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

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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-

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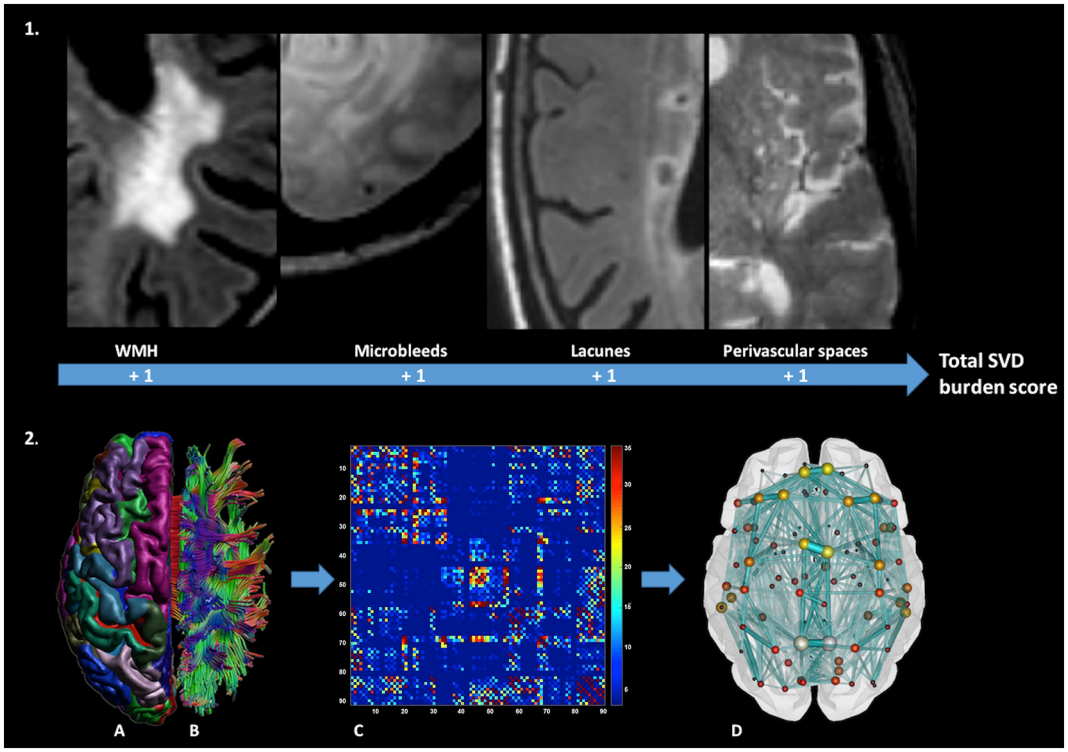

Fig. 1. Flowchart of construction of SVD burden score and structural network reconstruction.
Panel 1 depicts the calculation of the total small vessel disease burden score. One point is added to the score for the presence for (1) Deep WMH (Fazekas grade ≥ 2) or perivascular WMH (Fazekas grade 3), (2) 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

ganglia PVS by trained and experienced raters (RH under supervision of JdB) according to the STRIVE criteria (Wardlaw et al., 2013). Perivascular and deep WMH were rated using the Fazekas scale on the FLAIR sequence (Fazekas et al., 1987). Lacunes were defined as hypointense areas between 2 and 15 mm on both FLAIR and T1-weighted images with a hyperintense rim on FLAIR images. CMB were defined as small, homogenous, round, focal areas of hypointense areas on T2*-weighted images. Basal ganglia PVS were defined as small linear hyperintensities on T2-weighted images. PVS were rated according to a semi-quantitative scale ranging from 0 to 4 (Doubal et al., 2010). Subsequently, a total SVD score was constructed for each patient according to a previously developed scale, see Fig. 1 (Huijts et al., 2013; Staals et al., 2014; Staals et al., 2015). This score summarizes the presence or severity of each of four SVD MRI markers: beginning confluent to confluent deep WMH (deep WMH Fazekas grade ≥ 2) and/or irregular periventricular WMH extending into the deep white matter (periventricular WMH Fazekas grade 3) (one point); presence of lacunes (one point); presence of CMB (one point); and moderate to severe PVS in the basal ganglia (grade 2–4 on semi-quantitative scale) (Doubal et al., 2010) (one point). Due to motion artifacts, CMB and basal ganglia PVS could not be scored for 2 patients. For these 2 patients, CMB and basal ganglia PVS were not included in the calculation of the total SVD score.

