

# Small Vessel Disease and Cognitive Impairment: The Relevance of Central Network Connections

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**Abstract:** Central brain network connections greatly contribute to overall network efficiency. Here we examined whether small vessel disease (SVD) related white matter alterations in central brain network connections have a greater impact on executive functioning than alterations in non-central brain network connections. Brain networks were reconstructed from diffusion-weighted MRI scans in 72 individuals ( $75 \pm 8$  years) with cognitive impairment and SVD on MRI. The centrality of white matter connections in the network was defined using graph theory. The association between the fractional anisotropy (FA) of central versus non-central connections, executive functioning, and markers of SVD was evaluated with linear regression and mediation analysis. Lower FA in central network connections was more strongly associated with impairment in executive functioning than FA in non-central network connections ( $r = 0.41$  vs.  $r = 0.27$ ;  $P < 0.05$ ). Results were consistent across varying thresholds to define the central subnetwork (>50%–10% connections). Higher SVD burden was associated with lower FA in central as well as non-central network connections. However, only central network FA mediated the relationship between white matter hyperintensity volume and executive functioning [change in regression coefficient after mediation (95% CI):  $-0.15$  ( $-0.35$  to  $-0.02$ )]. The mediation effect was not observed for FA alterations in non-central network connections [ $-0.03$  ( $-0.19$  to  $0.04$ )]. These findings

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suggest that the centrality of network connections, and thus their contribution to global network efficiency, appears to be relevant for understanding the relationship between SVD and cognitive impairment. *Hum Brain Mapp* 37:2446–2454, 2016. © 2016 Wiley Periodicals, Inc.

**Key words:** diffusion tensor imaging; vascular brain injury; cognition; white matter; executive function

## INTRODUCTION

Small vessel disease (SVD), including white matter hyperintensities, lacunes, microbleeds, and global brain atrophy, is associated with cognitive dysfunction [Gorelick et al., 2011]. One potential mechanism through which SVD may affect cognition is by disrupting brain connectivity, thereby hampering the rapid exchange of information throughout the brain. Recent studies have examined this hypothesis using diffusion tensor imaging (DTI) based network analysis. Results demonstrate that patients with SVD have lower white matter network efficiency than controls and that global network efficiency is related to worse cognitive outcome, in particular in executive functioning and processing speed [Lawrence et al., 2014; Reijmer et al., 2013b; Reijmer et al., 2015].

Healthy brain networks have high global and local efficiency, defined by an optimal balance between maximal connectivity and minimal axonal volume or “wiring cost” [Bullmore and O. Sporns, 2009]. This type of network organization is also referred to as a small-world organization [Watts and S. H. Strogatz, 1998]. In small-world networks, white matter connections differ widely from each other in terms of their centrality within the network. White matter connections with high network centrality participate in a large number of short communication paths between distant brain regions [Kaiser and C. C. Hilgetag, 2006; Latora and M. Marchiori, 2001]. Because central white matter connections facilitate short path communication, they are expected to carry a large proportion of the total information flow [Kaiser and C. C. Hilgetag, 2006;

van den Heuvel et al., 2012] and can be considered the “highways” of the brain.

Using computational models, researchers have shown that lesions in highly central network regions have a greater impact on functional network dynamics and overall network efficiency [Alstott et al., 2009; de Reus and M. P. van den Heuvel, 2014; Irimia and J. D. Van Horn, 2014]. This may imply that SVD-related white matter lesions in central network regions also have a greater impact on cognitive functioning than white matter lesions elsewhere in the brain. This might explain why in patients with SVD, the location of the lesion appears to be relevant in explaining cognitive outcome apart from total lesion volume [Biesbroek et al., 2013; Duering et al., 2011; Viswanathan et al., 2010].

Here we hypothesize that SVD-related white matter alterations in central network connections are more strongly associated with executive functioning than alterations in non-central network connections. Secondly, we hypothesize that the degree to which central network connections are disrupted, mediates the relationship between markers of SVD and executive functioning. We tested our hypotheses in a population of older adults evaluated for cognitive impairment with various degrees of SVD.

