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Global and regional functional connectivity maps of neural oscillations in focal epilepsy

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Abstract

Introduction: Intractable focal epilepsy is a devastating disorder with profound effects on cognition and quality of life. Epilepsy surgery can lead to seizure freedom in patients with focal epilepsy, but sometimes fails due to an incomplete delineation of the epileptogenic zone (EZ). Brain networks in epilepsy can be studied between seizures with resting-state functional connectivity (RSFC) analysis, but previous investigations using functional MRI or electrocorticography have produced inconsistent results. Magnetoencephalography (MEG) allows noninvasive whole-brain recordings, and can be used to study both long-range network disturbances in focal epilepsy and regional connectivity at the EZ.

Methods: In MEG recordings from presurgical epilepsy patients, we examined: i) global functional connectivity map alterations in patients vs. controls, and ii) regional functional connectivity map patterns at the region of resection, compared to the non-epileptogenic hemisphere in the same patient.

Results: Sixty-one patients were studied, including 30 with mesial temporal lobe epilepsy and 31 with focal neocortical epilepsy. Compared to 31 controls, epilepsy patients had decreased RSFC in widespread regions, including peri-sylvian, posterior temporo-parietal, and orbitofrontal cortices ($p < 0.01$, FDR-corrected). Decreased mean global connectivity was significantly related ($p < 0.01$, linear regression) to longer duration of epilepsy and higher frequency of consciousness-impairing seizures. Furthermore, patients with increased regional connectivity within the area of resection (n = 24) were significantly more likely to achieve seizure post-operative seizure freedom (87.5% with Engel I outcome) than those with neutral (n = 15, 64.3%

seizure free) or decreased (n = 23, 47.8% seizure free) regional connectivity ($p < 0.02$, chi-square).

Conclusions: Widespread global decreases in functional connectivity are observed in patients with focal epilepsy, which may reflect the deleterious long-term effects of recurrent seizures. Furthermore, enhanced regional functional connectivity maps at the area of resection may help predict seizure outcome and aid surgical planning.

Introduction

Epilepsy affects approximately 1% of the population, and seizures are refractory to medical treatment in 30% of those individuals, leading to significant morbidity and mortality.[8,30] In medically-refractory epilepsy, localization and surgical resection of the epileptogenic zone (EZ) leads to seizure freedom in approximately 60-80% of patients with mesial temporal lobe epilepsy (MTLE) and about one-half of individuals with focal neocortical epilepsy (FNE).[20,49] This leaves significant room for improvement in surgical outcomes, as seizure freedom is the single greatest predictor of quality-of-life in epilepsy.[14,43] Failures in the surgical treatment of epilepsy stem in part from an incomplete understanding of epileptic brain networks,[15] as most cases of failed epilepsy surgery involve incomplete delineation and resection of the epileptogenic zone (EZ) from which seizures originate.[19,24] Studying the networks involved in epilepsy may lead to enhanced techniques for localizing the EZ, improved ability to predict surgical outcomes, and a better understanding of the effects that recurrent seizures have on various brain regions.

The pathophysiological underpinnings of seizure generation likely involve both abnormal brain structures and aberrant connections between these regions, resulting in large-scale network instability.[15,35,60] Furthermore, aberrant brain network activity in epilepsy likely contributes to devastating cognitive and neuropsychological sequelae that are frequently suffered in this disorder.[30,31,38] Abnormal network connections can be studied using resting-state functional connectivity (RSFC) analysis, which is performed between seizures (interictal period), avoiding the challenges associated with diagnostic recordings during the ictal period. However, functional connectivity studies in focal epilepsy have thus far produced inconsistent findings. The majority of these investigations have utilized functional magnetic resonance imaging (fMRI), and while some studies have found only decreased connectivity in focal epilepsy patients,[28,42,44,55] others

report increased connectivity in some networks juxtaposed by decreases in others.[29,40,41,61] In contrast, most RSFC studies utilizing intracranial electroencephalography (EEG) have suggested predominantly increased connectivity in relation to the EZ and surrounding structures.[1,3,32,59] Differences between study techniques and analysis methods may contribute to these variable findings. For instance, fMRI only allows indirect estimation of neuronal activity through blood oxygenation patterns, but does permits whole-brain connectivity analysis, whereas intracranial EEG provides direct neuronal recordings from the human brain, but only from the area of invasive electrode coverage.[18,33,58] More direct approaches to noninvasively map RSFC in focal epilepsy are needed, to examine both global connectivity throughout the entire brain, as well as regional connectivity related to EZ.

Magnetoencephalography (MEG) is a powerful noninvasive technique for mapping activity throughout the brain through the detection of magnetic fields produced by electrophysiological signals.[7,27] It allows more direct measurement of neuronal activity at a significantly higher temporal resolution than fMRI, and possesses high spatial resolution without signal deterioration by the skull and scalp that is present in scalp EEG.[7,27] MEG has been used to study RSFC in numerous brain disorders,[27] including pre-operative neurosurgical patients,[27,53] and recordings are already performed in many pre-surgical epilepsy patients to aid with the localization of interictal epileptic spikes.[23,50] Overall, MEG is well suited for non-invasive, whole-brain connectivity analysis in surgical epilepsy patients. A few groups have reported MEG-based connectivity analyses in epilepsy, although these have examined only global network organization without interrogating EZ connectivity,[34,54] or regional sensor-based calculations without whole brain source-space analysis.[57]

Recently, we have developed techniques to extract from MEG data, global functional

connectivity maps across the whole brain (REFs to Guggisberg, Hinkley, Tarapore etc.) as well as regional functional connectivity maps and its relationship to behavioral outcomes (REFS to Martino, Guggisberg etc.), Here we report the first MEG-based study of RSFC in focal epilepsy to examine both whole brain connectivity and regional connectivity maps associated with the EZ. We investigate 61 pre-surgical patients with medically-refractory MTLE or FNE, comparing global connectivity maps in these individuals to age, gender, and handedness matched controls, and relating connectivity alterations to duration and severity of epilepsy. Furthermore, within individual patients, we examine regional connectivity maps related to the EZ vs. the non-epileptogenic hemisphere, relating connectivity patterns to long-term seizure outcome after surgery.

Methods

Subjects

Study subjects were selected from 310 patients referred for MEG as part of a clinical epilepsy evaluation at the University of California, San Francisco (UCSF) Biomagnetic Imaging Laboratory (BIL) between June 1, 2004 and June 30, 2013. Among these patients, 174 individuals also underwent surgical resection for medically-refractory epilepsy at our institution following MEG recordings, and were considered for inclusion in the study. Patients were then excluded for age < 18 at the time of MEG (n = 45), a history of resective brain surgery prior to MEG (n = 24), a lack of awake resting-state data (eg., MEG performed only for task-based cortical mapping) (n = 21), extensive MEG artifact from a metallic object such as dental implants (n = 4), or post-operative follow-up of < 1 year (n = 8). Finally, we excluded patients with a

history of infiltrative and/or malignant brain tumor such as glioma (n = 11), but included those with pathology confirming a benign, non-infiltrating brain lesion, such as meningioma or cavernous malformation. The remaining 61 adults who received MEG followed by surgical resection for focal epilepsy, including 30 patients with MTLE and 31 individuals with FNE, were included for analysis. Patients were 52.5% female, 82.0% right-handed, and mean age at the time of MEG recordings was 34.7 years (range 18-67). Thirty-one control subjects matched for age, gender, and handedness were recorded during the same time period, and had no known history of epilepsy or other neurological disorder. Controls were 51.5% female, 83.9% right-handed, with mean age of 34.2 years (range 18-63). All procedures and subject consents in the study were in full compliance with UCSF clinical research policies, with research protocol approval by the UCSF Committee on Human Research.

MRI and MEG recordings

Magnetic resonance imaging (MRI) studies were performed on a 3-T scanner (Excite, GE) using an 8-channel head coil. To provide anatomical head models for MEG analysis, a high-resolution 3D T1-weighted whole-brain volume was acquired using a fast spoiled gradient-recalled echo in a steady state inversion recovery (FSPGR-IR) sequence (TR 6.3 msec, TE 1.5 msec, TI 400 msec, and flip angle 15°), slice thickness 1.0 mm, matrix size 256 × 256, and FOV 230 × 230 mm with skin-to-skin coverage to include the nasion and preauricular points, as well as T2-weighted FLAIR images (TE 126 msec, TR 10 seconds, and TI 2200 msec) with 220-mm FOV, 47–48 3.0-mm contiguous slices at a 256 × 256 matrix. All MR images were interpreted by a board-certified attending neuroradiologist.

