

Identifying Rate-Limiting Nodes in Large-Scale Cortical Networks for Visuospatial Processing: An Illustration using fMRI

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Abstract

■ With the advent of functional neuroimaging techniques, in particular functional magnetic resonance imaging (fMRI), we have gained greater insight into the neural correlates of visuospatial function. However, it may not always be easy to identify the cerebral regions most specifically associated with performance on a given task. One approach is to examine the quantitative relationships between regional activation and behavioral performance measures. In the present study, we investigated the functional neuroanatomy of two different visuospatial processing tasks, judgement of line orientation and mental rotation. Twenty-four normal participants were scanned with fMRI using blocked periodic designs for experimental task presentation. Accuracy and reaction time (RT) to each trial of both activation and baseline conditions in each experiment was recorded. Both experiments activated dorsal and ventral visual cortical areas as well as dorsolateral

prefrontal cortex. More regionally specific associations with task performance were identified by estimating the association between (sinusoidal) power of functional response and mean RT to the activation condition; a permutation test based on spatial statistics was used for inference. There was significant behavioral–physiological association in right ventral extrastriate cortex for the line orientation task and in bilateral (predominantly right) superior parietal lobule for the mental rotation task. Comparable associations were not found between power of response and RT to the baseline conditions of the tasks. These data suggest that one region in a neurocognitive network may be most strongly associated with behavioral performance and this may be regarded as the computationally least efficient or rate-limiting node of the network. ■

INTRODUCTION

It is now generally accepted that complex mental functions are often subserved by large-scale, spatially distributed neurocognitive networks (Lin, Nein, & Lin, 1999; Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Haxby et al., 1991). Many of these networks have recently been investigated using functional neuroimaging techniques such as positron emission tomography (PET) (Fox & Raichle, 1984) and functional magnetic resonance imaging (fMRI) (Bullmore, Rabe-Hesketh, et al., 1996; Ogawa, Lee, Kay, & Tank, 1990). Inferences about the roles of cerebral structures are commonly based on regional differences in the activation maps obtained from different tasks. Although this “subtraction” approach yields important information regarding the anatomical substrates of task performance, it does not always elucidate the relative contribution of each activated area to different aspects of a task. One complementary way to accomplish this is to examine the

quantitative relationships between regional activation and behavioral performance measures (e.g., Honey, Bullmore, & Sharma, 2000; Tagaris et al., 1996).

We have chosen to study visuospatial processing systems because although there is a large body of published literature on visuospatial tasks, the specific contributions of the (usually) multiple areas involved in overall performance of these tasks are not always clear. For example, posterior parietal and extrastriate visual cortices are engaged in the mental rotation of objects as demonstrated by PET (Alivisatos & Petrides, 1997), fMRI (Cohen et al., 1996; Tagaris et al., 1996), and event-related potential (ERP) (Perronet & Farrah, 1989) techniques. However, they are also involved in performance on other visuospatial processing tasks such as those involving judgements of axis/line orientation (Taira, Kawashima, Inoue, & Fukuda, 1998; O'Donnell, Swearer, Smith, Hokama, & McCarty, 1997; Hannay et al., 1987; Benton, Varney, & Hamsher, 1978). Which of these two regions is specifically critical to performance on each of these rather different tasks remains an open question.

In their computational model of mental rotation, Just and Carpenter (1992) proposed that the degree of

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mental computation and extent of information maintenance required would scale with a concomitant consumption of neural resources. More recently, Carpenter, Just, Keller, Eddy, & Thulborn (1999) proposed that the amount of cortical activation required for visuospatial processing is related to the amount, as well as to the type, of computational demand. This proposal was based in part on an observed linear relationship between fMRI (i.e., blood oxygen level dependent [BOLD]) activation in intraparietal, fusiform, and inferotemporal regions and increasing angular disparity on the Shepard–Metzler mental-rotation task. Carpenter et al. equated increasing angular disparity with greater task demand and larger resource utilization as it results in a monotonic increase in the average decision time (Shepard & Cooper, 1982; Shepard & Metzler, 1971). A control condition that had a lower computational demand for object recognition and rotation processes and a similar demand for visual scanning produced less activation in the parietal and inferotemporal regions, although considerable activation in the precentral and middle frontal gyri.

