodrigue, & Acker, 2003; Schmidt et al., 1993, 1995). Additionally, whether a differentiation between white matter regions is important has barely been examined and, when it has, inconsistent results have been reported. One study observed an increase in number of perseverations on the Wisconsin Card Sorting Test as a result of frontal WMH (Raz, et al., 2003), whereas another observed a reduction in performance on an executive composite score irrespective of WMH location (Tullberg et al., 2004).

Aging coincides with an increase in cardiovascular risk factors such as hypertension and diabetes that are known to affect cognition, including EF. Hypertension, diabetes mellitus, and cardiovascular disease, for example, have all been related to executive dysfunctioning (Knopman et al., 2001; Kuo et al, 2005; Raz et al., 2003; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003; Vicario, Martinez, Baretto, Diaz Casale, & Nicolosi, 2005; Wolfe, Worrall-Carter, Foister, Keks, & Howe, 2006). One underlying mediator of the association between cardiovascular risk factors and cognition is that these risks, as does
aging, induce structural brain changes (Carmelli et al., 1999). More specifically, age, hypertension, diabetes mellitus, smoking, and a history of cardiovascular disease have all been denoted as risk factors for WMH (Jeerakathil et al., 2004; Lazarus, Prettyman, & Cherryman, 2005; Longstreth et al., 2005; Ylikoski et al., 1995). Presumably, by affecting the vasculature, they increase the risk of ischemia (Pantoni & Garcia, 1997). As such, part of the mediated effect of these risks on cognition may occur through WMH development.

The present study focuses on several issues. First of all, the effect of WMH on various EF domains (i.e. Flexibility, Fluency, Inhibition, Planning, Set shifting, Working memory) will be assessed, with the emphasis on differentiated white matter regions. The precise contribution of aging and various cardiovascular risk factors to WMH will also be established. Finally, it will be examined to what extent the association between WMH and EF is mediated by aging and cardiovascular risk factors.

Methods

Subjects

One hundred and seventy-two subjects participated. The recruitment of participants for this study was accomplished in cooperation with the Sint Lucas Andreas Hospital in Amsterdam, the Netherlands. The selection procedure of the subjects was as follows. As aging poses the major risk for WMH (Ylikoski et al., 1995), and white matter volume starts declining during the fifth decade of life (Bartzokis et al., 2001; Walhovd et al., 2005), age was restricted to a minimum of 50 years for inclusion. Medical records from elderly visiting the outpatient clinic (e.g. of cardiology or internal medicine) were screened to select subjects suffering from and free from cardiovascular risks. The following variables were considered risks: a history of hypertension, hypercholesterolemia, diabetes mellitus (DM), cardiovascular disease (CVD: myocardial infarction, congestive heart failure, coronary artery disease, atrial fibrillation) and smoking behaviour. To additionally include participants free from any of these risks, participants under treatment at the department of neurology (e.g. for locomotor problems) or spouses or friends from participants under treatment were included; all fulfilled at least the age criterion.

A prerequisite for subjects to participate was to be free of neurodegenerative disease (e.g. dementia, Parkinson’s disease), stroke, alcohol or other substance abuse, or psychiatric disease. 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 (Grut, Fratiglioni, Viitanen, & Winblad, 1993). Premorbid IQ, assessed with the NLV (Dutch version of the NART, Schmand, Bakker, Saan, & Louman, 1991), and depressive symptoms as assessed with the SCL-90 (Arrindell & Ettema, 1986), were furthermore measured. 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 = 172)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>68.9 (8.9)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>61.7</td>
</tr>
<tr>
<td>IQ (mean ± SD)</td>
<td>99.4 (13.5)</td>
</tr>
<tr>
<td>MMSE (mean ± SD)</td>
<td>27.9 (1.6)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>40.1</td>
</tr>
<tr>
<td>DM (%)</td>
<td>34.3</td>
</tr>
<tr>
<td>CVD (%)</td>
<td>64.5</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>51.2</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>18.0</td>
</tr>
</tbody>
</table>

*CVD = cardiovascular disease; DM = diabetes mellitus; MMSE: Mini Mental State Examination

Executive functions

The neuropsychological battery completed by the participants consisted of the following EF domains: Flexibility, Fluency, Inhibition, Planning, Set Shifting, Strategy and Working Memory. Domain scores using standardized z-scores were calculated. Scores were transformed such that a higher score always represented better performance.

