Identification of a strategic brain network underlying processing speed deficits in vascular cognitive impairment

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A B S T R A C T

Patients with vascular cognitive impairment (VCI) commonly exhibit deficits in processing speed. This has been attributed to a disruption of frontal-subcortical neuronal circuits by ischemic lesions, but the exact mechanisms and underlying anatomical structures are poorly understood. We set out to identify a strategic brain network for processing speed by applying graph-based data-mining techniques to MRI lesion maps from patients with small vessel disease. We studied 235 patients with CADASIL, a genetic small vessel disease causing pure VCI. Using a probabilistic atlas in standard space we first determined the regional volumes of white matter hyperintensities (WMH) and lacunar lesions (LL) within major white matter tracts. Conditional dependencies between the regional lesion volumes and processing speed were then examined using Bayesian network analysis. Exploratory analysis identified a network of five imaging variables as the best determinant of processing speed. The network included LL in the left anterior thalamic radiation and the left cingulum as well as WMH in the left forceps minor, the left parahippocampal white matter and the left corticospinal tract. Together these variables explained 34% of the total variance in the processing speed score. Structural equation modeling confirmed the findings obtained from the Bayesian models. In summary, using graph-based models we identified a strategic brain network having the highest predictive value for processing speed in our cohort of patients with pure small vessel disease. Our findings confirm and extend previous results showing a role of frontal–subcortical neuronal circuits, in particular dorsolateral prefrontal and cingulate circuits, in VCI.

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Introduction

Vascular brain lesions are the second most common cause of dementia (Gorelick et al., 2011; O’Brien et al., 2003) and have been shown to modify the clinical expression of Alzheimer’s disease (Iadecola, 2010). Subcortical ischemic vascular disease, the most common cause of vascular cognitive impairment (VCI), is characterized by the presence of lacunar infarcts and white matter lesions which are both mediated by small vessel disease (Pantoni, 2010). Affected individuals typically show impaired executive functions with relative preservation of memory (Charlton et al., 2006; Jokinen, 2006; Peters et al., 2005).

Deficits in information processing are particularly common in patients with VCI, even in early disease stages (Benisty et al., 2012; Charlton et al., 2006; Dichgans, 2009), which has led many investigators to focus on this particular aspect (Prins et al., 2005; Zieren et al., 2013). However, the mechanisms underlying slowed information processing in VCI remain poorly understood.

MRI imaging and autopsy studies have identified two major determinants for the clinical expression of ischemic lesions: The total burden of lesions (lesion volume) and lesion location (Gold, 2009). Using a voxel-based lesion–symptom mapping approach in patients with pure small vessel disease we recently identified the anterior thalamic radiation (ATR) and the forceps minor (Fmin) as being strategic locations for processing speed. This was further confirmed by analyzing regional volumes of lesions within these white matter tracts (Duering et al., 2011). Together the results suggested a strategic role of frontal-subcortical neuronal circuits (Cummings, 1995; Tekin and Cummings, 2002) in VCI Studies...
in other cohorts identified additional white matter structures that are relevant for processing speed and in fact, processing speed is increasingly regarded as a network function (Wen et al., 2011). Yet, the network aspect of processing speed requires investigating multiple structures and therefore incorporating a multitude of variables into statistical models.

The majority of studies exploring lesion-deficit relationships have used multivariate linear models. However, regression models suffer from methodological problems, in particular multicollinearity and over-fitting (Hawkins, 2004). Data-mining techniques, such as probabilistic graphical models, are better suited for exploring large multivariate datasets. Probabilistic models enable to discover interactions and to learn from noisy observations. Bayesian networks are graph-based models describing the conditional dependencies between multiple interacting quantities (e.g., ischemic lesions in multiple white matter tracts and processing speed). In such graphs, nodes depict the quantitative variables and arcs depict probabilistic conditional dependencies between them (Korb and Nicholson, 2010). The algorithm decomposes the joint probability distribution of the entire system into a set of local conditional distributions to examine individual components. Bayesian graph representations are explicit and intuitive and the probabilistic approach ensures robustness, making Bayesian network analysis suitable for medical applications (Herskovits and Gerring, 2003).

