



Of Blobs and Buzzes: Does SISCOM Imaging Actually Help SEEG Planning?

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Neurovascular Networks in Epilepsy: Correlating Ictal Blood Perfusion With Intracranial Electrophysiology

Krishnan B, Tousseyn S, Nayak CS, Aung T, Kheder A, Wang ZI, Wu G, Gonzalez-Martinez J, Nair D, Burgess R, Iasemidis L, Najm I, Bulacio J, Alexopoulos AV. *Neuroimage*. 2021;231: 117838. doi: 10.1016/j.neuroimage.2021.117838

Perfusion patterns observed in Subtraction Ictal SPECT Co-registered to MRI (SISCOM) assist in focus localization and surgical planning for patients with medically intractable focal epilepsy. While the localizing value of SISCOM has been widely investigated, its relationship to the underlying electrophysiology has not been extensively studied and is therefore not well understood. In the present study, we set to investigate this relationship in a cohort of 70 consecutive patients who underwent ictal and interictal SPECT studies and subsequent stereo-electroencephalography (SEEG) monitoring for localization of the epileptogenic focus and surgical intervention. Seizures recorded during SEEG evaluation (SEEG seizures) were matched to semiologically-similar seizures during the preoperative ictal SPECT evaluation (SPECT seizures) by comparing the semiological changes in the course of each seizure. The spectral changes of the ictal SEEG with respect to interictal ones over 7 traditional frequency bands (0.1 to 150 Hz) were analyzed at each SEEG site. Neurovascular (SEEG/SPECT) relations were assessed by comparing the estimated spectral power density changes of the SEEG at each site with the perfusion changes (SISCOM z-scores) estimated from the acquired SISCOM map at that site. Across patients, a significant correlation ($P < 0.05$) was observed between spectral changes during the SEEG seizure and SISCOM perfusion z-scores. Brain sites with high perfusion z-score exhibited higher increased SEEG power in theta to ripple frequency bands with concurrent suppression in delta and theta frequency bands compared to regions with lower perfusion z-score. The dynamics of the correlation of SISCOM perfusion and SEEG spectral power from ictal onset to seizure end and immediate postictal period were also derived. Forty-six (46) of the 70 patients underwent resective epilepsy surgery. SISCOM z-score and power increase in beta to ripple frequency bands were significantly higher in resected than non-resected sites in the patients who were seizure-free following surgery. This study provides for the first time concrete evidence that both hyper-perfusion and hypo-perfusion patterns observed in SISCOM maps have strong electrophysiological underpinnings, and that integration of the information from SISCOM and SEEG can shed light on the location and dynamics of the underlying epileptic brain networks, and thus advance our anatomico-electro-clinical understanding and approaches to targeted diagnostic and therapeutic interventions.

Commentary

Successful epilepsy surgery requires accurate identification of the epileptogenic zone, which typically overlaps with the ictal onset zone (IOZ). Subtraction Ictal SPECT Co-registered to MRI (SISCOM) has been an important part of the presurgical evaluation for decades, but it has never been a “magic bullet,” and is only one of several tools needed to find the IOZs.^{1,2} Fortunately, the introduction of stereo-electroencephalography (SEEG) now allows us to sample ictal activity in regions of interest more freely. Therefore, SISCOM has taken on a more powerful role by demonstrating areas of ictal hyperperfusion that may guide subsequent SEEG targeting. It is thought that due to neurovascular coupling, hyperperfusion during a seizure is a marker for excess electrical activity. However, this hypothesis has not been well studied in patients with epilepsy.

In the presently highlighted study, Krishnan and colleagues³ sought to correlate ictal SEEG activity with the SISCOM intensity and relate these findings to surgical outcomes in patients with drug resistant epilepsy. They studied 70 individuals who underwent SISCOM imaging followed by SEEG recordings. Simultaneous SEEG and ictal SPECT is typically impractical, so the authors focused on those SEEG seizures that most closely matched the duration and semiological evolution of the ictal SPECT events. Since SEEG detected seizure onset occurs a couple seconds earlier than scalp EEG, they used the time of first clinical change to temporally align the seizures. Based on this alignment, they were able to approximate SEEG changes around the time of peak tracer uptake phase (15–20 seconds after tracer injection). It is worth mentioning, however, that neurovascular coupling is not instantaneous, so perfusion during tracer uptake is





predominantly related to the preceding several seconds of SEEG activity. As with SISCOP, the authors found that their ictal SEEG power analysis was critically dependent on first normalizing each contact to its own interictal activity. They defined SEEG “boost power” as being above interictal baseline, whereas “suppressed power” is defined as being below this threshold. SISCOP activity was threshold using a Z-score of 1.5 to define whether a region was hyperperfused, hypoperfused or normally perfused.