MEG recordings were performed inside a magnetically shielded room, with a 275 channel whole-head axial gradiometer system (VSM MedTech, Port Coquitlam, British Columbia). Data were recorded from each patient in a passband of 0–75 Hz (600 Hz sample rate). A recording epoch of 1-minute duration not limited by artifact or interictal epileptic spike activity, and with the subject awake but resting with eyes closed, was selected for subsequent analysis. The position of the head in the MEG dewar relative to the MEG sensors was determined via indicator coils before and after each interval to ensure adequate sampling of the entire magnetic field. The data were bandpass filtered offline at 1–70 Hz.

Signal analysis algorithms

For the majority of connectivity analyses, alpha (8-12 Hz) activity was used, given that spectral power typically peaks in the alpha band during the awake resting state, and alpha-band imaginary coherence has been well-established as a measure of functional connectivity.[27,52] However, confirmatory analyses were also performed using delta (1-4 Hz), theta (4-8 Hz), beta (12-30 Hz), or gamma (30-55 Hz) band activity where specified. An adaptive spatial filtering algorithm was used to reconstruct the electromagnetic neural activity at each brain voxel from the signal recorded by the entire MEG sensor array. The details of this algorithm are described elsewhere.[57] In brief, the raw MEG data were bandpass filtered with a fourth-order Butterworth filter, and the spatial covariance matrix of the data was calculated from the entire recording of 1 minute in duration. We also computed the lead-field matrix for each voxel in the brain, corresponding to the expected magnetic field pattern for a unit dipole in a particular orientation at a particular location. From the spatial covariance of the data and the lead-field matrix, a spatial

weight matrix was then obtained for optimal estimation of the signal power in each voxel. The activity at each time in each voxel was then calculated as the linear combination of the spatial weighting matrix with the sensor data matrix. Thus, all sensors contributed in some degree to all voxel time series estimates from which we analyzed functional connectivity.

We utilized the method of imaginary coherence for estimating functional connectivity, which overcomes estimation biases arising from seed-blur, or crosstalk or volume conduction, as described previously in detail.[27,45,47] Many commonly used measures of functional connectivity (eg., coherence, phase locking value, synchronization likelihood) overestimate the magnitude of true connectivity because of common references and volume connection. By omitting the real component of coherence, which is dominated by similarities with zero time lag, we remove potentially spurious associations and limit the analysis to the imaginary component of coherence, which represents more realistic neural oscillatory interactions between brain areas occurring at non-zero time lags.

Functional connectivity maps

A 3D grid of voxels with an 8-mm spatial resolution covering the entire brain was created for each subject and recording, based on a multiple local sphere head model of coregistered structural 3D T1-weighted FSPGR-IR MR images. Although the sensitivity of MEG is significantly reduced for deeper sources, our analysis includes them and reports findings from deep structures as well subject to the same statistical tests as voxels in the rest of the brain. Alignment of structural and functional images was ensured by marking 3 prominent anatomical points (nasion and preauricular points) on the subject's head in the MR images and localizing 3

fiducials attached to the same points before and after each MEG scan. MEG oscillation frequencies between 1 and 20 Hz (1-55 Hz for beta and gamma band analyses) were used for calculation of the spatial weighting matrix and the voxel time series. For the calculation of imaginary coherence, the entire frequency bin of interest (usually alpha, 8-12 Hz) for each subject was averaged. The alpha peak, representing the point of greatest power density between 8 and 12 Hz during the resting state, was recorded for each subject. For imaginary coherence calculations, a frequency resolution of 1.17 Hz (512 frequency bins) was used. Imaginary coherence at each voxel of interest was estimated by averaging across all its Fisher Z-transformed connections.

Two different connectivity maps were generated for each patient: i) a patient-specific map (P-image) of global connectivity including all voxels throughout the brain, compared to that in control subjects, and ii) a region-specific map (R-image) of regional connectivity including only voxels within the region of resection, compared to corresponding voxels in the contralateral hemisphere of the same patient. P-images were obtained by analyzing all pairwise connections between voxels of 2 cm^3 extension for each patient, resulting in approximately 30,000-60,000 voxel pairs in total depending on the individual's head size, and compared to the mean of those obtained from all control subjects. From the point of view of a single voxel, the P-image reflects the mean imaginary coherence between that voxel and every other voxel in the brain. Thus, a significant alteration in connectivity of that voxel means that its connectivity to the rest of the brain has changed. For group analysis of P-images, patients were assigned to one of four groups based on the side of resection (left or right) and type of focal epilepsy (MTLE or FNE), and each group was compared to healthy control subjects matched for age, gender, and handedness. Patient and subject P-images were spatially normalized to the Montreal Neurological Institute

atlas template according to the coregistered structural MRI, using the toolbox Statistical Parametric Mapping 8 (SPM8) for MATLAB (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/).

Regional connectivity maps (R-images) were generated by analyzing all connections within the area of resection and a centered, equally spaced, whole-brain grid of each fourth voxel within the entire set of voxels (~10,000-100,000 voxel pairs in total, depending on the individual head and tumor size). The region for analysis was individually selected and drawn for each patient to represent the entire area of surgical resection. The limits of the resection area were defined by examination of the post-operative MRI, in addition to review of the operative report. Resections were planned to include the presumed EZ, as determined pre-operatively by the comprehensive clinical epilepsy team, and avoid eloquent cortex, where possible. For MTLE cases, anatomic anterior temporal lobectomy including both mesial structures (hippocampus, amygdala, entorhinal cortex) and the lateral cortex of the anterior temporal lobe was performed, and thus these regions were included in the regional analysis. For FNE cases involving resection of a focal discrete lesion devoid of functional neural elements (eg., ganglioglioma, cavernous malformation), a 1-2 cm rim of cortex surrounding the lesion was also included in the regional analysis, as seizures likely originate within peri-lesional parenchyma. As an internal control, the imaginary coherence was also calculated for connections between corresponding voxels contralateral to resection of resection (in the presumably non-epileptogenic hemisphere), and the same whole-brain voxel grid.

Interictal spike modelling

Interictal spikes were not included in data epochs used for functional connectivity analysis, but

were analyzed separately. Spikes were visually identified by a certified EEG technologist (MM) and were confirmed by a board-certified clinical neurophysiologist and epileptologist (HEK). EEG spikes were identified based on the criteria defined by the International Federation of Clinical Neurophysiology (IFCN) for EEG epileptiform discharges.[12] MEG spikes were chosen for analyses based on duration (< 80 ms), morphology, field map, and lack of associated artifact. The onset of each spike, defined as the rising deflection of the first sharp negativity from the baseline, was marked and ECDs were fit using commercial software provided by CTF Systems (VSM MedTech, Port Coquitlam, British Columbia). Only sources with a goodness of fit higher than 90% were accepted. Co-registration of dipoles to MRI scans was performed using fiducials (nasion and preauricular points) to produce magnetic source images (MSI) of dipoles superimposed on anatomic images. The authors then inspected these results and classified the spike dipoles according to their location and orientation.

Spikes were considered specific to the region of resection if the dipole location and orientation indicated spike source in the same lobe or lobar region, with no appreciable (>10%) dipole source estimates observed in other lobes or sublobar regions. Spikes were considered non-specific in the setting of another distal region with >10% dipoles, or discordant if >50% of dipoles were contralateral. Spike localization and the determination of regional specificity were performed while blinded to the patient's connectivity findings or seizure outcome.