**Flexibility:** The Trail Making Test (TMT) (Reitan, 1958) was employed to assess flexibility performance. The TMT-A consists of 25 encircled numbers that are randomly distributed on a sheet of paper. The subject is required to sequentially connect these numbers. With the TMT-B, both numbers and letters are distributed. This time, the subject is instructed to alternate between the numbers and letters (e.g., 1, A, 2, B, 3, etc.). Both completion time of part B corrected for part A (TMT-B/TMT-A) and TMT-B number of errors were considered.

**Fluency:** Both Category Fluency and the Controlled Oral Word Association Test (COWAT) (Benton, Hamsher, & Sivan, 1983) were examined. Subjects were instructed to generate as many words as possible within 1 minute. For Category Fluency total number of words for both ‘animal’ and ‘profession’ was used. The COWAT score consisted of the total number of words beginning with a specific letter (Dutch equivalent of ‘fas’).

**Inhibition:** Both the Colour (C) and Colour/Word (C/W) cards of the Stroop test (Stroop, 1935) were assessed. For the C card, 10 rows, with each row containing
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10 coloured blocks, are presented, and the subject is required to name the colours of the blocks as fast as possible. On the C/W card, instead of coloured blocks, colour names are printed in an incongruent colour, and the subject is required to name the colours in which the words are printed. Completion time of the C/W card corrected for the C card (time C/W – time C) and the number of errors on the C/W card were noted.

**Planning:** Stockings of Cambridge (SOC; CANTAB), a computerized version of the Tower of London test, was used to assess planning ability. Two displays with coloured balls are presented, and subjects have to adjust one display so that it matches the other one, in a minimal number of moves (ranging from 2-step problems to 5-step problems). The subject is instructed to first think about the moves to be performed before starting moving the coloured balls. A maximum number of moves (5, 7, 9, and 12 moves for 2, 3, 4 and 5-step problems respectively) is allowed before the trial terminates and the next problem is introduced. Two different outcomes were of interest. First of all, the number of problems solved in minimal moves was noted. Secondly, the initial thinking time was calculated, which represents the time prior to the execution of the first move corrected for motor speed (Robbins et al., 1998). As such, it is a measure of planning time.

**Set Shifting:** The Intra/Extra Dimensional Set Shifting (IED; CANTAB) test was employed to measure set shifting ability. The test starts with the presentation of four boxes in which two stimuli (shapes) are displayed, one correct and one incorrect. The subject has to find out which of the two shapes is the correct one and, once found, has to continue choosing the ‘correct shape’ (stage 1). When the computer establishes full comprehension of the rule (after six successive trials), the rule is changed (the previous incorrect shape is now correct, stage 2). Successful comprehension induces stages 3 and 4, in which irrelevant information (white lines presented respectively next to and superimposed on the shapes) is additionally presented that must be ignored. In stage 5 a shift towards the other shape is required. In stage 6 an intradimensional shift is initiated, with novel stimuli but the same principle (shapes remain the correct dimension). A reversal to the alternate shape is required in stage 7. Finally, in stage 8 novel stimuli are presented but this time an extradimensional (ED) shift towards the white lines is required. Successful completion of this stage induces a shift to the opponent line (stage 9). When a stage was not completed after 50 consecutive trials, the test terminated. In case a subject failed to complete a stage prior to stage 9, a total of 25 errors was noted for each following uncompleted stage. This test is about set shifting and rule generation, and the ED shift has frequently been denoted as a computerized Wisconsin Card Sorting Test. Number of stages completed, the number of errors made prior to the ED shift (ID errors) and the number of errors needed to complete the ED shift (ED errors) were of interest.

**Working Memory:** The Spatial Working Memory test (SWM; CANTAB) was included to examine working memory. 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. When
a token has been found, 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. Two different outcome measures as representatives of working memory function were of interest. The first was 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 that search trial. Secondly, the number of ‘within errors’ was calculated which represents the number of times a subject re-opens a previously examined box within a single search sequence.

MRI-Images

A 1.5 Tesla scan was used to obtain brain MRIs (General Electric, Millwaukee, USA). Whole brain axial and coronal fluid attenuated inversion recovery (FLAIR) (repetition time [TR] = 10000 msec, echo-time [TE] =150 msec, inversion time [TI] =2200 msec, slice thickness 5 mm, interslice gap 0 mm, 24 slices) and axial T2-weighted fast spin echo (TR=6500 msec, TE = 102 msec, echo train 24, slice thickness 5 mm, interslice gap 1 mm, 22 slices) were acquired to allow detailed visualization of WMH.

