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The influence of cerebral small vessel disease on default mode network deactivation in mild cognitive impairment

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ABSTRACT

Introduction: Cerebral small vessel disease (CSVD) is thought to contribute to cognitive dysfunction in patients with mild cognitive impairment (MCI). The underlying mechanisms, and more specifically, the effects of CSVD on brain functioning in MCI are incompletely understood. The objective of the present study was to examine the effects of CSVD on brain functioning, activation and deactivation, in patients with MCI using task-related functional MRI (fMRI).
Methods: We included 16 MCI patients with CSVD, 26 MCI patients without CSVD and 25 controls. All participants underwent a physical and neurological examination, neuropsychological testing, structural MRI, and fMRI during a graded working memory paradigm.
Results: MCI patients with and without CSVD had a similar neuropsychological profile and task performance during fMRI, but differed with respect to underlying (de)activation patterns. MCI patients with CSVD showed impaired deactivation in the precuneus/posterior cingulate cortex, a region known to be involved in the default mode network. In MCI patients without CSVD, brain activation depended on working memory load, as they showed relative 'hyperactivation' during vigilance, and 'hypoactivation' at a high working memory load condition in working memory related brain regions.
Conclusions: We present evidence that the potential underlying mechanism of CSVD affecting cognition in MCI is through network interference. The observed differences in brain activation and deactivation between MCI patients with and without CSVD, who had a similar 'clinical phenotype', support the view that, in patients with MCI, different types of pathology can contribute to cognitive impairment through different pathways.

1. Introduction

Mild cognitive impairment (MCI) is a clinical construct that classifies individuals with cognitive impairment and high risk of dementia (DeCarli, 2003; Petersen, 2004; Albert et al., 2011). While MCI is a heterogeneous condition, it was found that Alzheimer's disease (AD) and Vascular dementia (VaD) are the most common clinical endpoints, and consequently either Alzheimer pathology, cerebral vascular pathology, or a combination of the two, underlies the great majority of MCI cases (Petersen et al., 2001; Meyer et al., 2002; Mitchell and Shiri-Feshki, 2009). The most common type of cerebrovascular pathology is cerebral small vessel disease (CSVD). The consequence of this condition on the brain parenchyma is damage to the white matter and subcortical gray matter structures, visible on MRI as white matter hyperintensities (WMH) and lacunar infarcts (Pantoni, 2010). In MCI patients, CSVD has been associated with cognitive deficits including reduced mental speed, impaired executive functioning, and deficits in working and episodic memory (Galluzzi et al., 2005; Nordahl et al., 2005; Nordlund et al., 2007; Luchsinger et al., 2009; Villeneuve et al., 2011). Whereas Alzheimer pathology is known to cause cognitive deficits by affecting cortical brain regions, the mechanisms through which CSVD contributes to cognitive impairment are still a matter of debate. It has been postulated that the link between CSVD and cognitive impairment lies in frontal lobe functioning, CSVD causing cognitive impairment through disconnection of cortico-striatal loops resulting in frontal lobe dysfunction (Cummings, 1993; Pugh

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and Lipsitz, 2002; Tullberg et al., 2004). This hypothesis is supported by results from a recent task-related functional MRI (fMRI) study in healthy elderly with CSVD, that showed an association between the extent of vascular burden, impaired brain deactivation and lower functional connectivity in the prefrontal cortex (Mayda et al., 2011). While the analyses in this study were limited to frontal regions of interest (ROI) and effects of CSVD on brain functioning in the rest of the brain remained unclear, the study does postulate a relationship between structural white matter integrity and neural network functioning underlying cognitive deterioration. Several recent studies have examined this relationship within the default mode network (DMN) (for a review see Damoiseaux and Greicius, 2009), a network of brain regions including the medial prefrontal cortex, posterior cingulate cortex (PCC)/precuneus, anterior cingulate cortex (ACC), hippocampus and inferior parietal lobule, found to be actively suppressed, i.e. deactivated, during the performance of cognitive tasks (Raichle et al., 2001; Greicius et al., 2003; Buckner et al., 2008). These studies using a combination of resting state fMRI and diffusion tensor imaging (DTI) show that functional connectivity and network functioning are largely dependent on white matter structural integrity (Damoiseaux and Greicius, 2009).

The objective of this study was to examine the role of CSVD on brain functioning in MCI. For this purpose we assessed fMRI activation as well as deactivation patterns during an n-back working memory paradigm in MCI patients with and without CSVD. This paradigm is heavily dependent upon the frontal lobe (Braver et al., 1997), and was previously found to be effective in examining deactivation within the DMN in MCI (Kochan et al., 2010). We hypothesized that the presence of CSVD in MCI will result in differences in brain functioning, and, considering the findings of reduced functional connectivity in healthy elderly with CSVD (Mayda et al., 2011), as well as a relationship between DMN functioning and white matter integrity (Damoiseaux and Greicius, 2009), we furthermore hypothesized that CSVD will affect brain regions involved in network functioning. To address this hypothesis we examined specifically deactivation during cognitive functioning in regions involved in the DMN in MCI patients with CSVD, MCI patients without CSVD and controls by means of ROI analysis. This ROI analysis was based on a priori defined brain regions known to be involved in the DMN, in conjunction with results in controls.

