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Independent contribution of individual white matter pathways to language function in pediatric epilepsy patients

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ABSTRACT

Background and purpose: Patients with epilepsy and malformations of cortical development (MCDs) are at high risk for language and other cognitive impairment. Specific impairments, however, are not well correlated with the extent and locale of dysplastic cortex; such findings highlight the relevance of aberrant cortico-cortical interactions, or connectivity, to the clinical phenotype. The goal of this study was to determine the independent contribution of well-described white matter pathways to language function in a cohort of pediatric patients with epilepsy.

Materials and methods: Patients were retrospectively identified from an existing database of pediatric epilepsy patients with the following inclusion criteria: 1. diagnosis of MCDs, 2. DTI performed at 3 T, and 3. language characterized by a pediatric neurologist. Diffusion Toolkit and Trackvis (http://www.trackvis.org) were used for segmentation and analysis of the following tracts: corpus callosum, corticospinal tracts, inferior longitudinal fasciculi (ILFs), inferior fronto-occipital fasciculi (IFOFs), uncinate fasciculi (UFs), and arcuate fasciculi (AFs). Mean diffusivity (MD) and fractional anisotropy (FA) were calculated for each tract. Wilcoxon rank sum test (corrected for multiple comparisons) was used to assess potential differences in tract parameters between language-impaired and language-intact patients. In a separate analysis, a machine learning algorithm (random forest approach) was applied to measure the independent contribution of the measured diffusion parameters for each tract to the clinical phenotype (language impairment). In other words, the importance of each tract parameter was measured after adjusting for the contribution of all other tracts.

Results: Thirty-three MCD patients were included (age range: 3–18 years). Twenty-one patients had intact language, twelve had language impairment. All tracts were identified bilaterally in all patients except for the AF, which was not identified on the right in 10 subjects and not identified on the left in 11 subjects. MD and/or FA within the left AF, UF, ILF, and IFOF differed between language-intact and language-impaired groups. However, only parameters related to the left uncinate, inferior fronto-occipital, and arcuate fasciculi were independently associated with the clinical phenotype.

Conclusions: Scalar metrics derived from the left uncinate, inferior fronto-occipital, and arcuate fasciculi were independently associated with language function. These results support the importance of these pathways in human language function in patients with MCDs.

1. Introduction

Patients with epilepsy and malformations of cortical development (MCDs) are at high risk for language and other cognitive impairment. Specific deficits, however, are not well correlated with the extent and locale of dysplastic cortex, highlighting the import of aberrant cortico-cortical interaction, or connectivity, to the clinical phenotype (Krsek et al., 2009). Given that surgical resection of focal epileptogenic lesions has become a frequent choice in management of the patient with intractable focal seizures, delineation of those pathways crucial to language function would be of great potential value to optimal patient management.

With the advent of diffusion-weighted imaging, the microstructural properties of a tissue of interest can be non-invasively probed at a spatial scale that is otherwise unattainable using even the most advanced structural MR techniques. Diffusion tensor imaging (DTI) is a variation on the theme of DWI which quantifies water motion in three orthogonal

Abbreviations: AF, arcuate fasciculus; BA, Broca's area; DWI, diffusion-weighted imaging; DTI, diffusion tensor imaging; FA, fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MCDs, malformations of cortical development; MD, mean diffusivity; UF, uncinate fasciculus; WA, Wernicke's area.

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dimensions and, therefore, is better able to capture the anisotropic tendencies of diffusion in highly organized tissues such as cerebral white matter (Basser et al., 1994). Diffusion tractography is an extension of DTI in which the directional tendencies of water diffusion are used to create three dimensional representations of white matter tracts based on their structural coherence (Lee et al., 2005; Melhem et al., 2002). In many instances, the functional role of the constructed pathways is at least in part known, which enables assessment of brain parenchymal abnormalities in terms of functional systems (Catani et al., 2008; Vishwas et al., 2010).

Numerous scalar metrics can be derived from the tensor and used to probe the microstructural character of individual white matter pathways; the most commonly referenced are MD and FA. MD provides a measure of overall incoherent motion within a voxel without regard for direction and reflects tissue organization at the cellular level (Chenevert et al., 2000). Increased MD is a common manifestation of white matter pathology of diverse etiology (Vishwas et al., 2010; Lochner et al., 2012; Della Nave et al., 2008). By contrast, FA provides a measure of the degree to which a single direction of water motion dominates overall diffusivity in a voxel. As such, FA has been shown to be a relatively robust measure of white matter integrity (Lee et al., 2012; Beppu et al., 2012; Qiu et al., 2010; Ptak et al., 2003; Deppe et al., 2007).

Abnormalities within several white matter pathways have been reported in patients with language dysfunction (Harvey et al., 2013; McDonald et al., 2008; Mills et al., 2013). However, great potential exists to detect indirect associations (epiphenomena) between a proposed biomarker and a particular cognitive function, particularly in patient populations whose cerebral connectivity and brain function are both extensively abnormal. Furthermore, the ability to apply quantitative information garnered from such imaging techniques toward management of an individual patient has, to date, proved elusive. We sought to use a random forest approach, a form of machine learning, to overcome these two commonly encountered challenges in quantitative imaging.