Two independent raters (PS and AAG), with both good to excellent intra-rater reliability (kappa > 0.85), scored the MRI scans. The degree of WMH was rated according to a highly validated semiquantative visual rating scale (Scheltens et al., 1993). Since the focus of the present study is on detailed WMH scores, PVH scores were calculated separately for the frontal and occipital caps and periventricular bands. The DWMH scores were examined separately in the frontal, temporal, parietal, and occipital lobes. Examples of varying degrees of WMH are presented in Figure 1.

![Figure 1. Axial FLAIR images of subjects with increasing rates of WMH severity.](image-url)
Statistical Analyses

All statistical analyses were performed using SPSS version 11.5 (SPSS, Inc., Chicago, IL). Violations of normality were subjected to either natural logarithmic, square root, or rank transformation.

Firstly, partial correlations between the EF domains and the white matter variables were calculated, controlling for sex, IQ, and depressive symptoms, in order to examine whether a general association between EF and white matter (irrespective of location) exists. Since two raters scored all MRI variables, a dichotomised variable, representing the two raters, was controlled for as well. Due to the low prevalence of occipital (8.6%) and temporal (29.6%) DWMH, these variables were dichotomised into absent (score 0) and present (score 1) scores.

To determine the unique contributions of the white matter subscores to EF, the white matter subscores that significantly correlated with an EF domain were subjected to hierarchical multiple regression analyses with stepwise selection, controlling for sex, IQ, depressive symptoms, and rater.

In order to examine the overall effect of aging and the cardiovascular risk factors on WMH, these factors (age, hypertension, CVD, DM, hypercholesterolemia, smoking behaviour) were entered in hierarchical multiple regression analyses, controlling for sex and rater. Frontal, lateral, and occipital PVH, as well as frontal and parietal DWMH, were analysed using a linear regression analyses. Collinearity statistics revealed low multicollinearity among the predictors. Associations between cardiovascular risk factors and occipital and temporal DWMH were analysed by means of logistic regression.

Hierarchical multiple linear regression analysis with the EF domains were repeated, to examine to what extent aging and the cardiovascular risk factors account for the association between WMH and EF. Controlling for confounders (sex, IQ, depressive symptoms, rater), the effects of aging and the cardiovascular risk factors were examined by means of stepwise selection, after which the previous significant contributing WMH subscore(s) was entered.

Results

White matter and Executive Functions

Correlations between the EF domains and white matter subscores are presented in Table 2. The Fluency domain revealed a marginal significant correlation with temporal DWMH only ($r = -0.15, p = .07$). Significant correlations of Flexibility with temporal DWMH ($r = -0.24, p < .01$) and occipital DWMH ($r = -0.175, p < .05$) were noted. Inhibition performance correlated significantly with nearly all white matter subscores: lateral ($r = -0.25, p < .01$) and occipital ($r = -0.24, p < .01$) PVH, and frontal ($r = -0.23, < .01$), parietal ($r = -0.25, < .01$), temporal ($r = -0.22, < .01$),
and occipital ($r = -0.20, p < .05$) DWMH, and, marginally, frontal PVH ($r = -0.16, p = .055$). Working memory performance was significantly related to several white matter variables: frontal ($r = -0.23, < .01$), parietal ($r = -0.17, < .05$), and occipital ($r = -0.19, < .05$) DWMH, as well as lateral ($r = -0.22, p < .01$) and, marginally, frontal ($r = -0.14, = .09$) PVH. The Set Shifting domain revealed a significant correlation with occipital DWMH ($p = -0.20, p < .05$). Finally, the Planning domain did not correlate with any white matter subscore.

Results from the hierarchical multiple linear regression analyses revealed that, after controlling for sex, IQ, depressive symptoms, and rater, temporal DWMH did not significantly predict the Fluency domain. Temporal DWMH turned out to be the most important predictor of Flexibility performance ($\beta = -0.25, p < .01$). Lateral PVH ($\beta = -0.22, p < .05$) significantly contributed to Inhibition performance. Frontal DWMH turned out to be the most important predictor of Working Memory ($\beta = -0.23, p < .01$). Finally, the Set Shifting domain revealed a sole significant association with occipital DWMH ($\beta = -0.19, p < .05$). As the Planning domain did not reveal a significant correlation with any of the WMH subscores, it was not further examined here.

