Comparative Evaluation for Brain Structural Connectivity Approaches: Towards Integrative Neuroinformatics Tool for Epilepsy Clinical Research

Sheng Yang, BS¹, Curtis Tatsuoka, PhD², Kaushik Ghosh, PhD³, Nuria Lacuey-Lecumberri, MD², Samden D. Lhatoo, MS, FRCP², Satya S. Sahoo, PhD¹

¹Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, OH; ²Neurological Institute, University Hospitals Case Medical Center, Cleveland, OH; ³Department of Statistics, University of Nevada, Las Vegas, NV; ⁴Department of Neurology, Case Western Reserve University, Cleveland, OH

Abstract

Recent advances in brain fiber tractography algorithms and diffusion Magnetic Resonance Imaging (MRI) data collection techniques are providing new approaches to study brain white matter connectivity, which play an important role in complex neurological disorders such as epilepsy. Epilepsy affects approximately 50 million persons worldwide and it is often described as a disorder of the cortical network organization. There is growing recognition of the need to better understand the role of brain structural networks in the onset and propagation of seizures in epilepsy using high resolution non-invasive imaging technologies. In this paper, we perform a comparative evaluation of two techniques to compute structural connectivity, namely probabilistic fiber tractography and statistics derived from fractional anisotropy (FA), using diffusion MRI data from a patient with rare case of medically intractable insular epilepsy. The results of our evaluation demonstrate that probabilistic fiber tractography provides a more accurate map of structural connectivity and may help address inherent complexities of neural fiber layout in the brain, such as fiber crossings. This work provides an initial result towards building an integrative informatics tool for neuroscience that can be used to accurately characterize the role of fiber tract connectivity in neurological disorders such as epilepsy.

1. Introduction

Recent advances in neuroscience technologies to study brain connectivity are providing new techniques to better understand the role of both structural and functional networks in complex neurological disorders [1]. The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative aims to replicate the success of the Human Genome Project (HGP) and bring together similar resource and scientific expertise to accelerate our understanding of the human brain from cellular to neural circuit dynamics. The development of novel neuroscience technologies, such as molecular, genetic, anatomic, electrical and optical recording tools, are driving new insights into neural cells, brain circuit maps, and dynamics of brain interconnections in both healthy persons and patients suffering from severe neurological disorders [1]. These technologies, including informatics tools, are leading to better diagnostic and therapeutic approaches in many neurological disorders, such as depression, Alzheimer’s Disease, and epilepsy. In this paper we focus on epilepsy, which is the most common serious neurological disorder affecting 50 million patients worldwide with 5.1 million people in the United States diagnosed with epilepsy or seizure disorder [2].

Epilepsy is known to be a disorder of cortical network organization that leads to disruption of network activity with generation and propagation of abnormal electrical signals called seizures [3]. Epileptic seizures may be initiated at specific brain locations, which are called focal seizures, or may involve the whole cortex, which are called generalized seizures. The localization of brain regions involved in the three stages of seizures, namely onset, propagation, and termination, serves as a vital tool in diagnosis and treatment of epilepsy patients. Further, about 30% of epilepsy patients do not respond to treatment methods. These patients are considered for surgical intervention and undergo a systematic presurgical evaluation, which involves: (a) identification of brain regions involved in seizure onset that may be removed for seizure freedom, and (b) mapping of brain regions that involve important functions such as the speech center that need to be preserved during surgery [4-6]. The accurate characterization of the temporal and spatial features of seizure networks is an important unresolved problem in epilepsy clinical research, which has led researchers to use both functional and structural connectivity approaches to address the challenge.
Functional networks in epilepsy are computed using linear or nonlinear coupling measures over electroencephalogram (EEG) data that are recorded using either scalp electrodes or intracranial electrodes [7-11]. However, functional networks computed from EEG data present only a partial view of the brain connectivity, since the propagation of seizure to different portions of the brain requires either direct or indirect structural connections. Although there has been some work on correlating slow time scale of fMRI and Blood Oxygen Level Dependent (BOLD) to structural network, the role of structural network in functional networks computed from fast time scale measurements such as EEG is not well understood [3]. Therefore there is a clear need for integrative analysis of functional network and structural connectivity information to: (a) accurately characterize seizure networks, (b) their extent, and (c) analyze the brain connectivity properties across different categories of epilepsy. This integrative brain connectivity approach can address the unique challenges associated with understanding seizure network characteristics through systematic analysis of multi-modal neurological data (Figure 1 illustrate the overall view of this integrative approach).

