
Analysis of connectivity in the resting state of the default mode of brain function: a major role for the cerebellum?

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Abstract: Low frequency (< 0.1 Hz) oscillations in resting state fMRI signal have been studied for some years and are now attracting interest in terms of their relationship to the so-called 'default mode' of the brain. The default mode network is identified as those brain areas which are active during rest and is believed to be associated with background environmental surveillance. In this study, we carry out a comprehensive analysis of the default mode network in the resting state across the whole brain, using a combination of model-based and data-driven approaches: a cosine basis set approach, the independent component analysis (ICA) and functional connectivity analysis. The correlated regions with low frequency fluctuations revealed by all three methods include a number of key nodes of the proposed default-mode network. Most importantly we have also identified the cerebellum and angular gyrus as possible major default mode nodes.

Keywords: functional magnetic resonance imaging; fMRI; connectivity; resting state; low frequency fluctuations; default mode network; independent component analysis; ICA; cerebellum.

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1 Introduction

Much of our understanding of brain function comes from studies using specific cognitive tasks. However, task-related increases in neuronal metabolism are usually small (<5%) when compared with the large resting energy consumption in the brain (Raichle and Mintun, 2006). Resting-state functional magnetic resonance imaging (fMRI), a promising technique for measuring brain activities during rest, has attracted much attention in the past few years (for a review see Fox and Raichle, 2007). Subjects are usually instructed simply to lie still in the scanner and refrain from falling asleep. Low frequency (<0.1 Hz) fluctuations (LFF) in resting state blood oxygen level dependent (BOLD) signal and the spatial patterns of coherent BOLD activity provide a mechanism for mapping functional connectivity of the human brain at rest (Biswal et al., 1995).

Biswal et al. (1995) first described functional connectivity in the motor cortex of the human brain at rest. The temporal signal from a region in the motor cortex was used as the input function to the correlation analysis, revealing a high degree of temporal correlation with the opposite hemisphere in the resting brain. This may reflect correlated fluctuations in blood oxygenation or blood flow between the hemispheres, mediated by neuronal connections through the corpus callosum and commissural pathways (Maldjian, 2001).

Most studies of resting state connectivity analysis have been performed with a predefined 'seed' region of interest (Fransson, 2005; Greicius et al., 2003). The correlations with other brain regions can be obtained directly from the linear regression statistical map. However, this method is dependent on the a priori definition of a seed region. Independent component analysis (ICA) is a well established and robust technique for analysing resting state BOLD data (Beckmann et al., 2005; De Luca et al., 2006; Esposito et

al., 2006, 2008; Garrity et al., 2007; van de Ven et al., 2004). This data-driven technique decomposes BOLD signal data into different components of functional brain networks such as motor, auditory, visual and language systems. Interestingly, researchers have found that some brain regions were more active at rest than during task performance. This finding suggests the existence of an organised baseline pattern of brain function during the resting state: the so-called 'default mode network' of the brain, which is active during rest but becomes consistently deactivated by a range of cognitive tasks and is believed to be associated with background environmental surveillance (Raichle et al., 2001). Previous studies have identified a default mode network which is associated with the posterior cingulate cortex (PCC), medial, prefrontal, parahippocampal and inferior parietal cortices and ventral anterior cingulate cortex (vACC) (Fransson, 2005, 2006; Raichle et al., 2001; Greicius et al., 2003; Greicius and Menon, 2004; McKiernan et al., 2003; Fox et al., 2005; Buckner and Vincent, 2007). The default mode network has been found to link with self-referential and reflective activity that specifically includes episodic memory retrieval, inner speech, mental images, emotions and planning of future events (Fransson, 2005; Greicius et al., 2003). The default mode signal sources have been found to be almost identical spatially in sleeping, anaesthetised and awake subjects (Kiviniemi et al., 2000, 2005b; Buckner and Vincent, 2007).

In this study, we carry out a comprehensive analysis of the default mode network in the resting state across the whole brain, using a combination of model-based and data-driven approaches: a cosine basis set approach, the ICA and functional connectivity MRI (fcMRI) analysis. The discrete cosine basis set is used to model the linear combination of LFF and detect all the voxels in the brain having significant LFF across all subjects. Secondly we use

data-driven method – ICA to obtain the default mode component for each subject. The resting state functional connectivity was then characterised.

