Relating Structural and Functional Connectivity to Performance in a Communication Task

Jeffrey T. Duda¹, Corey McMillan², Murray Grossman², and James C. Gee³

¹ Department of Bioengineering, University of Pennsylvania, USA
jtduda@seas.upenn.edu

² Department of Neurology, University of Pennsylvania, USA

³ Department of Radiology, University of Pennsylvania, USA

Abstract. Measures from event-related functional MRI, diffusion tensor imaging tractography and cognitive performance in a language-based task were used to test the hypothesis that both functional and structural connectivity provide independent and complementary information that aids in the identification of network components most related to the neurobiological basis for language and cognitive processing. Structural connectivity was measured by averaging fractional anisotropy (FA) over a geometric fiber bundle model that projects local white matter properties onto a centerline. In the uncinate fasciculus FA was found to predict performance on a measure of decision-making regarding homonym meaning. Functional synchronization of BOLD fMRI signals between frontal and temporal regions connected by the uncinate fasciculus was also found to predict the performance measure. Multiple regression analysis demonstrated that combining equidimensional measures of functional and structural connectivity identified the network components that most significantly predict performance.

1 Introduction

In this paper functional subnetworks in the brain are examined using MRI to measure both structural connectivity (SC) and functional connectivity (FC). Additionally, the influence on behavior of both SC and FC is examined to determine the degree to which each provides unique information as well as how this information may be used to identify the parts of a network that are most influential on behavioral performance. FC involves co-activation of brain regions during performance of a task while brain recruitment is monitored with fMRI. SC is related to the long tract white matter projections that may integrate recruited brain regions biologically. The use of diffusion tensor imaging (DTI) in tract-specific studies has received much attention recently and has demonstrated the utility of atlas-based methodologies [1,2]. Geometric models of fiber bundles are typically used to create arc-length parameterizations of diffusion properties [3,4,5]. Statistical analysis of diffusion properties of fiber bundles may be enhanced by reducing dimensionality by projecting local properties onto a skeleton [2] or medial-axis [1]. Inspired by the success of these approaches, we

developed an atlas-based approach for using diffusion tensor tractography to determine geometric models of fiber bundles that connect functionally defined cortical regions of interest. Combining FC and SC, and further integrating behavioral data, provides important insight into the nature of the relationship between structure and function in the brain and their respective roles in determining behavior [6,7,8]. In this study, we demonstrate how SC and FC may be used to examine small, functionally defined subnetworks in the brain during performance of a common language task. Functionally defined cortical regions are used along with a population-averaged diffusion tensor atlas to identify the white matter pathways that provide the basis for biological connectivity. A centerline-based method is used to provide a geometric model that facilitates the equidimensional comparison of FC and SC within a network. Behavioral data are used to identify the relative contributions of function and structure, and the degree to which each provides unique insight into behavior.

2 Methods

Functionally defined cortical regions and the white matter pathways that connect them are used to measure both structural and functional connectivity in individual subjects. Multiple regression analysis of cognitive performance scores is then used to determine the components of the subnetworks that most influence performance and the relative predictive strengths of the connectivity measures. A set of ten subjects (6 female, mean age of 23.5 years) had T1, functional and diffusion tensor images acquired. These are used to examine the relationship between structure and function and their relationship to performance in the functional task.

2.1 Subnetworks in the Brain

We investigate a hypothesis that suggests language processing is supported by the interaction of two cortical subnetworks [9]. This hypothesis specifically focused on the strategic process of minimizing ambiguity during language production, defined as an individuals use of an unambiguous word (e.g. "cage") instead of a semantically ambiguous word (e.g. "pen") to make the meaning of an utterance more clear. The cortical regions and MNI coordinates of peak activation are listed in figure 1. A forced choice paradigm in which subjects were instructed to make the choice that resulted in the most clear sentence meaning (e.g. reduced ambiguity) was used. The proportion of unambiguous choices was used as the measure of cognitive performance. It has been proposed that this process of minimizing ambiguity relies on the recruitment of two subnetworks: a lexical semantic network situated in posterolateral temporal cortex (PLC) and anterior temporal cortex (ATC) to support retrieval of a word form; a strategic decision-making network to support probabilistic resources in the dorsolateral prefrontal cortex (DLPFC) (e.g. evaluating the likelihood that a word like "pen" has multiple meanings), risk-based resources in orbital frontal cortex (OFC) (e.g. using

"pen" in an ambiguous context has a higher "risk" of being misinterpreted), and an integration mechanism in inferior parietal cortex (IPC) that brings together probabilistic and risk information to inform a decision. To evaluate the biological feasibility of these networks, the current work evaluated the white matter connections between the activated regions and measured FC between all regions.

