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ORIGINAL ARTICLE

SPECT postprocessing for epileptogenic focus localization: SISCOM versus ISAS

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Abstract

Objective: Ictal SPECT can be used as an estimate for the epileptogenic zone in people with focal epilepsy. Subtraction of ictal and interictal SPECT scans reveals the area with significant ictal hyperperfusion. Some methods use a control database to also correct for physiological variance. This control database is ideally scanner specific, but it is not trivial to obtain such a database because of ethical issues. In this study, we used a publicly available control database to compare ictal-interictal SPECT analyzed by SPM (ISAS) with the most commonly used subtraction ictal SPECT co-registered to MRI (SISCOM).

Methods: Ictal and interictal SPECTs of 26 patients (age range: 7–50 years, 15 adults, 11 children) with focal drug resistant epilepsy in workup for epilepsy surgery were retrospectively analyzed using both SISCOM and ISAS. The control database for ISAS was obtained from the ISAS website. Two groups of blinded reviewers determined the location of ictal hyperperfusion in all datasets. Results were compared between subtraction algorithms and with the resected area (if available) or the suspected epileptogenic zone. The number of significant clusters and the locations of maximum hyperperfusion were compared between algorithms.

Results: The location of ISAS and SISCOM hyperperfusion was the same in 14 patients (54%). ISAS localized in 6 patients where SISCOM did not. Compared to the resected area or suspected epileptogenic zone, SISCOM correctly localized in 55%, while ISAS did in 65% (not significantly different). ISAS shows significantly less clusters than SISCOM. The maximum hyperperfusion was in the reviewer's location in 65% for ISAS and 38% for SISCOM.

Significance: ISAS using a publicly available control database gives comparable or better results than SISCOM. ISAS results are easier to interpret than SISCOM results. We show that ISAS is a reliable alternative for SISCOM, which could easily be implemented in epilepsy surgery clinics.

Plain Language Summary: We explored the effectiveness of ISAS as an alternative to the widely used SISCOM for assessing SPECT scans in epilepsy

surgery candidates. Utilizing a publicly available control database, we compared the two methods in 26 patients. The results indicate that ISAS might offer increased accuracy and interpretability, making it a promising option, especially for centers without access to a specific control dataset.

KEYWORDS
epilepsy surgery, ISAS, normal database, SISCOM, SPECT

1 | INTRODUCTION

Ictal single photon emission tomography (SPECT) imaging is a nuclear medicine imaging technique that can be used in preoperative localization of the epileptogenic zone during the workup for epilepsy surgery.[1] It is particularly valuable in patients who do not show abnormalities on MRI, when localizing the ictal onset in the EEG is challenging or when there is a discrepancy between imaging, EEG, or clinical findings.[2] It involves using radioactive technetium (Tc99-m) labeled either to hexamethylpropyleneamine oxime (HMPAO) or ethyl cysteinate dimer (ECD). The tracer is injected immediately after seizure onset and accumulates in brain regions with the highest blood perfusion. At seizure onset, these regions are presumed to be the epileptogenic zone. For diagnostic purposes, an interictal scan is also performed, serving as a baseline for comparison with the ictal scan.

To analyze these images, subtraction ictal SPECT co-registered to MRI (SISCOM) is the most commonly used method. In SISCOM, the interictal scan is subtracted from the ictal scan, the mean value of the resulting image is computed and all voxels above a certain standard deviation threshold are considered to show significant ictal hyperperfusion.[3,4] This method is user-friendly and is available as open-source software.[5] However, SISCOM does not correct for physiological variance in cerebral blood flow. Normal variation in blood flow can result in significant differences between two SPECT scans of the same person, even without a seizure during the tracer injection for one of those scans. Consequently, SISCOM often shows multiple areas of significant ictal hyperperfusion, making interpretation challenging. By using a normal database in the statistical model, the results are also corrected for this normal variation in blood flow. Ictal-Interictal SPECT Analyzed by SPM (ISAS)[6] compares the patient's two scans to two scans of each healthy control in the dataset. Statistical Ictal SPECT co-registered to MRI (STATISCOM)[7] uses a similar approach, by comparing the subtracted image of the patient to subtracted images of healthy control subjects. Therefore, ISAS or STATISCOM only display hyperperfusion due to the seizure, while SISCOM also reflects normal variation. This also implies that the perfusion difference between the ictal and interictal scans needs to be larger to show up as significant in ISAS or STATISCOM compared to SISCOM. ISAS and STATISCOM outperformed SISCOM in localizing the epileptogenic zone when utilizing a scanner and protocol-specific control database.[8–10] However, obtaining such a database of SPECT scans from healthy control subjects is challenging for most institutions. Injection with a radioactive tracer is an invasive procedure requiring ethical approval and informed consent, particularly when applied to healthy volunteers due to the radiation dose.

Key points

- Ictal-interictal SPECT analyzed by SPM (ISAS) with a public control database showed more localized results than subtraction ictal SPECT co-registered to MRI (SISCOM).
- The conclusion of ISAS and SISCOM was the same in 54% of datasets.
- SISCOM localized correctly in 55% and ISAS in 65%. ISAS results were easier to interpret than SISCOM results.

