The electrophysiological basis of negative BOLD in default mode network

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Introduction: The default mode network (DMN) [1], which includes medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), precuneus and the left and right inferior parietal lobules (IPLs), has been widely investigated using fMRI. The network is characterised by high intrinsic correlation between BOLD signals measured at separate network nodes in the resting state, implying functional connectivity within the network even in the absence of a task. BOLD deactivations have also been frequently observed across the network in tasks requiring a response to external stimuli, suggesting that the network is most active during the 'resting state' and activity is attenuated when the task requires attention to external stimuli. This has lead to a hypothesis that the DMN is responsible for introspection (i.e. 'daydreaming'). However, despite the large BOLD literature relating to DMN, relatively few studies have probed the electrodynamic effects that underlie the observed negative BOLD changes. Using intracranial EEG recordings a decrease in γ band activity has been observed in regions of the DMN during an externally driven task [2,3]. These results agree with the prediction that, as increased γ is associated with an increased BOLD response [e.g. 4,5], a decreased BOLD response may be linked with reduced γ activity. Intracerebral recordings provide the most direct measure of neuronal activity and yield high signal to noise, however their invasive nature typically restricts recruitment to subjects with potentially confounding neurological pathology. In this study, we employ both fMRI and magnetoencephalography (MEG) as a multi-modal non-invasive means to study task induced deactivation in the DMN. A 2-back working memory task is employed to induce changes in DMN nodes. The high spatial resolution afforded by ultra-high field (7T) fMRI is used to define the locations of DMN nodes and to show that BOLD responses in those areas decrease during the task relative to rest. Source space projected MEG data from the same subjects are then generated at each MR-defined network node to investigate the electrophysiological basis of negative BOLD effects. Our results show decreased neural oscillatory activity in the high β and γ frequency bands in the DMN during the working memory task. Our results are in agreement with previous work [6,7].

Methods: Seven healthy subjects took part in the MEG experiment; six of those also took part in the fMRI experiment. Within both the MR and MEG scanners two experiments were performed. Initially there was a 5 minute eyes open resting state scan during which subjects were asked to remain still and relaxed. Participants then completed a 2-back working memory experiment; a single trial comprised 30s rest followed by 30s of a 2-back task. In the 2-back task letters were presented sequentially to the subject (1 every 2 seconds) via projection onto a back projection screen. If the letter displayed matched the letter presented 2 letters (i.e. 4s) previously, the participant was asked to press a button using their right index finger. A total of 12 trials were recorded in both modalities. BOLD fMRI data were acquired using a 7 T Philips Achieva MR system. 24 contiguous echo planar images (TR/TE 1500/25ms, 1.5x1.5x3mm^3 resolution, 198x192 x72mm^3 FOV, SENSE factor 3) were acquired giving whole brain coverage. Homogeneous B_0 was achieved using a parcellated shimming procedure. MEG data were acquired using the 3rd order gradiometer configuration of a 275 channel MEG system, at a sampling rate of 600Hz. Co-registration of MEG sensor space data to anatomical MRI was achieved using head digitisation (Polhemus Isotrack).

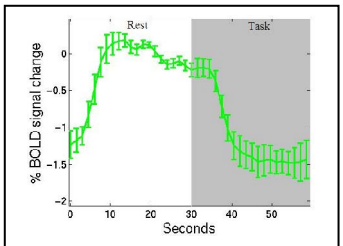

Figure 1 Mean % BOLD signal change averaged across subjects and trials for voxels in the DMN

Data Analysis: Pre-processing of fMRI data was carried out in SPM5. Data were motion corrected, corrected for non-neuronal physiological artifacts using RETROICOR and smoothed spatially using a 4mm Gaussian kernel. Each subject's anatomical image was coregistered to the MNI brain (FSL) and a seed voxel in PCC selected. Seed based correlation analysis was applied to the resting state data resulting in a correlation map showing resting state connectivity between the seed and all other voxels in the brain. For each subject this map revealed the spatial signature of the DMN.

