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Progressive contralateral hippocampal atrophy following surgery for medically refractory temporal lobe epilepsy

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ABSTRACT

Objective: Determine the extent and time course of volumetric changes in the contralateral hippocampus following surgery for medically refractory temporal lobe epilepsy (TLE).
Methods: Serial T1-weighted MRI brain scans were obtained in 26 TLE patients pre- and post-temporal lobe epilepsy surgery as well as in 12 control subjects of similar age. Patients underwent either anterior temporal lobectomy (ATL) or selective amygdalohippocampectomy (SAH). Blinded, manual hippocampal volumetry (head, body, and tail) was performed in two groups: 1) two scan group [ATL (n = 6); SAH (n = 10)], imaged pre-surgery and on average at 5.4 years post-surgery; and 2) longitudinal group [ATL (n = 8); SAH (n = 2)] imaged pre-surgery and on post-operative day 1, 2, 3, 6, 60, 120 and a delayed time point (average 2.4 years).
Results: In the two scan group, there was atrophy by 12% of the unresected contralateral hippocampus ($p < 0.001$), with atrophy being most pronounced (27%) in the hippocampal body ($p < 0.001$) with no significant differences seen for the hippocampal head or tail. In the longitudinal group, significant atrophy was also observed for the whole hippocampus and the body with atrophy seen as early as post-operative day #1 which progressed significantly over the first post-operative week (1.3%/day and 3.0%./day, respectively) before stabilizing over the long-term to a 13% reduction in total volume. There was no significant difference in atrophy compared by surgical approach (ATL vs. SAH; $p = 0.94$) or side ($p = 0.31$); however, atrophy was significantly more pronounced in patients with ongoing post-operative seizures (hippocampal body, $p = 0.019$; whole hippocampus, $p = 0.048$). There were no detectable post-operative neuropsychological deficits attributable to contralateral hippocampal atrophy.
Significance: Significant contralateral hippocampal atrophy occurs following TLE surgery, which begins immediately and progresses over the first post-operative week. The observation that seizure free patients had significantly less atrophy of the contralateral hippocampus after surgery suggests the possibility of an early post-operative imaging marker to predict surgical outcome.

1. Introduction

Surgical treatment of medically refractory, temporal lobe epilepsy (TLE) with mesial temporal sclerosis (MTS) is associated with a high rate of seizure control, with rates of seizure freedom ranging between 41 and 72% depending on the length of follow-up (Cohen-Gadol et al., 2006; de Tisi et al., 2011; McIntosh et al., 2004; Samuel et al., 2001). It remains difficult to predict which patients will continue to experience seizures post-operatively. Moreover, post-operative neuropsychological consequences (e.g. verbal or non-verbal memory deficits) need to be balanced against long-term seizure benefit.

High resolution, structural magnetic resonance imaging (MRI) demonstrates diffuse pre-operative gray matter atrophy in TLE relative to healthy controls, which may be associated with cognitive dysfunction (Keller and Roberts, 2008). Though present throughout the brain, atrophy is most pronounced in the temporal lobe ipsilateral to the epileptic focus (Keller and Roberts, 2008; Keller et al.,

Abbreviations: ATL, anterior temporal lobectomy; MTS, mesial temporal sclerosis; TLE, temporal lobe epilepsy; SAH, selective amygdalohippocampectomy.

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2002), and quantitative, MRI-based, pre-surgical manual volumetry has consistently shown that hippocampal atrophy—sometimes undetectable visually—correlates well with the epileptogenic focus (Cendes et al., 1993a, 1993b; Jack et al., 1990; Watson et al., 1997). Gray matter changes following TLE surgery, however, are much less thoroughly described with largely inconsistent results based exclusively on comparisons between a single pre-operative and a single post-operative scan (Fernandes et al., 2014; Noulhiane et al., 2006). For example, one recent longitudinal study identified mild post-operative contralateral hippocampal atrophy in 47 TLE surgery patients imaged post-operatively at a single delayed time point (mean 4-years, range 0.5–9.6 years)(Fernandes et al., 2014). In contrast, an earlier report which compared contralateral hippocampal volumes at 6-months following TLE surgery in 24 patients with unilateral MTS to those in 16 healthy controls did not find any significant difference in hippocampal volumes (Noulhiane et al., 2006). Both of these reports studied the hippocampus as a whole and did not look at hippocampal subcomponents.

