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Longitudinal hippocampal and extra-hippocampal microstructural and macrostructural changes following temporal lobe epilepsy surgery

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ABSTRACT

Objectives: 1) Characterize the evolution of microstructural changes in the contralateral, non-operated hippocampus—using longitudinal diffusion tensor imaging (DTI)—following surgery for temporal lobe epilepsy (TLE). 2) Characterize the downstream extra-hippocampal volumetric changes of the fornix and mammillary bodies after TLE surgery. 3) Examine the relationship between these measures and seizure/cognitive outcome.

Methods: Serial structural and DTI brain MRI scans were collected in 25 TLE patients pre- and post-surgery (anterior temporal lobectomy, ATL – 13; selective amygdalohippocampectomy, SelAH – 12) and in 12 healthy controls. Contralateral hippocampal fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were computed with manual hippocampal tracings as volumes of interest following co-registration to anatomical images. Fornix and mammillary body volumetry was performed by manual segmentation.

Results: After surgery, the non-resected hippocampus showed significant postoperative decline in FA ($p = 0.0001$), with increase of MD ($p = 0.01$) and RD ($p = 0.0001$). In contrast to the timing of our previously reported volume changes where atrophy is observed in the first week, diffusion changes occurred late, taking 1–3 years to develop and are not significant at one week after surgery. Diffusion changes are accompanied by delayed limbic circuit volume loss in the mammillary bodies (35%; $p < 0.0001$) and fornix (24%; $p < 0.0001$) compared to baseline. There was no correlation between postoperative diffusion or structural changes and memory score nor did the degree of postoperative change in hippocampal DTI parameters, mammillary body volume or fornix volume vary significantly based on seizure outcome.

Significance: Differences observed in the timing of postoperative volume (first week) and FA/MD (one year) changes would suggest that early contralateral hippocampal atrophy is not secondary to fluid shifts (dehydration) while the late DTI changes suggest ongoing microstructural changes extending beyond the early post-operative period. Postoperative hippocampal diffusion changes are accompanied by delayed mammillary body and fornix volume loss which did not differ when stratified by seizure outcome nor was correlated with degree of hippocampal diffusion change. Finally, we did not identify any significant correlation between postoperative diffusion parameter change and memory performance.

1. Introduction

Surgical treatment of medically refractory temporal lobe epilepsy (TLE) with mesial temporal sclerosis (MTS) is associated with excellent short term seizure control compared to non-operative treatment (Wiebe et al., 2001). However, seizure control decays over time, such that by 10 years after surgery less than half of patients remain seizure free (de Tisi et al., 2011; McIntosh et al., 2004). Reliable prediction of post-operative seizure outcome remains challenging. Recently, using longitudinally-obtained structural MRI scans in patients undergoing surgery for TLE, early and progressive post-operative volume loss of the non-resected (i.e., contralateral) hippocampus was identified (Elliott et al., 2016). This post-operative contralateral hippocampal volume loss was significantly more pronounced amongst patients with seizure recurrence at two years after surgery but was uncorrelated with surgical approach or neurocognitive outcome. At present, the mechanisms underlying this phenomenon of contralateral hippocampal volume loss are not yet known. Whether post-operative atrophy extends beyond the contralateral hippocampus, especially within structures having direct hippocampal connections, is also an open question.

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Diffusion tensor imaging (DTI) is a quantitative MRI approach which can be used to assess microstructural changes within brain regions of interest. In the hippocampus, DTI is a sensitive measure of microstructure which may provide information which is both complementary and partially overlapping to volumetry. Hippocampal DTI measures depend on the disease process in question and in the case of TLE are related to seizure lateralization (Bernhardt et al., 2016; Ercan et al., 2016; Fellgiebel et al., 2004; Fellgiebel and Yakushev, 2011; Förster et al., 2012; Gong et al., 2008; Kantarci, 2014; Kimiwada et al., 2006; Londono et al., 2003; Nazem-Zadeh et al., 2014; Szabo et al., 2014; Wieshmann et al., 1999; Yuce et al., 2016). Specifically, the hippocampus ipsilateral to seizure focus is generally found to have increased mean diffusivity (MD; a measure of the magnitude of rotationally invariant diffusion of water) and reduced fractional anisotropy (FA; a measure of directionality of water diffusion) relative to healthy controls (Bernhardt et al., 2016; Salmenpera et al., 2006). TLE DTI findings in the hippocampus contralateral to the seizure focus are more disparate, with some reports showing no difference from healthy controls (Assaf et al., 2003), and others showing reduced FA alone (Kimiwada et al., 2006; Liacu et al., 2010) or reduced MD alone (Thivard et al., 2005). In one prior study, contralateral hippocampal diffusivity changes were found to be at least partially reversible following either selective amygdalohippocampectomy (SelAH) or anterior temporal lobectomy (ATL) in 23 patients, based on a single post-operative scan (mean delay 8 months post-operatively) using a coarse region-of-interest drawn on native MD maps (Pfeuty et al., 2011). Interestingly, recovery of hippocampal diffusivity was suggested to correlate with postoperative improvement in measures of verbal and non-verbal memory—thought to be largely hippocampally mediated.