In this paper, we describe our work towards development of an integrative analysis platform for structural and functional connectivity analysis using de-identified patient data from the Epilepsy Monitoring Unit (EMU) at the University Hospital Case Medical Center (UHCMC). Our work is part of a multi-center project to identify biomarkers for a poorly understood condition called Sudden and Unexpected Death in Epilepsy (SUDEP). The Center for SUDEP Research (CSR) is funded by the National Institute of Neurological Disorders and Stroke (NINDS) and involves 14 EMUs across the United States and the United Kingdom. The CSR project is collecting multi-modal neurological data from enrolled patients, which includes genetic, MRI, electrophysiological signal data, and demographic information, to support large cohort studies in epilepsy. In contrast to existing work on computing functional networks in epilepsy patients, this paper performs a comparative evaluation of two different approaches for computing structural networks using diffusion MRI data recorded from an epilepsy patient.

2. Background: Computing Brain Structural Networks

The structure and layout of brain has been studied using diffusion MRI with many advanced techniques being developed over the past decade [5, 12-15]. Diffusion-weighted imaging (DWI) uses the displacement characteristics of water molecules in presence of biological tissues, specifically neural tissues, which affect the direction of their movement. Molecular displacement of water is greater in a direction parallel to nerve fibers as compared to a direction perpendicular to the fiber tracts due to the hindrance of nerve cell membranes [12]. This anisotropy of water molecule displacement is projected into 3-dimensional (3D) space for each 3D position in the brain leading to
a 6D image to map the complete diffusion characteristics of water molecules [12]. A variety of MR imaging techniques have been developed ranging from Diffusion Spectrum Imaging (DSI) that provide high quality data for neural fibers in presence of complex layouts (e.g. fiber crossings) to simple Diffusion Weighted Imaging (DWI) that provide data at the voxel level in the 3D space of brain.

Broadly, diffusion MRI allows in vivo structural brain mapping and detection of microstructural disruption of white matter through fiber tractography [16]. However, we are not aware of any work that has comparatively evaluated the effectiveness of different approaches to study structural networks in epilepsy patients. Therefore, in this paper we present a comparative evaluation of two approaches for computing fiber tracts using de-identified epilepsy patient data. In the following sections, we briefly describe the clinical context of the patient who was diagnosed with a relatively uncommon type of insular epilepsy. We also describe the details of the statistical modeling techniques used to compute fiber tracts as background knowledge to prepare for the work described in subsequent sections.

2.1 Fiber tracking using diffusion MRI

Fiber tracking using diffusion MRI data identifies fiber tracts between regions of interest (ROI) based on the anisotropic diffusivity of water [16]. The anisotropic diffusion is usually modeled as 3 x 3 matrix of vectors called a diffusion tensor (D). The diffusion tensor can be related to diffusion weighted signal intensity S by the following equation:

\[ S = S_0 \exp(-b r_i^T D r_i), \quad i=1, \ldots, n \quad (1) \]

where, \( b \) is the diffusion weighting factor, which is a function of the strength, duration, and temporal spacing of the diffusion gradients; \( r \) is the vector of diffusion gradient; and \( S_0 \) is the signal intensity without diffusion gradients. The eigenvectors can be calculated from the diffusion tensor by “diagonalizing” the diffusion tensor (D). The three eigenvectors and the corresponding eigenvalues \( \lambda_1, \lambda_2, \) and \( \lambda_3 \) describe the directions and lengths of the diffusion paths, which are modeled as ellipsoids. This process can be represented using notation defined in [16] as follows:

\[
\begin{bmatrix}
\lambda_1 & 0 & 0 \\
0 & \lambda_2 & 0 \\
0 & 0 & \lambda_3
\end{bmatrix} = R \cdot D \cdot R^T,
\]

where \( D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\
D_{xy} & D_{yy} & D_{yz} \\
D_{xz} & D_{yz} & D_{zz} \end{bmatrix} \quad (2) \]

and \( R \) is a matrix composed of eigenvectors of the system \( D \) and \( R^T \) is the transpose of the \( R \). We refer to the [16] for further details, including mean diffusivity [16]. Fiber tracking approaches using diffusion MRI data are usually categorized into two types: (a) Deterministic fiber tracking, and (b) Probabilistic fiber tracking. We briefly describe the details of these two approaches in the following sections.