2.2 Analysis of fMRI

For the examination of FC the previously cortical regions were examined. A region-growing process was used to create 5 regions of equal volume. Each peak activation coordinate was used as a seed for the region growing algorithm in which each region was grown iteratively by examining neighboring voxels in the region and adding each of the 8-connected neighbors in a template-based brain mask created in MNI space. The process iterated until each region had a volume of 480mm^3 . In each subject, an average time-course BOLD fMRI signal was calculated for each activated region. To estimate FC between regions, a Pearson's correlation coefficient was calculated using each regions' averaged signal.

2.3 Analysis of DTI

Diffusion tensor tractography in individual subjects is highly subject to false-positive connections, but recent work has shown that the improved SNR provided by a population atlas provides an appropriate space for identifying fiber bundle geometry [10]. To achieve this, a multivariate atlas was created from a data set consisting of 26 healthy young adults for whom both high resolution T1 images and DTI were acquired. The 10 subjects examined in this study were all included in this atlas-building data set. The set of all subjects' high resolution T1 weighted images were registered to the template using Symmetric Normalization as implemented in Advanced Normalization Tools [11]. This was accomplished through the use of a multi-resolution, non-rigid registration algorithm to optimize a cross correlation metric under the constraints of a diffeomorphic transformation model [11]. A brain mask of the template was propagated to each subject's T1 weighted image. These skull-stripped T1 weighted images were then registered to the FA image derived from each subject's diffusion tensor image. The intra-subject transforms were composed with the T1 atlas transforms in order to transform the each subjects' tensor data into template space using the preservation of principle technique along with log-Euclidean linear interpolation.

The diffusion tensor component of the atlas was used to perform whole brain, deterministic fiber tractography [12]. Landmarks were manually placed in the T1 component of the atlas in order to extract well defined white matter fiber bundles [13]. The functionally activated regions were warped from MNI space into the template space and dilated by 5mm to extend into the white matter for use as target regions to identify fiber bundles that connected two regions of interest. A popular approach to avoiding partial voluming bias is to incorporate a centerline or skeletonization technique in which an FA value at each point is determined by finding the maximum FA in the local neighborhood [2,1]. Here

we use a template-fiber approach where an elliptical cross-section is defined at each point along the centerline and used to identify local maxima. For each white matter tract, the atlas-based tractography provided a bundle of streamlines, each of which was parametrized by arc-length to extend from 0.0 to 1.0. A BSpline was then fit to the set of all points from all streamlines in each bundle to obtain a single centerline that lies in the core of the fiber pathway of interest. For each point along the model pathway, a tangent was calculated and used to determine a perpendicular plane. The intersection of this plane with each of the streamlines in the bundle defines a set of points. The normal and binormal vectors were used to re-parameterize the intersection points into 2D coordinates. Graham's scan method was used to determine the convex hull that encloses the set of intersection points [14], and least-squared method was applied to the points on the hull to define an elliptical cross-section [15]. These model pathways were then used to examine each subject's FA image. At each point along the average pathway, the maximum fractional anisotropy within the associated elliptical cross-section was projected to the centerline. To obtain a single SC value for the entire fiber bundle, the FA values were averaged over the length of the centerline.

2.4 Relating Structure and Function to Behavior

Behavioral data was used to explore the extent to which FC and SC provide unique and relevant information regarding behavior. The proportion of responses in which subjects minimized ambiguity was used to identify the components of the network that most directly influence performance in the functional task. Multiple regression analysis was performed to examine the relationship between FC and SC between regions for which there exists a direct white matter connection. Both FC and SC were used as independent variables to quantify their relationship to the behavioral scores.

3 Results

The functionally activated regions illustrated in figure 1 were used to identify the white matter tracts of interest revealing a biological network made up of the uncinate fasciculus (UF), arcuate fasciculus (AF), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior frontal-occipital fasciculus (IFO) and an inferior-superior fiber bundle running along the arcuate fasciculus that will be referred to as the vertical aspect of the arcuate fasciculus (AFv). The elliptical cross-sections used to define local maxima along each template fiber are illustrated in figure 1 and are consistent with known neuroanatomy. The results of the SC and FC measurements are summarized in table 1. The posterior lateral temporal cortex (PLC) had the highest average FC values. This region also has the highest number of white matter connections as it directly connects to every other cortical region in the network.

