Functional Connectivity: Integrating Behavioral, Diffusion Tensor Imaging, and Functional Magnetic Resonance Imaging Data Sets

Abigail A. Baird, Mary K. Colvin, John D. VanHorn, Souheil Inati, and Michael S. Gazzaniga

Abstract

■ In the present study, we combined 2 types of magnetic resonance technology to explore individual differences on a task that required the recognition of objects presented from unusual viewpoints. This task was chosen based on previous work that has established the necessity of information transfer from the right parietal cortex to the left inferior cortex for its successful completion. We used reaction times (RTs) to localize regions of cortical activity in the superior parietal and inferior frontal regions (blood oxygen level-dependent [BOLD] response) that were more active with longer response times. These regions were then sampled, and their signal change used to predict individual differences in structural integrity of white matter in the corpus callosum (using diffusion tensor imaging). Results show that shorter RTs (and associated increases in BOLD response) are associated with increased organization in the splenium of the corpus callosum, whereas longer RTs are associated with increased organization in the genu. ■

INTRODUCTION

Central to research in neuroscience is the exploration of the relationship between function and structure in the human brain. Advances in magnetic resonance technologies have allowed investigators to collect both structural and functional data from human subjects in vivo. In terms of cerebral function, blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI) has been used to measure localized cortical activity (Kwong et al., 1992; Ogawa et al., 1992). fMRI signal intensity relies upon changes in the balance of oxyhemoglobin to deoxyhemoglobin in the capillary and venous vascular beds as a function of nearby neuronal activity and is derived from the complex interaction between cerebral blood flow, cerebral blood volume, and oxygen consumption rate. This technique has become a reliable means by which to localize and study cortical function (Sereno, 1998).

More recently, diffusion tensor imaging (DTI) has been increasingly used to explore and characterize white matter structure in vivo (see LeBihan, 2003). Stated simply, DTI takes advantage of the fact that bipolar magnetic field gradient pulses cause 3-D displacement of water molecules within a given area, termed *diffusion*. Anisotropy is a measure that quantifies the extent to which diffusion varies along the sampled axes. Fractional anisotropy (FA) provides information about the shape of the diffusion tensor at each voxel. Thus, it shows the differences between an isotropic diffusion (where the diffusion tensor is represented by a sphere) and a linear diffusion (cigar-shape ellipsoid). Its range is between 0 and 1; 0 means an isotropic diffusion and 1 means a highly directional diffusion (Basser & Pierpaoli, 1996). FA values are thought to reflect microstructural obstacles that might limit diffusion in certain directions. Examples of such obstacles include the integrity of axonal cell membranes, the amount and integrity of myelin around the axons, as well as the number and size of axons. In sum, it has been suggested that FA in white matter originates roughly from the presence and coherence of oriented structures. In practice, higher FA values have been related to increases in white matter organization/integrity (see Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999).

To date, a small number of studies have combined fMRI and DTI data to examine the structure–function relationship. Toosy et al. (2004) found that FA values in the optic radiations correlated with BOLD activity in the visual cortex (in response to a photic stimulation paradigm). The authors interpreted these results as indicating that functional activity within cortical regions is constrained by the structural properties of the anatomical connections subserving those regions. The coregistration of FA and BOLD data has also been used in small number of studies. This method, established by Werring

Dartmouth College

et al. (1999), has most recently been used to generate seed points for a fiber tracking study of connectivity in the human motor cortex (Guye et al., 2003). Simply, Guye et al. (2003) used statistical mappings of BOLD response to place seed points for fiber tracking in the white matter adjacent to the gray matter activated by a motor task. Using this technique, the investigators were able to generate probabilistic connectivity maps from M1 to a number of regions in the cortex and subcortex. Finally, it has been reported that FA values in fronto-parietal white matter correlate strongly with BOLD response (during a working memory task) in closely located gray matter in the superior frontal sulcus and inferior parietal lobe (Oleson, Nagy, Westerberg, & Klingberg, 2003). Taken together, these previous investigations underscore the relevance and utility of combining these types of data.