**Deterministic Fiber Tracking**

This method uses the primary eigenvector as the fiber paths from each region of interest (ROI) to the next ROI in 3 dimensional spaces. When the path reaches the next ROI, the direction of the fiber tract pathway is modified to align with the primary eigenvector of the next ROI. The path of the neural tract is constrained to turn only along regions that are more likely to have brain connectivity pathways. The eigenvectors and eigenvalues derived from the diffusion tensor \( D \) can be used to quantify the fractional anisotropy (FA), which measures the orientation of the fiber in each ROI. FA is computed from the eigenvalues, which are derived from the diffusion tensor \( D \) in Equation 2 as follows:

\[
FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \overline{\lambda})^2 + (\lambda_2 - \overline{\lambda})^2 + (\lambda_3 - \overline{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad (3)
\]
The fiber tracts are computed using the Fiber Assignment by Continuous Tractography (FACT) algorithm [17]. However, there are multiple factors, for example noise during data acquisition and complex layout of the fiber structures including fiber crossing, which reduces the effectiveness of deterministic fiber tractography. The probabilistic tractography approach attempts to address some of these limitations.

**Probabilistic Fiber Tracking**

The probabilistic fiber tracking method takes into consideration the distortion introduced during data acquisition and produces a connectivity index for each ROI. The probability distribution used for probabilistic fiber tracking is computed using Bayesian estimation methods [16]. The Bayesian approach is considered to be an appropriate approach as the uncertainty in modeling of key parameters that reflect fiber direction can be represented as posterior probability distributions using this approach. For the probability-based approach, the quality and precision of fiber tract information is closely dependent on the posterior probability distributions used in fiber tract generation. However, the convergence of estimation methods is a challenge associated with this approach due to the limited b-values and non-informative prior distributions. In addition, probabilistic fiber tracking is believed to be computationally more expensive as compared to deterministic fiber tracking as it uses multiple samples at each ROI to compute the fiber tract.

Given the advantages and disadvantages of each of these two approaches, there is a clear need to comparatively evaluate these approaches using a common dataset that can help researchers to select the most appropriate approach for fiber tracking in their experiments, including studies to characterize seizure networks in epilepsy patients. This paper uses data collected during pre-surgical evaluation from a 44 years old female with intractable focal epilepsy. This patient had a relatively uncommon form of insular epilepsy with 4-10 seizures per day. We used the FMRIB Software Library (FSL) [18] to compute fiber tracks using both the deterministic and probabilistic fiber tracking methods using the de-identified patient data. In the following section, we describe the approach used to compute fiber tracts.

**3. Methods**

Epilepsy patients admitted to the UHCMC EMU are scanned on a 3T Siemens Magnetom TIM Trio scanner (Siemens Medical Solutions USA; Malvern PA, USA). Images are acquired with maximum gradient strength of 40 mT/m using a 12-channel head matrix coil. High-resolution T1 anatomic images are acquired at 1x1x1 mm³ resolution with an MPRAGE sequence (FOV 224x256x176 mm³, TR 2600ms, TE 3.02ms, FA 8°, GRAPPA factor 2). The diffusion MRI data are collected using a diffusion weighted single-shot spin-echo sequence with following parameters (b = 1000s/mm², voxel resolution = 2x2x2 mm, number of slices = 64, matrix=128x128, and 64 non-collinear directions with two average values). The data are stored using the Digital Imaging and Communications in Medicine (DICOM) file format. The DICOM imaging files obtained from the scanner represent the slices of axial views of brain along the vertical axis. We apply the dcm2nii software to convert the DICOM files into the Neuroimaging Informatics Technology Initiative (NIITI) file format [19], which aggregates the slices as a volume. The data is processed using the FSL tool. Figure 2 illustrates the workflow used to process the diffusion MRI data after image acquisition, including brain extraction and image registration, which is followed by applying the protocols for computing probabilistic and deterministic fiber tracking.

**3.1 Image Processing Phase**

The diffusion MRI data is processed using the FSL tool. In the first phase of image processing, the FSL Brain Extraction Tool (BET) is used to remove non-brain tissue from the raw diffusion MRI image, which may have different contrast and geometry. In the next phase, the image is placed in the Montreal Neurological Institute (MNI) MNI152 “standard space” followed by the use of Eddy Current Correction feature of FSL to remove the stretches and shears induced by the gradient coils in the diffusion weighted images. There are two cost functions available for image registration in the FSL tool, namely FMRIB’s Linear Image Registration Tool (FLIRT) and FMRIB Non-linear Image Registration Tool (FNIRT). In order to co-register the physical position in DWI with anatomical MRI, for example simple head motion, we use FLIRT. After image registration, the FSL tool is used to perform both deterministic and probabilistic fiber tracking in the next phase.
Figure 2: The workflow used to analyze diffusion MRI data for computing fiber tracks using two approaches: (a) Deterministic fiber tracking, and (b) Probabilistic fiber tracking in epilepsy patients.