The regions with low frequency fluctuations revealed by all three methods include a number of key nodes of the proposed default mode network and most importantly we identified the cerebellum and angular gyrus as possible major default mode nodes. The cerebellum has significant functions in both cognitive and affective domains and the angular gyrus is crucial for random episodic memory access needed for inner rehearsals and a sense of self. This work strongly integrates the cerebellum and angular gyrus within the concept of a default mode network.

2 Subjects and methods

2.1 Subjects

Eighteen healthy adults (seven female) between the ages of 20 and 40 years (mean age 27.8 years) took part in the study with full informed written consent in compliance with the Declaration of Helsinki (1964). The subjects had no neurological, psychological or oculomotor abnormalities and no abnormalities were found on their structural MRI scans.

2.2 Experimental design

All scanning took place in the Wellcome Trust Clinical Research Facility (WTCRF, Manchester UK) using a 1.5 T Philips *Inera* Scanner with a six channel phased array head coil. For the resting state scanning, subjects were instructed to keep their eyes closed for five minutes during the scan, not to think of anything particular and to stay awake.

The functional scans were acquired with gradient echo echo planar imaging with the following parameters: FOV = 220 mm, acquisition matrix = 64×64 , TR = 2.10 seconds, TE = 37 msec, voxel size = $3.5 \times 3.5 \times 5$ mm, slice thickness = 4.5 mm with 0.5 mm slice gap, 29 slices. fMRI data were obtained in radiological convention, exported from the scanner in Philips' proprietary PAR/REC format and converted into ANALYZE format using MRicro (C. Rorden, University of South Carolina: <http://www.mricro.com>). All the experimental fMRI data were then pre-processed in statistical parametric mapping software (SPM2) (Wellcome Department of Imaging Neuroscience: <http://www.fil.ion.ac.uk/spm/>) in the normal routine: spatial realignment of head motion, normalisation into the Montreal Neurological Institute (MNI) coordinates and finally smoothing using a 10 mm full width half maximum Gaussian filter.

2.3 Extracting the low frequency fluctuations

As discussed in the introduction, the occurrence of LFF in resting-state fMRI time series has come to the attention of researchers. These fluctuations arise mainly from metabolic demands in the resting brain and may represent changes of

local blood flow secondary to fluctuations in firing rates in distributed neural networks. These spontaneous signals can be characterised by oscillations in the frequency interval below 0.1 Hz, unrelated to cardiac and respiratory effects and synchronised in time across different brain regions (Biswal et al., 1995; Kiviniemi et al., 2004; Mayhew et al., 1995). There are a number of approaches to extract the regions with significant components in the low frequency bandwidth, two of which we have used here: cosine basis set and ICA.

2.3.1 Cosine basis set

LFF in fMRI time-series were modelled by a discrete cosine basis set consisting of 41 regressors spanning the frequency range of 0.008~0.05 Hz. The discrete cosine basis set provides an effective model of the linear combination of all signal changes within this frequency change. Details of the methodology can be found in Fransson (2005), with the original frequency range of 0.012~0.1 Hz. Power spectral density analysis of random fMRI time course from the resting state shows that the dominant frequency power range is below 0.05 Hz (figure not shown). Therefore in this study we focus on the frequency range of 0.008~0.05 Hz. Very slow signal changes below 0.008 Hz are not of interest as they are related predominantly to scanner drift. By switching the repetition time (TR) of fMRI images and separating signal sources with ICA, Kiviniemi et al. (2005a) found that the very low frequency BOLD signal fluctuations (<0.05 Hz) in the occipital cortex are a true physiological fluctuation, not a result of signal aliasing. This evidence gives support for the frequency band selection in our study.

The data were high-pass filtered (cutoff at 128s) and global drifts were removed using proportional scaling. Since the LFF are mainly < 0.1 Hz in resting state BOLD signal, we low pass filtered all resting state data with a cutoff frequency at 0.1 Hz. A general linear model (GLM) for fixed effect analysis was then used to generate effects of interest for each participant separately using the cosine basis set as the design matrix. As there are 41 different contrasts in the design matrix and we have to test multiple linear hypotheses with all multidimensional contrasts, F-contrasts were used to compute the cross correlation of each time course of a given voxel with all 41 basis functions. Eventually statistical parametrical maps were constructed to show all voxels synchronised linearly with the slow physiologic BOLD signal oscillations within the frequency range spanned by the basis set. Individually SPM maps were created with a threshold of $F = 3.04$ corresponding to a P value of 0.05, FWE (family-wise-error)-corrected for multiple subjects analysis.

