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RESEARCH ARTICLE

Planning for selective amygdalohippocampectomy involving less neuronal fiber damage based on brain connectivity using tractography

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Abstract

Temporal lobe resection is an important treatment option for epilepsy that involves removal of potentially essential brain regions. Selective amygdalohippocampectomy is a widely performed temporal lobe surgery. We suggest starting the incision for selective amygdalohippocampectomy at the inferior temporal gyrus based on diffusion magnetic resonance imaging (MRI) tractography. Diffusion MRI data from 20 normal participants were obtained from Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org). A tractography algorithm was applied to extract neuronal fiber information for the temporal lobe, hippocampus, and amygdala. Fiber information was analyzed in terms of the number of fibers and betweenness centrality. Distances between starting incisions and surgical target regions were also considered to explore the length of the surgical path. Middle temporal and superior temporal gyrus regions have higher connectivity values than the inferior temporal gyrus and thus are not good candidates for starting the incision. The distances between inferior temporal gyrus and surgical target regions were shorter than those between middle temporal gyrus and target regions. Thus, the inferior temporal gyrus is a good candidate for starting the incision. Starting the incision from the inferior temporal gyrus would spare the important (in terms of betweenness centrality values) middle region and shorten the distance to the target regions of the hippocampus and amygdala.

Key Words: *nerve regeneration; epilepsy; selective amygdalohippocampectomy; diffusion tensor imaging; tractography; connectivity; betweenness centrality; magnetic resonance imaging; network analysis; temporal lobe surgery; neuronal fibers; neural regeneration*

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Introduction

Epilepsy is a neurological disorder affecting 1% of the world population (World Health Organization, 2006). It is characterized by epileptic seizures that can vary between brief and long periods of convulsions (Chang and Lowenstein, 2003; World Health Organization, 2006). Two-thirds of epilepsy patients receive medication to control seizures. Patients who are not suitable candidates for medication might undergo surgery, neurostimulation, or dietary change (Wiebe and Blume, 2001). Surgical treatment of epilepsy can be classified into the following procedures: temporal lobe resection, hemispherectomy and corpus callosotomy. Half of the patients who select surgery undergo temporal lobe resection. Early attempts at temporal lobe resection involved removal of large amounts of neocortex, which led to significant side effects (McEvoy and Harkness, 2005). Some scholars have proposed resection of only small portions of the neocortex focusing on the hippocampus and amygdala, known as selective amygdalohippocampectomy (Wieser and Yaşargil, 1982; Yasargil et al., 1993). This study focuses on this more selective procedure.

Diagnosis of epilepsy is typically made with electroencephalography and various neuroimaging techniques. Neuroimaging techniques include positron emission tomography (PET), single-photon emission computerized tomography (SPECT), and magnetic resonance imaging (MRI) (Spencer and Burchiel, 2012). Diffusion tensor imaging (DTI) is an MRI technique that can reveal information about *in vivo* neuronal fibers using anisotropic water diffusion in white matter. It has been used to visualize fiber connections in epilepsy patients (Colnat-Coulbois et al., 2010; Radhakrishnan et al., 2011; Faber et al., 2013). DTI suffers from a few limitations including the inability to distinguish efferent and afferent connections; however, it is the only practical option to assess *in vivo* fiber information (Campbell and Pike, 2014). DTI data is processed with a computer algorithm known as