Evaluation of clinical data and seizure outcomes

For all patients, we retrospectively reviewed outpatient and inpatient provider notes, diagnostic and laboratory reports, operative records, and pathology reports. Clinical and demographic data

including patient gender, age, handedness, surgical history, the results of neuroimaging or electrographic diagnostic studies, and the side and region of surgery were recorded. Details regarding patients' epilepsy history and seizure semiology, including epilepsy duration and seizure type and frequency, were obtained from pre-operative assessments by epileptologists. Seizure types investigated included consciousness-impairing (complex-partial and generalized tonic-clonic) seizures and consciousness-sparing (simple-partial) seizures, based on epileptologist assessment. Surgical decisions were made by a comprehensive team of epileptologists, neurosurgeons, neuropsychologists, neuroradiologists, and other practitioners. Surgical specimens were analyzed by neuropathologists. Seizure outcome was determined by the latest patient follow-up with the epileptologist using the Engel classification system, with Engel class I outcome or "seizure freedom" used to signify post-operative freedom from all disabling seizures, and Engel class II-IV outcomes signifying varying degrees of persistent seizures.[16]

Statistical analyses

Group analysis of P-images for MTLE or FNE patients was performed by comparison to an equal number of age, gender, and handedness-matched control subjects with voxel-wise *t*-tests, corrected for multiple comparisons with a 5% False Discovery Rate (FDR) modified for dependency. All normalized P-image (whole-brain connectivity map) voxels of epilepsy patients with Z-transformed connectivity estimates greater than or less than the 95% confidence interval of the values of control subjects, after FDR correction, were considered significantly abnormal. Mean imaginary coherence of all voxels in the brain was calculated as an estimate of global functional connectivity. Individual unpaired *t*-tests with Bonferroni correction for multiple comparisons were used to compare global connectivity in each frequency band between MTLE

patients, FNE patients, and controls. Factors were examined for potential association with mean imaginary coherence via multivariate analysis using a generalized step-wise linear regression model. Generalized linear regression was used to generate voxel-wise maps of connectivity as a function of epilepsy duration or seizure frequency across all patients. For R-images (regional connectivity maps), patients were designated as having increased connectivity ($t > 0.2$), decreased connectivity ($t < -0.2$), or neutral connectivity ($-0.2 > t > 0.2$), based on mean *t*-scores across all voxel-wise comparisons of imaginary coherence in the region of analysis vs. contralateral voxels. Regional connectivity pattern was related to postoperative seizure outcome (Engel I vs. Engel II-IV outcome), interictal MEG spike findings (spikes specific to resection region vs. discordant/nonspecific vs. not modelled) and neurological outcome (presence vs. absence of new post-operative neurological deficit) with individual chi-square tests. All statistical analyses were performed using SPSS 20 (IBM, Somers, NY) and statistical significance was assessed at $p < 0.05$, unless otherwise specified.

Results

We analyzed global and regional RSFC maps in sixty-one patients who underwent resection for medically-refractory focal epilepsy, including 30 individuals with MTLE and 31 patients with FNE. Patient demographics and epilepsy characteristics are summarized in Table 1.

Widespread decreased connectivity in epilepsy patients compared to controls

To generate whole-brain global functional connectivity maps (P-images) for patients vs. control

subjects, we calculated alpha-band imaginary coherence between all reconstructed brain voxels using resting-state MEG recordings. Group analysis of MTLE patients reveals decreased RSFC compared to controls in widespread regions, without areas of increased connectivity (Fig. 1). In patients with left-sided MTLE, decreased connectivity is observed in the right lateral frontal, bilateral posterior temporal, bilateral parieto-occipital, and right peri-sylvian neocortices. We also observe decreased connectivity in deep structures such as the basal forebrain, basal ganglia, anterior thalamus, posterior orbitofrontal cortex, posterior cingulate/precuneus, and right anterior insula, subject to the same statistical analyses (Fig. 1A). Similar large decreases in connectivity are seen in patients with right MTLE, affecting the peri-sylvian region, lateral frontal neocortex, basal forebrain, basal ganglia, anterior thalamus, orbitofrontal cortex, and insula (Fig. 1B). No prominent connectivity alterations are noted in the mesial temporal structures of MTLE patients vs. controls. Whole-brain RSFC maps in FNE patients also reveal various regions of decreased connectivity compared to controls, including the peri-sylvian, parieto-occipital, and posterior temporal neocortex, and subcortically in the basal forebrain, basal ganglia, and anterior thalamus (Fig. 2).

Given consistently decreased connectivity in epilepsy patients vs. controls, we calculated the mean of the global functional connectivity maps across all brain voxels in each subject, to create a single "global mean connectivity" metric with which to relate other factors of interest. Overall, global mean alpha-band connectivity was significantly decreased in patients with MTLE (0.044 ± 0.006 [mean ± SEM], arbitrary units) and FNE (0.043 ± 0.007) compared to controls (0.049 ± 0.004) ($p < 0.01$ for each comparison), but there was no significant difference in connectivity between MTLE and FNE patients ($p = 0.48$) (*t*-tests with Bonferroni correction). We also measured the alpha peak from resting-state power spectra of all subjects, and found a

lower alpha peak frequency in individuals with MTLE (9.6 ± 0.1 Hz [mean ± SEM]) or FNE (9.8 ± 0.1) than in controls (10.2 ± 0.1 Hz) ($p < 0.05$ for each comparison), but no difference in alpha peak frequency between MTLE and FNE patients ($p = 0.3$) (*t*-tests with Bonferroni correction). In addition to alpha-band activity, we compared mean imaginary coherence across subjects in the delta, theta, beta, and gamma frequency bands, revealing decreased global connectivity in epilepsy patients across all bands except gamma (Fig. 3). Overall, these results suggest marked disruption in global RSFC in patients with focal epilepsy.

Decreased global mean functional connectivity is related to duration and severity of epilepsy

We then interrogated various factors for potential association with global mean RSFC (ie, alpha-band imaginary coherence), including both categorical (gender, handedness, side of surgery, MTLE or FNE, and lesional vs. non-lesional epilepsy) and continuous variables (age, duration of epilepsy, frequency of consciousness-impairing and consciousness-sparing seizures, and numbers of current and previous anti-epileptic medications). Seizure frequency was stratified by seizures which impair consciousness (complex-partial and generalized tonic-clonic seizures) vs. those that spare consciousness (simple-partial seizures), given previous evidence of impaired cortical function with consciousness-impairing seizures.[17] Multivariate analysis revealed that duration of epilepsy (Fig. 4A) and frequency of consciousness-impairing seizures (Fig. 4B) are negatively associated with global connectivity, while other variables show no significant relationship. Furthermore, voxel-wise maps of RSFC regressed by epilepsy duration (Fig. 4C) or seizure frequency (Fig. 4D) reveal a negative relationship to connectivity in the frontal lobes,

particularly the left prefrontal and orbitofrontal cortex. These findings suggest that RSFC alterations in focal epilepsy are quantitatively related to severity of illness.

Regional connectivity maps of the area of resection predicts seizure outcome

Focal epilepsy patients may have decreased global RSFC compared to controls, but how do regional connectivity maps at the EZ differ from other brain regions within individual patients? To address this question, we generated regional connectivity maps (R-images) for each patient, measuring imaginary coherence of the area of resection. Specifically, these maps investigate long-range connectivity between the region of resection and the rest of the brain, compared to corresponding voxels in the non-epileptogenic hemisphere. Figure 5 depicts an example regional connectivity map of a 34-year old right-handed female with MTLE, showing increased connectivity in the right mesial temporal lobe, with a smaller area of diminished connectivity in the lateral temporal cortex. In contrast, Figure 6 displays a regional connectivity map of a 55-year old right-handed female with FNE from a right frontal meningioma, in which only decreases in connectivity are seen surrounding the lesion. Connectivity at the resection region was predominantly increased (mean voxel *t*-score > 0.2) in 24 patients (39.3%), mostly decreased ($t < 0.2$) in 23 patients (37.7%), and neutral ($-0.2 < t < 0.2$) in 15 individuals (24.5%).

We then asked if regional connectivity at the resection area is related to post-operative seizure outcome. After mean (± SEM) post-operative follow-up of 2.9 ± 0.4 years (range 1-10 years), 41 (67.2%) patients were free of disabling seizures (Engel class I outcome), while 20 (32.8%) individuals continued to experience seizures (Engel class II-IV outcome). As shown in Figure 7, seizure freedom was achieved in 87.5% of patients with increased connectivity at the

region of resection, but in only 64.3% of individuals with neutral connectivity, and in 47.8% of patients with decreased connectivity ($X^2 = 8.5$, $p = 0.015$). This finding implies that increased connectivity at the resection region is associated with favorable seizure outcome, and raises an interesting question: In patients with decreased connectivity at the resection region, are seizure outcomes poor because the true EZ was not fully resected?