For task-induced fMRI experiments, a one sample t-test is applied as a secondary random effects analysis in order to obtain mean activation for all subjects to each resultant contrast. However, there are no external stimuli in the resting state scan and all the effects of 41 regressors have to be compared. Therefore the t-test group analysis is not ideal for the resting state data. Instead a binary mask was used to perform the group analysis. The 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 LFF across all subjects. The group activations are shown on a T1-weighted anatomical template with the anatomical identification of areas being processed in the anatomy toolbox provided by SPM2 (Slice overlay program, author: Matthew Brett).

2.3.2 Group ICA

An alternative to the model-based cosine basis set approach is to use model-free ICA. ICA separates the fMRI data into a set of spatially distinct networks and their temporal time courses. ICA is powerful for revealing independent, temporally synchronous regions, from which functional connectivity can be inferred. In this study, the group ICA of fMRI toolbox (GIFT) (<http://icatb.sourceforge.net/>) was used to perform group ICA on the resting state data.

Spatial ICA was carried out for each of the 18 subjects using the GIFT software. The fMRI data were preprocessed in SPM as above. The initial dimensions (i.e., number of time points) were then reduced to 20 using principal component analysis with the minimum description length criteria modified to account for slowly varying signals (Rissanen, 1978). The data were then decomposed into 20 components by independent component estimation with the infomax algorithm (Garrity et al., 2007).

Although components are calculated according to variance, all the information is unrelated. The components were sorted with some assumptions as to their physical meaning in order to extract those components of most interest. The default mode component was identified by spatially correlating all the components with a spatial template generated by the LFF binary mask. All the activated voxels in a group component were converted into set of connected regions of interest (ROIs) and their MNI anatomical locations were compared to those in the existing LFF binary mask. The default mode component was selected as the component that most significantly correlated spatially with the template. The selected default mode component from each subject was then loaded into SPM2 to perform a second level group analysis. The group component spatial map is superimposed on a T1-weighted anatomical image for visualisation.

2.4 Connectivity map

The objective of fMRI is to detect interregional temporal correlations of BOLD signal fluctuations. It is usually done on a region of interest (ROI) basis, in which a hypothesised seed ROI is chosen. A single cubic ROI (10.5 mm linear dimension: 27 voxels) positioned in the seed area is used to extract the mean BOLD signal intensity. The correlations with other regions can be obtained directly from the linear regression statistical map.

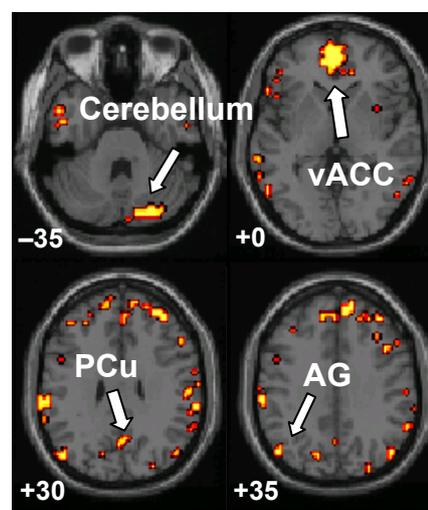
Seed ROIs consistent with the default mode hypothesis were selected from the binary resting state group map (i.e., from areas with significant low frequency components in all subjects). The time courses of all voxels from individual ROIs in the resting-state data were preprocessed by three steps. Firstly, voxel time series were globally scaled to minimise the effect of global drift by dividing each time point's value by the mean value of the whole brain image at that time point. Secondly, the scaled waveforms were band-pass filtered ($0.008 < f < 0.15$ Hz) to reduce the effect of low frequency drift and high frequency noise. Finally the scaled and filtered time courses were averaged to produce the principle ROI intensity waveform. The resulting waveform was then used as a linear regressor 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 all subjects.

3 Results

3.1 Low frequency fluctuations: default mode nodes?

In individual subjects, spontaneous fluctuations in the resting-state BOLD signal were detected throughout the brain, predominately in vACC, PCC/precuneus area and dorsolateral prefrontal cortex (PFC). We used a relatively high threshold of $F = 3.04$ corresponding to a P value of 0.05, FWE-corrected for the binary mask analysis. Only voxels of high F value for all subjects survive in the final group mask. Figure 1 shows the multi-subject (group binary mask) of the significant low-frequency signal oscillation areas superimposed on anatomical images. The numbers below each image refer to the z plane MNI coordinates in mm from the AC/PC line. The left hemisphere of the brain corresponds to the left side of the image.