In this study, we utilized a publicly available database of healthy control subjects provided on the ISAS website (http://spect.yale.edu), and compared ISAS with SISOM, as well as with the clinically suspected epileptogenic zone. Without the need for a scanner and protocol-specific control database, ISAS would be easier to implement in other centers.

Subtraction results are clinically interpreted by a nuclear medicine physician who examines the images alongside information about injection delay and seizure semiology. This process can be subjective. To simplify interpretation, we conducted quantitative analyses on the SISCOM and ISAS results.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients were selected from two time spans: (1) all patients who underwent ictal and interictal SPECT in our center between January 1, 2017 and February 1, 2018 and (2) all patients who underwent ictal and interictal SPECT between January 1, 2013 and December 31, 2016, and subsequently underwent epilepsy surgery. Due to the retrospective nature of the study, primarily aimed to directly improving patient care, the need for written informed consent was waived by the Medical Ethics Committee for the UMC Utrecht, provided that data were handled in a coded manner. Data are not openly available for this reason.

2.2 | SPECT imaging

For the ictal SPECT, patients were monitored with video-EEG, and 21 MBq/kg of ^{99m}Tc-HMPAO was injected as soon as possible after the clinical or encephalographic onset of the seizure. The SPECT scan was performed within 3 hours after injection. The interictal SPECT was performed either when no seizure occurred during the presumed ictal session (approximately 11 MBq/kg) or at least 1 week after the ictal SPECT. All scans were conducted on a Siemens Symbia TruePoint SPECT–CT scanner. Scans were acquired over 360° to collect 60 views in a 256 × 256 matrix with a zoomfactor of 1.23. Images were reconstructed using SyngoMI VB10E. Chang attenuation correction was applied. The resulting images had a resolution of 1.9 × 1.9 × 1.9 mm. Ictal and interictal SPECTs were registered to a 3D T1 MRI for anatomical reference.

2.3 | Subtraction methods

Ictal and interictal SPECTs were postprocessed by SISCOM and ISAS. SISCOM was applied as described in,[3] in summary: the ictal and interictal SPECT images were registered to each other and scaled to similar intensity values by using grand mean normalization. The interictal scan was subtracted from the ictal scan, the subtraction was masked to isolate brain voxels, and the distribution of intensity values was assessed. Values exceeding two standard deviations were considered significant, as recommended by.[11] ISAS was applied according to the procedure outlined in,[6] in summary: ictal and interictal SPECT images were registered to the MNI standard brain. Subsequently, both scans were masked to only contain voxels inside the brain, smoothed using a Gaussian filter with 16 mm at full-width-half-maximum, and scaled to similar intensity values by using grand mean normalization. A database comprising 28 scan from 14 healthy subjects (8 female, 12 right-handed, average age 33 [range: 24–48]) was obtained from the ISAS website (http://spect.yale.edu). These healthy subjects received 20 mCi of ^{99m}Tc-HMPAO and underwent scans conducted with a Picker PRISM 3000 XP, with an image resolution of 2.67 × 2.67 × 2.12 mm. These control database scans were also registered to the MNI standard brain for comparative purposes. The preprocessed ictal and interictal patient scans were compared to the normal database using a generalized linear model (GLM) with a flexible factorial design. A *t*-test with $p < 0.001$ identified regions displaying significant ictal hyperperfusion. We assessed the quality of the ISAS algorithm with the publicly available normal database through leave-one-out analysis (Appendix A), confirming its reliability.

Both methods were integrated in our in-house software, which enabled revision of the results both in all slices as well as projected on the 3D rendered cortex. Hyperperfusion maps were de-normalized and visualized on the patient's own MRI. No extent threshold was applied. The SPM12 scripts used for ISAS analysis are available on Github (https://github.com/NvanKlink/ISAS-SPECT).

2.4 | Image review

The two methods performed on 26 patients resulted in 52 datasets to be reviewed. All datasets were reviewed by two groups of reviewers who are accustomed to interpret subtraction images (team 1 MH + NT: two nuclear medicine physicians with >5 years' experience in epilepsy imaging, team 2 CF + TG: a neurophysiologist and a physician assistant, experts in epilepsy imaging and surgery). The datasets were normalized in such a way that a threshold of 1 corresponded to a standard deviation value of 2 for SISCOM and a *t*-value of 3.85 for ISAS. This way the reviewers were blinded to the type of method used. The reviewers assigned, if possible, the location(s) of hyperperfusion on the lobar level (left and right frontal, temporal, central, parietal, occipital, opercular/insula), as they would do for clinical analysis. One or two locations could be assigned. If more than two areas were prominent, or no area could be found, the dataset was considered nonlocalizing. The final localization of a dataset was determined by concordance between two reviewers. A Cohen's kappa score was calculated for 13 possible choices (6 lobes in both hemispheres and nonlocalizing). Only when a location was rated by both reviewers, the result was used. If the two disagreed, the dataset was considered nonlocalizing. Significant hyperperfusion could therefore

be localized in two lobes which could be either independent foci or one hyperperfused area spanning two lobes.