To further elucidate the relationship between regional connectivity and epileptogenicity of resected tissue, we examined interictal spike localization from MEG recordings, as we have previously observed that localization of MEG spikes to the resection area predicts seizure freedom in our surgical patient population.[23] Among the 45 patients with successful modelling of interictal spikes, spike localization was specific to the resection region in 28 (62.2%) patients, and non-specific or fully discordant with the resection region in 17 (37.8%) individuals. Increased connectivity at the resection region was observed in 57% of 28 patients with spikes specific to the area, but in only 12% of 17 patients with discordant or non-specific spike localization. Of note, connectivity analysis was performed using MEG data segments without interictal spikes. Together, these findings imply that increased regional connectivity at the resection area may reflect true epileptogenicity, and a greater likelihood of post-operative seizure freedom.

Finally, we observed no mortality or severe peri-operative morbidity in our surgical series, but 10 (16.4%) patients did have a new or worsened neurological deficit immediately after surgery. We did not detect a relationship between the presence of a new neurological deficit and regional connectivity pattern at the resection region ($X^2 = 2.2$, $p = 0.33$). Post-operative neurological deficits included 8 patients with transient expressive or receptive aphasia, one

individual with slight hand clumsiness and proprioceptive deficit, one patient with both transient mild aphasia and right superior quadrantanopsia, and a case of expected dense hemianopia after occipital resection. In two additional individuals with hemiparesis, the deficit with stable compared to pre-operative baseline.

Discussion

The present study is the first to utilize MEG-based brain-space RSFC analysis to examine both global functional connectivity map alterations in focal epilepsy, as well as regional connectivity map patterns related to the EZ, allowing novel insights into the impact of epilepsy on resting state functional of oscillatory networks. In both MTLE and FNE patients, we observed decreased connectivity in widespread regions compared to controls. Although the majority of our analyses measured connectivity in the alpha-band, global connectivity reductions were also seen in most other frequency bands. We observed larger connectivity decreases in patients with a longer duration of epilepsy or higher frequency of consciousness-impairing seizures, suggesting a quantitative relationship between disease severity and RSFC alterations. While regional connectivity patterns of the area of resection differed between patients, increased connectivity significantly predicted seizure freedom after surgery. Overall, our results suggest that MEG-based RSFC analysis can provide useful information related to the impact of disease on brain networks, and may aid in surgical planning and outcome prediction in focal epilepsy.

Most prior studies of RSFC in epilepsy have been performed using fMRI, with several showing widespread decreases in connectivity in focal epilepsy patients vs. controls.[28,42,44,55] However, some fMRI studies have also noted local increases in connectivity related to the EZ,

alongside decreases in long-range connectivity.[29,40,41] Regional increases in connectivity are supported in part by intracranial EEG data, which show predominantly elevated connectivity in relation to the EZ and surrounding structures.[1,3,32,59] However, intracranial EEG studies are inherently limited to the area of electrode coverage, and thus do not permit whole-brain connectivity analysis. MEG provides a unique opportunity to non-invasively study both whole-brain and regional connectivity, utilizing a more direct measurement of neuronal activity than fMRI.[7,27] Our results build upon previous studies, and suggest that focal epilepsy leads to decreased long-range connectivity, but may be associated with increased regional connectivity at the EZ in certain patients.

How might recurrent seizures lead to decreased long-range connectivity? While our current analyses examine network status during the interictal state, divergent effects of seizures on local vs. long-range networks have also been described during the ictal period. Intracranial EEG and single positron emission computed tomography (SPECT) studies in MTLE patients have shown that during focal limbic seizures, fast spike activity and increased cerebral blood flow (CBF) in the mesial temporal lobe are starkly contrasted by slow wave activity and decreased CBF in the distal fronto-parietal neocortices.[4,5,25] Furthermore, rat models of focal seizures have shown increased neuronal activity, CBF, and oxygen consumption at the EZ during seizure activity are juxtaposed by ictal decreases in all of these parameters in distal cortical regions.[21] These long-range neocortical effects of focal seizures appear to involve ictal recruitment of the thalamus, septal nuclei, and other subcortical regions, and can be prevented if seizure activity remains confined to the limbic structures.[22] Together, these previous human and rodent studies suggest that long-range neocortical inhibition during focal seizures may result from aberrant activity in subcortical activating systems – a phenomenon termed the ‘network

inhibition hypothesis'.[11,17]

It is possible that over time, recurrent seizures result in diminished long-range connectivity between subcortical and cortical structures, which may in turn contribute to known deleterious effects of epilepsy including gray matter atrophy, cortical hypometabolism, neuropsychological sequelae, and cognitive impairment.[6,13,30,31,38] This hypothesis is supported by the quantitative relationship we observed between epilepsy duration and decreased global connectivity in the present study. We also observed alpha slowing in patients compared to controls, which has previously been described in individuals with neurocognitive disorders.[26,37] Next, we found the frequency of consciousness-impairing seizures, but not consciousness-sparing seizures, to be related to long-range interictal connectivity decreases. This observation is in line with previous studies of ictal network dysfunction in MTLE patients, in which consciousness-impairing seizures are associated with depressed fronto-parietal cortical function (characterized by sleep-like activity on EEG and reduced CBF), but neocortical function appears relatively spared during consciousness-sparing seizures.[4,5,25] Unique pathophysiological network effects have also been observed in rodents during seizures which cause transient behavioral arrest.[21,22] Overall, there is compelling evidence that focal epilepsy leads to long-range network dysfunction, both during and between seizures.

In our regional connectivity map analyses, post-operative seizure freedom was more common in patients with increased connectivity at the resection area compared to those with decreased connectivity. Why do patients with decreased connectivity at the resection region continue to have seizures after surgery? One possible explanation is that increased regional connectivity predicts accurate localization of the true EZ, leading to seizure freedom, while decreased connectivity suggests incomplete delineation of the EZ, leading to persistent seizures.

Our observation that patients with increased connectivity at the resection zone are more likely to harbor interictal spike in that region lends support to the hypothesis that increased connectivity reflects regional epileptogenicity. If this observation is supported by further study, functional connectivity analysis may have a promising role in predicting surgical outcome and confirming localization of the EZ during the pre-operative epilepsy surgery evaluation.

Interestingly, while increased connectivity at the resection zone may predict favorable seizure outcome in epilepsy patients, we previously reported dissimilar results in glioma surgery, where increased connectivity predicted poor neurological outcome.[53] Specifically, glioma patients with increased regional connectivity at the area of resection were more likely to experience a new post-operative neurological deficit than those with decreased connectivity. Of note, we did not find an association between connectivity at the resection bed and new neurological deficit in the present study of epilepsy surgery. It is possible that increased regional connectivity in glioma represents the *physiological connectivity* of eloquent cortex infiltrated by tumor, while elevated connectivity in epilepsy reflects *pathophysiological connectivity* related to epileptogenic tissue. Future study of RSFC in tumor-related epilepsy may shed more light on this issue.

Limitations related to both our techniques and study design should be addressed. First, given that MEG source localization may be more challenging with deeper regions, some have argued that MEG has diminished utility in evaluating mesial temporal structures in MTLE.[39,48] Innovative source reconstruction algorithms are rapidly evolving, allowing improved localization of the neural sources underlying electromagnetic signals,[9,10,46,56] and previous studies of interictal spike mapping have also demonstrated favorable localization with MEG in MTLE patients.[2,23,36,51] Nevertheless, further studies validating MEG source modelling of mesial

temporal signals will be important going forward, along with continued innovation in reconstruction procedures. Next, given the retrospective nature of our study, possible selection bias must be considered in the interpretation of clinical outcomes, and prospective study of functional connectivity in pre-surgical epilepsy evaluation represents a worthwhile future endeavor. Finally, it is important to recognize that epilepsy patients comprise a heterogeneous population, both with regard to EZ pathophysiology, and the various anti-epileptic medications used to treat seizures. Each patient in our series was taking at least one anti-convulsant agent at the time of recordings, and had tried multiple medication regimens in the past, as is the case in previous studies of functional connectivity in intractable epilepsy. The impacts of anti-epileptic drugs on functional connectivity are not yet known, and are likely significant. Ethical considerations limit the ability to administer these medications to control subjects, or to discontinue them in epilepsy patients for research purposes. However, medication weaning is often a part of inpatient pre-surgical video-EEG monitoring, and connectivity analyses during this time window may be revealing in the future.