Figure 1 The multi-subject (group binary mask) of the significant low-frequency signal oscillation in the resting state from the cosine basis set (see online version for colours)



Notes: AG = angular gyrus, ACC = anterior cingulate cortex, PCu = precuneus

The following areas are mainly present in the mask (Figure 1): precuneus, vACC, angular gyrus, superior frontal gyrus, inferior frontal gyrus, middle temporal gyrus, inferior temporal gyrus and cerebellum. These detected regions include a number of key nodes of the proposed default mode network. Their presence across all subjects in our resting state analysis adds support to the concept of a default mode network.

3.2 Default mode component

The so-called ‘default mode’ component of all subjects was one of the independent components that most spatially correlated with the a priori mask of Figure 1. Maps of the default mode component are shown in Figure 2. The most significant clusters of this component are shown in Table 1: medial frontal gyrus, superior frontal gyrus, posterior cingulate extending dorsally into the precuneus, temporal medial gyrus and cerebellum.

Figure 2 Default mode component from group ICA analysis. (see online version for colours)

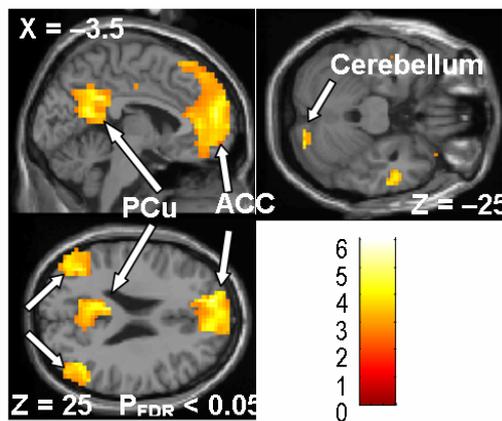


Table 1 Default mode component from group ICA analysis

Area	BA	L/R	k_E	Z	MNI peak
Superior medial frontal	9	L	297	4.36	-14 42 20
		R	154	4.17	11 53 5
Precuneus	7	L	90	3.67	-7 -67 35
		R	47	3.28	4 -56 20
Superior frontal	9	L	56	4.34	-14 49 20
		R	18	3.17	18 56 35
Middle frontal	8	L	54	3.09	-21 21 40
		R	32	3.40	49 -60 25
Angular	39	L	76	3.67	-42 -63 25
		R	32	3.40	49 -60 25
		L	39	3.70	-42 -63 25
		R	21	3.26	56 -4 -25
Cerebellum	19	L	30	2.97	-25 -84 -40
		R	85	3.28	25 -84 -25

Notes: BA – Brodmann area, L – left, R – right, k_E – cluster size

As the ICA analysis finds the most significant pattern according to the covariance, the areas shown in the default mode component could be thought as the most ‘active’ brain regions in the resting state. Moreover, these spatially correlated brain regions are all associated with one time course. The finding of the significant regions in the default mode component during rest is in good agreement with the areas of LFF by cosine basis set (Table 1).

3.3 Connectivity maps

To further investigate the connectivity patterns of the default mode network, we applied functional connectivity analysis. As discussed above, certain brain regions, including precuneus and vACC, consistently show greater activity during resting states than during cognitive tasks. The cerebellum (centre voxel MNI coordinates [32 -78 -30]) and angular gyrus ([-50 -72 31]) were selected for the connectivity analysis along with precuneus ([0 -60 38]) and vACC ([-4 56 0]), as we hypothesise that these play an important role in the default mode network. The four selected regions for the connectivity analysis are labelled in Figure 1 and Figure 2.

Figure 3 Resting state connectivity map from seed region cerebellum [32 -78 -30] (see online version for colours)

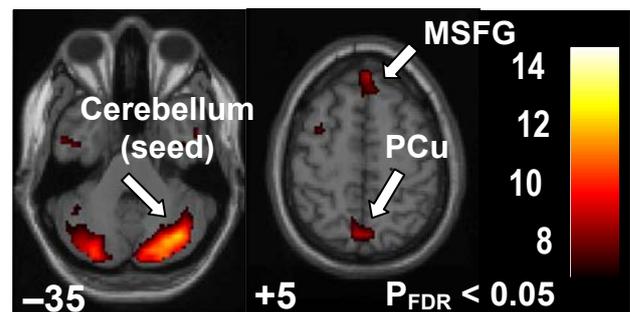


Figure 4 Resting state connectivity map from seed region [-4 56 0] vACC (see online version for colours)

