Demonstration of the central role of the subcortex in the developing brain by identifying "hubs" in the network organisation of functional connectivity

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Introduction: We describe and demonstrate a novel fMRI analysis technique for characterising the network hierarchy of functional connectivity in the brain. Recent studies have shown that this network displays a small-world network (SWN) topology [1,2,3], which is a special class of sparse network characterised by a high *clustering coefficient* (i.e. nodes cluster together into tightly interconnected sub-networks) coupled with the presence of *hub nodes (*key nodes linking different sub-networks together into higher-level networks) [4]. The hub-nodes represent the most critical points for the efficient functioning of SWN [5] and, therefore, are of particular interest in understanding the operation of such systems.

A well known man-made network with SWN properties is the world-wide-web, and a widely used tool for exploring this network is Google's PageRank (PR) algorithm [6], which provides an efficient method for ranking web-pages based upon their interconnections. The PR algorithm assigns a rank to a web-page based upon a weighed-sum of the ranks of pages that link to it – so that progressively higher ranks propagate from the base-level sub-graphs to the top-most hubs of the network. In this work we demonstrate the application of the PR algorithm to detect functional connectivity hubs using a whole-brain voxel-based analysis of fMRI data.

Method: *Subjects & Data*: We analysed 15 minutes of resting-state fMRI data from 5 adults (3 men, ages 21-22, mean 21.6±0.55 years) and 5 children (4 boys, ages 7-10, mean 8.8±1.3 years old). BOLD-weighted images were acquired on a 3 tesla GE Signa LX scanner using a gradient-echo EPI sequence (25 slices; 128x128 matrix; TE=40ms; TR=3.6s (adults); TR=3s (children)). The data were pre-processed with SPM8 using: slice-timing correction, realignment, spatial normalisation and spatial smoothing (8mm FWHM). Motion-related variance was also estimated and removed using multiple linear regression of the realignment parameters. *Connectivity Analysis*: We formed a directed graph modelling the network of functional connections between voxels in the brain, where the existence of a connection was inferred from the correlation between low frequency (0.01–0.08 Hz) BOLD signal changes [7]. One-thousand out-going connections were chosen for each voxel based upon the strongest correlations. The PR algorithm was then used to provide a ranking for each voxel in the network. In brief, this requires finding a vector of ranks, $\mathbf{r}$, such that $\mathbf{r} = \mathbf{C}\mathbf{r}$, where $\mathbf{C}$ is the connectivity matrix of the network. This amounts to finding an eigenvector with an eigenvalue of one, and the PR algorithm describes an efficient iterative method for solving this problem [8]. This analysis was implemented using C++ and processed on a 2.83GHz Intel Core2 Quad CPU with 1.5 GB of memory running Ubuntu Linux.

Results: The analysis revealed a markedly different connectivity pattern for the children compared to the adults. In children the highest ranking voxels were in sub-cortical structures (the thalamus and putamen), whereas in adults the highest ranks were restricted to cortical areas, including primary sensorimotor, visual and auditory cortices and the cingulate gyrus (*Figure 1*). The processing time for each subject was approximately 15 minutes to construct the whole-brain connectivity graph and 10 seconds to perform the ranking computation.

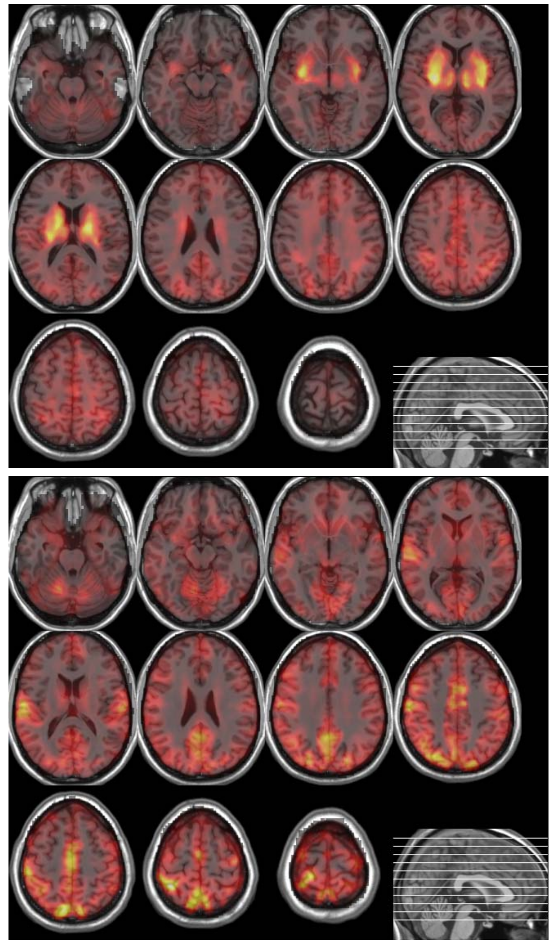

Figure 1: Group connectivity maps for children (top) and adults (bottom). The colour indicates the average rank assigned by the PR algorithm, with hotter colours indicating higher ranks. These maps reveal prominent high ranks in the subcortical structures in children but not in adults.

Discussion: We have demonstrated the use of an efficient algorithm to enable localisation of whole-brain functional connectivity hubs at a voxel-level, which differs from most other published network analyses of fMRI connectivity that have been based upon regions-of-interest. Our findings suggest that the functional connectivity of the brain moves from a more centralised network organisation in young children to a more distributed organisation in adults. This finding extends upon the results from another recent connectivity study that described a shift from a local towards a more distributed network organisation of cortical regions in children compared with adults [9]. The putamen and thalamus are both strongly and widely connected to the cortex so our data suggests that these structures play a more prominent role in the integration of cortical networks in children. These maturational changes in functional connectivity may explain the age-related onset and remission of some neurological disorders such as certain types of childhood epilepsy. We also suggest that this analysis technique may assist in localising SWN changes in diseases such as schizophrenia and Alzheimer's disease [10,11,12,13].

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