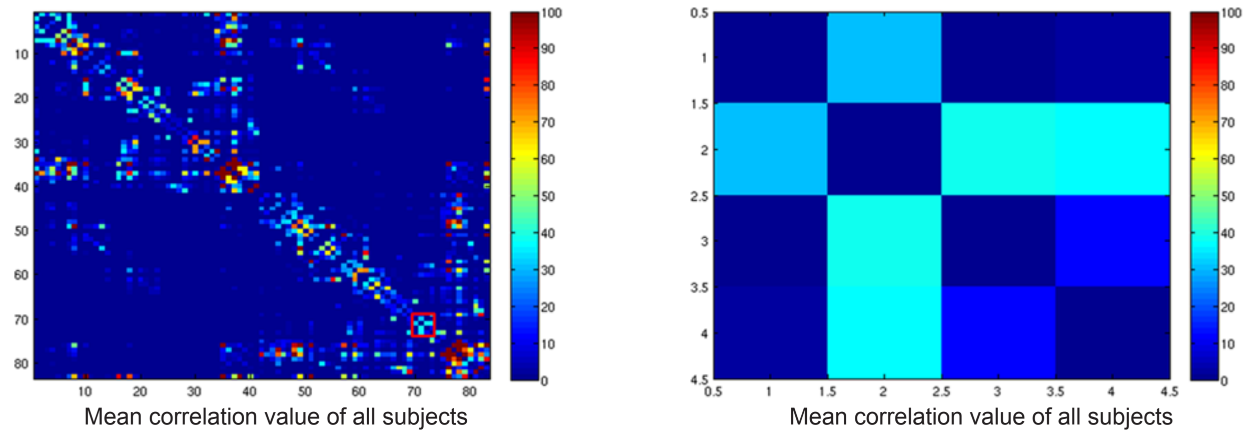

Figure 3 Whole brain fiber connectivity and its subset regarding temporal regions from 20 normal control subjects.
Left subplot: Temporal regions (rows 70–73), hippocampus (row 81), and amygdala (row 82) are of interest. The fibers of temporal regions are enclosed in a red rectangle in the lower right corner. A magnified version of the red rectangle is given in the right sub-figure. Right subplot: Inferior temporal gyrus (row 1), middle temporal gyrus (row 2), bankssts (row 3, not needed for analysis), and superior temporal gyrus (row 4) are shown. Rows refer to value assignment in the vertical axis in the left sub-figure. The axis value varies between 1 and 83. Each axis value corresponds to one row in the correlation matrix. Regions were obtained from Deskian-Killiany atlas (Desikan et al., 2006).

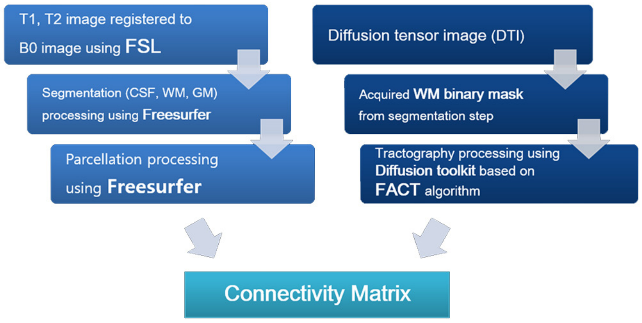

Figure 1 An overview of the pre-processing steps to assess brain connectivity.
FSL: Functional Magnetic Resonance Imaging of the Brain Software Library; CSF: cerebrospinal fluid; WM: white matter; GM: gray matter; FACT: Fiber Assignment by Continuous Tracking.

tractography to extract fiber information (Filler, 2009). Connectivity analysis is used to process fiber information, and the brain is considered a complex network (Hagmann et al., 2007). Many parameters, including the betweenness centrality (BC) of network graphs, are available to characterize the brain network. BC is a local parameter that quantifies the importance of a given node in terms of brain network structure. A region with high BC is considered to play an important role in brain circuitry (Hagmann et al., 2007; Bullmore and Sporns, 2009). Connectivity derived from DTI is known as structural connectivity, as DTI reflects actual structural connections *via* neuronal fibers between regions.

Surgical approaches to amygdalohippocampectomy differ greatly in terms of amount of resection involved. Anterior temporal lobectomy involves removal of the whole anterior temporal lobe. It is technically easier for the surgeon, but patients may suffer from neuropsychological deficits (McEvoy and Harkness 2005), including visual (superior temporal gyrus), memory (middle temporal gyrus), and auditory processing (inferior temporal gyrus) deficits (Mishkin et al., 1983; Goodale and Milner, 1992; Chao et al., 1999; Cabeza and Nyberg, 2000; Creem and Proffitt, 2001; Onitsuka and Shenton, 2004; Redcay, 2008; Jou et al., 2010; Acheson and Hagoort, 2013). Selective amygdalohippocampectomy involves resecting parts of the temporal lobe, typically the middle temporal lobe, and thus might affect memory function (Engel, 1996; Spencer and Burchiel, 2012). Transsylvian amygdalohippocampectomy involves the least amount of resection, but is the most difficult approach for the surgeon. It has benefits of better cognitive outcome in terms of intelligence quotient (IQ). The number of patients receiving transsylvian amygdalohippocampectomy is significantly less than the anterior temporal lobectomy and selective amygdalohippocampectomy (Adada, 2008). This study focuses on selective amygdalohippocampectomy, which is the middle ground between anterior temporal lobectomy and transsylvian amygdalohippocampectomy. Improving selective amygdalohippocampectomy could have major neuroprotective implications as it might involve less neuronal fiber damage. Armed with fiber information, a better way to plan amygdalohippocampectomy is to minimize fiber damage, and therefore reduce alterations in complex brain circuitry. Incision for amygdalohippocampectomy starts from the temporal region and proceeds to the target regions of the hippocampus and amygdala. The focus of this study was to identify the optimal incision starting location (*e.g.*, the superior, middle or inferior temporal gyrus) for amygdalohippocampectomy with fiber information derived from DTI tractography.