3.2 Connectivity Analysis of DWI Data using Deterministic and Probabilistic Fiber Tracking

To compute the deterministic fiber tracts, we use DTIFIT, which is part of FMRIB’s diffusion toolbox in FSL that fits a diffusion tensor model at each voxel. We obtain the directional information of fiber from the diffusion ellipsoid of the tensor generated by deterministic tractography equation (2), which was described earlier in Section 2, by calculating the eigenvector corresponding to the largest eigenvalue at each ROI. In this paper, we use the conservative streamline tracking technique (STT), since STT models the propagation of a fiber through the major eigenvector fields of the brain. The fiber tracking orientation position results from the interpolation of the directions of the 8 neighboring voxels that are weighted by the proportionate position (linear nearest neighbor interpolation):

\[ \mathbf{v}_{\text{new}}(i,j,k) = \sum_{w=1}^{8} a_w \mathbf{v}(l_w, m_w, n_w) \]

\( \mathbf{v}_{\text{new}}(i,j,k) \) for the 8 neighboring voxels. The factors \( a_w \) are the respective 8 weighting factors for the interpolation. The fiber tracking based on FA maps is performed by the option DTIFIT.

The probabilistic tractography in FSL is generated using an approach developed in [20] that relies on the Bayesian estimation methods. Two features in FSL namely BedpostX and ProtrackX utilize this approach to obtain the estimated parameters of fiber orientation. The BedpostX feature uses Markov Chain Monte Carlo (MCMC) sampling methods to simulate posterior distributions on diffusion parameters at each voxel (e.g., spherical angles of fiber orientation, the number of crossing fibers, and volume fraction of fiber bundle). Based on the results from the BedpostX method, the ProtrackX procedure is applied to perform the tractography analyses. Specifically, the posterior distribution of fiber orientation from BedpostX and ProtrackX is used to repeatedly sample from a series of voxel-level distributions to obtain a group of streamlines that either pass through or do not reach a target voxel.
Therefore, all voxels will have a connectivity measure between the specific voxel and the seed voxel (voxel-to-voxel), which is computed as the proportion of simulated fiber tracts that pass through that voxel from the seed voxel.

In our study, we computed the connectivity distributions between two ROIs corresponding to the left and right insula that were involved in the onset and propagation of the seizure networks. This notion of connectivity between the two insula in this particular patient corresponds to general approach of identifying connections between ROIs representing different brain locations. The seeds for fiber tracking are specified within a given ROI and the tracts are generated probabilistically as described earlier. The proportions of tracts that pass through a second ROI (i.e. pass through any voxel in that ROI) can be computed to create a map of the structural connectivity in the patient. The results from the two approaches to compute fiber tracts were visually reviewed and compared by domain experts to identify the specific approach that resulted in a higher quality image of the structural connectivity.

4. Results

The corpus callosum is the main structural connection between the left and right insula. In our previous study, we have used cortico-cortical evoked potential (CCEP) to establish significant functional connectivity between homotopic left and right anterior insula for the same epilepsy patient as used in this study [21]. The fiber tracts results described in this paper map the structural connectivity between the two insula for the first time using diffusion MRI data. Building on the results presented in this paper, we propose to correlate the spatio-temporal properties of the CCEP results with the structural connectivity values between the two insula in the next step of this integrative analysis framework. This will enable us to gain a better understanding of the role of different structural connectivity paths in seizure propagation and potentially in seizure onset as well as termination. Therefore, the comparative evaluation of the two-fiber tracking approaches described in this paper has a well-defined and significant clinical research application in epilepsy.

![Image](image-url)

**Figure 3** RGB FA map dependent on major eigenvector V, using DTIFIT. The colors red, green, and blue encode the directions of principal axis of the fibers. Red represents left-right alignment, green represents the anterior-posterior alignment, and blue represents the superior-inferior alignment. The mask of probabilistic tractography in Figure 4 highlights the part of pathway in FA map between two ROIs. The FA map is shown on sagittal (left), coronal (middle) and axial (right) axes.

