Structural network alterations and neurological dysfunction in cerebral amyloid angiopathy

Yael D. Reijmer,1 Panagiotis Fotiadis,1 Sergi Martinez-Ramirez,1 David H. Salat,2 Aaron Schultz,2 Ashkan Shoamanesh,1 Alison M. Ayres,1 Anastasia Vashkevich,1 Diana Rosas,3 Kristin Schwab,1 Alexander Leemans,4 Geert-Jan Biessels,5 Jonathan Rosand,1 Keith A. Johnson,3,6 Anand Viswanathan,1 M. Edip Gurol1 and Steven M. Greenberg1

Cerebral amyloid angiopathy is a common form of small-vessel disease and an important risk factor for cognitive impairment. The mechanisms linking small-vessel disease to cognitive impairment are not well understood. We hypothesized that in patients with cerebral amyloid angiopathy, multiple small spatially distributed lesions affect cognition through disruption of brain connectivity. We therefore compared the structural brain network in patients with cerebral amyloid angiopathy to healthy control subjects and examined the relationship between markers of cerebral amyloid angiopathy-related brain injury, network efficiency, and potential clinical consequences. Structural brain networks were reconstructed from diffusion-weighted magnetic resonance imaging in 38 non-demented patients with probable cerebral amyloid angiopathy (69 ± 10 years) and 29 similar aged control participants. The efficiency of the brain network was characterized using graph theory and brain amyloid deposition was quantified by Pittsburgh compound B retention on positron emission tomography imaging. Global efficiency of the brain network was reduced in patients compared to controls (0.187 ± 0.018 and 0.201 ± 0.015, respectively, P < 0.001). Network disturbances were most pronounced in the occipital, parietal, and posterior temporal lobes. Among patients, lower global network efficiency was related to higher cortical amyloid load (r = −0.52; P = 0.004), and to magnetic resonance imaging markers of small-vessel disease including increased white matter hyperintensity volume (P < 0.001), lower total brain volume (P = 0.02), and number of microbleeds (trend P = 0.06). Lower global network efficiency was also related to worse performance on tests of processing speed (r = 0.58, P < 0.001), executive functioning (r = 0.54, P = 0.001), gait velocity (r = 0.41, P = 0.02), but not memory. Correlations with cognition were independent of age, sex, education level, and other magnetic resonance imaging markers of small-vessel disease. These findings suggest that reduced structural brain network efficiency might mediate the relationship between advanced cerebral amyloid angiopathy and neurologic dysfunction and that such large-scale brain network measures may represent useful outcome markers for tracking disease progression.

1 Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
2 Athinoulia A. Martinos Centre for Biomedical Imaging, Massachusetts General Hospital, Boston, MA, USA
3 Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
4 Image Sciences Institute, University Medical Centre Utrecht, Utrecht, The Netherlands
5 Department of Neurology, Brain Centre Rudolf Magnus, University Medical Centre Utrecht, Utrecht, The Netherlands
6 Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Correspondence to: Steven M. Greenberg, MD, PhD,
J.P. Kistler Stroke Research Centre,
175 Cambridge Street,
Suite 300,
Boston, MA, USA, 02114
E-mail: sgreenberg@mgh.harvard.edu
Introduction

Vascular cognitive impairment due to cerebral small vessel disease represents a major public health threat to rapidly ageing populations (Savva et al., 2010; Arvanitakis et al., 2011). However, the development of effective treatment to modify or prevent vascular cognitive impairment is hampered by the absence of a clear understanding of how individual small brain lesions produce cognitive impairments and how to measure brain injury in a clinically meaningful way (Greenberg et al., 2014).