Understanding the specific structural consequences of TLE surgery may ultimately be clinically useful, as they may help to predict the likelihood of poor post-operative seizure control or neuropsychological deterioration on the basis of early post-operative imaging findings. In this study, the first objective was to characterize the extent and time course of changes found in the contralateral hippocampus, including its subcomponents of head, body, and tail, following TLE surgery in patients scanned longitudinally at short intervals within the first post-operative week and beyond. The second objective was to investigate the relationship between post-operative contralateral hippocampal volume and neurocognitive outcomes, surgical approach, resected side and seizure control.

2. Methods

This study was approved by the University of Alberta Health Research Ethics Board and informed consent was obtained from all participants.

2.1. Participants

Our study included 26 patients with medically refractory TLE who underwent surgery at the University of Alberta Hospital from 2005 to 2014 and group of 12 control subjects of similar age with no history of epilepsy or any other neurologic or psychiatric disease. Participants were referred through the comprehensive epilepsy program. Each patient had a standard preoperative assessment including MRI, ictal and inter-ictal long-term video electroencephalography (EEG) and neuropsychological evaluation. On the basis of this evaluation participants either underwent an anterior temporal lobectomy (ATL) or selective amygdalohippocampectomy (SAH) 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 are offered SAH as an option. The majority of cases had subjective evidence of unilateral MTS on MRI (visually detectable hippocampal atrophy, or abnormal hippocampal shape/internal architecture with or without increased signal on T2/FLAIR sequences) (n = 23) with concordant evidence from surface EEG-video telemetry and neuropsychiatric evaluation. The remaining three cases included one participant with imaging evidence of bilateral MTS (surgical side with more severe visible atrophy than non-surgical side), one with an isolated right inferior frontal lesion and one with no detectable lesion. 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

Patients were imaged in two distinct groups, either: i) as part of a two-scan group (N = 16) having a single preoperative and a single delayed postoperative scan (average inter-scan interval 5.4 ± 3.2 years, range 0.4–8.6); or ii) as part of an intensively imaged longitudinal group (N = 10) scanned on postoperative days 1, 2, 3, 6, 60, 120 and a delayed time point (average 2.4 ± 1.5 years, range 1.0–5.7) in order to better characterize the early time course of postoperative hippocampal volume change. Sutures were used to close skin in the longitudinal group instead of staples for high quality MRI scanning in the immediate post-operative period. To investigate variability of hippocampal volumes in the non-operated, non-epileptic brain, nine healthy subjects (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) as controls for the two-scan group, while three 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 longitudinal group.

Images for all patients and controls were acquired on a Siemens Sonata 1.5T scanner (Siemens Healthcare, Erlangen, Germany) using an eight-element head coil. 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.

2.3. Volumetric analysis

Volumetric analysis was performed using manual segmentation by a single trained observer (author C.E.). DISPLAY software (Montreal Neurological Institute, Montreal, Canada) was used to delineate anatomical boundaries of the structures of interest in three orthogonal planes simultaneously on 3D MPRAGE images (Bonilha et al., 2004). The observer was blinded to surgical status (i.e., pre-resection, post-resection or control) and time point (i.e., post-operative day) by ensuring that anonymized images of patients were interspersed with controls in random order. Images were zoomed in to the structure of interest such that the resection cavity (or lack thereof) was not visible. The hippocampal formation was traced using a protocol described by Malykhin and colleagues with previously demonstrated robust inter- and intra-rater reliability (Malykhin et al., 2007). Segmentation yielded whole hippocampal volume (WHV), as well as hippocampal head (HHV), body (HBV) and tail (HTV) volumes for each subject (Supp. Fig. 1). To evaluate the possibility of mechanical deformation causing spurious atrophy of periventricular structures—say, due to dural opening and/or cerebrospinal fluid egress during resection—the volume of the caudate nucleus was measured using a manual protocol described by Looi and coworkers (Looi et al., 2008). The caudate nucleus is not directly connected to the mesial temporal lobe and would not be expected to change in volume due to disconnection following temporal resection.

2.4. Defining a variability threshold for hippocampal volume

To identify a conservative threshold beyond which changes from baseline in the longitudinal surgical group would represent a real change (attributable to a surgical effect rather than measurement error), a normal variation range for hippocampal (and sub-regional)