The present study was designed to further examine Carpenter et al.'s (1999) proposal with respect to visuospatial processing. In addition to a mental rotation task, we selected a task requiring judgements of line orientation (Benton et al., 1978). Both tasks are known to depend on similar large-scale neurocognitive networks, although performance on these tasks may depend on somewhat different visuospatial processes. The quantitative relationships between behavioral performance and regions of cerebral activation identified by fMRI were investigated to determine the areas critically associated with each task. Response latencies were utilized as the measure of performance on each task.

RESULTS

Performance Data

Accuracy (percentage of trials correct), mean reaction time (RT) for correct responses, and the correlation between accuracy and RT, are shown for each task in Table 1. For both visuospatial tasks it is apparent that (a) the subjects performed at ceiling level in the control condition, namely, they achieved accuracies greater than 95%; and (b) the mean RT is longer, and accuracy is less,

for the task condition. Only in the task conditions were there significant (negative) correlations between mean RT and accuracy.

Generic Brain Activation Maps

Robust activation in large-scale distributed cortical networks was found for both the line orientation and mental rotation tasks. In the judgement of line orientation task, significant activation was observed in the precuneus (approximate Brodmann's area [BA] 7), extrastriate visual cortex (BA 19), and middle frontal gyrus (dorsolateral prefrontal cortex; BA 9); see Figure 1 and Table 2. Similar areas were significantly activated, albeit to a lesser degree, in the mental rotation task; see Figure 2 and Table 3. It can be seen that the main areas of activation that were common to the two tasks were the superior parietal lobe/precuneus, extrastriate visual cortex, and middle frontal gyrus.

Relationships Between RT and Power of Activation

A significant linear relationship between mean RT and power of functional response to the judgement of line orientation task was identified in the right ventral extrastriate cortex (BA 18, 19; see Figure 3). A significant linear relationship between mean RT and power of functional response to the mental rotation task was identified in bilateral (predominantly right-sided) superior parietal lobule (BA 7; see Figure 4). In both cases, increased power of functional response was predicted by prolonged RT.

To explore the relationship between RT and power of response more closely, estimates of standardized power (FPQ) observed at Talairach coordinates in these areas of significant behavioral–physiological association were simply plotted against RT (see Figures 5 and 6). The data for the judgement of line orientation task were extracted from the right ventral extrastriate cortex at Talairach coordinates (x, y, z ; mm) 30, $-78, -6$; the data for the mental rotation task were extracted from the right superior parietal lobule at Talairach coordinates (x, y, z ; mm) 8, $-70, 55$. As indicated by prior nonparametric hypothesis testing at cluster level, the power of response was significantly (and specifically) correlated with RT at each of these index voxels. In the ventral extrastriate

Table 1. Measures of Performance During Scanning on Activation and Baseline Conditions of Line Orientation and Mental Rotation Experiments

	<i>Line Orientation</i>		<i>Mental Rotation</i>	
	<i>Task</i>	<i>Control</i>	<i>Task</i>	<i>Control</i>
Mean RT in msec (<i>SD</i>)	2009 (428)	1029 (223)	2083 (311)	961 (113)
Accuracy in percent (<i>SD</i>)	81.5 (12.8)	96.4 (7.1)	89.6 (21.8)	98.3 (4.4)
Accuracy/latency correlation (<i>R</i> value)	-.77 (.003)	-.11 (.74)	-.74 (.006)	.10 (.76)

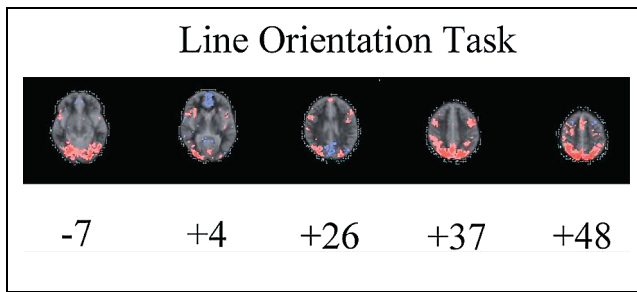


Figure 1. Judgement of line orientation: generic brain activation map showing voxels with significant median power of periodic response ($N = 12$). Red voxels showed significant power of response with signal maximum during the activation condition (on average over subjects); blue voxels were activated with signal maximum during the baseline condition. The voxel-wise probability of false positive activation $p < .0005$; the search volume $V = 20,515$ voxels; the expected number of false positive voxels $PV < 11$. The locations of the main regional foci of functional activation are detailed in Table 2. The right side of the brain is shown on the left side of each map.