Conclusions

Using MEG-based functional connectivity map analysis in focal epilepsy, we observed decreased RSFC in widespread neocortical and subcortical regions in patients vs. controls. Global reductions in functional connectivity were related to epilepsy duration and frequency of consciousness-impairing seizures, and thus may reflect the deleterious long-range effects of seizures on brain networks over time. At the area of resection, however, increased regional connectivity predicted seizure freedom after surgery. Overall, our results suggest that MEG-

based RSFC analysis in focal epilepsy may lead to a better understanding of brain network dysfunction in this disorder, and may help guide surgical planning and outcome prediction.

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Tables

Table 1: Patient characteristics

Age	*years*	34.7 ± 1.5
Gender	Male	29 (47.5)
	Female	32 (52.5)
Handedness	Right	50 (82.0)
	Left	11 (18.0)
Duration of epilepsy	*years*	19.0 ± 1.8
Region of epilepsy	MTLE	30 (49.2)
	FNE	31 (50.8)
	Lateral Temporal	15 (24.6)
	Frontal	8 (13.1)
	Parietal	3 (4.9)
	Occipital	1 (1.6)
	Multiple lobes	4 (6.6)
Seizure frequency	*no. per week,* total	7.1 ± 1.2
	consciousness-impairing	5.0 ± 0.9
	consciousness-sparing	2.1 ± 0.7
Anti-epileptic drugs failed	*no.*	4.4 ± 0.3
Current anti-epileptic drugs	*no.*	2.0 ± 0.1
History of generalized seizures	Yes	37 (61)
	No	24 (39)
MRI findings	Abnormal	51 (83.6)
	Normal	10 (16.4)
Side of surgery	Left	35 (57.4)
	Right	26 (42.6)
Pathology	MTS	19 (31.1)
	Gliosis only	17 (27.9)
	FCD	11 (18 .0)
	Tumor	9 (14.8)
	Other	5 (8.2)

Data are N (%) for categorical variables or mean ± SEM for continuous variables. N = 61 patients. FCD: focal cortical dysplasia; FNE: focal neocortical epilepsy; MTLE: mesial temporal lobe epilepsy; MRI: magnetic resonance imaging; MTS: mesial temporal sclerosis.

Figures

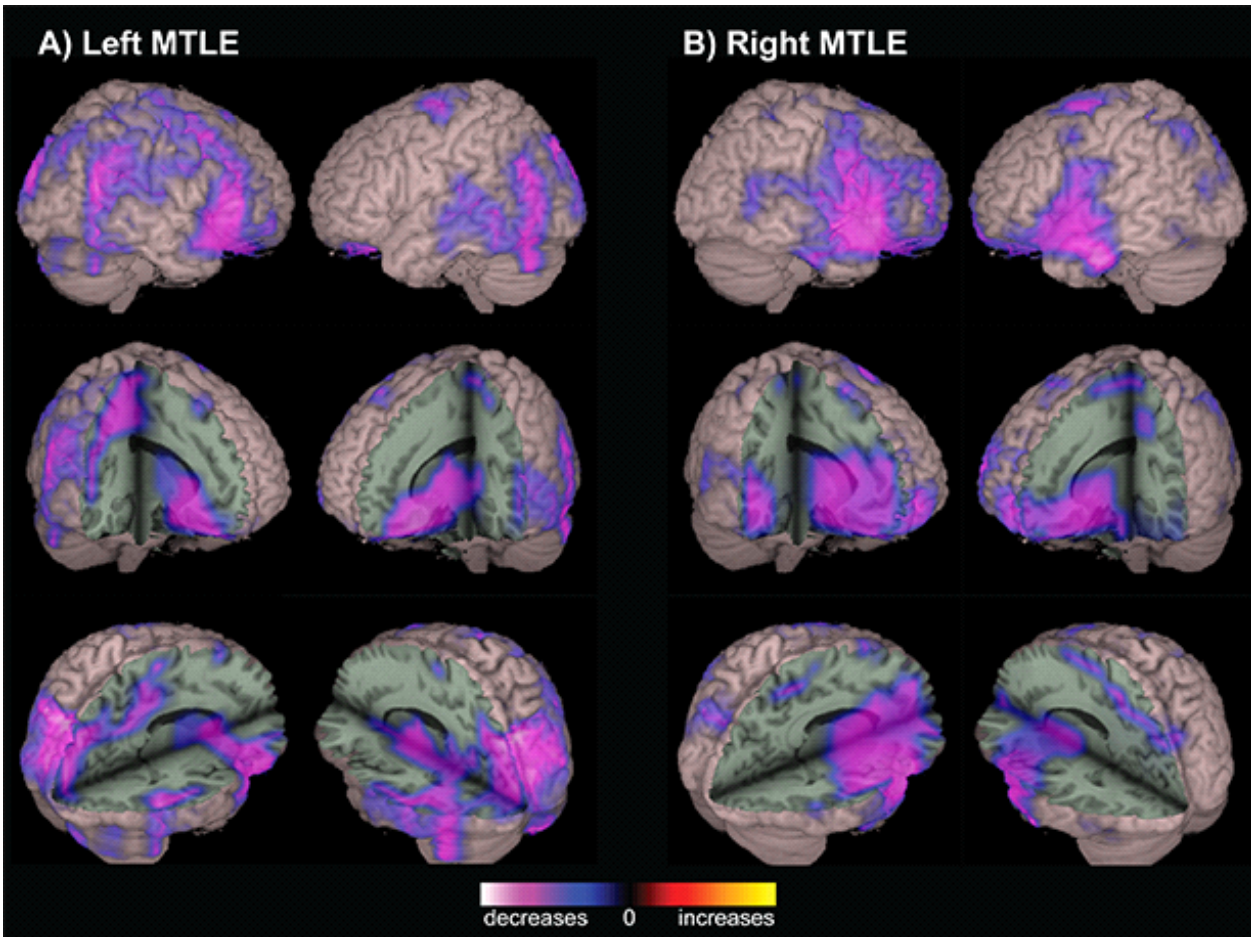

Figure 1: Decreased functional connectivity in MTLE patients. A) Compared to control subjects, patients with left MTLE demonstrate decreased RSFC in widespread regions including right lateral frontal, bilateral posterior temporal, bilateral parieto-occipital, and right peri-sylvian neocortex, as well as basal forebrain, basal ganglia, anterior thalamus, posterior orbitofrontal cortex, posterior cingulate/precuneus, and right anterior insula. B) Similar connectivity decreases are observed in patients with right MTLE, most prominent in the peri-sylvian and lateral frontal neocortex, as well as the basal forebrain, basal ganglia, anterior thalamus, orbitofrontal cortex, and insula. In both left and right MTLE, no regions of increased connectivity are observed, and significant connectivity alterations are not seen in the mesial temporal structures. Connectivity maps represent *t*-tests (threshold $p < 0.01$, FDR-corrected) of alpha-band imaginary coherence in patients with left (N = 18) or right (N = 12) MTLE compared to controls, overlaid on a 3D-rendered template brain. FDR: false discovery rate; MTLE: mesial temporal lobe epilepsy; RSFC: resting-state functional connectivity.