## MATERIALS AND METHODS

### Patients

Participants were recruited through the memory clinic as part of a study on the role of vascular risk factors in early cognitive impairment. This study is a sub-study of the Massachusetts Alzheimer’s Disease Research Center (MADRC) longitudinal cohort [Donovan et al., 2014]. In addition to the standard MADRC work up patients underwent a dedicated research MRI scan. Inclusion criteria were >50 years, mild cognitive complaints or mild dementia, a cognitive dementia rating (CDR) scale of 0.5 or 1.0 at the baseline visit, no prior history of symptomatic stroke or other neurological condition, and no contraindications for MRI. For the present study, only participants with a research MRI scan and cognitive testing within one year were selected (n = 72). All participants provided informed consent in accordance with the Partners Human Research Committee before undergoing any study procedures.

Demographic and clinical variables, including measures of blood pressure and body mass index, were collected. Medical history and medication use were evaluated with a

### Abbreviations

AAL	Automated anatomical labeling atlas
CDR	Cognitive dementia rating
CI	Confidence interval
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FLAIR	Fluid attenuation inversion recovery
ICV	Intracranial volume
MADRC	Massachusetts Alzheimer’s Disease Research Center
MNI	Montreal Neurological Institute
MPRAGE	Magnetization-prepared rapid acquisition gradient echo
SVD	Small vessel disease
SWI	Susceptibility weighted image
WMH	White matter hyperintensities

standardized questionnaire. The complete cognitive assessment has been described elsewhere [Donovan et al., 2014]. For the present study we selected executive functioning as the outcome measure, because of its previously reported association with SVD [Gorelick et al., 2011] and global network efficiency [Lawrence et al., 2014; Reijmer et al., 2015]. Tests for executive functioning included the Category Fluency (animals, vegetables), the Letter Fluency (F,A,S), and the Trail Making Test form B corrected for form A, and the Digit Span Test backwards. Raw cognitive test scores were transformed into standardized z-scores and averaged to obtain one cognitive outcome measure.

### MRI Data Acquisition

All MRI data were collected on a Siemens Trio-TIM 3 Tesla scanner equipped with a 12-channel phased-array head coil. The imaging protocol included a single shot spin echo planar imaging diffusion sequence (TR = 8040, TE = 84 ms, a flip angle of 90°, FOV: 256 × 256 × 128 mm, acquired isotropic voxel size 2 × 2 × 2 mm, 60 isotropically distributed diffusion-sensitizing gradients with a b-value of 700 s/mm<sup>2</sup> and 10 non-diffusion weighted images), a high-resolution T1-weighted multi-echo magnetization-prepared rapid acquisition gradient echo (MPRAGE) anatomical image (TR = 2300 ms, TE = 2.98, and voxel size 1 × 1 × mm), a 3D Fluid attenuation inversion recovery (FLAIR) image (TR = 6000 ms, TE = 455 ms, TI = 2100 ms, and voxel size 1x1x1 mm), and a susceptibility weighted image (SWI; TR = 27 ms, TE = 20 ms, and voxel size 0.9 × 0.9 × 1.5 mm).

### DTI Data Processing and Network Reconstruction

The diffusion MRI data sets were processed and analyzed in *ExploreDTI* (<http://www.exploredti.com>) [Leemans et al., 2009]. Data preprocessing, including correction of subject motion and eddy current-induced geometric distortions and tensor estimation, was performed as described previously [Leemans and Jones, 2009; Reijmer et al., 2012]. During this processing procedure, all brain scans were rigidly normalized to Montreal Neurological Institute (MNI) space during the motion-distortion correction step to maximize the uniformity of brain angulation across subjects [Rohde et al., 2004]. Note that the normalization to MNI space was performed by concatenating the transformation matrices with those derived from the previous correction step (subject motion and eddy current distortions), obviating the need of an additional interpolation step. Given that the diffusion properties are rotationally invariant, this rigid transformation to MNI space does not affect fiber tractography results. Whole-brain deterministic streamline fiber tractography was performed using constrained spherical deconvolution [Jeurissen et al., 2011; Tax et al., 2014; Tournier et al., 2007]. Fibers were recon-

structed by starting seed samples uniformly distributed throughout the data at 2 mm isotropic resolution with a maximum deflection angle of 45° and a fiber orientation distribution threshold of 0.1, and a maximum harmonic degree of 4 [Tournier et al., 2007].