cortex, RT to the judgement of line orientation task was significantly correlated with power of functional response ($R = .58$, $df = 10$, $p = .05$) but RT to the baseline task was not significantly correlated with power of functional response ($R = .15$, $df = 10$, $p = .64$). Likewise, in the superior parietal lobule, RT to the mental rotation task was significantly correlated with power of functional response ($R = .59$, $df = 10$, $p = .04$) but RT to the baseline task was not ($R = -.33$, $df = 10$, $p = .32$).

DISCUSSION

A combination of specific and more general processes is integral to the execution of a complex mental task. This is reflected by the activation commonly observed across widespread neural networks identified in functional

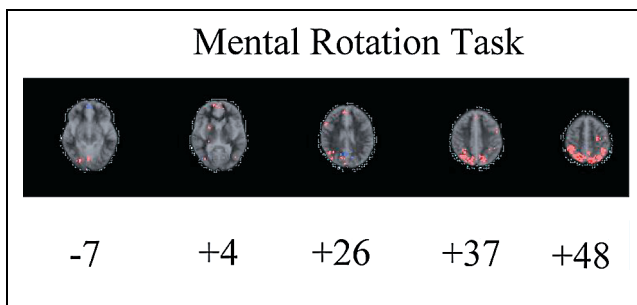


Figure 2. Mental rotation: generic brain activation map showing voxels with significant median power of periodic response ($N = 12$). Red voxels showed significant power of response with signal maximum during the activation condition (on average over subjects); blue voxels were activated with signal maximum during the baseline condition. The voxel-wise probability of false positive activation $p < .0005$; the search volume $V = 21,302$ voxels; the expected number of false positive voxels $PV < 11$. The locations of the main regional foci of functional activation are detailed in Table 3. The right side of the brain is shown on the left side of each map.

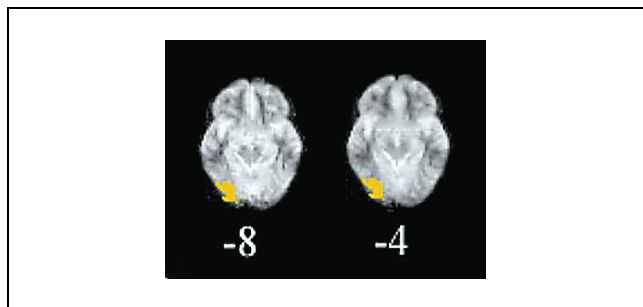


Figure 3. Judgement of line orientation: association between mean RT and power of functional response ($N = 12$). The cluster-wise probability of false positive activation $p < .005$; the search volume $V = 126$ clusters; the expected number of false positive clusters $PV < 1$. The right side of the brain is shown on the left side of each map. The yellow voxels denote the areas of significant association.

neuroimaging studies. However, the exact role of an activated area within a delineated network may be unclear. We therefore examined the quantitative relationships between BOLD activation and behavioral performance on two visuospatial tasks in a fMRI experiment in order to determine the critical regions involved in task execution.

Inspection of the coordinates of the activation foci revealed similar neural networks were involved in performance on both the line orientation and mental rotation tasks, consistent with previously published results (e.g., O'Donnell et al., 1997; Cohen et al., 1996; Perronet & Farrah, 1989; Hannay et al., 1987). When the physiological responses were correlated with RT data from the respective tasks, areas more specifically associated with performance on each task were identified. The cerebral region, or neurocognitive network node, specifically associated with the line orientation task was located in the right ventral extrastriate cortex; whereas the region most strongly associated with the mental rotation task was located in the superior parietal cortex. In neither of these regions was power of functional response significantly associated with RT to the baseline

