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Spike-Associated Networks Predict Postsurgical Outcomes in Children with Refractory Epilepsy

Joshua J Bear, MD[1,2], **Jenifer L Sargent, BS**[3], **Brent R O'Neill, MD**[4], **Kevin E Chapman, MD**[5], **Debashis Ghosh, PhD**[6], **Heidi E Kirsch, MD**[7,8], **Jason R Tregellas, PhD**[9,10]

[1]Department of Pediatrics, Section of Neurology, Children's Hospital Colorado

[2]Department of Pediatrics, University of Colorado Anschutz Medical Campus

[3]Neuroscience Institute, Children's Hospital Colorado

[4]Department of Neurosurgery, University of Colorado and Children's Hospital Colorado

[5]Department of Pediatric Neurology, Phoenix Children's Hospital

[6]Department of Biostatistics and Informatics, Colorado School of Public Health

[7]Department of Radiology and Biomedical Imaging, University of California, San Francisco

[8]Department of Neurology, University of California, San Francisco

[9]Department of Psychiatry, University of Colorado Anschutz Medical Campus

[10]Research Service, Rocky Mountain Regional VA Medical Center

Abstract

Introduction: Up to half of children undergoing epilepsy surgery will continue to have seizures despite a cortical resection or ablation. Functional connectivity has shown promise in better identifying the epileptogenic zone (EZ). We hypothesized that cortical areas showing high information outflow during interictal epileptiform discharges (IEDs) are part of the EZ.

Methods: We identified 22 children with focal epilepsy who had undergone stereo electroencephalography (SEEG), surgical resection or ablation, and had ≥1 year of post-surgical follow-up. The mean phase slope index, a directed measure of functional connectivity, was calculated for each electrode contact during IEDs. The positive predictive value (PPV) and negative predictive value (NPV) for a seizure-free outcome were calculated based on whether or not high information outflow brain regions were resected.

Results: Resection of high outflow (z-score ≥ 1) and very high outflow (z-score ≥ 2) electrode contacts was associated with higher seizure freedom (high outflow: chi-squared statistic = 59.1, $p < 0.001$; very high outflow: chi-squared statistic = 31.3, $p < 0.001$). The PPV and NPV for seizure freedom based on resection at the electrode level increased at higher z-score thresholds with a peak PPV of 0.86 and a peak NPV of 0.9.

Corresponding Author: Joshua J Bear, 13123 East 16th Avenue, Box B-155, Aurora, CO 80045, Phone: 720-777-6138, Fax: 720-777-7285, joshua.bear@cuanschutz.edu.

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Conclusions: Better identification of the EZ has the potential to improve epilepsy surgery outcomes. If the surgical plan can be modified to include these very high outflow areas, more children might achieve seizure freedom. Conversely, if deficits from resecting these areas are unacceptable, ineffective surgeries could be avoided and alternative therapies offered.

Keywords

Epilepsy surgery; Epileptogenic zone; Pediatric epilepsy; Intracranial EEG; Functional connectivity

Of an estimated eight million children with epilepsy globally, 30-40% are refractory to anti-seizure medications[1,2]. For many, epilepsy surgery offers the potential for seizure freedom, lower morbidity and mortality, and improvements in quality of life across psychosocial and cognitive domains.[3] Unfortunately, many children continue to have seizures after surgery. In recent cohorts, for whom the latest imaging techniques were available, the seizure freedom rate ranged from a high of 87% for temporal lobe epilepsies to as low as nearly 50% for extra-temporal epilepsies.[4] In other words, nearly half of children in some cohorts will continue to have seizures after undergoing neurosurgery. As such, there is a clear need for improvement, either through better identification of the anatomic regions needing resection or better prediction of surgical failures.

Functional connectivity and network analysis methods are rapidly growing research areas in epilepsy surgery.[5] Much attention in this area has been focused on non-invasive techniques, such as functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG), to aid in presurgical planning. However, functional connectivity can also be measured from intracranial EEG recordings, including both traditional electrocorticography and stereo EEG (SEEG), prior to resection. Studies of intracranial EEG-based functional connectivity in adult[6] and pediatric[7] epilepsies have suggested that a higher overall connectivity is associated with persistent seizures.

In addition to subject level predictions, efforts have also been made to define connectivity-based biomarkers that identify which electrode contacts should be included in the resection. In a study of 15 adults, the resection of highly central nodes in ictal networks was associated with seizure freedom.[8] A larger study using a similar technique, however, found that the *existence* of these highly central network nodes was associated with worse outcomes even when they were resected.[6] In a recent multicenter study of 28 adults, electrode-specific features were able to predict postsurgical outcomes based on resection with a positive predictive value (PPV) of 0.89 and a negative predictive value (NPV) of 0.80.[9]

This study examined connectivity changes occurring during interictal epileptiform discharges, or “spikes”, as a means of identifying the epileptic network and predicting postsurgical outcomes. We previously demonstrated that a similar technique, using whole-brain MEG rather than intracranial EEG, was able to noninvasively identify nodes within the epileptic network.[10] In this work, we are extending the study of spike-associated networks (SANs) to SEEG with the goal identifying methods to improve surgical outcomes in children with refractory focal epilepsy. We hypothesize that brain regions in the epileptogenic

zone (EZ), the minimum brain tissue that must be resected to achieve seizure freedom,[11] demonstrate high information outflow during interictal spiking activity.