Current MRI markers of small vessel disease-related brain injury include white matter T2 hyperintensities, lacunes, global atrophy, microbleeds, and microinfarcts (Wardlaw et al., 2013). Although these markers have been related to cognitive outcome in population-based (Prins et al., 2005) and stroke cohorts (Gregoire et al., 2011; Patel et al., 2013), correlations are generally relatively weak or inconsistent across studies (van der Vlies et al., 2012; Kloppenborg et al., 2014). One explanation for the small effect sizes might be that the cumulative effect of these small, spatially distributed lesions, rather than the individual lesions themselves, determines their impact on cognition. This is consistent with findings from autopsy studies showing multiple concurrent pathologies in cases with dementia (Schneider et al., 2007). Whole-brain connectivity might be particularly vulnerable to the effects of multiple spatially distributed brain lesions. Brain connectivity has particular relevance to neurological functions that are preferentially affected in patients with small vessel disease, such as information processing speed, executive functioning and gait, which depend on the rapid communication between widespread brain regions (Hachinski et al., 2006; Viswanathan and Sudarsky, 2012; Duering et al., 2014).

In the present study we aimed to address these possibilities by analysing large-scale structural brain network measures reconstructed from diffusion-weighted images as a marker of small vessel disease-related brain injury. We applied this approach to cerebral amyloid angiopathy (CAA), a form of small vessel disease associated with intracerebral haemorrhage (ICH) and an important contributor to vascular cognitive impairment independent of ICH (Viswanathan and Greenberg, 2011). A CAA cohort has several inherent advantages for this analysis, including its characteristic pattern of posterior-predominant small vessel disease lesions such as lobar microbleeds, white matter hyperintensities, and small asymptomatic infarcts (Rosand et al., 2005; Auriel et al., 2012; Zhu et al., 2012; Thanprasertsuk et al., 2014), and the ability to detect the vascular disease itself by molecular amyloid imaging.

Although Pittsburgh compound B (PiB) cannot differentiate between vascular amyloid and parenchymal amyloid plaques, several PiB PET studies have provided convincing evidence that PiB retention in patients with CAA is indeed largely driven by vascular amyloid burden (Johnson et al., 2007; Greenberg et al., 2008; Gurol et al., 2012). Our unifying hypothesis was that structural connectivity measures are reduced in patients with CAA and that they constitute a pathway between vascular amyloid and clinical dysfunction. To that end, our specific aims were to show that: (i) the efficiency of the network is reduced in individuals with CAA compared to similar aged controls; (ii) that the posterior predominance of CAA-related vascular pathology (Nelson et al., 2013) is reflected in the pattern of local network disturbances; (iii) that individual MRI and PET markers of CAA-related brain injury would be associated with reduced global network efficiency; and (iv) that global network efficiency correlates with neurological function measured by tests of processing speed, executive functioning, and gait velocity.

Materials and methods

Study design

This study is a cross-sectional analysis of data from an ongoing single-centre longitudinal cohort study on the natural history of CAA. The Institutional Review Board approved the study and informed consent was obtained from all participants or their surrogates.

Study participants

Thirty-eight non-demented patients with probable ($n=34$) or definite ($n=4$) CAA defined by the Boston criteria (Knudsen et al., 2001) who underwent research MRI between May 2006 and April 2013 were included in this study. Seventeen patients had a symptomatic ICH before enrolment, but all research imaging was performed at least 6 months after the ICH in these patients. CAA participants underwent a clinical evaluation, extensive cognitive testing (described below) and research 1.5 T MRI scan including a T1-weighted 3D spoiled gradient recalled-echo (SPGR), fluid attenuated inversion recovery (FLAIR), susceptibility-weighted imaging and diffusion-weighted imaging sequence (Auriel et al., 2014). Twenty-nine control subjects without CAA, with similar ages, were selected from among cognitively normal participants in the National Alzheimer’s Coordinating Centre-based Longitudinal Cohort (Dumas et al., 2012) and the Harvard Cooperative Program on Ageing at MGH (Salat et al., 2006) and underwent the same clinical evaluation and MRI protocol as the patient group. Exclusion criteria of both groups were

Keywords: small vessel disease; mild cognitive impairment; stroke: imaging; amyloid imaging; executive function; tractography

Abbreviations: CAA = cerebral amyloid angiopathy; ICH = intracerebral haemorrhage; PiB = Pittsburgh compound B
dementia, a diagnosis of cerebrovascular disease other than CAA, and contraindication to functional MRI (metallic implant/devices, claustrophobia or seizure history). Controls were excluded if they had a history of neurological or psychiatric disorder, a history of stroke or haemorrhage, or serious cardiovascular disease.

