Resecting critical nodes from an epileptogenic circuit in refractory focal-onset epilepsy patients using subtraction ictal SPECT coregistered to MRI

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OBJECTIVE The purpose of this study was to assess the positive predictive value of postresection outcomes obtained by presurgical subtracted ictal SPECT in patients with lesional (MRI positive) and nonlesional (MRI negative) refractory extratemporal lobe epilepsy (ETLE) and temporal lobe epilepsy (TLE). Specifically, outcomes were compared between partial versus complete resection of the regions of transient hyperperfusion identified using subtraction ictal SPECT coregistered to MRI (SISCOM) in relation to the ictal onset zone (IOZ) that was confirmed by electrocorticography (ECoG). That is, SISCOM was used to understand the long-term postsurgical outcomes following resection of the IOZ that overlapped with 1 or more regions of ictal onset–associated transient hyperperfusion.

METHODS The study cohort included 44 consecutive patients with refractory ETLE or TLE who were treated between 2002 and 2013 and underwent presurgical evaluation using SISCOM. Concordance was determined between SISCOM localization and the IOZ on the basis of ECoG monitoring. In addition, the association between the extent of the resection site overlapping with the SISCOM signal and postresection outcomes were assessed. Postsurgical follow-up was longer than 24 months in 39 of 44 patients.

RESULTS The dominant SISCOM signals were concordant with ECoG and overlapped the resection site in 32 of 44 (73%) patients (19 ETLE and 13 TLE patients), and 20 of 32 (63%) patients became seizure free. In all 19 ETLE patients with concordant SISCOM and ECoG results, the indicated location of ictal onset on ECoG was completely resected; 11 of 19 patients (58%) became seizure free (Engel Class I). In all 13 TLE patients with concordant SISCOM and ECoG results, the indicated ECoG focus was completely resected; 9 of 13 patients (69%) became seizure free (Engel Class I). Complete resection of the SISCOM signal was found in 7 of 34 patients (21%). Of these 7 patients, 5 patients (72%) were seizure free (Engel Class I). Partial resection of the SISCOM signal was found in 16 of 34 patients (47%), and 10 of these 16 patients (63%) were seizure free (Engel Class I) after more than 24 months of follow-up.

CONCLUSIONS Concordance between 1 or more SISCOM regions of hyperperfusion with ECoG and at least partial resection of the dominant SISCOM signal in this refractory epilepsy cohort provided additional useful information for predicting long-term postresection outcomes. Such regions are likely critical nodes in more extensive, active, epileptogenic circuits. In addition, SPECT scanner technology may limit the sensitivity of meaningful SISCOM signals for identifying the maximal extent of the localizable epileptogenic network.

<http://thejns.org/doi/abs/10.3171/2015.6.JNS141719>

KEY WORDS ictal onset zone; electrocorticography; temporal lobe epilepsy; subtraction ictal SPECT coregistered to MRI; epileptogenic network; extratemporal epilepsy; magnetic resonance imaging

EPILEPSY is estimated to affect between 2.5 and 3 million people in the United States, with a prevalence of 5 to 10 persons per 1000.³² It has been shown that about 47% of patients with a new diagnosis of focal-onset epilepsy are successfully treated with the first antiepileptic

drug (AED) prescribed.¹⁹ Therapeutic failure of 2 AEDs is defined as drug-resistant epilepsy.^{2,5} Approximately 20% to 40% of patients with epilepsy are likely to have drug-resistant epilepsy.^{4,26,27} Patients with a unilateral lesion on high-resolution MRI that is concordant with the

ABBREVIATIONS aECoG = acute electrocorticography; AED = antiepileptic drug; ECoG = chronic electrocorticography; EEG = electroencephalography; ETLE = extratemporal epilepsy; IOZ = ictal onset zone; SISCOM = subtraction ictal SPECT coregistered to MRI; SPGR = spoiled gradient recalled; TLE = temporal lobe epilepsy.

SUBMITTED July 28, 2014. **ACCEPTED** June 17, 2015.

INCLUDE WHEN CITING Published online March 18, 2016; DOI: 10.3171/2015.6.JNS141719.

electroencephalography (EEG) findings and seizure semiology have the best outcomes after resection.^{13,31,34} Unfortunately, 20% to 30% of temporal lobe epilepsy (TLE) patients and 20% to 50% of extratemporal lobe epilepsy (ETLE) patients demonstrate the absence of an underlying lesion on high-resolution MRI.^{6,16,18} Resective targeting of the ictal onset zone (IOZ) is most challenging in patients with nonlesional MRI and focal-onset epilepsy. Previous postresection outcome studies report seizure freedom to be the greatest after resection in lesional TLE patients, where 75% to 85% of patients achieve Engel Class I after 2 years of follow-up (Engel classification: Class I, seizure free; Class II, rare disabling seizures; Class III, worthwhile improvement; and Class IV no worthwhile improvement).^{3,9} Patients with lesional ETLE have seizure-free rates (Engel Class I) of around 60% (at 1-year follow-up).³¹ In contrast, patients with nonlesional TLE demonstrate outcomes with seizure-free rates (Engel Class I) ranging from 41% to 65% (at 2-year follow-up).^{1,14,24,30} Patients with nonlesional ETLE exhibit the lowest seizure-free outcomes, ranging from 24% to 42% (at 2-year follow-up).^{8,20,23} A better understanding is necessary to evolve our approach toward recognizing the IOZ as a critical node in a larger epileptogenic network in order to achieve better seizure-free rates, particularly in nonlesional focal-onset epilepsy.

