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White matter integrity in small vessel disease is related to cognition

Anil M. Tuladhar[a,b,1], Anouk G.W. van Norden[c,1], Karlijn F. de Laat[d], Marcel P. Zwiers[b], Ewoud J. van Dijk[a], David G. Norris[b,e,f], Frank-Erik de Leeuw[a,g,*]

[a] Donders Institute for Brain, Cognition and Behaviour, Centre for Neuroscience, Department of Neurology, Radboudumc, PO Box 9101, Nijmegen 6500 HB, The Netherlands
[b] Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging, Radboud University Nijmegen, PO Box 9101, Nijmegen 6500 HB, The Netherlands
[c] Department of Neurology, Amphia Ziekenhuis, Breda, The Netherlands
[d] Department of Neurology, HagaZiekenhuis, Den Haag, The Netherlands
[e] Erwin L. Hahn Institute for Magnetic Resonance Imaging, University of Duisburg-Essen, Essen, Germany
[f] MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands
[g] Donders Institute for Brain, Cognition and Behaviour, Centre for Neuroscience, Department of Psychiatry, Radboud University Nijmegen Medical Centre, PO Box 9101, Nijmegen 6500 HB, The Netherlands

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ABSTRACT

Cerebral small vessel disease, including white matter hyperintensities (WMH) and lacunes of presumed vascular origin, is common in elderly people and is related to cognitive impairment and dementia. One possible mechanism could be the disruption of white matter tracts (both within WMH and normal-appearing white matter) that connect distributed brain regions involved in cognitive functions. Here, we investigated the relation between microstructural integrity of the white matter and cognitive functions in patients with small vessel disease. The Radboud University Nijmegen Diffusion tensor and Magnetic resonance Cohort study is a prospective cohort study among 444 independently living, non-demented elderly with cerebral small vessel disease, aged between 5500 and 85 years. All subjects underwent magnetic resonance imaging and diffusion tensor imaging scanning and an extensive neuropsychological assessment. We showed that loss of microstructural integrity of the white matter at specific locations was related to specific cognitive disturbances, which was mainly located in the normal-appearing white matter ($p < 0.05$, FWE-corrected for multiple comparisons). The microstructural integrity in the genu and splenium showed the highest significant relation with global cognitive function and executive functions, in the cingulum bundle with verbal memory performance. Associations between diffusion tensor imaging parameters and most cognitive domains remained present after adjustment for WMH and lacunes. In conclusion, cognitive disturbances in subjects with cerebral small vessel disease are related to microstructural integrity of multiple white matter fibers (within WMH and normal-appearing white matter) connecting different cortical and subcortical regions.

1. Introduction

Cerebral small vessel disease (SVD) manifests on conventional MR images (i.e. T1 and FLuid Attenuated Inversion Recovery (FLAIR)) as white matter hyperintensities (WMH) and lacunes of presumed vascular origin (Wardlaw et al., 2013). These SVD markers are commonly observed in the elderly population. SVD is related to cognitive impairment and may, in some, ultimately lead to dementia (de Groot et al., 2000; Vermeer et al., 2003). This is supposedly due to the disruption of important white matter (WM) tracts. Despite the high prevalence of SVD (de Leeuw et al., 2001; Vernooij et al., 2007), relatively few develop evident cognitive decline or dementia (Vermeer et al., 2003). Other factors, apart from WMH and lacunes, presumably play a role in the transition from relative intact cognitive performance to severe cognitive decline in these few individuals. One of these factors could be the (loss of) microstructural integrity of the largest part of the WM; the on FLAIR imaging normal-appearing white matter (NAWM) surrounding the SVD. Pathological studies have demonstrated loss of microstructural integrity in the NAWM (Grafton et al., 1991) that cannot be visualized with conventional imaging, but can be investigated with diffusion tensor imaging (DTI).

DTI provides information on the microstructural integrity of the WM. DTI measures the local water diffusion profiles by: fractional anisotropy (FA), which represents a normalized ratio of diffusion directionality; mean diffusivity (MD), which reflects the overall magnitude of water diffusion; axial diffusivity (AD), which reflects the diffusivity parallel to the WM tracts and radial diffusivity (RD), which is the diffusivity perpendicular to these tracts (Pierpaoli et al., 1996). Loss of

* Corresponding author. Tel.: +31 243613396; fax: +31 243541122.
E-mail address: FrankErik.deleeuw@radboudumc.nl (F.-E. de Leeuw).
[1] Authors contributed equally to this work.

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microstructural integrity is typically reflected by a reduction in FA and/or an increase in MD (Sen and Basser, 2005); the latter can result from different combinations of changes in AD and RD. Few studies in patients with cerebral SVD demonstrated a relation between higher MD and lower FA and loss of cognitive function (Della Nave et al., 2007; Nitkunan et al., 2008; O'Sullivan et al., 2001b; O'Sullivan et al., 2004; Xu et al., 2010). These studies had, however, small sample sizes and were not able to properly adjust for possible confounders. One large population-based cohort study demonstrated relation between microstructural integrity of both WMH and NAWM and cognitive function. However, the regional differences of microstructural integrity were not taken into account (Vernooij et al., 2009).

We hypothesized that cognitive performance in subjects with SVD would not only be related to loss of WM microstructural integrity within the WMH, but also to specific areas within the NAWM. We conducted DTI using tract-based spatial statistics (TBSS) analyses to investigate the location of microstructural WM loss related to cognitive disturbances. Also, additional adjustments for the WMH and lacunes were made to examine whether the associations in the WM were primarily explained by the typical manifestations of SVD on conventional MRI.