The aim of the current study was to identify a strategic brain network for processing speed deficits in patients with cerebral small vessel disease. Specifically, we sought to investigate associations and inter-relationships between the regional volumes of ischemic lesions in major white matter tracts and processing speed using advanced and robust statistical methods. We hypothesized that the ATR and Fmin would be part of the network and that the application of advanced and robust statistical methods. We hypothesized that the ATR and Fmin would be part of the network and that the application of graph-based methods would allow identifying an extended network involving additional white matter structures.

Methods

Study cohort and neuropsychological testing

The study cohort consisted of 328 patients with genetically or biopsy confirmed CADASIL recruited through a prospective study conducted at the Medical Center of the University of Munich (Munich, Germany) and at Hospital Lariboisière (Paris, France) (Duering et al., 2011; Viswanathan et al., 2010).

52 subjects were excluded from the current analyses due to quality control of MRI scans. The reasons were: insufficient image quality e.g., through motion artifacts (N = 15), territorial infarctions (N = 5), and difficulties registering images to standard space (N = 24). An additional 41 patients had to be excluded because of failure to adequately perform or complete the neuropsychological tests required for the processing speed compound score (see below). The final sample available for the lesion-deficit analysis consisted of 235 subjects.

Neuropsychological testing was performed blinded to clinical information on the previous or same day as the MRI examinations. Analyses were done on a previously published compound score for processing speed, incorporating the timed measures of the trail making tests part A and B and the block design test (Duering et al., 2011). For the compound score, raw test scores were first transformed into age- and education-corrected Z-scores based on reference values from healthy subjects (Tewes, 2006; Tombaugh, 2004). Next, the processing speed compound score (speedscore) was calculated as the mean of the three Z-scores.

MR imaging and generation of lesion maps

MRI was performed on 1.5 Tesla systems: Siemens Vision (Munich) and General Electric Medical Systems Signa (Paris and Munich). Sequence parameters are detailed in the supplementary methods. The procedures for generating lesion maps have been previously described (Duering et al., 2011). In brief, lesion maps for lacunar lesions (LL) and white matter hyperintensities (WMH) were generated using custom 2D and 3D imaging editing tools from BioClinica SAS (Lyon, France). Lacunar lesions were identified based on size and signal characteristics (isointens to cerebrospinal fluid). Special care was taken to distinguish lacunar lesions from enlarged perivascular spaces, considering their shape, location and typical orientation along perforating vessels (Douhal et al., 2010). WMH were segmented on FLAIR images using a semi-automated procedure with intensity thresholding and manual corrections. The intra- and inter-rater reliability for these procedures and the Dice coefficient as a measure for overlap between raters has been shown to be high (Duering et al., 2011; Viswanathan, 2006; Viswanathan et al., 2010).

Estimation of regional lesion volumes within distinct white matter tracts

The regional volumes of lesions mapping on major white matter tracts were calculated using the Johns Hopkins University (JHU) International Consortium for Brain Mapping (ICBM) probabilistic white matter atlas (JHU-ICBM-tracts, Hua et al., 2008) in Montreal Neurological Institute (MNI) 152 space. The normalization procedure to MNI 152 standard space involved tools from the Functional MRI of the Brain software library (FSL) (Smith et al., 2004; Woolrich et al., 2009) and lesion masking (Brett et al., 2001) and has been previously described (Duering et al., 2011).

Regional lesion volumes were calculated for each white matter tract from the atlas (see supplementary Table A.1) and separately for WMH and LL. To account for inaccuracies during normalization and for inter-individual variations in white matter tracts we used a probabilistic approach: individual lesion voxels in standard space were assigned to the underlying white matter tracts according to the probability of each tract within the voxel (supplementary fig. A.1).

Assessment of brain volume

Whole brain volume was estimated from native T1 images using the SIRENAX program (Smith et al., 2002; 2004), part of FSL. Results were rigorously checked and parameters optimized if necessary. Even after manual correction, the brain extraction algorithm failed on some images. As a result, brain volume could only be obtained for 217 (92.3%) of the subjects. Intracranial cavity was segmented by a 3D image segmentation algorithm on the T2 sequence followed by manual corrections. Normalized brain volume was then calculated by dividing the whole brain volume by intracranial cavity.

