Triggered Seizures for Ictal SPECT Imaging: A Case Series and Feasibility Study

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Ictal SPECT is an informative seizure imaging technique to tailor epilepsy surgery. However, capturing the onset of unpredictable seizures is a medical and logistic challenge. Here, we sought to image planned seizures triggered by direct stimulation of epileptic networks via stereotactic electroencephalography (sEEG) electrodes. Methods: In this case series of 3 adult participants with left temporal epilepsy, we identified and stimulated sEEG contacts able to trigger patient-typical seizures. We administered 99mTc-HMPAO within 12 s of ictal onset and acquired SPECT images within 40 min without any adverse events. Results: Ictal hyperperfusion maps partially overlapped concomitant sEEG seizure activity. In both participants known for pericentral aphasia, SPECT imaging revealed hyperperfusion in the speech cortex lacking sEEG coverage. Conclusion: Triggering of seizures for ictal SPECT complements discrete sEEG sampling with spatially complete images of early seizure propagation. This readily implementable method revives interest in seizure imaging to guide resective epilepsy surgery.

Key Words: human epilepsy; seizure imaging; ictal SPECT; seizure triggering; stereotactic electroencephalography

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Delineating brain areas of seizure onset and propagation is a necessary step toward tailoring surgery for focal epilepsy (1). Ictal SPECT is a key method to capture a spatially complete view of propagating seizures by imaging areas of accompanying parenchymal hyperperfusion (1–3). However, the unpredictable timing of fleeting seizures renders ictal SPECT acquisitions logistically challenging and resource-intensive. In practice, neurologists reduce antiseizure medications to hasten the occurrence of seizures. Their prompt detection requires continuous visual monitoring of the electroencephalogram. Until then, nuclear medicine staff must stand ready to inject a radiotracer, critically within seconds of seizure onset, which rarely succeeds without delay (4). Moreover, maintaining ready-to-inject radiotracer over days incurs issues with isotope production, transport and storage, as well as radioprotection (5). Thus, because of growing cost and time constraints in health care, most epilepsy centers, including ours, abandoned this informative technique (6).

Here, we conducted a feasibility study modifying the original ictal SPECT method to address these practical issues. In most patients with epilepsy undergoing invasive stereotactic electroencephalography (sEEG) monitoring, patient-typical seizures can be triggered using direct electric stimulation (7). This procedure contributes to localizing ictogenic tissue but also offers temporal control over the occurrence of seizures. We used this untapped opportunity to image planned seizures.

MATERIALS AND METHODS

Participants

Three male participants undergoing invasive sEEG investigations for the clinical purpose of localizing their seizures gave their written informed consent in accordance with the Declaration of Helsinki. The Ethics Committee of the Canton Bern, Switzerland, approved this prospective feasibility study (KEK 2021-01337).

Electrophysiology

sEEG leads (DIXI Medical) were implanted under general anesthesia in cerebral areas of interest for recording (Natus Quantum), mapping, and stimulation (ISIS neurostimulator; Inomed Medizintechnik GmbH). We systematically screened all gray-matter sEEG contacts for minimal stimulation parameters able to trigger the patient-typical seizure (biphasic 1-ms square pulses; frequency, 60 Hz; duration, 1–4 s; intensity, 2–6 mA; Table 1). Epileptiform discharges without symptoms and symptoms without epileptiform discharges were disregarded.

Seizure Triggering and SPECT Acquisition

One day after triggering a first patient-typical seizure (confirmed as such against spontaneous seizures), stimulation was repeated at the identified trigger site with a connected syringe containing the freshly produced 99mTc-hexamethylpropyleneamine oxime (HMPAO) (medeo AG; Table 1). Upon the onset of an electroclinical seizure, the radiotracer was injected, followed by SPECT imaging within 21–39 min on a prebooked Symbia Intevo Bold system (Siemens Healthineers) (Fig. 1A). Potential spillover was assessed with a Geiger counter.