To test a novel method of combining DTI and fMRI data sets, we chose to examine individual differences on an object recognition task. One remarkable aspect of the human visual system is the proficiency with which it is able to recognize objects, even when they are presented from unusual visual perspectives. Neuropsychological studies of patients with brain damage (Davidoff & Warrington, 1999; Warrington & Taylor, 1973) as well as functional neuroimaging studies (Sugio et al., 1999; Kosslyn et al., 1994) have reliably established the role of the right hemisphere, particularly right parietal cortex, in recognizing objects viewed from an unusual orientation (Figure 1). In contrast, the left parietal cortex has been shown to be involved in recognizing objects presented in canonical representations (Warrington & Taylor, 1973), and the left inferior frontal cortex, in object naming (for a review, see Humphreys, Price, & Riddoch, 1999). Thus, naming objects presented in a prototypical perspective is mediated by the left hemisphere and does not require interhemispheric integration, whereas naming objects presented in an unusual orientation does require interhemispheric integration (Warrington & James, 1988; Warrington & Taylor, 1978). Although there are likely multiple routes of interhemispheric communication involved in object recognition (Kosslyn et al., 1994; Warrington & James, 1988), the pathway necessary for recognizing objects presented in unconventional views is thought to pass through the splenium of the corpus callosum, a region known to connect right and left parietal regions. Patients with selective lesions to this posterior callosal region can normally name objects when they are presented in conventional views, but are impaired when the objects are presented in unusual orientations (Rudge & Warrington, 1991).

In the current experiment, we asked whether the difference between the time required by participants to name objects presented in either prototypical or unusual perspective could predict individual differences in BOLD response in regions previously demonstrated to directly relate to performance on this task. Further, we investigated whether these individual differences in reaction time (RT) and accompanying BOLD response could reveal anything about functional connectivity and information transfer within the intact brain. Specifically, we expected that naming objects presented at unusual perspectives would produce greater differences in activity within the left and right superior parietal regions, as well as the left and right frontal regions. We also hypothesized that individual differences in cortical activity would relate positively to callosal organization, particularly within the splenial region. In sum, we predicted that increased behavioral efficiency on this task (as measured by RT) would be associated with cortical activity (as measured by BOLD) and that increased activity in multiple cortical regions would be associated with greater callosal organization (as measured by FA).

RESULTS

Cortical regions of interest (ROIs) were defined in 15 subjects using a correlational analysis based on the time required to name objects presented from unusual perspectives. Four regions were selected based on both anatomical specificity, as per our a priori hypotheses, and statistical significance: right superior parietal cortex ($x = 57, y = -54, z = 33$), left superior parietal cortex, ($x = -39, y = -78, z = 39$), right inferior frontal cortex ($x = 45, y = 12, z = 36$), and left inferior frontal cortex ($x = -45, y = 30, z = 27$) (see Table 1). The area under the curve was used to determine a mean activa-

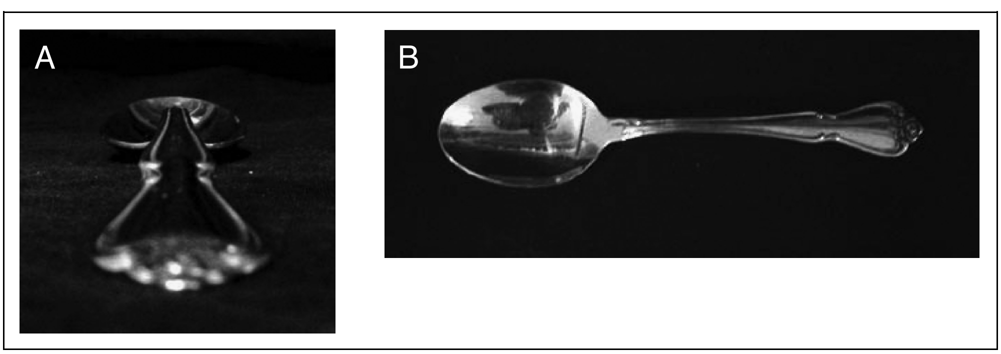

Figure 1. Example of object used in the present study. The object depicted is a spoon shown in both (A) unusual and (B) usual perspectives.