Methods

This was a retrospective observational study. Patients from Children's Hospital Colorado (CHCO) were included if they had undergone SEEG monitoring and subsequent surgical resection or ablation with at least one year of postsurgical follow-up. The study was reviewed by the Colorado Multiple Institutional Review Board and determined to be exempt.

Participant Identification and Extraction of Clinical Data

The charts of all children who had undergone both SEEG monitoring and subsequent epilepsy surgery were reviewed. Study participants were included if the surgery was a resection, disconnection, or ablation. For these participants, clinical data including the age at epilepsy diagnosis, presurgical full-scale intelligence quotient (FSIQ) and/or general ability index (GAI), age at surgery, pathology results, last clinic follow-up, and postsurgical outcome were extracted. Children without at least one year of clinical follow-up were excluded. Postsurgical outcomes were categorized as seizure(sz)-free (Engel class I) or sz-persist (Engel class ≥ II).

Electrophysiology and Neuroimaging Data Review and Co-Registration

All SEEG data were recorded as part of the subjects' standard epilepsy surgery evaluations. The locations and total number of SEEG electrodes were tailored to each patient according to his or her presurgical evaluation and multidisciplinary epilepsy surgery conference discussions. Intracranial data were recorded at a minimum sampling rate of 500 Hz using 8-to-16-contact electrodes. Thirty minutes of interictal SEEG data from at least four hours before or after any seizures were imported into Brainstorm.[12] Intracranial EEG-based functional connectivity measures with 24 hours separation versus 1 hour separation from seizures has not been found to differ.[13]

Interictal epileptiform discharges (IEDs) including spikes, sharp waves, polyspikes, and their complexes—hereafter referred to broadly as "spikes"—were visually identified by a board certified epileptologist (JJB) and manually marked at the first change from baseline (Figure 1). The scorer was given a study-specific subject number and the EEG data without any clinical information during this visual review. IEDs were only marked if they were separated from other discrete IEDs by at least one second. In areas with continuous slowing and sharply contoured waveforms, as is common in some epileptogenic tissue including cortical dysplasias, IEDs were only marked when they stood out in amplitude and morphology from the rest of the electrographic background. When there were multiple spike populations, the single predominant population defined by the number of occurrences was selected for analysis. When an IED was seen in multiple regions, the beginning of the earliest discharge was marked. Non-functioning electrode contacts identified by visual review were excluded.

Neuroimaging data including presurgical MRI, implantation computed tomography (CT), and postsurgical imaging (MRI or CT) were imported into Brainstorm. All imaging studies were co-registered to each individual's presurgical MRI. Electrode positions and contacts

were manually marked on the implantation CT. Based on a combination of visual review of the EEG tracing and the co-registered neuroimaging data, every electrode contact was classified by whether it was intra- or extracerebral and whether or not it was included in the resection cavity.

Measuring Spike-Associated Networks (SANs)

Generating SAN connectivity matrices.—For every subject, 0.5-second epochs beginning with each spike were extracted from the SEEG recordings. A multitaper approach using discrete prolate spheroidal sequences was used to decompose the time series data into the time-frequency domain. The phase-slope index (PSI) between each electrode contact with all other contacts was calculated from activity in the beta frequency band (13–30 Hz), generating a spike-specific connectivity matrix. The PSI is a directed measure of functional connectivity, which allows estimation of information flow within the network, derived from the imaginary component of coherency.[14] By measuring the imaginary component of coherency, the PSI mitigates effects of zero time-lag correlations, which most often represent artifact and volume conduction. This reduces the impact of external artifacts while also minimizing the connectivity contributions from white matter contacts. Beta activity was selected because it is prominently represented in intracranial EEG with a high signal-to-noise ratio, particularly compared to higher frequencies in the gamma range and above. Additionally, spikes themselves with a duration of 20–70 milliseconds exist within the beta frequency range. The 0.5-second duration was chosen for its high temporal resolution while still being of adequate duration to obtain a reliable connectivity estimate in the beta band.[15] Connectivity matrices were then averaged within each subject to reduce noise and improve the signal-to-noise ratio for the SAN.

Quantitative network features.—For each subject, the mean absolute value of the PSI for all contacts was calculated as the subject's overall connectivity strength. Contact-specific connectivity strengths were calculated as the mean strength of all connections from the contact of interest to every other contact. Each electrode contact's overall connectivity could be positive (indicating a net outflow of information) or negative (indicating a net inflow of information). Baseline functional connectivity values and event-related connectivity changes often vary from one individual to the next. To facilitate meaningful inter-subject comparisons, connectivity values for all contacts were z-normalized within each subject. Contacts were considered "high outflow" if the z-normalized PSI value was ≥ 1 and "very high outflow" if the z-normalized PSI value was ≥ 2.

