NeuroImage: Clinical 19 (2018) 963–969

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

The cumulative effect of small vessel disease lesions is reflected in structural brain networks of memory clinic patients

Rutger Heinen[a,1], Naomi Vlegels[a,*,1], Jeroen de Bresser[b,c], Alexander Leemans[d], Geert Jan Biessels[a], Yael D. Reijmer[a], On behalf of the Utrecht Vascular Cognitive Impairment study group

[a] Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[b] Department of Radiology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[c] Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands
[d] Image Sciences Institute, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Cerebral small vessel disease
Vascular cognitive impairment
Diffusion-weighted imaging
Cognition
Magnetic resonance imaging

ABSTRACT

Background and purpose: Mechanisms underlying cognitive impairment in patients with small vessel disease (SVD) are still unknown. We hypothesized that cognition is affected by the cumulative effect of multiple SVD-related lesions on brain connectivity. We therefore assessed the relationship between the total SVD burden on MRI, global brain network efficiency, and cognition in memory clinic patients with vascular brain injury.

Methods: 173 patients from the memory clinic of the University Medical Center Utrecht underwent a 3 T brain MRI scan (including diffusion MRI sequences) and neuropsychological testing. MRI markers for SVD were rated and compiled in a previously developed total SVD score. Structural brain networks were reconstructed using fiber tractography followed by graph theoretical analysis. The relationship between total SVD burden score, global network efficiency and cognition was assessed using multiple linear regression analyses.

Results: Each point increase on the SVD burden score was associated with 0.260 [−0.404 - -0.117] SD units decrease of global brain network efficiency ($p < .001$). Global network efficiency was associated with information processing speed (standardized B = −0.210, $p = .004$) and attention and executive functioning (B = 0.164, $p = .042$), and mediated the relationship between SVD burden and information processing speed ($p = .027$) but not with executive functioning ($p = .12$).

Conclusion: Global network efficiency is sensitive to the cumulative effect of multiple manifestations of SVD on brain connectivity. Global network efficiency may therefore serve as a useful marker for functionally relevant SVD-related brain injury in clinical trials.

1. Introduction

Small vessel disease (SVD) is a common cause of cognitive decline and dementia (Gorelick et al., 2011). However, the mechanisms underlying cognitive impairment in SVD remain largely unknown. A proposed mechanism is that SVD-related lesions (such as white matter hyperintensities (WMH), lacunes, cerebral microbleeds (CMB), and perivascular spaces (PVS)) affect structural brain connectivity and thereby the efficiency of the brain network to process information. Due to recently developed techniques, we can now estimate the efficiency of the brain network using diffusion MRI and graph theory analyses. Several studies have shown that global network efficiency is related to reduced processing speed and executive functioning in patients with SVD (Reijmer et al., 2013; Reijmer et al., 2015; Lawrence et al., 2014; Tuladhar et al., 2016). In these studies, associations between network efficiency and cognition were found to be stronger than between individual MRI markers of SVD and cognition (Patel and Markus, 2011). One reason for the strong associations between network efficiency and cognition, could be a sensitivity of network efficiency to the cumulative effect of multiple types of SVD-related injury on brain connectivity (Sun et al., 2014). In previous studies a total SVD burden score was used to capture these multiple types of SVD-related injury (Huijts et al., 2013; Staals et al., 2014; Staals et al., 2015). To date, the association between increasing SVD burden and brain network efficiency has not yet been assessed in memory clinic patients. In the current study, we used a previously developed total SVD score that combines various well-

* Corresponding author: Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, the Netherlands.
E-mail address: n.vlegels@umcutrecht.nl (N. Vlegels).
[1] Contributed equally to this work.

https://doi.org/10.1016/j.nicl.2018.06.025
Received 14 March 2018; Received in revised form 23 May 2018; Accepted 17 June 2018
Available online 19 June 2018