**Diffusion tensor imaging processing and network reconstruction**

High angular resolution diffusion imaging (HARDI) scans (60 directions, b-value 700, 10 b0 images, voxel size 2 × 2 × 2 mm³) were obtained on a 1.5 T MRI scanner (Siemens) and were analysed and processed in ExploreDTI (www.exploredti.com). The HARDI scans were corrected for subject motion and eddy current induced geometric distortions as described previously (Leemans and Jones, 2009). The diffusion tensors were calculated using the RESTORE approach (Chang et al., 2012). For each data set, whole-brain white matter tractography was performed using deterministic streamline constrained spherical deconvolution (CSD)-based tractography (Jeurissen et al., 2011). The CSD method can model multiple fibre populations within a voxel and therefore allows fibre tracking to proceed through crossing fibre regions (Jeurissen et al., 2012; Reijmer et al., 2012). Fibres were reconstructed by starting seed samples uniformly throughout the white matter at 2 mm isotropic resolution with a maximum deflection angle of 45° and a fibre orientation distribution threshold of 0.1. The whole-brain fibre tract reconstructions were parcellated into 90 cortical and subcortical grey matter regions using the automated anatomical labelling atlas (AAL; Tzourio-Mazoyer et al., 2002). Two brain regions or nodes were considered to be connected if a fibre bundle was present with two 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 of that connection (Fig. 1). Fractional anisotropy is a commonly used metric to examine the microstructural aspects of brain connectivity (van den Heuvel and Sporns, 2011) and has been shown to be sensitive to CAA-related white matter injury (Salat et al., 2006).

To account for the effects of ICH on structural connectivity, we also performed reconstruction limited to the ICH-free

![Figure 1](https://academic.oup.com/brain/article-abstract/138/1/179/339045)
hemisphere, resulting in a $45 \times 45$ connectivity matrix for each subject. In this analysis, we followed the same procedure for patients with CAA without ICH and control subjects by excluding one hemisphere such that half of the patient and control group had a network based on the right hemisphere and half on the left hemisphere.

**Network characteristics**

Organizational properties of the brain networks were calculated using the brain connectivity toolbox (https://sites.google.com/site/bcnet), (Rubinov and Sporns, 2010). Global network efficiency was chosen as the primary outcome measure in this study as it has shown the most robust relationships with cognition in previous diffusion tensor imaging network studies (Wen et al., 2011; Reijmer et al., 2013a, b). Global efficiency is calculated as the inverse of the shortest path lengths (i.e. the minimum number of fractional anisotropy-weighted connections between each pair of brain regions) (Rubinov and Sporns, 2010) and quantifies how efficiently information is exchanged over the network. Local differences in network connectivity were assessed by the mean nodal strength (i.e. the mean fractional anisotropy of the connections projecting to each individual node).

To evaluate overall network topology independent of network strength, we also calculated network properties from the unweighted connectivity matrices. Unweighted measures included network density, i.e. the observed number of connections divided by the number of possible connections, and the betweenness centrality of each node. Nodes with a high betweenness centrality are central nodes that participate in many short paths and indicate nodal ‘hubs’.

**Neuroimaging markers of amyloid load and CAA-related brain injury**

Microbleeds were identified on axial susceptibility-weighted imaging sequences by an experienced rater (S.M.R.) as described previously (Martinez-Ramirez et al., 2013). White matter hyperintensity segmentation on FLAIR MRI scans was performed using a semi-automated method (Gurrol et al., 2006). We have previously reported a high interrater concordance for microbleeds (Greenberg et al., 1999), and white matter hyperintensity (Gurrol et al., 2006) measurements. Total brain volumes were obtained from the T1-weighted SPGR images using Freesurfer (http://surfer.nmr.mgh.harvard.edu) (Fischl and Dale, 2000) and included the brain tissue within the cranium, excluding the brainstem, ventricles, CSF and choroid plexus. All brain volumes were visually inspected for segmentation errors. For individuals with an ICH, the volume estimates of the ICH-free hemispheres were used and multiplied by 2. To account for between-subject differences in head size, brain volumes were expressed as percentage of intracranial volume.