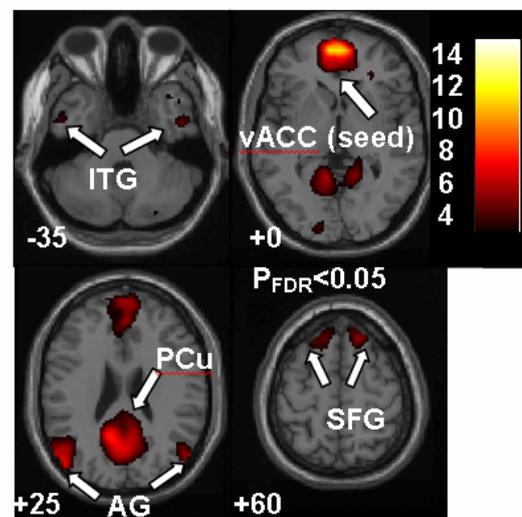


Figure 5 Resting state connectivity map from seed region precuneus [0 -60 38] (see online version for colours)

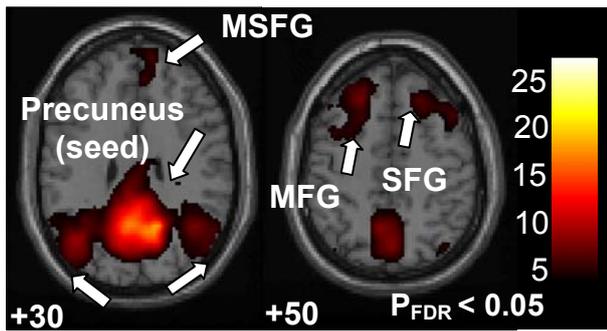


Figure 6 Resting state connectivity map from seed region angular gyrus [-50 -72 31] (see online version for colours)

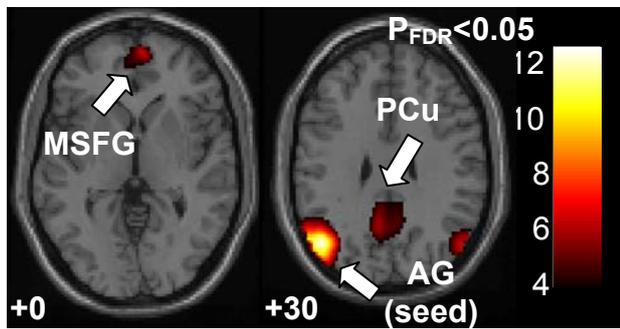


Table 2 Brain regions that significantly correlated with the seed region cerebellum [32 -78 -30] during resting state

Area	BA	L/R	k_E	Z	MNI peak
Cerebellum	19	R	358	6.58	35 -74 -30
		L	205	6.00	-32 -81 -25
Thalamus		L	36	5.96	-14 -28 10
		R	26	5.44	11 -28 5
Calcarine		L	16	5.28	0 -95 -10
Hippocampus	35	L	10	5.57	-21 -39 0
Precuneus	7	R	34	5.34	4 -56 65
		L	73	5.74	-4 -46 75
Superior medial frontal	8	L	26	5.30	0 42 50
		R	27	5.35	7 35 60
Inferior temporal	20	L	22	5.24	-53 -4 -35
Middle temporal	20	L	21	5.39	-53 -32 -15

Table 3 Brain regions that significantly correlated with the seed region vACC [-4 56 0] during resting state

Area	BA	L/R	k_E	Z	MNI peak
Superior medial frontal	10	R	139	5.99	4 56 0
		L	164	6.01	-4 56 0
Anterior cingulum	24	L	114	5.53	0 53 0
		R	72	4.44	7 49 15

Table 3 Brain regions that significantly correlated with the seed region vACC [-4 56 0] during resting state (continued)

Area	BA	L/R	k_E	Z	MNI peak
Precuneus	7	L	132	5.12	-11 -56 20
		R	132	4.71	4 -63 30
Calcarine	29	L	90	5.05	-11 -60 10
		R	61	4.39	14 -56 10
Angular	39	L	73	4.99	-49 -74 30
		R	30	3.88	53 -74 30
Middle temporal	39	L	20	3.77	-49 -70 20
		R	19	3.94	56 -70 20
Superior frontal	8	R	30	3.99	18 32 60
		L	63	3.97	-18 32 50
Inferior temporal	20	R	26	3.76	53 -7 -35

