Default Network Connectivity During a Working Memory Task

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Abstract: The default network exhibits correlated activity at rest and has shown decreased activation during performance of cognitive tasks. There has been little investigation of changes in connectivity of this network during task performance. In this study, we examined task-related modulation of connectivity between two seed regions from the default network posterior cingulated cortex (PCC) and medial prefrontal cortex (mPFC) and the rest of the brain in 12 healthy adults. The purpose was to determine (1) whether connectivity within the default network differs between a resting state and performance of a cognitive (working memory) task and (2) whether connectivity differs between these nodes of the default network and other brain regions, particularly those implicated in cognitive tasks. There was little change in connectivity with the other main areas of the default network for either seed region, but moderate task-related changes in connectivity occurred between seed regions and regions outside the default network. For example, connectivity of the mPFC with the right insula and the right superior frontal gyrus decreased during task performance. Increased connectivity during the working memory task occurred between the PCC and bilateral inferior frontal gyri, and between the mPFC and the left inferior frontal gyrus, cuneus, superior parietal lobule, middle temporal gyrus and cerebellum. Overall, the areas showing greater correlation with the default network seed regions during task than at rest have been previously implicated in working memory tasks. These changes may reflect a decrease in the negative correlations occurring between the default and task-positive networks at rest. *Hum Brain Mapp 32:1029–1035, 2011.*

Key words: working memory; fMRI; default mode network; posterior cingulate; medial prefrontal cortex; insula; cognition

INTRODUCTION

It has been hypothesized that the brain maintains a "default mode" in the absence of cognitive demands [Gusnard et al., 2001a,b; Raichle et al., 2001], perhaps representing a state of readiness to respond to environmental contingencies [Raichle and Gusnard, 2005]. Early investigation of the default mode implicated specific brain structures, including the posterior cingulate/precuneus (PCC), medial prefrontal cortex (mPFC), and angular gyrus, as

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being of particular interest because (1) they had been consistently shown to decrease activity associated with a change from "resting" baseline to engagement in cognitive tasks [Mazoyer et al., 2001; Shulman et al., 1997], and (2) they were also known to increase activity during introspectively oriented tasks [Johnson et al., 2002].

More recently, it has been demonstrated that the brain regions primarily associated with the default mode exhibit correlated, low-frequency (~0.1 Hz) oscillations during rest [Fox et al., 2005; Fransson, 2005]. In addition to the PCC, mPFC and bilateral angular gyrus, some studies have also implicated middle temporal gyrus [Damoiseaux et al., 2007], medial temporal cortex [Greicius et al., 2004], and anterior cingulate [Garrity et al., 2007; Greicius et al., 2007] as part of the default network. Further, activity in the network during rest is argued to be negatively correlated ("anticorrelated") with activity in unimodal sensory cortices [Tian et al., 2007] and in "task positive" brain areas associated with the performance of cognitive tasks, including bilateral inferior parietal cortex, frontal eye fields, medial temporal lobes, dorsolateral prefrontal cortex, and insula [Fox et al., 2005; Fransson, 2005]. These task positive regions may comprise two distinct networks, each of which correlates negatively with the default network at rest, but which do not correlate strongly with each other [Dosenbach et al., 2007; Seeley et al., 2007]. The implication of these findings has been challenged by recent work that suggests that negative correlations may be influenced by preprocessing strategies, particularly the use of global scaling [Murphy et al., 2009]; however, there is also evidence that these observed negative correlations actually do represent a biological phenomenon [Fox et al., 2009].

Other investigators have suggested that the default network might actually comprise distinct subnetworks, as activity in the PCC and mPFC at rest appears to correlate with other areas of the default network (including each other) at rest, but also to show different patterns of negative correlation with task-positive areas [Uddin et al., 2008]. These authors also used Granger causality analyses to show that nodes of the default network modulate activity in task-positive networks, rather than being modulated by areas associated with the task-positive networks. This finding provides experimental support for Raichle and Gusnard's [2005] conjecture that one function of the default mode may be to maintain a state of readiness to respond to relevant environmental stimuli.

