On connectivity within the Default Mode Network: an ICA and tractography approach

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Introduction:
This abstract describes a detailed examination of the connectivity within the Default Mode Network (DMN). It is based on high quality resting state fMRI and Diffusion Weighted Imaging (DWI) scans from 47 subjects. The connectivity sub-regions of the Posterior Cingulate (PC) to the other regions of the DMN were investigated in order to test the hypothesis that the connectivity of sub-regions within this network is localized in hubs or nodes, in accordance with the small-world properties found for larger scale networks.

Data and Methods:
rs-fMRI and DWI data were acquired at 3T during one session on a Siemens Magnetom Trio system using a 32 channel head coil The resting state scan used a five echo multi echo EPI with acquisition parameters: TR = 2000 ms, TE = 6.9, 16.2, 25, 35 and 44 ms, flip angle 80°, 39 slices, 3.5 mm isotropic resolution, 1030 volumes, scan time 35 minutes (giving sufficient power to perform analysis at the single subject level), GRAPPA factor 3, 6/8 partial Fourier. The DWI acquisition parameters were: TR = 13000 ms, TE = 101 ms, 70 slices, 2.0 mm isotropic resolution, 256 directions at b = 1500 and 24 directions at b = 0. These data were acquired from 47 healthy subjects. rs-fMRI preprocessing involved realignment, merging of the five echoes, and spatial normalization to MNI space using functions from SPM5 (Wellcome Department of Imaging Neuroscience, University College London, UK). Non-brain regions were removed using the Brain Extraction Tool from FSL (fMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl). The data were filtered in the temporal domain with a 6th order Butterworth band pass filter. The diffusion data were preprocessed using an in-house toolbox capable of correcting artifacts induced by subject movement and cardiac pulsation. [1]
An ICA was performed on a group level to define the DMN, similar to the work by Damoiseaux *et al.*[2] The data from the first 12 subjects was temporally concatenated, and an ICA was performed using FSL-MELODIC, set to obtain 25 Independent Components (ICs). The memory requirement for this analysis is relatively heavy because of the large number of time points. Only the first 12 subjects were used because of memory limitations on the computer system used. The DMN ended up as a single component, and its regions were used as ROIs for both the resting state and the diffusion data analysis. An second ICA was performed on a single subject level using FSL-MELODIC set to obtain 75 ICs. The ICs containing artifacts, white matter, and regions outside the brain were discarded. The remaining components were used to create a detailed parcellation of the DMN into smaller sub-regions, after the overlap between IC regions was resolved. Small regions of overlap (less than 100 voxels) were removed by sharing the overlapping voxels between neighboring regions. Larger overlaps were designated as separate regions. The resulting regions were used to parcellate the DMN.
This parcellated DMN was used for a partial correlation analysis as explained by Salvador et al.[3]. This analysis was used to explore the connectivity within the DMN in more detail. The DMN parcellation and the subsequent partial correlation analysis allow for the examination of detailed and localized connectivity between DMN regions. The connectivity between the DMN regions was examined in a pair-wise fashion. Resulting hotspots indicate the presence of hubs of connectivity within the DMN. This is accomplished by examining the Partial Correlation Coefficients (PCCs) between the sub-regions of a given pair of DMN regions for each subject. For every sub-region, the highest PCC to any sub-region of the other region is obtained. The results of this analysis should indicate the locations within the larger regions that are stronger connected to sub-regions of the other larger region. These PCCs can be averaged over the complete group of subjects, to locate the hubs of connectivity, which were then compared to the DWI fiber tracking results.
DWI data was analyzed using FSL and Camino to perform spatial normalization and Q-ball deterministic tractography. Tracts that intersect two DMN ROIs were generated for every subject. The resulting tracts were transformed to MNI space to allow for easy comparison to rs-fMRI results. This was partly based on work by Greicius *et al.*. [4]

Results:
The DMN parcellation was successfully performed for every subject. On average, this divided the Medial Frontal Cortex (MFC) into 48 and the Posterior Cingulate (PC) into 98 sub-regions. This large number of regions results from the use of the long resting state scan, and the increased power this brings. Figure 1 shows the results from the resting state analysis to the left, and the deterministic tractography results to the right. The resting state analysis found several regions with a higher average PCC, shown in the top half of the left image. The bottom half of the resting state image highlights the regions that are statistically significant, shown in red in the right image. The tracts show a high correspondence to the anterior hotspot in the PC, but not to the posterior hotspot. Figure 2 depicts the results from the right hippocampus, which are very similar to the results from the left hippocampus (not shown). For both the left and right hippocampus, the tractography results closely match the hotspots found with the resting state analysis.

Conclusion and Discussion
The resting state results show that there do seem to be node regions in the PC that are more important in facilitating the connections between the DMN regions. These results partially coincide with the tractography results of the PC-MFC connection, and greatly coincide with the results of the PC-hippocampus connection. This is in line with the general small-world structure of the brain. In a small-word network, clusters are more strongly interconnected with each other, but only connect through a few central points to other clusters.

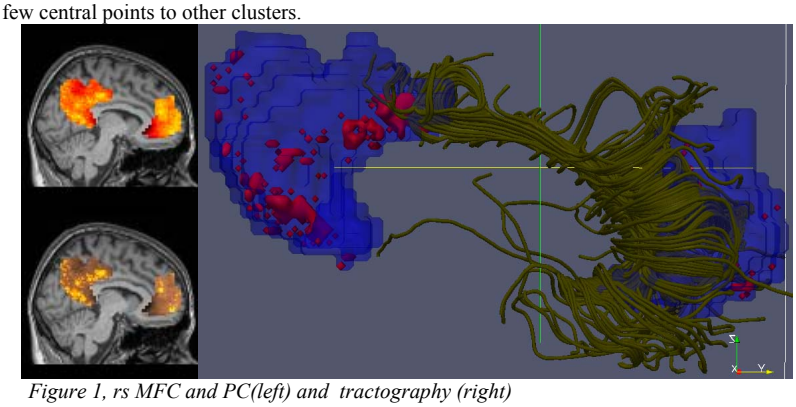

Figure 1, rs MFC and PC(left) and tractography (right)

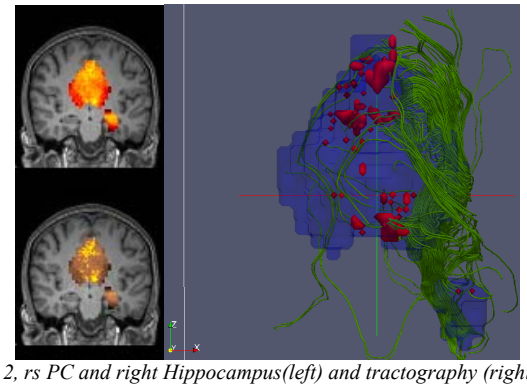

Figure 2, rs PC and right Hippocampus(left) and tractography (right)

References:
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[3] R. Salvador *et al.*, Neurophysiological Architecture of Functional Magnetic Resonance Images of Human Brain. *Cerebral Cortex* September 2005
[4] M. Greicius *et al.*, Resting-State Functional Connectivity Reflects Structural Connectivity in the Default Mode Network, *Cerebral Cortex* April 2008