Table 1. Regions of Interest

Region of Activation	*Brodmann's Area*	*Coordinates* *x*	*y*	*z*	*Z score*	*Volume (mm^3)*
Left parietal	7	−39	−78	39	2.60	216
Right parietal	7	57	−54	33	2.75	513
Left frontal	9	−45	30	27	2.86	216
Right frontal	9	45	12	36	2.47	162

Clusters of 5 or more contiguous voxels whose global maxima meet a Z threshold of 2.91, $p < .005$, uncorrected, are reported. Coordinates are from the atlas of Talairach and Tournoux (1988).

tion in each region for each subject. These values were then submitted to a second analysis to examine functional connectivity.

To isolate white matter regions that might underlie the functional connectivity associated with this task, we performed a voxelwise multiple regression analysis in SPM using the changes in BOLD signal measured in the 4 cortical ROIs as the independent variables, and the FA as the dependent measure. This method was used to explore the idea that individual variation in RT and concomitant cortical BOLD response during the task would predict the extent of white matter organization within the pathways that enable communication between these regions. Our results from this analysis revealed a large and highly significant region (threshold set to $p < .005$, uncorrected) within the splenium area of the corpus callosum, a region known to connect the right and left parietal cortices. This region was significantly associated with relatively faster RTs and relatively less BOLD response. When the directionality of the regression was reversed, such that significant cortical regions were associated with longer RTs and increased BOLD response, an area in the genu portion of the callosum was observed (threshold set to $p < .005$, uncorrected). This region of the corpus callosum has been consistently implicated in information transfer between the frontal lobes (see Figure 2A,B and Table 2).

The time required to recognize objects at unusual views was also used in a simple regression analysis to investigate regions of white matter integrity that might be predicted by individual differences in RTs (see Table 2). When the statistical threshold was set at $p < .005$, no significant regions were observed, however, when the threshold was lowered to $p < .1$, it became evident that RT was related to differences in regions of the corpus callosum very similar to those detected by our multiple regression analysis.

DISCUSSION

The present study set out to examine the feasibility of combining fMRI and DTI data sets. Individual differences in RT on a task requiring subjects to name objects presented from an unusual perspective were used to determine cortical activity. Longer RTs were found to be associated with increases in both frontal and parietal cortices. Statistical analysis yielded 4 cortical regions of activity (in the frontal and parietal cortices) from which individual activation values were extracted using an ROI analysis. These values were then used as independent variables in a voxelwise multiple regression analysis, where each subject's FA values were the dependent measure. This analysis yielded a region in the splenium of the corpus callosum that was significantly associated with decreased BOLD response in the 4 ROIs. Additionally, a region in the genu of the corpus callosum was found to significantly relate to increased BOLD response in the 4 ROIs.

Information transfer across the hemispheres was examined by means of a task known to require both right parietal and left inferior frontal participation. Previous research has established that the successful naming of objects viewed from an unusual perspective relies on the functional integrity of both the right parietal (Warrington & Taylor, 1973) and left inferior frontal cortex (Humphreys et al., 1999), as well as the presence of the splenial portion of the corpus callosum (Rudge & Warrington, 1991). Although our results affirm these findings, they significantly extend the previous literature by demonstrating the functionality of the above-described network in the intact brain. Furthermore, there appears to be a behavioral continuum for performance on this task that is neurologically discernable. The current results suggest that an individual's ability to name objects viewed from unusual perspectives can be predicted by the efficiency of this network, measured by regional cortical activity as indexed by BOLD response and white matter integrity as indexed by FA measurements in the splenium of the corpus callosum.

Although previous neuropsychological research has suggested that an intact splenium is necessary for naming objects viewed in unusual orientations, additional research on the object naming abilities of patients with posterior callosal lesions has provided mixed results. Some patients with selective splenial lesions can name objects (Intriligator, Henaff, & Michel,