While all seizures showed elevated boost power, the investigators found that voxels with higher SISCOP signal had especially high boost power in faster frequencies. There was elevated β -ripple boost power in hyperperfused vs hypoperfused areas, with the greatest difference being at the middle of seizure with boosted γ /high- γ range power. Ictal fast activity is a powerful indicator of the IOZ, and the authors found a strong correlation with increased SISCOP activity and boosted high γ -ripple activity at seizure onset. At the time of peak tracer uptake, SEEG showed a broad-band boost power in all frequencies above the δ band. The authors also studied suppressed power, since suppressed slow activity can be a component of some IOZ “fingerprints”.⁴ Concordantly, Krishnan et al found that areas of high SISCOP signal also had suppressed low frequency (δ -theta) power. In contrast, suppressed γ -ripple activity was correlated low SISCOP signal. As expected, there was an abrupt loss of boost power after the seizure, although areas of hypoperfusion tended to have a bit more residual postictal theta- α power compared to hyperperfused regions. These SEEG/SISCOP correlations were similar irrespective of the time to injection, temporal vs extratemporal focus, secondary generalization, or surgery outcomes.

Finally, the authors focused on surgical results. They found that surgical successes tended to have higher SISCOP Z-scores in the resection bed, compared to surrounding tissue, but this was not true in surgical failures. Moreover, successful resections tended to include a greater proportion of hyperperfused SEEG contacts. The authors also found that areas of resection in surgical successes tended to have greater boost theta-ripple power. While resected areas from surgical failures also had increased fast activity compared to surround regions, this boost power was limited to the γ /high- γ band. Finally, the previously mentioned suppression of ictal δ -theta activity did not reliably differentiate successes from failures.

Overall, this study by Krishnan and colleagues does provide novel and compelling evidence of neurovascular coupling between perfusion on SISCOP maps and SEEG findings. Of course, there are limitations to this study and questions for further contemplation. The authors’ approach will necessarily be biased towards areas of hyperperfusion, given that the intracranial electrode targeting occurred after the SISCOP data were available, but this may be somewhat mitigated by the broad sampling strategy with an average of 13 electrodes and 153 contacts per patient. Hippocampal seizures can have slightly different SEEG patterns at ictal onset, so it is also notable that only fraction of their cases had hippocampus-involving IOZs.

Next, while patients who had a favorable surgical outcome did have higher SISCOP Z-scores in the region of resection, further suggesting hyperperfusion in true epileptogenic regions, only 56 patients actually had resection/laser ablation, and only 46 of these had a post-operative MRI to confirm whether voxels/contacts were actually resected. This may limit the generalizability of these results, but the size of this patient subset is likely still adequate to draw interesting conclusions.

What are the clinical implications of this study? The authors’ results do increase confidence about the utility of this technique to delineate regions to consider targeting when planning an SEEG study. However, surgical resection should not be performed based on SISCOP findings alone, in particular because the hyperperfused region is often much larger than the ONZ. This may be particularly true if tracer injection is delayed to a point when seizure activity has spread far beyond the ONZ.⁵ It is also important to recognize that hyperperfusion is common in subcortical regions such as basal ganglia,⁶ and some contralateral activations are not uncommon and have been described in insular⁷ and mesial temporal lobe epilepsy.⁸ Therefore, integration of SISCOP results with other clinical, electrophysiological, and imaging findings remains critical in surgical planning. Nonetheless, this work paves the way to a greater, patient-specific, understanding of epilepsy networks. SISCOP hyperperfusion can indicate areas of ictal spread, and/or high functional connectivity to the IOZ. Subtraction ictal SPECT co-registered to MRI-directed SEEG planning allows more complete electrographic sampling of salient areas which may help us better define specific SEEG power “fingerprints” to differentiate areas of ictal onset vs early spread. Moreover, using SISCOP hyperperfusion to identify areas of high functional connectivity to the IOZ⁹ may eventually allow us to find subordinate IOZ nodes in some networks, thereby preventing surgical failures. Epilepsy surgery evaluations require a multi-modal approach, and the work by Krishnan et al provides insight into how we can use these different tests to provide synergistic, rather than simply additive, progress in our quest for consistently successful epilepsy surgeries. In a nutshell, showing that hyperperfused areas on SISCOP are electrically involved during a seizure is an expected albeit welcome validation of what one anticipates: the common challenge of both SISCOP and SEEG is translating their findings into an actionable surgical plan that leads to seizure freedom.

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