In the present study, we retrospectively analyzed the clinical history profiles including duration of epilepsy, video EEG (noninvasive and invasive) and MRI findings, subtraction ictal SPECT coregistered to MRI (SISCOM) data, seizure semiology, sites and sizes of resection, pathological findings, and postsurgical seizure outcomes in a cohort of patients with lesional and nonlesional ETLE and TLE. The aim of our study was to assess the positive predictive value of resecting SISCOM regions of transient hyperperfusion that were associated with the IOZ. Also, the long-term postsurgical outcomes in patients with both MRI-positive and MRI-negative ETLE and TLE were compared.

Methods

Patients

A total of 567 presurgical SPECT studies (243 patients) were performed at our center between 2002 and 2013. Our study included a cohort of 44 patients from this presurgical group who underwent resective epilepsy surgery. The mean age of the patients in our cohort was 29 years (range 11–57 years; SEM 1.8) (Table 1). Patients underwent follow-up for a mean of 5 years (range 2–10 years). All patients in our cohort were assessed using chronic intracranial electrode electrocorticography (ECoG) monitoring and/or acute intraoperative electrocorticography (aECoG). The placement of the electrodes for invasive monitoring was determined during an epilepsy surgery management conference at our institution. Multiple factors were analyzed to generate the hypothesis for intracranial electrode placement and targeting the IOZ. To facilitate localization of the IOZ, we employed seizure semiology, MRI, chronic noninvasive scalp video-EEG monitoring, magnetoencephalography, SISCOM, positron emission tomography, and neurocognitive testing (Table 2).

TABLE 1. Characteristics of the study participants

Characteristic	Value*
Resections	44
Age (yrs)	
Range	11–57
Mean	29
Male	23 (52%)
Female	21 (48%)
Rt-handed	38 (86%)
Lesional temporal epilepsy	17 (38%)
Nonlesional temporal epilepsy	1 (2%)
Lesional extratemporal epilepsy	14 (32%)
Nonlesional extratemporal epilepsy	12 (27%)

* Values are shown as n (%) unless otherwise stated.

We included patients based on the following inclusion criteria: 1) diagnosis of drug-resistant, focal-onset epilepsy based on presurgical evaluation that included SISCOM; and 2) resective epilepsy surgery performed with a postoperative follow-up of ≥ 24 months (mean follow-up 5 years). The predominant reasons for exclusion from the study were 1) patient underwent less than 24 months of follow-up (except patients who remained as Engel Class IV [no worthwhile improvement]), or 2) no interictal SPECT was acquired. Forty-four patients met all of the inclusion criteria and were analyzed in this study. One ETLE patient in the study had undergone a previous resection prior to a second resection. In 25 (61%) patients, postresection MRI was performed. Preresection subtraction ictal SPECT was coregistered to the patient's postresection MRI study, which was acquired at least 12 months postoperatively. This technique accounted for brain shift following resection. This strategy was used to determine the regions of transient hyperperfusion in comparison with the extent of resection.

High-Resolution MRI

High-resolution, gapless, pre- and postgadolinium, volumetric, spoiled gradient recall (SPGR) MR images of the brain were obtained for each patient. The MRI examination was performed using a 1.5- or 3-T scanner (Siemens). A gapless, SPGR, T1-weighted sequence data set for each patient was acquired at a slice thickness of 1.0 or 1.6 mm.

Noninvasive Video-EEG Monitoring

Chronic, noninvasive video-EEG monitoring was performed in each patient using the International 10-20 system for electrode placement, including anterior temporal and sphenoidal electrodes if appropriate. AEDs were lowered during chronic monitoring, all patients were electrographically monitored to record the typical seizures, and video recordings were generated to monitor semiology.

SISCOM

SPECT was performed on each patient during video-EEG monitoring using Ceretec (^{99m}Tc-HMPAO) or Neurolite (^{99m}Tc-ECD) at a dose of 24 to 26 mCi (adjusted for