Imaging Data

Postoperative CT images were coregistered to a preoperative T1-weighted MRI scan using the Lead-DBS toolbox (version 2.5.2) in
MATLAB 2020a (The MathWorks) to compute the coordinates of sEEG contacts. We computed a SPECT deviation map for each participant and detected volumes with a z-value of at least 2.25 as hyperperfusion clusters using a normal database (8)—that is, normalization to whole-brain activity provided by the Hermes BRASS software (version 6.1.3; Hermes Medical Solutions; Fig. 1B) as a reference. We computed patient-specific cortical reconstruction with FreeSurfer (Harvard) for covisualization with the hyperperfusion clusters and sEEG contacts (Fig. 2).

**Electrophysiologic Data**

We computed bipolar traces of adjacent contacts and filtered signals with a 1- to 410-Hz bandpass filter. To estimate seizure power per bipolar contact, a z-value was calculated as follows: \((LL_{\text{post}} - LL_{\text{pre}}) / (SD(LL_{\text{pre}}))\), where LL is the line length of the sEEG signal over a running window of 1 s, averaged over 60 s before (pre) and after (post) seizure onset (9). Seizure-triggering stimulation was excluded from this calculation.

### RESULTS

Within a few attempts over 3–8 min, we successfully triggered seizures in 3 participants, replicating the patient-typical seizure semiology and electrographic pattern on sEEG (Table 1). In each case, we injected \(^{99m}\text{Tc}-\text{HMPAO} \ (<520 \text{ MBq})\) within 9–12 s of

### TABLE 1

Characteristics of Participants, Trigger Parameters, SPECT Acquisition Data, and Clinical Value

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristic</th>
<th>Participant 1</th>
<th>Participant 2</th>
<th>Participant 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants and their epilepsy</td>
<td>Age and sex</td>
<td>20-y-old man</td>
<td>50-y-old man</td>
<td>48-y-old man</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Left mesiotemporal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td>Hippocampal sclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure onset zone from sEEG</td>
<td>Entorhinal cortex, anterior and posterior hipparcampus</td>
<td>1 s</td>
<td>2 s</td>
<td>4 s</td>
</tr>
<tr>
<td>Spontaneous seizure symptoms*</td>
<td>Gustatory aura → oral and manual automatisms → aphasia</td>
<td>2 mA</td>
<td>2 mA</td>
<td>6 mA</td>
</tr>
<tr>
<td>Triggered seizures</td>
<td>Symptoms</td>
<td>Identical up to aphasia</td>
<td>Identical up to aphasia</td>
<td>Identical up to tunnel vision</td>
</tr>
<tr>
<td>Antiseizure medication</td>
<td>Half-dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation intensity</td>
<td>2 mA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation duration</td>
<td>1 s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of awareness</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure propagation*</td>
<td>Entorhinal → anterior and posterior hippocampus → amygdala → temporal pole</td>
<td>151 s</td>
<td>94 s</td>
<td>188 s</td>
</tr>
<tr>
<td>SPECT</td>
<td>Delay</td>
<td>12 s</td>
<td>9 s</td>
<td>7 s</td>
</tr>
<tr>
<td>Seizure onset to injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection to image</td>
<td>21 min</td>
<td>22 min</td>
<td>39 min</td>
<td></td>
</tr>
<tr>
<td>Radiotracer production to image</td>
<td>3 h 13 min</td>
<td>2 h 26 min</td>
<td>1 h 38 min</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>406 MBq</td>
<td>489 MBq</td>
<td>511 MBq</td>
<td></td>
</tr>
<tr>
<td>Hyperperfusion</td>
<td>Mesiotemporal, superior temporal, frontobasal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Resection</td>
<td>Selective amygdalohippocampexctomy, left</td>
<td>None because of cognitive risk</td>
<td>Selective polectomy and amygdalectomy</td>
</tr>
<tr>
<td>Seizure outcome</td>
<td>Engel class ID at 1 y</td>
<td>NA</td>
<td>Engel class IV at 1 y</td>
<td></td>
</tr>
<tr>
<td>Cognitive outcome</td>
<td>Improved</td>
<td>NA</td>
<td>Unchanged</td>
<td></td>
</tr>
</tbody>
</table>

*Arrows indicate sequence of symptoms or involved areas, which can be complete or partial across seizures in same participant. NA = not applicable.
Involvement of brain areas lacking electrode coverage to limit the early seizure propagation unique. In the temporal), each triggered seizure was patient-specific, and the imaged early seizure propagation unique. In the first 2 cases, ictal SPECT offered complementary information to sEEG and revealed early involvement of brain areas lacking electrode coverage to limit the risk of complications in potentially eloquent cortex. In the third case, sEEG and ictal SPECT provided overlapping information.