Statistical analysis

Statistical analysis was conducted with the R software package (version 2.13.2). We analyzed Bayesian networks of conditional dependencies between the processing speed compound score, age, and regional lesion volumes for each white matter tract to reveal the major determinants for processing speed impairment. Continuous variables of processing speed, age, and regional lesion volumes of WMH and LL were standardized. Gaussian linear Bayesian network analysis for continuous data was applied as implemented in the R/bnlearn package (version 2.9) (Scutari, 2010). The most probable network was identified using the Tabu learning algorithm in combination with the Bayesian Gaussian likelihood equivalent (BGe) scoring criteria (Daly and Shen, 2007; Heckerman et al., 1995; Korb and Nicholson, 2010; Russell and Norvig, 2009). The analysis was carried out hypothesis-free, with the following two exceptions: In order to limit analyses to biologically relevant structure-function dependences, where ischemic lesions impact on processing speed and not vice versa, we defined processing speed as a dependent variable. For similar reasons, age was defined as independent variable.
To assess the robustness of the final strategic network to sampling variability, the network construction was confirmed using a bootstrapping approach: the strength of each arc was calculated as a relative frequency of the arc appearance in 3000 networks obtained through resampling. Reasonable confidence is indicated by an arc frequency of 50% and higher (Friedman et al., 1999). The significance of the conditional dependencies was estimated by partial correlations. For an excellent model fit included: non-significant p-value for chi-squared goodness of fit statistic (>0.05), ratio of chi-square statistic to degrees of freedom (chi/df)<2 (Ullman, 2001), root mean square error of approximation (RMSEA)<0.08 (MacCallum et al., 1996), comparative fit index (CFI)>0.95 (Hu and Bentler, 1999; Ullman, 2001). The CFI is one of the most popularly reported fit indices, because it is least affected by sample size (Fan et al., 1999; MacCallum et al., 1996).

To compare the results of the graph-based analysis with a common linear regression approach we conducted both univariate and multivariate linear regression analysis. To find the most predictive regressors we used a stepwise forward selection based on the adjusted R-square criterion.

Results

Demographic, clinical and imaging characteristics of the study cohort are provided in Table 1. Overall, there were 903 lacunar lesions (LL) present in 158 (67.2%) subjects. White matter hyperintensities (WMH) were detected in all subjects. Lesion prevalence maps for WMH and LL are depicted in Fig. 1. The regional volumes of LL and WMH in distinct white matter tracts (supplementary fig. A.1) are given in supplementary Table A1.

<table>
<thead>
<tr>
<th>Characteristics of the study cohort (n=2135).</th>
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<tbody>
<tr>
<td>Demographic characteristics</td>
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<tr>
<td>Age, median (IQR, range) [years]</td>
</tr>
<tr>
<td>Female, n (%)</td>
</tr>
<tr>
<td>Clinical features</td>
</tr>
<tr>
<td>Symptomatic, n (%)</td>
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<tr>
<td>Migraine history, n (%)</td>
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<tr>
<td>Prior clinically apparent stroke, n (%)</td>
</tr>
<tr>
<td>Vascular risk factors</td>
</tr>
<tr>
<td>Smoking*, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
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<tr>
<td>Hypercholesterinaemia, n (%)</td>
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<tr>
<td>Diabetes, n (%)</td>
</tr>
<tr>
<td>Clinical scores</td>
</tr>
<tr>
<td>MDRS, median (IQR, range)</td>
</tr>
<tr>
<td>mRS, median (IQR, range)</td>
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<tr>
<td>NIHSS, median (IQR, range)</td>
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<tr>
<td>Speedscore, median (IQR, range)</td>
</tr>
</tbody>
</table>

Imaging characteristics

| Normalized LL volume, median (IQR, range) [%] | 0.00511 (0.022, 0–0.0404) |
| Normalized WMH volume, median (IQR, range) [%] | 2.6 (0–26) |
| Normalized brain volume, median (IQR, range) | 0.826 (0.076, 0.623–0.957) |

Exploratory Bayesian network analysis

To identify a strategic network of major white matter tracts relevant for processing speed and to account for possible co-lineari ties and interactions between variables we used Bayesian network analysis. In a first step, we analyzed all white matter tracts represented in the JHU probabilistic atlas while combining lesions from corresponding white matter structures of the left and right hemisphere into a single imaging variable. Considering both WMH and LL we found processing speed to be jointly associated with three variables, each defined by lesion type and location: LL in the cingulum and WMH in the forceps minor (Fmin), the parahippocampal white matter (PHWM) and the corticospinal tract (CST) (supplementary fig. A.2).