TABLE 2. Clinical data of all patients included in the study

Pt No.	Age (yrs)/Sex	Ep Dur (yrs)	Handedness	MRI Finding	Pathology	Scalp EEG	ECoG Onset	Inj Time (sec)	No. of Szs During Inj	SISCOM Focus	Surgery	ECoG/SISCOM Concord	Complete/Partial Resection	Outcome (Engel class)*
1	32/M	Rt	31	Normal	Glios	Bilat frontal	1) Lt mesiofrontal, lt orbitofrontal; 2) surrounding prior resection	11	3	Lt ant cingulate cortex	1) SFG, MFG, sparing lt MFG; 2) lt anterior frontal	No	NA	IVb
2	45/F	Rt	38	Cavernoma, Lt H	Glios	Rt frontal	Rt mesiofrontal	62	11	Rt post supra-marginal gyrus/STG	Rt frontal, IFG, MFG, SFG	No	NR	Ia
3	50/M	Rt	45	Lt MTS	MTS	Lt temp	Lt ant temp	NA	2	Lt ant temp/H	Lt ant temp; STG, MTG, ITG, AHC	Yes	Complete	Id
4	12/M	Rt	5	Normal	Inflam-mation	Bilat frontal	Rt mesiofrontal, rt posteroinf-rior frontal	21	1	Rt ant insula	Rt frontal, SFG + ant corpus callosotomy	Yes	NA	Ib
5	27/M	Rt	26	Rt frontoparietal cortical efface-ment	FCD	Bilat frontal (rt>lt)	Rt mesiofrontal	20	2	Rt basal frontal	Rt basal frontal	Yes	Partial	IVb
6	29/M	Rt	8	Lt temp tumor	Epidermoid cyst	Lt temp	Lt ant temp, lt post temp	12	4	Lt ant temp	Lt ant temp; STG, MTG, ITG, tumorectomy, AHC	Yes	Partial	Ia
7	51/F	Rt	45	Normal	Hemorrhage	Bilat frontal, lt temp	Lt mesiofrontal	8	2	Lt mesiofrontal	Lt mesiofrontal	Yes	Partial	Ic
8	24/F	Rt	17	Normal	Heterotopia	Rt temp, rt frontal H	Rt orbitofrontal	44	8	Rt frontal	Rt SFG, IFG + partial MFG + ant mesio-temp + rt ant temp	Yes	Complete	IVb
9	31/M	Rt	14	Rt frontal tumor	FCD	Lt temp & lt frontal	Lt ant inferior temp	72	2	Lt anterobasal temp	Lt ant temp; STG, MTG, ITG, AHC	Yes	Partial	Ia
10	57/M	Lt	50	Lt-sided tumor	Inflam-mation	Lt frontal	Lt mesial frontal	11	16	Lt mesiofrontal	Lt hemispherectomy	Yes	Partial	IVa
11	40/F	Rt	21	Lt MTS + tumor	MTS, heterotopia	Lt temp & midpost rt frontal	Lt temp	23	1	Lt hippocampus	Lt temp; STG, MTG, ITG, AHC	Yes	Partial	Ia
12	39/0	Rt	19	Rt frontal tumor	Glios	Rt temp & rt basal frontal	Rt ant, middle temp, rt basal frontal	22	1	Rt basofrontal, rt temp	Rt ant temp; STG, MTG, ITG, AHC	Yes	Complete	IVa
13	14/F	Rt	3	Normal	Hemorrhage	Bilat frontal	Rt lateral frontal, rt orbitofrontal	11	1	Lt paramesial premotor cortex	Rt frontal	No	Partial	Ia
14	41/F	Rt	36	Rt FCD	FCD	Nonlocaliz-able	Rt mesial frontal	54	10	Rt mesiofrontal	Rt frontal; SFG	Yes	Complete	Ia

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Pt No.	Age (yr)/Sex	Ep Dur (yrs)	Hand-edness	MRI Finding	Pathology	Scalp EEG	ECoG Onset	Inj Time (sec)	No. of Szs During Inj	SISCOM Focus	Surgery	ECoG/SISCOM Concord	Complete/Partial Resection	Outcome (Engel class)*
15	11/M	Rt	2	Lt cingulate tumor	Neurocytoma	Lt temp	Lt frontal, SFG	330	5	Lt mesiofrontal	Lt frontal; SFG, Lt parietal tumor resection	Yes	Partial	Ia
16	28/M	Lt	27	Normal	FCD	Lt frontal	Lt basal frontal	41	3	Lt basal frontal	Lt frontal; SFG, MFG, IFG	Yes	Complete	Ib
17	50/F	Rt	46	Lt MTS	MTS	Lt frontal	Lt mesial temp, Lt ant frontal	17	6	Lt ant temp	Lt temp; STG, MTG, ITG, AHC	Yes	Partial	Ia
18	36/F	Rt	30	Rt frontal tumor	Giant cell astrocytoma	Bilat frontoparietotemp multifocal	Rt ant mesial frontal	11	1	Rt post frontal	Rt ant frontal, tumor resection	No	NA	IVb
19	17/F	Rt	15	Ischemia or demyelination	Gliosis	Lt temp	Lt basal temp	40	1	Lt basal temp	Lt ant temp; STG, MTG, ITG, AHC	Yes	NR	IIIa
20	33/F	Rt	25	Normal	Gliosis	Rt temp	Rt ant temp	3	NA	Rt ant temp	Rt ant temp, AHC	Yes	Partial	IIIb
21	10/F	Lt	3	Lt frontal tumor	Meningioma	Bilat frontal, rt frontopolar	Lt ant frontal	22	1	Rt hippocampal frontal	Lt frontal tumor	No	NR	Ia
22	49/M	Rt	46	Rt MTS	Rt MTS + heterotopia	Rt H, post quadrant	Rt posterolateral temp	21	1	Rt posterolateral temp	Rt ant temp; STG, MTG, ITG, AHC	Yes	NA	Ia
23	27/M	Rt	4	Rt MTS	MTS	Rt ant temp, Lt frontotemp	Rt ant temp	21	3	Bilat temp	Rt temp; STG, MTG, ITG, AHC	No	NR	Ia
24	16/F	Lt	15	Lt temp tumor	Inflammation	Lt post quadrant, rt frontal	Lt frontocentrotemp	10	1	Lt post basal temp	Lt AHC & resection of scar around the prior stroke cavity	Yes	NR	IIIa
25	23/F	Rt	12	Bilat FCD (lt occipital lobe) MTS	Gliosis	Lt occipital, lt temp	Lt ant mesial temp	12	3	Lt ant temp	Lt ant temp; STG, MTG, ITG, AHC	Yes	NA	Ila
26	25/M	Rt	15	Normal	Gliosis	Rt mesiofrontal, Rt temp	Rt mesial frontal	87	3	Rt basal frontal	Rt frontal	Yes	Partial	IVc
27	13/M	Rt	4	Ischemia or demyelination	Inflammation	Rt frontal	Rt lateral frontal	3	NA	Rt lateral frontal	Rt frontal back to the area of precentral sulcus	Yes	NR	IVc
28	27/M	Rt	14	Normal	Gliosis	Bilat frontal	Rt mesial frontal	375	NA	Rt basal frontal, rt mesiofrontal	Rt SFG, cingulate sulcus	Yes	NR	Ia
29	27/M	Rt	14	Normal	NA	NA	Rt orbitofrontal	11	10	Rt orbitofrontal	Rt orbitofrontal, MFG	Yes	Partial	Ia