Table 4 Brain regions that significantly correlated with the seed region precuneus [0 -60 38] during resting state

Area	BA	L/R	k_E	Z	MNI peak
Precuneus	7	L	294	6.95	-7 -56 40
		R	257	6.90	11 -60 35
Middle temporal	39	L	55	5.09	-63 -25 -15
		R	92	4.28	53 -60 15
Angular	39	L	116	5.18	-39 -67 30
		R	156	4.87	42 -56 30
Superior frontal	8	R	56	4.44	21 28 55
		L	88	4.61	-18 32 50
Cerebellum		L	17	4.60	-7 -49 0
		R	26	3.62	32 -77 -40
Superior medial frontal	10	L	62	4.02	0 60 0
Middle frontal	8	R	71	4.14	11 60 25
		L	92	4.72	-21 28 50
		R	65	4.30	35 25 55

Table 5 Brain regions that significantly correlated with the seed region angular gyrus [-50 -72 31] during resting state

Area	BA	L/R	k_E	Z	MNI peak
Angular	39	L	130	6.17	-46 -70 30
		R	61	4.57	53 -70 35
Middle temporal	39	L	47	5.03	-49 -67 20
		L	96	4.87	-7 -60 20
precuneus	7	R	59	3.99	7 -56 25
		L	26	4.33	-7 -63 20
Calcarine	29	L	26	4.33	-7 -63 20
Middle occipital	39	L	54	5.71	-46 -74 35
Superior medial frontal	10	L	24	3.63	0 60 0
		R	52	4.53	7 60 0

Maps of the resting state connectivity for the four selected seed regions are shown in Figures 3–6, with areas that significantly correlate with the seed region shown in red. Maps are superimposed on T1-weighted images. Extent thresholds were set at $P_{FDR} < 0.05$, except for the cerebellum seed map in Figure 3 which is set at the more conservative threshold of $P_{FWE} < 0.05$. At equivalent threshold of $P_{FDR} < 0.05$, the cerebellum shows the strongest and most extensive connections. Tables 2–5 show the most significant clusters that correlated with the seed region cerebellum, vACC, precuneus and angular gyrus respectively during resting state, labeled with Talairach atlas references in descending order of the cluster's z score.

The cerebellum (Figure 3, Table 2) showed significant resting-state connectivity with the following regions: hippocampus, thalamus, medial frontal gyrus, anterior cingulate gyrus, precuneus, superior frontal gyrus, medial temporal gyrus. The vACC (Figure 4, Table 3) showed significant resting-state connectivity with medial frontal gyrus, angular gyrus, anterior cingulate gyrus, superior frontal gyrus, inferior temporal gyrus, medial temporal gyrus. The precuneus (Figure 5, Table 4) showed significant resting-state connectivity with medial temporal gyrus, superior frontal gyrus, anterior cingulate gyrus, inferior temporal gyrus, medial frontal gyrus. The angular gyrus (Figure 6, Table 5) showed significant resting-state connectivity with precuneus, right angular gyrus, superior frontal gyrus, medial frontal gyrus.

Taken together, our results demonstrate that these brain regions with LFF show significant functional connectivity during the resting state, thus providing the most compelling evidence for the existence of a default mode network.

4 Discussions

The temporal and spatial characteristics of LFF in resting state fMRI signal were investigated in the present study. An explicit modelling of the possible contents of spontaneous LFF in resting-state revealed a number of key nodes of the proposed default mode network.

4.1 Spontaneous low-frequency fluctuations

The spontaneous LFF in BOLD fMRI time-series were modelled by a discrete cosine basis set consisting of regressors equally spaced in frequency. Importantly, we focused on the very low frequency range below 0.05 Hz as power spectral analysis results showed strong presence components in this frequency range. The group mask map shows all the areas with strong occurrence of LFF, of particular interest are the vACC, precuneus/PCC, angular gyrus and cerebellum in all subjects. Several other PET and fMRI studies have shown that the precuneus/PCC and the vACC consistently decrease their activity in a variety of cognitive tasks, all have in common the fact that they direct the subjects' attention toward externally generated events and suppress attention toward internally generated processes (McKiernan et al., 2003; Binder et al.,

1999; Raichle et al., 2001). The results of this study show that the regions that decrease their activity during goal-directed attention-demanding tasks also have spontaneous fluctuation in the resting state.

