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Functional connectivity between task-positive and task-negative brain areas and its relation to working memory performance

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Abstract

Functional brain imaging studies have identified a set of brain areas typically activated during cognitive tasks (task-positive brain areas) and another set of brain areas typically deactivated during cognitive tasks (task-negative brain areas). Negative correlations, or anticorrelations, between task-positive and task-negative brain areas have been reported at rest. Furthermore, the strength of these anticorrelations appears to be related to cognitive function. However, studies examining anticorrelations have typically employed global regression or similar analysis steps that force anticorrelated relationships to exist between brain areas. Therefore the validity of these findings has been questioned. Here we examine anticorrelations between a task-negative region in the medial frontal gyrus/anterior cingulate cortex and dorsolateral prefrontal cortex, a classic task-positive area, using an analysis that does not include global regression. Instead, we control for whole-brain correlations in the group-level analysis. Using this approach, we demonstrate that the strength of the functional connection between the medial frontal cortex and the dorsolateral prefrontal cortex is related to cognitive function and that this relationship is not an artifact of global regression.

Introduction

Functional brain imaging has revealed one set of brain areas that show increases in activity and a separate set of areas that show decreases in activity during performance of a wide range of different types of cognitive tasks. Adopting the terminology of Fox, et al [1], we refer to these brain areas as task-positive and task-negative regions respectively. Task-positive regions include dorsolateral prefrontal, precentral, and inferior parietal cortices [2,3]. Task-negative regions include posterior cingulate cortex, lateral parietal areas and a medial frontal region incorporating parts of the medial frontal gyrus and the ventral anterior cingulate cortex [4,5]. These task-negative regions have sometimes been referred to as the default-mode network.

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In the resting state, anticorrelations have been reported between task-negative and task-positive regions [1,6,7]. This has been interpreted as evidence that the resting brain shifts between two different modes of processing, one which engages the task-positive regions, and one which engages the task-negative regions [1,6]. This interpretation of the data is nicely expressed by Fox, et al [1]. “While correlations may serve an integrative role in combining neuronal activity subserving similar goals or representations, anticorrelations may serve a differentiating role segregating neuronal processes subserving opposite goals or competing representations”. We would like to suggest that anticorrelations can also serve an integrative role, allowing regions to share and process information together, just as deactivation in a brain area can reflect increased engagement of that area with other regions [8].

The strength of anticorrelation between task-positive and task-negative brain areas has been reported to be inversely correlated with intraindividual variability (IIV) in response time [9]. IIV is inversely related to stable behavioural performance and greater IIV is generally associated with poorer cognitive function. Thus, in that study, stronger anticorrelations were associated with better cognitive function. Similarly, in our unpublished data, we see correlations between working memory performance (that is, percent correct on a 3-back task) and the strength of anticorrelations between task-positive and task-negative brain areas. This apparent relationship with cognitive function motivates our interest in the functional relationship between task-positive and task-negative brain areas.

However, previous studies examining anticorrelations between task-positive and task-negative brain areas have employed preprocessing steps in which the time-course of the whole brain (or the whole slice) are removed via regression or orthogonalization. These analyses can introduce anticorrelations between brain areas [10]. It is therefore possible that the anticorrelations between task-positive and task-negative brain areas, and their relationships to performance, are artifacts of the analysis. On the other hand, if global regression (or some other form of global/ slice mean time-course removal) is not employed in the functional connectivity analyses, positive whole-brain correlations are seen. The source of this whole-brain correlation is not clear, but its magnitude can vary from subject to subject. If not adjusted for, this whole-brain correlation could potentially hide true relationships between the strength of specific functional connections and behaviour.

To the extent that whole-brain correlations are caused by cardiac and respiratory fluctuations, it may be possible to reduce them by methods designed to remove these noise sources from the imaging data. Although some of these methods require simultaneous recording of cardiac and respiratory fluctuations [11–15], other methods have been proposed that extract estimates of these noise sources directly from the imaging data [16,17]. However, it is possible that cardiac and respiratory fluctuations are not the only factors contributing to whole-brain correlations.