Statistical Analysis

Clinical variables in the sz-free and sz-persist group were compared using two-tailed t-tests for continuous predictor variables and Fisher's exact test of independence for nominal predictors if there were only two categories. For nominal predictors with more than two categories, for example surgical lobe and pathology results, the Freeman-Halton extension of Fisher's exact test was used. The chi-squared test was used to test the relationship between electrode contact resection and postsurgical outcome among the high outflow and very high outflow contacts separately. Positive predictive values (PPV) and negative predictive values (NPV) were calculated from these contingency tables. In post-hoc analysis, PPV and

NPV were graphed against a spectrum of PSI z-scores. P-values ≤ 0.05 were considered statistically significant.

Results

Twenty-two children met all inclusion criteria. Eleven children (50%) were seizure free ("sz-free") and eleven (50%) had persistent seizures ("sz-persist") after at least one year of follow-up. There were no significant differences in clinical variables, including gender, age of epilepsy onset, duration of epilepsy prior to surgery, or general cognitive function between the sz-free and sz-persist groups (Table 1). In the subject level analyses, there were no differences in mean absolute connectivity strength or in the number of electrodes and electrode contacts implanted between the sz-free and sz-persist groups. Subjects who achieved seizure freedom did have a significantly greater total number of electrode contacts resected ($t = 3.4$, $p = 0.003$). Clinical and connectivity characteristics for individual subjects are shown in Table 2. Additional clinical, neuroimaging, and neurophysiology details are available in Supplemental Table 1.

Resection of high outflow and very high outflow electrode contacts was associated with seizure freedom (high outflow: chi-squared statistic = 59.1, $p < 0.001$; very high outflow: chi-squared statistic = 31.3, $p < 0.001$). Examined another way, resected contacts in the sz-free group had a significantly higher connectivity strength than unresected contacts ($t = 4.02$, $p < 0.001$). This was not observed in the sz-persist group ($t = 0.009$, $p = 0.99$). Contingency tables for both groups are shown (Table 3). The PPV and NPV for seizure freedom generally showed an increasing trend at higher z-score thresholds. The peak PPV of 0.86 for seizure freedom was achieved with resection of electrode contacts with a connectivity z-score ≥1.8. Similarly, the NPV (the probability of persistent seizures when contacts were *not* resected) had a peak of 0.90 at a z-score threshold ≥ 2.5. Figure 2 shows the connectivity values and outcome probabilities at the electrode contact level. Z-transformed connectivity values for every contact, grouped by postsurgical outcome and colored by resection status, are shown in Figure 2A. The very high outflow contacts highlight the differences between resection status and postsurgical outcome. NPV and PPV values across a range of z-score thresholds are shown in Figure 2B.

Postsurgical neuroimaging was not available for seven subjects. Six out of the seven subjects had temporal lobectomies. At our institution, the surgical approach to temporal lobectomies is standardized, and review of the operative notes and discussion with the operating surgeon confirmed that all of the included cases followed our standard approach, allowing confident classification of resection status. Nonetheless, we were concerned about the potential bias introduced by misclassification of resected electrodes. We therefore performed a re-analysis excluding these subjects. Because five of the six temporal lobectomy subjects were in the sz-free group, their exclusion dropped the baseline seizure freedom rate to 0.33 (5 sz-free, 10 sz-persist). Resection of the very high outflow contacts led to a peak PPV to 0.74 while the peak NPV was 0.95. This remains statistically significant (high outflow: chi-squared statistic = 72.3, $p < 0.001$; very high outflow: chi-squared statistic = 25.4, $p < 0.001$).

Moving from contact-level data back to individual subjects, the total number of and difference between resected and unresected very high outflow electrode contacts for each subject are shown in Figure 3. Notably, only 2 out of 12 children in whom the majority of very high outflow contacts *were not* resected achieved seizure-freedom. Conversely, 8 of 9 children in whom at least half of the very high outflow contacts *were* resected achieved seizure freedom.

Discussion

For some children with refractory epilepsy, surgery can provide a cure when no other relief is possible. Unfortunately, identifying the epileptogenic zone (EZ) often remains elusive. The postsurgical seizure freedom rate in children with refractory epilepsy who require intracranial EEG monitoring appears to be around 50% based on several recent studies including this one. In this study, we examined the use of momentary changes in functional connectivity induced by interictal spikes as a biomarker of epileptogenicity that could be used to improve postsurgical outcomes.

