NeuroImage: Clinical 18 (2018) 425–432

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

A comparison of functional and tractography based networks in cerebral small vessel disease

Andrew J. Lawrence[a,1,2,3], Daniel J. Tozer[a,*,1], Emmanuel A. Stamatakis[b], Hugh S. Markus[a]

[a] Stroke Research Group, Department of Clinical Neurosciences, University of Cambridge, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK
[b] Division of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK

ARTICLE INFO

Keywords:
Small vessel disease
MRI
Network analysis
Reproducibility diffusion imaging
Functional connectivity

ABSTRACT

Objective: MRI measures of network integrity may be useful disease markers in cerebral small vessel disease (SVD). We compared the sensitivity and reproducibility of MRI derived structural and functional network measures in healthy controls and SVD subjects.

Methods: Diffusion tractography and resting state fMRI were used to create connectivity matrices from 26 subjects with symptomatic MRI confirmed lacunar stroke and 19 controls. Matrices were constructed at multiple scales based on a multi-resolution cortical atlas and at multiple thresholds for the matrix density. Network parameters were calculated over the multiple resolutions and thresholds. In addition the reproducibility of structural and functional network parameters was determined in a subset of the subjects (15 SVD, 10 controls) who were scanned twice.

Results: Structural networks showed a highly significant loss of network integrity in SVD cases compared to controls, for all network measures. In contrast functional networks showed no difference between SVD and controls. Structural network measures were highly reproducible in both cases and controls, with ICC values consistently over 0.8. In contrast functional network measures showed much poorer reproducibility with ICC values in the range 0.4–0.6 overall, and even lower in SVD cases.

Conclusions: Structural networks identify impaired network integrity, and are highly reproducible, in SVD, supporting their use as markers of SVD disease severity. In contrast, functional networks showed low reproducibility, particularly in SVD cases, and were unable to detect differences between SVD cases and controls with this sample size.

1. Introduction

Cerebral Small Vessel Disease (SVD) is the most common pathology underlying vascular cognitive decline and dementia (Pantoni, 2010). A number of features can be seen on MRI imaging including lacunar infarcts, T2-white matter hyperintensities, cerebral microbleeds, and more diffuse white matter changes seen on Diffusion Tensor Imaging (DTI) (Schmidt et al., 2010). It has been suggested that damage to white matter tracts leads to disruption of complex networks connecting cortical and sub-cortical regions (Lo et al., 2010; Reijmer et al., 2013). Recently it has become possible to estimate the disruption of such networks using MRI techniques. Structural networks can be constructed via tractography using DTI datasets and these have been shown to be abnormal in patients with SVD, with the extent of disruption correlating with cognitive decline (Lawrence et al., 2014). Mediation analysis has suggested conventional MRI markers of SVD cause cognitive decline via structural network disruption, and recently the degree of network disruption was found to be a significant predicator of future dementia risk (Lawrence et al., 2014). Network integrity can also be assessed using functional connectivity, which utilises resting-state blood oxygen level dependent (BOLD) MRI. Temporal correlations of signal fluctuations in different cortical regions are assessed, and provide an estimate of brain connectivity of these regions (Biswal et al., 1995). Abnormalities of functional connectivity have been reported in SVD, and it has been suggested they may correlate with cognitive impairment (Farràs-Permanyer et al., 2015).

In this study we compared functional and structural connectivity measures in SVD compared with age matched controls, and re-scanned

* Corresponding author at: Box 83, R3 Clinical Neurosciences, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK.
E-mail addresses: djt54@medschl.cam.ac.uk (D.J. Tozer), eas46@cam.ac.uk (E.A. Stamatakis), hsm32@medschl.cam.ac.uk (H.S. Markus).
[1] These authors contributed equally to the manuscript.
[2] Present address: Physcological Medicine, KCL Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK.
[3] Statistical Analysis conducted by Dr. Andrew Lawrence, PhD, University of Cambridge.

https://doi.org/10.1016/j.nicl.2018.02.013
Received 19 September 2017; Received in revised form 19 January 2018; Accepted 7 February 2018
Available online 08 February 2018

both patients and controls on a further occasion to determine reproducibility of both measures.

2. Methods

2.1. Participants

The study was approved by East of England - Cambridge East research ethics committee (reference: 14/EE/0014). All participants provided written, informed consent. Twenty-six participants with symptomatic SVD were recruited from acute and outpatient stroke services at a single teaching hospital. Inclusion criteria were: 1) history of clinical lacunar stroke syndrome (Bamford et al., 1991) with MRI evidence of an anatomically appropriate lacunar infarct, 2) presence of confluent White Matter Hyperintensities (Fazekas scale ≥ 2) (Fazekas et al., 1987). Exclusion criteria were any cause of stroke other than small vessel disease specifically: 1) evidence of larger subcortical infarctions (> 1.5 cm) on MRI as these are often embolic; 2) cortical infarction on MRI; 3) large artery disease - carotid, vertebral or intracranial stenosis > 50%; 4) cardioembolic source for embolism (moderate or higher risk according to the Trial of Org 10172 in Acute Stroke Treatment criteria (Adams Jr et al., 1993). In addition patients with any major central nervous system disease other than SVD. In addition 19 stroke-free control subjects were recruited, for these the exclusion criteria were: 1) a medical history of stroke; 2) any major central nervous system disease.

