Different Epileptic Brain Networks in Unilateral Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis Identified by the Whole Brain Tract-Based Automatic and Surface-based Analyses

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Introduction:

Previous structural magnetic resonance studies found widespread gray matter (GM) and white matter (WM) abnormalities in patients with unilateral mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS) [1, 2]. Therefore, MTLE with HS was regarded as a network disorder [3]. In the present study, we proposed a surface-based analysis and a tract-specific analysis over the whole brain to detect, respectively, the GM and WM alterations in unilateral MTLE with HS. Since the sclerotic hippocampus may generate epileptic activities and spread via the WM tracts to other extratemporal regions [4], we hypothesized that the WM alterations due to MTLE with HS might affect the averaged cortical thickness of the connected GM regions. In addition, we assumed that left and right MTLE with HS should exhibit different epileptic networks.

Methods:

The subjects consisted of 25 adults with clinical diagnosis of MTLE with unilateral HS (13 left HS, age: 36.39±8.66 years; 12 right HS, age: 39.33±9.5 years) and 18 age-, sex- and handedness-matched healthy adult controls (age: 36.38±8.65 years). MR scanning was performed on a 3T MRI system (TIM Trio, Siemens) with a 32 channel phased-array head coil. DSI was acquired using a twice-refocused balanced echo diffusion echo planar imaging (EPI) sequence, TR/TE = 9600/130 ms, FOV = 200 × 200 mm, image matrix size 80 × 80, and 2.5 mm slice thick. A total of 102 diffusion encoding gradients with the maximum diffusion sensitivity bmax = 4000 s/mm^2 were sampled on the grid points in a half sphere of the 3D q-space with $|q| \leq 3.6$ units [5]. T1-weighted imaging was performed using a 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence: repetition time (TR) / echo time (TE) = 2000 ms/3 ms, flip angle = 9°, FOV = 256 × 192 × 208 mm^3, acquisition matrix = 256 × 192 × 208, resulting in isotropic spatial resolution of 1 mm^3. The surface-based analysis pipeline consists of several stages: T1-weighted image registration, the B1 bias field estimation, the main body of WM estimation, the WM, GM, and pial surface estimation [6]. We further subdivided each hemisphere into 6 sub-cortical regions, 38 cortical gyri, and brain stem by an automatic parcellation [7] to compute volume of sub-cortical regions and averaged cortical thickness of cortical gyri. Whole brain tractography was reconstructed by tract-based automatic analysis (TBAA). The procedure of TBAA method was briefly described as follows. 1) Study subjects were coregistered to create a study specific template (SST) using large deformation diffeomorphic metric mapping (LDDMM) [8]. 2) The SST was coregistered to the DSI template. 3) Sampling coordinates of 74 tracts were transformed from the DSI template to individual DSI datasets via the transformation matrix between DSI template and SST as well as the transformation between SST and individual DSI. 4) Generalized fractional anisotropy (GFA) values were sampled in the native DSI space using the transformed sampling coordinates and a 2D array of GFA profiles, named connectogram, was created for each subject.

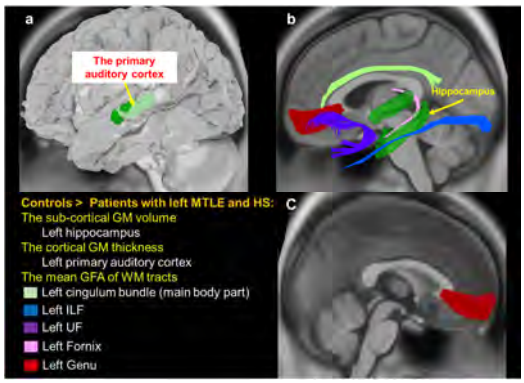

Figure 1: Comparisons of the sub-cortical GM volume, the cortical GM thickness and mean GFA of WM tracts between controls and patients with left MTLE and HS.

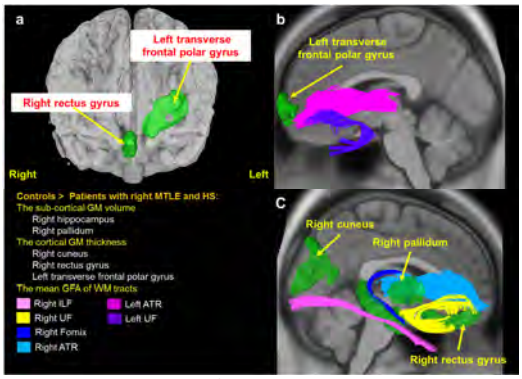

Figure 2: Comparisons of the sub-cortical GM volume, the cortical GM thickness and mean GFA of WM tracts between controls and patients with right MTLE and HS.

