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Decreased neurite density within frontostriatal networks is associated with executive dysfunction in temporal lobe epilepsy

Anny Reyes [a,b], Vedang S. Uttarwar [b], Yu-Hsuan A. Chang [b], Akshara R. Balachandra [b], Chris J. Pung [b], Donald J. Hagler Jr. [b], Briana M. Paul [c,d], Carrie R. McDonald [a,b,e,*]

[a] San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA
[b] Center for Multimodal Imaging and Genetics, University of California, San Diego, CA, USA
[c] Department of Neurology, University of California — San Francisco, San Francisco, CA, USA
[d] UCSF Comprehensive Epilepsy Center, San Francisco, CA, USA
[e] Department of Psychiatry, University of California, San Diego, CA, USA

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ABSTRACT

Objective: Executive dysfunction is observed in a sizable number of patients with refractory temporal lobe epilepsy (TLE). The frontostriatal network has been proposed to play a significant role in executive functioning, however, because of the complex architecture of these tracts, it is difficult to generate measures of fiber tract microstructure using standard diffusion tensor imaging. To examine the association between frontostriatal network compromise and executive dysfunction in TLE, we applied an advanced, multishell diffusion model, *restriction spectrum imaging* (RSI), that isolates measures of intraaxonal diffusion and may provide better estimates of fiber tract compromise in TLE.
Methods: Restriction spectrum imaging scans were obtained from 32 patients with TLE [16 right TLE (RTLE); 16 left TLE (LTLE)] and 24 healthy controls (HC). An RSI-derived measure of intraaxonal anisotropic diffusion (neurite density; ND) was calculated for the inferior frontostriatal tract (IFS) and superior frontostriatal tract (SFS) and compared between patients with TLE and HC. Spearman correlations were performed to evaluate the relationships between ND of each tract and verbal (i.e., D-KEFS Category Switching Accuracy and Color–Word Interference Inhibition/Switching) and visuomotor (Trail Making Test) set-shifting performances in patients with TLE.
Results: Patients with TLE demonstrated reductions in ND of the left and right IFS, but not SFS, compared with HC. Reduction in ND of left and right IFS was associated with poorer performance on verbal set-shifting in TLE. Increases in extracellular diffusion (isotropic hindered; IH) were not associated with executive dysfunction in the patient group.
Significance: Restriction spectrum imaging-derived ND revealed microstructural changes within the IFS in patients with TLE, which was associated with poorer executive functioning. This suggests that axonal/myelin loss to fiber networks connecting the striatum to the inferior frontal cortex is likely contributing to executive dysfunction in TLE.

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1. Introduction

Up to 75% of patients with temporal lobe epilepsy (TLE) exhibit significant executive dysfunction on standard neuropsychological measures [1]. Given the impact of executive dysfunction on overall quality of life [2], there is an emerging interest in understanding the neural underpinnings of executive dysfunction in TLE. Widespread structural and functional abnormalities in TLE have been well-documented, with patients demonstrating alterations in white matter microstructure, cortical thinning, reduced regional brain activity, and glucose hypometabolism within the frontal lobe [3–5]. Despite the identification of these structural and functional changes within frontal networks, relatively few studies have directly linked these changes to impairments in executive functioning in TLE (for review see Stretton & Thompson [1]).

The frontostriatal network, consisting of parallel anatomical loops connecting frontal cortex to the striatum, has been proposed to play a critical role in executive functions [6–8]. Microstructural changes within this network have been identified in several clinical populations and linked to impairments in decision making, inhibition, set-shifting, emotion regulation, and reward processing [9–11]. Despite compelling evidence that the frontostriatal network contributes to executive

* Corresponding author at: Altman CTRI Building, Floor #: 4W 9452 Medical Center Drive, La Jolla, CA 92037, USA.
E-mail address: camcdonald@ucsd.edu (C.R. McDonald).

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dysfunction in other clinical populations, only one study has examined frontostriatal contributions to executive dysfunction in TLE [12]. Riley and colleagues applied probabilistic tractography to nine patients with left TLE (LTLE) and reported that reduced *connection strength* between the left caudate and the dorsolateral prefrontal cortex was associated with slower set-shifting performance. Although *connection strength* (i.e., the proportion of overall connectivity to a region) has been employed in previous studies as a surrogate for fiber tract integrity [13,14], the authors acknowledge that the challenge of reliably reproducing the frontostriatal tracts prevented the use of more conventional tractography measures in their study.

Conventional diffusion tensor imaging (DTI) has provided great insight into the integrity of well-defined deep white matter tracts. However, this approach has limitations when defining pathways that fan out to connect neocortex with subcortical gray matter (e.g., frontostriatal tracts). Because of considerable fiber divergence within these pathways, which leads to low diffusion anisotropy and hence, less defined paths, Gaussian diffusion may not properly describe these paths [15]. To better model complex non-Gaussian diffusion in tissue, advanced diffusion methods, including *diffusion kurtosis imaging* (DKI), *diffusion spectrum imaging* (DSI), and *restriction spectrum imaging* (RSI), have been developed [16–19]. These techniques may provide better estimates of fiber tract compromise in regions with complex fiber orientation and structure, including tracts with high dispersion. In addition, multicompartment models (e.g., DSI, RSI) provide more specific measures of disease pathology relative to standard DTI by separating the intracellular (i.e., intraaxonal) compartments associated with axonal/myelin integrity from the extracellular (i.e., extra-axonal) compartment that likely reflects water shifts in the extracellular matrix [17,20]. To this end, we have recently shown that one advanced diffusion model, RSI, may provide a more specific measure of temporolimbic network pathology in TLE relative to DTI due to its ability to isolate anisotropically-restricted diffusion associated with axonal/myelin loss [17]. Given our previous findings, we propose that RSI is also well-positioned to capture microstructural changes within frontostriatal tracts that may be a strong marker of cognitive dysfunction in TLE.