In summary, at rest, the nodes of the default network show correlated low-frequency oscillations and appear to drive activity in other brain areas that become active during the performance of cognitive tasks. During such tasks, activation in areas of the default network decreases. To date, however, there has been relatively little work investigating whether patterns of correlation among the nodes of the default network also change during task performance, as compared with rest. The default network has been shown to maintain low-frequency connectivity during passive visual fixation [Fox et al., 2005; Fransson, 2005], during a low-demand "oddball" task [Calhoun et al., 2008; Garrity et al., 2007], as well as during light sedation [Greicius et al., 2008]. Yet few previous studies have examined the connectivity of the default network during a more demanding cognitive task. Fransson [2006] used a PCC seed region to compare areas showing correlation during rest and during a working memory task and found that both the spatial extent of the brain areas of the default network and the strength of the correlations between the seed region and other areas of the network were greater during rest than during the working memory task [Fransson, 2006]. Fransson and Marrelec [2008], using partial correlations, showed that there was some reduction in connectivity within the default network between the task and rest conditions, but that connectivity in the network was largely preserved. Similarly, Hampson et al. [2006] found that connectivity between the PCC and mPFC was maintained during the performance of a working memory task. Buckner et al. [2009] identified a number of highly-connected cortical "hubs" that included areas of the default network and suggest that the characteristic pattern of connectivity of these hubs is maintained during cognitive tasks, though they did not directly compare task and rest conditions. Thus, previous research examining connectivity of the default network suggests that there is still connectivity within the network during performance of a cognitive task, but that the degree of connectivity may be modulated.

In this study, we used psychophysiological interaction (PPI) analyses, as implemented in SPM2 software, to examine task-related alterations in the connectivity between each of two seed regions in the default network (PCC and mPFC) and the rest of the brain. PPI analyses are designed to measure context-sensitive changes in connectivity between two or more brain regions [Friston et al., 1997], by comparing connectivity in one context (in the current study, a working memory task) with connectivity during another context (in this case, rest). The results of these analyses are interpreted as providing information about the modulation of connectivity due to the effects of a psychological variable. In this study, the psychological variable in question was increased cognitive demand (during the working memory task). PPI analyses provide a potentially valuable resource for investigating default network connectivity, adding to resting-state functional connectivity analyses, because they are able to assess the effects of cognitive demands (in the current study, working memory) on patterns of connectivity observed during rest. It should also be noted that resting-state connectivity studies often focus on spontaneous fluctuations in the low-frequency range (<0.1 Hz), while PPI analyses are not generally filtered to include only connectivity within a specific frequency range. Thus if the change from rest to task involves not only changes in connectivity, but a shift to a higher frequency range, these changes will still be detectable using PPI analyses.

The purpose of this study was to determine (1) whether connectivity within the default network differs between a resting state and performance of a cognitive (working

memory) task and (2) whether connectivity differs between these nodes of the default network and other brain regions, particularly those implicated in cognitive tasks. We used seed regions in the mPFC and the PCC, as both of these nodes of the default network have been reliably shown to decrease in activation, relative to baseline, during cognitive tasks, and such a difference is a prerequisite for the PPI method. On the basis of previous finding [Fransson, 2006; Fransson and Marrelec, 2008], we hypothesized that during the working memory task, both seed regions would show greater connectivity than at baseline with areas previously implicated in working memory function and task-positive regions more generally. We also hypothesized that, based on the resting-state differences observed by Uddin et al. [2008], the specific areas showing alterations in connectivity with the seed region between baseline and task conditions would differ for the PCC and the mPFC. Such differences might reflect the contribution of each node to the performance of the cognitive task, possibly via the node's influence on "task positive" regions.