To facilitate the comparison of structure and function, the functional analysis was limited to examining FC between regions that were determined to have direct

Fig. 1. A) Functionally activated cortical regions were used to determine an MNI coordinate of peak activation in posterior lateral temporal cortex (PLC=-64 x -38 x 6), anterior temporal cortex (ATC=-54 x 22 x -6), dorso-lateral prefrontal cortex (DLPFC=-50 x 20 x 42), inferior parietal cortex (IPC=-32 x -64 x 58) and orbital frontal (OFC=-54 x 2 x -34) B) The cortical regions were used to identify white matter fiber bundles that connected any two regions of interest. This resulted in the identification of the uncinatus fasciculus (yellow), arcuate fasciculus (pink), orbito frontal-occipital fasciculus (orange), inferior longitudinal fasciculus (purple), superior longitudinal fasciculus (light blue) and a vertical aspect of the arcuate fasciculus (green)

biological connections. For each participant, a behavioral score was determined by the ratio of times that they correctly chose the unambiguous alternative. The mean score was 0.717 ± 0.14 . For each white matter tract the FC and SC values were used as independent variables in multiple linear regression on the behavior scores, using R. The resulting p-values, summarized in figure 2, were FDR corrected and connectivity in the UF was found to be most significantly correlated ($p = 0.014, r^2 = 0.810$) to performance. In order to examine relative strengths, SC and FC are standardized against one another to calculate their beta coefficients which gives $\beta_{FC} = 0.425$ and $\beta_{SC} = 0.681$. To illustrate the

Table 1. Functional connectivity was measured using a Pearson’s correlation for each pair of regions (upper triangular values) and structural connectivity was measured for each pair of regions that had a direct white matter connection by examining FA (lower triangular values)

	IPC	DLPFC	OFC	ATC	PLC
IPC	-	0.59 ± 0.29	0.61 ± 0.14	0.49 ± 0.26	0.49 ± 0.22
DLPFC	0.62 ± 0.07	-	0.27 ± 0.33	0.49 ± 0.19	0.69 ± 0.12
OFC	-	-	-	0.38 ± 0.36	0.68 ± 0.15
ATC	-	-	0.50 ± 0.10	-	0.60 ± 0.24
PLC	0.64 ± 0.08	0.66 ± 0.07	0.68 ± 0.05	0.60 ± 0.12	-

Fig. 2. Both structural and functional connectivity in each connection were used in a multiple linear regression analysis of performance. FDR-corrected p-values are shown here. Connectivity in the uncinate ($p = 0.014$) was most significantly correlated to performance.

Fig. 3. Regression analysis of cognitive performance was examined independently to examine correlations with (A) structural connectivity and (B) functional connectivity for the uncinate fasciculus

unique contributions of each connectivity measure, both both FC and SC in the UF were independently used as independent variable in a regression analysis of performance. Correlating SC to performance resulted in $p = 0.003, r^2 = 0.657$ while FC to performance resulted in $p = 0.034, r^2 = 0.379$. These results are illustrated in figure 3. A regression analysis using SC to predict FC resulted in $p = 0.308, r^2 = 0.020$.

4 Discussion

This study demonstrated that SC and FC provide unique and converging evidence for identifying the components of a brain network that are most significantly related to cognitive performance. The use of geometric models for white

matter fiber bundles provided a robust framework for quantifying tract-wide metrics of structural integrity that directly correlated to a behavioral measure. FC between regions was quantified using the Pearson's correlation of average BOLD fMRI signals. Using these connectivity measures in a multiple regression analysis implicated the UF as being the network component that most directly influences performance. When examined independently, both SC and FC in the UF significantly correlated to performance, but the relatively weak correlation between SC and FC suggests that each provides unique information about network connections.

The identification of the UF as the network connection that most mediates performance is interesting as it provides the connection between a region commonly associated with language processing (ATC) and a region commonly implicated for decision-making (OFC). A connection between these regions supports the hypothesis that ambiguity minimization is supported by the interaction of two cortical subnetworks. The UF provides the only direct connection between these regions, but an indirect connection is provided by the ILF and IFO which both connect to the PLC, a region associated with language processing. While the UF is not the only direct connection between the OFC and a language processing region, it is the shortest connection, and is thus consistent with studies of both SC [16] and resting-state FC [17] that have revealed evidence suggesting that shorter connective distances are associated with higher connectivity.

The use of template fibers with elliptical cross-sections provided an effective geometric model for examining white matter fiber bundle properties, but a great deal of opportunity exists for the development of more biologically relevant measures of SC. Here, these models were purely template-based and used to examine FA in individual subjects. Using these template-based models as a basis for fitting subject-specific models from subject-space tractography could potentially provide a more sensitive measure of SC and could provide a framework that explicitly examines the geometry of white matter pathways as well as the properties of the underlying tissue. Additionally, the use of metrics that leverage the expected fiber orientation provided by the geometric model may be useful as they incorporate more widespread information about the fiber tract as opposed to the purely local measure provide by FA [18].

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