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Pt No.	Age (yrs)/Sex	Ep Dur (yrs)	Hand-edness	MRI Finding	Pathology	Scalp EEG	ECoG Onset	Inj Time (sec)	No. of Szs During Inj	SISCOM Focus	Surgery	ECoG/ SISCOM Concord	Complete/ Partial Resection	Outcome (Engel class)*
30	37/F	Rt	10	Ischemia or demyelination	NA	Rt frontal, lt post quadrant	Rt mesial frontal	9	4	Rt mesiofrontal	MST, leg area over to the lateral convexity rt frontal	Yes	NA	Ic
31	20/F	Rt	3	Normal	MTS	Rt mesio-temp	Rt temp	3	NA	Rt basal temp	Rt temp	Yes	NA	Ib
32	24/F	Rt	19	Rt FCD	Gliosis	Nonlocalizable rt mesio-frontal, also bilat frontal spikes	Rt mesial frontal	129	3	Rt dorsolateral frontal	Rt frontal; SFG using bipolar & resection	No	NA	IIla
33	41/F	Rt	39	Rt temp, rt occipital, & rt parietal FCD	FCD	Rt parietal quadrant	Rt temp, seizure foci in rt parietal & rt occipital	28	2	Rt parietal	Rt temp, rt parietooccipital	Yes	Complete	Ib
34	25/M	Rt	6	Lt temp tumor	Old hemorrhage	Lt temp, rt frontal	Lt temp	76	5	Rt STG	1) Lt temp; 2) Rt neurospace concordant w/ SISCOM	No	NR	IIc
35	15/M	Rt	8	Normal	Subdural hematoma	Rt frontal	Rt mesial frontal	15	5	Rt mesiofrontal	Rt mesiofrontal	Yes	NA	Ib
36	35/F	Rt	29	Bilat MTS	Gliosis	Rt fronto-temp	Rt ant frontal, rt temp	NA	5	Nonlocalizing/nonlateralizing	Rt frontal; MFG, IFG	No	NR	Ib
37	20/M	Rt	12	Rt H w/ double cortex	NA	Nonlocalizable rt parietal sharp waves	Rt parietal	13	5	Rt parietal	NA	Yes	NR	IVa
38	11/F	Rt	10	Lt frontal FCD	NA	Lt frontal	Lt lateral frontal	12	2	Rt mesiofrontal	NA	No	Complete	IIlb
39	32/M	Rt	25	Normal	NA	Lt temp	Lt temp, ant temp	3	NA	Lt ant temp	Lt basal temp	Yes	Partial	Ia
40	24/F	Lt	19	Normal, sinus disease	Gliosis	Nonlocalizable bilat frontal slowing	Rt mesiofrontal	11	13	Rt mesiofrontal	Rt mesial frontal	Yes	NA	IVb
41	31/F	Rt	24	MTS	MTS	Lt fronto-temp	Lt ant temp	9	5	Lt antero-basal temp region	Lt ant temp STG, MTG, ITG	Yes	Complete	Ia

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TABLE 2. Clinical data of all patients included in the study

Pt No.	Age (yrs)/Sex	Ep Dur (yrs)	Hand-edness	Rt	MRI Finding	Pathology	Scalp EEG	ECoG Onset	Inj Time (sec)	No. of Szs During Inj	SISCOM Focus	Surgery	ECoG/SISCOM Concord	Complete/Partial Resection	Outcome (Engel class)*
42	44/M	41	Rt		Lt MTS	MTS	Nonlocalizable	Lt ant temp & lt basal temp	30	6	Lt basal frontal region	Lt ant temp STG, MTG, ITG, AHC	No	NR	Ia
43	20/M	5	Rt		Rt frontal encephalomalacia	NA	Bilat mesial frontal	Rt prefrontal cortex	118	42	Rt basal frontal	Rt frontal & STG	Yes	Partial	Ic
44	24/M	4	Rt		Rt arachnoid cyst	Gliosis	Lt temp	Lt ant polar temp region	39	2	Lt basal temp region	Lt temp STG, MTG, ITG	Yes	NA	IVb

AHC = amygdalohippocampectomy; ant = anterior; Concord = concordance; Ep Dur = epilepsy duration; FCD = focal cortical dysplasia; H = hemisphere; HF = hippocampus; IFG = inferior frontal gyrus; Inj = injection; ITG = inferior temporal gyrus; MFG = middle frontal gyrus; mid = middle; MST = multiple subpial transection; MTG = middle temporal gyrus; MTS = mesial temporal sclerosis; NA = not available; NR = not resected; post = posterior; Pt = patient; SFG = superior frontal gyrus; STG = superior temporal gyrus; Szs = seizures; temp = temporal.

