Functional connectivity during the resting state in the default-mode network: A major role for the cerebellum?

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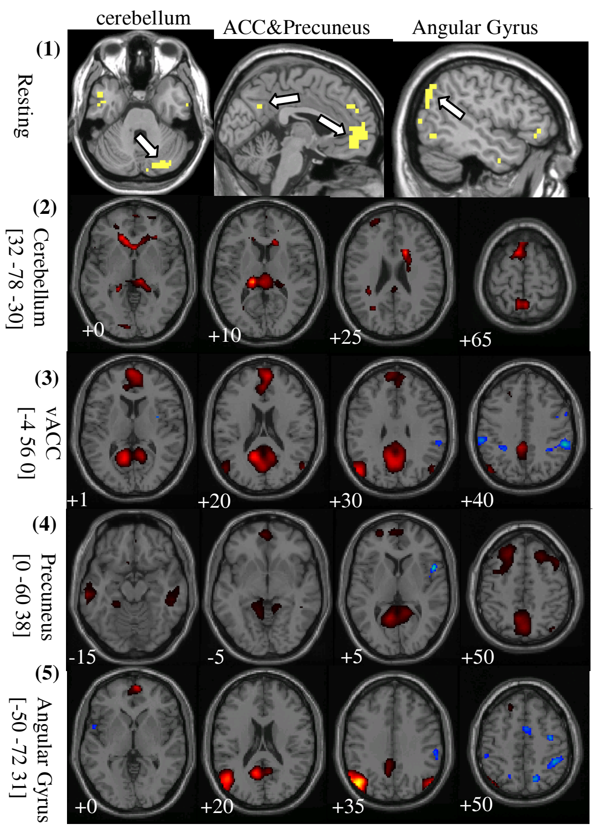
Introduction: Low frequency (< 0.1 Hz) oscillations in resting state BOLD signal have been studied for some years[1], and are now attracting interest in terms of their relationship to the so-called 'default-mode' of the brain[2,3,4]. The default-mode network is identified as those brain areas which become de-activated by a range of cognitive tasks and is believed to be associated with background environmental surveillance[2]. Previous studies have identified such a network, associated most notably with the posterior cingulate cortex (PCC) and ventral anterior cingulate cortex (vACC)[3,4]. Here we extend this prior work by firstly identifying nodes which share common low frequency oscillations across all subjects (precuneus, vACC, angular gurus [AG] and cerebellum), and then characterizing their resting state functional connectivity. The results are interpreted in terms of the default-mode network.



Methods: Whole brain images were acquired on a 1.5T Philips Gyroscan Intera [multi-slice EPI; FOV = 220mm, acquisition matrix = 64 x 64, TR/TE 2100/37, 3.5mm^3 voxels, slice thickness = 4.5mm with 0.5mm slice gap]. Subjects (n=18, aged 20-40, 7 females) were instructed to keep their eyes closed for 5 minutes during the scanning. fMRI data were processed using SPM2.

Low-frequency fluctuations in BOLD signal were modelled by a discrete cosine basis set consisting of 41 regressors spanning 0.008–0.05 Hz[4]. Spectrum analysis of BOLD signal reveals that the dominant frequency power range is within 0~0.05Hz. Very slow signal changes below 0.008 Hz are not of interest as they are related predominantly to scanner drift. SPM maps were created with a threshold of F=3.04 corresponding to a P value of 0.05, FWE-corrected. A binary mask was created from each individual F-contrast image by setting each voxel value to one if the corresponding F value exceeded 3.04. A final group analysis mask was calculated by multiplying the binary values of all of the individual masks. The result found all the voxels in the brain having significant low-frequency fluctuations across all subjects.

Seed ROIs (7mm^3) consistent with the default-mode hypothesis were selected from the binary resting state group map (i.e. from areas with significant low frequency components in all subjects). The time courses from individual ROIs in the resting-state data were then globally scaled, averaged, and band-pass filtered 0.008<f<0.15 Hz. The resulting time series were then used as linear regressors in a whole-brain SPM analysis to form individual functional connectivity correlation maps. Group functional connectivity maps were then obtained from a second-level random effects analysis across subjects.

Results: The top panel of Figure 1 shows the group binary mask of the low-frequency signals superimposed on anatomical images. The following areas are present in the mask: precuneus, vACC, AG, superior frontal gyrus, inferior frontal gyrus, middle temporal gyrus, inferior temporal gyrus and cerebellum). The cerebellum, ACC, precuneus, and AG were particularly selected for the default-mode connectivity analysis (white arrows). All coordinates used are MNI coordinates. Maps of the resting-state connectivity for the four selected seed areas are shown in the lower panels, with significant correlations shown in red and anti-correlations in blue. Maps are superimposed on T1-weighted images. The numbers below each image refer to the z plane MNI coordinates. The left hemisphere of the brain corresponds to the left side of the image. Height and extent thresholds were set at P<0.001, except for the cerebellum which is FWE 0.05 corrected. At equivalent thresholds, the cerebellum shows the strongest and most extensive connections. Table 1 shows the 4 most significant clusters in the correlation map for each seed region, labeled with Talairach atlas references in descending order of the cluster's t score.

Table 1. *Areas significantly correlated with specified seed ROIs*

Cerebellum	**-21 -39 0** Hippocampus	Ventral ACC	**-11 56 20** Medial Frontal Gyrus	Precuneus	**-63 -25 -15** Medial Temporal Gyrus	Left Angular Gyrus	**-7 -60 20** Precuneus
	18 14 25 Medial Frontal Gyrus		**-49 -74 30** Angular Gyrus		**-21 28 50** Superior Frontal Gyrus		**53 -70 35** Right Angular Gyrus
	-14 32 0 Anterior Cingulate Gyrus		**-7 21 10** Anterior Cingulate Gyrus		**-4 56 -5** Anterior Cingulate Gyrus		**7 60 0** Superior Frontal Gyrus
	4 -56 65 Precuneus		**18 32 60** Superior Frontal Gyrus		**53 -32 -15** Inferior Temporal Gyrus		**-18 32 50** Superior Frontal Gyrus

Conclusion: The resting state regions revealed in our experiment include a number of key nodes of the proposed default-mode network, originally revealed from analyzing the areas deactivated by cognitive tasks. Their presence across all subjects in our resting state analysis adds support to the concept of a default-mode network, and we have further demonstrated important functional connectivities among these regions and other regions likely to be important in surveillance. We have also identified the cerebellum and AG as possible major default-mode nodes. The AG, which is crucial for random episodic memory access, is understandably important for default-mode functioning. Because of the role of the cerebello-cerebral pathway, the uniqueness of cerebellar deficit syndrome and the importance of the cerebellum in central timing mechanisms and motor imagery, it is accepted that the cerebellum has significant functions in both cognitive and affective domains. The evolutionary advantage of an on-line cerebellum as part of the default-mode network is obvious if preparedness and inner rehearsals are one of its main putative functions. This work strongly integrates the cerebellum within the concept of a default-mode network.

Reference

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