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An investigation into the functional and structural connectivity of the Default Mode Network

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ABSTRACT

Connectivity analyses based on both resting-state (rs-)fMRI and diffusion weighted imaging studies suggest that the human brain contains regions that act as hubs for the entire brain, and that elements of the Default Mode Network (DMN) play a pivotal role in this network. In the present study, the detailed functional and structural connectivity of the DMN was investigated. Resting state fMRI (35 minute duration) and Diffusion Weighted Imaging (DWI) data (256 directions) were acquired from forty-seven healthy subjects at 3 T. Tractography was performed on the DWI data. The resting state data were analysed using a combination of Independent Component Analysis, partial correlation analysis and graph theory. This forms a data driven approach for examining the connectivity of the DMN. ICA defined regions of interest were used as a basis for a partial correlation analysis. The resulting partial correlation coefficients were used to compute graph theoretical measures. This was performed on a single subject basis, and combined to compute group results depicting the spatial distribution of betweenness centrality within the DMN. Hubs with high betweenness centrality were frequently found in association areas of the brain. This approach makes it possible to distinguish the hubs in the DMN as belonging to different anatomical association systems. The start and end points of the fibre tracts coincide with hubs found using the resting state analysis.

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Introduction

Resting state functional MRI (rs-fMRI) has developed into a major tool for examining functional connectivity in the brain. In 1995, Biswal et al. showed the similarity between the functional activation map of a finger tapping experiment, and the correlation map to a seed placed inside that activation map (Biswal et al., 1995). Initially, this type of research generally followed the methods developed by Biswal et al., and used seed voxels and correlation maps (Fox and Raichle, 2007).

One resting state network (RSN) of particular interest is the Default Mode Network (DMN) (Buckner et al., 2008; Raichle et al., 2001). A meta-study of Positron Emission Tomography (PET) data found that regions of this network: the Medial Frontal Cortex (MFC), Inferior Parietal Lobule (IPL), Medial Temporal Lobe (MTL), and the Precuneus/Posterior Cingulate Cortex (Pc/PCC), show reduced metabolic activity during activation (Shulman et al., 1997). From a cognitive point of view, parts of the DMN are involved in processes such as episodic memory (Greicius et al., 2003, 2004). However, its higher activation during inactivity has seen it described as an important part of the idling mode of the brain (Raichle et al., 2001; Raichle and Snyder, 2007). Seed-based techniques are capable of detecting a number of RSNs, including the DMN (Cole et al., 2010). However, these methods include some bias in the form of the seed selection. This specificity to the seed voxel selection can be an advantage for some research questions (van den Heuvel and Hulshoff Pol, 2010). However, when searching for RSNs it becomes a disadvantage, because the resulting RSN map can be very sensitive to the location of the seed voxel (Cole et al., 2010). Exploratory data-driven techniques, like Independent Component Analysis (ICA) (Beckmann et al., 2005; Comon, 1994; Kiviniemi, 2003; McKeown et al., 1998) can avoid some of these disadvantages. Results obtained using ICA suggest that there are at least 10 large scale RSNs, having long range connections throughout the entire brain (Beckmann et al., 2005; Damoiseaux et al., 2006), and importantly, if sufficient data are acquired, higher order ICA can be used to detect more components (Kiviniemi et al., 2009).

In recent years graph theoretical measures have been introduced as a means of describing the network structure of the brain. These techniques have been applied both to resting state data (Salvador et al., 2005) and to fibre tracking data (Hagmann et al., 2008). Graph theory

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can be used to find hubs of connectivity, by identifying regions with high betweenness centrality. It has furthermore revealed that brain networks have a small world topography (Achard et al., 2006; Salvador et al., 2005; van den Heuvel et al., 2008b). Previous work on the graph theoretical structure of the brain using both resting state fMRI (van den Heuvel et al., 2008a) and fibre-tracking data (Hagmann et al., 2008; van den Heuvel et al., 2012) have identified the Pc/PCC region of the DMN as a major hub. This is in agreement with existing anatomical knowledge that parts of the Pc/PCC are so called Heteromodal Association Areas (HAAs), having many connections with other parts of the brain and being associated with advanced stages of information processing (Bassett et al., 2008). The unique role of HAAs is to bind multiple brain regions into distributed integrated networks (Achard et al., 2006; Mesulam, 1998; Nieuwenhuys et al., 2008).

The connectivity of the DMN has been investigated on the scale of the larger DMN regions. Fransson and Marrelec used partial correlation coefficients to investigate the large scale connectivity between regions of the DMN and found that the Pc/PCC region showed a heightened connectivity to other regions in the network (Fransson and Marrelec, 2008). Greicius et al. have previously investigated the use of both functional and anatomical connectivity of the DMN and showed that regions that have a high degree of functional connectivity are likely directly connected anatomically (Greicius et al., 2009), reflecting results previously obtained from other regions of the brain (Koch et al., 2002; Skudlarski et al., 2008). Van den Heuvel et al. investigated the link between this anatomical and functional connectivity and found that the DTI fibre path integrity of the cingulum tract is highly correlated with the functional connectivity of the regions it connects (van den Heuvel et al., 2008a). The present work expands on this previous literature, by performing a graph theoretical analysis of the functional connectivity pattern at a finer spatial scale than has hitherto been attempted, and relating this to the anatomical connectivity in the network. To this end, resting state fMRI data were obtained. These resting state data were used to perform single-subject ICA runs. The resulting regions were used for a detailed analysis of the organisation of the DMN, and to compute group averages and hubs of connectivity. High angular resolution Diffusion Weighted Imaging (DWI) data were also obtained in order to explore the relationship between the anatomical connectivity of the DMN using both deterministic and probabilistic tractography and its internal hub structure. Deterministic tractography provided a clear visualisation of the streamlines between regions, probabilistic tractography was added in order to verify the simpler method of deterministic tractography.