Table 2. Correlations between white matter and the EF domains

<table>
<thead>
<tr>
<th></th>
<th>Flexibility</th>
<th>Fluency</th>
<th>Inhibition</th>
<th>Planning</th>
<th>Working Memory</th>
<th>Set Shifting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal PVH</td>
<td>-0.045</td>
<td>-0.0425</td>
<td>-0.158</td>
<td>-0.082</td>
<td>-0.140</td>
<td>0.1375</td>
</tr>
<tr>
<td>Lateral PVH</td>
<td>-0.097</td>
<td>-0.051</td>
<td>-0.253**</td>
<td>0.061</td>
<td>-0.2245*</td>
<td>-0.066</td>
</tr>
<tr>
<td>Occipital PVH</td>
<td>-0.135</td>
<td>-0.028</td>
<td>-0.239**</td>
<td>-0.075</td>
<td>-0.131</td>
<td>0.001</td>
</tr>
<tr>
<td>Frontal DWMH</td>
<td>-0.045</td>
<td>0.113</td>
<td>-0.229**</td>
<td>-0.104</td>
<td>-0.230**</td>
<td>-0.0865</td>
</tr>
<tr>
<td>Parietal DWMH</td>
<td>0.073</td>
<td>-0.124</td>
<td>0.247**</td>
<td>-0.007</td>
<td>-0.175*</td>
<td>-0.079</td>
</tr>
<tr>
<td>Temporal DWMH</td>
<td>-0.240**</td>
<td>-0.148</td>
<td>-0.216**</td>
<td>0.016</td>
<td>-0.137</td>
<td>-0.132</td>
</tr>
<tr>
<td>Occipital DWMH</td>
<td>-0.175*</td>
<td>-0.1015</td>
<td>0.199*</td>
<td>-0.038</td>
<td>-0.1885*</td>
<td>-0.196*</td>
</tr>
</tbody>
</table>

Partial correlations between the EF domains and white matter subscores were calculated while controlling for sex, IQ, depressive symptoms, and rater of WMH. DWMH: deep white matter hyperintensities; PVH: periventricular hyperintensities; WMH: white matter hyperintensities.

*: $p < .05$

**: $p < .01$

White matter variables and risk factors (Table 3)

Controlling for sex and rater, the risk factors additionally explained 9.9% in observed variance in frontal PVH ($p < .05$). Age turned out to be a significant predictor of frontal PVH ($\beta = 0.26, p < .01$), with a marginal effect of smoking behaviour ($\beta = 0.13, p = .09$). A significant increase of 14.3% ($p < .001$) in lateral PVH variance could be attributed to the risk factors, which was largely due to age ($\beta = 0.30, p < .001$) and hypertension ($\beta = 0.20, p < .05$). The risk factors further predicted 8.4% in occipital PVH variance ($p < .05$), with age as a significant contributor ($\beta = 0.25, p < .01$). 13.8% in frontal DWMH variance was
accustomed for by the risk factors ($p < .001$), with a strong age effect ($\beta = 0.28, p < .001$) and a marginal effect of hypercholesterolemia ($\beta = 0.16, p = .07$). An increase of 10.5% ($p < .01$) in parietal DWMH variance resulted after the risk factors entered, with age ($\beta = 0.26, p < .01$) as a significant contributor. A significant age effect was noted for temporal DWMH (OR = 1.07, $p < .01$), with a marginal effect of smoking behaviour (OR = 2.737, $p = .05$). Age was furthermore a significant predictor of occipital DWMH (OR = 1.07, $p < .05$), with a marginal effect of hypertension (OR = 3.125, $p = .09$).

