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Short Communication

Presurgical hyperconnectivity of the ablation volume is associated with seizure-freedom after magnetic resonance-guided laser interstitial thermal therapy

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ABSTRACT

Purpose: Magnetic Resonance-guided Laser Interstitial Thermal Therapy (MRgLITT) is an emerging minimally-invasive alternative to resective surgery for medically-intractable epilepsy. The precise lesioning effect produced by MRgLITT supplies opportunities to glean insights into epileptogenic regions and their interactions with functional brain networks. In this exploratory analysis, we sought to characterize associations between MRgLITT ablation zones and large-scale brain networks that portended seizure outcome using resting-state fMRI.

Methods: Presurgical fMRI and intraoperatively volumetric structural imaging were obtained, from which the ablation volume was segmented. The network properties of the ablation volume within the brain's large-scale brain networks were characterized using graph theory and compared between children who were and were not rendered seizure-free.

Results: Of the seventeen included children, five achieved seizure freedom following MRgLITT. Greater functional connectivity of the ablation volume to canonical resting-state networks was associated with seizure-freedom ($p < 0.05$, FDR-corrected). The ablated volume in children who subsequently became seizure-free following MRgLITT had significantly greater strength, and eigenvector centrality within the large-scale brain network.

Conclusions: These findings provide novel insights into the interaction between epileptogenic cortex and large-scale brain networks. The association between ablation volume and resting-state networks may supply novel avenues for presurgical planning and patient stratification.

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1. Introduction

Magnetic Resonance guided Laser InterstitialThermal Therapy (MRgLITT) is a minimally-invasive alternative to open resective neurosurgery for treatment of intractable localization-related epilepsy. The technique has rapidly gained popularity across North America, with several reports of superior peri-operative indicators, such as length of stay and patient comfort, with comparable seizure outcomes [1]. The targeted lesions produced by MRgLITT also supply an opportunity to glean insights into the interactions between epileptogenic brain regions and functional brain networks. The fact that the ablation volumes produced by MRgLITT are well-demarcated and easily identifiable intraoperatively affords the opportunity to study these interactions. Unlike resective procedures, there is also minimal disruption of normal brain tissue, thereby circumventing technical issues surrounding brain shift, and collateral brain injury due to retraction or via the corridor of dissection.

Here, we sought to characterize the functional relations between the volume of MRgLITT ablation and functional brain networks in children who were and were not rendered seizure-free post-operatively. We hypothesized that, irrespective of location or pathology, the ablation volume of children who subsequently became seizure-free would possess differential functional interactions with the brain's intrinsic networks, which could be further studied for improvement of presurgical planning and patient stratification.

2. Methods

Seventeen children undergoing MRgLITT with preoperative resting-state fMRI from 2011 to 2016 were identified. The children had heterogeneous pathologies and epileptogenic zone locations and the procedure was tailored to the individual patient based on multi-modal preoperative investigations (**Supplementary Materials**). The primary outcome of interest was seizure-freedom (i.e. Engel Class 1) with minimum one-year follow-up. The study was approved following Research Ethical Board review.

2.1. Functional MRI acquisition and preprocessing

Data were collected using a 1.5 T scanner (Philips, the Netherlands) with a single channel transmit/receive head coil, as previously published [2]. The data were analyzed using standard FMRIB Software Library (FSL) tools. Slice-timing and motion correction were performed and the functional data was aligned to each subject's high-resolution anatomical T1-weighted images. Data underwent spatial smoothing using a 5 mm FWHM Gaussian kernel and was bandpass filtered with a lower cut-off frequency of 0.01 Hz. Independent component analysis (ICA) maps were then used to denoise the data [3].

2.2. MRgLiTT ablation segmentation

Tracing of ablation sites was performed using the subject's intraoperative structural imaging and a public domain tool, ITK-SNAP v1.4.1 [4]. The software program provides semiautomatic segmentation using an active contour model with predetermined seed points extended to ablation boundaries. All segmentations were manually examined for accuracy by two authors (N.B.S. and S.S.). The estimated epileptogenic lesion on the pre-ablation MRI scan was manually segmented for volumetric comparison with the MRgLITT ablation volume.

2.3. Generation of adjacency matrices

The timeseries of 14 nodes of three resting-state networks, the default mode (DMN), salience (SAL) and dorsal attention networks, were extracted using coordinates from the literature [5], co-registered to each subject's individual fMRI using a two-step registration including the subject's anatomical T1. The timeseries of the volume that was subsequently ablated was also extracted from each subject's presurgical fMRI. Pairwise relations between combinations of nodes were plotted as an adjacency matrix, with mutual information (MI) used as the index of functional connectivity. Mutual information is a dimensionless quantity that describes the reduction of uncertainty about one random variable given knowledge of another. A value of zero suggests that two variables are statistically independent, whereas higher values suggest greater reduction in the uncertainty in the prediction of one variable given observation of another [6]. This non-linear measure was chosen to mitigate the effects of potentially variable hemodynamic response functions within epileptogenic cortices, compared to non-epileptogenic brain regions [7].

2.4. Network properties in seizure-free and non-seizure-Free patients

Adjacency matrices were created for each subject, from which node- and graph- specific network properties were calculated [8]. Differences in connectivity of the ablation volume between seizure-free and non-seizure-free children was compared using non-parametric permutation testing and displayed using BrainNet viewer [9]. The overall efficiency of the graph and the "hubness" of the ablation volume were respectively calculated, as strength and eigenvector centrality of the node [8]. The hub properties of a node reflect its importance within the embedded network. Strength is a non-sensitive measure of the sum of the weights of the edges around a given node while eigenvector centrality allocates greater importance to nodes that have neighbours that are themselves of high importance. These measures were compared between seizure-free and non-seizure-free children across a variety of network thresholds. False discovery rate (FDR) was used to correct for multiple comparisons, with $q < 0.05$ deemed statistically significant. All analyses were performed in MATLAB (Natick, MA).

3. Results

Of the 17 children included in the study, 5(30%) achieved seizure-freedom. There were no significant differences between seizure-free and non-seizure-free children with respect to any electrophysiological or neuroimaging variable (Table 1). There were also no differences with respect to temporal vs. extra-temporal ($p = 0.6$), mesial (mesial temporal, cingulate, mesial frontal, precuneus) vs. non-mesial location ($p = 0.32$). Children who were not seizure-free following ablation were attempted on a significantly greater number of antiepileptic drugs ($p = 0.001$).

3.1. No difference in segmentation volumes between seizure-free and non-seizure free children

All segmented ablation volumes are presented in a common standard space in Fig. 1**A**. No differences were observed between the ablation volumes of children who subsequently became seizure-free and those who did not (Fig. 1**B;** seizure-free: 5142 mm [2]; not seizure-free 5114 mm [2]; $p = 1.0$). Children who were not seizure-free were more likely to have a repeat procedure for residual disease than those who became seizure-free ($p = 0.05$), although there was no significant difference between the two cohorts with respect to the volume of residual disease ($p = 0.98$) or the percentage overlap between the ablation volume and lesion volume (**Supplementary Materials**, $p = 0.47$).

3.2. Children who are seizure-free demonstrate greater connectivity of the ablation volume to resting-state networks

Using non-parametric permutation testing, comparing seizure-free and non-seizure-free cohorts, the ablation volume was found to be significantly hyperconnected to the large-scale networks of children who subsequently became seizure-free (Fig. 1A). Following FDR