A threshold free cluster weighted (TFCW) method was used following Smith's approach [9] to estimate weighted scores ($S(p) = \sum_{h=h_0}^{h_5} e_p(h)$, where e_p is the cluster extent level which survives at the given threshold h at step p) of effect size of each step between two groups. A 98% cut-point of the histogram of TFCW scores was then estimated to determine the most different clusters between these two groups. The most different clusters were then used to sample GFA profiles and computed mean GFA values. Mann Whitney U-test was performed to investigate the difference in volume of sub-cortical regions, cortical thickness of cortical gyri, and mean GFA of 74 WM tracts between controls and patients. Bonferroni correction was applied to control the p value from multiple comparison problem.

Results:

In sub-cortical regions, both left and right MTLE with HS patients showed significant volume reduction in the ipsilateral hippocampus ($p < 0.001$, corrected). Patients with right MTLE and HS had a tendency of volume reduction in the right pallidun ($p = 0.046$, uncorrected). In cortical gyri, there was no significant difference in the averaged cortical thickness between controls and patients after Bonferroni correction. Patients with left MTLE and HS showed slightly thinner cortical thickness in the left primary auditory cortex ($p = 0.048$, uncorrected) (Figure 1a); right MTLE and HS showed mild cortical thickness reduction in the right cuneus ($p = 0.008$, uncorrected) and rectus gyrus ($p = 0.035$, uncorrected), and the left transverse frontal polar gyrus ($p = 0.048$, uncorrected) (Figure 2a, c). In altered WM microstructural integrity, we found significant mean GFA reduction in the left cingulum bundle (main body part), fornix, inferior longitudinal fasciculus (ILF), uncinate fasciculus (UF), and genu in patients with left MTLE and HS ($p < 0.05$, corrected) (Figure 1b). Patients with right MTLE and HS showed significant mean GFA reduction in the right fornix and ILF, the bilateral UFs, and the bilateral ventral anterior thalamic radiations (ATR) ($p < 0.05$, corrected) (Figure 2b, c).

Conclusions:

Using the surfaced-based analysis and TBAA method to assess, respectively, the WM and GM alterations over the whole brain, this work demonstrated different epileptic brain networks between left and right MTLE with HS. The results of right MTLE with HS demonstrated the possible epileptic pathway: the Fornix, UF and ATR may contribute to be a pathway to propagate the epileptic activity from the hippocampus to the orbito-frontal and middle frontal gyrus, which involves the rectus and transverse frontal polar gyri [7]. In the contrast, left MTLE with HS exhibit the ipsilateral alterations in the limbic tracts (Fornix, UF, and cingulum bundle) and the superior temporal gyrus. The epileptic pathway in left MTLE with HS may be related to Papez circuit [10]. Both patient groups showed the ipsilaterally impaired Fornix, implying that Fornix may play a role of output pathway of the sclerotic hippocampus. Compared to left MTLE with HS, right MLTE with HS also showed more widespread GM alterations in the frontal and occipital lobes. In conclusion, we successfully identified different epileptic networks in left and right MTLE with HS, and found more extensive WM and GM alterations in right MLTE with HS than in left MLTE with HS. Future work will include the clinical data (i.e. seizure duration and type) into our analysis to investigate the epileptogenic progress of the altered WM and GM in unilateral MTLE with HS.

References:[1] Keller et al. (2008) Epilepsia. [2] Liu et al. (2012) NeuroImage: Clinical. [3] Engel et al. (2013) Curr. Opin. Neurol. [4] Seifert et al. (2002) Epilepsia. [5] Wedeen et al. (2005) Magn Reson Med. [6] Fischl and Dale. (2000) Proc Natl Acad Sci U S A. [7] Desikan et al. (2006) NeuroImage. [8] Hsu et al. (2012) NeuroImage. [9] Smith et al. (2009) NeuroImage. [10] Papez. (1937) The Journal of neuropsychiatry and clinical neurosciences.