2.5 | Comparison to clinical interpretation and surgery

The SISCOM and ISAS results were compared to the suspected epileptogenic zone. In patients who became seizure free after surgery, the suspected epileptogenic zone was the resected area. For other patients the suspected epileptogenic zone was derived based on all clinical information gathered during presurgical evaluation and following the hypothesis of the multi-disciplinary team. This information included (in order of priority): location of unsuccessful surgery, invasive EEG findings, relevant MRI lesion, noninvasively estimated epileptogenic zone, based on seizure semiology, noninvasive video-EEG seizure onset area, abnormalities on positron emission tomography (PET), magnetoencephalography (MEG) or EEG-fMRI, and interictal video-EEG abnormalities. The location of the suspected epileptogenic zone for each patient was derived from notes of the multidisciplinary team meetings. When the patient was denied epilepsy surgery or invasive EEG because no hypothesis could be formed, no suspected epileptogenic zone was defined.

2.6 | Quantitative analysis

We determined the location of maximum hyperperfusion and the corresponding statistical value, for both SISCOM and ISAS. These locations were compared between algorithms and with the reviewer's location. We also compared the number of significant voxel clusters for SISCOM and ISAS, by counting of connected significant voxels in each dataset using the *bwconncomp* function in MATLAB 2022b.

2.7 | Statistics

The differences in the number of localizing datasets between adults and children and fast and slow injections were analyzed with a Fisher's exact test. The difference in the ability of SISCOM and ISAS to identify the suspected epileptogenic zone was assessed with a McNemar's test. The difference in maximum hyperperfusion voxel values between correct and incorrect locations was confirmed to be normally distributed (Shapiro Wilk test) and therefore analyzed with an independent samples *t*-test. Additionally, the number of significant voxel clusters, also normally distributed, was compared using a *t*-test. All statistical analyses were performed using R version 4.3.1, and a p-value < 0.05 was considered significant.

3 | RESULTS

3.1 | Patients

Inclusion of patients from the two recruitment periods is visualized in Figure 1. In total, we included 26 patients with ictal and interictal SPECT who were on average 24 years old (range: 7–50). Fifteen patients were adults and 11 were children (Table 1). Eleven patients were MRI negative, and 9 showed multiple possible foci. Eighteen patients underwent epilepsy surgery, and in 12 patients this was

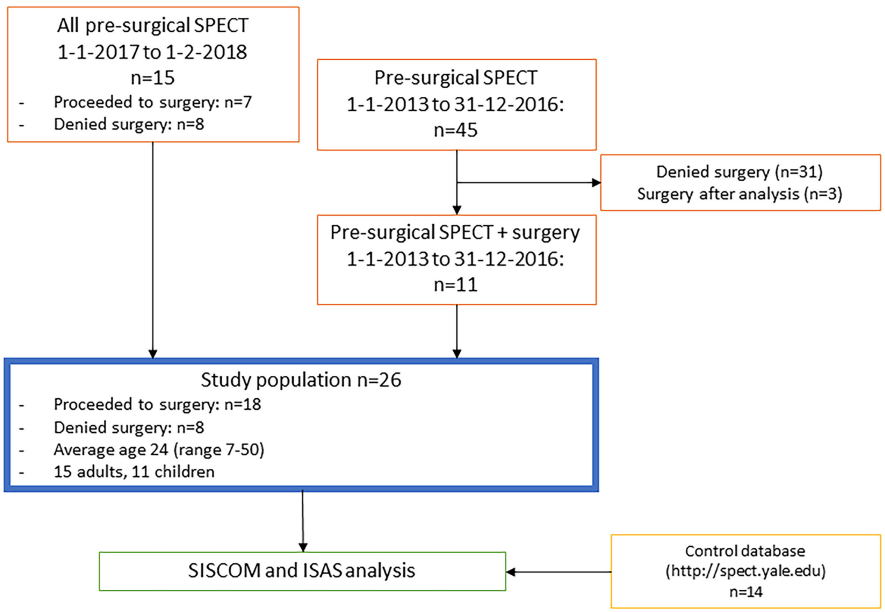

FIGURE 1 Flow chart of patient inclusion. The initial patient cohort with all SPECT patients was extended with SPECT patients who underwent subsequent resection, to increase the number of patients with surgical outcomes.

TABLE 1 Patient characteristics.