2.4. Total brain volume

For all patients, segmentations of grey matter, white matter and cerebrospinal fluid were obtained for an earlier study with FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/) (Fischl et al., 2002) using the 3D T1-weighted sequence. All brain volume segmentations underwent a visual quality check and were manually edited if needed. Manual edits consisted of correcting for large ventricles, correcting the brain mask and correcting for WMH. Total brain volume was defined as the sum of the grey and white matter volumes. To normalize total brain volume for variations in head size, total brain volume was adjusted for intracranial volume. Normalized total brain volumes were generated from linear regression of the residuals (Voevodskaya et al., 2014).

2.5. Diffusion MRI processing and tractography

Brain networks were reconstructed as described previously (Reijmer et al., 2013; Reijmer et al., 2015), using *ExploreDTI* version 4.8.6 (http://www.exploredti.com) (Leemans et al., 2009). Preprocessing of the data included correction for subject motion and eddy current induced geometric distortions followed by robust tensor estimation (including adjustment of the B-matrix) (Leemans and Jones, 2009; Veraart et al., 2013; Tax et al., 2015). During the motion-distortion correction, all scans were rigidly registered to Montreal Neurological Institute space. For each patient, whole-brain white matter tractography was performed using constrained spherical deconvolution (CSD)-based tractography, which allows for the reconstruction of pathways that go through crossing fiber regions (Jeurissen et al., 2011; Tax et al., 2014; Tournier et al., 2007; Jeurissen et al., 2013). Fiber tracts were reconstructed by starting seed samples uniformly distributed throughout the white matter of the brain at a 2 mm isotropic resolution. Fiber tracts were terminated when they deflected in an angle of $> 45^{\circ}$ or if they entered a voxel with a fiber orientation distribution threshold of < 0.1. Brain network nodes were defined using the automated anatomic labeling (AAL) template (Tzourio-Mazoyer et al., 2002), resulting in 90 cortical and subcortical brain regions. Two brain regions were considered to be connected if two end points of a reconstructed fiber bundle lay within both regions. This resulted in a 90×90 binary connectivity matrix. For all patients, each connection was multiplied by the mean fractional anisotropy (FA) of that connection which resulted in a 90×90 weighted connectivity matrix. For a graphical representation, see Fig. 1.

2.6. Brain network characteristics

Characteristics of the organization of the reconstructed structural brain networks were computed using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010). First, the degree of the structural brain network was calculated on the binary connectivity matrices. Degree is defined as the number of connections per node (Rubinov and Sporns, 2010). Next global efficiency was computed on the FA-weighted connectivity matrices. Global efficiency reflects the ability to rapidly exchange information between distributed brain regions (Rubinov and Sporns, 2010). Global efficiency was calculated as the inverse of the characteristic path length. The characteristic path length quantifies the average number of connections between regions along the shortest path. The shorter the path length, the higher the efficiency of the network (Rubinov and Sporns, 2010). Global network efficiency was transformed into standardized z-scores to ease interpretation of the results.

2.7. Cognitive testing

All patients underwent standardized neuropsychological testing. The present study focused on the domains “information processing speed” and “attention and executive functioning” as these are among the most frequently impaired cognitive domains in patients with VCI (Prins et al., 2005). Information processing speed was assessed by completion time of the Trail Making Test (TMT) A (Corrigan and Hinkeldy, 1987) and completion time of the Stroop Color Word test I and II (Stroop, 1935), and the Digit symbol-coding test (Moses et al., 1997). Attention and executive functioning was assessed by the ratio of completion time of the TMT-A and TMT-B (Corrigan and Hinkeldy, 1987), and completion time of the Stroop Color Word test part III (adjusted for part I and II) (Stroop, 1935), and two verbal fluency tasks: category naming and lexical fluency (Deelman et al., 1980). *Z*-scores were calculated for each test using the means and standard deviations of the present sample and averaged for tests comprising one cognitive domain.

2.8. Statistical analysis

The relationship between the total SVD score and global brain network efficiency was evaluated with multiple linear regression analysis (resulting in unstandardized betas with a 95% confidence interval and *p*-values ($\alpha = 0.05$)). Next, correction for possible confounding effects of age, sex, vascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, and current smoking) and normalized total brain volume was performed by adding those variables as covariates in the model. Correction was also performed for the degree of the network. In a sensitivity analysis, the regression was repeated in patients without a clinical diagnosis of Alzheimer's disease (AD). To verify whether the associations with the total SVD burden score were not driven by WMH, the most common SVD marker in our cohort, we recalculated SVD-scores without WMH. To check whether the tractography was affected by WMH, we assessed the association between WMH severity and number of network connections.