To investigate the full network we next performed a second analysis accounting for all variables with corresponding white matter tracts from the left and right hemisphere treated separately (supplementary fig. A.3). Here, processing speed was found to be jointly associated with the same white matter tracts (all on the left side) as in the combined analysis with the addition of LL in the left anterior thalamic radiation (ATR). Thus, only these five white matter tracts were informative in predicting processing speed and emerged as a strategic brain network (Fig. 2).

Confirmatory analysis

To investigate the robustness of the relationships within the strategic brain network we performed 3000 bootstrap replications of the Bayesian network (Fig. 2). The relative frequencies of the arcs appearances in the strategic network ranged from 50%, reflecting a good confidence level, to 100% indicating an excellent level of confidence.

The significance of conditional dependencies between processing speed and its primary determinants derived from the Bayesian approach was confirmed by calculating partial correlations, thereby controlling for the effect of the other variables (Table 2). The strongest negative partial correlations were found for WMH in the CST and for LL in the cingulum (−0.35 and −0.22, respectively). LL in the anterior thalamic radiation and WMH in the forceps minor (−0.18 and −0.14, respectively) showed a moderate negative partial correlation. Of note, the PHWM showed a positive partial correlation with processing speed. A good model fit was confirmed by structural equation modeling (p-value = 0.05, chi/df = 2.4, RMSEA = 0.08, CFI = 0.99) while resulting in the same order of partial loadings (Fig. 3 and Table 3).

Linear regression models

As a final step we compared the results obtained by the Bayesian networks analysis with linear regression models, which are subject to over- or under-fitting as they ignore collineari ties and interactions. In univariate linear models 31 (75.6%) of the variables significantly (p<0.05) correlated with processing speed (supplementary Table A2). Multivariate linear regression analyses identified 8 imaging variables, which were significantly associated with processing speed and together explained 37% of the variance (Table 4 and supplementary fig. A.4). This linear model included all five variables that had been identified by the Bayesian network analysis. Two of the three additional variables showed a positive correlation with processing speed, suggesting a better performance with higher regional lesion volume. For comparison, the five primary determinants identified by the Bayesian network analysis alone explained 34% of the processing speed variance. When adding normalized brain volume as a known imaging predictor of VCI to the model, the explained variance increased from 34% to 38% (n = 217).
The maps are color-coded according to the lesion probability and superimposed onto the MNI 152 T1 template. L = left, R = right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Discussion

In this study we set out to disentangle the relationships between ischemic lesions in multiple distinct white matter tracts and processing speed as the predominantly affected cognitive domain in VCI. Using a graph-based approach we identified a strategic network of white matter tracts, which best determines impaired processing speed. This brain network, discovered through an explorative Bayesian network analysis, was confirmed by structural equation modeling. Our findings confirm and extend previous results showing a role of frontal–subcortical neuronal circuits in vascular cognitive impairment.

The ATR and Fmin had already been identified by our previous voxel-based approach (Duering et al., 2011). Importantly, the current study was based on the regional volume of LL and WMH within major white matter tracts while considering the contributions from all white matter tracts and their inter-relations. This provides strong and independent evidence for the strategic role of the ATR and Fmin with regard to processing speed deficits. The left CST likewise came up in our previous analysis and other studies also found an association between executive functions and structural integrity of the CST (Duinkerken et al., 2012; Kinnunen et al., 2011). However, this likely reflects a motor component of the applied tests, all of which require manual skills. The fact that the signal was seen on the left side would be consistent with this interpretation.

In addition to these WM tracts, the Bayesian network analysis identified the cingulum as a relevant structure contributing to slowed information processing. Several studies support the role of the cingulum in executive functions in general (Kantarci et al., 2011; O’Sullivan et al., 2005; Schermuly et al., 2010; Skranes et al., 2009) and processing speed in particular (Dineen et al., 2008; Sasson et al., 2012). Interestingly, a previous study analyzing DTI metrics in CADASIL patients (O’Sullivan et al., 2005), found white matter integrity in the left cingulum to correlate with processing speed dependent tests. Our data extend this knowledge by demonstrating a strategic role of LL, i.e. chronic cavitating infarcts, within the cingulum. We further found lesions within the PHWM to determine processing speed in our study sample. To our knowledge, there are no reports linking the PHWM to processing speed. However, together the results on the ATR, Fmin, and cingulum strengthen the concept that the disruption of frontal–subcortical neuronal circuits, in particular dorsolateral prefrontal and cingulate circuits, plays an important role in VCI related to subcortical ischemic lesions (Cummings, 1993). This does not imply actual brain connectivity between the identified structures in our statistical network. However, our analysis suggests that lesions within these structures jointly drive cognitive impairment.

