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The role of white matter hyperintensities and medial temporal lobe atrophy in age-related executive dysfunctioning

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ABSTRACT

Various studies support an association between white matter hyperintensities (WMH) and deficits in executive function in nondemented ageing. Studies examining executive functions and WMH have generally adopted executive function 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 affected as a result of WMH. Furthermore, atrophy of the medial temporal lobe (MTA) is frequently observed in ageing. Nevertheless, in previous studies of nondemented ageing MTA was not considered when examining a relationship between white matter and executive function. The goal of the present study was to examine how WMH and MTA relate to a variety of executive functions, including flexibility, fluency, inhibition, planning, set shifting, and working memory. Strong correlations were observed between WMH and MTA and most of the executive functions. However, only MTA was related to flexibility and set shifting performance. Regression analysis furthermore showed that MTA was the strongest predictor of working memory, after which no further significant association with WMH was noted. Alternatively, both MTA and periventricular hyperintensities independently predicted inhibition performance. These findings emphasize the importance of MTA when examining age-related decline in executive functioning.

1. Introduction

Normal ageing is associated with a decline in cognitive functions, including executive function (Keys & White, 2000; MacPherson, Phillips, & Della Sala, 2002). White matter hyperintensities (WMH), indicative of reduced white matter integrity, are frequently observed in ageing and might mediate the decrement in executive function (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 is extensively connected to both cortical and subcortical regions (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 executive function (Royall et al., 2002). By reducing the functional connectivity of the PFC with other (sub-)cortical regions, WMH have been found to induce deficits in executive function (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 executive function has been well established, several issues regarding this relationship require elucidation. The term executive function has been used as a single construct including a variety of functions such as working memory, inhibition, and flexibility. Previous studies mostly focused on a single or only a few tests as representative of the entire executive function domain (e.g. Baum, Schulte, Girke, Reischies, & Felix, 1996; Gunning-Dixon & Raz, 2003; Marshall et al., 2006; Shenkin et al., 2005). Moreover, whether all executive functions are affected by WMH remains indefinite. For example, findings regarding the relationship between WMH and flexibility, measured with the Trail Making Test part B (TMT-B), or fluency performance, are inconsistent (Bartres-Faz et al., 2001; Baum et al., 1996; DeCarli et al., 1995; Dufouil, Alperovitch, & Tzourio,

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2003). Whether planning, another executive function that is strongly affected by ageing (Andres & Van der Linden, 2000; Phillips, Kliegel, & Martin, 2006; Robbins et al., 1998), relates to WMH in the aged population is unclear. Set shifting performance constitutes another function within the executive 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).

Next to WMH, mild atrophy of the medial temporal lobe (MTA) is observed in ageing (Raz, Rodrigue, Head, Kennedy, & Acker, 2004; Yonelinas et al., 2007). The medial temporal lobe is well known for its role in episodic memory. Next to the typical involvement in memory and learning, however, it is known that interactions between the medial temporal lobe, including the hippocampus, and prefrontal brain areas exist (Laroche, Davis, & Jay, 2000). Although traditionally referred to as a medial temporal lobe function, previous studies do point to an involvement of the PFC and of executive function in memory performance (e.g. Ranganath, Johnson, & D'Esposito, 2003; Rossi et al., 2006; Simard, Rouleau, Brosseau, Laframboise, & Bojanowsky, 2003). Furthermore, indirect projections of the PFC, through the thalamus, to the hippocampus have been identified in rats (Vertes, Hoover, Szigeti-Buck, & Leranth, 2007). Functional connectivity between the PFC and medial temporal lobe has been suggested by previous studies showing an excitatory effect of hippocampal activity on PFC functioning (Laroche et al., 2000). This implies that the medial temporal lobe may be involved in functions characteristic of the prefrontal cortex, including executive functions. Confirmative of this idea, MTA has been related to a decrease in fluency ability, a test of executive function, in an aged study sample that included demented subjects (Launer et al., 1995). Similarly, another study reported MTA to predict executive functioning in patients with mild cognitive impairment (van der Pol et al., 2007). Final evidence for involvement of the medial temporal lobe in executive function comes from a study showing a direct association between these functions and dopamine D2 receptor binding in the hippocampus (Takahashi et al., 2007). One possible rationale for these observations focuses on the multidisciplinary nature of executive functions and the tests employed to measure them. The term 'executive function' refers to the "high-order functions operating in non-routine, i.e. novel, complex, and/or conflicting situations" (Godefroy, 2003). In order for these functions to operate necessitates the integration of diverse cognitive functions. This indicates that intact executive functioning is partly dependent on other cognitive functions, such as memory. Indeed, previous studies point to a role of memory performance in executive function tasks (e.g. Giovagnoli, 2001). The medial temporal lobe is a structure highly important for memory. Therefore, by affecting memory functions, MTA may also induce a deficit in executive function.