DISCUSSION

To our knowledge, this is the first study establishing the feasibility of triggering ictal SPECT on demand with direct electric stimulation of the epileptic cortex. Triggering seizures for SPECT imaging was previously explored in psychiatric patients undergoing electroconvulsive therapy (10) and epileptic patients receiving pentylene-tetrazole (11). However, these prior methods did not generalize, given the unclear clinical utility and safety of these procedures. With this case series, we show that triggering of seizures with direct electric stimulation for ictal SPECT imaging is convenient, spares resources, and can be clinically useful.

The presented method is limited to patients with epilepsy undergoing invasive sEEG monitoring. As such, it cannot guide electrode placement but may contribute to the planning of resective surgery. Of note, we used a normal non-age-matched database for the calculation of deviation maps. Although we could identify ictal hyperperfusion areas, further optimization with the subtraction of patient-specific interictal SPECT is required. To establish the clinical value, future studies should compare triggered and spontaneous ictal SPECT as predictors of postsurgical outcomes, as well as delineate their added value over other imaging modalities.

As proposed by previous retrospective work (15,16), the maximum ictal hyperperfusion did not overlap perfectly with the seizing parenchyma (Fig. 2), suggesting a potential regional impairment of neurovascular coupling (17) and potential ictal hypoperfusion areas (16). As shown here, delineating ictogenic parenchyma with high temporal resolution (sEEG) and spatial continuity (ictal SPECT) may offer a deeper understanding of seizure propagation pathways and help plan resections around eloquent cortex.

CONCLUSION

Nuclear medicine and sEEG for recording and stimulation are broadly available at specialized epilepsy centers. In our opinion, SPECT imaging of seizures can be rapidly readopted in controlled conditions that mitigate its previous logistic drawbacks. Novel data generated with this technique in larger cohorts could contribute to refinement of resection planning, improving seizure and cognitive outcomes in epilepsy surgery.

DISCLOSURE

Maxime Baud holds shares with Epios, Ltd., a medical device company based in Geneva. No other potential conflict of interest relevant to this article was reported.
FIGURE 2. sEEG–SPECT comparison: patient-specific cortex reconstruction (FreeSurfer, left-hemisphere, frontal and inferior view) with sEEG bipolar contacts and SPECT deviation map (orange to yellow, more intense) for participants 1 (A), 2 (B), and 3 (C). Amygdala and hippocampus contours (adapted from FreeSurfer) are shown as dark gray overlays. sEEG bipolar contacts (plotted at anatomic centers of bipoles) are color-coded from white to blue according to amount of ictal activity recorded over 1 min (line length relative to baseline). Red bolt depicts stimulated bipole. sEEG traces are shown for selected channels of interest with their anatomic location. Brackets regroup channels from same lead. Note relationship between stimulus artifacts and direct beginning of epileptic discharges. A = amygdala; Ent = entorhinal cortex; HippA = hippocampus anterior; HippP = hippocampus posterior; P-1 = participant 1; P-2 = participant 2; P-3 = participant 3; Parahipp = parahippocampal gyrus; STG = superior temporal gyrus; TP = temporal pole; WM = white matter.
ACKNOWLEDGMENT

We thank Sandy Feruglio for setting up the clinical database for this study.

KEY POINTS

QUESTION: Is ictal SPECT able to map seizures triggered by direct electric stimulation?

PERTINENT FINDINGS: We successfully triggered and imaged patient-typical seizures with SPECT in a prospective case series of 3 participants with left temporal epilepsy. Our combined sEEG/SPECT approach revealed early seizure propagation pathways, beyond discrete electrophysiologic exploration.

IMPLICATIONS FOR PATIENT CARE: Triggering of patient-typical seizures for on-demand ictal SPECT may broadly reinstate this often-abandoned imaging technique and help tailor resective epilepsy surgeries.

REFERENCES