The whole-brain fiber tract reconstructions were parcellated into 90 cortical and subcortical gray matter regions using the automated anatomical labeling atlas (AAL [Tzourio-Mazoyer et al., 2002]). Two brain regions were considered to be connected if a fiber bundle was present with their end points located in these regions, resulting in a 90 × 90 binary connectivity matrix. A weighted connectivity matrix was obtained by multiplying each connection by the mean fractional anisotropy (FA) of that connection. FA is a commonly used metric to examine the microstructural aspects of brain connectivity [van den Heuvel and Sporns, 2011] and has shown to be sensitive to SVD-related white matter injury [Lawrence et al., 2014; Reijmer et al., 2015].

### Network Characteristics

Organizational properties of the brain networks were calculated using the brain connectivity toolbox (<http://www.brain-connectivity-toolbox.net>) [Rubinov and Sporns, 2010]. The *global efficiency* is calculated as the mean of the inverse of the shortest path lengths (i.e., the minimum number of FA-weighted connections between each pair of brain regions) and quantifies how efficiently information is exchanged over the network [Rubinov and Sporns, 2010].

The *centrality* of white matter connections was defined as the fraction of all shortest paths in the unweighted network that contain a given connection (also referred to as “edge betweenness centrality,” see for the exact calculation: <http://www.brain-connectivity-toolbox.net>). Thus, connections with high values of centrality participate in a large number of shortest paths and therefore contribute to the global efficiency of the network. Here we assume the existence of one central subnetwork that is constant across participants. We therefore first calculated the average brain network of the study sample by including those connections that occurred in more than 2/3 of the participants [de Reus and van den Heuvel, 2013]. Connections with the highest centrality within the average network (> threshold value) were selected and used to create a connectivity matrix representing the central subnetwork. Since the threshold value is arbitrary, analyses were repeated for different thresholds varying between 50% and 10% of connections with highest centrality. The population average central subnetwork was then used as a template to select the central subnetwork for each participant.

### Imaging Markers of SVD

Well-known MRI markers of SVD selected for this study include microbleeds, lacunes of presumed vascular origin,

white matter hyperintensities of presumed vascular origin (WMH), and global brain atrophy [Wardlaw et al., 2013]. Microbleeds and lacunes were defined on the axial SWI and FLAIR sequences respectively by an experienced rater (GB) as described previously [Wardlaw et al., 2013]. We have previously reported a high inter-rater concordance for microbleeds measurements [Greenberg et al., 1999]. For each lacune we also calculated the volume by manual outlining on the axial FLAIR sequences. WMH volume was calculated using an automated method similar to Hedden et al., [2012]. First, each subject’s T2-FLAIR image was registered to the T1-weighted GRE image. A threshold intensity method was then applied to the skull-extracted FLAIR to create a binary map of all the contiguous voxels that satisfied that threshold. The threshold optimal for this dataset was the mean intensity + 1.8 SD. From the resulting binary mask, the contiguous voxels that fell outside the white matter were excluded and the volume of the remaining clusters was calculated. All the results generated by this algorithm were manually checked to verify their accuracy. Total brain volume was obtained from T1-weighted GRE images using SPM8 [Ashburner and K. J. Friston, 2000] and was calculated by taking the sum of the grey and white matter probabilistic tissue maps and multiplying this by the voxel volume (1 mm<sup>3</sup>). Intracranial volume (ICV) was calculated as the sum of total brain volume and cerebrospinal fluid. All segmented volumes were visually inspected for segmentation errors.

### Analyses

To illustrate the impact of subtle microstructural loss within central connections on global network efficiency (E<sub>glob</sub>) in patients’ networks compared to random networks and across various thresholds for network centrality, we simulated a “central network attack.” The central attack was performed by lowering the FA of each patient’s central connections by 0.02. A drop in FA of 0.02 corresponded with a decrease of 1 SD within the whole study sample. We choose to lower the FA by a certain value instead of removing the complete connection like in previous studies [de Reus and M. P. van den Heuvel, 2014; Irimia and J. D. Van Horn, 2014], because the effect of SVD on the white matter is often subtle—within the range of 1 SD—and does not always result in complete disappearance of connections [Reijmer et al., 2013a]. We computed the decrease in E<sub>glob</sub> before vs. after the attack ( $\Delta E_{glob}$ ).  $\Delta E_{glob}$  was compared to the distribution of  $\Delta E_{glob}$  after attacking an equal number of randomly selected non-central connections (1,000 permutations; “non-central attack”). The central and non-central attack was repeated on randomly organized networks for each individual patient. That is, for each patient, a random network was constructed that contained the same number of connections and mean strength as observed physiologic network, but with a different organization. Random networks were