The results from the two approaches used to compute the fiber track between the left and right insula clearly show that as expected the corpus callosum is the primary structure linking the two insula. However, the quality of the pathway information computed using the deterministic approach (Figure 3) is not as good as the results from the probabilistic fiber tracking approach (Figure 4) in terms of clarity and ease of interpretation. In our future work, we propose to develop a more rigorous and systematic approach to represent the quality of fiber tract connectivity, which can accurately capture the quality of the results. The fiber tractography map in Figure 3 represents the alignment of the fibers using the three colors of red (for left-right alignment), green (for anterior-posterior alignment), and blue (for superior-inferior alignment).
alignment), and blue (superior-inferior alignment). Figure 4 shows the “heatmap” of probability values with a clear structure linking the left and right insula. The colors correspond to the probability values derived from the fiber tracking computations with “warmer” colors representing higher probability.

![Figure 4](image)

**Figure 4** Probabilistic connectivity pathway generated by ProbttrackX. The pathway is overlaid by high-resolution anatomical T1-weighted image. “Seed” regions of left and right insula are used to find the connectivity between these two ROIs, and the threshold of pathway selection is the connectivity value above 10. The pathway is shown on sagittal (left), coronal (middle) and axial (right) projection.

5. Discussion

Highly accurate fiber tractography algorithms are being increasingly used to compute structural connectivity in human brain in many neuroscience projects, especially in context characterizing and understanding how brain functions are affected or modulated by structural connections. For example, the Human Connectome project is a large multi-center initiative funded by the NIH to create structural connectivity map using data from 1200 healthy adults using noninvasive neuroimaging [14]. The Human Connectome project uses four imaging modalities, namely resting state functional MRI (fMRI), diffusion MRI, task-evoked fMRI, and structural MRI for acquire the data. Similarly, there has been lot of work in using structural connectivity in context of various neurological disorders, including traumatic brain injuries (TBI). Our work is an initial step towards establishing a well-defined protocol with preliminary results illustrating the advantages and disadvantages of using the well-known approaches for computing fiber tracts in the epilepsy disease domain. Using DWI data from a focal epilepsy patient, we use the publicly available FSL tool to compute fiber connectivity between the left and right insula, where seizure occurrence was noted using EEG data [21]. Our results demonstrated that probabilistic fiber tracking approach results in relatively better structural connectivity images as compared to images generated from deterministic fiber tracking techniques. We also note that deterministic fiber tractography approach has several limitations in presence of complex layouts of fiber tracts, such as fiber crossings, therefore probabilistic fiber tracking may be a more appropriate approach to compute fiber tracts involving complex layout.

Limitations and future work

Our study used coarse-level masks of the two insula to compute the fiber tracts, which cannot be directly correlated to functional connectivity measures computed from EEG data recorded from specific contacts on intracranial electrodes. Therefore, to address this issue we are working on defining precise ROIs around the recording contacts of intracranial electrodes that will be used as seed and target ROIs for probabilistic fiber tracking. In addition, we developing a modification of the standard probabilistic fiber-tracking algorithm used in the FSL tool to improve the accuracy of the fiber tractography results. We believe this will enable us to develop more accurate models of structural connectivity in epilepsy patients to perform integrative analysis together with functional connectivity data derived from EEG signal data.
6. Conclusions
We present a comparative evaluation of two approaches used to compute fiber tract-based structural connectivity in epilepsy, which will enable the development of an integrative approach to combine the structural and functional brain connectivity data for more accurate characterization of seizure networks. Integrative analysis of the complementary modalities of brain connectivity data is critical in the broader context of understanding human brain from cellular to neural circuit dynamics. Using de-identified diffusion MRI data from an epilepsy patient with relatively rare insular epilepsy, we found that probabilistic fiber tractography approach generates better quality structural connectivity images as compared to deterministic fiber tractography approach. In the future, we aim to refine our fiber-tracking algorithm to use more accurate ROIs defined around recording contacts of the intracranial SEEG electrodes. In addition, we propose to develop a more systematic approach to compare the structural connectivity images generated by different fiber tractography approaches.

Acknowledgement
This research was supported by the Center for SUDEP Research (CSR) project funded by NIH-NINDS (grant number U01NS090405) and the NIH-National Institutes of Biomedical Imaging and Bioengineering (NIBIB) Big Data to Knowledge (BD2K) grant (1U01EB020955).