2. Methods and materials

2.1. Study population

The Radboud University Nijmegen Diffusion tensor and Magnetic resonance imaging Cohort (RUN DMC) study prospectively investigates the risk factors and clinical consequences of brain changes among 503 non-demented elderly with cerebral SVD. The selection procedure of the participants and study protocol were described previously in detail (van Norden et al., 2011). In short, on the basis of established research criteria SVD was defined as the presence of lacunes and/or WMH on neuroimaging (Erkinjuntti, 2002). Symptoms of SVD include acute symptoms, such as TIAs or lacunar syndromes, or subacute manifestations, such as cognitive and motor (gait) disturbances and/or depressive symptoms (Roman et al., 2002). Inclusion criteria were: (a) age between 50 and 85 years; and (b) cerebral SVD on neuroimaging. The main exclusion criteria were dementia (American Psychiatric Association, 2000), (psychiatric) disease interfering with cognitive testing or follow-up, WMH or SVD mimics and MRI contraindications or known claustrophobia. Consecutive patients referred to the Department of Neurology between October 2002 and November 2006 were selected for participation. Participants were selected for participation in the study by a three-step approach. After reviewing the medical history, 1004 individuals were invited by letter. Of those 1004, 7these numbers seem odd the way they are displayed. Is this correct??27 were eligible after contact by telephone and 525 agreed to participate. In 22 individuals exclusion criteria were found during their visit to our research center, yielding a response of 71.3% (503/705). For the present study, 59 subjects were additionally excluded because of territorial infarcts ($n = 55$) and inadequate quality of the MRI image ($n = 4$), resulting in a final population of 444 participants. All participants signed an informed consent form. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.

2.2. Measurement of cognitive function

Cognitive function was assessed by a standardized neuropsychological test battery and has been described in detail elsewhere (van Norden et al., 2011). Performance across tests was made comparable by transforming raw test results in *z*-scores. We calculated compound scores for seven cognitive domains. Global cognitive function was evaluated by the Mini Mental State Examination (MMSE) and the cognitive index. The cognitive index is a compound score that was calculated as the mean of the *z*-scores of the 1-letter subtask of the Paper–Pencil Memory Scanning Task, the mean of the reading subtask of the Stroop test, the mean of the Symbol–Digit Substitution Task and the mean of the added score on the three learning trials of the Rey Auditory Verbal Learning Test and the delayed recall of this last test (Vermeer et al., 2003). Verbal memory is a compound score of the mean of two *z*-scores from the Rey Auditory Verbal Learning Test; one for the added scores of the three learning trials of this test, and one for the delayed recall of this test. Visuospatial memory is a compound score of the mean of the *z*-scores of the immediate recall trial and the delayed recall trial of the Rey's Complex Figure Test. Psychomotor speed was calculated as the mean of the *z*-scores of the 1-letter subtask of the Paper–Pencil Memory Scanning Task, the reading subtask of the Stroop test and the Symbol–Digit Substitution Task. Fluency was calculated from the mean of the *z*-scores of both verbal fluency tasks. Concept shifting was calculated as the *z*-score of the third subtask of the Stroop. Attention is a compound score of the *z*-score of the total time of the Verbal Series Attention Test (de Groot et al., 2000).

2.3. Magnetic resonance imaging scanning protocol

MRI scans of all participants were acquired on a single 1.5-T MRI. The protocol included, among other sequences, the following whole brain scans: 3D T1 magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR/TE/TI 2250/3.68/850 ms; flip angle15°; voxel size $1.0 \times 1.0 \times 1.0$ mm), a fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE/TI 9000/84/2200 ms; voxel size $1.0 \times 1.2 \times 5.0$ mm, interslice gap 1 mm) and DTI sequences (TR/TE 10,100/93 ms; voxel size $2.5 \times 2.5 \times 2.5$ mm; 4 unweighted scans, 30 diffusion weighted scans with b-value 900 s/mm^2).

2.4. Conventional magnetic resonance imaging analysis

WMH were manually segmented on FLAIR images and the number of lacunes was rated according to a standardized protocol (van Norden et al., 2011). In addition, the visual Fazekas scale was used on the FLAIR images to rate the severity of changes in the white matter (Fazekas et al., 1987). All imaging analyses were performed by two trained raters blinded to clinical information. In a random sample of 10%, interrater variability for total WMH volume yielded an intra-class correlation coefficient of 0.99. The probability map of the white matter hyperintensities were created using a method previously described by de Laat and colleagues (de Laat et al., 2011). In short, we registered the WMH maps to the T1 images using the transformation matrix from the registration parameters of skull-stripped FLAIR images to the T1-images that were obtained using Functional MRI of the Brain linear image registration tool (http://www.fmrib.ox.ac.uk/fsl/fnirt). Next, we normalized the WMH maps non-linearly to the group-specific template using the transformation parameters of T1 images to the group-specific template obtained from Functional MRI of the Brain non-linear registration tool (http://www.fmrib.ox.ac.uk/fsl/flirt). Finally, we averaged the normalized WMH maps to create a probability map of the WMH of the study population (Fig. 1).

We computed gray (GM) and WM tissue and cerebrospinal fluid (CSF) probability maps using SPM 5 unified segmentation routines on the T1 MPRAGE images (Ashburner and Friston, 2005). Total GM, WM and CSF volumes were calculated by summing all voxel volumes that had a $p > 0.5$ for belonging to that tissue class. Total brain volume (TBV) was taken as the sum of total GM and WM. Intracranial volume (ICV) was a summation of all tissue classes. To normalize for head size, TBV was expressed as percentage of total ICV.

2.5. DTI analysis

Tract-based spatial statistics (TBSS) is a relatively new method that mitigates the limitations of VBM analysis (Smith et al., 2006). This analysis is restricted to those WM voxels that constitute the skeleton (core) of the brains connectional architecture. This skeleton can be matched