* Engel classification: Ia, completely seizure free since surgery; Ib, nondisabling, simple partial seizures only after surgery; Ic, some disabling seizures after surgery, but free of disabling seizures for at least 2 years; Id, generalized convulsions with AED discontinuation only; IIa, initially free of disabling seizures, but has rare seizures now; IIb, worthwhile seizure reduction; IIc, prolonged, seizure-free intervals amounting to greater than half of the follow-up period, but for less than 2 years; IVa, significant seizure reduction; IVb, no appreciable change; IVc, seizures worse after surgery.

body weight). The radiotracer was injected for the ictal SPECT studies with an autoinjector (MedRad) used by a specially trained nuclear medicine technologist (V.P.) while at the patient's bedside during seizure onset. The technologist was trained to inject at the clinical and/or electroencephalographic seizure onset, whichever came first. The seizure-onset and ending times were always noted. Also, the time from the beginning of injection up to the complete depression of the syringe plunger was noted. We retrospectively calculated the time of the radiotracer injection following seizure onset by reviewing the video-EEG recordings for all patients. To avoid injection during the postictal state, a minimum of 15 seconds was required between the end of radiotracer injection and the end of the seizures, as described above. Baseline SPECT was obtained by performing an interictal injection after a seizure-free period of ≥ 24 hours. Brain SPECT scans were obtained within 2 hours after injection using a Siemens E.CAM Dual-Detector gamma camera with BiOCORE fan beam collimators. Thirty-two views per detector (total 64) were acquired using 80,000 counts per view, circular orbit, and "step and shoot" mode. Images were reconstructed by Syngo Siemens AG software using a 128×128 matrix with a Butterworth filter. DICOM isotropic datasets with a voxel size of 3.9 mm were created and transferred to Analyze software (AnalyzeDirect). Analyze version 10 was used to perform ictal and interictal SPECT thresholding, normalization, subtraction, and coregistration to the patient's MRI study. Finally, the brain was segmented from the extracerebral structures, as identified on the patient's volumetric MRI study. The cerebral surface of the binary ictal SPECT was matched to the cerebral surface of the binary MRI. The resulting registered transformation matrix was then applied to the subtraction SPECT data set in order to coregister it to the processed MRI study. Complete, gapless, SISCOM image sets were presented to a blinded, board-certified epilepsy neurologist (M.A.R.) who determined the SISCOM region of transient hyperperfusion for each patient in this study.

Invasive Recording

The ECoG electrode placement plan (subdural grid electrodes and/or depth electrodes) was confirmed using head CT. In 41 patients, chronic bedside ECoG monitoring was performed to investigate the clinical electrocerebral IOZ based on the patient's stereotypic seizure. For 3 patients, aECoG monitoring alone provided enough information to establish the IOZ.

Pathology

A pathological diagnosis of the resected specimens, such as gliosis, focal cortical dysplasia, heterotopias, tumor, or mesial temporal sclerosis, was determined for 38 of 44 (86%) patients (Table 2).

Postoperative Seizure Outcomes

Postoperative outcomes were determined by following 38 patients for a period greater than 24 months (mean follow-up 5 years; range 2–10 years) after resection. We classified the postresection outcomes into 4 classes and subclasses according to Engel's classification.¹¹ At the time

of our analysis, 5 patients in our study received a follow-up period of 17 to 18 months. However, these patients remained classified as Engel Class IV. One of the patients in our study was observed for only 12 months. However, this patient remained in Engel Class IVc (no worthwhile improvement, worsening of seizures after surgery).

Postresection MRI

We obtained postresection MRIs for 34 of 44 (77%) patients. We coregistered the preresection SISCOM on postresection MRI in order to evaluate the extent of resection of the identified SISCOM region of hyperperfusion. Using traditional SISCOM processing with Analyze, we could not achieve accurate registration of the preresection SISCOM signals on the postresection MRI studies for all patients. Postresection MRI findings were considerably different from preresection MRI findings due to the creation of new cortical boundaries, particularly in the area of resection. In addition, the craniotomy flap altered the skull shape in some patients. Consequently, clean object extraction could not be achieved in several postresection MRI data sets, resulting in poor registration. To solve this problem, we employed a different postprocessing method. We performed 3-dimensional voxel registration using Analyze between the original fused preresection SISCOM, which was used as the base, and the postresection MRI, which was used as the match. We first performed manual registration to achieve similar alignment in all 3 planes (transverse, coronal, and sagittal). We then performed autoregistration using the register tab in the 3-dimensional voxel registration window in Analyze. This process perfectly aligned the two 3-dimensional objects, so that each voxel in the new fused image represented the same voxel of the base (preresection SISCOM) and match (postresection MRI).

The intensities of the base and match were modified as follows. The minimum intensity of the base image was increased in order to make the preresection MRI disappear and reduce the maximum of the base in order to improve the SPECT signal. This technique prevented the preresection brain tissue boundary from filling the resection site. Thus, the fused image demonstrated the properties of the SPECT signal of the base, but not the MRI properties of the base. Lastly, we reduced the maximum intensity of the match to intensify the postresection MRI. This technique enabled us to better visualize the resection site. This process resulted in the accurate registration of the preresection, SISCOM hyperperfusion signals over the postresection MRI, and, at the same time, improved the intensity of the resection site.

