Ictal SPECT statistical parametric mapping in temporal lobe epilepsy surgery

N.J. Kazemi, MBBS
G.A. Worrell, MD, PhD
S.M. Stead, MD, PhD
B.H. Brinkmann, PhD
B.P. Mullan, MD
T.J. O'Brien, MD
E.L. So, MD

Address correspondence and reprint requests to Dr. Elson L. So, Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905
eso@mayo.edu

ABSTRACT

Objective: Although subtraction ictal SPECT coregistered to MRI (SISCOM) is clinically useful in epilepsy surgery evaluation, it does not determine whether the ictal-interictal subtraction difference is statistically different from the expected random variation between 2 SPECT studies. We developed a statistical parametric mapping and MRI voxel-based method of analyzing ictal-interictal SPECT difference data (statistical ictal SPECT coregistered to MRI [STATISCOM]) and compared it with SISCOM.

Methods: Two serial SPECT studies were performed in 11 healthy volunteers without epilepsy (control subjects) to measure random variation between serial studies from individuals. STATISCOM and SISCOM images from 87 consecutive patients who had ictal SPECT studies and subsequent temporal lobectomy were assessed by reviewers blinded to clinical data and outcome.

Results: Interobserver agreement between blinded reviewers was higher for STATISCOM images than for SISCOM images ($\kappa = 0.81$ vs $\kappa = 0.36$). STATISCOM identified a hyperperfusion focus in 84% of patients, SISCOM in 66% ($p < 0.05$). STATISCOM correctly localized the temporal lobe epilepsy (TLE) subtypes (mesial vs lateral neocortical) in 68% of patients compared with 24% by SISCOM ($p = 0.02$); subgroup analysis of patients without lesions (as determined by MRI) showed superiority of STATISCOM (80% vs 47%; $p = 0.04$). Moreover, the probability of seizure-free outcome was higher when STATISCOM correctly localized the TLE subtype than when it was indeterminate (81% vs 53%; $p = 0.03$).

Conclusion: Statistical ictal SPECT coregistered to MRI (STATISCOM) was superior to subtraction ictal SPECT coregistered to MRI for seizure localization before temporal lobe epilepsy (TLE) surgery. STATISCOM localization to the correct TLE subtype was prognostically important for postsurgical seizure freedom. *Neurology*® 2010;74:70-76

GLOSSARY

CI = confidence interval; **ECD** = ethyl cysteinate dimer; **HMPAO** = hexamethyl propylene-amine-oxime; **SISCOM** = subtraction ictal SPECT coregistered to MRI; **SPM** = statistical parametric mapping; **STATISCOM** = statistical ictal SPECT coregistered to MRI; **TLE** = temporal lobe epilepsy.

Early methods of ictal SPECT interpretation relied on a visual comparison of ictal and interictal SPECT images to detect focal hyperperfusion changes (these represented potential sites of ictal hyperperfusion).¹ SPECT imaging subsequently was improved by subtraction ictal SPECT with coregistration on MRI (SISCOM).²⁻⁵ With SISCOM, ictal SPECT data are subtracted from interictal SPECT data,^{6,7} and the “difference image,” which shows the focus of altered perfusion, is coregistered with the patient’s MRI for anatomic correlation. A recent study that compared several functional imaging modalities showed that positive SISCOM has the greatest association with seizure-free outcome after focal epilepsy surgery.⁸

Despite the validation of its clinical usefulness, SISCOM detection of abnormal perfusion is based a priori on a defined threshold of perfusion changes, and it does not account for the expected variability in voxel intensities between 2 serial images from an individual. To account for this random variation between images, our group developed a method that used statistical

From the Departments of Medicine, Surgery, and Neurology (N.J.K., T.J.O.), Royal Melbourne Hospital, University of Melbourne, Victoria, Australia; the Departments of Neurology (G.A.W., S.M.S., E.L.S.) and Radiology (B.P.M.), Mayo Clinic, Rochester, MN; and 3D Medical Imaging LLC (B.H.B.), Byron, MN.

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parametric mapping (SPM) analysis to compare a patient's ictal–interictal subtraction difference data with that of 2 nonictal SPECT studies from each of 26 control subjects.⁹ A similar approach subsequently was developed and evaluated by others using control data from pairs of SPECT scans of each of 7 non-neurologic patients, but their method was not compared with other more established methods such as SISCOM.¹⁰ The aim of this study was to objectively compare our new method of SPM analysis of ictal–interictal difference data (statistical ictal SPECT coregistered to MRI [STATISCOM]) with SISCOM by using the same raw SPECT data from each patient.