Methods

Subjects and data acquisition

Forty-seven subjects (age mean/std: 22.7/2.4, 24 male, 44 right handed) were scanned after giving informed written consent in accordance with the guidelines of the local ethics committee. All scans were acquired at 3 T on a Siemens Magnetom Trio system at the Donders Centre for Cognitive Neuroimaging. T1 anatomical, resting state fMRI and DWI data were acquired in one session. For the resting state scan, the scanner room was completely darkened. Lights were turned off and blinds pulled down. Subjects were instructed to relax, keep their eyes open, stay awake and try not to think about anything specific or dwell on one particular subject. Because this resting state scan was much longer than is usual, the subjects were monitored to ensure that they stayed awake. An infra-red camera normally used for eye tracking was used for this purpose.

Resting state fMRI data were acquired at 3 T using a Multi Echo - Echo Planar Imaging (ME-EPI) (Poser et al., 2006; Speck and Hennig, 1998) sequence with a Siemens 32 channel head coil. Voxel size was $3.5 \times 3.5 \times 3.5$ mm^3, flip angle = 80°, TR = 2000 ms, TEs = 6.9, 16.2, 25, 35 and 45 ms, matrix size 64×64, 39 slices, 1030 volumes, GRAPPA factor 3, 6/8 partial Fourier. Total scanning time for the resting state protocol was 35 min. The DWI protocol used the optimized acquisition order described by Cook et al. (2007). The DWI acquisition parameters were: voxel size $2.0 \times 2.0 \times 2.0$ mm^3, matrix size 110×110, TR = 13,000 ms, TE = 101 ms, 70 slices, 256 directions at b = 1500 s/mm^2 and 24 directions at b = 0. Finally, the T1 structural scan used an MPRAGE protocol, with acquisition parameters: voxel size $1.0 \times 1.0 \times 1.0$ mm^3, matrix size 256×256, 192 slices, TR = 2300 ms, TE = 3.03 ms, TI = 1100 ms, flip angle = 8°.

Preprocessing

rs-fMRI preprocessing was performed using Matlab scripts, and FSL's FEAT toolbox (fMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The multi-echo sequence that was used generates a volume for every echo at every time point. These echoes were combined as described by Poser et al. to allow the use of standard fMRI preprocessing tools (Poser et al., 2006). Of the 1030 combined volumes, the first six were discarded to allow the system to reach a steady state. Motion correction was performed prior to combining the multiple echoes using SPM5 functions (Wellcome Department of Imaging Neuroscience, University College London, UK). FEAT preprocessing involved the removal of non-brain regions using the Brain Extraction Tool (BET); 5 mm FWHM Gaussian spatial smoothing; spatial normalisation to Montreal Neurological Institute (MNI) space; a 0.01 Hz high pass filter, to remove low frequency scanner drifts; and ICA denoising. DWI preprocessing was performed with an in-house toolbox that corrects for artefacts induced by subject motion and cardiac pulsation (Zwiers, 2010). This toolbox uses a spatially informed tensor estimation technique that can robustly estimate the underlying tensor model from diffusion data that contains artefacts.

Analysis

Default Mode Network

Independent Component Analysis as implemented in FSL's MELODIC was applied to the time domain concatenated data of all subjects (Beckmann and Smith, 2004; Beckmann et al., 2005). This group analysis was set to obtain 30 components, with the DMN ending up as one component. The purpose of this analysis was to obtain a mask of the main regions of the DMN at the group level, for use in a detailed examination of the connectivity within this network.

ICA

The single subject resting state data were subsequently analysed using MELODIC. MELODIC was applied to the 4D Nifti files containing the preprocessed data, set to obtain 75 Independent Components (ICs) for each subject. The long measurement time, ICA denoising, and the large number of time points gives an increase in power, which makes this high number of components possible even at the single subject level. MELODIC was set to generate 75 ICs to keep the number of components manageable, though in principle more could have been generated by letting MELODIC determine by itself how many components to use (Beckmann et al., 2005). When this was tested, MELODIC found around 300 components per subject.

Parcellation

The single subject ICs related to functional anatomy were manually selected, and any components containing artefacts, white matter and regions outside of the brain were rejected. Regions within these components smaller than 100 voxels were removed to reduce clutter. The remaining components were masked with the DMN mask, and form the basis of the individual DMN parcellation. Each component was split into its constituent regions. Some of these regions overlapped with regions from other components. For the purposes of this work, the two regions that overlap will be called the parent regions. To

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