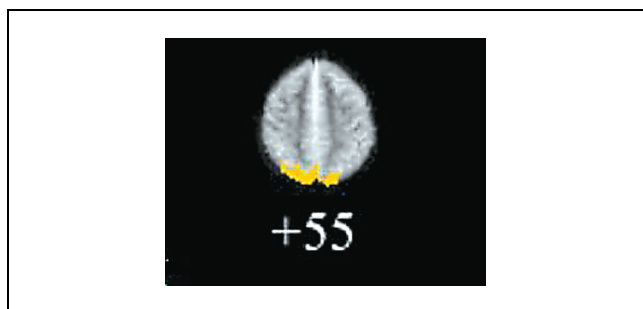


Figure 4. Mental rotation: association between mean RT and power of functional response ($N = 12$). The cluster-wise probability of false positive activation $p < .005$; the search volume $V = 55$ clusters; the expected number of false positive clusters $PV < 1$. The right side of the brain is shown on the left side of each map. The yellow voxels denote the areas of significant association.

Table 2. Significant Generic Brain Activation Areas in the Line Orientation Experiment ($p < .0005$)

Region	Talairach Coordinates			BA	Side	Max (FPQ)	No. of Voxels
	<i>x</i>	<i>y</i>	<i>z</i>				
Ventral extrastriate cortex	23	-67	-7	19	R	2.5	391
Precuneus	-17	-61	48	7	L	3.2	240
Medial frontal gyrus	-46	3	37	6	L	2.3	36
Dorsolateral prefrontal gyrus	-46	19	26	46	L	2.0	15
Inferior frontal gyrus	52	11	4	9	R	1.9	28
Inferior frontal gyrus	52	8	26	44	R	2.0	15

conditions of these experiments, suggesting that these associations are task-specific and do not merely reflect, for example, an association between power of response and some nonspecific subjective variable such as level of attention or speed of processing.

There are considerable prior data to suggest that the superior parietal cortex may play a key role in the computations of mental rotation. Evidence from monkey studies indicates that the superior parietal cortex projects to the lower bank of the intraparietal sulcus and the adjacent inferior parietal cortex (e.g., Seltzer & Pandya, 1982). Alivisatos and Petrides (1997) suggested that the activation observed in the superior parietal cortex and inferior parietal lobule in their PET study of mental rotation represented the process of cognitive spatial transformations. In an fMRI study of mental rotation, Tagaris et al. (1996) found that superior parietal activation increased with a higher proportion of errors in performance. They hypothesized that the increase in error-rate and concomitant increase in activation could be due to an increased difficulty in, and therefore increased demands for, information processing at several stages during performance of the task. A similar result was found by Carpenter et al. (1999) who used increasing angular disparity to manipulate task

difficulty, hence, utilization of neural resources. This graded task design was suggested by data from mental rotation tasks that showed a monotonic increase in the average decision time with increasing angular disparity (Carpenter et al., 1999; Shepard & Cooper, 1982; Shepard & Metzler, 1971).

For the purpose of the present study we used RT (for correct responses) as the behavioral performance measure. There are several good reasons for using RT as an index of performance. For example, it is a continuous variable with no ceiling effect and takes into account individual differences. In the psychology literature, RT has classically been associated with the rate of information processing, or computation, occurring continuously throughout the components involved in performance on a particular task (e.g., McClelland, 1979). Moreover, there is a well-documented relationship between response time and accuracy as was found in the present study. Consequently, we speculate that what makes the cortical regions with a significant relationship between activation and RT in the present study "critical" may be their association with computational efficiency on each task. In other words, we propose that within each network there will be one region that is least efficient computationally and therefore makes the greatest de-

Table 3. Significant Generic Brain Activation Areas in the Mental Rotation Experiment ($p < .0005$)

Region	Talairach Coordinates			BA	Side	Max (FPQ)	No. of Voxels
	<i>x</i>	<i>y</i>	<i>z</i>				
Precuneus	14	-64	42	7	R	2.4	144
Precuneus	-6	-64	48	7	L	2.2	45
Inferior parietal lobule	-38	-42	48	40	L	1.8	17
Dorsal extrastriate cortex	32	-72	20	19	R	1.8	11
Ventral extrastriate cortex	35	-72	4	19	R	1.6	21
Inferior frontal gyrus	52	11	26	44	R	1.8	4
Precuneus	-6	-58	37	7	L	1.8	17
Precuneus	17	-69	37	7	R	1.8	36
Lingual gyrus (visual cortex)	26	-78	-7	18	R	1.6	5