#	Age (years)/ gender	MRI	Injection time/seizure duration (s)	ISAS	SISCOM	Suspected epileptogenic zone	Surgery	Engel outcome (months follow-up)	Pathology
1	44/m	Tissue loss bilateral frontal	11/21	L temporal	No focus	No hypothesis	No		
2	33/m	Gliosis R parieto-occipital	56/122	R occipital	R occipital	R temporal	No		
3	13/m	NA	14/106	No focus	No focus	No hypothesis	No		
4	23/m	NA	26/177	No focus	No focus	No hypothesis	No		
5	13/m	MTS R	12/90	R temporal + parietal	R temporal	R temporal	Yes	2A (40)	MTS Wyler 3
6	28/f	Multiple tubers	15/25	No focus	No focus	L frontal	Yes	2C (25)	FCD ILAE 2B
7	30/f	NA	16/76	L temporal	No focus	L temporal	Yes + sEEG	3A (13)	NA
8	14/f	NA	14/58	L temporal	L temporal	L temporal	Yes + cECoG	4B (12)	NA
9	24/f	Multiple tubers	10/63	L temporal	L temporal + frontal	L frontotemporal	No		
10	49/m	NA	15/28	No focus	R temporal	R temporal	Yes	1A (37)	NA
11	7/f	Tissue loss L parieto-occipital + frontal	14/60	L temporal	L temporal	L temporal	Yes	1A (26)	No specimen
12	22/f	NA	3 s postictal/15	L temporal	No focus	No hypothesis	No		
13	34/m	Tissue loss L parieto-occipital + frontal	10/40	L opercular + parietal	No focus	L parietal	Yes + cECoG	3A (25)	Gliosis
14	50/m	NA	10/126	R temporal + parietal	R parietal + temporal	No hypothesis	No		
15	17/m	NA	8/135	R frontal	No focus	No hypothesis	No		
16	14/m	Multiple tubers	14/94	No focus	No focus	R temporal	Yes + cECoG	1B (85)	FCD ILAE 2B
17	13/m	MTS R	40/83	R temporal	R temporal	R temporal + parietal	Yes	1A (21)	MTS Wyler 4 + gliosis
18	33/f	NA	3/15	L temporaal + frontal	L frontal	L frontal	Yes + cECoG	1C (32)	NA
19	22/m	Tumor L temporal	8/71	No focus	No focus	L parietal	Yes + cECoG	1A (1)	Ganglioglioma WHO1
20	19/m	NA	5/80	No focus	No focus	L frontal	Yes + cECoG	2B (19)	NA
21	17/m	Tissue loss bilateral parietal	18/211	L central	No focus	L parietal	Yes + cECoG	1A (63)	Gliosis
22	17/m	MTS L	36/539	L temporal + parietal	L temporal	L temporal	Yes + sEEG	1A (16)	MTS Wyler 3

TABLE 1 (Continued)

#	Age (years)/ gender	MRI	Injection time/seizure duration (s)	ISAS	SISCOM	Suspected epileptogenic zone	Surgery	Engel outcome (months follow-up)	Pathology
23	21/m	FCD L fronto-opercular	15/118	No focus	R opercular/ insular	L opercular	Yes + cECoG	2B (51)	FCD ILAE 2B
24	17/m	FCD R + L frontal	8/20	R opercular/ insular	R opercular/ insular	R opercular	Yes + cECoG	1A (13)	FCD ILAE 2B
25	34/f	NA	40/240	R parietal	R parietal	R parietal	Yes + cECoG	3B (38)	FCD ILAE 2A
26	9/m	Periventricular heterotopia L, MTS L, tissue loss R periventricular	12/60	L temporal	L temporal	L temporal	Yes	1A (17)	MTS Wyler 3

Abbreviations: cECoG, chronic electrocorticography; f, female; FCD, focal cortical dysplasia; ISAS, ictal-interictal SPECT analyzed by SPM; L, left; m, male; MTS, mesiotemporal sclerosis; NA, no abnormalities; R, right; sEEG, stereo EEG; SISCOM, ictal SPECT co-registered to MRI.

preceded by invasive EEG. Average tracer injection time after seizure onset was 17 s (range: 3–56 s) after onset of the clinical or electrographic seizure (whichever came first). One injection was in the postictal stage (Table 1).

3.2 | Interrater agreement

The reviewers agreed on the conclusion of the dataset in 41 of 52 datasets (79%, Cohen's kappa 0.78). This included agreement on 32 foci and 9 datasets without focus. In the other 11 datasets, the reviewers pointed to different foci, and these datasets were reported as 'no focus' for this study. The kappa was slightly higher for ISAS (0.81) than for SISCOM (0.74) (Table 2).

3.3 | ISAS – SISCOM Comparison

The result of SISCOM and ISAS was the same in 14 patients (54%, Figure 2). In 8 patients (31%) SISCOM and ISAS showed the same location, and in 6 (23%) both were nonlocalizing. ISAS was localizing in 6 patients (23%) where SISCOM was not. Conversely, SISCOM was localizing in 2 patients (8%) where ISAS was not. In one of them, ISAS would show the same location if the threshold would be lowered. In the other patient, SISCOM showed the wrong location. An example of a localizing patient with both SISCOM and ISAS, only in SISCOM and only in ISAS, is shown in Figure 3. There were no patients in whom SISCOM and ISAS showed completely different locations.

SISCOM was localizing in 14 of 26 datasets (54%), and ISAS was localizing in 18 of 26 datasets (69%). The control database only consisted of adult scans, while our dataset contained 11 children (average age 14, range 7–17). SISCOM was localizing in 7 children (63%) and ISAS in 9 (81%). This was not significantly different from the number of localizing datasets in adults (Fisher's Exact test $p = 0.45$ for SISCOM and $p = 0.39$ for ISAS). There was no difference in localizing results between fast (≤30 s) and slow injections (Fisher's Exact test $p = 0.33$ for SISCOM and $p = 0.14$ for ISAS). Also considering injections in the first quarter of the seizure as 'fast' did not show differences in localizing results between fast and slow seizures (Fisher's exact test $p = 0.65$ for SISCOM and $p = 1$ for ISAS).

3.4 | SISCOM – ISAS – Clinical hypothesis comparison

The results of SISCOM and ISAS compared to the suspected epileptogenic zone are shown in Table 3. Six

	SISCOM		ISAS	
	Agreed	Disagreed	Agreed	Disagreed
Localization	14	1	18	1
Nonlocalizing	6	5	3	4
Total	20	6	21	5
Cohen's kappa	0.74		0.81	

Abbreviations: ISAS, ictal-interictal SPECT analyzed by SPM; SISCOM, ictal SPECT co-registered to MRI.