**TABLE I. Characteristics of the study sample**

	N=72
Age	74.6 ± 8.4
Sex, % men	58
Years of education	16.0 ± 2.5
MMSE	28 (14–30)
Total brain volume, cc	985 ± 109
WMH, cc	6.8 (1.1–61.8)
Lacunes, % present	24
Lacunes volume, cc <sup>a</sup>	0.01 (0.001–0.12)
Microbleeds, % present	29
Microbleeds, nr <sup>a</sup>	2 (1–14)

Data are given as mean ± SD, percentages, or as median (range).

<sup>a</sup>If present.

ICV = intracranial volume. WMH = white matter hyperintensities.

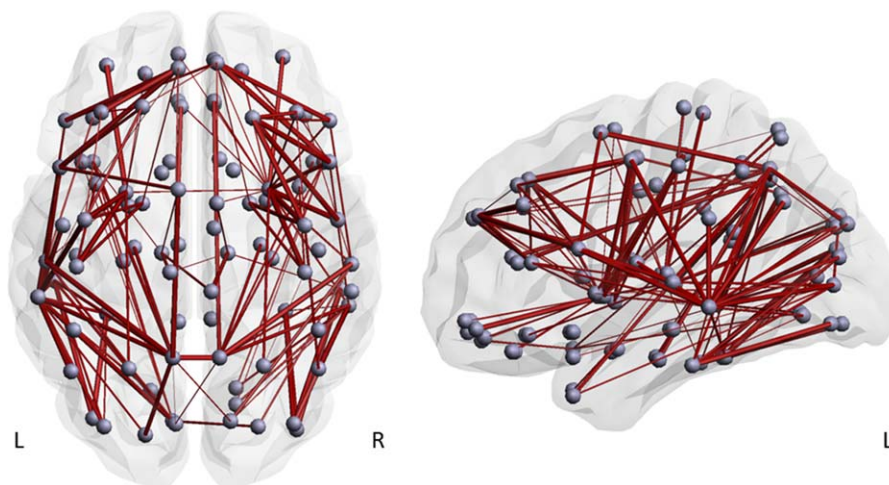
generated by randomly shuffling the connections between regions of each patient’s network.

Secondly, we examined the relationship between the mean FA of central vs. non-central connections and executive functioning by calculating the Pearson correlation adjusted for age, sex, and education level. Analyses were repeated for varying threshold values to define the number of central connections (> 50, 40, 30, 20 and 10%). A *P*-value of 0.01 was considered significant (Bonferroni-corrected). The Bonferroni correction is likely overly conservative however, since the correlations are not independent from each other. We also tested whether the correlation coefficient of central FA was significantly greater than the correlation coefficient of non-central FA with Steiger’s *z*-statistic [Steiger, 1980].

Thirdly, we tested whether the association between MRI markers of SVD and executive functioning was significantly mediated by the FA of central or non-central connections. For these mediation analyses, we used the threshold for central connections showing the strongest correlation with cognition in the previous analysis. We selected SVD markers that were significantly related to FA and executive functioning in linear regression models. WMH volume was log transformed to obtain a normal distribution. ICV was entered as covariate in models with total brain volume and WMH volume to correct for differences in head size. We computed the bias-corrected 95% confidence intervals (CI) for the size of the specific mediating “effects” with bootstrapping (1000 samples) [Preacher and Hayes, 2008]. The mediating effect is said to be present if the 95% CI does not contain zero [Preacher and Hayes, 2008].