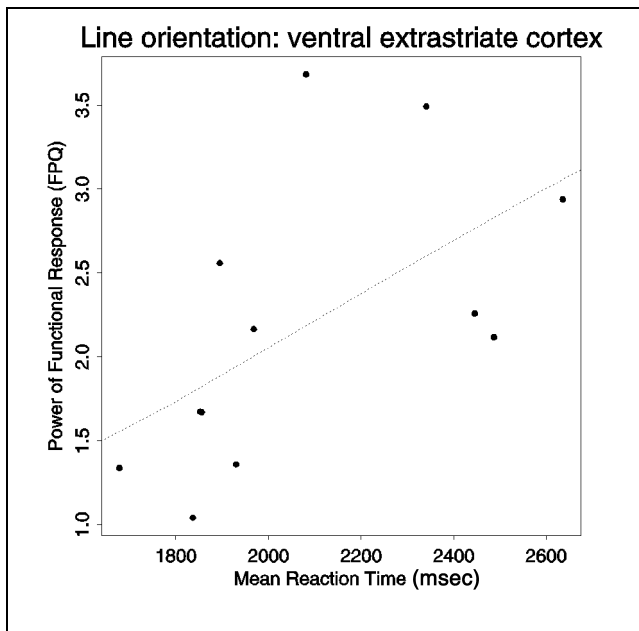


Figure 5. Judgement of line orientation task: Scatterplot of power of functional response (FPQ) versus mean RT in right ventral extrastriate cortex (Talairach coordinates (x, y, z ; mm) 30, $-78, -6$). Dotted line indicates fitted linear regression model (Equation 1).

mands on resources for activation and limits the rate at which the network as a whole can perform the task. This fits neatly with the theoretical assumption that computational efficiency is reflected in the consumption of neural resources (Carpenter et al., 1999).

By this interpretation, the computationally least efficient region or node involved in performance on the line orientation task was located in the ventral visuospatial pathway. Lesion and neuroimaging studies in humans indicate that this pathway is dedicated to elementary form analysis or local feature extraction (see Beason-Held et al., 1998; Doyon & Milner, 1991). Therefore, the process of detecting the matching line orientation within the semicircular arrangement of radial lines may be the rate-limiting step with respect to overall performance on this task. This node or region may also be the source of the N1 component identified in ERP studies as being sensitive to stimulus orientation, especially oblique lines (e.g., O'Donnell et al., 1997).

Conversely, the rate-limiting step in performance of the mental rotation task may be the process of spatial transformations, located according to these and other data in the dorsal (parietal) visuospatial pathway (e.g., Carpenter et al., 1999; Alivisatos & Petrides, 1997; Cohen et al., 1996). Shepard and Metzler (1971) found that the average decision time on their mental rotation task increased linearly and monotonically with increasing angular disparity. They subsequently suggested that, in order to make a decision, subjects align the two objects by imagining one of them passing through intermediate orientations.

It has been argued that the visuospatial systems should be regarded as a dynamic and flexible configuration of several specialized large-scale neural networks, and that the relative amount of activation in each area depends both on the nature and amount of computational demands that a specific task entails (Carpenter et al., 1999; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999). Our data are consistent with this proposal. Furthermore, we suggest that the association between rate of task performance and power of functional response can be used empirically to identify the most computationally inefficient or rate-limiting nodes in a network and that the location of these nodes may vary between regions of a generic network for visuospatial processing as a function of task-specific computational demands.

METHODS

Subjects

Each visuospatial processing task was performed by 12 normal right-handed males; 8 subjects performed both tasks. The age range was 16–43 years (mean age = 29.25 years). Informed consent was obtained according to the guidelines set by the Ethics Committee (Research) of the Institute of Psychiatry and the Maudsley Hospital, London, UK.