To assess the association between the total SVD score/global network efficiency and cognition, multiple linear regression analyses were performed. Correction was performed for possible confounding effects of age, sex and education and subsequently for vascular risk factors and normalized total brain volume. Correction was performed for normalized total brain volume and degree of the structural brain network.

Finally, a mediation analysis was performed using the PROCESS (v2.16.3) macro (Hayes, 2013) in SPSS to test whether the relationship between SVD burden and cognition was mediated by global network efficiency. The indirect effect of the mediation was tested with 5000 bootstrapping samples and 95% confidence interval.

Table 1
Patient characteristics.

	Total SVD score				
	0 N = 6	1 *N* = 47	2 *N* = 65	3 *N* = 37	4 *N* = 18
Age in years	64 ± 10	69 ± 10	73 ± 10	76 ± 11	71 ± 12
Female sex, %	33	47	43	49	39
Level of education[a]	5 (3–7)	5 (1–7)	5 (2–7)	5 (2–7)	6 (2–7)
MMSE	27.5 (25–28)	26 (7–30)	27 (17–30)[b]	26 (21 − 30)	27 (21–30)[c]
Vascular risk factors					
Hypertension, %	100	96	89	95	100
Hypercholesterolemia, %	100	89	63	62	78
Diabetes Mellitus, %	33	47	25	40.5	44
Current smokers, %	50	32[b]	9[b]	8	22
Neuroimaging markers					
Basal ganglia PVS score	1 (1)	2 (2–3)	2 (1–3)	3 (2–4)	3 (2–3)
WMH Fazekas scale grade					
Periventricular	1 (1)	1 (0–3)	2 (0–3)	2 (1–3)	2.5 (1–3)
Deep	1 (0–1)	1 (0–3)	1 (0–3)	2 (1–3)	2.5 (1–3)
Total SVD score					
Presence of lacunes, %	-	-	32	59.5	100
Presence of microbleeds, %	-	-	32	57	100
Basal ganglia PVS (grade 2–4)	-	98	98.5	100	100
Moderate to severe WMH (Fazekas: PV = 3 or Deep ≥2)	-	2	37	84	100

Data are given as mean ± SD, percentages or median (range). Abbreviations: MMSE = Mini Mental State Exam; PVS = Perivascular Spaces; WMH = White Matter Hyperintensities; PV = periventricular.

[a] Verhage scale: (1) less than six years of primary education, (2) finished six years of primary education, (3) six years primary education and less than two years of low level secondary education, (4) four years of low level secondary education, (5) four years of average level secondary education, (6) five years of high level secondary education, (7) university degree (Verhage, 1964).

[b] 2 missing.

[c] 1 missing.

3. Results

3.1. Patient characteristics

Patient characteristics are shown in Table 1. 98% of the patients had some degree of WMH (Fazekas grade 1 or more), with 58% having moderate to severe WMH (Fazekas grade 2–3). Almost all patients (96%) had moderate to severe PVS (PVS score grade 2–4). Mean ± SD total brain volume of the patients was 962 ± 108 (normalized for intracranial volume 959 ± 96 cm^3). As a reference, non-normalized brain volumes in non-demented elderly controls have been estimated at 1013 ± 96 cm^3, using the same method (Heinen et al., 2016).

3.2. Relationship between total SVD score and global network efficiency

The analysis between total SVD score and structural brain network measures showed that with each point increase in total SVD burden on MRI, there was a decrease in global network efficiency (regression coefficient: B [95% CI] = −0.260 [−0.406 - -0.114], p = .001, see Fig. 2). In other words, there was a dose-response relationship between the cumulative effect of SVD markers and global network efficiency. After controlling for age, sex, vascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus and current smoking) and normalized total brain volume this association remained significant (B = −0.239 [−0.390 - -0.089], p = .002). The association between total SVD burden and global network efficiency was not changed by controlling for degree of the network (B = −0.285 [−0.366 - -0.204], p < .001), indicating that the association with network efficiency was not driven by variations in the network density. A sensitivity analysis in patients without a diagnosis of AD showed similar results (B = −0.361 [−0.523 - -0.199], p = < .001). Exclusion of WMH from the total SVD score showed that the association with global efficiency was not primarily driven by WMH (B = −0.247 [−0.445 - -0.050], p = .014). Because 96% of the sample obtained a point for the presence of basal ganglia PVS, we re-calculated the total SVD score using a stricter cut-off value (i.e. > 20 PVS, 45% of the sample). The adapted total SVD score, however, did not change the association with global network efficiency (B = −0.208 [−0.328 - -0.088], p = .001).