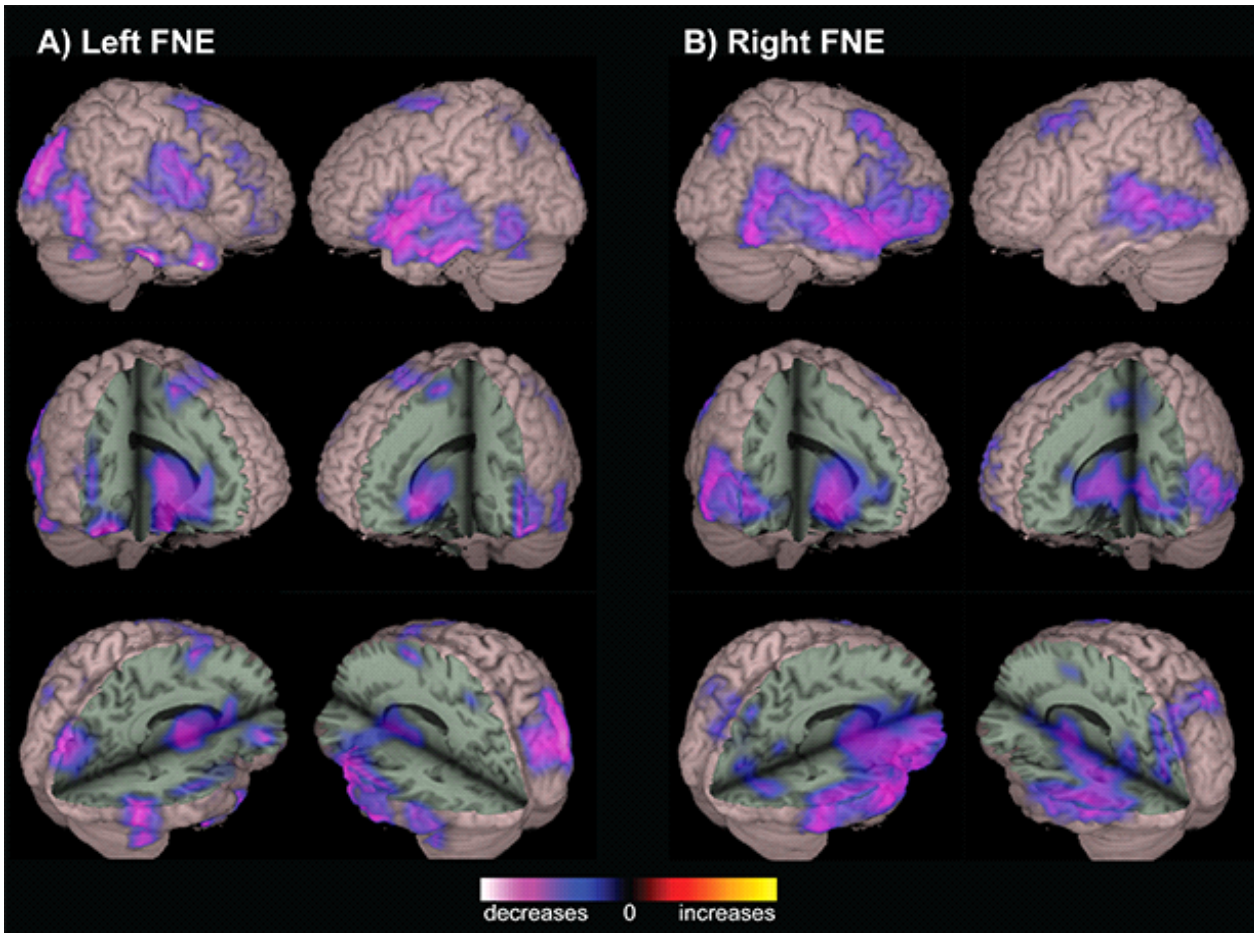

Figure 2: Decreased functional connectivity in FNE patients. A) In left FNE patients, decreased RSFC is observed in several locations compared to controls, including left peri-sylvian, right parieto-occipital, and bilateral posterior temporal neocortex. Subcortical decreases are seen in the basal forebrain, basal ganglia, and anterior thalamus. B) Decreased connectivity is also observed in patients with right FNE, including right peri-sylvian and inferior frontal, as well as posterior temporal, lateral frontal, and parieto-occipital neocortex, as well as the anterior thalamus and right insula. No regions of significantly increased connectivity are seen in left or right FNE. Connectivity maps represent *t*-tests (threshold $p < 0.01$, FDR-corrected) of alpha-band imaginary coherence in patients with left (N = 17) or right (N =14) FNE compared to controls, overlaid on a 3D-rendered template brain. FDR: false discovery rate; FNE: focal neocortical epilepsy; RSFC: resting-state functional connectivity.

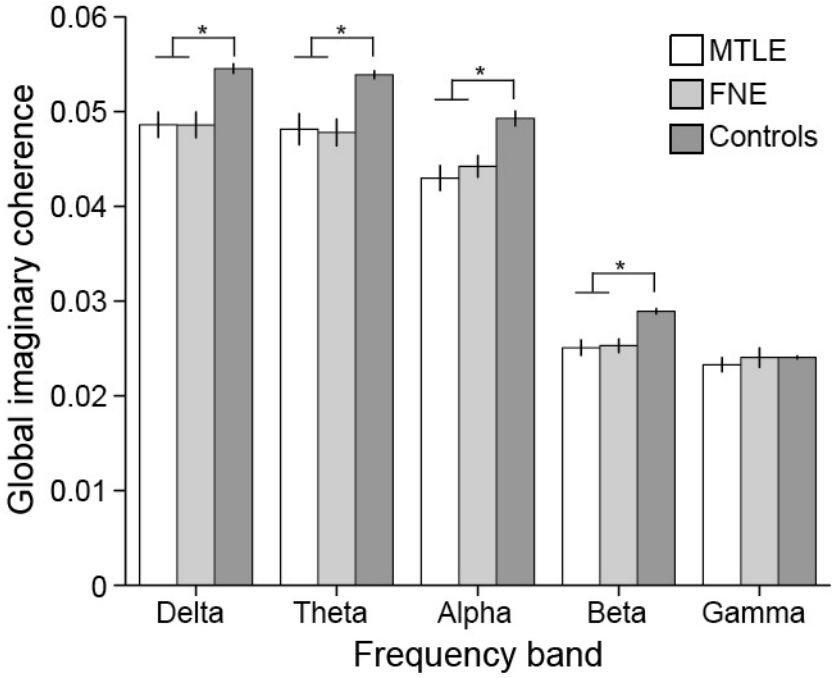

Figure 3: Global functional connectivity in decreased in focal epilepsy patients. Global functional connectivity, estimated by mean imaginary coherence across all brain voxels, is significantly decreased in epilepsy patients in the delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-30 Hz) frequency bands compared to controls. No difference in global connectivity is observed in the gamma (30-55 Hz) band. Data are mean ± SEM (arbitrary units). *$p < 0.05$, *t*-tests with Bonferroni correction.