Looking at intracranial EEG-derived SANs, we found a strong relationship between the resection of brain regions showing high information outflow and surgical outcome. Specifically, we observed a PPV for a seizure-free outcome as high as 0.86 when brain regions associated with high outflow were included in the resection. Conversely, when these regions were not resected, the NPV for a seizure-free outcome was as high as 0.9. With the overall cohort rate of seizure freedom being 0.5, these numbers suggest that a substantial improvement in outcomes is possible.

Even if resection of high outflow contacts leads to the predicted rate of seizure freedom, resection is not always possible. Surgical plans are driven not just by the likelihood of seizure freedom but also by the acceptability of postsurgical deficits. We often see families who favor a smaller resection—and the lower likelihood of seizure freedom—because potential deficits from the surgery are not acceptable. In our cohort, subjects 16 and 22 had limited surgeries for this reason, potentially contributing to their persistent seizures. In such cases, the current findings could still be helpful. If it could be shown, for example, that the majority of high outflow contacts were in an area of cortex that could not be resected, which this study suggests would result in a probability of seizure freedom as low as 10%, we might counsel the family differently and offer another option such as neurostimulation.

SANs have several strengths. First, using interictal connectivity data allows a preliminary estimation of the EZ in the absence of seizures. While SANs are unlikely to eliminate the need to capture seizures, they might increase our confidence to proceed with fewer seizures captured. This could reduce the risk of complications from prolonged recordings.[16] In addition, we will rarely proceed to surgery even when seizures are not captured during the SEEG monitoring. One subject in our cohort, Subject 12, was such a case where a single semiologically *atypical* seizure was captured after 14 days of recording. The standard interictal data supported epileptogenicity in the right temporal lobe, and ultimately a right temporal lobectomy was performed with persistent seizures. The SAN identified several electrode contacts in the temporo-parietal junction, posterior to the clinically

hypothesized EZ and planned surgery. As with the more limited resections mentioned above, we might have reconsidered offering this surgery if we knew that there was only a 10% chance of seizure freedom. Another benefit of SANs is the relative simplicity of incorporating the technique into a clinical workflow compared to more complicated multi-feature computational methods. Furthermore, highly predictive single-feature methods such as the SAN can subsequently be added back to multi-feature models with the potential for even greater accuracy.

There are a few considerations to address before applying this technique clinically. The modest size of our cohort limited our ability to control for more complex clinical interactions. For example, we were not powered to test differences in prediction accuracy between different epilepsy etiologies, specific MRI findings, anatomic distribution electroclinical hypotheses regarding the epileptogenic zone, or interictal and ictal electrographic patterns. Several of these potentially confounding clinical features, such as a diffuse electrographic onset and multifocal seizures, were present in both the sz-free and sz-persist group. Another clinical factor complicating the analysis is the matter of resection size. The total number of resected contacts did differ between the sz-free and sz-persist group, and larger resections are associated with an increased likelihood of seizure freedom[17]. A larger cohort would be necessary, however, to properly assess the effect these clinical features have on SAN predictions of the epileptogenic zone.

Despite the modest size of our cohort, our data add to a small but growing number of studies that have made similar observations using related techniques. The largest study using SEEG in adults consistently identified relative entropy, another measure of functional connectivity based on the randomness and spectral richness between two signals, to be a highly predictive measure of postsurgical outcome.[9] Similarly, in the only other pediatric study, which studied a slightly smaller cohort using electrocorticography grids rather than SEEG, increased mean connectivity was identified as one of two critical features for predicting postsurgical outcomes.[7] Including the present study, these three studies—representing 67 patients across a spectrum of ages, etiologies, EEG recording methods, and specific connectivity measures—all suggest that resecting highly connected regions is positively associated with seizure freedom.

Directed connectivity measures can elucidate the direction of information flow throughout epileptic networks. However, directed functional connectivity also presents unique considerations. In this cohort, we used the mean information outflow from a node as the indicator of its importance in the network. This measure, however, is prone to potential bias based on how widely connected a given node is. For example, electrical activity arising from the hippocampus often propagates to temporal neocortex before spreading more broadly throughout the brain[18]. This could lead to the contacts in the temporal neocortex having a higher mean outflow than those in the hippocampus despite being a secondary step in the network. This phenomenon could explain both subjects who achieved seizure freedom despite having unresected very high outflow contacts. The SAN identified two contacts in the anterior insula in subject 19. This patient did have two seizures that arose from this area, but she had 150 other seizures that arose from the mesial temporal structures and then spread

to this area, suggesting that the epileptogenicity in the anterior insula was being driven by the mesial temporal lobe.