We also computed the median fractional anisotropy of the total white matter of each subject using a normalized white matter atlas (Mori et al., 2008) to evaluate whether the correlations with network efficiency added explained variance on top of median white matter fractional anisotropy. VoxelS were selected with a minimal fractional anisotropy threshold of 0.2. In individuals with an ICH, the median fractional anisotropy of the ICH-free hemisphere was computed.

A subsample of the patient group ($n=29, 76\%$) had PiB PET imaging. PiB PET acquisitions and processing were performed as described (Gurrol et al., 2013). PET data were reconstructed with ordered set expectation maximization, corrected for attenuation, and each frame was evaluated to verify absence of head motion. The distribution volume ratio was calculated to express specific PiB retention with cerebellar cortex as the reference tissue. To obtain the distribution volume ratio in specific cortical regions, each subject’s PiB PET data were normalized and parcellated into four different lobes (frontal, parietal, temporal, and occipital) (Johnson et al., 2007; Gurrol et al., 2012). Total distribution volume ratio was defined as the mean of all four cortical regions of interest. In cases with ICH, distribution volume ratio estimates from the ICH-free hemisphere were used.

**Cognitive and gait testing**

Measures of cognitive functioning among the subjects with probable CAA were assessed using a standardized test battery. Tests include verbal memory (immediate and delayed memory score of the Hopkins Verbal Learning Test; Brandt, 1991), processing speed (Trail Making Test A: Corrigan and Hinkley, 1987; Symbol Substitution Test: Wechsler, 1997), and executive functioning (Trail Making Test B, Digit Span Test backwards: Wechsler, 1987; Verbal Fluency Test: Tombaugh et al., 1999). Each cognitive test score was transformed into z-scores using the mean and standard deviation (SD) of the whole population and averaged across tests to obtain one average z-score per cognitive domain. Cognitive data were not available in three patients: one who declined cognitive testing, one a non-native English speaker, and one who had aphasia as a result of the ICH. Raw cognitive test scores and corresponding age-, sex-, and education-adjusted normative scores are presented in Supplementary Table 2.

Gait was assessed using the speed velocity measure of the Timed Get Up and Go Test (Podsiadlo and Richardson, 1991). Data on gait velocity were available from 31 patients with CAA (82%).

**Statistical analysis**

Patient characteristics were compared between individuals with CAA and controls using independent samples $t$-test for continuous variables and Fisher’s exact test for proportions. The number of microbleeds and white matter hyperintensities volume were non-normally distributed and therefore log-transformed. Measures of brain network organization and network efficiency were compared between CAA patients and controls using ANOVA, adjusted for age. To evaluate whether the posterior predominant pattern of CAA pathology is reflected in the pattern of local network disturbances in directly connected tracts, we compared the mean connectivity strength of each individual node between patients and controls. Nodes within ICH-containing hemispheres were excluded from this analysis. $P$-values of nodal comparisons were adjusted for multiple hypotheses testing using the false discovery rate (FDR) correction (Benjamini and Hochberg, 1995).

To test whether structural network alterations form a mechanistic link between vascular amyloid and clinical manifestations, we analysed the relationship between global network
efficiency and (i) measures of CAA-related brain injury (i.e. MRI markers of small vessel disease burden and brain amyloid on PiB PET imaging); and (ii) cognitive and gait performance within the CAA group. The relationship between network connectivity and PiB uptake was further examined by testing whether patients with predominantly posterior PiB-uptake (posterior distribution volume ratio > frontal distribution volume ratio) also showed predominantly posterior network disturbances. Posterior was defined as the mean of the occipital, parietal and temporal lobe. The mean strength of posterior and frontal nodes was compared between patients with and without predominantly posterior PiB-uptake and controls using an independent samples t-test. Lastly, we examined whether global network efficiency explained variance in cognition/gait on top of other MRI markers with stepwise linear regression analyses. Potential predictors including age, sex, education level, white matter hyperintensities volume, median fractional anisotropy, microbleeds, total brain volume, and global efficiency were sequentially entered in the model and kept if they explained additional variance compared to the previous model (P-value change $R^2 < 0.05$).