Here we present an approach for computing connectivity-behaviour relationships that adjusts for the effects of whole-brain correlations without employing global regression or similar preprocessing steps. The approach computes correlation maps without any adjustment for whole-brain correlations. The magnitude of whole-brain correlations are then estimated in a post-processing step that fits the histogram of the data with a Gaussian curve and identifies the mean. This post-processing normalization step is based on the method introduced by Lowe’s group to evaluate the strength of connectivity in individual subjects [18]. Rather than adjusting the distribution of the maps directly, however, the maps are left unchanged, and an estimate of whole-brain correlation is obtained for each subject. The influence of whole-brain correlation can then be controlled for in the subsequent across-subject analyses.

This method is used to examine whether resting state connectivity between a key task-negative brain area located in medial frontal cortex (MFC) and a classic task-positive brain area located bilaterally in the dorsolateral prefrontal cortex (DLPFC) is related to working memory performance. These two regions were chosen because they were the most deactivated and most activated, respectively, during the working memory task. We hypothesized that there is a relationship between the strength of this connection and cognitive function that is not an artifact of global regression, and expected this relationship to be revealed using the new method described here that adjusts for whole-brain correlation without the use of global regression.

Methods

The subjects, acquisition parameters, and experimental paradigm for this dataset are summarized briefly below, and described in more detail in Hampson, et al. [8].

Subjects

Data from nine healthy subjects (5 women, 4 men, ages 25–45) were analyzed.

Functional Imaging Data Acquisition

Data was collected in a GE (Waukesha, WI) 1.5T Signa scanner. Each functional scan involved the collection of 128 volumes, the first four of which were discarded (TR=1500ms, TE=50ms, flip angle = 70, 64X64 matrix, 20cmX20cm field of view). Each subject participated in two block-design scans alternating between a verbal 3-back task and a baseline control task. In addition, five resting state scans were collected.

Data Analyses

All analyses were conducted using in-house software written in Matlab (<http://www.mathworks.com/>).

Preprocessing—Data were motion corrected using the SPM algorithm (<http://www.fil.ion.ucl.ac.uk/spm/>), spatially filtered using a Gaussian filter with a 2 pixel full-width at half-maximum. Pixels with a value less than one fifth the maximum median value were set to zero. Finally, data from the resting runs were band-pass filtered, preserving frequencies between 0.01 and 0.1 Hz.

Activation analyses (Block design paradigm)—Images from the two block-design scans were assigned to task or baseline blocks after adjusting for hemodynamic delay. For each subject, at each pixel, percent signal change across conditions was computed in each of the two scans separately, and averaged across the scans, yielding a map representing that subject's percent signal change in the block-design scans. These maps were transformed to Talairach space, and a t-test across subjects on the percent signal changes with condition for each pixel yielded a composite map of the significance of activations/deactivations to the block-design task.

Region definitions—All regions of interest were defined in the same manner as a prior study on this data set [8]. Task-negative seed region: To maximize power, the MFC seed region was defined functionally in a subject-specific manner, based on deactivations in their block-design scans. To avoid large differences in the size of the seed region used across subjects, a fixed threshold was not adopted, rather, each subjects 8 most deactivated pixels falling within the medial frontal gyrus (BA 9/10) or the ventral anterior cingulate cortex (BA 24/32 below $z = 26$) were used. Task-positive ROIs: The left dorsolateral prefrontal cortex (lt DLPFC) ROI was defined to include all activated pixels ($P < 0.005$) in the composite map falling within left BA 9 or left BA 46 of the prefrontal cortex. Similarly, the right dorsolateral prefrontal cortex

(rtDLPFC) ROI was defined to include all activated pixels ($P < 0.005$) in the composite map falling within right BA 9 or right BA 46 of the prefrontal cortex. The bilateral DLPFC was defined as the union of the right and left DLPFC ROIs. **Task-negative ROI:** One additional task-negative ROI was defined to include all deactivated pixels in the composite map ($p < 0.005$) falling in the posterior cingulate cortex (PCC). This ROI was included to allow a comparison with previously published findings of connectivity-behaviour correlations between MFC and PCC that were computed using a slightly different analysis strategy, including slice mean removal and less stringent filtering [8]. These ROIs are shown in Figure 1.