Subjects and Methods

Participants and imaging data

DTI data used in the preparation of this paper were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). Up-to-date

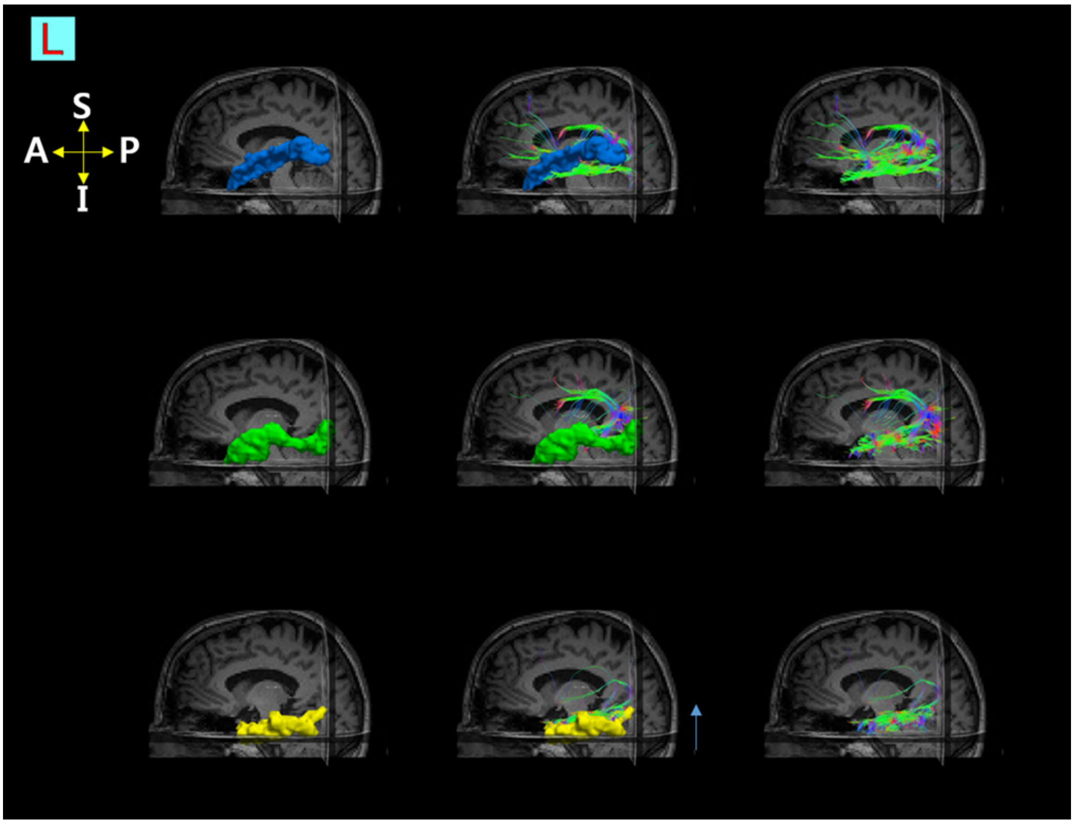

Figure 2 An example of extracted fiber touching inferior (bottom row), middle (second row), and superior (top row) temporal regions from one of 20 normal control subjects.

Top row: Superior temporal gyrus region of interest (ROI; left), extracted fiber touching the region overlaid with the ROI (middle), and extracted fibers (right). Second row: Middle temporal gyrus ROI (left), extracted fiber touching the region overlaid with the ROI (middle), and extracted fibers (right). Bottom row: Inferior temporal gyrus ROI (left), extracted fiber touching the region overlaid with the ROI (middle), and extracted fibers (right). Fibers are shown in three colors: Red represent fibers running from left to right or from right to left; blue represent fibers running from superior to inferior direction or from inferior to superior direction; green represent fibers running from anterior to posterior direction or from posterior to anterior.