The correlated regions with LFF revealed in our experiment include a number of key nodes of the proposed default mode network, mainly including frontal regions along the midline, lateral and medial parietal regions extending in to posterior cingulate and retrosplenial cortex, and the medial temporal lobes. The consistent presence across all subjects in our resting state analysis adds support to the concept of the default mode, that these regions are involved crucially in self-referential mental processing during resting state baseline conditions.

4.2 Default mode network: a major role for the cerebellum?

The vACC, precuneus/PCC, angular gyrus and cerebellum were used as the seed points for connectivity analysis. We have demonstrated important functional connectivity among these regions and other regions likely to be important in surveillance. The finding of the connectivity network during rest is in good agreement with recent functional connectivity studies of the resting brain (Fransson, 2005; 2006, Greicius et al., 2003).

We have also identified the cerebellum and angular gyrus as possible major default mode nodes. Although the cerebellum has not been previously identified as part of the default mode network, there are strong theoretical reasons for considering that it should be. The cerebellum can be thought of as an oscillation dampener that maintains function at a homeostatic level and that failure of this gives rise to dysfunction in the form of 'overshooting' or 'undershooting' involving multiple domains from pure movement through to affect and cognition. An example of the deficit state is perhaps the cerebellar cognitive affective syndrome (Schmahmann, 2000).

The extensive connectivity of the cerebellum with motor and association cortex lends itself to have such an expanded role. The cerebral cortex and cerebellum are connected to each other through a feed forward limb comprising cerebropontine fibres and pontoerebellar fibres while the feed back limb comprises of the cerebellothalamic and thalamocortical fibres. Numerous papers have documented that the pons receives projections from association areas in the dorsolateral and dorsomedial prefrontal cortex (Schmahmann and Pandya, 1995, 1997), posterior parietal region (Brodal, 1978; Glickstein et al., 1985; May and Andersen, 1986; Schmahmann and Pandya, 1989), superior temporal polymodal (Schmahmann and Pandya, 1991), posterior parahippocampal (Schmahmann and Pandya, 1993) and dorsal prefrontal regions (Fries, 1990; Schmahmann and Pandya, 1993), as well as from the cingulate gyrus (Vilensky and van Hoesen, 1981). There is an attractive conceptual notion that through the pontocerebellar projection, the associative cortices are linked with the lateral cerebellar hemispheres (Leiner et al.,

1986, 1993). This fits well with the postulated functional topography of the cerebellum that implicates the lateral part of the neocerebellum (lateral hemispheres and dentate nucleus) in executive, visual-spatial, linguistic, learning and memory functions and the medial part of neo-cerebellum (vermis and fastigial nucleus) in autonomic regulation, affect and emotional memory (Schmahmann, 2004).

Perception of time and timing are useful to predict and anticipate events, as well as to organise and plan sequences of actions. Cerebellar activity has been linked to event expectancy (Mauk et al., 2000). The cerebellum might have a role in slow timing rather than fast timing. A cerebellar pathway might also be involved in the visual perception of motion. The inferior lateral part of the cerebellum was activated during mental counting as well as during imagery of certain movement sequences (Decety et al., 1990). Indeed, greater cerebellar activation has been reported in healthy adults when sensory cues guide movements than when the same movements are self-generated (Jueptner et al., 1996).

Therefore the cerebellum has significant functions in both cognitive and affective domains (with unique cerebellar deficit syndrome), in central timing mechanisms and perception of motion (visual and imagery). The angular gyrus is crucial for random episodic memory access needed for inner rehearsals and a sense of self. The evolutionary advantage of an on-line cerebellum and angular gyrus as part of the default-mode network is obvious if we accept that preparedness, surveillance, inner rehearsals and awareness of self are the main putative functions of default mode network. This work strongly integrates the cerebellum and angular gyrus within the concept of a default mode network.

4.3 Group ICA

The other important work in this study was to apply group ICA to the resting state images. ICA is a method of blind source signal separation, and allows one to extract or 'unmix' unknown source signals which are linearly mixed together. For fMRI data, temporal and spatial ICA are possible, but spatial ICA is by far the most common approach and has been successfully applied to fMRI single subject or single session analyses. ICA was proved to be a powerful tool for the extraction of functional connectivity patterns of synchronised neural activity from fMRI time series (Esposito et al., 2006; McKeown et al., 1998). A model was proposed to extend ICA to group fMRI studies in (Calhoun et al., 2001). More recently group ICA has gained increased attention as its effective evaluation of the default-mode network. (Esposito et al., 2006) used group level ICA to explore the variability of the default mode network related to the engagement of task. (Garrity et al., 2007) applied group ICA to explore the default mode functional connectivity in schizophrenia.

