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

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ABSTRACT

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.

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.

MR 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

Abbreviations: VCI, vascular cognitive impairment; LL, lacunar lesions; WMH, white matter hyperintensities; ATR, anterior thalamic radiation; Fmin, forceps minor; CST, corticospinal tract, PHWM, parahippocampal white matter.

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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 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 during 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 (Doubal 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 SIENAX 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.