Functional connectivity maps—The reference time-course for a given subject was computed by averaging the time-course across all 8 pixels in their functionally defined MFC seed region for each scan individually. Maps of whole brain correlation to that reference time-course were computed in three different ways:

Strategy 1: Using removal of global time-course: For each resting state scan, the reference time-course was partial correlated with the time-course of every other pixel in the brain, removing the effects of the global time-course. The equation for this

partial correlation is: $r_{\text{partial}} = (r_{rp} - r_{pg} * r_{rg}) / \sqrt{(1 - r_{pg}^2)(1 - r_{rg}^2)}$ where r_{rp} is the correlation between the reference timecourse and the pixel timecourse, r_{pg} is the correlation between the pixel timecourse and the global timecourse, and r_{rg} is the correlation between the reference timecourse and the global timecourse. The resulting correlations were transformed to a Gaussian distribution via Fisher's transformation, and averaged across scans.

Strategy 2: No adjustment for globally synchronized fluctuations: For each resting state scan, the reference time-course was correlated with the time-course of every other pixel in the brain, and the correlations were transformed to a Gaussian distribution via Fisher's transformation, and averaged across scans.

Strategy 3: No adjustment for global time-course in individual subject maps, but whole-brain correlation estimated (for later use in group level analyses): For each resting state scan, the reference time-course was correlated with the time-course of every other pixel in the brain, and the correlations were transformed to a Gaussian distribution via Fisher's transformation, and averaged across scans. Because the global time-course was not removed, the Gaussian distribution was not centered on zero. For each scan individually, the Gaussian distribution was fit (to full-width at half maximum) with a Gaussian curve, and an estimate of the mean of the distribution was obtained (Δ_{ij} for each scan i of subject j , shown in Figure 2), but the distribution was not altered. Δ_{ij} was averaged across scans to yield one number for each subject representing their whole-brain correlation, $\Delta_j = \sum_i \Delta_{ij} / 5$. This vector (one value per subject) is referred to as Δ .

Assessing strength of functional connectivity—For the first two connectivity analyses described above (with and without global regression), strength of correlation between MFC and each of the four ROIs (right DLPFC, left DLPFC, bilateral DLPFC, and PCC) was assessed as the average z-transformed correlation across all pixels in that ROI within the Talarach transformed correlation map to the seed region. T-tests were used to assess the significance of these connections across subjects. In addition to these ROI analyses, a composite map of correlations to the MFC was computed on the maps created without global regression.

Correlations between behavior and connectivity to the four ROIs—Working memory performance for each subject was assessed as the average percent correct on a 3-back working memory task. For each of the four functional connections examined, and for each of

the three types of functional connectivity analysis strategies employed, subject performance was correlated across subjects with the strength of subjects' resting connectivity. In the case of the last method (Strategy 3), a partial correlation was performed, removing the effects of the Δ vector (see Figure 2 and text above for the definition of Δ). The Δ vector represents the mean correlation in the brain to the MFC seed region in each subject. Thus, this partial correlation adjusts for mean correlation in the brain.

Pixel-wise connectivity-behaviour correlations—Correlation to the MFC seed region was related to working memory performance at each pixel in the brain, using the three analysis strategies described above, once again adjusting for delta via partial correlation when using Strategy 3.

Results

When functional connectivity was assessed using the removal of global time-course, the correlation between MFC and right DLPFC was significantly negative ($p = 0.002$) and the connectivity to left DLPFC was negative, but did not reach significance ($p=0.1$). When DLPFC was treated as a single, bilateral region, it was significantly negatively correlated to MFC ($p = 0.006$). When global time-course was not removed, these functional connections were significantly positive ($p = 0.05$ lt DLPFC, $p = 0.04$ rt DLPFC, $p = 0.04$ bilateral DLPFC) as were connections to most other parts of the brain due to the large whole-brain correlations. The correlation between MFC and PCC was significantly positive whether global regression was ($p=0.003$) or was not ($p=0.000006$) employed. To illustrate the magnitude of whole-brain correlation, a composite map of correlations to MFC computed without the removal of global timecourse is provided in Figure 3. Consistent with a prior report[10], but in contrast to another one[19], when global timecourse is not removed, our maps of correlations to a task-negative seed region do not show negative correlations in any task-positive regions.