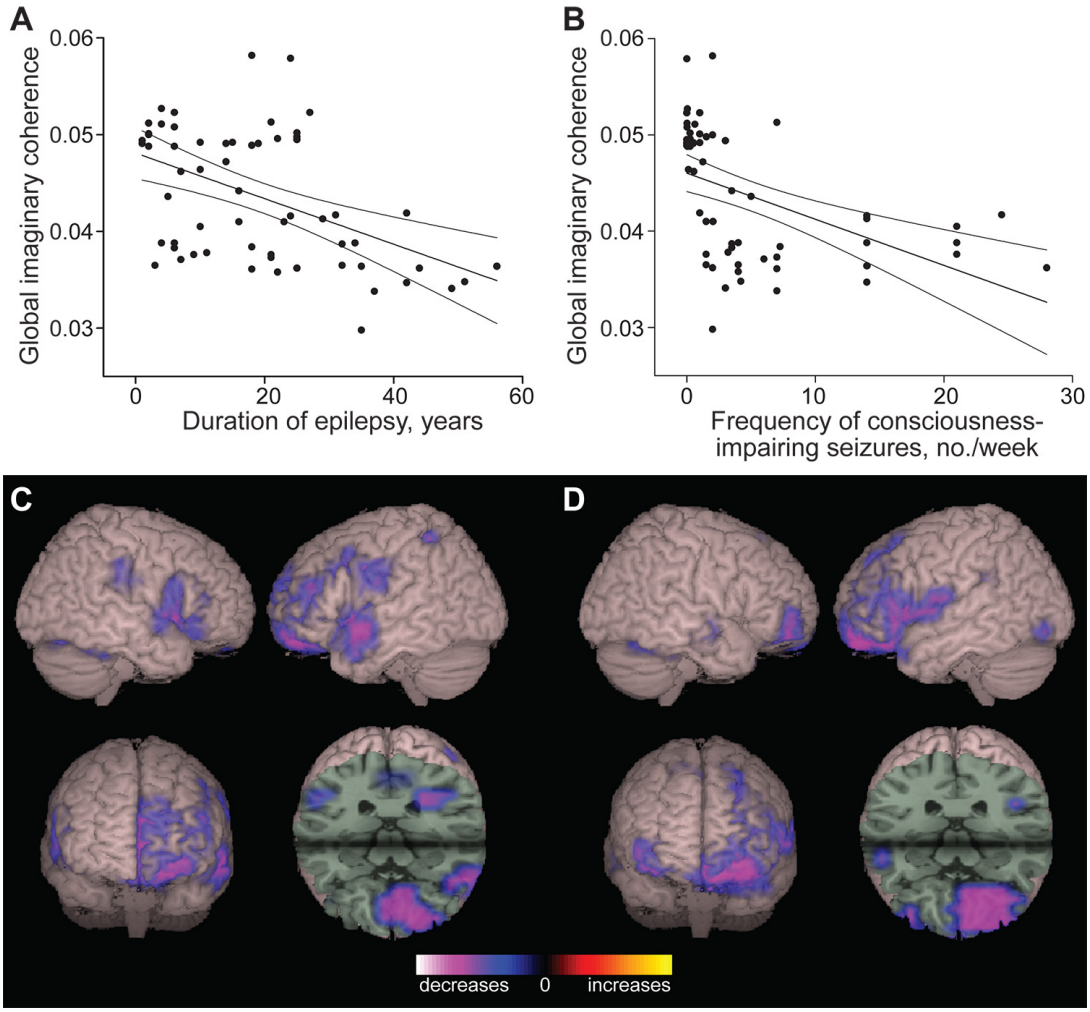

Figure 4: Longer epilepsy duration and higher seizure frequency are associated with decreased connectivity. A) Global functional connectivity, estimated by mean imaginary coherence across all brain voxels, is negatively related to epilepsy duration in patients with focal epilepsy ($R^2 = 0.229$, $p < 0.001$). B) A negative relationship is also observed between the frequency of consciousness-impairing seizures and mean imaginary coherence ($R^2 = 0.121$, $p < 0.01$). For A-B, units are arbitrary, N = 61 patients with MTLE and FNE, and line of best fit is shown with 95% CI. C, D) Regional maps of RSFC regressed by epilepsy duration (C) or seizure frequency (D) reveal a negative relationship to connectivity in the frontal lobes, particularly left prefrontal and orbitofrontal cortex. For C-D, connectivity maps represent linear regression analysis (threshold $p < 0.01$, FDR-corrected) of alpha-band imaginary coherence in all 61 patients, overlaid on a 3D-rendered template brain. CI: confidence interval; FNE: focal neocortical epilepsy; MTLE: mesial temporal lobe epilepsy; RSFC: resting-state functional connectivity.

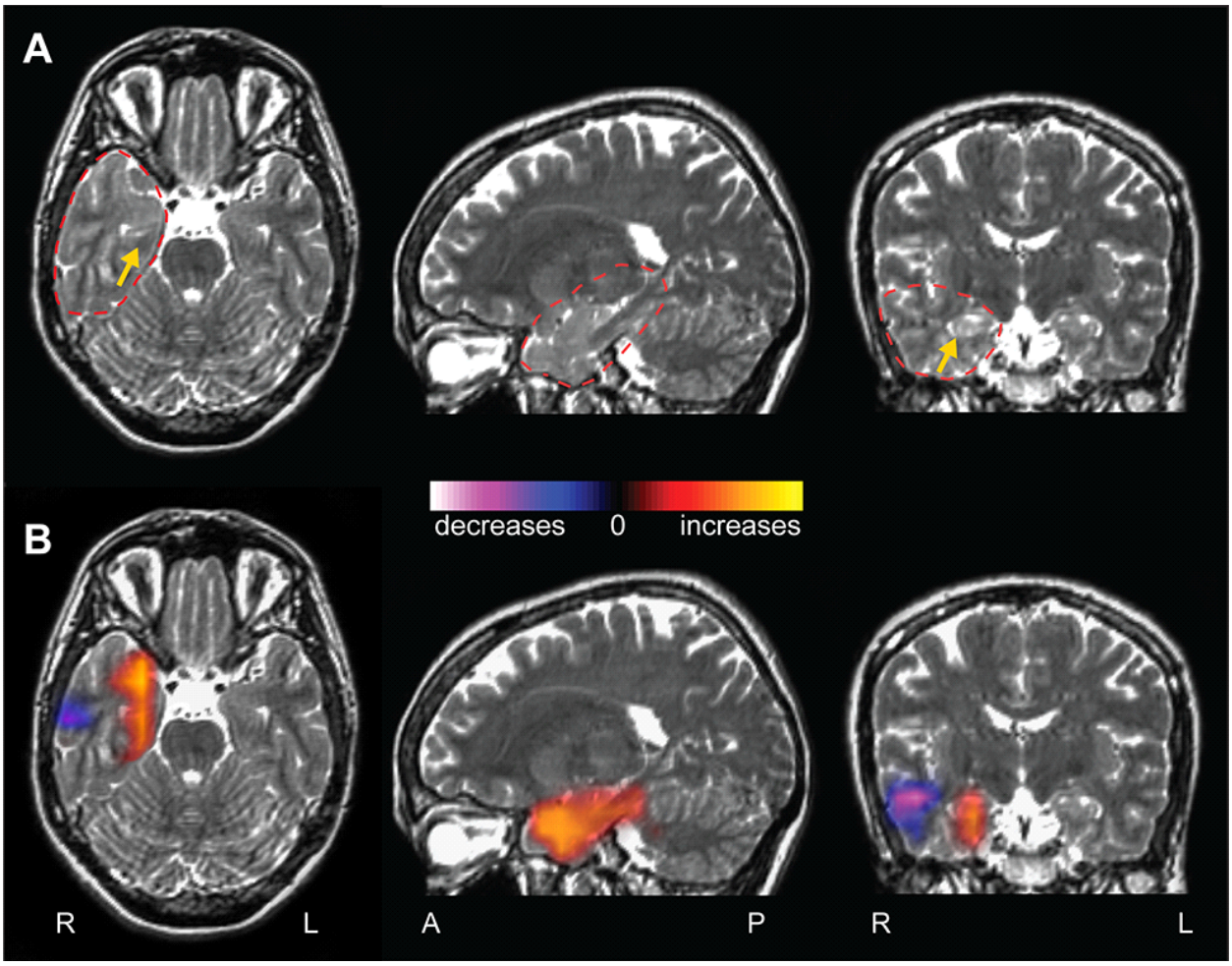

Figure 5: Example patient with increased connectivity at the resection region. A) T2-weighted MRI images from a 34-year old right-handed female suffering from intractable complex-partial and secondarily-generalized seizures for 21 years. The right anterior hippocampus shows slight T2 signal hyperintensity and blurred cytoarchitecture compared to the left side, suggestive of mesial temporal sclerosis (yellow arrow). Dashed red line represents region used for connectivity analysis. B) A regional functional connectivity map (L-image) shows increased connectivity between the mesial temporal lobe and the rest of the brain, compared to corresponding voxels in the contralateral hemisphere. A smaller area of decreased connectivity is also seen in the lateral temporal cortex. MRI: magnetic resonance imaging.