METHODS **Standard protocol approval, registration, and patient consent.** The study was approved by the Mayo Clinic Institutional Review Board. Written consent was obtained from the 11 control subjects. Otherwise, patient consent was not required in this retrospective clinical study.

Study subjects. Study patients were identified by medical record review. All subjects met the following eligibility criteria: 1) age 13 years and older; 2) no prior epilepsy surgery; 3) ictal and interictal SPECT studies performed from January 1, 1997, through December 1, 2005; 4) SPECT radioligand injected during the seizure (and before secondary generalization, if it occurred); 5) SPECT data sufficient for SISCOM and STATISCOM analysis; and 6) subsequent anterior temporal lobectomy with amygdalohippocampectomy.¹¹ Control subjects were 11 healthy volunteers (6 women) without a history of epilepsy, and each underwent 2 serial SPECT studies.

Classification of temporal lobe epilepsy subtypes. We categorized patients into 3 subtypes of temporal lobe epilepsy (TLE). First, patients with mesial TLE subtype had MRI evidence of hippocampal atrophy or other mesial temporal lesions. If patients were without lesions on MRI, intracranial EEG showed mesial temporal seizure onset. All patients with mesial TLE subtype did not have epileptogenic lesions elsewhere or conflicting neurophysiologic data. Second, patients with lateral neocortical TLE subtype had MRI evidence of epileptogenic lesions in the lateral temporal neocortex, without epileptogenic lesions elsewhere or conflicting neurophysiologic data. If patients were without lesions on MRI, intracranial EEG showed lateral temporal neocortical seizure onset. Third, patients with indeterminate seizure subtype had no lesions on MRI, and intracranial EEG was not performed; therefore, the TLE subtype could not be ascertained.

Control data. For the control subjects, SPECT difference data were calculated by subtracting one study from the other (both studies were conducted in each volunteer). The difference data from the 11 volunteers served as the control against which each patient's ictal–interictal difference data were compared.

SPECT and SISCOM study procedure. ^{99m}Tc-labeled ethyl cysteinate dimer (ECD) was injected IV as soon as seizure onset was noted during a prolonged video-EEG monitoring ses-

sion. SPECT imaging was performed within 1 to 3 hours after the injection. Interictal SPECT imaging was performed when the patient had been seizure-free for at least 24 hours after the ictal SPECT imaging, as confirmed by continuous video-EEG monitoring.

Our method of SPECT image acquisition and reconstruction has been published previously.² The SISCOM method used 2 reconstructed and processed SPECT images from each individual. Images were coregistered to each other, one image was subtracted from the other to produce a difference SPECT image, and the difference image was coregistered to MRI. This process was performed with commercial image analysis software (ANALYZE 8.0, Biomedical Imaging Resource, Mayo Foundation, Rochester, MN),² except for the SPECT-to-SPECT coregistration, which was performed using the automated image registration algorithm.¹² SPECT signals that were at least 2 standard deviations from the median value in the subtraction SPECT were used to detect hyperperfusion and hypoperfusion foci.

STATISCOM procedure. Voxel-based analysis was performed using SPM2 software.¹³ SPM analysis was performed using MATLAB (version 7.1; The Mathworks, Natick, MA). The difference SPECT image (derived as described above) and a mean, normalized SPECT image from each SPECT pair were imported into SPM2. Spatial normalization was achieved by warping the difference SPECT image into the standardized brain SPECT template provided by SPM2, using the mean, normalized image as the source image. Warping was achieved with a 12-parameter affine transform, using the General Linear Model and the Random Effects Model. The warp modified the difference image into the standard SPECT brain space; each voxel in the brain space was $2 \times 2 \times 2$ mm. The brain mask provided by SPM2 was applied to the warped image to remove extracerebral pixels. The masked, spatially normalized images were smoothed by convolution with an isotropic Gaussian kernel of 16 mm.

Each subject's processed difference image was compared with that of the 11 controls. Statistical analysis was performed using a group comparison through an unpaired, 2-sample *t* test with the SPM contrast set to "1 – 1" to identify ictal hyperperfusion and "–1 1" to identify ictal hypoperfusion with respect to the control group. No standardization to mean global uptake was necessary because normalization to a mean cerebral pixel intensity of 100 was already performed on all SPECT images during processing of SISCOM images (with ANALYZE software). The threshold for significance was set to $p < 0.001$ (uncorrected) for individual voxels. At the cluster level, only voxels with a threshold level of $p < 0.05$ (corrected) were deemed significant. The cluster extent threshold was set to 125, which was equivalent to the spatial resolution of SPECT in tissue.¹⁴ The resultant *t* statistics data were transformed to normally distributed *Z* scores in the form of 3-dimensional SPM images and displayed on a standard Montreal Neurological Institute MRI template provided by SPM2.