Random forests are an ensemble learning method for classification that operate by constructing a multitude of decision trees at training time and outputting the class that is the mode of the classes output by individual trees (Breiman, 2001). At a fundamental level, this approach is based on bootstrap aggregating, or bagging, in which numerous models are fitted using individual bootstrap samples then combined by averaging. A strength of this particular technique is its ability to estimate the independent contribution of an individual variable while accounting for the contribution of all other variables. This estimate of variable importance is accomplished by measuring the error for each data point over the forest compared to that error which results when that variable is negated during bagging. Another strength of the random forest algorithm lies in its ability to provide an unbiased measure of classification accuracy. During each bootstrap iteration, approximately one third of the cohort is omitted at random from the training set – this omitted portion of the dataset is considered "out-of-bag" – classification of out-of-bag individuals is then predicted based on the generated model.

The goals of this study were two-fold: 1. to quantify the independent contribution of well-described white matter pathways to language function in a cohort of pediatric patients with epilepsy and 2. to measure the accuracy of the random forest algorithm with respect to classification of language phenotype in an individual patient.

2. Methods

This health insurance portability and accountability act-compliant study was approved by the local institutional review board. Patients were identified retrospectively from an existing database of pediatric patients undergoing clinical evaluation as part of the institutional multidisciplinary epilepsy work-group. The following inclusion criteria were applied: 1. pediatric age group (≤18 years), 2. diagnosis of malformation of cortical development established by MRI, 3. MRI of the brain performed at 3 T, including DTI, and 4. language development characterized by a pediatric neurologist. Refinements to the above-defined population were based on the following exclusion criteria: 1. motion or other degradation to image quality and 2. increase in confidence in the clinical determination of language delay; patients younger than 3 years of age were also excluded.

Patients were divided initially into three groups based on characterization of their language development by a pediatric neurologist: 1. intact: age-appropriate, 2. mild-to-moderate impairment: delayed by comparison to peers (either expressive or receptive), and 3. profound impairment: absence of oral language. This three-point scale was selected as it has been shown to provide both a clinically meaningful and a reproducible estimate of language function (Im et al., 2014). Twenty-one MCD patients had intact language, 9 mild-to-moderate impairment, and 3 profound impairment.

2.1. Magnetic resonance imaging

All imaging was performed on two 3 Tesla magnets (Siemens, Tim Trio, Erlangen, Germany). The following sequences were obtained: 1. sagittal magnetic preparation rapid acquisition gradient echo (TR/TE: 2530 ms/3.39 ms; 1 acquisition; flip: 7°, inversion time: 1100 ms; acceleration: 2; voxel (mm): $1 \times 1 \times 1$), 2. axial fast spin echo T2-weighted (FSE; TR/TE: 11,730 ms/89 ms; 2 acquisitions; flip: 120°; acceleration: 2; voxel (mm): $0.6 \times 0.4 \times 2.5$), 3. axial fluid attenuation inversion recovery (FLAIR; TR/TE: 9000 ms/137 ms; 1 acquisition; flip: 150°; FOV: 22 cm; voxel (mm): $0.7 \times 0.7 \times 4$), and 4. axial single-shot echo planar imaging DTI (EPI; TR/TE (ms): 7000/90; flip: 90°; 1 acquisition; voxel (mm): $2 \times 2 \times 2$). For DTI, 35 image sets were acquired, five without diffusion weighting (b_0) and thirty with non-collinear diffusion-weighting gradients (b value: 1000 s/mm^2). All images were visually inspected for artifacts, including subject motion.

2.2. Image processing and analysis

A single user experienced in tractography performed tract reconstruction, segmentation, and analysis. Maps of MD and FA were created using Diffusion Toolkit (http://www.trackvis.org). For each voxel, a tensor matrix was derived. After diagonalization of the matrix, eigenvalues were obtained and MD and FA were quantified for each pixel according to standard equations (Basser and Pierpaoli, 1996). Diffusion Toolkit (http://www.trackvis.org) was also used for deterministic tract reconstruction using a Fiber Association by Continuous Tracking algorithm (FACT; 35 degree angular threshold). A DWI mask was used to remove cerebrospinal fluid, a process which has been shown to effectively prevent spurious tract reconstruction (Vishwas et al., 2010). Trackvis (http://www.trackvis.org) was then used for segmentation and analysis of the following major commissural, projection, and intra-hemispheric association pathways: 1. corpus callosum, 2. corticospinal tracts, 3. arcuate fasciculi, 4. inferior longitudinal fasciculi, 5. inferior fronto-occipital fasciculi, and 6. uncinate fasciculi. Regions of interest for tract segmentation were placed manually on the color FA maps cross-referenced to the b_0 images according to previously described methods (Wakana et al., 2007). Mean MD and mean FA were then calculated for each identifiable tract.

2.3. Data analysis and statistics

Statistical testing was performed using R statistical software package, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Wilcoxon rank sum test (corrected for multiple comparisons) was used to assess potential differences in tract parameters between language-impaired and language-intact patients (alpha: 0.05 corrected).