**Results**

**Between-group comparisons**

We analysed structural network measures in 38 patients with CAA and 29 similar aged control subjects (Table 1). Overall, CAA patients had greater white matter hyperintensity volume and lower fractional anisotropy than controls ($P < 0.05$). Age- and sex-adjusted comparison in network parameters showed no substantial difference in network density and the location of major network hubs (Table 2 and Supplementary Table 1), but global network efficiency was reduced in patients with CAA compared to controls ($P < 0.001$, Table 2). The between-group difference in global efficiency remained present when restricting the analysis to ICH-free hemispheres ($P = 0.01$, Table 2). We also observed no difference in global efficiency of the ICH-free hemispheric network between CAA patients with and without ICH ($0.195 \pm 0.022$ and $0.196 \pm 0.024$, respectively $P = 0.94$), indicating that the ICH had no major effects on efficiency in the contralateral hemisphere.

Figure 2 shows network nodes with lower nodal strength in CAA compared to controls ($P < 0.05$, FDR corrected). The strongest differences in connectivity of nodes appeared in occipital, posterior parietal, and posterior temporal cortex. There were no nodes with a significantly higher global efficiency in patients with CAA compared with control subjects. Affected nodes in patients with CAA did not differ from unaffected nodes with respect to average number of connections ($P = 0.89$) or total connectivity strength ($P = 0.56$).

**Relationship between network measures and neuroimaging markers of CAA-related brain injury**

Within the CAA group, lower global efficiency was correlated to increased age ($r = -0.63$, $P < 0.001$), greater white matter hyperintensity volume ($r = -0.57$, $P < 0.001$), and lower total brain volume ($r = 0.39$, $P = 0.02$). When restricting our analyses to the ICH-free hemispheres, similar correlations were observed with age ($r = -0.64$, $P < 0.001$), white matter hyperintensity volume ($r = -0.68$, $P < 0.001$) and total brain volume ($r = 0.39$, $P = 0.02$). Global efficiency tended to decline with increasing number of microbleeds ($r = -0.31$, $P = 0.06$).

Among the 29 patients with CAA who received PiB PET imaging, global network efficiency correlated with global mean distribution volume ratio in analysis of whole-brain efficiency ($r = -0.43$; $P = 0.02$; Fig. 3) or when restricting to the ICH-free hemispheres ($r = -0.52$; $P = 0.004$). CAA patients with predominantly posterior PiB-uptake (posterior distribution volume ratio > frontal distribution volume ratio, $n = 14$) also demonstrated predominantly posterior network disturbances: this subgroup of patients showed lower strength of posterior nodes compared to controls (mean difference $\pm$ SEM: $-0.16 \pm 0.007$, $P = 0.02$), whereas no difference was found in frontal node strength ($-0.005 \pm 0.007$, $P = 0.46$). The remaining subgroup of CAA patients ($n = 15$) showed greater frontal as well as posterior PiB retention compared to patients with

### Table 1 Characteristics of the study sample

<table>
<thead>
<tr>
<th></th>
<th>Controls $n = 29$</th>
<th>CAA $n = 38$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.3 ± 7.1</td>
<td>68.9 ± 9.9</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>69</td>
<td>82</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>ICH, %</td>
<td>45</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Microbleeds, n</td>
<td>-</td>
<td>35 (1–729)</td>
<td></td>
</tr>
<tr>
<td>White matter hyperintensity volume, % ICV</td>
<td>0.1 (0–2.1)</td>
<td>1.3 (0.1–6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total brain volume, % ICV</td>
<td>66 ± 3</td>
<td>62 ± 4</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Fractional anisotropy white matter</td>
<td>0.39 ± 0.03</td>
<td>0.36 ± 0.03</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

ICV = intracranial volume.