Attenuating effects of age and cardiovascular risk factors

For each EF component, it was examined whether previous WMH effects could be replicated while concurrently controlling for age and cardiovascular risk factors. For Flexibility, age entered as a significant predictor ($\beta = -0.26, p < .01$), after which the significant effect of temporal DWMH ($\beta = -0.19, p < .05$) was replicated. Although both age ($\beta = -0.28, p < .001$) and smoking behaviour ($\beta = -0.16, p < .05$) entered as significant predictors of Inhibition performance, lateral PVH still significantly contributed to performance as well ($\beta = -0.14, p < .05$). Age ($\beta = -0.35, p < .001$) and smoking behaviour ($\beta = -0.24, p < .01$) also predicted Working Memory performance, diminishing the effect of frontal DWMH ($\beta = -0.11, p = .15$). Finally, age entered as significant predictor of Set Shifting ($\beta = -0.30, p < .001$), after which the effect of occipital DWMH was marginally significant ($\beta = -0.14, p = .07$).
Table 3. Predictive values of aging and cardiovascular risk factors on WMH.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Frontal PVH</th>
<th>Lateral PVH</th>
<th>Occipital PVH</th>
<th>Frontal DWMH</th>
<th>Parietal DWMH</th>
<th>Temporal DWMH</th>
<th>Occipital DWMH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta R^2$</td>
<td>$\beta$</td>
<td>$\Delta R^2$</td>
<td>$\beta$</td>
<td>$\Delta R^2$</td>
<td>$\beta$</td>
<td>$\Delta R^2$</td>
</tr>
<tr>
<td>Age</td>
<td>0.099**</td>
<td>0.258**</td>
<td>0.084*</td>
<td>0.245**</td>
<td>0.283***</td>
<td>0.255***</td>
<td>1.07*</td>
</tr>
<tr>
<td>DM</td>
<td>0.114</td>
<td>-0.053</td>
<td>0.128</td>
<td>0.038</td>
<td>-0.012</td>
<td>1.17</td>
<td>0.39-3.50</td>
</tr>
<tr>
<td>CVD</td>
<td>-0.046</td>
<td>0.021</td>
<td>0.090</td>
<td>0.043</td>
<td>0.117</td>
<td>1.18</td>
<td>0.34-4.07</td>
</tr>
<tr>
<td>Hyp.chol</td>
<td>0.104</td>
<td>0.055</td>
<td>0.003</td>
<td>0.156</td>
<td>0.047</td>
<td>0.45</td>
<td>0.17-1.19</td>
</tr>
<tr>
<td>Hypert.</td>
<td>0.063</td>
<td>0.201*</td>
<td>-0.022</td>
<td>0.053</td>
<td>0.083</td>
<td>1.75</td>
<td>0.70-4.38</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.132</td>
<td>0.090</td>
<td>0.032</td>
<td>0.119</td>
<td>0.020</td>
<td>2.74</td>
<td>0.99-7.60</td>
</tr>
</tbody>
</table>

A hierarchical regression analysis, controlling for sex and rater of WMH, was applied to all PVH variables, as well as to frontal and parietal DWMH. Temporal and occipital DWMH were analysed using a hierarchical logistic regression analysis. CVD: cardiovascular disease; DM: diabetes mellitus; DWMH: deep white matter hyperintensities; Hyp.chol: hypercholesterolemia; Hypert: hypertension; PVH: periventricular hyperintensities.

*: $p < .05$

**: $p < .01$

***: $p < .001$
Discussion

This paper addresses several issues regarding the relationship between various EF tests and WMH, associations between age, cardiovascular risk factors and white matter variables, and possible attenuating effects of aging and cardiovascular risk factors on the associations between WMH and EF.

First of all, WMH associations were present with several EF domains, with the exception of the Planning domain. Whereas Inhibition and Working Memory revealed significant correlations with nearly all white matter regions, Flexibility, Fluency, and Set Shifting correlated with more posterior DWMH regions (i.e. temporal and occipital DWMH). The strongest predictors of EF performance differed across domains: frontal DWMH related to working memory, temporal DWMH to Flexibility, occipital DWMH to Set Shifting, and lateral PVH to Inhibition. How risk factors may contribute to WMH was furthermore explored. Age turned out to be the major predictor of WMH: all WMH variables were directly relatable to age. Frontal DWMH additionally proved sensitive to hypercholesterolemia and lateral PVH to hypertension. Age and the cardiovascular risk factors furthermore accounted for part of the EF-WMH relationships.

The observation that a variety of white matter regions were related to the EF components can be interpreted in various ways. It can be suggested that, conform previous observations (Tullberg et al., 2004), WMH affect EF irrespective of their location. This suggestion can be supported considering the nature of EF tests in more detail. Next to a specific involvement of the prefrontal cortex (PFC), EF also requires the integration of various basic cognitive functions and, as such, non-frontal cortical and subcortical brain regions. This suggests that non-frontal brain damage may equally induce executive dysfunctioning (Stuss, Shallice, Alexander, & Picton, 1995). Although frontal WMH has been implicated to be strongly involved in EF (Nordahl et al., 2006), overall WMH burden is important as well (Nordahl et al., 2006; Tullberg et al., 2004). This indicates that a disruption in any part of the white matter reduces the functional connectivity and, hence, disables the integration of cognitive functions and thereby EF.