References
[1] Bargmann, C., Newsome, W., Anderson, D., et al., "BRAIN 2025: a scientific vision," US National Institutes of Health 2014.
[2] US Center for Disease Control and Prevention (CDC). (2012). Behavioral Risk Factor Surveillance System (BRFSS). Available: http://www.cdc.gov/brfss/about/brfss_today.htm Retrieved on October 15, 2015.
[3] Kramer, M.A., Cash S.S., "Epilepsy as a disorder of cortical network organization.." Neuroscientist, vol. 18, pp. 360-372, 2012.
[4] Rosenow, F., Lüders, H., "Presurgical evaluation of epilepsy," Brain, vol. 124, pp. 1683-1700, 2001.
[5] Diehl, B., Piao, Z., Tkach, J., et al., "Cortical stimulation for language mapping in focal epilepsy: correlations with tractography of the arcuate fasciculus.," Epilepsia, vol. 51, pp. 639-46, 2010.
[6] Kahane, P., Minotti, L., Hoffmann, D., et al., "Invasive EEG in the definition of the seizure onset zone: depth electrodes," in Handbook of Clinical Neurophysiology. vol. 3, F. Rosenow, Luders, H., Ed., ed Amsterdam: Elsevier BV, 2004, pp. 109-133.
[7] Ansari-Asl, K., Senhadji,L., Bellanger, J., et al., "Quantitative evaluation of linear and nonlinear methods characterizing interdependencies between brain signals," Physical Review E. statistical, nonlinear, and soft matter physics, vol. 74, p. 031916, 2006.
[8] Wendling, F., Chauvel, P., Biraben, A., et al., "From intracerebral EEG signals to brain connectivity: identification of epileptogenic networks in partial epilepsy.," Frontiers in systems neuroscience, vol. 4, 2010.
[9] Wendling, F., Bartolomei, F., Senhadji, L., "Spatial analysis of intracerebral electroencephalographic signals in the time and frequency domain: identification of epileptogenic networks in partial epilepsy.," Philosophical Transactions Maths Physics Engineering Science, vol. 367, pp. 297-316, 2009.
[10] Bartolomei, F., Chauvel, P., Wendling, F., "Epileptogenicity of brain structures in human temporal lobe epilepsy: a quantified study from intracerebral EEG.," Brain, vol. 131, pp. 1818-30, 2008.
[11] Bourien, J., Bellanger, J.J., Bartolomei, F., et al., " Mining reproducible activation patterns in epileptic intracerebral EEG signals: application to interictal activity.," IEEE Trans. Biomed. Eng, vol. 51, pp. 304-315, 2004.
[12] Hagmann, P., Jonasson, L., Maeder, P., et al., "Understanding Diffusion MR Imaging Techniques: From Scalar Diffusion-weighted Imaging to Diffusion Tensor Imaging and Beyond," RadioGraphics, vol. 26, pp. s205-23, 2006.
[13] Mori, S., van Zijl, P.C., "Fiber tracking: principles and strategies - a technical review.," NMR in Biomedicine, vol. 15, pp. 468-80, 2002.
[14] Marcus, D.S., Harwell, J., Olsen, T., et al., "Informatics and data mining tools and strategies for the human connectome project.," Frontiers in Neuroinformatics, vol. 5, 2011.
[15] Swann, N.C., Cai, W., Conner, C.R., et al., "Roles for the pre-supplementary motor area and the right inferior frontal gyrus in stopping action: electrophysiological responses and functional and structural connectivity.," Neuroimage, vol. 59, pp. 2860-70, 2012.
[16] Mukherjee, P., Berman, J.I., Chung, S.W., et al., "Diffusion tensor MR imaging and fiber tractography: theoretic underpinnings.," American Journal of Neuroradiology (AJNR), vol. 29, pp. 632-41, 2008.

[17] Mori S, Crain, B.J., Chacko, V.P., et al., "Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging.," Annals of Neurology, vol. 45, pp. 265-269, 1999.

[18] Jenkinson, M., Beckmann, C.F., Behrens, T.E., Woolrich, M.W., Smith, S.M., "FSL," Neuroimage, vol. 62, pp. 782-90, 2012.

[19] The Neuroimaging Informatics Technology Initiative(NIfTI), http://nifti.nimh.nih.gov/, Retrieved on October 15, 2015.

[20] Behrens, T.E., Berg, H.J., Jbabdi, S., et al., "Probabilistic diffusion tractography with multiple fibre orientations: What can we gain?," Neuroimage, vol. 34, pp. 144-155, 2007.

[21] N. Lacuey, Zonjy, B., Kahriman, et al., "Homotopic reciprocal functional connectivity between anterior human insulae," Brain Structure and Function, pp. 1-7, 2015.