### Table 2 Between-group differences in brain network parameters

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>CAA</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Network density (%)</td>
<td>24.6 ± 1.6</td>
<td>24.0 ± 2.9</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Average network weight</td>
<td>0.286 ± 0.017</td>
<td>0.304 ± 0.017</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global efficiency whole brain</td>
<td>0.201 ± 0.015</td>
<td>0.187 ± 0.018</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global efficiency ICH-free hemisphere</td>
<td>0.205 ± 0.018</td>
<td>0.194 ± 0.023</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Global network efficiency measures are given as mean ± SD of age- and sex-adjusted z-scores. Network density of the whole brain network indicates the total number of connections divided by the total number of possible connections within the network.
predominantly posterior PiB ($P < 0.01$), suggestive of more severe global CAA pathology. In line with the higher global PiB uptake, those patients also showed lower frontal and posterior node strength than controls (posterior: $-0.023 \pm 0.007$, frontal: $-0.018 \pm 0.006$, $P < 0.009$).

**Relationship between network measures and neurological function in CAA**

Whole-brain global efficiency was correlated with worse performance on cognitive tests measuring processing speed ($r = 0.58; P < 0.001$) and executive functioning ($r = 0.54; P = 0.001$), but not memory ($r = 0.18$, $P = 0.31$; Fig. 4). The associations with speed and executive functioning remained independent after controlling for potential confounders as detailed above ($P < 0.05$; Supplementary Table 3), indicating that the network-derived global efficiency measure carried additional information beyond these conventional structural small vessel disease measures. The correlation with speed also remained independent after controlling for average network strength ($P = 0.03$), while the relationship with executive functioning became a trend ($P = 0.14$). The strength of the correlations with cognition did not change when restricting the analyses to global efficiency of the ICH-free hemispheres (Supplementary Table 3).

Gait velocity was measured in a subsample of 31 subjects with CAA and correlated with global efficiency of the ICH-free hemispheres ($r = 0.41$, $P = 0.02$), though not whole-brain global efficiency ($r = 0.30$, $P = 0.11$). The relationship between gait velocity and efficiency of the ICH-free hemisphere was not independent of median fractional anisotropy ($P = 0.193$; Supplementary Table 3).

**Discussion**

The present study shows reduced global efficiency of structural brain networks in patients with CAA compared with controls, independent of ICH. CAA-related reductions in global network efficiency were related to cortical amyloid burden, MRI markers of small vessel disease, and worse cognitive and gait performance, supporting our view that microstructural alterations can be a link between vascular pathology and clinical manifestations. Importantly, the associations with cognition remained independent after controlling for white matter hyperintensity load, microbleeds, brain volume, or median fractional anisotropy, suggesting that network measures can explain additional variance not captured by these currently used MRI markers.

Our findings of lower structural network efficiency and its association with neurological outcome are consistent with previous reports in patients with Alzheimer’s disease (Lo et al., 2010), diabetes (Reijmer et al., 2013a) and small vessel disease (Lawrence et al., 2014). The consistency of these findings across different populations, despite subtle differences in image processing, suggests that diffusion-based network measures are indeed sensitive to clinically relevant brain injury.

The current results support a model in which CAA leads to multiple types of spatially distributed brain lesions which together impact the strength and efficiency of the brain network. Although the exact pathophysiological mechanism underlying structural network disturbances in these patients remain to be established, several of our findings point towards an important role of CAA-related pathology. First, reductions in brain connectivity were most pronounced in tracts projecting onto the occipital and posterior temporal cortex, whereas subcortical tracts were less affected. This pattern of brain injury is consistent...
with reports from post-mortem and imaging studies showing a posterior lobar predominance of vascular amyloid deposition (Nelson et al., 2013), white matter hyperintensity burden (Zhu et al., 2012; Thanprasertsuk et al., 2014), and PiB uptake (Johnson et al., 2007) in patients with CAA.

