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Frontal gray matter abnormalities predict seizure outcome in refractory temporal lobe epilepsy patients

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ABSTRACT

Developing more reliable predictors of seizure outcome following temporal lobe surgery for intractable epilepsy is an important clinical goal. In this context, we investigated patients with refractory temporal lobe epilepsy (TLE) before and after temporal resection. In detail, we explored gray matter (GM) volume change in relation with seizure outcome, using a voxel-based morphometry (VBM) approach. To do so, this study was divided into two parts. The first one involved group analysis of differences in regional GM volume between the groups (good outcome (GO), e.g., no seizures after surgery; poor outcome (PO), e.g., persistent postoperative seizures; and controls, N = 24 in each group), pre- and post-surgery. The second part of the study focused on pre-surgical data only (N = 61), determining whether the degree of GM abnormalities can predict surgical outcomes. For this second step, GM abnormalities were identified, within each lobe, in each patient when compared with an ad hoc sample of age-matched controls. For the first analysis, the results showed larger GM atrophy, mostly in the frontal lobe, in PO patients, relative to both GO patients and controls, pre-surgery. When comparing pre-to-post changes, we found relative GM gains in the GO but not in the PO patients, mostly in the non-resected hemisphere. For the second analysis, only the frontal lobe displayed reliable prediction of seizure outcome. 81% of the patients showing pre-surgical increased GM volume in the frontal lobe became seizure free, post-surgery; while 77% of the patients with pre-surgical reduced frontal GM volume had refractory seizures, post-surgery. A regression analysis revealed that the proportion of voxels with reduced frontal GM volume was a significant predictor of seizure outcome ($p = 0.014$). Importantly, having less than 1% of the frontal voxels with GM atrophy increased the likelihood of being seizure-free, post-surgery, by seven times. Overall, our results suggest that using pre-surgical GM abnormalities within the frontal lobe is a reliable predictor of seizure outcome post-surgery in TLE. We believe that this frontal GM atrophy captures seizure burden outside the pre-existing ictal temporal lobe, reflecting either the development of epileptogenesis or the loss of a protective, adaptive force helping to control or limit seizures. This study provides evidence of the potential of VBM-based approaches to predict surgical outcomes in refractory TLE candidates.

1. Introduction

Temporal lobe epilepsy (TLE) is the most frequent type of refractory epilepsy, which commonly leads to surgical treatment (Engel, 2001). However, the successful rate of brain surgery to obtain complete seizure freedom is only about 66% in this population at 1 year (Spencer and Huh, 2008; Tellez-Zenteno et al., 2005), dropping to less than 50% after 10 years (de Tisi et al., 2011). It has been suggested that poor seizure control is the result of multiple factors, including insufficient resection, or the existence of other extra-temporal ictal generators likely stemming from occult or unknown pathology elsewhere in the brain. Therefore, developing more reliable predictors of clinical (seizure) outcome following epilepsy brain surgery is an elusive, but critical continuous clinical goal. To date, the most commonly used predictors are clinical characteristics such as the presence of a lesion such as ictal mesial temporal sclerosis (MTS) or the size of the resection (see review by Zhang et al., 2013). Nevertheless, in the last years, new promising predictors of clinical outcomes in refractory TLE have been described based on pre-surgery MRI measures. For instance, using resting-state functional connectivity, Xu et al. (2014) found that compared with poor outcomes, a successful surgical outcome in TLE was associated with larger interhemispheric homotopic functional connectivity (FC) differences, pre-surgery. Using structural imaging techniques, recurrent post-surgical seizures have been associated with atrophy in multiple areas such as the thalamus (Keller et al., 2015a; Keller et al., 2015b),

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temporopolar, and insular cortices, (Bernhardt et al., 2010; Bernhardt et al., 2015), along with abnormal white matter tracts emerging from the thalamus (Keller et al., 2015b). In a study using voxel-based morphometry (VBM), Yasuda et al. (2010) found that poor seizure outcome (PO) was associated with a larger pattern of preoperative gray matter (GM) atrophy than good seizure outcome (GO). Importantly, these authors also studied GM change post-surgery, and observed that GO patients displayed an increase in GM postoperatively, compared to PO patients.

Such results suggest that protective neuroplastic mechanisms, a form of functional or structural reserve, may exist in patients that will become seizure free post-surgery. While these results are promising both for understanding the basis of a positive response to the surgery and improving the prediction of surgical outcome, to date, they have not yet been reproduced nor tested at the individual level, which is the major limitation in terms of clinical application.

Accordingly, the current investigation was undertaken to test the association between GM volume and seizure outcome following procedures such as standard anterior temporal lobectomy (ATL) or laser ablation of the MTS, all toward the goal of advancing our ability to use GM measures as predictors of outcome. Based on VBM, we first report on GM volume differences between good and poor outcome groups both prior to and after brain surgery. Second, we focus on pre-surgical individual whole brain GM volume and seek to determine a pattern distinguishing patients with a good versus poor seizure outcome. Based on a prior report (Yasuda et al., 2010), in addition to our initial group results, we hypothesized that individual good or poor outcomes can be identified on a pre-surgical basis by using the level of GM volume loss relative to a large normative age-matched control group. The overarching goal of this work is to try to identify a new structural GM measure, conceptualized as an index of either structural vulnerability or reserve, easily computed as part of pre-surgical workups, capable of reliably predicting individual seizure outcomes in refractory TLE patients.

