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White matter structural connectivity changes correlate with epilepsy duration in temporal lobe epilepsy

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ABSTRACT

Purpose: Temporal lobe epilepsy (TLE) is thought to be a network disease and structural changes using diffusion tensor imaging (DTI) have been shown. However, lateralized differences in the structural integrity of TLE, as well as changes in structural integrity with longer disease duration, have not been well defined.
Methods: We examined the fractional anisotropy (FA) and mean diffusivity (MD) in the hippocampus, as well as its primary (cingulum and fornix) and remote (uncinate and external capsule) connections in both right and left TLE. Changes in diffusion measures over the disease course were examined by correlating FA and MD in the various structures with epilepsy duration. The potential for each measure of anisotropy and diffusivity as a marker of TLE laterality was investigated using random forest (RF) analysis.
Results: MD was increased in the bilateral hippocampus, cingulum, fornix and the right external capsule in both left and right TLE compared to controls. In addition, left TLE exhibited an increased MD in the ipsilateral uncinate fasciculus and bilateral external capsules. A decrease in FA was seen in the left cingulum in left TLE. RF analysis demonstrated that MD of the right hippocampus and FA of the left external capsule were important predictors of TLE laterality. An association of increased MD with epilepsy duration was seen in the left hippocampus in left TLE.
Conclusion: Evidence of disrupted white matter architecture in the hippocampus and its primary and remote connections were demonstrated in TLE. While changes in the hippocampus and cingulum were more prominent in right TLE, remote changes were more prominent in left TLE. MD of the right hippocampus and FA of the left external capsule were found to be the strongest structural predictors of TLE laterality. Changes associated with duration of epilepsy indicated that changes in structural integrity may be progressive over the disease course. This study illustrates the potential of structural diffusion tensor imaging in elucidating pathophysiology, enhancing diagnosis and assisting prognostication.

Introduction

Temporal lobe epilepsy (TLE) is the most common form of epilepsy in adults and is thought to be a network disease (Engel et al., 2013; Spencer, 2002). Diffusion tensor imaging (DTI) has been used to study the underlying white matter structural integrity in TLE, finding changes in temporal and extratemporal white matter structures (Arfanakis et al., 2002; Govindan et al., 2008; Gross, 2011; Gross et al., 2006; Thivard et al., 2005). The reason for white matter changes in TLE is unclear. However, various mechanisms have been suggested, including changes related to the underlying epileptogenic process, axonal degeneration due to seizures or epileptiform discharges, and compensatory white matter reorganization (Gross, 2011; Otte et al., 2012).

Measures often used to quantitate levels of white matter integrity include the fractional anisotropy (FA) and mean diffusivity (MD) (Le Bihan et al., 2001). FA is a measure of directional diffusivity in white matter, which is often decreased in white matter pathology including edema and inflammation. Normal white matter has

Abbreviations: TLE, temporal lobe epilepsy; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; FDR, false discovery rate; CE, change-in-estimate; ST, significance testing; RF, random forests; EC, external capsule; TR, repetition time; TE, echo time; FOV, field of view; NSA, number of signals averaged.

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axons arranged in tracts imparting a high directional diffusivity (high FA), while degenerated tracts have reduced directional diffusivity (low FA) (Basser and Pierpaoli, 1996). MD measures the overall motion of water molecules without respect to directionality (Le Bihan et al., 2001). A recent meta-analysis of 13 DTI studies in TLE found that the MD is increased and the FA reduced in TLE compared to healthy controls (Otte et al., 2012). DTI changes were more prominent in the tracts closely connected with the affected temporal lobe, including the cingulum and fornix (Otte et al., 2012). The major input to the hippocampus is the entorhinal cortex, which receives inputs from the cingulum, and the major output of the hippocampus is the fornix. We planned to study changes in (1) the hippocampus; (2) tracts directly connected to the hippocampus, including the cingulum and fornix; and (3) remote tracts previously identified as most significantly involved in DTI studies of TLE, including the external capsule and uncinate fasciculus (Otte et al., 2012). In addition to the recognized propensity to involve ipsilateral, rather than contralateral, white matter in TLE, there has been evidence to suggest that white matter changes may differ in left and right TLE, although studies investigating lateralized differences in structural integrity have been limited in both number and sample size (Ahmadi et al., 2009; Focke et al., 2008; Kemmotsu et al., 2011). Left TLE has been shown to have more structural compromise than right TLE, which has been suggested to be related to greater vulnerability of the left hemisphere to injury and progressive effects (Kemmotsu et al., 2011). Left TLE has also been noted to have more widespread involvement, compared to a restricted ipsilateral involvement in right TLE, using FA measurements (Ahmadi et al., 2009). These patterns, however, were restricted to the scope of the specific tracts studied, and the relationship of these patterns to hippocampal changes is not yet clear. Due to limited evidence on lateralized differences in structural integrity between left and right TLE (Besson et al., 2014), we examined lateralized changes separately. In addition, we investigated the relative importance of structural changes in primary versus remote hippocampal inputs and outputs for serving as a marker of TLE laterality. One study has found that FA measurements in the uncinate and parahippocampal gyrus may lateralize TLE into left and right TLE in 90% of cases (Ahmadi et al., 2009). However, despite emerging evidence that differences in anisotropy and diffusivity may be useful for lateralizing TLE, the relative importance of affected regions for lateralizing TLE remains relatively unexplored.