Alternatively, the observation that not all WMH subregions correlated with the EF domains and that WMH subregions most strongly involved in EF varied across different domains, supports a differentiation between the white matter regions. Previous literature suggests that PVH may be most important for EF (e.g. de Groot et al., 2000; van den Heuvel et al., 2006; Ylikoski et al., 1993). These studies, however, mostly focused on tests of EF that place heavy demands on mental speed, such as the Stroop test. It could be argued that mental speed, which requires specific frontal lobe involvement (Demakis, 2004; Leskelä et al., 1999), constitutes the previous observed associations between EF and PVH. As such, it is not surprising that Inhibition performance, as assessed with the Stroop test, related most strongly to PVH. In contrast, DWMH variables were involved in various other EF domains. For Flexibility performance, as assessed with the TMT-B, a specific role of the temporal lobe in task performance has been
WMH Related Decline in Executive Functions

implicated (Zakzanis, Mraz, & Graham, 2003), which might explain the involvement of temporal DWMH in Flexibility performance in the present study. With regard to working memory, studies indicate typical prefrontal and parietal cortex activation in task performance (Cabeza & Nyberg, 2000). Despite that various WMH subregions significantly correlated with working memory performance, the strength of these associations was diminished after frontal DWMH entered the analysis. The use of compensatory strategies in the aged population may explain the strongest contribution of frontal white matter to working memory performance. Compensatory strategies commonly include an increase in brain activation as well as the recruitment of additional brain regions in cognitive task performance to cope with decrements in cognitive capacity that accompany aging. For working memory, a specific increase in frontal activity in older compared to younger subjects has been reported (Grossman et al., 2002; Mattay et al., 2006). These increasing demands placed on the frontal lobe may explain why frontal white matter was the strongest predictor of Working Memory performance in the present study population.

Another question of the present study concerned how age and cardiovascular risk factors contribute to WMH. When examined together, the risk factors significantly predicted the degree of WMH. Conform previous research, age turned out to be the most important predictor of WMH (Ylikoski et al., 1995), revealing a significant association with each WMH subscore. Despite that only some additional significant effects of the cardiovascular risk factors were observed, it can be concluded that, overall, age and the cardiovascular risk factors were related to WMH. Aging and the cardiovascular risk factors furthermore accounted for part of WMH-EF association, although overall the significant relationship between EF and WMH was retained. As such, the association between WMH and EF seems quite robust.

Quite surprising is the observation of a small effect of hypertension in the present study only. Hypertension, next to aging, poses a major risk factor for both WMH (Artero et al., 2004; Dufouil et al., 2001; van Dijk et al., 2004) and executive dysfunctioning (Harrington, Saxby, McKeith, Wesnes, & Ford, 2000; Saxby et al., 2003; Singh-Manoux & Marmot, 2005). We observed a significant effect for lateral PVH only, without significant contributions to other WMH subscores and EF domains. One explanation for this apparent contradiction may be that nearly all hypertensive subjects were taking antihypertensive medication (97%) and the majority had controlled blood pressure (BP) levels (i.e. 63% had systolic BP <160 and diastolic BP < 90, data not shown), which significantly reduces the risk of WMH (Dufouil et al., 2001; Fukuda & Kitani, 1995) and cognitive decline (Hanon et al., 2006; Murray et al., 2002; Skoog et al., 2005). If this is the case, the present study was not capable of indicating ‘true’ effects of hypertension on both WMH and EF. Alternatively, an interpretation might be that the effect of treated hypertension on WMH and EF is small at most. However, further research is needed to elucidate this possibility.

The present study provides more insight into the relationship between various EF and WMH, and how this association may be mediated and attenuated by age
and cardiovascular risk factors. First of all, we confirmed WMH to relate to various EF domains, although the nature of the association may vary with each domain. Presumably, the association between executive dysfunctioning and WMH is specified by the cognitive abilities that comprise that function. Furthermore, significant effects of age and cardiovascular risk factors were observed for the white matter subscores, with age as a strong predictor of each WMH subscore. Finally, although the relationship between EF and WMH was slightly modified when additionally controlling for age and cardiovascular risk factors, overall the results support robust associations between WMH and EF domains exist in the aged population. The precise mechanisms underlying the associations between WMH and EF, with the focus on the diverse cognitive abilities addressed by each EF domain, require elucidation and should be explored in future studies.