Experimental Design

Both experiments adopted a blocked periodic AB design, with five cycles of alternating 30-sec epochs of

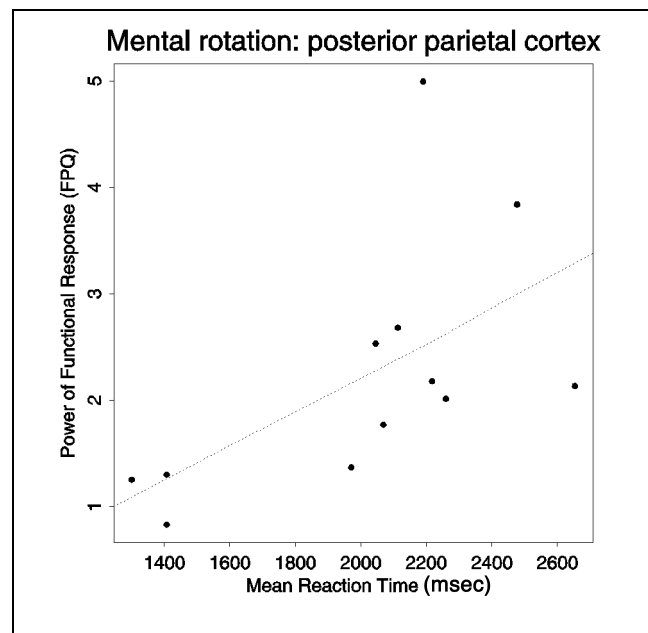


Figure 6. Mental rotation task: Scatterplot of power of functional response (FPQ) versus mean RT in right superior parietal cortex (Talairach coordinates (x, y, z ; mm) 8, $-70, 55$). Dotted line indicates fitted linear regression model (Equation 1).

baseline (B) and activation (A) conditions, giving a total experimental duration of 5 minutes. The baseline condition was always presented first. The tasks were presented visually from a personal computer via an LCD projector to a screen at the foot of the bed on which subjects lay supine during scanning.

The judgement of line orientation task was presented with a fixed intertrial interval of 3.75 sec, i.e., eight trials per epoch. In each trial of the activation condition, the subjects were shown two stimulus lines in the top half of the screen, and an exemplar consisting of nine radial lines arranged in a semicircle in the bottom half of the screen (Figure 7). In each trial of the baseline condition, subjects were asked to ascertain whether the two stimulus lines were on the same level, the lines being always horizontal and thus not involving angle judgement. The two corresponding lines in the exemplar were highlighted for comparison. In the activation condition, the two stimulus lines could be represented by any two of the nine radial lines in the exemplar. The subject had to decide whether these two stimulus lines matched the two highlighted lines in the exemplar.

Subjects performing the mental rotation task were shown two L's in the task condition, situated in the top and bottom halves of the screen (Figure 8). Each L was positioned on one of the four sides of an imaginary

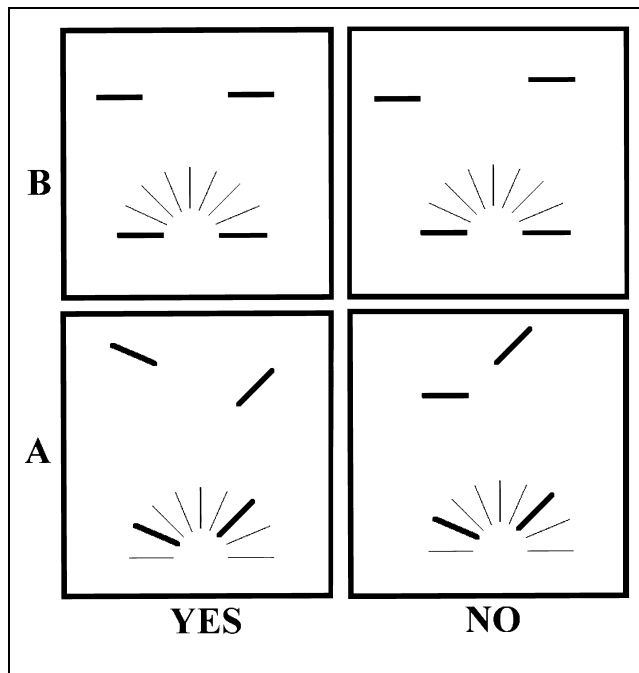


Figure 7. Judgement of line orientation. Examples of baseline (B) and activation (A) trials eliciting “yes” and “no” responses. In the baseline condition, the subject simply decides whether the upper two lines in the display are on the same horizontal level; in the activation condition, the subject decides whether the upper two lines are at the same angles to the horizontal as the pair of lines highlighted in the semicircular array of lines below.