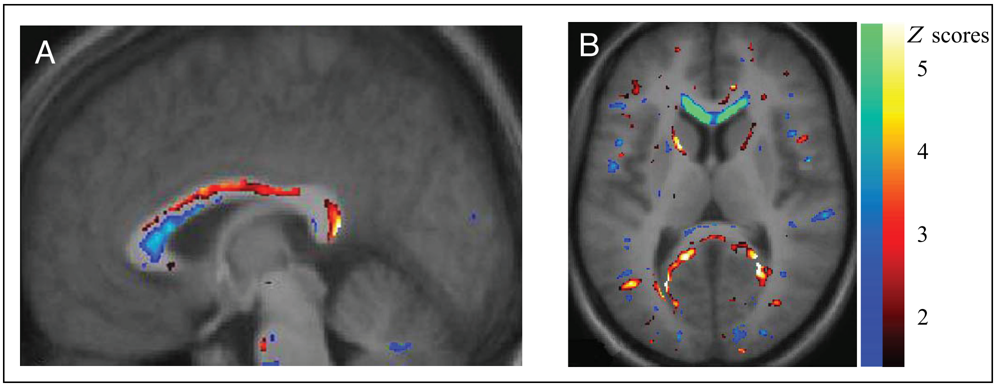

Figure 2. *Z* scale statistical maps illustrating regions of significance based on FA. Positive *Z* scores are depicted in warm color scale, negative in cool color scale. Results from a multiple regression analysis isolated the splenium of the corpus callosum as being associated with relatively faster RTs, and decreased BOLD response. In contrast, the genu of the corpus callosum was significantly associated with longer RTs and increase BOLD response in cortical ROIs on a task that required individuals to name objects presented from unusual perspectives. Results are presented in both the (A) sagittal and (B) axial planes.

2000), whereas others demonstrate complete left hemianomia, which is not limited to objects shown in unusual perspectives (for a review, see Suzuki et al., 1998). The fact that increased FA in the anterior callosal region was significantly associated with increasingly poor performance on the task (see Figure 2) may reflect the existence of multiple callosal channels between the perceptual identification systems of the right hemisphere and the semantic association systems of the left hemispheres. This would be consistent with Geschwind's (1965) proposal that objects' rich somesthetic associations enable object naming via anterior

Table 2. Individual Data

Subject Number	*Genu FA (Dimensionless Units)*	*SD*	*Splenium FA (Dimensionless Units)*	*SD*	*Unusual RT (msec)*	*SD*	*Usual RT (msec)*	*SD*
1	0.6065	0.1148	0.7554	0.0936	1249.59	333.60	850.76	190.40
2	0.7027	0.0738	0.6681	0.0531	1109.10	394.00	818.59	199.10
3	0.7301	0.1206	0.7950	0.0506	927.17	264.20	687.87	150.60
4	0.7742	0.0905	0.6974	0.0504	1282.73	294.70	981.32	145.90
5	0.7721	0.0786	0.7087	0.0626	921.32	228.60	690.74	88.80
6	0.7960	0.1335	0.8176	0.0693	1236.76	301.20	891.66	412.60
7	0.8073	0.1032	0.5993	0.0730	1060.09	284.50	810.92	158.50
8	0.6241	0.0818	0.4758	0.1807	1337.25	334.80	995.00	302.00
9	0.3223	0.0805	0.4500	0.1646	1202.21	95.80	916.94	119.60
10	0.4804	0.0743	0.4066	0.1426	1125.44	308.10	901.48	338.80
11	0.7172	0.0930	0.8088	0.0694	714.53	156.30	592.44	66.10
12	0.7988	0.0935	0.6820	0.0704	1070.52	266.30	776.10	122.30
13	0.7912	0.1040	0.7392	0.0750	1053.19	327.60	856.54	249.60
14	0.3465	0.1144	0.7162	0.0492	1479.16	264.20	1397.32	300.20
15	0.6558	0.0709	0.7282	0.0512	1079.33	301.90	819.89	220.50
Total Mean	0.6617	0.0952	0.6699	0.0837	1123.23	277.05	865.84	204.33
Total SD	0.1606	0.0193	0.1302	0.0432	187.67	73.45	183.20	99.10

ROI data were collected per individual from both the splenium and genu of the corpus callosum. The anterior region was 2160 mm^3 and the posterior region was 1701 mm^3, both regions contained voxels whose global maxima meet a z threshold of 2.91, $p < .005$.

