Analysis of Structural Connectivity of the Human Language Pathways Using Diffusion and Functional Magnetic Resonance Imaging

A. Mishra[1], A. T. Newton[1], A. W. Anderson[1], J. C. Gore[1], V. L. Morgan[1], and Z. Ding[1]

[1]VUIIS, Vanderbilt University, Nashville, TN, United States

Introduction

Involvement of frontal and temporal cortical regions in human language processing was reported by Broca and Wernicke over a century ago. Electrophysiological investigations on primates along with tracer injection studies suggest that there might be two connections between the auditory cortices and the prefrontal area [1]. In this work we focused on a quantitative assessment of the human auditory and language systems *in vivo* to have a deeper insight beyond this structural connectivity. The specific purpose of the study is to examine the strength of structural connections among functionally active language regions with integrated functional and diffusion magnetic resonance imaging (MRI). Two fiber pathways connecting *i*) Broca's area to the pre-motor region and *ii*) Broca to Wernicke's area were considered for this analysis.

Methods

Twelve healthy adults were imaged with three different imaging protocols (T$_1$-weighted, diffusion weighted and fMRI) with full brain coverage on a dedicated 3T Philips scanner (Netherlands). The high resolution T$_1$ weighted data (1x1x1 mm^3) were primarily used to aid in accurate localization of functionally active language regions and fiber pathways connecting them. Functionally active regions (Fig. 1) were extracted using standard t-tests on motion- and slice-time corrected fMRI data (3.75x3.75x5 mm^3) acquired when subjects were performing designated language tasks. Resulting t-maps were thresholded and co-registered with T$_1$ weighted data, both of which were then co-registered with diffusion weighted images (DWI, 2x2x2 mm^3) using SPM2. Fibers were tracked with diffusion tensor images (DTI) that were reconstructed from DWI, using the detected functional regions as seeds. As these regions reside in the gray matter that has low fractional anisotropy (FA) and ambiguous dominant directions, tractography was carried out based on a probabilistic method, as described by Eqn. 1-3 below. Specifically, at each step of fiber tracking, a unit random vector r_i is added to the major eigenvector v_i, but its relative magnitude is inversely related the local FA value. In the gray matter where FA is low, r_i carries more weight hence allowing more possible tracking directions than in white matter where FA is high. This probabilistic tracking algorithm is similar in nature to that in [2] but is associated with adaptive modulation and an anisotropic interpolation [3]. The initial seeds are the voxels within a sphere centered on the centroid of the activated region with a radius of 3 mm. The connecting fibers are those which terminated on any voxel in the target region. The fibers were traced from each end for both expected regions of connectivity.
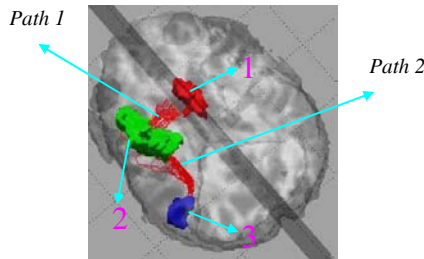

Fig. 1 3-D view of functionally active regions. 1. Pre-motor, 2. Broca & 3. Wernicke's region

$$s_{i+1} = s_i + \Delta t . \delta_i \qquad (1)$$

$$\delta_i = \frac{\tau . v_i + r_i}{\|\tau . v_i + r_i\|}, \{\delta_i . \delta_{i-1} > 0.2, if\, FA > 0.2\} \quad (2)$$

$$\tau = \tau_{min} + (\tau_{max} - \tau_{min}) . \frac{e^{FA} - 1}{e - 1} \qquad (3)$$

$$where\ \tau_{min} = 0.3, \quad \tau_{max} = 3.0$$

s_i – time varying position vector, Δt –step size

δ_i – unit vector modulated with a random vector r_i

and i is the discrete time step

Case No.	Path 1 Volume	Path2 Volume
1	1156.2	1401.6
2	1308.2	1728.6
3	1273.2	1156.2
4	2347.8	1483.3
5	1319.9	1647
6	1413.4	1214.7
7	1343.1	1086.3
8	2079.2	1191.4
9	1343.1	1039.6
10	1798.9	1401.6
Mean	1538.3	1335
Stdev	397.83	235.53

Table 1. Volume of connecting fiber bundle (mm^3), *Path1:* Pre-motor to Broca's area. *Path2:* Broca to Wernicke's area.

Results

The process was repeated for 100 iterations from both regions or until at least 50 fibers were tracked, as we observed the connecting fibers were either repeated or had very similar shape after 100 iterations. Fig. 1 shows typical fiber connections between language regions (denoted with different colors). The strength of structural connectivity is measured by the volume of the fiber bundle connecting them. The volume of fiber bundle was calculated by approximating the cross-sectional area of the bundle on planes normal to mean pathway. The fiber tracking was effectively performed on ten normal subjects all having left dominant hemisphere in which we observed strong connections in both fiber pathways (*Path1:* Pre-motor to Broca's area and *Path2:* Broca to Wernicke's area). Quantitative measures of the connection strength are shown in Table 1. We have not observed any direct fiber connections between Pre-motor and Wernicke's area in this study, which implies functional connections between them may be mediated by Broca's area.

Discussions

This is our initial attempt to quantify the structural connectivity between language related regions. The probabilistic approach employed is particularly advantageous in this analysis because we are interested in connecting areas that are located in the gray matter and hence susceptible to the effects of noise and partial volume averaging. An adaptive addition of a random vector increases the chance of tracking any possible fiber pathways that connect functionally active regions. However, the effect of random vector added to the major eigenvector is significantly reduced in white matter due to its high FA value. As a result the fibers more closely follow the direction of major eigenvector.

Acknowledgements

References

[1] Kass J. H. *et. al.,* What and Where Processing in Auditory Cortex [News]. *Nat. Neurosci.* 2, 1045-1047, 1999.

[2] Hagmann P. *et. al.,* DTI Mapping of Human Brain Connectivity: Statistical Fiber Tracking and Virtual Dissection, *NeuroImage,* 19, 545-54, 2003.

[3] Mishra A. *et. al.,* Unified Framework for Anisotropic Interpolation and Smoothing of Diffusion Tensor Images, *NeuroImage,* 31, 1525-35, 2006.