There was no relationship between number of network connections and WMH severity (B = 0.048 [−0.176–0.273], p = .671), indicating that WMH severity did not significantly affect the tractography results.

3.3. Relationship between total SVD score, global network efficiency and cognition

The analysis between total SVD score and cognition showed that the total SVD score tended to be associated with performance on both information processing speed (B = −0.123 [−0.273–0.026], trend p = .105) and attention and executive functioning (B = −0.140 [−0.289–0.008], trend p = .064), albeit not significantly (see Fig. 3). After correction for age, sex, education and vascular risk factors the effect remained non-significant (information processing speed B = −0.115 [−0.254–0.025], p = .106; attention and executive functioning: B = −0.119 [−0.273–0.035], p = .129). As can be seen in Fig. 4, global efficiency was associated with both information processing speed (B = 0.265 [0.115–0.414], p = .001) and attention and executive functioning (B = 0.171 [0.019–0.324], p = .028). After correction for age, sex, education, vascular risk factors and normalized total brain volume, this effect remained significant for information processing speed (B = 0.223 [0.087–0.359], p = .001) and attention and executive functioning (B = 0.175 [0.021–0.330], p = .027). Lastly, correcting for the degree of the structural networks did not change the results (information processing speed: B = 0.320 [0.082–0.588], p = .009; attention and executive functioning: B = 0.298 [0.056–0.539], p = .016).

3.4. Mediation analysis

The association between SVD burden and cognition was similar as reported in a previous study (Staals et al., 2015). Albeit, not significant

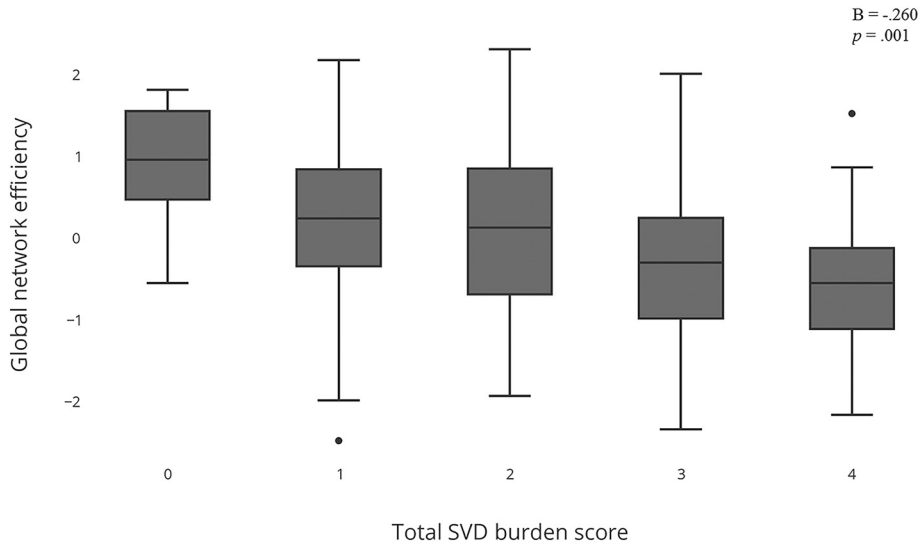

Fig. 2. Relationship between total SVD score and global network efficiency. Boxplots showing the relationship between total small vessel disease burden score and global network efficiency (z-scores) in patients with vascular cognitive impairment.

in our study. This could be due to a lower number of subjects. Nevertheless, a valid indirect mediation effect can still be established in the absence of a significant total effect as was shown in previous studies (Shrout and Bolger, 2002; Hayes, 2009; Zhao et al., 2010). In the current study, mediation analysis showed that global network efficiency mediated the relationship between SVD burden and information processing speed (indirect effect B = −0.059 [−0.126 - -0.017], p = .027), but not the relationship between SVD burden and attention and executive functioning (indirect effect B = −0.035 [−0.089 - -0.005], p = .12).