callosal channels when the splenium is damaged. This idea is further supported by the work of Sidtis, Volpe, Holtzman, Wilson, and Gazzaniga (1981), who demonstrated that following partial posterior callosal commissurotomy, transfer of sensory information between the hemispheres was nonexistent; however, the transfer of more cognitive information (i.e., semantic and episodic information) remained intact. The authors concluded that this preservation of function was the result of sparing of anterior portions of the callosum during the sectioning. The present results lend strong support to this, clearly demonstrating that in the intact brain there exist multiple routes by which information can travel from one hemisphere to the other and that these routes vary in their efficiency. In the case where performance on the naming of objects presented at unusual angles was slower, it is conceivable that individuals were recruiting greater cognitive resources (as evidenced by the relatively increased BOLD response) and relying principally on the interaction of the frontal cortices to perform the task. Conversely, it is likely that individuals who demonstrate relatively faster performance are able to do so because they are relying more heavily on the transfer of information between the parietal cortices, and thus making relatively greater use of relatively faster perceptual systems to accomplish the task more efficiently.

Conclusion

By using behavior to predict cortical activity, which was then used to predict white matter integrity, these data represent an important advance in the available methods for combining magnetic resonance data sets to examine functional connectivity. Traditional methods have used behavior (e.g., RT) to predict BOLD response and/or FA across subjects. The present study underscores the utility of a stepwise process whereby more of the variance across individuals was accounted for by using an index of cortical activity (derived from RT) to index FA. These results suggest that behavioral performance on a task is related to cortical activity in multiple regions, as well as the integrity of the fibers connecting them. Although the interpretation of these results must remain preliminary, the present findings demonstrate the feasibility of using unique and convergent neuroimaging techniques to examine specific behavioral phenomena.

METHODS

Participants

Fifteen normal right-handed adults (9 women, mean age = 25.9 years) participated in the experiment. All participants gave informed consent. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Participants either received monetary compensation or volunteered as part of an fMRI workshop. Data from 3 additional participants were excluded because of technical difficulties.

Experimental Task

Trial onsets were time-locked to the beginning of volume acquisition, so that each trial was the length of 1 TR (3 sec). During each trial, a digital photograph of a common object was presented in either a prototypical (usual) or an unusual perspective for 1500 msec. Stimuli were created based on those used by Warrington and Taylor (1973). The present study replicated these stimuli in digital photograph form (instead of line drawings). On each trial, participants immediately pressed the response button upon determining the name of the object, and then said the name aloud. To minimize priming effects, the unusual orientation always preceded the usual orientation of the same object. Because our a priori hypotheses were based on response to the unusual views, analyses were based exclusively on data from the unusual view condition.

During each of the 2 functional runs, 25 usual, 25 unusual, and 24 fixation trials were pseudorandomly intermixed. The fixation trials were included to introduce jitter into the time series so that unique estimates of the hemodynamic responses for the trial types of interest could be computed (Ollinger, Shulman, & Corbetta, 2001).

Behavioral Apparatus and Imaging Parameters

Visual stimuli were presented using an Apple G3 laptop computer running PsyScope 1.2.5 software (Cohen, MacWhinney, Flatt, & Provost, 1993). Stimuli were projected to participants with an Epson (model ELP-7000) LCD projector onto a screen positioned at the head end of the bore and viewed through a mirror mounted on the head coil. Participants' naming times were recorded using hand-held, fiber-optic buttons interfaced with a PsyScope button box (New Micros, Dallas, TX).

All images were acquired using a 1.5-T scanner (General Electric Medical Systems Signa CV/Nvi LX8.4, Waukesha, WI) with a standard head coil. Anatomical images were acquired using a high-resolution 3-D spoiled gradient recovery sequence (128 sagittal slices, TR = 7.7 sec, TE = 3 msec, flip angle = 15°, voxel size = 1 × 1 × 1.2 mm). Functional images were collected in runs using a gradient spin-echo, echo-planar sequence sensitive to BOLD contrast (T2*) (TR = 3 sec, TE = 40 msec, flip angle = 90°, 3.75 × 3.75 mm in-plane resolution). During each functional run, 88 volumes of axial images (25 slices, 4.5 mm slice thickness, 1-mm skip between slices) were acquired.