The lack of postsurgical neuroimaging for several subjects is also an important limitation. However, excluding these subjects from the analysis did not affect the relative improvements or statistical significance of the predictive power of the SAN technique. The lack of a gold standard for measuring the EZ is a limitation in all studies of novel techniques in epilepsy surgery. Lacking a gold standard, we make inferences based on outcomes. If seizures stop after surgery, then the brain tissue removed contained the EZ. We cannot know whether the whole region needed to be resected or if the resection could have been smaller. Similarly, all intracranial EEG techniques result in limited sampling of the cortex. Even if a perfect connectivity-based measure of the EZ was developed, results would depend on where the EEG contacts were placed. Patients could have persistent seizures if the EZ extends to unresected parts of the brain not included in the sampled areas. This could explain the persistent seizures in Subject 2 who had the second lowest number of total electrode contacts implanted. While the majority of her seizures appeared to arise from the temporal lobe, there were a few seizures during a cluster that had a broader onset that included the insula. This might have indicated a second focus or a remote focus spreading to both of these regions that was not being monitored. Similarly, depending on the z-score threshold chosen, the SAN technique will identify electrode contacts with high outflow connectivity values whether or not any contacts are truly in the EZ. As such there is a risk that the technique could identify healthy cortical tissue, particularly if the SEEG implantation plan is based on limited information or if an overly liberal connectivity threshold is used. Outcomes will continue to depend heavily on the strength of *a priori* hypotheses of the EZ based on scalp EEG, neuroimaging, and seizure semiology.

In summary, SANs retrospectively measured interictal SEEG recordings can predict seizure freedom with a PPV and NPV of up to 86% and 90% respectively at the electrode level. With the growing consensus that intracranial EEG-based functional connectivity measures can markedly improve post-surgical outcome predictions[6,7,9], it is time to begin prospectively examining the application of these methods to pediatric epilepsy surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest and Funding Sources

Dr. Kirsch serves as a consultant for Ricoh. The remaining authors report no conflicts interest. This work was supported in part by a grant from the National Institutes of Health, National Institute of Neurological Disorders and Stroke (NIH K12 NS089417). Dr. Tregellas is also supported by a Department of Veterans Affairs Clinical Science Research and Development Merit Review Award (I01CX001414) and Research Career Scientist Award (IK6CX002178).

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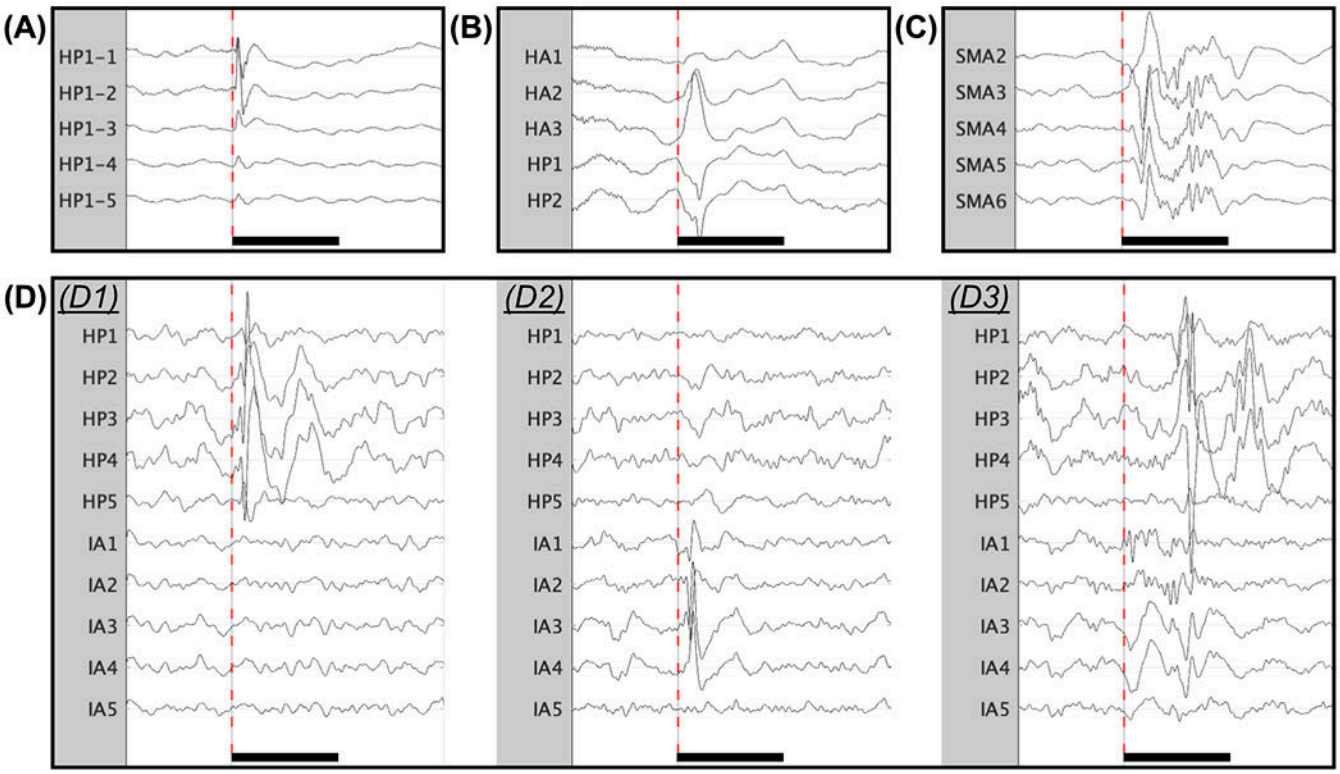

Figure 1.