METHODS

Two previous studies examining alterations in working memory function associated with posttraumatic stress disorder have been published using these data [Moores et al., 2008; Shaw et al., 2009]; however, the current study focuses only on data from the healthy participants who comprised the control group in the previous papers. Twelve right-handed adults (seven male, five female; mean age 40.41 ± 10.93) with normal color vision participated in this study, after giving written, informed consent. The cognitive paradigm was a visuo-verbal target detection task, involving working memory, that required participants to attend to a serially presented set of words on a computer monitor and respond to target stimuli by pressing a button. There were four variations of this task in each run; however, because we are interested in the effects of cognitive effort on default network connectivity, rather than in specific effects associated with a particular variation of the task, for this study we combined the variations to model a single "task" condition. The "baseline" condition consisted of periods of viewing either five asterisks in the center of the screen or a notice of which variation of the task would be performed next. Further details of this working memory (WM) paradigm are provided in Moores et al., 2008.

The study used a block design with four task periods per imaging run. Each task block was 32-s long. Each run began with 16 s of baseline, with 32 s of baseline between each of the four task blocks and a further 16 s of baseline at the end of the run. In total, 16 functional runs were collected for each participant, in order to provide sufficient power to detect between-group differences. In the current study, using only the healthy control group, only the first eight runs were used. This number of runs has previously been shown to be sufficient to power connectivity analyses [Shaw et al., 2009].

MRI data were acquired using a Siemens VISION (Magnotom 4000, Erlangen, Germany) 1.5T MRI scanner with a CP head coil. Functional scanning runs used a specialized, gradient echo echoplanar imaging (EPI) trapezoidal mosaic sequence developed by the Functional Imaging Laboratory at the Wellcome Department of Imaging Neuroscience, University College London, UK, in collaboration with Siemens [TR = 0.76 ms, TE = 50 ms, TD1 (echo time) = 20 ms, TD2 (measurement delay time) = 188.2 ms, flip angle = 90°, matrix = 64 × 64, pixel size = 5 mm × 5 mm, slice thickness = 4 mm with a 1 mm interslice gap, yielding 5 mm^3 isotropic voxels, number of slices = 34)]. Axial fMRI volumes were acquired over the whole brain every 3.494 s (80 acquisitions per run, for a total time per run of 4 min, 39 s). No stimuli were presented during the first three volumes of each run in order to allow steady-state magnetization to be achieved.

Image preprocessing steps and statistical analysis were conducted using Statistical Parametric Mapping (SPM2, Wellcome Department of Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm) and were based on methods previously developed for the analysis of default network connectivity in resting-state fMRI scans [Bluhm et al., 2007, 2008; Fransson, 2005]. For each subject, all functional images were realigned to the first image in the series to reduce the effects of head motion and resliced, and a mean functional image was created. Images were then coregistered to the mean functional image and normalized to the EPI template in SPM2. To compensate for residual within-subject variability, decrease high spatial frequency noise and allow for the application of Gaussian random field theory, the functional images were smoothed using a 12 mm full-width half-maximum (FWHM) isotropic Gaussian filter [Fransson, 2005]. The high pass filter cut-off is conventionally set at least twice the task frequency oscillation (62 s for this study from beginning of WM task instruction set to the beginning of each rest/fixation block), so the high pass filter cut-off was 128 s.

Prior to the connectivity analyses, a subtraction analysis was conducted in order to demonstrate that there were significant differences in activation between baseline and the WM task in areas that had previously been identified as seed regions of interest for assessing alterations in connectivity of the default network. For each individual subject, contrast images were created that identified voxels showing (1) increased and (2) decreased activity from baseline to task. These contrast images were then entered into a second-level (group) analysis using one-sample *t*-test in SPM2, which was thresholded at $p < 0.05$ using False Discovery Rate (FDR) correction, as implemented in SPM2, with an extent threshold of 10 voxels.