TABLE 2 Interrater agreement for localization of datasets by two teams of reviewers blinded for the method. Cohen's kappa score was calculated for 13 possible choices (6 lobes in both hemispheres and nonlocalizing).

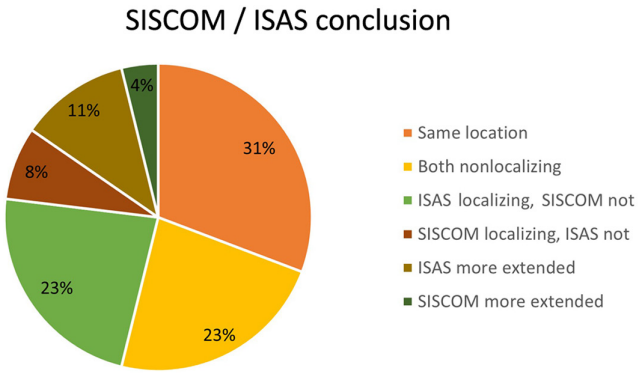

FIGURE 2 Correspondence between ISAS and SISCOM results, independent of the suspected epileptogenic zone. ISAS, ictal-interictal SPECT analyzed by SPM; SISCOM, ictal SPECT co-registered to MRI.

patients did not have a suspected epileptogenic zone. When only considering the 20 patients with a suspected epileptogenic zone, SISCOM correctly localized it in 11 (55%) and ISAS in 13 (65%) patients. This difference was not significant (McNemar's test $p=0.62$). Both SISCOM and ISAS correctly localized the resected area in 7 of the 8 seizure-free patients (Engel 1A). For patients who not became seizure free ($n=10$), ISAS localized to the resected area in 6 and SISCOM in 4 patients.

ISAS correctly localized in 3 patients in whom SISCOM was nonlocalizing. SISCOM correctly localized in 1 patient in whom ISAS was nonlocalizing, but would show the same localization if the threshold was lowered. Localization of SISCOM and ISAS was the same but incorrect in patient 2.

3.5 | Quantitative analysis

SISCOM showed significantly more clusters with significant voxels than ISAS ($t[25]=-7.66$ $p<0.001$, SISCOM average 57 clusters, ISAS 5 clusters).

The maximum hyperperfusion was in the cerebral neocortex in 18 patients in SISCOM, the other 8 showed the maximum in the cerebellum or thalamus. In 10 datasets (38%), the maximum hyperperfusion location was the same as the reviewers location. The datasets without correct localization had a significantly lower maximum standard deviation value ($t[24]=-2.70$, $p=0.01$). When a SISCOM hyperperfusion location had a standard deviation higher than 5.5, it was always in the same location as pointed out by the reviewers (Figure 4A).

Twenty-five of the 26 ISAS datasets showed a cerebral neocortical location of maximum hyperperfusion. One dataset did not show any significant voxel. In 17 datasets (65%), the maximum hyperperfusion location was the same as the reviewers location. The datasets without correct localization had a significantly lower maximum t-value ($t[23]=-3.19$, $p=0.004$). When an ISAS hyperperfusion location had a t-value higher than 10, it was always in the same location as pointed out by the reviewers(Figure 4B).

4 | DISCUSSION

In this study, we compared the clinically standard SISCOM algorithm with ISAS SPECT postprocessing using a publicly available control database. We showed additional value of the latter, revealing more localizing results than SISCOM, although not statistically significant due to the small population. These additional localizing results were all in agreement with the clinically suspected epileptogenic zone. Quantitatively, ISAS showed less voxel clusters than SISCOM and the most significant location in ISAS was correct in 65%, as opposed to 38% for SISCOM. Therefore, we conclude that ISAS might be more accurate than SISCOM, and ISAS results are easier to interpret than SISCOM results.

To our knowledge, we are the first to compare these methods aside from the original developers. Moreover, we are the first to use a public control database instead of the recommended in-house developed control dataset and still show additional value. This simplifies implementation of ISAS analysis in epilepsy surgery clinics.

The comparison with a control database in ISAS corrects for physiological variance in cerebral blood flow. We show that this correction is beneficial when looking for seizure related hyperperfusion. This is in line with