2. Methods

2.1. Participants

We recruited MCI patients, aged 65 years or older, from outpatient clinics of the departments of Geriatrics and Neurology of Erasmus MC, University Medical Center Rotterdam, the Netherlands, and 7 surrounding hospitals on the basis of criteria for MCI by Petersen (Petersen and Morris, 2005). These criteria include: 1) presence of cognitive complaint by patient or relatives; 2) impairment in one or more cognitive domains; 3) preserved overall general functioning, with possible increased difficulty in the performance of activities of daily living; and 4) absence of dementia according to the DSM-IV or NINCS ADRDA criteria for dementia. We screened 57 MCI patients for study eligibility. Exclusion criteria were a history of a neurological or psychiatric disorder negatively affecting cognition (e.g. major stroke, cerebral tumor or depression) and contraindication for MRI (e.g. metal implants and claustrophobia). After the initial screening we invited 55 MCI patients to participate in the present study. All patients underwent a standardized work-up, including physical and neurological examination, extensive neuropsychological assessment, structural and functional MRI scanning. After the MRI examinations, we excluded 2 patients due to physical inability or refusal to undergo MRI when presented with the MRI scanner, 1 MCI patient because of excessive head movement (movement more than 1 voxel, 3 mm), 2 patients with vision problems, and 8 patients based on insufficient fMRI task performance (as described below). We included the remaining 42 patients in our analyses. Controls (n = 25; 65 years or older) were either relatives of MCI patients, or were recruited through advertisement in the Erasmus MC, University Medical Center. The same in- and exclusion criteria applied to the controls, except that controls did not have cognitive complaints and a neuropsychological profile within normal boundaries. Controls underwent the exact same work-up as the MCI patients. All participants gave written informed consent to our protocol that was approved by the medical ethics committee of the Erasmus MC, University Medical Center, Rotterdam.

2.2. Structured interview and physical examination

We collected data on demographics, general functioning, activities of daily living and vascular risk factors by means of a structured interview. Level of education was assessed with a Dutch education scale ranging from 1 (less than 6 years elementary school) to 7 (academic degree) (Verhage, 1964). We defined hypertension as a systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 90 mm Hg or the use of antihypertensive medication, and determined *Apoliproprotein E* (*APOE*) genotype in all participants.

2.3. Neuropsychological assessment

Trained neuropsychologists administered a standardized battery of neuropsychological tests to all participants. The battery included the MMSE as a global cognitive screening method; the Dutch version of the Rey Auditory Verbal Learning Test, the 15-word verbal learning test (15-WVLT) and the stories of the Rivermead Behavioural Memory Test (RBMT) to assess memory; the Trail Making Test (TMT) part A and Stroop II as measures of cognitive processing speed; the TMT part B, Stroop III, the modified Wisconsin Card Sorting Test (WCST), and a phonological fluency task to assess executive functioning; the Boston Naming Test (BNT; 60 items version) and semantic fluency tasks (animals and occupations) to measure word finding difficulties and lexical retrieval; the subtest Block Design of the Wechsler Adult Intelligence Scale III and clock drawing to assess visuo-spatial and visuo-constructive ability respectively. For every neuropsychological test we calculated z-scores, using the mean and standard deviation of the test scores from the control group (z-score = individual test score minus mean divided by the standard deviation). Subsequently, we constructed composite scores for the following cognitive domains: memory (15 WVLT and RBMT immediate recall and delayed recall), information processing speed (TMTA and Stroop II), executive functioning (TMTB and Stroop III), and language (BNT and semantic fluency tasks). Visuo-spatial skills and visuo-constructive ability are each represented by a single neuropsychological test, and consisted of z scores of the Block Design test and clock drawing test respectively. We defined impairment in a cognitive domain as a z-score of −1.5 below the mean score of controls in that domain.

2.4. MRI acquisition protocol

We performed structural and functional MR imaging on a 3.0 T MRI scanner with an 8-channel head coil (HD platform, GE Healthcare, Milwaukee, US). High resolution 3 dimensional (3D) inversion recovery fast spoiled gradient recalled T1-weighted structural MRI was acquired in the axial plane with the following parameters: repetition time (TR) = 10.4 ms, echo time (TE) = 2.1 ms, inversion time (TI) = 300 ms, flip angle 18°, acquisition matrix 416 × 256, field of view (FOV) 250 × 175 mm^2. We acquired 192 slices with a slice thickness of 1.6 mm with 0.8 mm overlap in a total acquisition time of 4:57 min. T2-fluid attenuated inversion recovery (FLAIR) images were obtained with the following parameters: TR = 8000 ms, TE = 120 ms, TI 2000 ms, acquisition matrix 256 × 128 mm^2, FOV 210 × 210 mm^2. We acquired 64