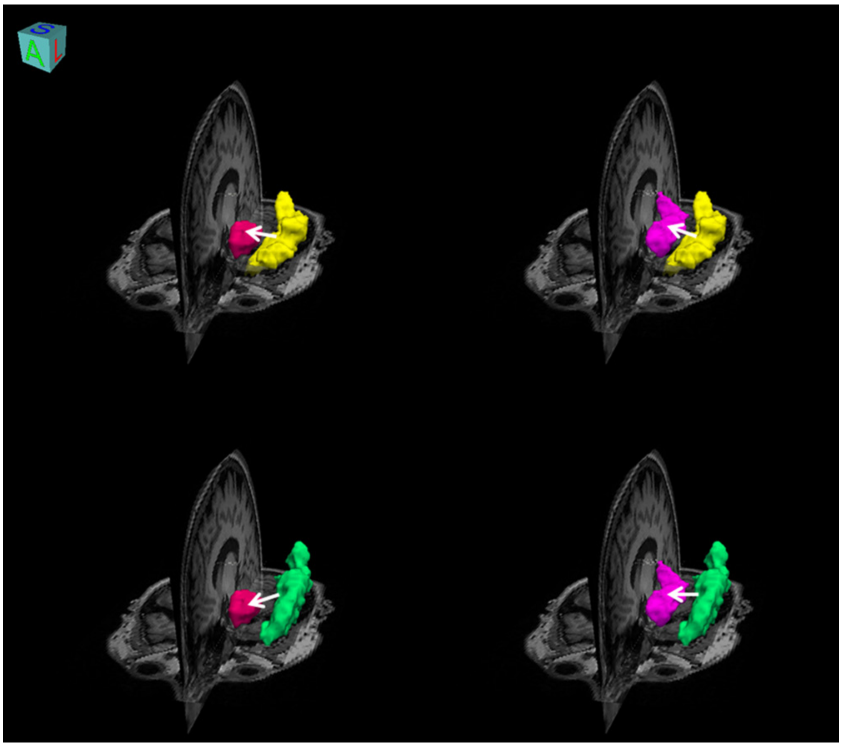

Figure 4 Visualization of distance among regions of interest (ROIs) from one of 20 normal control subjects.

The amygdala, hippocampus, inferior tempgral gyrus, and middle temproal gyrus were obtained from Deskian-Killiany atlas (Desikan et al., 2006). Upper left figure shows distance from the inferior temporal gyrus to the amygdala. Upper right figure shows distance from the inferior temporal gyrus to the hippocampus. Bottom left figure shows distance from the middle temporal gyrus to the amygdala. Bottom right figure shows distance from the middle temporal gyrus to the amygdala. Color assignment for the ROIs are as follows: red (amygdala), pink (hippocampus), yellow (inferior temporal region), and green (middle temporal). White arrows indicate the centroid of the ROIs. The lengths of the arrows are not to scale.

Table 1 Subject information

Sex (M/F, *n*)	13/7
Handedness (R/L/A, *n*)	16/3/1
Years of education (mean ± SD)	14.35±2.97
Age (mean ± SD, year)	45.10 ±6.68

M: Male; F: femal; R: right-handed; L: left-handed; A: ambidextrous.

Table 2 Number of fibers and betweenness centrality values of temporal regions from 20 normal control subjects

	Temporal gyrus		
Fiber connections	Inferior	Middle	Superior
Number of fibers			
Inferior temporal gyrus	0	30.7±15.6	2.5±6.4
Middle temporal gyrus	30.7±15.6	0	38.4±25.3
Superior temporal gyrus	2.5±6.4	38.4±25.3	0
Betweenness centrality	2	127.8	186.9

The data are expressed as the mean ± SD with the exception of values measured for betweenness centrality.

Table 3 Distances (mm) between the hippocampus, amygdala, inferior temporal gyrus, and middle temporal gyrus from 20 normal control subjects

	Hippocampus	Amygdala
Inferior temporal gyrus	28.25±2.05	38.64±2.97
Middle temporal gyrus	31.19±1.56	39.76±3.16
P value	< 0.0001	0.255

The data are expressed as the mean ± SD. Regions were obtained from Deskian-Killiany atlas (Desikan et al., 2006).

information of the research database is available (Marek et al., 2011)(Parkinson Progression Marker Initiative, 2011). We evaluated 20 normal subjects to assess connectivity prior to investigation of epilepsy patients. Subject baseline characteristics are described in **Table 1**. We studied a coherent group of middle-aged, moderately educated participants. Each subject received DTI with a 3 Tesla Siemens Trio Tim MR scanner with the following imaging parameters: voxel resolution = 1.98 × 1.98 × 1.98 mm^3, image matrix = 116 × 116 × 72, and flip angle = 90°. Sixty-five diffusion volumes with b = 1,000 s/mm^2, one with b =0 s/mm^2, and 64 diffusion directions were acquired. The subjects also received T1- and T2-weighted MR imaging. Details regarding T1 and T2 MR images are available (Marek et al., 2011). We obtained T1- and T2-weighted MR images as well as the pre-processing steps required in addition to DTI data.