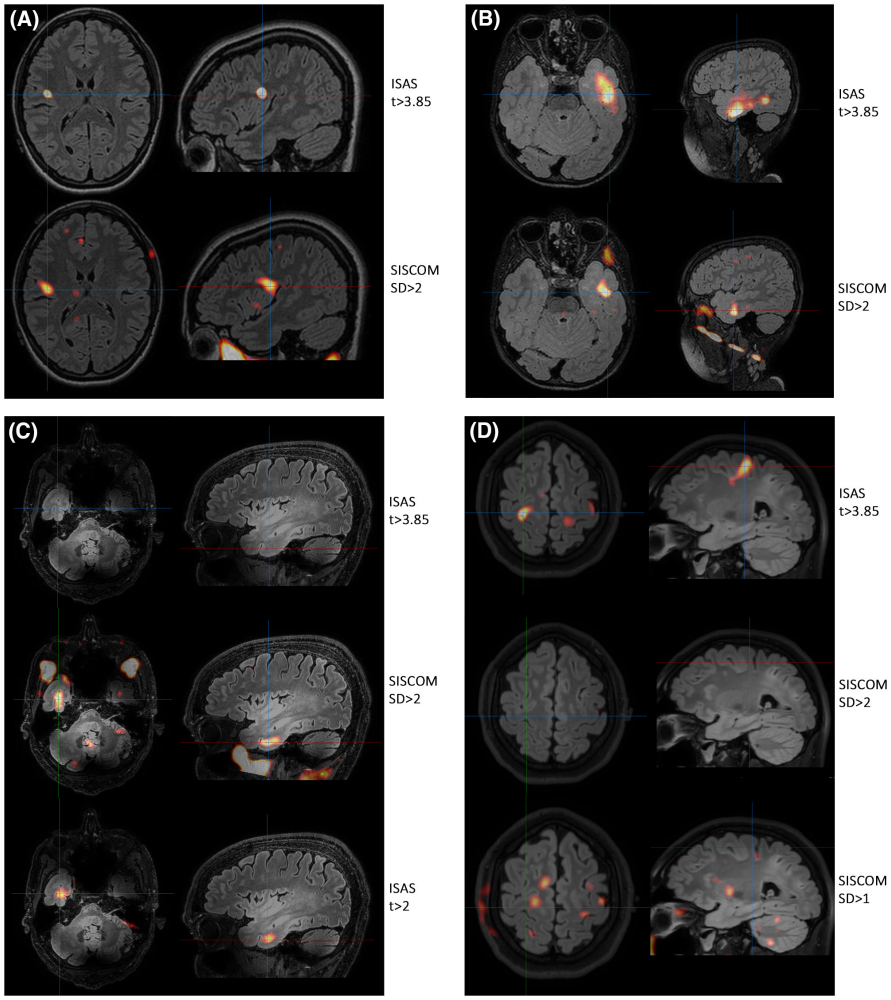

FIGURE 3 Patient examples of ISAS and SISCOM. (A and B) The same localization in both ISAS and SISCOM (patients 24 and 26), (C) SISCOM is localizing, but ISAS not. Interestingly, when lowering the ISAS threshold, the same location is revealed (patient 10), and (D) ISAS is localizing but SISCOM not. When lowering the SISCOM threshold, the location is still not clear (patient 21). ISAS, ictal-interictal SPECT analyzed by SPM; SISCOM, ictal SPECT co-registered to MRI.

TABLE 3 SISCOM and ISAS results compared to clinical suspected epileptogenic zone.

	SISCOM				ISAS			
	Correct	**Incorrect**	**No hypothesis**	**Total**	**Correct**	**Incorrect**	**No hypothesis**	**Total**
Localization	11	2	1	14 (54%)	13	1	4	18 (69%)
Nonlocalizing[a]		7	5	12 (46%)		6	2	8 (31%)

Abbreviations: ISAS, ictal-interictal SPECT analyzed by SPM; SISCOM, ictal SPECT co-registered to MRI.

[a]Nonlocalizing and correct is not possible. Nonlocalizing and incorrect if there was a suspected epileptogenic zone.

earlier studies on ISAS and STATISCOM, a similar algorithm that uses a control database,[4,6,7,9] although all these studies were carried out by groups that developed either SISCOM, ISAS or STATISCOM. One study comparing ISAS and STATISCOM showed slightly better results for STATISCOM; ISAS localized correctly in 59% of patients, STATISCOM in 63%.[9] We found the correct location with ISAS in 65% of patients.

The difference between SISCOM and ISAS is evident when analyzing the images: SISCOM shows on average 57 clusters with significant hyperperfusion, while ISAS presents only 5. The multitude of SISCOM clusters can be confusing, with most being nonrelevant. In contrast, ISAS showed fewer clusters, with the most significant cluster often aligning with the reviewers location, indicating that ISAS is easier to interpret than SISCOM.

We took a fairly liberal approach in generating the ISAS images, by using a *p*-value threshold of 0.001 on the voxel level, but no cluster-level threshold. This is an arbitrary choice and can be seen as a limitation of the study. Practically, this meant that all voxels with $t > 3.85$ were included in the result. Had we applied family wise error correction, this threshold would have increased to approximately 7.5. While this would have increased the number of datasets without significant voxels, it might also have increased the specificity of the ISAS results. In Figure 4B,