Correlations to performance

Correlations between functional connectivity and working memory performance are summarized in Table 1. When global time-course was removed in the functional connectivity analyses, the connection between left DLPFC and MFC was significantly negatively related to working memory performance ($p = 0.03$). The connection between right DLPFC and MFC was also negatively correlated with working memory performance, but this relationship did not reach significance ($p = 0.2$). Treating DLPFC as a single, bilateral region, its connection to MFC was significantly negatively related to working memory performance ($p = 0.04$). Finally, the connection between MFC and PCC was positively related to working memory performance ($p = 0.02$). This last result is consistent with that reported previously in which the same data set was analyzed using slice mean time-course removal rather than global time-course removal, and in which slightly different filtering was used [8].

When the data was not normalized for the global time-course, the only significant correlation between performance and the functional connectivity measures was a negative correlation between performance on the working memory task and the strength of the connection between MFC and left DLPFC ($p = 0.05$). However, when a partial correlation was used to remove the effects of the Δ vector, the significance of the connectivity-behaviour correlation increased for all four ROIs. In addition to a significantly negative correlation between performance and MFC-left DLPFC connectivity ($p = 0.03$), the partial correlations also revealed a significantly negative correlation between MFC-bilateral DLPFC connectivity and performance ($p = 0.04$), and a significantly positive correlation between MFC-PCC connectivity and performance ($p = 0.02$).

These results confirm our hypothesis that the relationship between working memory performance and the MFC-DLPFC connection is not an artifact of global regression.

Although the connectivity-behaviour relationships for the connections examined in this study were similar when using global regression and our alternate method (that adjusts for the whole-brain correlation during group level analysis), the two methods differed in many other areas of the brain. Differences between the methods are illustrated in Figure 4 where pixel-wise connectivity-behaviour relationships computed using the two methods are shown for a single slice. In both maps, a negative connectivity-behaviour correlation is apparent in left DLPFC, and a positive connectivity-behaviour correlation is apparent in PCC, consistent with our ROI analyses. However, the spatial pattern of connectivity-behaviour correlation differs for the two methods in other regions, as highlighted by circles in Figure 4. Caution must be used when interpreting results in regions where the two methods do not converge.

Discussion

The use of global regression, or similar approaches, such as the removal of slice mean time-course from the data, can introduce artifactual negative correlations into connectivity maps [10]. This is particularly a concern when studying the functional relationships between task-negative and task-positive brain areas, which appear as anticorrelations when global time-course is removed in the analysis, but which are not anticorrelated when global normalization is not employed. Here we describe an alternative approach for studying the relationships between task-positive and task-negative regions. This method does not remove the global time-course in the functional connectivity analysis, but adjusts for whole-brain correlation by estimating the magnitude of the whole-brain correlation in each subject, and adjusting for it in subsequent, group-level analyses. The method can be used when studying connectivity-behaviour correlations, or when comparing the strength of a specific connection between groups. Because the method does not employ global regression, it can be used to verify that findings obtained using global regression are not due to artifacts introduced by that analysis step.

The source of whole-brain correlations is unknown. They may be related to physiologic noise sources such as the cardiac or respiratory cycles, or may arise from the neural dynamics of brain systems. This work does not directly address this important question, but does estimate the strength of whole-brain correlations in each subject. By examining how such measures relate to other variables, some insight may be gained into the source of these whole-brain correlations. Here we use estimates of whole brain correlation based on seed region maps, which are therefore dependent on the choice of seed region used. The development of a measure of whole-brain correlation that is not seed region specific could have utility for studying the basis of these whole-brain correlations.