PPI Analysis

Connectivity analyses were conducted using the PPI analysis methodology implemented in SPM2. As with the

TABLE I. Baseline vs. task

MNI co-ordinates			z Score	Cluster size	Brain region
			A) Baseline greater than task		
2	−54	28	3.56	173	Posterior cingulate/precuneus
14	−74	2	4.57	468	Cuneus, precuneus
50	−68	30	3.33	31	Angular gyrus (BA 39)
−56	−22	−4	4.58	1257	Superior temporal gyrus (BA 21, 22)
52	−28	6	4.05	348	Superior temporal gyrus
−36	18	−24	3.22	10	Superior temporal gyrus (BA 38)
58	−52	8	3.79	181	Middle/superior temporal gyrus (BA 22, 39)
0	54	18	5.21	2539	Medial frontal gyrus (BA 10)
2	−26	60	3.30	35	Medial frontal gyrus (BA 6)
−62	−6	38	3.84	37	Precentral gyrus (BA 6)
44	32	−16	3.51	27	Inferior frontal gyrus (BA 11, 47)
−58	28	8	3.23	12	Inferior frontal gyrus (BA 45)
			B) Task greater than baseline		
−40	−42	48	5.98	3821	Inferior parietal cortex (BA 7, 40)
38	−38	44	3.49	86	Inferior parietal cortex (BA 40)
−48	−58	−16	4.60	560	Temporal cortex, fusiform gyrus (BA 37)
−18	−96	10	4.36	355	Middle occipital gyrus (BA 17, 18)
−36	−82	−10	3.30	22	Occipital cortex (BA 18,19)
−48	10	28	4.09	1572	Middle frontal gyrus (BA 6)
26	−2	70	3.38	19	Middle frontal gyrus (BA 6)
36	2	58	3.21	20	Middle frontal gyrus (BA 6)
36	10	26	3.43	44	Inferior frontal gyrus (BA 9)
60	2	38	3.27	19	Superior frontal gyrus (BA 6)
32	−56	−26	3.58	114	Cerebellum

subtraction analysis described above, each PPI analysis was conducted individually for each subject and the contrast image derived from this analysis was then entered into a one-sample *t*-test. At the individual subject level, for each subject, an average time course was extracted from the two seed regions of interest, defined as a 10 mm sphere around co-ordinates derived from a previous study of the default network [Fox et al., 2005]. The PPC analysis was centered at MNI coordinates $(x,y,z) = (-6, -50, 36)$ and the mPFC analysis at 0, 50 0. The time course for each separate seed region was then compared between baseline and task in the PPI analysis, resulting in contrast images for each seed region for each subject, which were then analysed in second-level group analyses using a one-sample *t*-test for each seed region, thresholded at $P < 0.001$, uncorrected. Data for the PCC seed region were available for only 11 of the 12 subjects, as one subject did not show significant task-related differences in activation in the seed region and PPI analyses require that there is a difference in activation between baseline and task conditions.

In order to better interpret the results of the PPI analyses, we also examined functional connectivity during each of the rest and task blocks separately, using the method of Fair et al. [2007]. Activity during rest-only and task-only periods were separately correlated with seed-region activity to determine whether the seed region was positively or negatively correlated with areas showing significant changes in connectivity in the PPI analysis.

RESULTS

Subtraction Analysis

Task-induced deactivations were observed in a number of areas previously implicated in the default network, including the medial frontal gyrus, PCC and right angular gyrus (Table I). Increased activity during the WM task was observed in a number of task positive regions, including bilateral inferior parietal cortex and middle frontal gyrus (BA 6).

Posterior Cingulate Connectivity

The PCC showed greater correlation during baseline than during the WM task with the left precuneus, middle temporal gyrus and parahippocampal/fusiform gyrus (Table II). Greater connectivity of this region during WM task than baseline was observed with bilateral inferior frontal gyrus (Table II, Fig. 1).

Medial Prefrontal Cortex

The mPFC showed greater correlation during baseline than during the WM task with the right superior frontal gyrus (BA 9) and regions of the right insula (Table III). Greater correlation of this region during task than rest was observed with the middle temporal gyrus, superior

TABLE II. Areas Showing Altered Connectivity With the Posterior Cingulate Between Task and Baseline Conditions

MNI co-ordinates			z Score	Cluster size	Brain region
A) Greater connectivity with PCC during Baseline					
−44	−44	−12	4.60	141	Parahippocampal and fusiform gyri
−10	−66	49	4.04	102	Middle temporal gyrus (BA 39)
−40	−60	24	3.72	15	Precuneus (BA 7)
B) Greater connectivity with PCC during Task					
−54	10	28	3.65	88	Inferior frontal gyrus (BA 6, 9)
50	6	46	3.41	88	Inferior frontal gyrus (BA 6, 8, 9)

parietal lobule, cuneus, inferior frontal gyrus (see Fig. 1) and regions of the cerebellum (Table III).