Analysis and Statistics

Concordance was determined between SISCOM localization and ECoG on the basis of an overlapping IOZ and called "concordance with the ECoG." Concordance was also determined between SISCOM localization and the resection site, or "concordance with the resection site." Two different concordance types are designated since resection usually involves a larger area than the IOZ, as determined by ECoG. Strict concordance criteria were used, where > 90% of the resected area must overlap with the SISCOM signal to be considered concordant. Concor-

dance was determined by a blinded, board-certified epilepsy neurologist (M.A.R.).

We coregistered preresection and subtracted ictal SPECT on postresection MRI to determine if the SISCOM signal was completely or partially removed. We determined if complete or partial resection impacted postoperative outcomes.

Our cohort of 44 patients underwent resective epilepsy surgery. All patients underwent follow-up for at least 2 years (mean follow-up 5.0 years; range 2–10 years). Five patients only received 17 to 18 months of follow-up at the time of our analysis, but these patients demonstrated Engel Class IV outcomes. One of the patients completed a follow-up of only 12 months, but achieved Engel Class IVc. The mean radiotracer injection time for all patients was 45 seconds (SEM 11.4) after electrocerebral seizure onset. In our cohort, all SPECT studies were performed during the patient's stereotypic seizures, as measured electrographically or clinically.

Results

ECoG Monitoring

ECoG concordant tissue was completely resected from all 44 patients. Of these 44 patients, 24 of 44 (55%) became seizure free (Engel Class I) after at least 2 years of follow-up after resection.

SISCOM Concordance

SISCOM was concordant with ECoG and the resection site in 32 of 44 (73%) patients, and 20 of these 32 (63%) became seizure free (Engel Class I after > 2 years follow-up). Of these 32 patients, 19 of 32 (59%) were ETLE and 13 of 32 (41%) were TLE (Fig. 1). The mean injection time was 46 seconds in the SISCOM ECoG concordant group (SEM 14.5).

SISCOM Concordant ETLE Group

In 19 ETLE patients with concordant SISCOM and ECoG results, ECoG delineated the epileptogenic source or focus, which was completely resected in all patients; 11 of 19 patients (58%) became seizure free (Engel Class I) (Table 3).

Among these 19 ETLE patients, 8 patients exhibited a lesion on MRI (focal cortical dysplasia, tumor, double cortex, or encephalomalacia). Only 6 of these 8 patients exhibited an MRI lesion and SISCOM focus that were both concordant with the ECoG results; only 3 of these 6 patients (50%) became seizure free (Engel Class I) (Table 3).

Also, among these 19 ETLE patients, 11 patients were MRI negative for lesions. For these patients, SISCOM facilitated the placement of the intracranial electrodes; 7 (64%) patients became seizure free (Engel Class I) (Table 3).

SISCOM Concordant TLE Group

In the 13 TLE patients with concordant SISCOM and ECoG results, the indicated ECoG focus was completely resected; 9 of 13 patients (69%) became seizure free (Engel Class I) (Table 3).

Among these 13 TLE patients, 11 patients had a lesion

TABLE 3. SISCOM concordant with ECoG and overlapping with the resection site in ETLE (n = 19) and TLE (n = 13)*

Engel Class	ETLE			TLE		
	SISCOM & Lesional MRI Concordant w/ aECoG/ECoG (n = 6)	SISCOM Concordant, Lesional MRI Nonconcordant w/ aECoG/ECoG (n = 2)	SISCOM Concordant w/ aECoG/ECoG, Nonlesional MRI (n = 11)	SISCOM & Lesional MRI Concordant w/ aECoG/ECoG (n = 8)	SISCOM Concordant, Lesional MRI Nonconcordant w/ aECoG/ECoG (n = 3)	SISCOM Concordant w/ aECoG/ECoG, Nonlesional MRI (n = 2)
I	3 (50%)	1 (50%)	7 (64%)	7 (88%)	1 (33%)	1 (50%)
II	0	0	0	0	1 (33%)	0
III & IV	3 (50%)	1 (50%)	4 (36%)	1 (12%)	1 (33%)	1 (50%)

* Values are shown as n (%).

(mesial temporal sclerosis, focal cortical dysplasia, or tumor) on MRI. Only 8 of these 11 patients demonstrated an MRI lesion and SISCOM focus that were both concordant with the ECoG results; 7 of these 8 patients (88%) became seizure free (Engel Class I) (Table 3).

Also, among these 13 TLE patients, 2 patients were MRI negative. For these patients, SISCOM guided the placement of the intracranial electrodes; 1 (50%) patient became seizure free (Engel Class I) (Table 3).

Nonconcordant Group

SISCOM was nonconcordant with ECoG but overlapped with the resection site in only 1 of 44 patients. This patient was diagnosed with nonlesional ETLE but did not exhibit a lesion on MRI. This patient demonstrated a worse outcome after resection and achieved Engel Class IV (> 2 years of follow-up, Fig. 1).

SISCOM was nonconcordant with ECoG and nonoverlapping with the resection site in 11 of 44 patients (Fig.