There has also been some evidence of white matter changes associated with the age of onset of epilepsy (Lin et al., 2008) and epilepsy duration (Govindan et al., 2008), although other studies failed to show evidence of such associations (Arfanakis et al., 2002; Gross et al., 2006; Thivard et al., 2005). In a recent study, however, Bernhardt et al. (2009) showed that structural changes exist in TLE beyond those attributable to normal aging. Improved understanding of progressive changes in the TLE network is of interest as (1) a measure of disease load, (2) a correlational tool with clinical measures including cognition and behavior (Yogarajah et al., 2010), and (3) identification of changes of interest that could help guide intervention using surgery or devices. However, few studies have investigated lateralized differences in the progression of structural integrity changes in left versus right TLE. Therefore, we further assessed for DTI changes correlated with the duration of epilepsy among separate left and right TLE groups.

The major aims of the current study were to (1) compare the MD and FA of the hippocampus, cingulum, fornix, uncinate fasciculus, and external capsule in left and right TLE to healthy controls; (2) investigate the potential of each of these measures for serving as a marker for TLE laterality; and (3) correlate these measures to epilepsy duration in left and right TLE.

Material and methods

Subjects

The study population included 28 controls (average age, 37.8 ± 8.9 SD (y)) and 28 TLE patients (17 left TLE, average age, 37.3 ± 11.6 SD (y); average epilepsy duration, 13.9 ± 17.0 SD (y); average age of disease onset, 23.6 ± 13.7 SD (y); 11 right TLE, average age, 44.6 ± 12.8 SD (y); average epilepsy duration, 26.1 ± 22.0 SD (y); average age of disease onset, 18.7 ± 20.8 SD (y)). Epilepsy patients were recruited from the Baylor College of Medicine comprehensive epilepsy center following clinical evaluation, video-EEG monitoring, and high-resolution MR imaging between July 2011 and June 2014. Exclusion criteria included patients with disabling cognitive impairment or other neurological co-morbidities. None of the patients had a seizure in the 24 h preceding imaging. Control subjects were recruited through local advertisements and word-of-mouth, and were selected to match patient groups in age, gender, and educational background as closely as possible. The study was approved by the Institutional Review Board. Written informed consent was obtained from all subjects prior to scanning.

Image acquisition

Imaging was performed on a Philips Ingenia 3.0T MRI scanner (Philips Medical Systems, Best, Netherlands) equipped with a 16 channel digital radiofrequency coil for signal reception. T_1-weighted imaging was performed as follows: TR = 2500 ms, TE = 4600 ms, FOV = 199 mm, matrix = 244 × 206, slice thickness = 1.4 mm, 284 slices. A spin-echo echo planar imaging based DTI sequence was acquired with the following acquisition parameters: FOV = 228 mm × 228 mm × 143 mm; acquired voxel size = 2 mm × 2 mm × 2.2 mm (i.e., 65 slices at 2.2 mm thick); TR/TE = 9400 ms/75 ms; parallel imaging acceleration factor = 2.5; *b*-values acquired: 0 (3 NSA) and 1000 (1 NSA along 32 directions) s/mm^2; chemical shift selective fat suppression. Slices were acquired in axial-oblique orientation.

DTI processing

Imaging data were acquired in PAR/REC format (Philips Healthcare, Best, Netherlands) and underwent DICOM-to-NIfTI format conversion with dcm2nii (http://www.mccauslandcenter.sc.edu/mricro/mricron/dcm2nii.html). Diffusion gradient directions were extracted using CATNAP (Landman et al., 2013). The FMRIB Software Library (FSL)'s Diffusion Toolkit (FDT) was then used for diffusion-weighted image pre-processing and fitting of the diffusion tensor (http://www.fmrib.ox.ac.uk/fsl/fdt/index.htm) (Behrens et al., 2003). For each subject, brain extraction was performed on non-diffusion weighted b0 images (b = 0 s/mm^2) and T_1-weighted images. Diffusion-weighted images were eddy-current corrected and co-registered to the b0 image in order to minimize head movement. Voxel-wise fitting of the diffusion tensor was then performed using FDT's dtifit (http://www.fmrib.ox.ac.uk/fsl/fdt/fdt_dtifit.html) (Behrens et al., 2003). To delineate the fornix, cingulum, external capsule, and uncinate fasciculus, the white matter of each subject's brain was parcellated in native diffusion space based on the anatomical labeling in the ICBM-DTI-81 atlas (Mori et al., 2008; Oishi et al., 2008). Right-left reversal and label-checking was manually performed after inspection (Rohlfing, 2013). To delineate the hippocampus, parcellation in native diffusion space based on the automated anatomical labeling (AAL) atlas was used (Tzourio-Mazoyer et al., 2002). Regions of interest in standard space were transformed to subject space using the inverse of the transformation matrix obtained by co-registering the