The 2-back data were processed using a GLM (SPM5) which compared activity in the rest to that during the task. Areas of significant BOLD contrast were observed in all subjects in all DMN nodes. To ensure that only voxels within the DMN were considered in later analyses, this thresholded image was masked using the DMN defined by the resting state connectivity map, on a subject by subject basis. An average DMN (defined across subjects) was generated in MNI space. The % change in BOLD signal within these nodes was calculated defining baseline as a 15-30s window during the rest period.

The 2-back and resting state MEG data were frequency filtered into frequency bands of interest using overlapping frequency filters (1-4, 2-6, 4-8, 6-10, 8-13, 10-15, 13-20, 15-25, 20-30, 25-40, 30-50, 35-60, 40-65, 50-70 and 20-60Hz). Locations of interest were defined based on the fMRI analysis as MPFC MNI(-12,56,36)mm; PCC MNI(-6,-58,12)mm; LIPL MNI(-49,-73,30)mm; RIPL MNI(52,-64,28)mm. MEG data were projected from sensor space onto each of these locations of interest using a beamformer spatial filtering technique. This yielded a timecourse of electrical activity for each node of the DMN. Each timecourse was Hilbert transformed to compute the analytic signal; the absolute value of the analytic signal was then derived giving the envelope of oscillatory power fluctuations within each frequency. This was then averaged across trials to generate a spectrum. The average Hilbert envelope amplitude over the duration of the rest period was then subtracted from the whole spectrum resulting in a mean difference spectrum for each DMN node showing task minus rest.

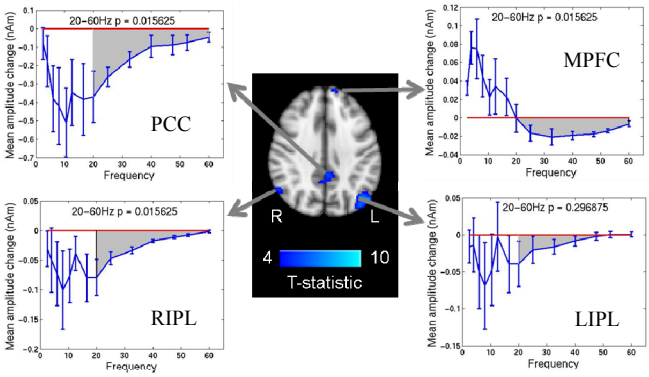

Figure 2 shows the mean DMN defined from the MR experiments overlaid onto a standard MNI brain. The subplots show the average MEG difference frequency spectra (error bars show SE across subjects) for each DMN node. The 20-60Hz frequency band is shaded.

Results: Figure 1 shows the mean timecourse of % BOLD change averaged across all subjects and voxels within the DMN. As shown, a clear decrease in BOLD amplitude is observed confirming previous results showing BOLD deactivation on task initiation. Figure 2 shows the spatial signature of the DMN averaged across subjects in MNI space (Centre). The four subplots show the mean MEG difference spectra for each DMN node. The map shows the distinctive nodes of the DMN including MPFC, PCC, and right and left IPL. Within PCC and left and right IPLs, decreased activity is noted in MEG across all frequency bands in the 2-back task compared with rest. In MPFC a decrease in activity is noted at high β and γ band but this is accompanied by an increase in the θ band.

Discussion and Conclusions: We have shown that a two-back working memory paradigm induces negative BOLD changes in the default mode network with a marked decrease in BOLD amplitude noted across all nodes. Most interestingly these negative BOLD changes are accompanied by decreases in neural oscillatory effects measured by MEG and this confirms a neural basis to DMN BOLD deactivation on task initiation. At three of the four DMN nodes we observed a general reduction in oscillatory power across all frequency bands, however in the MPFC we note an increase in oscillatory amplitude in the θ band with a concomitant decrease in the high β and γ bands. Increases in frontal θ oscillations have been well characterised in cognitive tasks [6], but it remains to be seen how the observed changes at different frequencies affect BOLD. Previous work [8] has shown that positive BOLD responses are more closely related to γ activity than to activity in lower frequency bands. Here we have shown a significant ($p<0.05$) high β/γ decrease in all but one of the DMN nodes and we hypothesise that, in agreement with other previous work [2,3], it is this γ decrease that is responsible for the negative BOLD effects observed across the DMN.

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