BRAIN (DYS)CONNECTIVITY IN MULTIPLE SCLEROSIS: NETWORK TOPOLOGY AND COGNITION

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Abstract: Using the Signed Differential Mapping voxelwise meta-analysis technique, we identify statistical consensus between studies for minimally-overlapping distributions of injury relating to physical disability and cognitive impairment in multiple sclerosis (MS). These findings form a basis for the study of brain network properties as potential markers of cognitive impairment in MS. We present our future plans to that end.

Previous Work

Purpose

- Several heterogeneous distributions of fractional anisotropy (FA) have been reported in relation to cognitive impairment and physical disability.
- We aimed to identify statistical consensus between published studies for distribution and functional relevance of white matter degradation in MS.

Methods

- Systematic identification of TBSS studies which: (1) compare FA in MS patients to healthy controls; (2) correlate FA in MS patients with physical disability; and (3) correlate FA in MS patients with cognitive performance.
- Voxelwise meta-analysis using the Signed Differential Mapping (SDM) technique [2]. SDM combines statistical maps of imaging data, weighting by the intra-study variance and the inter-study heterogeneity. A random-effects general linear model allows comparisons and meta-regressions.

Results

- Data from 495 patients and 253 controls across 8 studies were meta-analysed (Fig. 1).
- The number of DTI diffusion gradient directions had a significant moderating effect on the correlation between FA and clinical scores.
- There were over twice as many voxels with significant FA reduction in relation to cognition (753) than to physical disability (323).

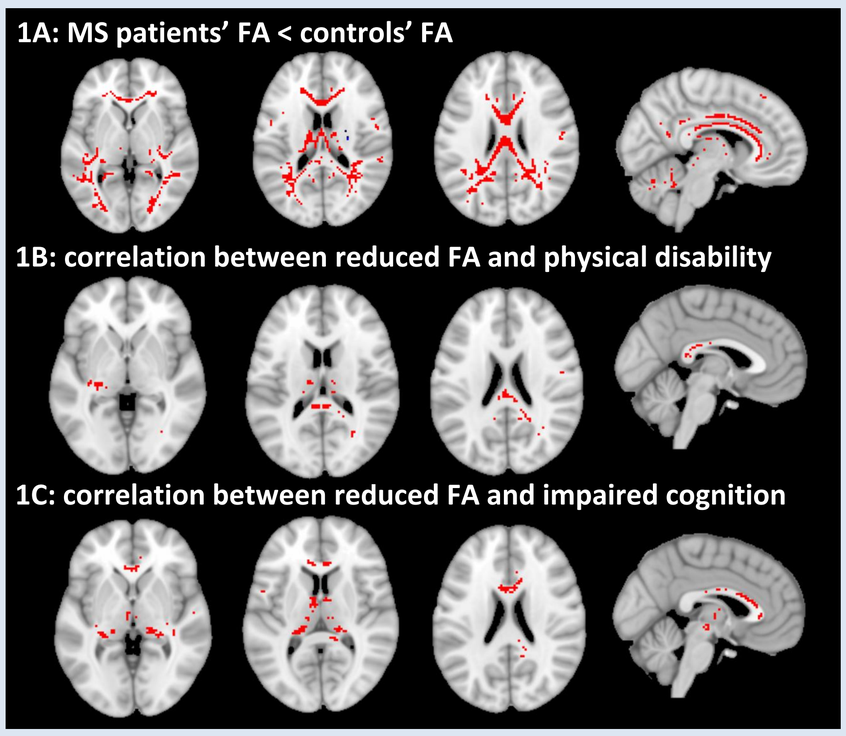
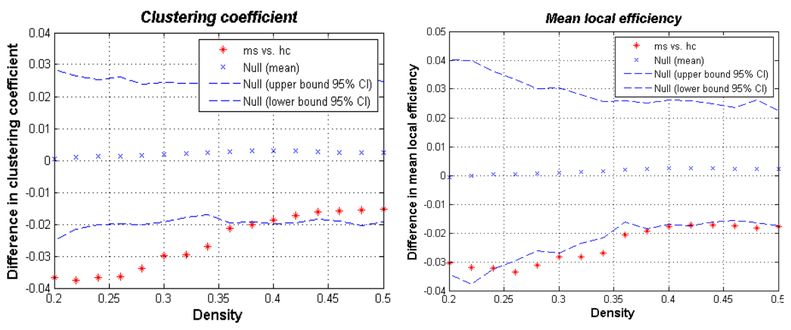