Diffusion tensor images (DTI) were acquired using a diffusion weighted single-shot spin-echo EPI sequence, using the following parameters: TR = 10 sec, TE, 88 msec, flip angle, 90°, slice thickness = 2.5 mm, FOV = 240 mm, matrix size = 128 × 128, 8 excitations, acquisition time (9 min, 20 sec). Diffusion weighting was performed along 6 independent directions, with b value 1000 sec/mm^2. A reference image (b = 0 sec/mm^2) was also acquired.

Data Analysis

Behavioral Data

For each trial, a time to name the presented object was recorded. These naming times were grouped by object orientation (usual or unusual). Within each group, only naming times within 3 *SD* from the mean were included (see Table 2). The time required to name usual objects was used in the final analysis.

Diffusion Tensor Imaging Data

Using software written by Dr. Inati, the averaged diffusion weighted images and 6 apparent diffusion coefficients were calculated, from which 6 independent elements of the diffusion tensor were determined for each voxel. Eigenvalues and eigenvectors of the tensor were calculated using a Jacobi transformation. FA was calculated from the eigenvalues as described by Basser and Pierpaoli (1998) and used for all subsequent analyses.

Functional Magnetic Resonance Imaging Data

fMRI data were analyzed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995). For each functional run, data were preprocessed to remove sources of noise and artifact. Functional data were corrected for differences in acquisition time between slices for each whole-brain volume, realigned within and across runs to correct for head movement, and coregistered with each participant's anatomical data. Functional data were then transformed into a standard anatomical space (3-mm isotropic voxels) based on the ICBM 152 brain template (Montreal Neurological Institute), which approximates the atlas space of Talairach and Tournoux (1988). Normalized data were then spatially smoothed (6 mm full width half maximum) using a Gaussian kernel. Analyses took place at 2 levels: First, within-subject activity was examined using a fixed-effects model; second, a random effects model (Holmes & Friston, 1998) was used to explore the data across subjects.

Statistical analyses were performed on individual subjects using a general linear model incorporating task effects modeled with a canonical hemodynamic response function and its temporal derivative (Friston et al., 1998), as well as mean, linear, and quadratic trends for each of the 2 runs. This model was used to compute parameter estimates (β) and t contrast images for each comparison (usual and unusual views) at each voxel.

To identify regions for which the level of activation across participants was related to the time required to name objects shown at unusual perspectives, a simple regression analysis was performed on the average images for the unusual view condition. Individual contrast images were submitted to a second-level, random-effects regression analysis to create mean t images (threshold $p < .005$, $t = 2.91$ uncorrected for multiple comparisons). Based on previous reports of increased BOLD response during sustained attention and cognitive effort (Coull, Frackowiak, & Frith, 1998; Barch et al., 1997), regions that were increasingly active with longer time on task were selected. An automated peak-search algorithm identified the location of peak activations based on voxelwise t values. An extent threshold of 5 contiguous voxels was applied to activated clusters meeting the voxel-level threshold.

For each participant, hemodynamic response functions (10 frames long) for each trial type were then estimated across each ROI using a finite impulse response formulation of the general linear model (Ollinger et al., 2001; Burock & Dale, 2000). The parameter estimates for this model (calculated using the least-squares solution to the general linear model) are estimates for the temporally evolving response magnitude at each of the 10 points in peristimulus time, selectively averaged across all occurrences of that peristimulus time interval. This approach has recently been implemented by Poldrack et al. as an add-on toolbox to the SPM analysis software (SPM ROI Toolbox, sourceforge.net/projects/spm-toolbox/). This method resulted in a single value for each region, per individual. These values were later used in a regression analysis to predict individual differences in diffusion anisotropy.

Regression Analysis

Single BOLD values in 4 ROIs (left and right frontal, left and right parietal) per subject were entered as independent variables in a regression analysis using SPM, the FA images of each subject were used as the dependent measure. This analysis yielded ROIs that were predicted by BOLD response, FA values were sampled per subject from these regions.

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Reprint requests should be sent to Abigail A. Baird, Department of Psychological and Brain Sciences, Dartmouth College, Moore Hall, Hanover, NH 03755, or via e-mail: abigail.a.baird@dartmouth.edu.

The data reported in this experiment have been deposited with The fMRI Data Center archive (www.fmridc.org). The accession number is 2-2005-118E6.

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