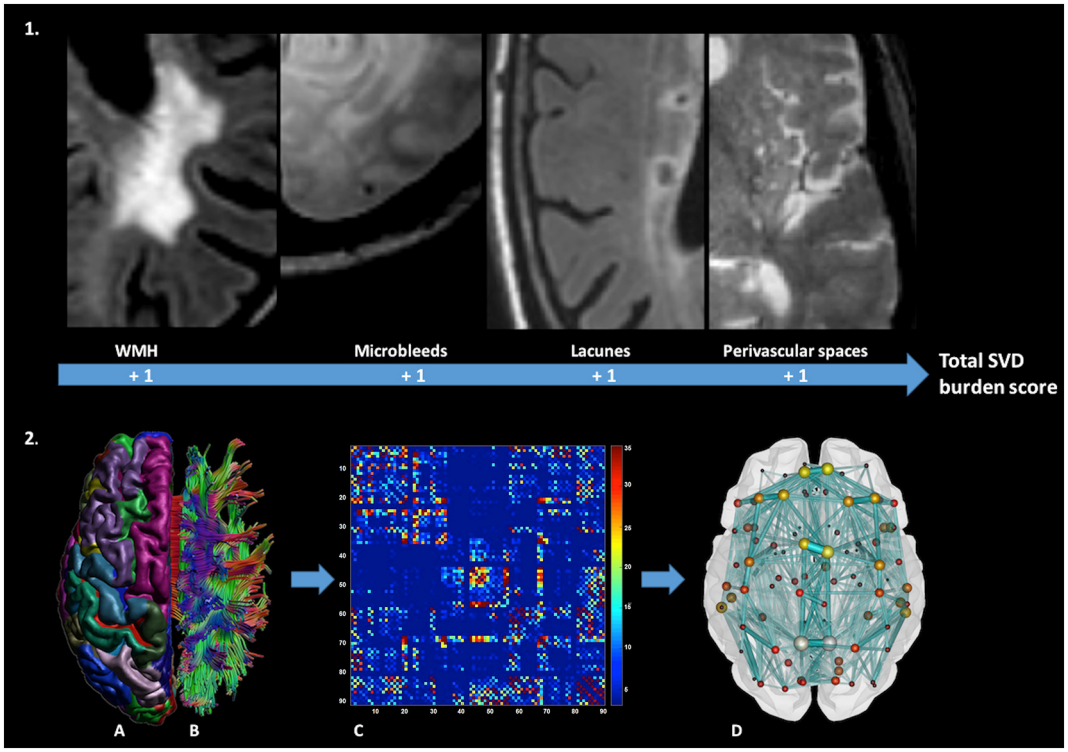

Fig. 1. Flowchart of construction of SVD burden score and structural network reconstruction.
Panel 1 depicts the calculation of the total small vessel disease burden score. One point is added to the score for the presence for (1) Deep WMH (Fazekas grade ≥ 2) or perivascular WMH (Fazekas grade 3), (2) Presence of microbleeds, (3) Presence of lacunes, and (4) > 10 perivascular spaces. Panel 2 depicts (A) The coregistration of an Automated Anatomical Labeling atlas (AAL) template, consisting of 90 cortical and subcortical brain regions to (B) the whole-brain Constrained Spherical Deconvolution (CSD)-based tractography, (C) For any two regions of the AAL template, it was established if a connection was present. Each connection was multiplied by the mean fractional anisotropy (FA) of that connection, resulting in a 90 × 90 weighted connectivity matrix. (D) The weighted connectivity matrix can be viewed as a graph composed of nodes (brain regions) and edges (white matter connections). Network measures such as global network efficiency were calculated on individual structural brain networks.

established MRI markers of SVD (Huijts et al., 2013; Staals et al., 2014; Staals et al., 2015) to test the relationship between SVD, global network efficiency, and cognition. We expected that with increasing SVD burden (i.e. a higher SVD burden score), global network efficiency would decrease. Secondly, we hypothesized that global network efficiency mediates the association between total SVD score and cognition (i.e. processing speed and executive functioning).

2. Methods

2.1. Study population

Patients in the current study were recruited from the memory clinic at the University Medical Center Utrecht (UMC Utrecht) between September 2009 and December 2013. This study sample has been described in detail earlier (Boomsma et al., 2017). In short, all patients that presented with cognitive complaints and vascular brain injury on MRI (i.e. possible VCI) were eligible to participate. In order to capture the whole spectrum of possible VCI, we defined no threshold for cognitive impairment or specific patterns of vascular brain injury. Vascular brain injury was operationalized as (Boomsma et al., 2017): either (1) WMH with a Fazekas scale grade ≥ 2, (2) Fazekas scale grade 1 combined with two or more vascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity or current smoking) (3) presence of ≥1 lacunar infarcts, (4) presence of ≥1 non-lacunar infarct (5) presence of ≥1 cerebral microbleeds or (6) presence of ≥1 intracerebral haemorrhage. All markers were rated according to the STRIVE criteria (Wardlaw et al., 2013). Absence or presence of possible co-existing neurodegenerative disorders did not play a role in the selection of patients (Boomsma et al., 2017). Patients with a primary etiology other than vascular brain injury or an etiology other than neurodegeneration were excluded. All patients underwent a one-day evaluation consisting of an interview, a physical and a neurological examination, neuropsychological assessment and a brain MRI scan. During the interview and physical examination, information on education, smoking, medical history, use of medication, BMI and blood pressure was collected. In total, 173 patients were included in the analyses. The study was approved by the institutional review board of the UMC Utrecht. All patients provided informed consent prior to any research procedures.

2.2. MRI data acquisition

All patients underwent a brain MRI scan using a Philips 3 T scanner (Achieva, Philips, Best, the Netherlands). The standardized MRI protocol included the following transversal 2D sequences (48 slices, voxel size: 0.96 × 0.96 × 3.00 mm^3): T2-weighted (repetition time (TR)/echo time (TE): 3198/140 ms), T2*-weighted (TR/TE: 1653/20 ms), and fluid-attenuated inversion recovery sequence (FLAIR; TR/TE/Inversion time: 11000/125/2800 ms). The MRI protocol also included a 3D T1-weighted sequence (192 slices, voxel size: 1.00 × 1.00 × 1.00 mm^3, TR/TE: 7.9/4.5 ms), and a diffusion-weighted sequence 48 slices, voxel size: 1.72 × 1.72 × 2.50 mm^3, TR/TE: 6600/73 ms, 45 gradient directions with a b-value of 1200 s/mm^2 and one with a b value of 0 s/mm^2(number of signal averages = 3).

2.3. Small vessel disease burden on MRI

MRI images were rated for the presence of WMH of presumed vascular origin, lacunes of presumed vascular origin, CMB, and basal