Examples of typical IEDs used in the study. (**A**) A hippocampal spike seen in Subject 1. (**B**) A hippocampal sharp wave seen in Subject 5. (**C**) A polyspike-and-wave complex seen in Subject 13. (**D**) Multiple populations of IEDs seen in Subject 6 including a polyspike-and-slow-wave complex in HP1–5 (**D1**), a spike in IA1-4 (**D2**), and a low amplitude polyspike in IA1–2 with concordant sharp wave in IA3–4 followed shortly by a polyspike-and-slow-wave complex in HP1–4 (**D3**). The IEDs at IA1–4 were the predominant population with 87 events while the HP1–4 IEDs were also abundant with 76 events. The vertical dashed line indicates the start of the 500 ms epoch used in the connectivity analyses, and the black horizontal bar indicates a period of 500 ms.

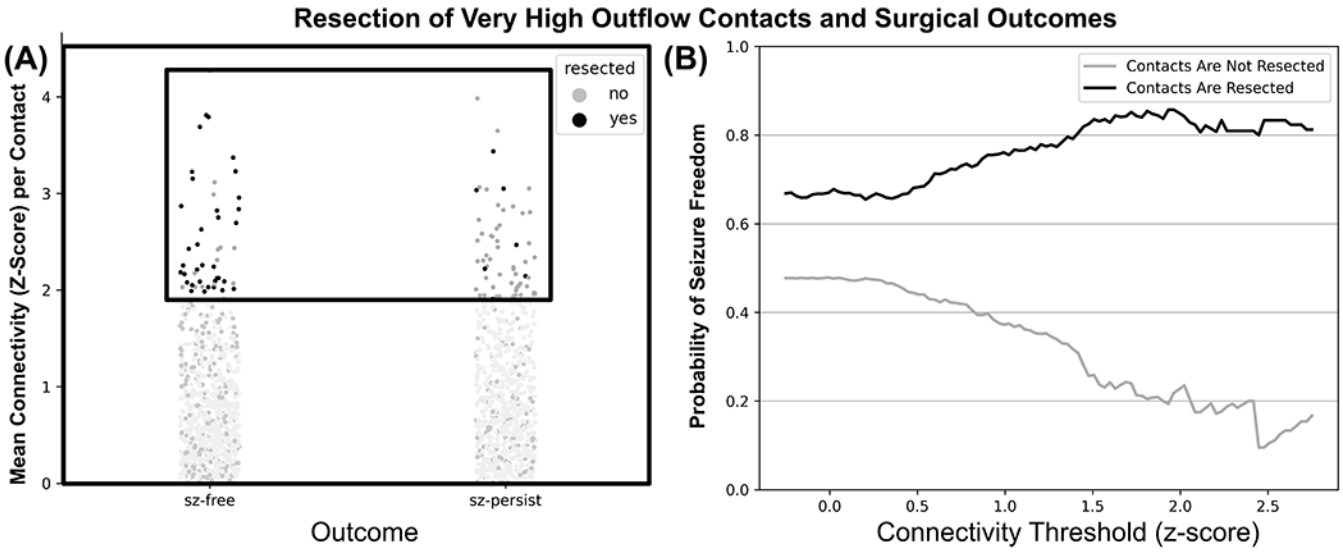

Figure 2.

Connectivity values and surgical outcomes based on whether or not given contacts were included in the resected area. (**A**) Categorical scatter plot showing the resection status and outcome of all contacts with a mean outflow connectivity. The black rectangle indicates those contacts classified as “very high outflow.” Note that these very high outflow contacts were significantly more likely to be resected (black dots) in the sz-free group and not resected (gray dots) in the sz-persist group. (**B**) Positive predictive values (black) and negative predictive values (gray, shown as 1 – NPV to match axes) of a seizure-free outcome based on the resection status of electrode contacts at increasing z-score thresholds.