Studies in other, mostly healthy cohorts have identified other white matter structures impacting on processing speed performance, including the superior and inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus and the uncinate fasciculus (Jacobs et al., in press; Konrad et al., 2009; Perry et al., 2009; Sasson et al., 2012; Turken et al., 2008). A recent study focusing on the network aspect of processing speed found that processing speed related to the connectivity of multiple brain regions (Wen et al., 2011). Some authors even suggest, that processing speed is a global function and determined by the shared integrity across all tracts rather than specific fiber connections (Penke et al., 2010). Yet, the current study, which incorporates lesions measurements from multiple white matter tracts in multiple brain regions, suggests that damage to frontal–subcortical neuronal circuits is of paramount importance for slowed processing speed in VCI.

Table 2

Partial correlations between processing speed and the five primary determinants as revealed by the Bayesian network analysis.

<table>
<thead>
<tr>
<th>Path</th>
<th>r_{partial}</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST left WMH → speedscore</td>
<td>−0.35</td>
<td>3.05E−8</td>
</tr>
<tr>
<td>Cingulum left LL → speedscore</td>
<td>−0.22</td>
<td>8.53E−4</td>
</tr>
<tr>
<td>ATR left LL → speedscore</td>
<td>−0.18</td>
<td>5.69E−3</td>
</tr>
<tr>
<td>Fmin WMH → speedscore</td>
<td>−0.14</td>
<td>3.24E−2</td>
</tr>
<tr>
<td>PHWM left WMH → speedscore</td>
<td>0.23</td>
<td>4.00E−4</td>
</tr>
</tbody>
</table>

CST = corticospinal tract, speedscore = processing speed compound score, ATR = anterior thalamic radiation, Fmin = forceps minor, PHWM = parahippocampal white matter.
WMH in the left PHWM was positive. This might result from the strategic network. Rather surprisingly, the partial effect of variable while controlling for the effects from all other variables using partial correlations we sought to assess the impact of each technique for exploratory and confirmatory analysis by structural equation modeling. Estimated effected sizes together with left and right 95% confidence intervals and standardized standard errors for the model shown in Fig. 1. Thus, while a bias owing to verbal skills cannot be entirely excluded, these findings support the prominent role of the left hemisphere in processing speed tasks.

To our knowledge, this is the first lesion-deficit analysis on subcortical ischemic lesions and cognitive performance using graph-based statistical methods. Bayesian network analysis has previously been successfully applied to MRI data to study the mechanisms of psychiatric sequelae of traumatic brain injury in children (Herskovits and Gerring, 2003) and mild cognitive impairment (Chen and Herskovits, 2006). Graph-based techniques account for interactions of variables in the model. Bayesian networks deal well with multicollinearity, providing an intuitive representation of complex relationships. This is especially important, as all regional lesion volumes in the strategic network were interconnected and highly correlated. The use of robust data-mining techniques for exploratory and confirmatory analysis can thus be regarded a main strength of this study.

The confidence of the network structure was confirmed by learning a large number of Bayesian networks from bootstrap samples. Using partial correlations we sought to assess the impact of each variable while controlling for the effects from all other variables from the strategic network. Rather surprisingly, the partial effect of WMH in the left PHWM was positive. This might result from the overall weak influence of lesions in the PHWM – as shown by the univariate negative correlation with the processing speed score (r = – 0.04, see supplementary Table A.2) – and indirect effects that were not captured by our approach. Thus for example, lesions in the PHWM might be an early indicator for more widespread ischemic pathology and ongoing compensatory mechanisms, which were not assessed in the current study. Alternatively, the finding on PHWM could be due to the relatively small sample size (see limitations below) and the fact that this structure includes the temporopolar white matter, which is commonly affected by WMH even in young asymptomatic mutation carriers. Of note, PHWM damage has been shown to influence the memory domain of cognitive impairment (Wang et al., 2012), which is relatively well preserved in CADASIL and in VCI in general.