Previous investigations have used DTI extensively to examine longitudinal postoperative microstructural changes in TLE including extrahippocampal structures such as the fornix, cingulum, external capsule, and uncinate fasciculus among others (Concha et al., 2007; Liu et al., 2013; McDonald et al., 2010; Schoene-Bake et al., 2009; Winston et al., 2014; Yogarajah et al., 2010). Although early postoperative scans (within 1–2 months of surgery) are uncommonly acquired, when available, changes in diffusion parameters including in the fornix are evident within this time frame or earlier (Liu et al., 2013; McDonald et al., 2010). However, such postoperative longitudinal analyses have not been extended to include volumetric analysis of the interconnected structures that form part of the circuit of Papez, such as the fornix and mammillary bodies—an important next step given the more direct relationship between MRI-evident volume loss and histologic cell loss (Fuerst et al., 2003; Watson et al., 1997). It also remains unclear to what extent surgery affects the fornix and mammillary bodies ipsilateral and contralateral to the side of surgery.

The first goal of this study was to characterize the evolution of the microstructural properties of the contralateral, non-operated hippocampus using DTI metrics over time following TLE surgery. The second aim was to characterize the downstream extra-hippocampal changes of volume in the mammillary bodies and fornix. The final objective was to examine the relationship between these measures and clinically relevant outcome variables of seizure and neurocognitive outcome, as well as hippocampal volume.

2. Methods

2.1. Participants

Our study included 25 patients with medically refractory TLE who underwent surgery at the University of Alberta Hospital from 2005 to 2014 and a group of 12 control subjects of similar age with no history of epilepsy or any other neurologic or psychiatric disease. These subjects make up a subgroup of patients who also had longitudinal DTI taken from a previously published article on hippocampal volumetric change after TLE surgery (Elliott et al., 2016) and include some of the same TLE subjects investigated using DTI changes of the fornix after surgery (Concha et al., 2010, 2009, 2007, 2005; Liu et al., 2013). This study was approved by the University of Alberta Health Research Ethics Board and informed consent was obtained from all subjects. Participants were referred through the comprehensive epilepsy program. Each patient had a standard preoperative assessment including MRI, ictal and interictal long-term video electroencephalography (EEG) and neuropsychological evaluation. On the basis of this evaluation, participants either underwent an anterior temporal lobectomy (ATL, n = 13) or selective amygdalohippocampectomy (SelAH, n = 12) by a single neurosurgeon (author B.M.W.). In our institution, only patients with clear cut MRI evidence of MTS accompanied by corroborative clinical and EEG findings were offered SelAH as an option. Subjects had evidence of MTS on MRI (visually detectable hippocampal atrophy, or abnormal hippocampal shape/internal architecture with or without increased signal on T2/FLAIR sequences) (n = 23) and/or surgical pathology (n = 23) with concordant evidence from surface EEG-video telemetry and neuropsychiatric evaluation. One participant had imaging evidence of bilateral MTS (surgical side having more severe visible atrophy than the non-surgical side). Two subjects were reported as non-lesional on MRI but surgical pathology was consistent with MTS. In seven cases, surgery was preceded by bitemporal stereoelectroencephalography (SEEG) evaluation when recommended by the comprehensive epilepsy team on the basis of ambiguous surface telemetry. In all seven cases SEEG demonstrated unilateral temporal ictal onset.

2.2. Image acquisition

All patients were imaged preoperatively (within 3 months prior to surgery) and postoperatively (mean post-operative interval 4.3 ± 3.0 years, range 0.4–8.6). A subset of patients (n = 10) were also imaged at frequent intervals on postoperative days 1, 2, 3, 6, 60 and 120 in order to better characterize early postoperative structural brain changes. Sutures were used to close skin instead of staples for high quality MRI scanning in the immediate post-operative period. Non-operated, non-epileptic healthy subjects (n = 9, average age 33.3 ± 13.1 years old; range 23–58; all but one right-hand dominant) were scanned on two separate occasions (average inter-scan interval 6.9 ± 2.1 years; range 3.6–9.1). In addition, 3 healthy subjects (20, 22, and 33-years of age, all right-hand dominant) were imaged longitudinally (i.e., at baseline and then in a delayed fashion on days 1, 2, 3, 6 and 60) as controls for the longitudinally imaged surgical subgroup.

All MRI data were acquired on a 1.5T Siemens Sonata (Siemens Healthcare, Erlangen, Germany) using an eight-element head coil at the Peter S. Allen MR Research Centre at the University of Alberta. Whole brain, axial, T1-weighted, three-dimensional magnetization-prepared rapid-acquired gradient echo (MPRAGE) images were obtained aligned to anterior-posterior commissural line with voxel size 1 mm × 1 mm × 1 mm, TR 1890 ms, TE 4.38 ms, and scan time 6:03 min. DTI was acquired using a dual spin-echo, single shot echo-planar imaging sequence with 52 axial-oblique slices with no inter-slice gap; TR = 6400 ms; TE = 88 ms; $2 \times 2 \times 2\,mm^3$ voxel resolution (interpolated to $1 \times 1 \times 2\,mm^3$) along six non-collinear diffusion sensitizing gradient directions with $b = 1000\,s/mm^2$; 1 $b = 0\,s/mm^2$; 8 averages for a scan time of 7:26 min.

2.3. DTI analysis of hippocampus

Raw data were imported and processed to correct for subject motion, DWI signal drift, eddy current and EPI deformations in ExploreDTI (version 4, Utrecht, The Netherlands)(Leemans et al., 2009). Diffusion metrics of interest included fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), which were calculated using previously determined hippocampal volumes from high resolution T1-weighted images (Elliott et al., 2016). Each tracing was used as a region of interest (ROI) following affine co-registration of