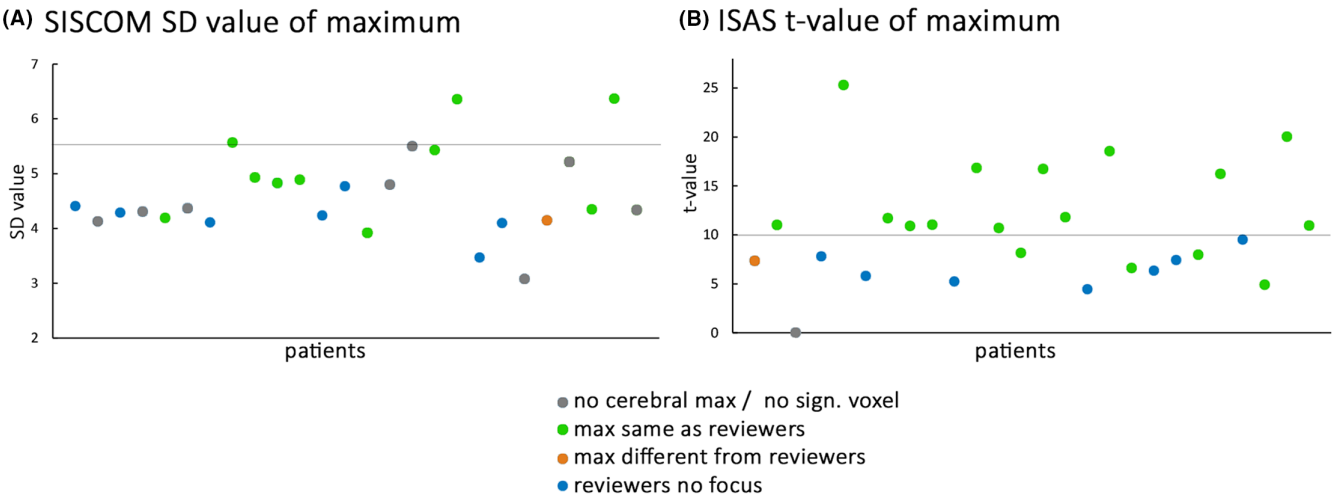

FIGURE 4 Analysis of the maximum hyperperfusion in SISCOM (A) and ISAS (B). (A) The SD value of the most significant SISCOM location was higher in patients in whom the reviewers found the same location (green dots) than in the patients in whom the maximum was not correct (gray, orange or blue dots). An SD value higher than 5.5 was always in the correct location. (B) The *t*-value of the most significant ISAS location was higher in patients in whom the reviewers found the same location (green dots) than in the patients in whom the maximum was not correct (gray, orange or blue dots). A *t*-value higher than 10 was always in the correct location. ISAS, ictal-interictal SPECT analyzed by SPM; SD, standard deviation; SISCOM, ictal SPECT co-registered to MRI.

we observe that datasets with low *t*-values were often nonlocalizing.

One goal was to investigate the feasibility of using a publicly available control database. The use of a protocol- and equipment-specific control database is likely superior to our strategy of using a generic control database. We were pleasantly surprised by the stability of our leave-one-out analysis and found no concerning results when comparing ISAS to SISCOM within a patient. The control database comprised only adult scans, potentially impacting our results in the children. Limited knowledge exists about metabolic and vascular differences with aging, but it seems that regional cerebral blood flow and metabolism reach adult values during adolescence.[12] Since the majority of our pediatric population were teenagers, this might explain the absence of differences between adults and children. We anticipate that the subtraction of ictal and interictal SPECT within one patient compensates for much of the age-related metabolic differences. The results of ISAS in children could potentially improve with an age-matched control database. Analyzing children's SPECT using ISAS with this adult database should be approached cautiously, despite observing no negative effects in our cohort.

Whether the SPECT postprocessing shows localizing results does not only depend on the algorithm used. The time of injection of the tracer after seizure onset is also a key factor in the success of the investigation.[13,14] Injection within 30 s after seizure onset is considered to be a fast injection and will increase the chance of a localizing result.[15] Therefore, we expected to find a difference in localizing ability between fast and slow injections, but our data did not show this. This may be biased because we only had 5 slow injections. We also calculated the difference between fast and slow injections when 'fast' was defined as 'within the first quarter of the seizure', but in this analysis there was also no difference in the chance of a localizing result. Injection time might be more important for SISCOM than for STATISCOM or ISAS, as late injections might lead to multiple foci of hyperperfusion related to both seizure-related and physiological responses, of which the latter are suppressed in STATISCOM and ISAS.[8] We could not differentiate between focal and bilateral tonic clonic seizures with the available data. One could hypothesize that bilateral tonic clonic seizures are less likely to show focal SPECT results, especially when the injection was in the bilateral tonic clonic phase.[16]

One limitation of this study is its comparison to the gold standard for identifying the epileptogenic zone,[17] which is the resected area in patients with postoperative seizure freedom. Initially, our patient cohort, spanning from 2017 to 2018, included only seven patients who underwent surgery, of whom two became seizure-free. To enhance the cohort size, we added SPECT patients who underwent subsequent resection from 2013 to 2016. SPECT is typically performed in complex focal epilepsy cases, without MRI abnormality or without clear ictal onset zone in the EEG. Consequently, the number of patients achieving seizure freedom after SPECT is notably low. Hence, we opted to use two gold standards for the epileptogenic zone: (1) the resected area in patients with postoperative seizure freedom and (2) the suspected epileptogenic zone in patients

without postoperative seizure freedom or without surgery. This second gold standard is not ideal, but a result of the complex patient cohort in whom SPECT is performed.

When only considering patients attaining seizure freedom after surgery, both SISCOM and ISAS correctly identified the epileptogenic zone in 7 out of 8 patients. This underscores the challenging nature of cases within our cohort, where only highly successful SPECT leads to surgery. Being a tertiary referral center for epilepsy surgery, our patients often return to their epilepsy clinic or general hospital, and subsequently, some are lost to follow-up. We included the last available outcomes from our center. Unfortunately, Patient 9 passed away 1 month after surgery due to reasons unrelated to the surgical procedure or seizures.

ISAS analysis using a publicly available control dataset, instead of a recommended in-house acquired control set, showed at least comparable results to clinical standard SISCOM analysis. Therefore, this study paves the way for a broader application of ISAS in centers that do not have the possibility to acquire such an in-house control dataset.