## RESULTS

Table I shows the group characteristics of the study sample. All the participants had some degree of WMH, and the majority had moderate to severe WMH (median



**Figure 1.**

Subnetwork of 20% most central white matter connections based on a mean network of the whole study sample. Light blue dots represent the 90 cortical and subcortical brain regions. Thicker connections indicate higher centrality. Results show that connections between the frontal, parietal, temporal, and occipi-

tal lobe have the greatest centrality and may therefore have a greater contribution to the overall information flow within the brain. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

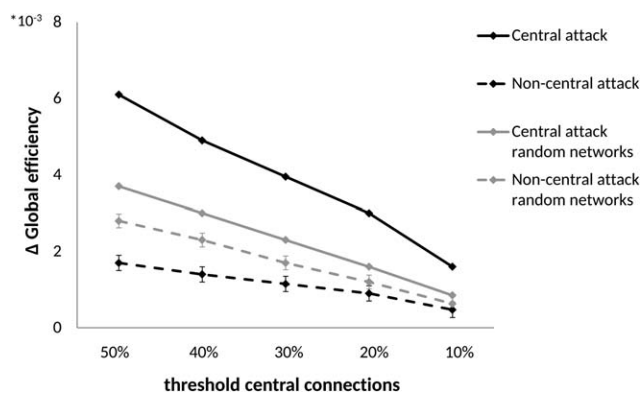
WMH 6.8 cc). In addition, 24% of the participants had a lacune and 29% had one or multiple microbleeds. This is consistent with previous studies suggesting that SVD is common in patients presenting with cognitive complaints and dementia [Gold et al., 2007].

### Structural Alterations in Central Network Connections and Network Efficiency

Figure 1 shows the central subnetwork containing 20% of the most central connections. Lowering the FA of central connections (central-attack) had a greater impact on global network efficiency than lowering the FA of non-central connections (non-central attack) ( $P < 0.001$  for all thresholds, Fig. 2). As expected, the impact of the central attack on global efficiency was much greater for the physiologic-based patient networks which have a small-world organization (black lines) than for randomly organized networks (grey lines;  $P < 0.001$  for all thresholds). The decrease in global efficiency was smaller when applying a stricter threshold to define the central connections. This is because stricter thresholds involve less connections being attacked.

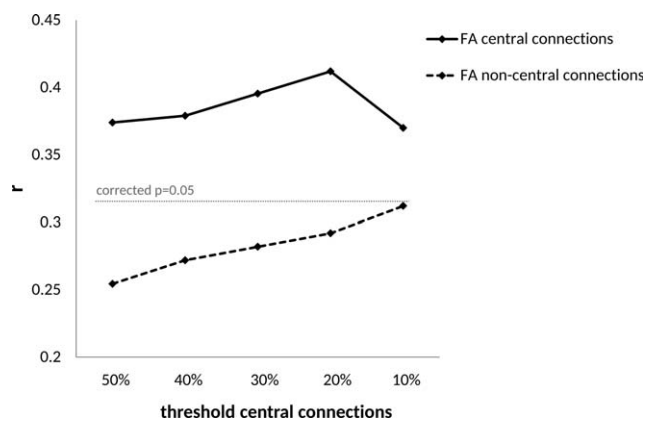
### Structural Alterations in Central Network Connections and Cognition

Lower FA in central as well as non-central connections was associated with worse executive functioning after adjusting for age, sex, and education level (uncorrected



**Figure 2.**

Difference in global efficiency after lowering the FA of central (solid line) and non-central (dashed line) network connections. Analyses were performed on the patient networks (black lines) and on randomly organized networks with similar matched number of connections and mean strength (grey lines). Network attacks were repeated for different thresholds varying between 50% and 10% of connections with highest centrality. Stricter thresholds indicate less connections being attacked and therefore have a lower impact on global efficiency (negative slope). Note that for each given threshold the number of central and non-central connections attacked was kept similar. Data illustrates that attacking central network connections has a much greater impact on global efficiency compared to attacking non-central connections (mean and 95% CI of 1000 permutations). The impact of a central attack is greater for patient networks than for randomly organized networks.



**Figure 3.**

Correlation between the mean FA of central connections (solid line) and non-central connections (dashed line) and executive functioning. Correlation coefficients are adjusted for age, sex, and education level. Analyses were repeated for different thresholds varying between 50% and 10% of connections with highest centrality. The grey line indicates the threshold for significance after Bonferroni correction.