4. Discussion

The present study showed a dose-response relationship between the total SVD burden on MRI and decreased global network efficiency in memory clinic patients with vascular brain injury. Furthermore, global network efficiency mediated the association between SVD burden and information processing speed. These findings indicate that the cumulative effect of different manifestations of SVD partly affect cognition by disrupting structural brain connectivity.

Our results complement earlier studies that assessed the relationship between SVD, structural network measures and cognition (Lawrence et al., 2014; Tuladhar et al., 2016; Staals et al., 2015). Lawrence et al. (2014) and Tuladhar et al. (2016) found a mediating role for global network measures in the relationship between individual SVD markers and cognition. Our results indicate that this mechanistic pathway might be better studied by considering the total burden of SVD than by individual markers. The greater the SVD burden, the lower the efficiency of the brain network to integrate information between remotely connected brain regions. The functional consequences of these network impairments seem to primarily involve information processing speed and executive functioning (Lawrence et al., 2014; Tuladhar et al., 2016). However, the mediation effect in our study was only significant for processing speed. While it is common to only perform mediation analysis in case of a significant total effect (as described by Baron and Kenny (1986)), which in our case would be a significant association between total SVD burden and cognition, recent studies have demonstrated that a valid indirect mediation effect can be established in the absence of a significant total effect (Shrout and Bolger, 2002; Hayes, 2009; Zhao et al., 2010).

SVD is a heterogeneous disease that manifests itself in different ways. We expected that a total SVD burden score could be better capable of capturing this heterogeneity than individual SVD markers. In the present study, we indeed found that the relationship between total SVD burden and structural brain connectivity was not driven by one of the common individual SVD markers, such as WMH, supporting the cumulative effect of SVD markers on the structural brain network. Staals et al. (2015) have shown that SVD markers also have a cumulative effect on cognition. However, the strength of the association between total SVD burden score and cognition in our sample and in the study of

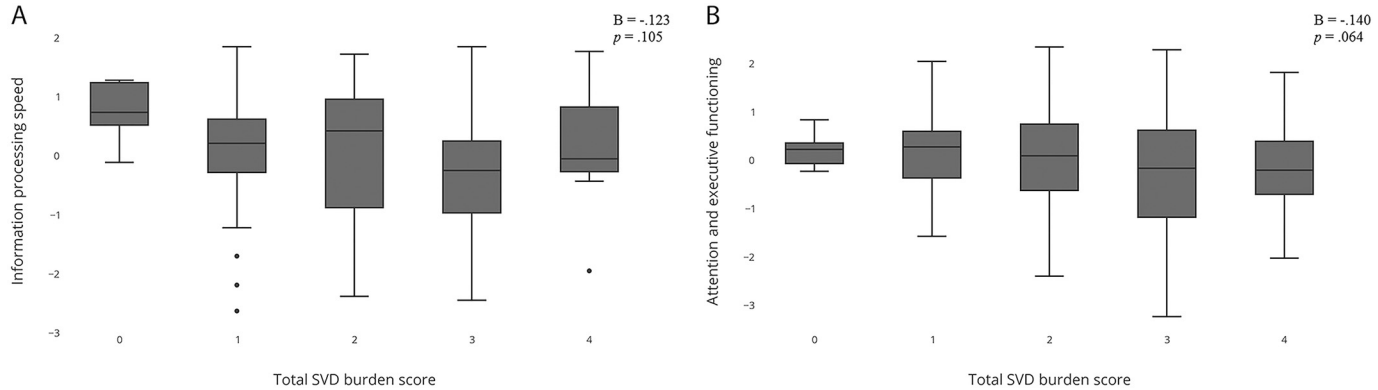

Fig. 3. Relationship between total SVD score and cognition. Boxplots showing the relationship between total small vessel disease burden score and information processing speed (A) and attention and executive functioning (B). Information processing speed and attention and executive functioning are shown as z-scores.