DISCUSSION

This study focused on two nodes of the default network, the PCC and the mPFC, and used PPI analyses to investigate alterations in connectivity patterns associated with the transition from a resting baseline condition to a cognitive (WM) task. PPI analyses are designed to compare alterations in the correlation of activity in a seed region of interest with activity in other areas, voxel-by-voxel, of the brain. The analysis assumes a difference in activation in the seed region between the two task conditions being compared. We found greater activation during baseline than during the WM task in areas previously associated with the default network, including our two seed regions. This replicated findings in previous studies [Mazoyer et al., 2001; Shulman et al., 1997]. Conversely, we found greater activation during the WM task, compared with baseline, in bilateral inferior parietal cortex and middle frontal cortex, again replicating the findings of previous research [Moores et al., 2008; Shaw et al., 2009]. These latter areas have also been identified as "task positive" regions that are negatively correlated with the default network at rest [Fox et al., 2005; Fransson et al., 2005], as well as being implicated specifically in WM tasks.

With regard to alterations in connectivity between rest and the cognitive task, we found relatively little alteration in connectivity between either the PCC or the mPFC and other areas of the default network. The default network itself was originally identified in part on the basis of studies that showed areas implicated in this network regularly decreased in activity from baseline to a variety of cognitive tasks [Gusnard and Raichle, 2001; Raichle et al., 2001], a finding replicated in this study. This decrease, however, appears to have relatively little impact on connectivity within the network.

In contrast to the lack of changes in functional connectivity observed within the default network, both seed regions showed differences in connectivity across task conditions with areas outside of the default network.

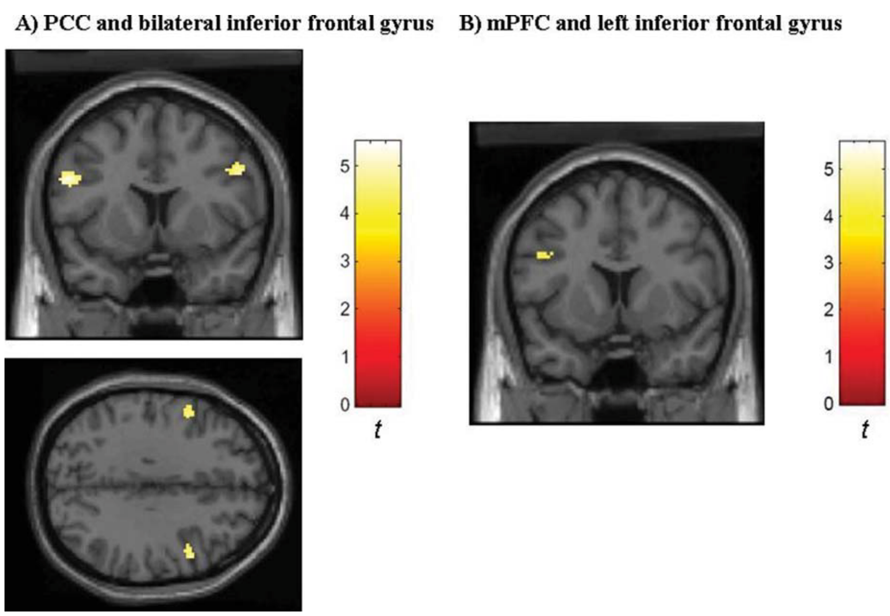

Figure 1.
Areas in bilateral inferior frontal gyrus showing greater connectivity with (**A**) PCC and (**B**) mPFC during performance of the working memory task.

