Identifying group differences in functional subnetworks: a novel whole-brain method applied to dyslexia

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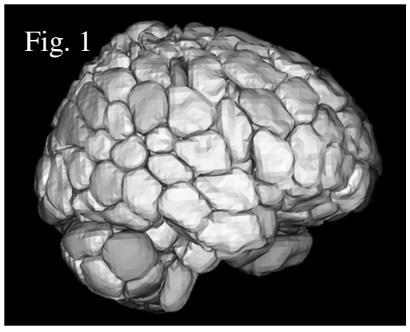
Introduction. Functional connectivity (FC) analyses of fMRI data are a powerful tool for characterizing brain networks and how they are disrupted in various neural disorders. However, many FC analyses limit themselves to examining one or a small number of seed regions chosen based on *a priori* information. Other studies that consider the whole brain frequently rely on anatomic atlases[1] to define network nodes, which may result in mixing distinct activation timecourses within a single node. Here, we improve upon previous methods by using a data-driven functional brain parcellation[2] to compare connectivity profiles of dyslexic versus control readers in the first whole-brain FC analysis of dyslexia.

Methods. Two large datasets of dyslexic readers (DFI) and non-impaired controls (NI) were analyzed, one containing young subjects (mean age 9, n=144) and the second older subjects (age 18-20, n=127). fMRI data were acquired at 1.5T; TR=1500 ms; TE=60 ms; FA=60°; slice thickness=7mm. Data were slice-time and motion corrected, head motion was balanced between groups, and the effect of a word-rhyming task was regressed out. Functional parcellation was done on data from NI subjects using a normalized cut algorithm to group voxels with similar timecourses into functional subunits[2], resulting in a whole-brain parcellation of 225 nodes (Fig. 1). Temporal correlations in BOLD signal between each pair of nodes were calculated, resulting in 225x225 matrix of *z*-transformed *r*-values for each subject. Groups were compared using the network-based statistic[3]: A t-test was performed on each cell of the matrix (representing a single connection, or "edge"), a t-score threshold was set, and the largest component of suprathreshold edges in each direction (NI>DFI and DFI>NI) was determined. Results were corrected for multiple comparisons using group-permutation testing (K=1000).



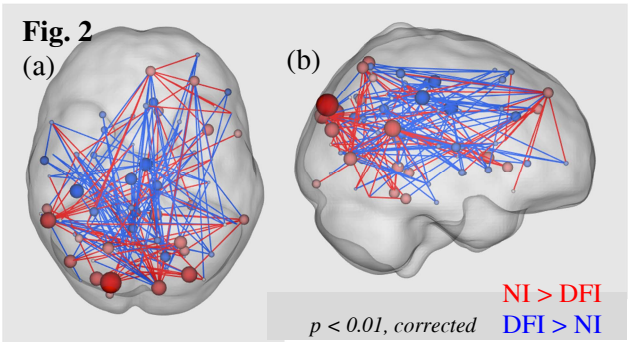


Fig. 1. Network nodes defined using a 225-region functional brain parcellation.
Fig. 2. An axial (a) and sagittal (b) depiction of subnetworks differentially connected in NI vs. DFI readers. Red = stronger in NI; blue = stronger in DFI.

Results. In younger subjects, we detected a subnetwork of 337 edges more strongly connected in the NI group, and a subnetwork of 415 edges more strongly connected in the DFI group ($p<0.01$, corrected). Many of the NI connections involved occipitoparietal and frontal areas, while the DFI subnetwork was more diffuse (Fig. 2). In older subjects, we detected a subnetwork of 312 edges more strongly connected in the NI group, and a subnetwork of 361 edges in the DFI group. Results from older readers showed similar trends for NI in occipitoparietal areas, and older DFI subjects showed increased connectivity between frontal regions and a left inferior frontal region (not shown).

Discussion. The occipitoparietal areas that were better connected in both younger and older NI readers are known to be involved in visual association, suggesting that these subjects are better able to process word forms based on their shapes. Many of these occipitoparietal connections involved frontal areas responsible for attention and executive control, suggesting that NI subjects are better able to modulate their attention to visual stimuli. In the older DFI subjects, persistent overconnectivity to a left-frontal phonology region indicates that these subjects continue to rely on laborious "sounding out" strategies instead of recognizing words via an automatic sight-based system. These connectivity results deepen our understanding of dyslexia, moving beyond magnitude of activation in isolated areas and highlighting the importance of between-region synchrony for successful reading. We believe this data-driven analysis method can be extended to examine differentially connected subnetworks in a range of neural disorders.

[1] Tzourio-Mazoyer et al., Neuroimage 2002; 15:273–289. [2] Shen et al., Neuroimage 2010; 50(3):1027−1035. [3] Zalesky et al., Neuroimage 2010; 53(4):1197−1207.