Secondly, we found a correlation between global network efficiency and amyloid burden on PiB PET imaging, suggesting that the vascular disease itself contributes to the observed network disturbances. The greater tendency for reduced frontal node strength in brains with relatively greater frontal PiB retention supports the possibility of regional association between worsened CAA burden and damage to the local structural network. PiB cannot differentiate between vascular amyloid and parenchymal amyloid plaques, thus we do not know to what extent parenchymal amyloid contributed to the PiB PET signal. However, the fact that global network efficiency was related to markers of small vessel disease on MRI (i.e. white matter hyperintensity volume, total brain volume, microbleeds) strengthens our view that the observed network alterations are a result of CAA-related brain injury.

Finally, global network efficiency was correlated with reduced processing speed, executive functioning, and gait velocity, but not with memory performance. This clinical profile is typically observed in patients with vascular cognitive impairment (Hachinski et al., 2006) and to a lesser degree in Alzheimer’s disease, supporting a primarily vascular mechanism underlying the network alterations. Importantly, global network efficiency explained changes in cognition beyond individual markers of small vessel disease, indicating that network measures provide information that is complementary to widely used conventional MRI biomarkers. One explanation for the relatively strong correlation with cognition is that diffusion-based network measures account for the total burden of brain injury, including microstructural tissue abnormalities such as microinfarcts not visible to the naked eye (Smith et al., 2012). Measures of global network efficiency also take into account the position of the connection within the network: central connections that participate in many shortest paths have a greater contribution to the overall efficiency (Alstott et al., 2009; van den Heuvel et al., 2012). These central connections may

Figure 4 Correlation plots. Correlation plots showing the relationship between global network efficiency and cognitive performance (z-scores) (A–C) and gait velocity (m/s) (D) in patients with CAA.
be specifically relevant for cognitive functions such as speed and executive functioning that rely on the global transfer and integration of information between distant brain regions. Indeed, a recent DTI network study showed that long-range association fibres connecting parietal, temporal, and frontal regions are primarily affected in small vessel disease patients with speed and executive deficits, but no memory impairment (Lawrence et al., 2014).

Strengths of our study include the collection of multimodal imaging in a well-described cohort of CAA patients in combination with the detailed assessment of cognitive functioning. Our study is limited, however, by the cross-sectional design and by the lack of PiB and cognitive data from our control group. Therefore we were not able to examine whether the observed correlations between network efficiency and cognition are specific to CAA. Another limitation is the possible confounding effect of Alzheimer pathology on our results. However, the pattern of local network disturbances in our sample differed from those found in Alzheimer’s disease. In patients with Alzheimer’s disease and amnestic mild cognitive impairment, alterations in network connectivity are primarily seen in temporal and frontal regions, whereas the occipital lobe is relatively spared (Lo et al., 2010; Shu et al., 2012), resembling the progression of Alzheimer-related pathology (Corder et al., 2000). Hub regions have also been shown to be particular vulnerable to Alzheimer’s disease (Buckner et al., 2005), but were not primarily affected in this sample of patients with CAA. These discrepancies suggest that the contribution of Alzheimer pathology to our results is limited. Finally, the optimal protocol for reconstructing network connectivity is still a matter of debate. Different grey matter parcellation methods (Reus, 2013), fibre tractography methods (Bastiani et al., 2012), and measures of connectivity strength (Fornito et al., 2013) have been suggested. The high correlation among weighted network measures makes it difficult to determine whether global efficiency is truly preferred as an outcome marker above other global network measures. Larger study samples are necessary to identify which network parameter is most sensitive to clinically relevant brain injury. Other than comparing different metrics and analytic techniques, future studies should examine whether our findings are generalizable to other vascular cognitive impairment populations and whether global network efficiency can predict cognitive decline.

In conclusion, this study supports the view that brain network alterations detected with diffusion-based methods can be one of the mechanistic links between vascular amyloid and neurological dysfunction in patients with CAA. In addition to providing new information about the biological basis of vascular cognitive impairment, diffusion-based network analysis may also prove to be a useful tool for measuring clinically meaningful disease progression in clinical trials or practice.

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Conflict of interest

Dr Rosand serves as a consultant for Boehringer Ingelheim. Drs Rosand, Greenberg, and Gurol receive research support from National Institutes of Health. The other authors report no conflicts.

Supplementary material

Supplementary material is available at Brain online.

References