$P < 0.05$  for all thresholds). The correlations between the FA of central connections and executive functioning remained significant after Bonferroni correction (corrected  $P < 0.05$  for all thresholds, Fig. 3). The correlation coefficient with executive functioning was consistently greater for the mean FA of central connections compared to non-central connections (difference between two correlation coefficients for threshold 50–20%:  $P < 0.05$ , threshold 10%:  $P = 0.10$ ).

The central subnetwork showing the strongest correlation with cognition is shown in Figure 1 (threshold value: 20% most central connections). The subnetwork was largely composed of connections between the frontal, parietal, temporal, and occipital lobe (80%) and less by within lobe connections (20%). The subsequent analyses were primarily evaluated using this central subnetwork. Secondary analyses were performed on the subnetworks with a threshold value of 10% and 30% (see Supporting Information).

### Mediation of the Association Between SVD and Cognition by Central Network Connections

Higher WMH load, smaller total brain volume, and the presence of lacunes were related to lower FA of central as well as non-central connections ( $P < 0.01$ , Table II). A trend was observed for the association between microbleeds and lower FA ( $P < 0.10$ , Table II). Higher WMH load and smaller total brain volume were also related to worse executive functioning (standardized  $\beta = -0.29$  (-0.52 to -0.05),  $P = 0.02$ ; and  $\beta = 0.57$  (0.28 to 0.85),  $P < 0.001$ , respectively). The presence or total volume of lacunes was not related to executive functioning ( $P > 0.45$ ). Also no association was found with the presence or number of microbleeds ( $P > 0.48$ ). In line with our hypothesis, the association between WMH volume and executive functioning was significantly mediated by the FA of central connections [change in  $\beta$  after mediation (95% CI): -0.15 (-0.35 to -0.02)], but not by the FA of non-central connections [change in  $\beta$ : -0.03 (-0.19 to 0.04)]. The association between total brain volume and executive functioning was not significantly mediated by the FA of central connections, but results showed a trend [change in  $\beta$ : 0.09 (-0.01 to 0.23)]. We did not observe a mediation effect for the FA of non-central connections [change in  $\beta$ : -0.01 (-0.05 to 0.13)]. Results were essentially similar when using the subnetworks with a threshold of 30% and 10%. For the direct and indirect effects of the mediation analyses for different thresholds of central FA see Supporting Information Figure S1, Table S1, Table S2.

### DISCUSSION AND CONCLUSION

Our results show that structural alterations in central network connections, which have a significant impact on global network efficiency, are more strongly associated with executive functioning than alterations in non-central network connections. Secondly, we found that although markers of SVD were associated with diffuse white matter alterations in both central and non-central network connections, only the degree to which central network connections were disrupted mediated the relationship between WMH volume and executive functioning.

**TABLE II. Association between markers of SVD and the FA of central and non-central white matter connections**

	FA central connections	FA non-central connections
WMH volume (log)	-0.59 (-0.81 to -0.37) <sup>b</sup>	-0.42 (-0.67 to -0.18) <sup>b</sup>
Total brain volume	0.59 (0.31 to 0.87) <sup>b</sup>	0.48 (0.19 to 0.77) <sup>b</sup>
Lacunar infarcts (yes/no)	-0.40 (-0.62 to -0.18) <sup>b</sup>	-0.36 (-0.58 to -0.14) <sup>b</sup>
Microbleeds (yes/no)	-0.21 (-0.45 to 0.03) <sup>a</sup>	-0.20 (-0.44 to 0.03) <sup>a</sup>

Standardized regression coefficients (95% CI) are given. WMH volume and total brain volume are adjusted for intracranial volume.

<sup>a</sup> $P < 0.10$ .

<sup>b</sup> $P < 0.01$ .

This is the first study to examine local associations between DTI parameters and cognition by defining “location” based on network properties rather than anatomically defined brain regions. Our findings support the hypothesis that the contribution of an affected edge to overall network efficiency can help to understand the basis of cognitive deficits that rely on the integration of information between different lobes, such as executive functioning. Patients with WMH showed diffuse network injury. However, the WMH-related injury in central network connections was particularly predictive of cognitive outcome. Because central white matter connections have a large impact on overall network efficiency, the results explain why global network efficiency has found to be more strongly related to executive functioning than total WMH volume [Lawrence et al., 2014; Reijmer et al., 2013a; Reijmer et al., 2015].