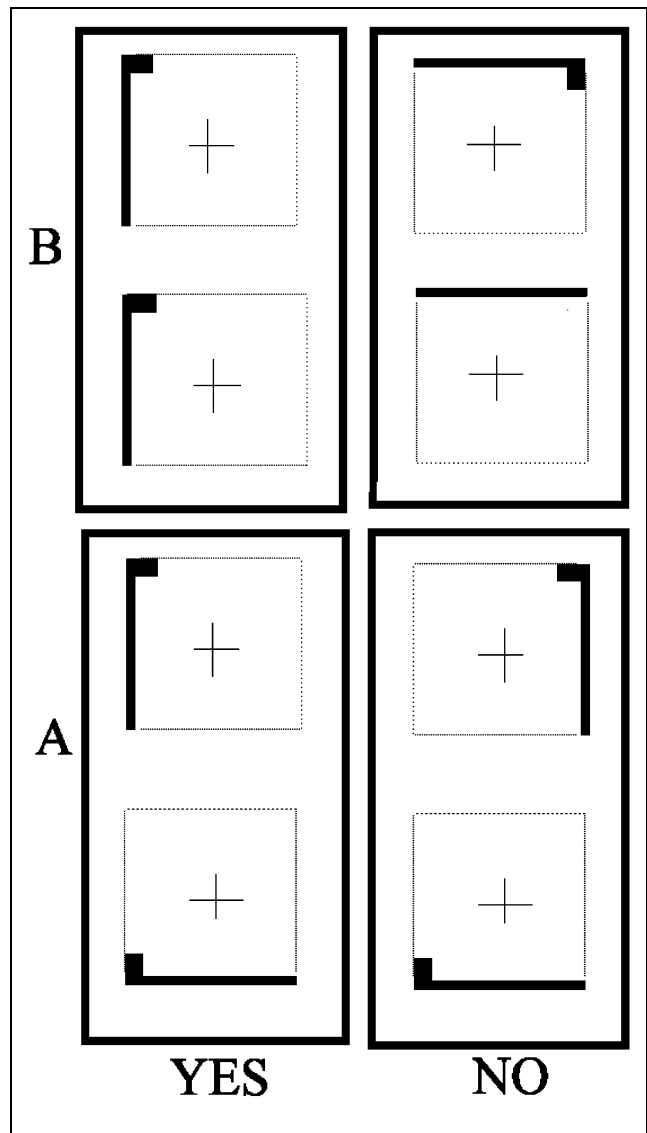


Figure 8. Mental rotation task. Examples of baseline (B) and activation (A) trials eliciting “yes” and “no” responses. In the baseline condition, the subject simply decides whether there are two L shapes displayed; in the activation condition, the subject decides whether the two L shapes can be rotated mentally to an identical configuration.

square, with the top and bottom L's in different positions. Each subject was asked mentally to rotate the bottom L to the same side of the square as the top L was situated, and then to determine whether the configurations of the two L's were the same. There were four possible configurations of the top L: inverted and non-inverted, and their mirror images. The subject indicated a match between the stimuli after rotation by right-handed button press. In the baseline condition, subjects were shown either a L and a l, or two L's. These were always parallel to each other, and the subjects were asked whether two L's had been shown, and to make a button press response only when this was the case. The interstimulus-interval was also 3.75 sec, eight trials per epoch.

In both experiments, the total number of correct responses that can be made was matched between control and task conditions, and balanced over the 5 minutes, to control for motor and visual aspects of the two tasks. Accuracy and latency (RT) of response to each trial was recorded by an MRI compatible button box interfaced to an external personal computer during scanning.

Image Acquisition

Gradient echo, echoplanar MR images were acquired with a 1.5-T GE Signa system retrofitted with Advanced NMR operating console with a quadrature, birdcage head coil. Head stabilization was achieved by mild restraint using foam pads and Velcro fastening over the forehead. One hundred T_2^* -weighted images depicting BOLD contrast (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Kwong et al., 1992; Ogawa et al., 1990) were acquired with an in-plane resolution of 3 mm (TR = 3 sec; TE = 40 msec) at each of 14 near-axial noncontiguous 7 mm thick slices (with 0.7 mm interslice gap) parallel to the anterior commissure–posterior commissure (AC–PC) line.