The present study focuses on several issues. First of all, the relationship between WMH and various executive functions (i.e. flexibility, fluency, inhibition, planning, set shifting, working memory) will be assessed. As WMH induces cortical disconnection, an inverse relationship between WMH and all executive functions is expected. Secondly, the effect of MTA will be examined and taken into account with regard to the relationship between executive functions and WMH. Reduced integrity of the medial temporal lobe, affecting connectivity with the prefrontal cortex and the presumed involvement in executive functions, is expected to also inversely relate to executive performance. Although interconnected, the functions of the PFC, which are impaired by WMH, include different ones from those exerted by the medial temporal lobe (Sloan, Good, & Dunnett, 2006). Therefore, a complementary relationship between WMH and MTA in task performance is expected.

2. Methods

2.1. Subjects

One hundred and sixty 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. Ageing poses the major risk for WMH (Ylikoski et al., 1995), and since 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. As this study is part of a larger study focusing on cardiovascular risk factors, medical records of elderly people visiting the outpatient clinic (e.g. of cardiology or internal medicine) were screened to select subjects with and without these risks. As such, most subjects (83.1%) had one or more of these risks, including a history of hypertension, hypercholesterolemia, diabetes mellitus, cardiovascular disease (myocardial infarction, congestive heart failure, coronary artery disease, atrial fibrillation), and smoking. These risk factors have been acknowledged as risks for WMH and MTA (Den Heijer et al., 2003, 2005; Jeerakathil et al., 2004; Lazarus, Prettyman, & Cherryman, 2005). A small percentage of participants (16.9%) consisted of healthy partners or neurological out-patients visiting the hospital for low back pain or a peripheral nerve problem; all were without a history of cardiovascular risk factors and all fulfilled the age criterion.

A prerequisite for subjects to participate was to be free of a history 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 $\geqslant 26$ was required for participation. Both premorbid IQ, assessed with the Dutch version of the National Adult Reading Test (Schmand, Bakker, Saan, & Louman, 1991) and education, assessed with an ordinal rating scale ranging from 1 (incomplete primary school) to 7 (university degree) (Heslinga, van den burg, & Saan, 1983), were measured. Using standardized z-scores, a single composite was calculated representing intelligence. Subject details are presented in Table 1. Approval for this study was obtained from the Sint Lucas Andreas medical ethics committee. All subjects signed an informed consent form.

2.2. Executive functions

The neuropsychological battery completed by the participants consisted of tests measuring the following executive functions: flexibility, fluency, inhibition, planning, set shifting, and working memory. A single score, using standardized z-scores, was calculated for each executive function. Scores were adjusted such that a higher score always represented better performance.

2.2.1. Flexibility

The Trail Making Test (TMT; Reitan, 1958) was employed to assess flexibility performance. The TMT-A consists of 25 encircled

Table 1
Subject characteristics ($N = 160$)

Variable	Value
Age (mean ± SD)	68.3 (8.7)
Sex (% male)	61.3
Education (mean ± SD)	4.5 (1.5)
IQ (mean ± SD)	99.9 (13.5)
MMSE (mean ± SD)	28.1 (1.4)

MMSE, Mini mental state examination.