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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APPENDIX A

Leave-one-out analysis

Methods

Before the ictal-interictal SPECT analyzed by SPM (ISAS) algorithm was implemented in our in-house software, it was tested in SPM. The steps of the algorithm as described on http://spect.yale.edu/indexSPM.html were implemented in SPM12 such that the sample analysis could be reproduced. To assure the stability of the results with a normal database of only 14 subjects, gathered from another SPECT scanner, we performed leave-one-out analysis. We ran the algorithm 14 times on one patient (patient 16, a 14-year-old male), each time excluding one of the normal subjects. We compared the result of hyperperfusion in pattern and location of maximum hyperperfusion.

Results

The location of maximum hyperperfusion in the 14 runs is shown in Figure A1. All images show the same distribution of significant voxels. Twelve of the 14 results show the maximum hyperperfusion in the right temporal lobe. One shows the maximum hyperperfusion in the right frontal lobe and one shows it in the left frontal lobe. These two also show significant voxels in the right temporal lobe, but not the maximum.

Conclusion

Based on the very similar pattern of significant voxels and the consistent location of the maximum hyperperfusion in 12/14 runs, we concluded that this ISAS algorithm with a normal database of 14 subjects from another scanner in another scanner gives reliable results. Therefore, we deemed it appropriate to use this algorithm and normal database in our study population.

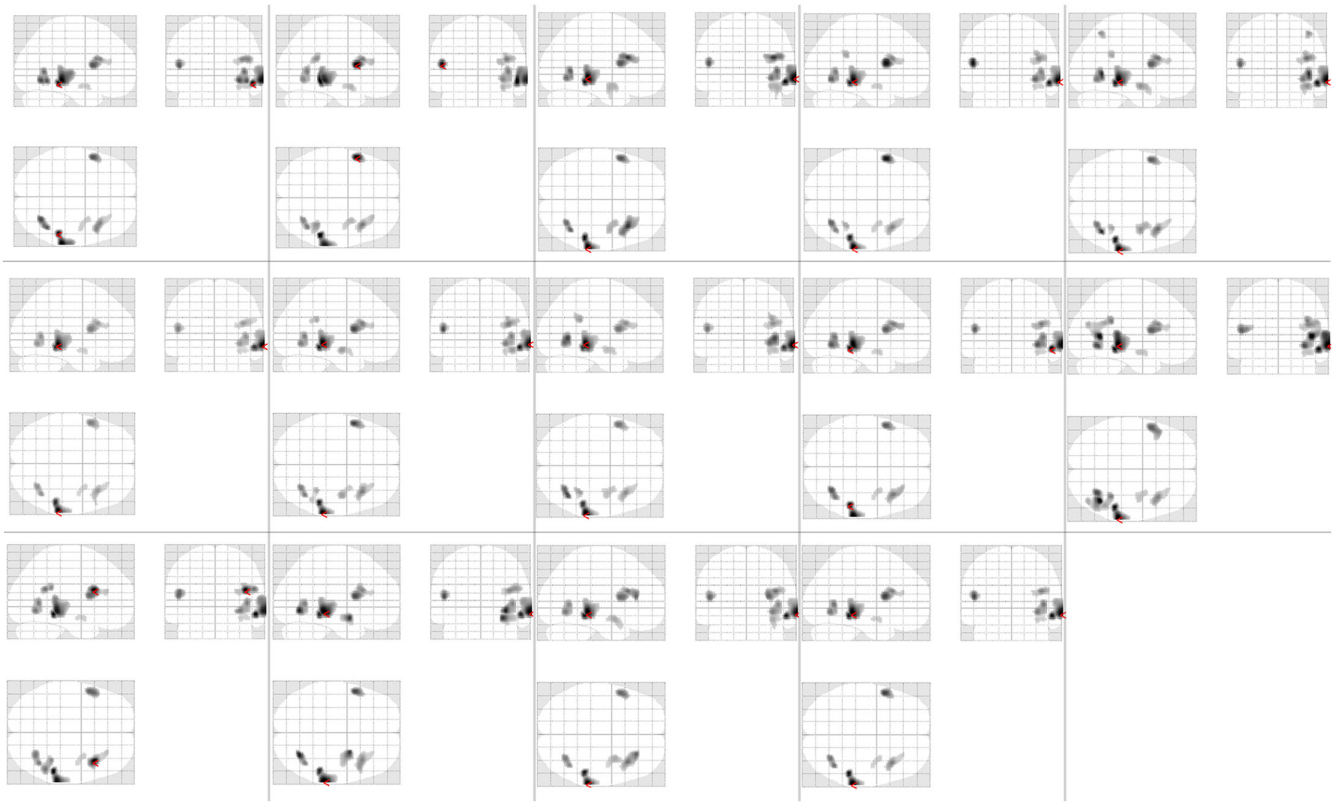

FIGURE A1 SPM result of each leave-one-out run of ISAS. The results for each run are shown in a minimum intensity projection in sagittal (upper left), coronal (upper right), and axial (lower left) view. Images are in neurological convention, left = left. The maximum hyperperfusion for each is indicated with a red arrow. ISAS, ictal-interictal SPECT analyzed by SPM.