2.2. MRI acquisition

Participants were imaged on a 3 T Verio MRI system (Siemens AG, Erlangen, Germany) employing a 32-channel receive-only head coil. In addition to conventional sequences (1 mm volumetric T1 weighted MPRAGE, 0.9375 × 0.9375 × 2 mm T2 weighted FLAIR, 0.86 × 0.86 × 5 mm T2* weighted gradient echo) for SVD marker identification and brain volume estimation, the following whole brain sequences were acquired:

1. Axial single shot T2*-weighted EPI sequence with diffusion-weighted images (b = 1000 $s{\cdot}mm^{-2}$) obtained in 63 non-collinear directions on the whole sphere. Eight non-diffusion weighted images (b = 0 $s{\cdot}mm^{-2}$) were acquired. TE/TR: 106/11700 ms, GRAPPA: 2, acquisition matrix 128 × 128, FOV: 256 × 256 mm, 63 contiguous 2 mm slices. Acquisition time 14.5 min.
2. Gradient recalled echo fieldmap, TR: 688 ms, TE1: 5.19 ms, TE2: 7.65 ms, flip angle: 60°. Geometry, slice order and phase encoding identical to 1.
3. Eleven minute axial multi-echo EPI resting state acquisition during which subjects were instructed to attend to a fixation cross. TR: 2430 ms, TE1/2/3: 13/31/48 ms, Flip angle: 90°, GRAPPA: 2, acquisition matrix: 64 × 64, FOV: 240 × 240 mm, 34 slices of 3.8 mm thickness, 10% slice gap. Reconstructed voxel dimensions: 3.75 × 3.75 × 4.18 mm. 269 volumes were acquired.

2.3. Test-retest reproducibility

To investigate the reproducibility of our MRI measures we acquired a second set of MRI data for a subset of participants. Fifteen SVD and 10 control participants were rescanned within 6 months of the original scan.

2.4. MRI processing

2.4.1. Cortical segmentation

Cortical reconstruction and volumetric segmentation of the T1-weighted images was performed using the Freesurfer suite (http://surfer.nmr.mgh.harvard.edu; version 5.3 (Fischl and Dale, 2000; Fischl et al., 2002)). Subcortical structures are segmented and the grey-white matter boundary estimated and refined. The cortical surface is parcellated into 33 regions per hemisphere on the basis of cortical folding patterns (Desikan et al., 2006).

2.4.2. Diffusion and rs-fMRI pre-processing

The diffusion data was pre-processed to produce a diffusion tensor for each voxel using FSL (Jenkinson et al., 2012) and other algorithms implemented in Python, details can be found in Appendix A.

The rs-fMRI data was analysed using the methods proposed by Kundu et al. (2012), this was followed by a pipeline involving steps from SPM (Friston et al., 1995) and CONN (Whitfield-Gabrieli and Nieto-Castanon, 2012) to remove residual effects of noise, movement and the confounding effects of CSF and WM signal, a signal time-course can then be obtained; see Appendix A for more details.

2.5. Network construction

2.5.1. Network nodes definition

Network nodes were defined from the Desikan-Killiany parcellation of cerebral cortex (Desikan et al., 2006). For the structural analysis the nodes are based on the white-grey matter surface, the ROIs were single voxel dilated with 26-connectivity to capture connectivity where streamlines terminated close to grey matter. For functional connectivity the measure of interest is the signal from the cortical region volume itself, so this is the ROI.

To investigate the effects of atlas resolution we employed a hierarchical multiresolution atlas (Daducci et al., 2012). The atlas was created according to Cammoun et al. (2012), the original Desikan-Killiany 68 GM-WM ROIs were partitioned to create a fine resolution atlas of approximately equal area regions (1.5 cm^2, $n = 998$). Then successive merges of neighbouring regions were employed to produce multiple atlas resolutions. Due to the low functional imaging resolution we omit the finest resolution atlas and investigate networks constructed at four atlas resolutions: 68, 114, 219 and 448 nodes.

2.5.2. Network connection definition

For the structural data whole brain deterministic tractography was conducted on the principal directions of the tensors. Streamlines were generated and two cortical regions A, B were connected where one or more streamlines terminating in region A also terminated in region B. The strength of this connection was weighted by the number and length of streamlines between the two regions. Details of the tractography processing and weighting are found in Appendix A.

The corresponding measure for the functional data is simply the correlation coefficient between the signal time-courses over the 269 volumes for any 2 regions.

2.6. Brain network analysis

Network analysis produces a number of measures of network integrity. We focussed on weighted global efficiency (E_{Global}), weighted clustering coefficient (C^w) and the total network strength (TNS) as these have previously been shown to be sensitive to structural network differences between SVD cases and controls in (Lawrence et al., 2014). Details on how these parameters are derived is in Appendix A.

2.7. Thresholding of connectivity matrices

There is a correlation coefficient between every pair of nodes in functional analysis and a threshold is required to distinguish connections from statistical noise. In contrast, structural networks are sparse with most pairs of nodes having no connection. Further, for structural data the distribution of connection weights decays exponentially such that the number of streamlines is very low for most connections (Hagmann et al., 2007). Thresholding is also commonly carried out in