The central subnetwork as defined in our study (Fig. 1) shows large similarities with the subnetwork described by Irimia and colleagues in young healthy male subjects [Irimia and J. D. Van Horn, 2014]. The authors found that removal of white matter network connections between the major lobes caused the most significant changes in global network characteristics [Irimia and J. D. Van Horn, 2014]. Also we found that the central subnetwork was largely composed of connections between lobes instead of within lobes (80% vs. 20%), which is in line with the theory of efficient global information processing [Bullmore and O. Sporns, 2009; Kaiser and C. C. Hilgetag, 2006; Latora and M. Marchiori, 2001]. Furthermore, in our study and in [Irimia and J. D. Van Horn, 2014] the effect on network efficiency was more pronounced for intra hemispheric compared to inter hemispheric connections. Figure 2 illustrates the effect of a central network attack on global network efficiency without complete removal of the connection, but by slightly lowering the FA of the connection. The results demonstrate that even subtle changes in the white matter that occur early in the disease process can have a profound impact on the global information flow within the brain if they occur in certain network connections. Importantly, the impact of a “central attack” was more profound for human networks than for random networks, because of their inherent organization.

The present study extends findings from earlier simulation studies [Alstott et al., 2009; de Reus and van den Heuvel, 2014; Irimia and Van Horn, 2014; van den Heuvel and Sporns, 2011] by showing the relationship between central network alterations and executive functioning in older adults with SVD. The association between central network FA and executive functioning was strongest when considering the top 20% of network connections based on their centrality (Fig. 3). A lower threshold (50-30% central connections) showed a weaker correlation with cognition; probably because of a reduced specificity of the subnetwork with respect to ‘centrality’. By contrast, a stricter threshold (10% central connections) most likely reduced

the correlation with cognition by excluding some important central connections mediating executive function. An open question for future studies is whether the optimal threshold observed in this study is also optimal for other SVD populations.

Disruptions in network connections did not significantly mediate the association between total brain volume and executive functioning, although a strong trend was observed for the mediating effect of FA in central connections. Besides a marker of SVD [Jouvent et al., 2010], global brain atrophy is also a marker of Alzheimer’s disease [Dickerson et al., 2009], which primarily affects cortical grey matter. Several studies have shown that SVD and Alzheimer’s disease pathology often co-occur in memory clinic populations [Gold et al., 2007]. In this context it is important to note that all participants in the study sample had at least some degree of SVD, mostly in the form of WMH with the majority of cases having moderate to severe WMH (Table I). Lacunes and microbleeds were common. However, most lacunes were very small and the number of microbleeds per patient was relatively low (Table I), which could explain why we did not find an association with cognition. Since the degree of amyloid plaques or tau pathology was not known, we were not able to examine the effect of Alzheimer-related pathology on these associations.

SVD is largely known to affect the white matter [Wardlaw et al., 2013]. We therefore focused in this study on network connections. However, central subnetworks have also been defined based on the characteristics of cortical ‘hub’ regions [Alstott et al., 2009; van den Heuvel and Sporns, 2011]. Cortical-based subnetworks may be particularly useful to study the impact of diseases that target the cortical gray matter, such as Alzheimer’s disease [de Haan et al., 2012].

Strengths of this study include the availability of high-resolution structural MRI data and detailed cognitive testing from a clinical cohort of patients with SVD and cognitive impairment. Our study also has several limitations. We were not able to control for possible age-related co-morbid conditions, such as Alzheimer disease, because of the lack of information on pathology and of an aged-matched control group. Furthermore, the optimal method to reconstruct structural brain networks is still a matter of debate [Sporns, 2014]. Nevertheless, the central subnetwork found in our study largely overlaps with the central subnetwork reported in a previous study that used a different tractography method and different nodal parcellation scheme [Irimia and Van Horn, 2014]. Finally, we were not able to validate our results in an independent patient sample. Future studies should evaluate whether our findings are replicable in other cohorts of patients with SVD.

In conclusion, white matter alterations in central network connections mediated the association between SVD and executive functioning in memory clinic patients.

Taking into account the contribution of white matter alterations to overall brain network efficiency may prove to be useful for understanding the link between SVD and higher order cognitive functions.

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