The STATISCOM technique was not developed in a commercial format. The analysis techniques are in the public domain.

Image reviews. SISCOM and STATISCOM images were assessed by two primary reviewers (E.L.S. and G.A.W.) who were blinded to all clinical, EEG, and brain MRI information. They identified up to 3 regions of hyperperfusion or hypoperfusion (in order of magnitude) in each SISCOM and STATISCOM study. SISCOM and STATISCOM images of each patient were not

presented together, so the review of one study would not be influenced by the other study. If the primary reviewers disagreed, a third reviewer (B.P.M.), also blinded to all findings, assessed the images. Agreement of the third reviewer with one of the primary reviewers was considered the final localization of hyperperfusion or hypoperfusion changes. If the third reviewer failed to agree with either primary reviewer, the study was considered nonlocalizing. After all studies were reviewed, we compared STATISCOM and SISCOM with the following variables: 1) interobserver agreement rate between the 2 primary reviewers; 2) rate of localization of perfusion change; 3) rate of correct localization to TLE subtype; 4) concordance rate between regions of localized perfusion change; and 5) epilepsy surgery outcome.

RESULTS Patient population and SPECT injection timing. A total of 453 consecutive patients underwent resective epilepsy surgery during the study period. Ictal and interictal SPECT studies were conducted in 106 temporal lobectomy patients who were 13 years or older and had no history of epilepsy surgery. SPECT data were incomplete or unavailable for analysis in 19 patients. Eighty-seven remaining patients (39 female [45%]) met all eligibility criteria for study inclusion. Median age at the time of the SPECT study was 34 years (range, 13–62 years). Median duration of the seizure in which ^{99m}Tc -ECD was injected was 77 seconds (range, 13–529 seconds). Median time from seizure onset to injection was 25 seconds (range, 7–166 seconds), and median time from injection to end of seizure was 49 seconds (range, 0–501 seconds). The seizure types occurring during ECD injection were complex partial seizures without secondary generalization ($n = 64$ [74%]), complex partial seizures with secondary, generalized tonic-clonic seizures ($n = 20$ [23%]), and simple partial seizures ($n = 3$ [3%]). Only 52 patients (60%) had a localizing MRI abnormality (i.e., 40 patients with mesial temporal sclerosis, 3 with dysembryonic neuroepithelioma, 2 with traumatic encephalomalacia, 2 with gangliocytoma, 1 each with ganglioglioma, oligodendroglioma, tuberous sclerosis, cavernous hemangioma, and gliosis with corpora

amylacea). Ictal scalp EEG showed localization to the frontotemporal region for 70 patients (80%).

Interobserver agreement rates. Interobserver agreement (κ statistic) between the 2 primary blinded reviewers was considerably higher for STATISCOM images (87%; $\kappa = 0.81$; 95% confidence interval [CI], 0.70–0.92) than it was for SISCOM images (60%; $\kappa = 0.36$; 95% CI, 0.20–0.54). The interobserver agreement for STATISCOM was 45% higher than that for SISCOM (95% CI, 25%–65%).

Lateralization and localization. STATISCOM localized a focus of abnormal perfusion in more patients than SISCOM (73/87 [84%] vs 57/87 [66%]; $p < 0.05$, χ^2 test; difference of 18%, 95% CI of the difference, 5.5%–31.3%). Sixteen patients with no SISCOM abnormality had an abnormal STATISCOM focus, whereas only one patient with no STATISCOM abnormality had a SISCOM focus. The rate of lateralizing the focus to the correct temporal lobe was higher with STATISCOM than with SISCOM (68/87 [78%] vs 52/87 [60%]; $p \leq 0.05$; difference of 18%, 95% CI of the difference, 4.6%–32.1%). Moreover, STATISCOM was markedly superior to SISCOM in localizing TLE subtypes (68% vs 24%). This effect was attributable to STATISCOM identifying significantly more mesial TLE seizures than SISCOM (65% vs 9%). The table shows the accuracy of STATISCOM and SISCOM localization of seizure onset for several TLE subtypes.

TLE subtype localization in patients with nonlesional MRI findings. MRI studies did not show a lesion in 35 patients (40%). Of these, 29 underwent intracranial EEG and therefore had known TLE subtype, as determined by study criteria. STATISCOM localized an abnormal focus in more nonlesional patients than SISCOM (25/29 [86%] vs 17/29 [59%]; $p = 0.02$). Moreover, when an abnormal focus was localized, STATISCOM correctly localized the focus to the TLE subtype (mesial TLE vs lateral neocortical TLE) in more patients than SISCOM (20/25 [80%] vs 8/17 [47%]; $p = 0.04$) (figures 1 and 2).