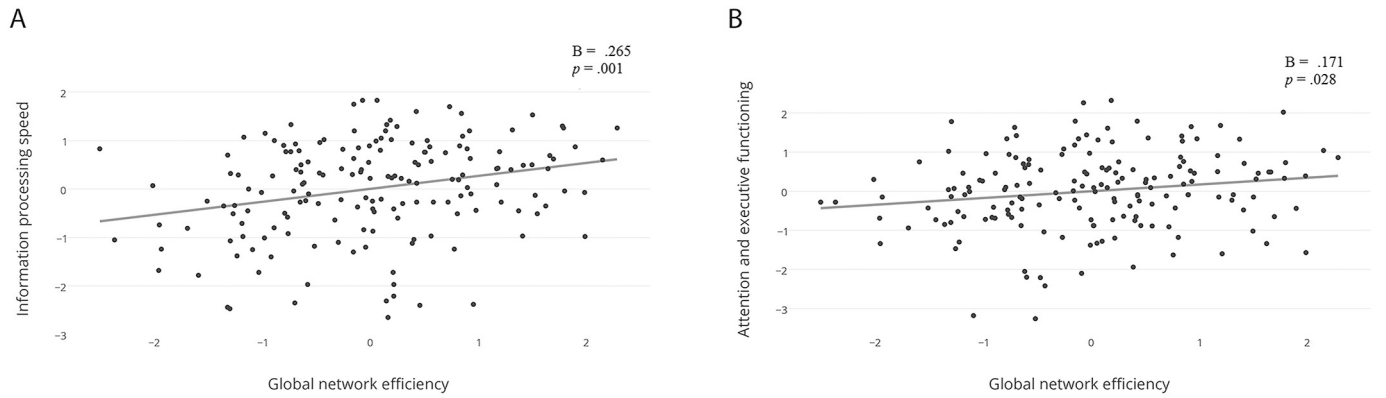

Fig. 4. Relationship between global network efficiency and cognition. Scatterplot showing the relationship between global network efficiency and information processing speed (A) and attention and executive functioning (B). Both global network efficiency and cognitive performance are shown as z-scores.

Staals et al. (2015) were modest, and in our case not significant, which can be explained by the smaller sample size.

Measures of global network connectivity quantify more than what is visible on conventional MRI. For example, diffusion MRI can also detect subtle changes in the so-called normal appearing white matter (NAWM). Diffusion abnormalities in the NAWM, such as decreased FA, are very common in patients with SVD and have been associated with SVD-related cognitive impairment (O'Sullivan et al., 2001; O'Sullivan et al., 2004; van Norden et al., 2012; Tuladhar et al., 2015). However, whether the diffusion abnormalities in the NAWM indeed reflect SVD-related pathology is not known. Alternatively, it may reflect white matter damage caused by non-vascular pathologies, such as neurodegeneration and age (Sun et al., 2014). In our view, diffusion measures and structural network measures should thus not be seen as a specific marker for SVD, but as a sensitive marker that integrates impairments in brain connectivity caused by multiple factors that together explain part of the cognitive performance in patients with SVD.

This study is the first to assess the association between total SVD burden, global network efficiency and cognitive performance in a relatively large sample of patients with different degrees of vascular brain injury. High quality, standardized structural MRI data were used in combination with detailed cognitive testing. One limitation of the DTI data is that only one b-zero image was acquired, which might have confounded the DTI estimates. Also regions in which WMH is present, have relatively low FA values (Bastin et al., 2009; Maniega et al., 2015). This may have affected the tractography results. However we found no association between WMH severity and number of network connections. A possible limitation to this study could be the selection of our patients. Since all patients were recruited from the memory clinic and no selection was made based on absence or presence of co-existing neurodegenerative disorders, patients with mixed diagnoses and mixed pathologies were included in this study sample. As vascular brain injury commonly co-occurs with other pathologies, this does reflect clinical practice. Moreover, a sensitivity analysis in which all patients with AD were excluded, showed that the cumulative effect of SVD markers on global network efficiency was even stronger in this subset of patients. Our sample was selected based on the presence of SVD, which explains why almost all patients had some degree of basal ganglia PVS (96%). However, recalculating the total SVD score for all patients with a higher cut-off for PVS did not change the results. The construction of the total SVD score might be another limitation of this study. The score takes neither location nor number of individual SVD marker into account. Also, the same weight is assigned to each marker. Future studies should evaluate whether the total SVD score can be improved by including such information.

5. Conclusion

Our findings support the hypothesis that global network efficiency is sensitive to the cumulative effect of multiple manifestations of SVD on brain connectivity and may therefore serve as a useful marker for functionally relevant disease progression in clinical trials.

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Disclosures

None.

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