Figure 1 (right). Weighted mean statistical maps. Thresholds were: uncorrected p < 0.005, z > 1 and cluster extent ≥ 10 voxels. MS diagnosis was significantly associated with widespread tract reductions in FA (1A). Poor physical disability scores were significantly associated with reduced FA in the right posterior cingulum, left callosal splenium, right inferior fronto-occipital fasciculus and left fornix crus (1B). Impaired cognition was significantly associated with reduced FA in the callosal genu, thalamus, right posterior cingulum and fornix crus (1C).

Proposed Work

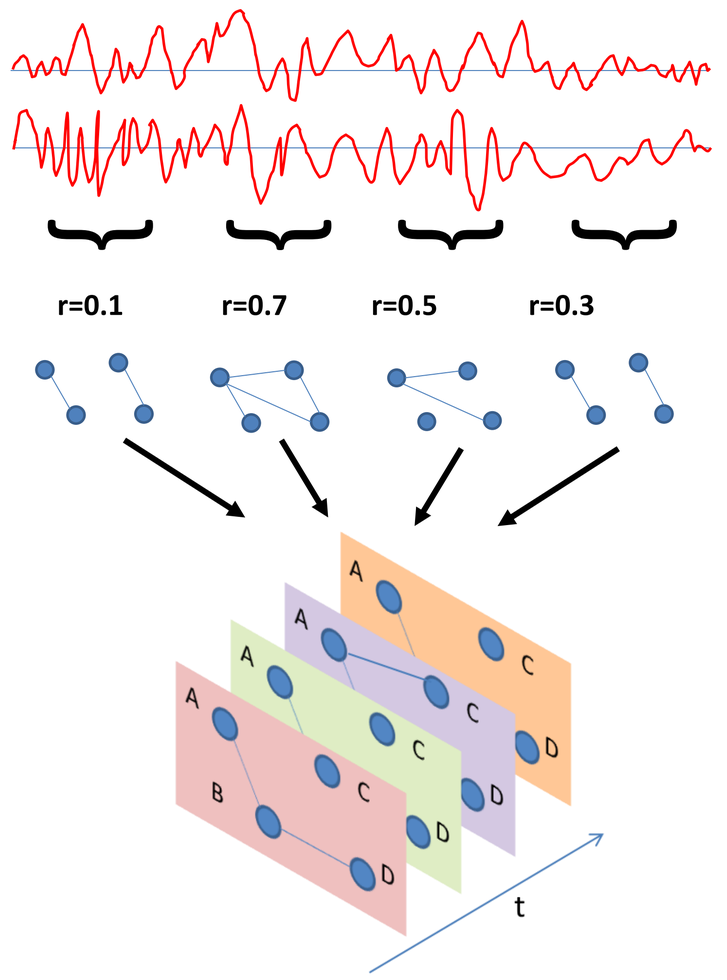
Graph Analysis

- Disruption to functional networks by disconnection of grey matter regions may be an important mechanism contributing to the symptomatology of MS, particularly cognitive dysfunction.
- We hypothesise that properties of those networks may be useful as outcome measures in clinical trials.
- An initial graph analysis of 15 MS patients and 15 controls showed significant differences between groups in several metrics: clustering ($p<0.01$), local efficiency ($p<0.05$). Assortativity and clustering correlated with disease duration ($p<0.05$), while density and mean degree correlated with disease severity ($p<0.05$).
- Metrics are calculated over a range of densities to establish their reliability:



- The biological plausibility of brain network density is an ongoing debate.

- **Dynamic network analysis will show changes to functional network organisation that occur during induction of cognitive fatigue:**



- We will determine the test-retest reliability of graph metrics between two scans, 1 month apart, in a cohort of 30 MS patients and 30 controls.
- The responsiveness of candidate markers to a cognitive intervention will also be tested.

Conclusion: Altered network topology is justified in theory as a potential marker of cognitive impairment and fatigability in MS and we will explore this further in future work.

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1. Smith SM et al, 2006. *NeuroImage* 31:1487-505.
2. Radua J et al, 2009. *European Psychiatry* 27:605-11.

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