We used structural equation modeling (SEM) to confirm the proposed network model. A specific strength of SEM is the ability to assess relationships between one or more independent and dependent variables. Stepwise multiple linear regressions captured three additional variables not contained in the graph-based models. Two of them showed a positive correlation with processing speed. Of note, however, regression models ignore interactions and can be affected by multicollinearity. Thus, these positive associations might be functionally irrelevant and a result of data overfitting. In accord with this, the explained variance in a linear model incorporating solely the five primary determinants identified by the network approach was only slightly lower (R square of 0.34 vs. 0.37). The results from the graph-based model can therefore be regarded as more robust compared with linear regression models, which are subject to multicollinearity. In other words, additional variables might have entered the linear model because of overfitting. Importantly, inclusion of normalized brain volume as a known predictor for VCI (Viswanathan et al., 2010) resulted in only minor improvement of the explained variance indicating that the variables identified by the graph-based approach already cover a large part of the explainable variance.

The effectiveness of our approach to disentangle causal relationships is illustrated by the results for age. Processing speed is known to decline with normal aging, which might in part relate to an age-related loss of white matter integrity (Burgmans et al., 2011). To account for the effects of normal aging we used reference data from healthy subjects and calculated age corrected Z-scores of processing speed. Still, there was a significant association between age and processing speed in univariate regression analysis. The graph-based model clarifies this relationship: here, age is not a direct predictor of processing speed but an upstream node of relevant regional lesion volumes.

Table 4
Stepwise linear regression model on processing speed.

<table>
<thead>
<tr>
<th>Model</th>
<th>Beta</th>
<th>p-value</th>
<th>Adjusted R square</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST left WMH</td>
<td>− 0.48</td>
<td>0.22</td>
<td>0.22</td>
</tr>
<tr>
<td>+ Cingulum left LL</td>
<td>− 0.25</td>
<td>0.28</td>
<td>0.28</td>
</tr>
<tr>
<td>+ ATR left LL</td>
<td>− 0.18</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>+ PHWM left WMH</td>
<td>0.18</td>
<td>0.33</td>
<td>0.33</td>
</tr>
<tr>
<td>+ IFO left WML</td>
<td>− 0.21</td>
<td>0.34</td>
<td>0.34</td>
</tr>
<tr>
<td>+ ATR left WML</td>
<td>0.32</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>+ SLF right LL</td>
<td>0.13</td>
<td>0.36</td>
<td>0.36</td>
</tr>
<tr>
<td>+ Fmin WMH</td>
<td>− 0.16</td>
<td>0.37</td>
<td>0.37</td>
</tr>
</tbody>
</table>

IFO = inferior fronto-occipital fasciculus, SLF = superior longitudinal fasciculus.
which grow larger with increasing age. Age can therefore be interpreted as a surrogate marker for disease progression. A vital aspect of this study was that we examined patients with pure vascular disease. By design we minimized a possible confounding effect from other pathologies such as inflammatory or age-related neurodegenerative disease. All of our patients had a proven diagnosis of CADASIL and the mean age of our cohort was 48 years, which is much below the usual age of onset for neurodegenerative disease. Thus, the cognitive symptoms can be clearly related to the underlying vascular pathology.

One limitation of our study is the relatively small sample size. Bayesian networks benefit from large sample sizes, allowing them to find conditional dependencies even in noisy data. With our current sample size, we cannot be certain to have identified all relationships within the data. The atlas-based approach can also be regarded as a limitation. Individual tractography in every subject would have better accounted for inter-individual differences in tract location. We partially addressed this issue by using a probabilistic approach for the projection of lesions onto tracts. Finally, the inclusion of a test assessing motor function of the dominant hand could have helped interpreting the results on the corticospinal tract.

Conclusions

In summary, using graph-based statistical models, we identified a strategic network of distinct white matter tracts having the greatest impact on processing speed in our sample of patients with pure small vessel disease. This network emphasizes the importance of frontal–subcortical neuronal circuits, in particular dorsolateral prefrontal and cingulate circuits, in vascular cognitive impairment.

Study funding

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Appendix A. Supplementary data

Supplementary data associated with this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2012.10.084.

References