In this study, we investigated the association between frontostriatal network integrity and executive dysfunction in TLE using an RSI-derived measure of axonal/myelin integrity (i.e., neurite density; ND). We selected two frontostriatal tracts, the inferior frontostriatal tract (IFS) and the superior frontostriatal tract (SFS), which connect the striatum to the inferior and superior frontal cortices, respectively. We hypothesize that patients with TLE would demonstrate lower ND within frontostriatal tracts relative to healthy controls (HC). We also hypothesize that reduced ND within the frontostriatal tracts would be associated with poorer performances on measures of executive functioning (verbal and visuomotor set-shifting) in TLE.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Boards at the UC San Diego and UC San Francisco, and informed consent was collected from all participants in accordance to the Declaration of Helsinki. Thirty-two patients with medically refractory TLE and 24 HC met inclusion/exclusion criteria for the study. A subset of the subjects were included in a previous study by Loi et al. [17]. All patients with TLE were recruited through referral from the UC San Diego or UC San Francisco Epilepsy Centers. Inclusion criteria for patients included a TLE diagnosis by a board-certified neurologist with expertise in epileptology, in accordance with the criteria defined by the International League Against Epilepsy, and unilateral seizure onset based on video-EEG telemetry, seizure semiology, and neuroimaging evaluation. Patients were excluded if there was evidence on video-EEG of multifocal seizure onset. In nine patients, magnetic resonance imaging (MRI) findings suggested the presence of ipsilateral mesial temporal sclerosis (MTS; six with left MTS and three with right MTS). Of the 32 patients, 16 patients demonstrated right temporal lobe seizure onset (RTLE) and 16 demonstrated left temporal lobe seizure onset (LTLE). Healthy controls were included if they were between the ages of 18 and 65 and had no reported history of neurological or psychiatric disease.

2.2. MRI acquisition

All patients were seizure-free per self-report for a minimum of 24 h prior to the MRI scan. Magnetic resonance imaging data were collected on a General Electric Discovery MR750 3 T scanner with an 8-channel phased-array head coil at the Center for Functional MRI at UC San Diego or the Surbeck Laboratory for Advanced Imaging at UC San Francisco. Image acquisitions were identical at both centers and included a conventional three-plane localizer, GE calibration scan, a T1-weighted 3D customized FSPGR structural sequence (repetition time (TR) = 8.08 ms, echo time (TE) = 3.16 ms, Inversion time (TI) = 600 ms, flip angle = 8°, field of view (FOV) = 256 mm, matrix = 256 × 192, slice thickness = 1.2 mm), and for standard diffusion MRI, a single-shot pulse-field gradient spin-echo echo-planar imaging (EPI) sequence (TE/TR = 96 ms/17 s, FOV = 24 cm, matrix = 128 × 128 × 48, axial). Diffusion data used for RSI analyses were acquired with b = 0, 500, 1500, and 4000 s/mm^2, with 0, 15, 15, and 15 unique gradient directions for each b-value, respectively (total RSI scan time = ~7 min). For use in nonlinear B_0 distortion correction, two additional b = 0 volumes were acquired with either forward or reverse phase-encode polarity.

2.3. RSI processing

All data were processed at the UC San Diego Center for Multimodal Imaging and Genetics (CMIG). Preprocessing of the diffusion data included corrections for distortions due to magnetic susceptibility (B_0), eddy currents, and gradient nonlinearities, as well as head motion correction and registration to the T1-weighted structural image. For B0 distortion correction, a reverse gradient method was used [21]. This method provides superior accuracy and better cross-modality registration relative to the field mapping approach. A detailed description of the image processing is provided elsewhere [22]. Restriction spectrum imaging utilizes a multi-b-shell acquisition in conjunction with a linear mixture model to isolate diffusion signals from separable hindered, restricted, and free water diffusion compartments within a voxel. Technical details describing the RSI mathematical framework are described in full elsewhere [16,23,24]. Restriction spectrum imaging-based measures were calculated from the 2nd and 4th order spherical harmonics of the cylindrically-restricted (ND) and isotropic hindered (IH) compartments. The cylindrically-restricted compartment obtained from our model is referred to as "neurite density" throughout this paper to remain consistent with the existing biophysical literature and our previous work [17,24]. However, it is of note that here, ND was modeled exclusively in white matter, and therefore, likely represents axonal projections rather than neurites. These measures were normalized by the square root of the sum of squares of all model coefficients, converting them into volume fractions. The RSI model was fit to the data using least-squares estimation with Tikhonov regularization [23].

2.4. Fiber tracts calculations

Fiber tract values for each of the RSI diffusion measures were derived using a probabilistic diffusion tensor atlas developed using in-house software written in MATLAB (i.e., AtlasTrack), which has been validated in HC and patients with TLE [25]. This method uses information from a single subject on the location and orientation of the tracts of interest. The diffusion measures were then derived from each participant's atlas using T1-weighted images and the orientation estimates from diffusion tensor calculations. A full description of the atlas and the steps

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