In this study the group ICA method was used to extract brain regions with significant LFF. An advantage of our use of cosine basis set and group ICA is that they allow for examination of LFF regions without specifying regions of

interest beforehand. In this study, group ICA analysis is consistent with the cosine basis set and functional connectivity analysis for the identification of the default-mode network and gives great support to our connectivity analysis. Also we have good agreement with the key regions of the default-mode component from (Garrity et al., 2007), only they have larger areas extending from the key regions, e.g., the angular gyrus extending anteriorly into the supramarginal gyrus. A possible explanation for this might stem from the experimental designs: an auditory oddball task was used in (Garrity et al., 2007) rather than the resting scanning in our study.

4.4 Future work

The connectivity maps in Figures 3–6 showed only the positive correlations with the seed regions. An interesting finding in the anti-correlation connectivity maps is the insula area (Brodmann Area 13), which is significantly anti-correlated with all the default mode nodes (not shown in the figures). Functionally speaking, the insula is believed to process convergent information to produce an emotionally relevant context for sensory experience. More specifically, the anterior insula is related more to olfactory, gustatory, visero-autonomic, and limbic function, while the posterior insula is related more to auditory-somesthetic-skeletomotor function (Ackermann and Riecker, 2004; Bamiou et al., 2003). Functional imaging experiments have revealed that the insula has an important role in pain experience and the experience of a number of basic emotions, including anger, fear, disgust, happiness and sadness (Mauguiere, 2004; Brooks and Tracey, 2007). The anti-correlated insula area could be an additional finding to the default mode theory. More work is needed in the future for the anti-correlation areas within the framework of default mode.

The advantage of using the cosine basis set analysis is its ease of use and implementation, and it also proved to be effective in detecting regions with strong LFF. However, the natural property of the fMRI BOLD time courses is that they are not reproducible in time. The cosine basis sets will identify regions with nearly periodic time series in the frequency range, which is a limitation for this modelling method. Moreover, the group analysis is given by a binary mask method instead of the second level t-test. It shows the common areas with LFF but cannot tell which areas are more significant statistically.

The 'resting state' is neither a static phenomenon nor reproducible in time. Rather, it may differ considerably between subjects and even within one subject (Goncalves et al., 2006). There is no control condition to compare to or any hypothesis driven models to use as regressor therefore data-driven methods need to be used in the resting state studies. Kiviniemi et al. (2004) compared methods for analyzing the nondeterministic flow fluctuations as Fast Fourier Transformation (FFT), cross correlation (CC), spatial principal component analysis (sPCA), and spatial independent component analysis (sICA). sICA was spatially most accurate but time consuming. The CC detected the

highest temporal synchrony but the subjective detection for reference vector produced excess variance of the detected volumes. The FFT and sPCA were not spatially accurate and did not detect adequate temporal synchrony of the voxels. Recently, partial least square was used to identify the functional connectivity of the medial temporal lobe relates to learning and awareness in PET study (McIntosh et al., 2003). Moreover wavelet method has also been introduced to fMRI studies (Bullmore et al., 2004). The discrete wavelet transform acquired from healthy volunteers in the resting state was used to estimate frequency dependent correlation matrices characterising functional connectivity between 90 cortical and subcortical regions in (Achard et al., 2006). After thresholding the wavelet correlation matrices to create undirected graphs of brain functional networks, a small world topology of sparse connections was found in the low-frequency interval 0.03–0.06 Hz. Inspired from all the research work above, there is scope for exploring these issues further in terms of signal processing and modelling resting state fluctuations.

Some functional connectivity studies related to pathology have been performed recently, including alzheimers disease (Greicius and Menon, 2004; Lustig et al., 2003); multiple sclerosis (Lowe et al., 2002); attention deficit/hyperactivity disorder (ADHD) (Zhu et al., 2005); schizophrenia (Garrity et al., 2007; Liang et al., 2006); autism (Cherkassky et al., 2006) and depression (Greicius et al., 2007). All of these studies confirmed the importance of functional deactivations or correlation differences among brain regions under different pathological conditions. However, whether functional connectivity is moderated by different antipsychotic drugs and in what manner is unknown. This would be a fruitful area for study.

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