FIG. 1. Classification hierarchy of patient outcomes after resective epilepsy surgery. Three main groups are represented: 1) SISCOM concordant with ECoG and overlapping with the resection site; 2) SISCOM nonconcordant with ECoG and nonoverlapping with the resection site in TLE patients; and 3) SISCOM nonconcordant with ECoG and overlapping with the resection site.

TABLE 4. Outcomes for SISCOM nonconcordant with aECoG/ECOG and nonoverlapping with the resection site (n = 11)*

Engel Class	ETLE		TLE	
	SISCOM Nonconcordant, Lesional MRI Concordant w/ aECoG/ECOG (n = 2)	SISCOM Nonconcordant, MRI Lesional Nonconcordant w/ aECoG/ECOG (n = 4)	SISCOM Nonconcordant, MRI Lesional Concordant w/ aECoG/ECOG (n = 5)	SISCOM Nonconcordant, Lesional MRI Nonconcordant w/ aECoG/ECOG (n = 0)
I	1 (50%)	1 (25%)	2 (40%)	0
II	0	0	1 (20%)	0
III & IV	1 (50%)	3 (75%)	2 (40%)	0

* Values are shown as n (%).

1). In the nonconcordant group, 4 of 11 (36%) patients achieved Engel Class I, 1 of 11 (9%) patients achieved Engel Class II (rare disabling seizures), 2 of 11 (18%) patients achieved Engel Class III (worthwhile improvement), and 4 of 11 (36%) patients achieved Engel Class IV. All of these 11 patients exhibited lesions on MRI (Table 4).

For the SISCOM nonconcordant group, the average injection time was 37 seconds (SEM 11.3).

Resection of SISCOM Focus

We coregistered the preresection subtraction ictal SPECT to each patient's postresection MRI in order to determine if the SISCOM signal(s) used to guide the placement of the intracranial electrodes preresection was completely, partially, or not resected. A 10% shifting of the adjacent brain postresection was assumed in the postresection MRI coregistrations. Postresection MRI studies were completed in 35 of 44 (80%) patients.

Complete resection of the SISCOM signal was found in 7 of 34 patients (21%). Of these 7 patients, 5 patients (72%) were seizure free (Engel Class I). Partial resection of the SISCOM signal was found in 16 of 34 patients (47%); 10 of these 16 patients (63%) were seizure free (Engel Class I) after more than 24 months of follow-up (Table 5).

The SISCOM signal was not resected in 11 of 34 (32%) patients. Four of these 11 patients (36%) were seizure free (Engel Class I) after more than 24 months of follow-up.

Pathology

The pathological findings (gliosis and focal cortical dysplasia) ($p = 0.1007$) were not significantly correlated with the outcomes of epilepsy surgery (Table 2).

Discussion

The success of epilepsy surgery depends on the accurate anatomical localization of the IOZ, which is indispensable to contributing to favorable outcomes. The IOZ is a com-

ponent of the ictal circuitry that is critically involved in the initiation of seizure. Scalp EEG and semiology are often not sensitive enough to accurately delineate the IOZ in rapidly propagating seizures. Consequently, the development of novel neuroimaging approaches is required to facilitate visualizing the IOZ, particularly in patients with ETLE. SISCOM can help identify the IOZ, though its limitations as an indirect measure of increased metabolic demand in the nearby epileptogenic cortex must be kept in mind. The probability of seizure freedom in our cohort is highest for lesions identified on MRI. Patients with MRI findings showing lesions in 1 temporal lobe that are concordant with ipsilateral ictal activity on EEG have the highest rate of seizure freedom after resective epilepsy surgery.^{13,31} In our cohort, 7 patients demonstrated underlying lesions in 1 temporal lobe (predominantly mesial temporal sclerosis), and a concordant abnormality on scalp EEG was noted in 6 of these patients; all 7 of 7 (100%) patients achieved Engel Class I with longer than 3 years follow-up (mean follow-up 4.9 years). SISCOM was concordant with the resection site in 6 of 8 (75%) of these patients.

It has been previously shown that the probability of seizure freedom (Engel Class I) at the 12-month follow-up after surgery is 2.7 times higher in TLE patients with MRI lesions in comparison with TLE patients without MRI lesions.³¹ Moreover, the probability of seizure freedom (Engel Class I) at the 12-month follow-up after surgery is 2.9 times higher in ETLE patients with MRI lesions in comparison with ETLE patients without MRI lesions.³¹ SISCOM impacted our postresection outcomes in the nonlesional ETLE and TLE patient groups. Also, the complete or partial resection of the SISCOM region of transient hyperperfusion plays a role in seizure freedom; 5 of 7 (72%) patients were seizure free after complete resection of SISCOM hyperperfusion-related signaling, and 10 of 16 (63%) patients were seizure free after the partial resection of similar SISCOM signals. In our study, 6 patients exhibited SISCOM signal foci localized with the resection site;

TABLE 5. Outcomes in patients with partial resection of the SISCOM focus in ETLE (n = 10) and TLE (n = 6)*

Engel Class	ETLE, Lesional MRI Concordant w/ aECoG/ECOG (n = 2)	ETLE, Lesional MRI Nonconcordant w/ ECOG (n = 2)	ETLE, MRI Nonlesional (n = 6)	TLE, Lesional MRI Concordant w/ aECoG/ECOG (n = 4)	TLE, Lesional MRI Nonconcordant w/ aECoG/ECOG (n = 1)	TLE, MRI Nonlesional (n = 1)
I	1 (50%)	1 (50%)	4 (67%)	3 (75%)	1	0
II	0	0	0	0	0	0
III–IV	1 (50%)	1 (50%)	2 (33%)	1 (25%)	0	1

* Values are shown as n (%).

these patients demonstrated poor surgical outcomes (Engel Class IV), and at least 1 SISCOM region not overlapping with the resection site (Fig. 2). Concordance between SISCOM with ECoG had a sensitivity of 72.7%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 14.3%.