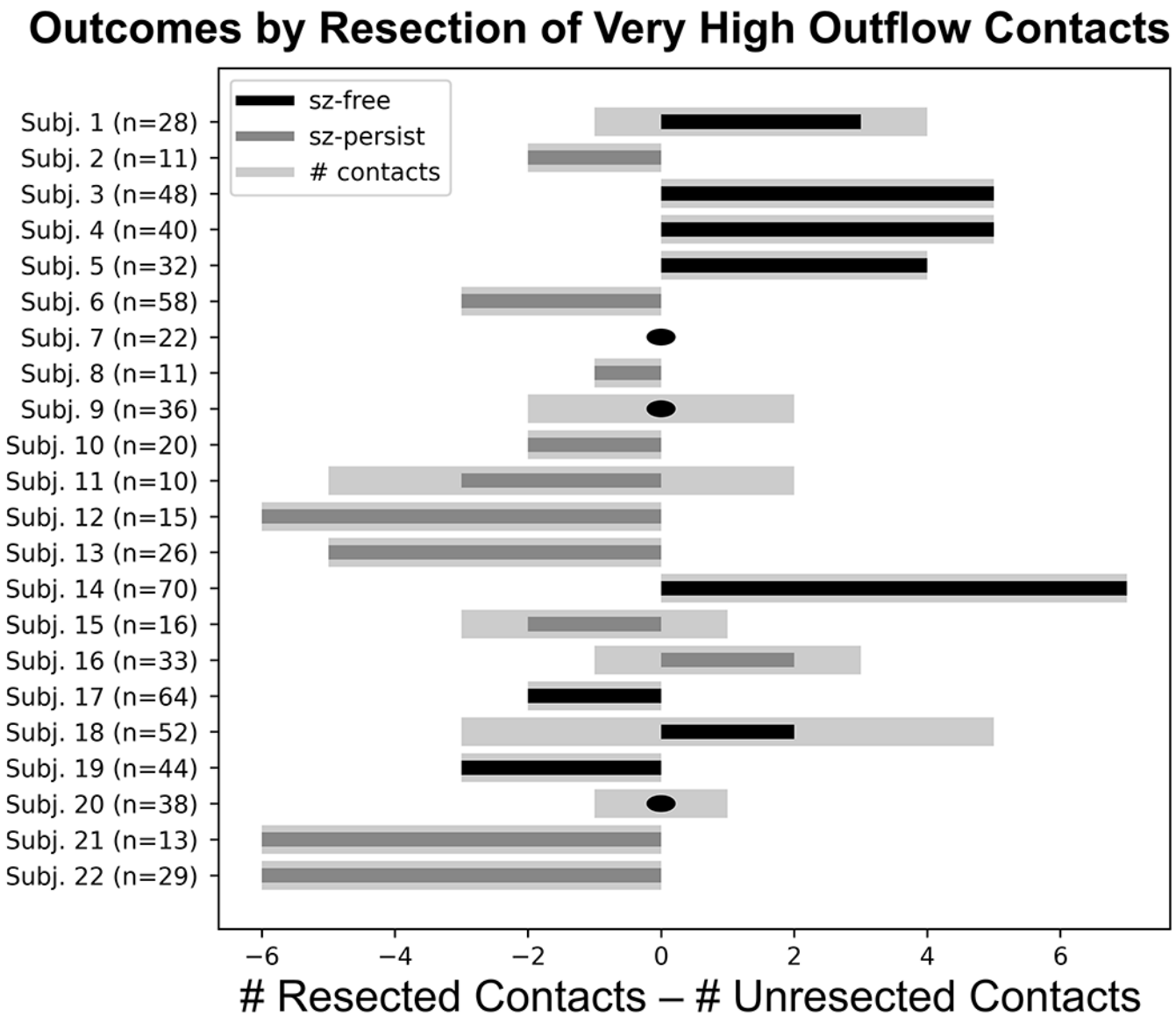

Figure 3.

Subject-level outcomes based on the number of very high outflow contacts included in the resection versus those not included in the resection. The black (sz-free) and gray (sz-persist) bars indicate the difference in the number of resected and unresected contacts. The light gray bars indicate the total number of resected (positive) and unresected (negative) contacts at z-score threshold ≥ 2 for each subject.

Table 1.

Clinical Characteristics and Outcomes

		Sz-Free	Sz-Persist	*p*-value
Total Subjects (n)		11	11	
Sex				1.00
	Female (*n*)	4	3	
	Male (*n*)	7	8	
FSIQ/GAI (mean)		84 +/− 14	84 +/− 19	0.94
MRI+ *(n)*		10	8	0.59
Age at Surgery (mean)		16 +/− 2	13 +/− 5	0.08
Age at Diagnosis (mean)		7 +/− 5	6 +/− 4	0.76
Duration of Epilepsy at Surgery (mean)		9 +/− 5	6 +/− 4	0.23
SEEG				
	Number of Electrodes (*n*)	13 +/− 3	13 +/− 2	0.68
	Intracranial Electrode Contacts (*n*)	161 +/− 41	162 +/− 34	0.98
	Contacts Resected (%)	28% +/− 13%	15% +/− 12%	**0.02**
	Contacts Resected (n)	43 +/− 15	22 +/− 14	**0.003**
Surgical Lobe (n)				1.00
	Temporal	6	5	
	Frontal	2	2	
	Parietal	1	1	
	Occipital	—	—	
	Multilobar	2	2	
Surgical Hemisphere (n)				0.39
	Right	8	5	
	Left	3	6	
Pathology (n)				0.51
	Hippocampal Sclerosis	2	1	
	Focal Cortical Dysplasia	2	3	
	Subtle Nonspecific Abnormalities	7	4	
	Normal Tissue	0	2	

Abbreviations: Sz, seizure; FSIQ, full scale intelligence quotient; GAI, general ability index; MRI+, likely explanatory lesion for subject's seizures visible on MRI; SEEG, stereo electroencephalography

Table 2.