The functional connection between MFC and DLPFC was an anticorrelation only when the global time-course was removed during analysis. In fact, there are no anticorrelations apparent in our composite map when functional connectivity is assessed without the removal of global timecourse, even at a very low threshold. This is consistent with a previous study that reported no anticorrelations to the PCC even at very low thresholds when global regression was not used [10] (albeit with a different task-negative seed region). On the other hand, a more recent study reported finding anticorrelations to the PCC at an uncorrected $p < 0.05$ [19]. The differences between these studies remain to be resolved.

It may be that task-positive and task-negative brain areas fluctuate in antiphase in terms of their neural activity patterns, and that this relationship is obscured by positive correlations in their hemodynamics when no global normalization is used. However, it is also possible that the

regions have no antiphase relationship in their neural activity patterns, and that global normalization introduces the appearance of one. Relevant to this question, a study examining local field potential (LFP) in cat homologues of human task-positive and task-negative regions reported periods of anticorrelated LFP power oscillations in task-positive and task-negative areas[20]. However these anticorrelations were present only approximately 20% of the time, and the power fluctuations in LFP were overall positively correlated between task-positive and task-negative areas.

Regardless of whether the functional relationships between task-positive and task-negative brain areas are anticorrelations, they appear to be relevant to cognitive function. We illustrate here that the strength of the MFC-DLPFC connection is related to working memory performance, and that this relationship is not an artifact of global regression. Thus, the functional connections between task-positive and task-negative regions, and their relations to human cognition, deserve further study.

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Figure 1.
A map of the regions of interest studied. Regions were identified based on activations and deactivations during the 3-back working memory task at an uncorrected threshold of $p < 0.005$.

Figure 2.

Illustration of the method for estimating whole-brain correlation to the seed region, Δ_{ij} , for a single run i of a single subject j . The histogram of the values in the seed region correlation map (after the Fisher transform has been applied to the r -values to transform them to Gaussian values) is plotted in red. The Gaussian curve which best fits this distribution (to full-width at half-maximum) is computed (shown in blue). The mean of that Gaussian curve is Δ_{ij} , an estimate of the whole-brain correlation in that run.

Figure 3. Composite map of correlations to the MFC at a threshold of $p < 0.05$, uncorrected. Positive correlations throughout the brain are apparent and there are no negative correlations in task-positive regions. This is true even when the threshold is reduced to $p < 0.5$.

Figure 4. Maps showing how connectivity to the MFC seed region is related to working memory performance when connectivity-behavior relationships are computed using two different approaches to adjust for synchronized global activity. A) Global timecourse is removed during the computation of functional connectivity in each subject (Strategy 1). B) No removal of global timecourse in the computation of functional connectivity maps, but the magnitude of whole-brain correlation (Δ) is adjusted for the group-level analysis (Strategy 3). These images depict the axial slice located at $z=14$ in Talairach coordinates, shown at an uncorrected threshold of $p<0.05$. Arrows indicate the location of the two ROIs where we found significant connectivity-behavior relationships: a negative relationship in left DLPFC (white arrow) and a positive one in PCC (black arrow). Here results from the two analyses converge. Differences in the two maps are also apparent in several locations, as highlighted by the red circles.

Correlation between performance on working memory task and functional connectivity (fc) to MFC seed region evaluated for the four regions of interest using three different analyses. P-values are not corrected for the number of connections examined.

Table 1

Analysis Strategy		Region of Interest			
		Lt DLPFC	Rt DLPFC	Bilat DLPFC	PCC
Strategy 1: Removing global time-course		r = -0.73 p = 0.03	r = -0.46 p = 0.2	r = -0.68 p = 0.04	r = 0.75 p = 0.02
		r = -0.67 p = 0.05	r = -0.54 p = 0.14	r = -0.58 p = 0.1	r = 0.54 p = 0.14
		r = -0.76 p = 0.03	r = -0.64 p = 0.09	r = -0.72 p = 0.04	r = 0.77 p = 0.02
Strategy 2: No removal of global time-course	Correlating fc to performance				
	Partial correlating fc to performance, removing Δ				