Surgical outcome. The median duration of postsurgical follow-up was 30 months (range, 0–93 months). Seventy-two patients (83%) had at least 12 months of follow-up; of these, 53 (74%) had a seizure-free outcome (Engel Class I), 9 (13%) had a favorable outcome (Engel Class II), and 10 (14%) had a nonfavorable outcome (Engel Class III or IV).

The probability of a seizure-free outcome was higher when STATISCOM correctly localized the TLE subtype compared with when it was incorrect or had an indeterminate result. Of the 53 patients with correctly localizing STATISCOM, 43 (81%) had a

Table Comparison of STATISCOM vs SISCOM for localization of temporal lobe seizure onset

TLE subtype	STATISCOM		SISCOM		p Value ^a	95% CI (proportion localized), %
	No.	%	No.	%		
Mesial	37/57	65	5/57	9	0.001	—
Neocortical	16/24	67	12/24	50	>0.05	—
Indeterminate	6/6	100	4/6	67	>0.05	—
Total	59/87	68	21/87	24	0.02	28.9%–58.5%

Abbreviations: CI = confidence interval; SISCOM = subtraction ictal SPECT coregistered to MRI; STATISCOM = statistical ictal SPECT coregistered to MRI; TLE = temporal lobe epilepsy.

^aMcNemar test of dependent proportions for TLE subtype.

After intracranial electrode implantation, the patient underwent right temporal lobectomy and subsequently became seizure-free. (Row A) Subtraction ictal SPECT coregistered to MRI shows multiple foci of increased perfusion in the coronal (left), sagittal (middle), and axial (right) planes. (Row B) Statistical ictal SPECT coregistered to MRI shows a dominant hyperperfusion focus at the right posterior neocortical temporal region in all planes.

seizure-free outcome, whereas 10 of the 19 patients (53%) with incorrect or indeterminate STATISCOM were seizure-free ($p = 0.03$; 95% CI, 5.4%–51.6%).

DISCUSSION In the current study, we were able to show the superiority of STATISCOM, an SPM-based method of SPECT analysis, over SISCOM. We developed STATISCOM to specifically address certain limitations of the SISCOM technique. We theorized that multiple foci of perfusion changes in an indeterminate SISCOM study may partly be due to random differences in SPECT images that are expected to occur between 2 serial SPECT studies. We addressed this limitation of SISCOM in a previous study using SPM to statistically compare the patient's ictal–interictal difference data against the difference data derived from pairs of nonictal SPECT studies from 26 control subjects.⁹ The 26 pairs of SPECT studies consisted of 16 pairs of interictal studies from patients with epilepsy and 10 pairs from healthy volunteers. In contrast, the control data of our current study were derived only from healthy volunteers because a previous report showed that such data would improve the sensitivity of SPM SPECT analysis.¹⁵

A previous study compared SPM SPECT analysis with subtraction SPECT analysis in 21 patients, but the authors reported that SPM SPECT analysis was

not superior.¹⁵ However, that study performed SPM analysis on ictal data only. In contrast, our method of STATISCOM used SPM to compare the difference data from a patient's ictal and interictal SPECT studies with that of 2 serial SPECT studies performed in healthy volunteers. The SPM analysis in the previous study¹⁵ may have been confounded by the phenomenon of “pseudonormalization,” which is defined as clinically significant ictal hyperperfusion at a seizure focus that has the appearance of normal perfusion. In these cases, the seizure focus is often hypoperfused relative to other brain regions during the interictal (baseline) state.¹⁶ When a focal seizure occurs, the perfusion may be increased compared with baseline, but the increment may only approach or barely exceed a global threshold value for hyperperfusion. Pseudonormalization reduces the sensitivity with which an imaging study can detect the focus of hyperperfusion that corresponds to focal seizure activity.

