Left Temporal Lobe Epilepsy Associated With Hippocampal Sclerosis And Reduced Functional Connectivity In The Default Mode Network

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Target audience: Researchers and physicians who work in the field of neuroscience, specifically epilepsy.

Purpose:

We hypothesized that medial temporal lobe epilepsy with left hippocampal sclerosis (HS) would yield altered functional connectivity (FC) between medial temporal lobes and other default mode network (DMN) nodes than healthy controls (HC) assessed by resting state (rs)-fMRI. We also examined accompanying structural changes, in patients with HS to study effect of volume loss on FC.

Material and Methods:

IRB was obtained for this study and all the participants gave signed consent form.

Subjects: Twenty-five patients with left HS (M/F: 13/12; 30.95±7.27 years) and 17 HC (M/F: 9/8; 29.31±8.11 years) (t-test; p>0.5) were included in the study. All patients were diagnosed on basis of clinical, electrophysiological and MRI findings.

Image Acquisition: All imaging data of the brain were obtained on a 3T MR scanner (Magnetom, Trio TIM system, Siemens, Germany) equipped with an 8-channel phase-array head coil. A T2* weighted gradient echo spiral pulse sequence (TR /TE: 2000/35 msec, FA 75°, FOV: 230 mm, matrix: 64 x 64, in-plane spatial resolution of 3.6 mm) was used while the subjects kept their eyes closed without a specific concentration. All participants also underwent structural 3D T1-weighted high resolution images (magnetization prepared rapid gradient echo-MPRAGE) (TR/TE: 1900/3.4 msec; FA: 90; FOV: 256mm; matrix: 224x256; distance factor: %50).

Data Processing and Analysis

-Preprocessing of the fMRI data: The rs-fMRI scans were preprocessed using SPM8 [1]. Preprocessing of the rs-fMRI data included realignment, slice-timing correction, coregistration and normalization (to Montreal Neurological Institute template (MNI)), and spatial smoothing with an 6 mm³ isotropic Gaussian kernel.

-Functional Connectivity Analysis: Using the CONN toolbox in MATLAB R2008a [2], we identified principal components associated with segmented white matter (WM) and cerebrospinal fluid (CSF) for each subject and entered WM, CSF and realignment parameters as confounds in a first-level analysis. The data were band-pass filtered to 0.008 Hz–0.09 Hz. For group analysis, we then used a region of interest (ROI) and seed-voxel analysis, and specified connectivity patterns separately for two 6 mm spherical clusters different seed ROIs located in bilateral parahippocampal cortex (PHC). CONN computed correlations between the specified seeds and the other four specified ROIs, located in medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC) and bilateral angular gyrus (AG) for roi-to-roi analysis. Correlation coefficient images were z-transformed, with one and two sample t-tests examining within- and between connectivity. Roi-to-roi results were computed as significant at a voxelwise threshold of level of p<0.001 uncorrected and a cluster-level threshold of p<0.05 FDR corrected. Next, we used a seed-to-voxel analysis to explore whether bilateral PHC was differentially connected to other brain regions outside of the DMN in patients group. Using the same seed ROIs in bilateral PHC defined above, temporal correlations were computed between these seeds and all the other voxels in the brain. Seed-to-voxel results are reported as significant at a voxelwise threshold of level of p<0.001 uncorrected and cluster-level threshold of p<0.05 FDR corrected. T-test and Fisher's Z-transformed correlations were used to compute differences in FC between the patients with HS and HC. For the individual seed-based connectivity, we applied psychophysiological interaction (PPI) analysis to examine functional coupling respectively between the bilateral PHC and other four specified ROI located in DMN regions. Volumes of interest (VOI) s were defined as spheres with 6 mm radius. To form a sphere mask around a voxel of interest, we used the fslmaths commands. The time-series was extracted from the voxel that was at the center of the activation cluster from the normalized fMRI file by using fslmeants command. We used FEAT toolbox [3] with the seed time-series file and calculated Z score values for each subject. To determine the effect of volume loss of temporal lobe and other possibly related cortical and subcortical structures, we also carried out a volume analysis using Freesurfer Version 4.5.1, as described by Fischl et al. [4, 5].

Results:

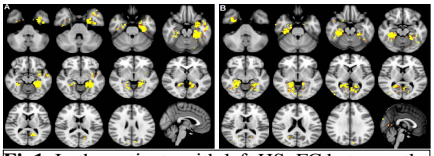

Fig1. In the patients with left HS, FC between the left PHC (A) and right PHC (B) and all other brain regions (seed-to-voxel analysis).

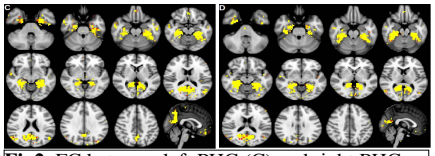

Fig2. FC between left PHC (C) and right PHC (D) to all other brain regions (seed-to-voxel) in controls.

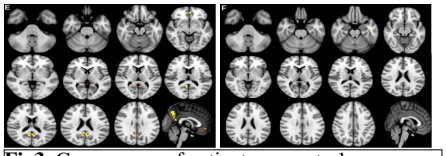

Fig3. Group maps of patients vs controls. Decreased FC between left PHC and all other brain regions in patients compared to controls is shown in E. Please note that no significant change in FC of the right PHC and all other brain regions in patients compared to controls, shown in F.

ROI-to-ROI analysis for the functional connectivity revealed marked reduction between left PHC-right PHC (t=8.41, p=0.0001) and there was no significant FC between PHC and other specified default mode regions in the left HS group. On the contrary, the healthy group showed significantly stronger connectivity between left PHC and bilateral AG, left PHC-right AG (t=5.69, p=0.0001) and left PHC-left AG (t=3.58, p=0.0027). The HC group also showed significantly stronger connectivity between left PHC and PCC (t=5.25, p=0.0001), and also between left PHC and MPFC (t=4.66, p=0.0004). In the group ROI-to-ROI analysis, there were significant reductions in FC of specified regions, especially between left PHC-PCC (t=3.72, p=0.001175), left PHC-MPFC (t=3.39, p=0.002193) and left PHC-right AG (t=3.36, p=0.001169) in the patients. Similar results are obtained from the seed-to-voxel analysis (Fig.1, Fig.2, and Fig.3). The patients had significantly decreased total cerebral cortex volume and subcortical gray matter nuclei, more prominent in the left hemisphere (all, p<0.05).

Discussion and Conclusion:

Resting state-fmri of the individual-based and group analyses, compatible to each other, showed decreased functional connectivity between left and right medial temporal lobes and between each medial temporal lobe with other DMN nodes in the patients with left hippocampal sclerosis. Given reduced cortical and subcortical volumes may also contribute and/or be associated with decreased FC between the medial temporal lobes and DMN nodes.

References:

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