2. Material and methods

2.1. Participants

2.1.1. TLE patients

A total of 61 patients with refractory TLE that underwent surgical intervention were recruited from the Thomas Jefferson University Comprehensive Epilepsy Center. The recruitment period was between 2007 and 2014, with eligible patients selected serially with no change in inclusion criteria or scanner software parameters during that time. Among eligible patients, a total of 48 (79%) were scanned both pre- and post-surgery. Patients received either a standard en bloc resection of their anterior temporal lobe (ATL, including a partial amygdalohippocampectomy [approximately 4–6 cm from the temporal pole with the size smaller for the patients with left (language dominant) TLE]) (N = 49), laser ablation of the ictal hippocampus (N = 7), or a neocortical resection with the mesial regions spared (N = 5). Using data collected at least 6 months post-surgery, patients were identified as either "good" (Engel Class I, n = 34, e.g., no seizure since the surgery) or "poor" outcome (Engel Class II or higher, n = 27, e.g., persistent post-surgical seizures) (GO and PO, respectively) (Engel et al., 1993). Details of the Thomas Jefferson Comprehensive Epilepsy Center algorithm for surgical decision making is described in Sperling et al. (1992). A combination of video/surface EEG (at least 96 h), MRI, PET, neuropsychological testing and, for a subgroup of patients (25%, n = 15), implanted electrodes and electrocorticography was used to lateralize the side of seizure focus. In order to become a good surgical candidate and be included in this study, a patient must have met the following inclusion criteria: failed at least three seizure medications; unilateral temporal lobe seizure focus; concordant MRI and/or PET findings of unilateral temporal lobe abnormality. TLE patients were excluded from the study for any of the following reasons: medical illness with central nervous system impact other than epilepsy; contraindications to MRI; multiple seizure foci (including bilateral temporal foci); extra-temporal seizures; psychiatric diagnosis other than an Axis-I Depression or Anxiety Disorder; or hospitalization for any Axis I disorder listed in the Diagnostic and Statistical Manual of Mental Disorders, IV. Patients provided written informed consent. Table 1 outlines the patients' demographic and clinical characteristics.

2.1.2. Healthy controls

A total of 119 healthy normal controls (NCs) were recruited from the Thomas Jefferson University community, in order to match the patient participants in age and gender. All controls were free of psychiatric or neurological (central nervous system) disorders based on a health screening measure. Among them, 24 were scanned twice with an average interval of 429 days (SD: 119) to match the pre- to post-scan interval for the patients. This study was approved by the Institutional Review Board for Research with Human Subjects at Thomas Jefferson University, and all participants provided a written informed consent.

2.2. MRI data acquisition

All participants underwent Magnetic Resonance Imaging on a 3-T X-series Philips Achieva clinical MRI scanner (Amsterdam, the Netherlands) using an 8-channel head coil. Both the NCs and the TLE patients underwent identical scanning sessions. In detail, each patient underwent a pre-surgical (mean = 114 days prior to surgery, N = 61) and post-surgical scan (m = 305 days after surgery, minimum of 6 months, N = 48). High resolution T1-weighted images were collected using an MPRage sequence (180 slices, 256 × 256 isotropic voxels; TR = 640 ms, TE = 3.2 ms, FOV = 256 mm, flip angle = 8°, voxel size = 1 × 1×1 mm). Subjects lay in a foam pad to comfortably stabilize the head, and were instructed to remain still throughout the scan.

2.3. Preprocessing analyses

In order to preprocess each individual T1 sequence, we used the VBM8 toolbox, available in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). To improve the probability of detecting areas with GM volume changes in relation to surgical outcome, the images of patients with right TLE were flipped left-to-right so that all data could be analyzed together and treated as ipsilateral and contralateral to seizure onset and surgical target area. In order to minimize left-to-right bias when comparing with controls, we also side flipped the same proportion of the healthy control sample. In this context, the left hemisphere was considered the ictal hemisphere.

T1-weighted images were preprocessed using a standard routine ("estimate and write"): the images were spatially normalized to the same stereotaxic space (A Fast Diffeomorphic Registration Algorithm (DARTEL) algorithm, MNI (Montreal Neurological Institute)-152), segmented into GM, white matter and cerebrospinal fluid, non-linearly modulated (aiming to correct to local volume changes during the normalization) and smoothed with an isotropic Gaussian kernel of 8 mm. A test of quality was performed to observe homogeneity and co-registration between the data. Also, post-surgery postprocessed T1s were individually checked to ensure that the normalization step was accurate and comparable to the pre-surgery postprocessed T1s (see Supplementary Fig. 1 for an example).

2.4. Prediction of seizure outcome

2.4.1. Creation of age-matched control templates

The group of controls was split into three groups based on their age: Under 30 (N = 44, minimum age: 18), Between 30 and 40 (N = 34),