The concept of SPM analysis of ictal–interictal SPECT difference data was also investigated previously by others¹⁴; they reported no correlation with surgical outcome. Our different study outcome may be due to several reasons. Their method of ictal–interictal SPECT analysis by SPM spatially normalized (i.e., warped) the ictal and interictal images to the SPM SPECT template before subtracting to ob-

Figure 2 Series of coronal images from a 47-year-old patient with medically intractable epilepsy and nonlesional MRI findings

(A) Subtraction ictal SPECT coregistered to MRI shows multiple foci of increased perfusion at the right and left temporal and extratemporal regions. (B) Statistical ictal SPECT coregistered to MRI shows a dominant hyperperfusion focus restricted to the right mesial temporal region. The patient has been seizure-free since undergoing right temporal lobectomy. Pathologic examination of the resected tissues showed mesial temporal sclerosis.

tain difference images. In contrast, interictal SPECT in our STATISCOM method undergoes rigid transformation only to the ictal image before subtraction. We avoided warping SPECT data to the SPM SPECT template before subtraction to reduce image blurring and to avoid compounding effects of 2 registration errors. Ictal SPECT studies have better localization value than postictal SPECT studies, but most patients in the other study¹⁴ had postictal SPECT injection; in contrast, all patients in our study had ictal SPECT injection. The SPECT radioligand may have affected outcome; the other study used ^{99m}Tc-labeled hexamethyl propylene-amine-oxime (HMPAO), and we used ^{99m}Tc-ECD. ^{99m}Tc-HMPAO must be constituted immediately before injection, and this delay results in more postictal injections than would occur with use of ^{99m}Tc-ECD.¹⁷

The conventional method of visually comparing ictal with interictal SPECT images has been reported to yield an abnormal focus in as many as 90% of patients with TLE,¹⁸ whereas the rate of STATISCOM detection (84%) and SISCOM detection (66%) of an abnormal focus in our study are lower. However, many conventional visual comparison studies were not blinded to the results of all other diagnostic information, and the reference for localization was scalp EEG findings. In contrast, blinded reviews have demonstrated that the yield of the conventional visual comparison method is much lower than SISCOM (39% vs 88%).⁴

The yield of SISCOM in our first validation study, conducted 12 years ago, was 88%,⁴ which was higher than the yield of 66% in the current study. The previous study involved patients who were evaluated at Mayo Clinic from 1993 through 1996. Our current study involved patients evaluated from 1997 through 2005. As with other major epilepsy centers, we experienced a remarkable change in the complexity of the patient population undergoing epilepsy surgery, beginning about the mid 1990s. At this time, many major epilepsy centers reported an increase in the number of patients treated with intracranial electrode implantation. These changes have been attributed to the increased availability of epilepsy surgery nationwide in the 1990s, which has resulted in major medical centers evaluating epilepsies that were more complex than those previously encountered.

Our study showed that STATISCOM results have prognostic implications for epilepsy surgery outcome. Compared with incorrect or indeterminate STATISCOM localization, correct localization of the STATISCOM focus to the TLE subtype was associated with a higher probability of seizure-free outcome. Post hoc analysis also showed that of the 72 patients who had

postsurgical follow-up of at least 1 year, 46 patients (64%) who had positive STATISCOM became seizure-free, whereas 33 patients (46%) with positive SISCOM became seizure-free ($p < 0.05$).

The absence of a relevant MRI lesion in patients with medically intractable epilepsy presents major challenges when localizing the seizure focus for epilepsy surgery.¹⁹ Such a condition often requires functional imaging tests (ictal SPECT or fluorodeoxyglucose PET) to help guide intracranial electrode implantation and resective surgery. We showed that STATISCOM localized an abnormal focus in more patients with nonlesional MRI findings than SISCOM. Furthermore, the rate of correct localization to TLE subtype with STATISCOM was almost twice that of SISCOM (80% vs 47%).

The reviewers in our study were not specifically blinded to the fact that all study subjects had TLE. Therefore, our results may have resulted in a higher yield of STATISCOM and SISCOM findings than if the reviewers had been specifically blinded to the type of epilepsy being evaluated. The results of our study are applicable to patients with TLE, and the value of STATISCOM in extratemporal epilepsy needs further evaluation.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Noojan J. Kazemi.

DISCLOSURE

Dr. Kazemi has received funding from the Australian National Health and Medical Research Council (NHMRC) (postgraduate medical scholarship). Dr. Worrell receives research support from the NIH [R01-NS63039-01 (PI)]. Dr. Stead and Dr. Brinkmann report no disclosures. Dr. Mullan estimates that 5% of his clinical practice is spent conducting nuclear medicine brain scanning for dementia and epilepsy. Dr. O'Brien serves on the editorial boards of *Epilepsia*, the *Journal of Clinical Neuroscience*, and *Epilepsy and Behavior*; has received speaker honoraria from Janssen and Sanofi-Aventis 2009; and receives research support from UCB, Abbott Laboratories, Janssen-Cilag, the Australian NHMRC, The Epilepsy Research Foundation, NARSAD, and the Royal Melbourne Hospital Neuroscience Foundation. Dr. So serves on the editorial boards of the *Journal of Clinical Neurophysiology* and *Epilepsy Research*.

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