Image pre-processing and connectivity analysis

Imaging data were pre-processed using FSL (Functional Magnetic Resonance Imaging of the Brain Software Library) and Freesurfer software (Fischl, 2012; Jenkinson et al., 2012). These steps were requirements for the fiber extraction software used in our study, CMTK and Diffusion Toolkit (Wang et al., 2007; Daducci et al., 2012). The extracted fiber information was entered into correlation matrices that were further analyzed with MATLAB (Mathworks Inc., Natick, MA, USA) for connectivity analysis.

This section explains the pre-processing steps required to extract fiber information from DTI data. There are excellent review papers on this procedure, and thus only a brief summary is given below for completeness (Daducci et al., 2012; Fischi-Gómez et al., 2014). For each subject, the T1- and T2-weighted images are registered to the non-diffusion-weighted image (b = 0) by a non-linear registration using FSL software (Jenkinson et al., 2012). Eddy-current correction and motion correction were performed using FSL. The registered T1-weighted image is segmented into white matter, grey matter and cerebrospinal fluid (CSF) using Freesurfer software (Fischl, 2012). Connectivity analysis requires specifying regions of interest (ROIs) such that correlations among them can be investigated. We transferred information from a pre-defined atlas onto the individual subject's image space to specify the ROIs *via* registration. A modified version of the Desikan-Killiany anatomical atlas, containing 83 cortical and sub-cortical regions, was adopted (Desikan et al., 2006; Cammoun et al., 2012). We considered the following five ROIs near the site of surgery: the amygdala, hippocampus, inferior temporal gyrus, superior temporal gyrus, and middle temporal gyrus. The overall procedures for image pre-processing are summarized in **Figure 1**.

Fiber information was computed using the FACT algorithm implemented with the Diffusion Toolkit and CMTK software (Daducci et al., 2012). The FACT algorithm propagated a line from the center of a seed voxel along the direction of the dominant vector, determined by the largest eigenvector of the tensor until the line exited to the next voxel. The starting point of the next voxel was the intercept of the previous voxel. Tracking was terminated when the algorithm entered a region where an abrupt change in fiber direction (*i.e.*, angle threshold more than 60°) was detected. The FACT algorithm propagated a line from one voxel to another. Every voxel was considered a seed voxel, and we retained only fibers that touched the pre-defined ROIs. Examples of extracted fibers touching inferior, middle, and superior temporal gyri are given in **Figure 2**. Given a set of ROIs within the brain, connectivity was assessed using the nodes and edges of the graph (Stam and Reijneveld, 2007; Bullmore and Sporns, 2009; Xia et al., 2014). Nodes were assigned ROIs that were transferred from the pre-defined atlas. Each edge value was assumed to be the number of fibers touching two ROIs, which was entered into the matrix as an element. The matrix is referred to as the correlation matrix. We adopted a simple network model where un-directed and un-weighted edges were considered. Once the correlation matrix was computed, BC values for the chosen ROIs were computed to quantify the relative importance of the chosen ROIs. BC is a local parameter that quantifies importance of a given node in terms of brain network structure. The BC of a given node is the number of shortest paths between any two other nodes that run through that node, which quantifies how much information might pass through that particular node.

Distance between regions

Optimal surgical planning would explore a path that travels the minimum distance between the incision-starting location and the target location. Distances are computed as Euclidean distances between the centroids of involved ROIs. We measured Euclidean distances among five ROIs from their respective centroids. Centroids are the anatomical centers of the ROIs, not the centers of the tissues being resected.