TABLE III. Areas Showing Altered Connectivity With the Medial Prefrontal Cortex Between Task and Baseline Conditions

MNI co-ordinates			z Score	Cluster size	Brain region
A) Greater connectivity with mPFC during Baseline					
20	46	44	4.46	45	Superior frontal gyrus (BA 9)
42	−10	14	3.46	50	Insula (BA 13)
38	−32	20	3.35	13	Insula (BA 13)
B) Greater connectivity with mPFC during Task					
4	−98	22	3.76	43	Cuneus (BA 18, 19)
14	−90	−26	3.61	14	Cerebellum
52	−62	−32	3.53	20	Cerebellum
−4	−88	−32	3.53	41	Cerebellum
−62	−18	−14	3.48	40	Middle temporal gyrus (BA 21)
32	−74	54	3.31	12	Superior parietal lobule (BA 7)
−46	10	28	3.20	22	Inferior frontal gyrus (BA 9)

Detection of these significant changes give us confidence that the lack of change in functional connectivity observed within the default network is not due to a lack of power. Increases in connectivity during the WM task tended to occur primarily in areas previously described as part of a task-positive network that is negatively correlated with the default network during rest [Fox et al., 2005; Fransson, 2005], though some differences occurred between the two seed regions in the specific areas where connectivity differed. For the PCC, increased task-related connectivity was observed with bilateral inferior frontal gyrus. Follow-up analyses of connectivity between the PCC and inferior frontal gyrus at rest and during the task suggest that the increased connectivity observed in the PPI analysis is actually due to a reduction in the negative correlations that exists at rest. A similar pattern of connectivity was seen between the mPFC and the left inferior frontal gyrus.

The mPFC also showed stronger correlations during WM task than at baseline with several regions of the cerebellum, which has previously been shown to be involved both in the control of motor functions and in working memory [Ben-Yehuda et al., 2007; Bellebaum and Daum, 2007], as well as being identified as positively correlated with areas of the default network at rest [Fox et al., 2005; Fransson, 2005; Greicius et al., 2004]. We found that the mPFC and the cerebellum were positively correlated both during rest and during task, which suggests that the PPI results reflect an increase of underlying ("default") connectivity between the cerebellum and the mPFC.

The differences observed in the connectivity patterns of these two seed regions reflect previous work by Uddin et al. [2008], who examined resting state connectivity and found that the medial prefrontal cortex had stronger negative correlations than the PCC with posterior regions in the temporal and parietal cortex. These authors used Granger causality analysis to show that the negative correlations were modulated by the nodes of the default network, rather than by the task-positive regions. We found that there was greater correlation between seed regions in the default network and areas of the task-positive network during the WM task than at rest.

In addition to the regions showing greater connectivity during task than rest, there were also areas that showed greater connectivity with the seed regions during rest than during task performance. Of particular interest here is the finding of greater connectivity at rest between the mPFC seed region and the insula, which reflected an increase in the strength of the positive connectivity between these areas at rest. Previous work has shown that the insula may be a critical node in a "salience network" [Seeley et al., 2007; Taylor et al., 2009] and that this function may be of particular importance in mental disorders, such as autism [Uddin and Menon, 2009], which, together with the current results, suggests that the insula may play an important role in the default network as well as contributing to the performance of cognitive tasks.

In summary, we found relatively little change in connectivity of either the mPFC or the PCC with other areas of the default network. These results suggest that the default network continues to function as a correlated network during cognitive tasks, as well as during rest, replicating the results of previous studies [Hampson et al., 2006; Fransson and Marrelec, 2008]. By contrast with the consistency in correlation within the default network, the relationships between nodes of the default network and areas previously identified as "task-positive" regions change during performance of cognitive tasks. Further research may determine whether these alterations in connectivity are driven by nodes of the default network, in the same way that the work of Uddin et al. [2008] has suggested that the default network governs activity in task-positive areas at rest. A better understanding of the task-dependent relationships between the default network and other brain regions and networks will help to elucidate the function of the default network itself.

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