Improved outcomes were seen with earlier surgery for intractable frontal lobe epilepsy.²⁸ In our study, the mean duration of frontal lobe epilepsy was 19.17 years. When the duration of frontal lobe epilepsy was < 5 years, 75% became seizure free (n = 4; 3 MRI lesion-positive and 1 MRI lesion-negative patients) (Engel Class I, mean year of follow-up postresection 7.7 years, range 6–10 years, SD 2.08). However, when the duration of frontal lobe epilepsy was ≥ 5 years, 59% became seizure free (n = 17; 7 MRI lesion-positive and 10 MRI lesion-negative patients) (Engel Class I, mean year of follow up postresection 7.3 years, range 3–11, SD 2.8).

According to previously published success rates for partial frontal lobectomy, favorable outcomes (Engel Class I) range from 15% to 35% in these trials.^{7,12,20,25,29,36} The only variable that was significantly associated with a favorable surgical outcome was a focal MRI abnormality in frontal lobe epilepsy.¹³ Elsharkawy et al. published a retrospective study investigating 97 patients with lesional frontal lobe epilepsy who underwent resection.¹⁰ This study reported the seizure freedom rates (Engel Class I) to be 54.6% at 6 months, 49.5% at 2 years, 47% at 5 years, and 41.9% at 10 years.¹⁰ In yet another series, 41% of nonlesional TLE patients showed excellent outcomes versus 72% when an MRI abnormality was present.²¹ Previous studies that

report favorable (Engel Class I) outcomes investigated patients with frontal lobe tumors or focal cortical dysplasias.³⁶ Other factors that predict seizure recurrence include incomplete resection of the epileptogenic lesion,^{7,10,17,33,36} predominantly generalized or poorly localized ictal EEG patterns on surface EEG,^{10,17,35} the lack of a subdural grid evaluation,^{10,17} acute postresection seizures,⁶ postoperative persistence of prolonged auras,^{10,17} history of febrile seizures,²¹ and the lack of a distinct MRI lesion.^{7,10,17,22,33,35}

The SISCOM results in our study patients influenced the planning of intracranial electrode placement. Therefore, our ECoG results were, in part, influenced by our SISCOM data. Also, all patients in our cohort underwent SISCOM as part of the presurgical evaluation. Therefore, potential selection bias toward patients with more localizable IOZ has to be regarded, and consequently resulted in more favorable postresection outcomes.

Conclusions

The goal of resective epilepsy surgery is long-term seizure freedom (Engel Class I or II). Seizure outcomes are time dependent and dynamic. All prognostic factors converge into one central theme: an epileptogenic zone that is well visualized and also electrically and semiologically restricted, in that its extent offers the best chance of seizure freedom when resected completely. However, SISCOM provides an indirect measure of localizing the IOZ, which often coincides with the critical nodes within the epileptogenic network.

These data confirm previous studies that demonstrate

FIG. 2. Presentation of patients with SISCOM foci localizing with the resection site. These patients demonstrated poor surgical outcomes (Engel Class IV), and at least 1 SISCOM region did not overlap with the resection site. Figure is available in color online only.

the utility of SISCOM by improving the outcomes of drug-resistant, focal-onset epilepsy in both ETLE and TLE patients. Concordance between SISCOM and ECoG and/or aECoG in this refractory epilepsy cohort provides useful additional information for predicting postresection outcomes. In addition, the limitations in SPECT scanner technology may contribute to the sensitivity of SISCOM for identifying the maximal extent of the critical nodes or the generators of the epileptogenic circuit. The predominant limitation of conventional SPECT technology is the voxel resolution, which is limited to 8 to 12 mm with inadequate attenuation correction. The limitations of the spatial resolution of SPECT are related to using only 2- and 3-head photon detectors to record low-energy single-photon events. Next-generation SPECT scanner systems with significantly improved resolution and complementary postprocessing techniques will facilitate identifying a greater extent of the critical nodes in an epileptogenic network.¹⁶ Such technology will augment guiding ECoG electrode placement in potentially extensive epileptogenic networks.

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Disclosures

Dr. Byrne reports that he is a consultant for Stryker and Integra.

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Conception and design: Jalota, Rossi, Byrne. Acquisition of data: Stein, Stoub, Balabanov, Bergen, Bermeo, Park, Smith. Analysis and interpretation of data: Jalota, Rossi. Drafting the article: Jalota, Rossi. Critically revising the article: Jalota, Rossi. Reviewed submitted version of manuscript: Jalota, Rossi, Byrne. Approved the final version of the manuscript on behalf of all authors: Rossi. Statistical analysis: Jalota, Rossi, Pylypyuk. Administrative/technical/material support: Rossi, Pylypyuk. Study supervision: Rossi.

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