Results

Neuronal fibers and BC

Whole-brain connectivity and its subset of temporal gyrus ROIs are given in **Figure 3**. The analysis of fibers touching five ROIs showed that there were no direct connections between the following: 1) temporal gyrus regions and the amygdala and 2) temporal gyrus regions and the hippocampus (**Figure 3**, **Table 2**). There would therefore be no difference among incision-starting points within the temporal gyrus as far as the direction fiber connections were concerned. Many connections existed between temporal gyrus regions, especially from the middle temporal gyrus (**Table 2**). In addition, analysis of BC values showed that the middle temporal gyrus (BC = 128) and superior temporal gyrus (BC = 187) have higher BC values than the inferior temporal gyrus (BC = 2). This implied that the middle temporal gyrus and superior temporal gyrus are the most important regions with crossing of many fiber connections, though these connections may not be from the hippocampus or amygdala. Starting the incision at the middle temporal gyrus or superior temporal gyrus will likely negatively affect such connections. A better location to start the incision would be the inferior temporal gyrus, which would least affect the existing connections in terms of BC values.

Distance of the surgical path

We compared the distances between the temporal gyrus regions and the hippocampus or amygdala. As we were interested in distances of the participant group specifically, we measured Euclidean distances between the five ROIs and their respective centroids. The distances between the inferior temporal gyrus and the hippocampus (28 mm) or amygdala (38 mm) were shorter than the distances between the middle temporal gyrus (MTG) and the hippocampus (31 mm) or amygdala (40 mm) (**Table 3**, **Figure 4**). The shortened distances were only significant in terms of P values for ITG/MTG-hippocampus, not for ITG/MTG-amygdala.

Choosing to start the surgery at the inferior temporal gyrus may not lead to a shortened surgical path for the target regions of the amygdala, but it will spare the middle temporal region suggested to be important by high BC values. Factoring in these observations, starting the incision from the inferior temporal gyrus would: 1) spare an important middle region in terms of BC values and 2) shorten the distance to the spatial location of the hippocampus.

Discussion

Brain surgery requires as much precision as possible since even small inconsistencies are likely to incur irreparable damage. Thus, accurate surgery planning is critical. Imaging guidance is a valuable option to improve accuracy in planning brain surgery. DTI is a tool to assess *in vivo* fiber information and can thus provide important cues for image guidance. DTI alone does not provide all the necessary information for accurate surgical planning, but having such information is a step towards multi-modal image guidance with improved performance.

We suggest starting the selective amygdalohippocampectomy incision from the inferior temporal gyrus so that important neuronal connections are spared and the distance between the starting and target points is shortened. DTI information can be used to improve planning accuracy. Many epilepsy patients undergo temporal lobe surgery as a last resort. The surgical procedure involves incision into the temporal region responsible for auditory, visual, and memory function. The surgery is likely to negatively affect such functions. The parameters gained from this study are likely to contribute to better surgical planning and limit damage to those essential functions. To validate our approach, a future clinical trial is required to compare different starting locations of selective amygdalohippocampectomy.

We adopted a deterministic tractography where each voxel can assume one primary fiber orientation. Probabilistic tractography is better equipped to deal with multi-fiber orientation situations and thus is potentially better than deterministic tractography (Descoteaux et al., 2009); however, deterministic tractography has been widely adopted and is effective at spotting general trends in fiber distribution among ROIs containing many voxels. We leave comparisons of probabilistic and deterministic tractography for future work.

Centroids of ROIs were used to compute the distances between temporal regions and the hippocampus/amygdala. A better option would be using the centroid of the tissues being resected. Our study is a retrospective study of images, and further investigation is needed to compute the centroid of the tissues being resected.

The main results of our study were derived from normal control cases, not epilepsy patients. We justified our choice of using normal control cases by citing that MD values of DTI were largely similar between normal control and epilepsy patients (Widjaja et al., 2013). Other studies adopted a similar approach and derived results from an normal control group (Colnat-Coulbois et al., 2010). The PPMI database did not have epilepsy cases, and thus we chose the normal control cases due to this practical limitation.

We adopted DTI to assess structural brain connectivity. Many studies computed functional brain connectivity from functional magnetic resonance imaging. Connectivity derived from functional magnetic resonance imaging reflects functional correlation between time series data of different regions, while connectivity derived from DTI reflects neuronal fiber connections between brain regions. Combining two types of connectivity information would allow us to better explore possible surgical paths. One study showed that correlation matrices of functional connectivity and structural connectivity were topologically similar, and thus the results of the analysis could be similar (Bullmore and Sporns, 2009). Our findings are likely to be valid even if we adopted additional functional connectivity. Further research is needed to quantify this issue.

Author contributions: *SHL, MK, and HP designed the study, analyzed the data and wrote the paper. SHL and HP were responsible for statistical analysis. All authors approved the final version of the paper.*
Conflicts of interest: *None declared.*

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