Image Analysis

After movement correction by realignment and regression of each realigned time series on the vector of estimated translations and rotations in three dimensions (Bullmore, Brammer, et al., 1999), a sinusoidal regression model was fitted by pseudogeneralized least squares to the fMRI time series observed at each voxel (Bullmore, Brammer, et al., 1996). This fitting procedure modeled the autocorrelated residuals of a preliminary ordinary least squares fit as a first order autoregressive AR(1) process. The estimated AR(1) coefficient was then used to prewhiten the time series before obtaining valid estimates of regression model parameters and their standard errors by a second ordinary least squares fit (Bullmore, Brammer, et al., 1996). The regression model included a pair of sine and cosine terms, with coefficients (γ , δ), at the fundamental frequency of alternation between control and task conditions (1/60 Hz). The sum of squared coefficients ($\gamma^2 + \delta^2$) provided an estimate of the power in the signal at the fundamental frequency, which was divided by its standard error to estimate the fundamental power quotient (FPQ). The sign of γ indicated the timing of a signal intensity increase relative to the experimental input function: in these data, $\gamma > 0$ indicated increased signal intensity during the baseline condition; $\gamma < 0$ indicated increased signal intensity during the activation condition (Bullmore, Rabe-Hesketh, et al., 1996). Maps representing standardized power of activation (FPQ) at each intracerebral voxel were registered in standard space (Talairach &

Tournoux, 1988) and smoothed by a 2-D Gaussian filter with full width at half maximum = 7 mm. The median FPQ over all subjects was computed at each voxel and tested for statistical significance by a permutation test procedure described in detail by Brammer et al. (1997). Generically activated voxels identified by this procedure were colored and superimposed on the grey-scale template EPI dataset used for spatial normalization to form a generic brain activation map. Generically activated voxels with median $\gamma < 0$, i.e., signal maximum occurred during the activation condition on average over all subjects, were colored red; activated voxels with median $\gamma > 0$ were colored blue. The one-tailed voxel-wise probability of false positive (Type 1) error was $p < .0005$ for all generic brain activation maps.

To explore the relationship between mean RT and power of functional response throughout the brain, we fitted a simple linear regression model at each intracerebral voxel in standard space:

$$FPQ_{ij} = \mu_i + \beta_1 RT_j + \varepsilon_{ij} \quad (1)$$

Here $FPQ_{i,j}$ is the standardized power of physiological response at the i th voxel in the j th subject; μ_i is the overall mean power of response at the i th voxel; RT_j is the mean RT of the j th individual; $\varepsilon_{i,j}$ is an error term. To test the null hypothesis that $\beta_1 = 0$, we used a permutation test at the level of suprathreshold voxel clusters, similar to that described in detail by Bullmore, Suckling, et al. (1999). In brief, the observed voxel statistic map of β_1 was thresholded against the 2.5 and 97.5 percentiles of the permutation distribution of β_1 , which had been ascertained by repeatedly (10 times) fitting the regression model at each voxel after random permutation of the vector of RTs, and pooling the resulting estimates of β_1 under the null hypothesis over all intracerebral voxels. Applying this probability threshold (two-tailed voxel-wise $p < .05$) at each voxel of the observed maps generated a number of suprathreshold voxel clusters that were spatially contiguous in 3-D. The sum of suprathreshold voxels in each such cluster was tested against a permutation distribution ascertained by applying the same probability threshold to each of the voxel statistic maps generated after random permutation of the RTs vector. The rationale for this nonparametric mode of inference is that test statistics for image analysis that incorporate spatial neighborhood information, such as 3-D cluster size, are generally more powerful than other possible test statistics, such as β_1 or $\beta_1/SE(\beta_1)$, which are informed only by data at a single voxel. Yet theoretical approximations to the null distributions of spatial statistics estimated in imaging data may be overconservative or intractable (Ashburner & Friston, 2000; Bullmore, Suckling, et al., 1999).

Another advantage of hypothesis-testing at cluster level is that the number of tests to be conducted, or search volume V , will generally be less by about two

orders of magnitude than the number of tests that would be required at voxel level. This means that satisfactory Type 1 error control can be attained with less risk of unacceptable Type 2 error. In almost all the analyses reported below, the cluster-wise probability of Type 1 error $p < .005$ was chosen because at this size of test the number of false positive tests PV was less than 1.

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The data reported in this experiment have been deposited in the National fMRI Data Center (<http://www.fmridc.org>). The accession number is 2-2001-111JJ.

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