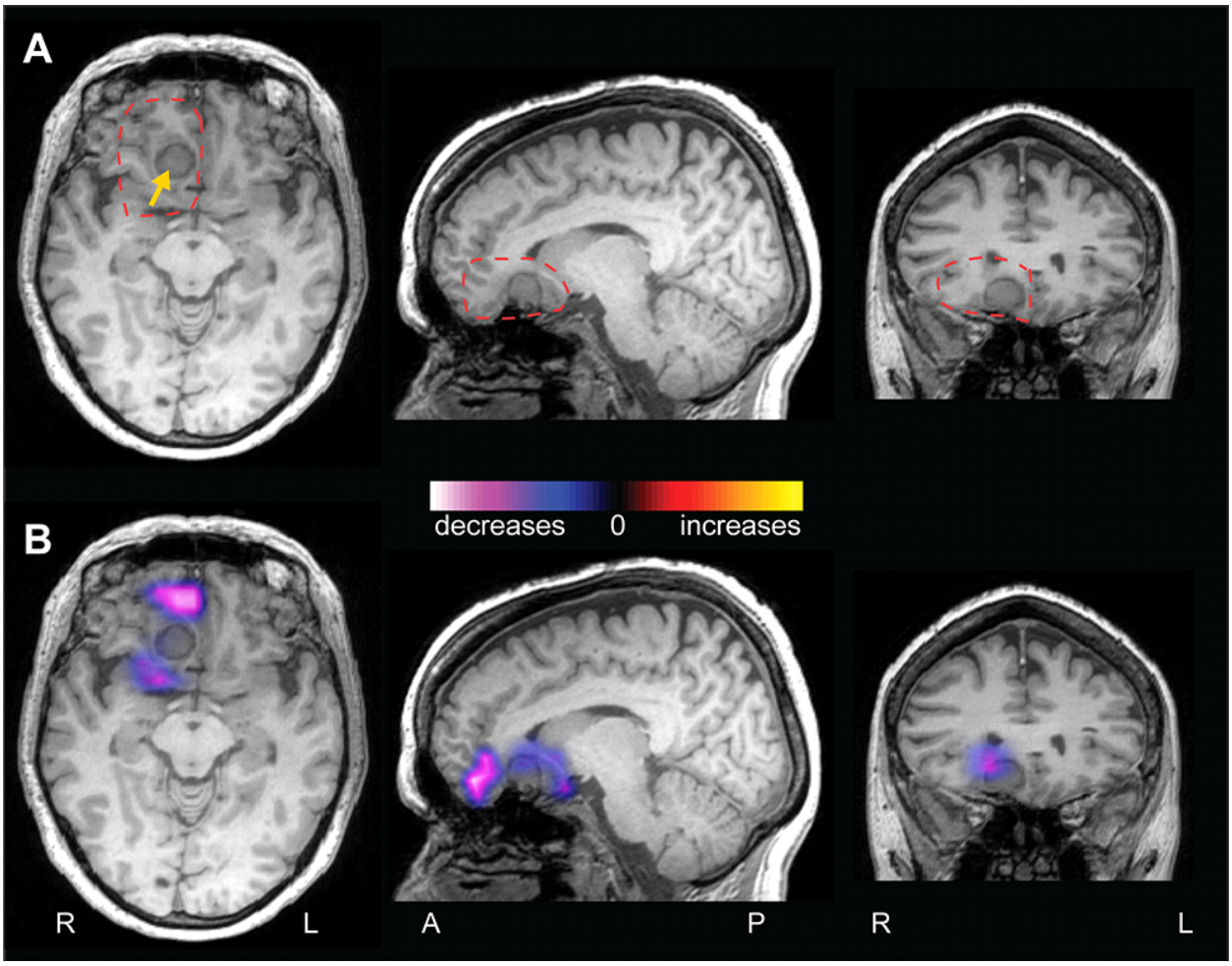

Figure 6: Example patient with decreased connectivity at the resection region. A) T1-weighted MRI images from a 55-year old right-handed female with a 7-year history of intractable complex-partial and secondarily-generalized seizures. An extra-axial lesion is at the medial floor of the right anterior fossa, consistent with meningioma (yellow arrow). Dashed red line represents region used for connectivity analysis. B) A regional functional connectivity map (L-image) shows decreased connectivity between cortex surrounding the lesion and the rest of the brain, compared to corresponding voxels in the contralateral hemisphere. No areas of increased connectivity are seen. MRI: magnetic resonance imaging.

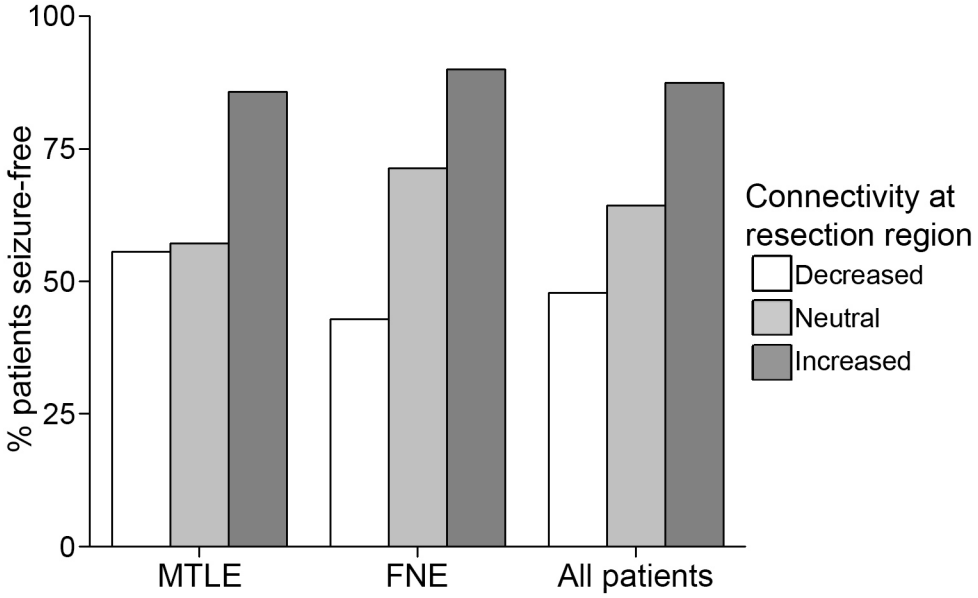

Figure 7: Increased connectivity at the resection region is associated with seizure freedom after surgery. Post-operative seizure freedom is more common in patients with predominantly increased connectivity at the resection region (mean voxel *t*-score > 0.2, N = 24) compared to those with neutral (-0.2 < *t* < 0.2, N = 15) or decreased (*t* < *0.2,* N = 23) connectivity ($X^2 = 8.5$, $p = 0.015$, all 61 patients). Results reflect regional connectivity between the resection region and the rest of the brain, compared to corresponding voxels in the non-epileptogenic hemisphere. FNE: focal neocortical epilepsy; MTLE: mesial temporal lobe epilepsy.

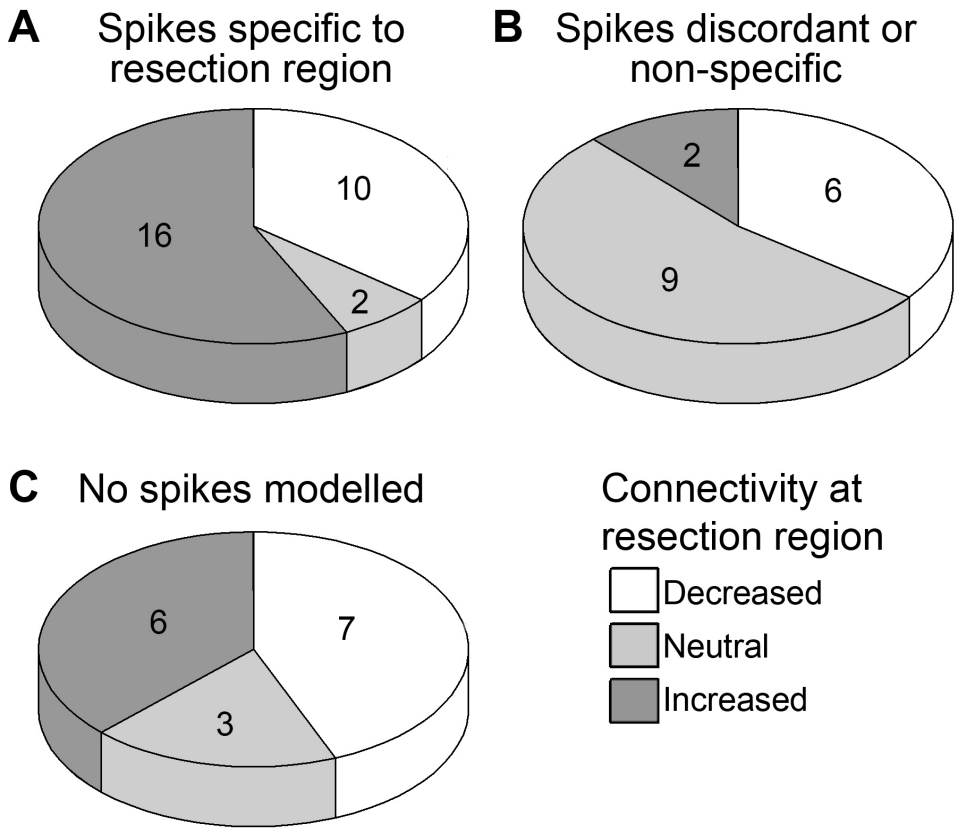

Figure 8: A resection region harboring localized interictal spikes is more likely to display increased connectivity. Functional connectivity at the resection region is increased in 57% of 28 patients with interictal spikes specific to that region, but in only 12% of 17 individuals with discordant or non-specific spikes. Regional connectivity is increased in 32% of 16 of patients in whom spikes were not observed (overall $X^2 = 16.0$, $p < 0.01$). N = 61 patients.