Individual Subject Clinical and Connectivity Characteristics

							Electrode Contacts					
Subject	**Age (y)**	**Sex**	**FSIQ/GAI**	**MRI**	**# of IEDs***	**# of Electrodes**	***n***	**% Resected**	**Conn. Strength†**	**Surgery Performed**	**Pathology**	**Outcome**
Subj. 1	15.5	F	90	+	102	13	106	26%	0.012	R temporal lobectomy	Hippocampal sclerosis	sz-free
Subj. 2	15	F	85	+	86	12	116	9%	0.010	L hippocampus laser ablation	Not sent	sz-persist
Subj. 3	15	M	93	+	99	13	126	38%	0.028	R temporal lobectomy	Immature neurons, moderate gliosis	sz-free
Subj. 4	18	F	72	+	38	11	131	31%	0.006	L temporal lobe, anterior/ inferior L insula resection	WM gliosis, cortical dyslamination	sz-free
Subj. 5	14	M	90	+	79	16	214	15%	0.010	R temporal lobectomy	Hippocampal sclerosis	sz-free
Subj. 6	17	F	89	−	87	10	118	49%	0.013	L Temporal lobectomy	FCD type Ic	sz-persist
Subj. 7	16	M	94	+	82	13	177	12%	0.028	L STG and inferior anterior insula resection	Equivocal FCD ILAE type Ia	sz-free
Subj. 8	9	M	72	+	64	9	127	9%	0.018	L superior frontal gyrus resection	FCD type IIb	sz-persist
Subj. 9	16	F	64	+	43	13	144	25%	0.016	L parietal lobe resection	Encephalomalacia, FCD type IIId	sz-free
Subj. 10	18	M	79	+	108	12	162	12%	0.017	R temporal lobectomy	Hippocampal sclerosis, moderate gliosis	sz-persist
Subj. 11	7	M	100	+	174	14	176	6%	0.021	L medial frontal lesionectomy	Normal tissue	sz-persist
Subj. 12	13	M	45	−	87	16	208	7%	0.019	R temporal lobectomy	Normal tissue	sz-persist
Subj. 13	2	M	n.p.	+	103	11	136	19%	0.035	R anterior insula resection	WM gliosis, mild cortical dyslamination	sz-persist
Subj. 14	17	M	71	+	67	8	116	60%	0.089	R frontal lobectomy	Meningeal fibrosis, equivocal dyslamination	sz-free
Subj. 15	15	M	86	+	117	16	206	8%	0.007	R lateral parietal lobe partial resection	Focal gliosis, adjacent FCD type IIId	sz-persist
Subj. 16	18	M	115	+	108	14	192	17%	0.015	R temporal lobe, insula resection	WM gliosis, tangential dyslamination	sz-persist
Subj. 17	13	M	62	+	44	16	199	32%	0.015	R frontal lobe disconnection	WM gliosis, equivocal tangential dyslamination	sz-free
Subj. 18	20	M	104	−	39	16	213	24%	0.005	R temporal lobectomy	WM gliosis, equivocal tangential dyslamination	sz-free

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Subj. 19	13	F	89	+	180	16	204	22%	0.012	R temporal lobectomy	Moderately-severe Chaslin's subpial gliosis	sz-free
Subj. 20	18	M	98	+	112	10	142	27%	0.010	R temporal lobectomy	Mild gliosis	sz-free
Subj. 21	7	M	74	+	136	14	176	7%	0.014	L temporal, hippocampal, basal frontal lobetomy	Perivascular inflammation, patchy neuronal loss	sz-persist
Subj. 22	17	F	92	−	94	12	160	18%	0.009	L temporal neocortex resection	Mild cortical dyslamination	sz-persist

*Represents the number of IEDs used in the connectivity analysis based on the defined selection criteria, not the total of number of IEDs in the recording.

†Connectivity strength shown as the mean absolute value of the phase slope index for every contact. Abbreviations: F, female; M, male; FSIQ, full scale intelligence quotient; GAI, general ability index; MRI, magnetic resonance imaging (+ indicates an MRI abnormality identified as a likely source of seizures); IEDs, interictal epileptiform discharges; Conn., connectivity; Subj., subject; R, right; L, left; sz, seizure; WM, white matter; FCD, focal cortical dysplasia; n.p., not performed.

Table 3.

Contingency tables of highly connected and very highly connected electrode contacts.

Highly Connected (z-score > 1) Contacts		
	Sz-Free	Sz-Persist
Resected	108	34
Not Resected	132	221
Very Highly Connected (z-score > 2) Contacts		
	Sz-Free	Sz-Persist
Resected	33	6
Not Resected	12	40