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A study of perfusion changes with Insula Epilepsy using SPECT

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ABSTRACT

Purpose: The non-invasive localisation of insular lobe epilepsy is a challenge. We aimed to determine if ictal SPECT is a reliable adjunctive test in insular cases and to explore its role in the tailoring of intracranial strategies.
Method: From a dataset of patients who underwent SEEG between December 2012 and December 2016, we collected patients with focal insular onset epilepsy. We examined semiology, EEG, PET and SPECT hyperperfusion pattern with SISCOM. We also reviewed relevant literature.
Results: 5 patients were identified, 4 females, from a dataset of 51 patients. Median age of seizure onset was 8 years old (8 months to 10 years). All patients had an ictal SPECT during pre-surgical work-up: median injection time was 7 s (3–17 sec) from clinical onset, and median seizure duration was 42 s (11–85 sec). Insula cortex showed focal hyperaemia in four patients, all bilateral, with the greatest hyperperfusion contralateral to the ictal onset in two cases, using SISCOM threshold at 1.5 standard deviation. Other sites with hyperaemia included basal ganglia and middle temporal gyrus. The SEEG confirmed insular onset seizures in all the cases. All patients had epilepsy surgery and were seizure free at 21 to 50 months follow up. The results from the literature review showed frequent hyperperfusion in structures outside insula and frequently over the contralateral hemisphere.
Conclusions: This study highlights the technical limitations of SPECT when attempting to assess seizures arising from the insula. Our findings and the literature show ictal SPECT can be localising but falsely lateralising in seizures arising from the insula.

1. Introduction

The non-invasive localisation of insular lobe epilepsy (ILE) continues to pose a challenge. The suggestion of insular cortex involvement is often based upon recognition of the described clinical semiology [1–4]. Non-invasive neurophysiological investigation is often non-localising and at times discordant to the hypothesis of insular lobe involvement [5]. With these difficulties, many cases progress to intracranial EEG evaluation to achieve a surgical solution.

Ictal SPECT has the potential to localise seizure onset in non-lesional cases and compliment the investigations of lesional cases with discordant data [6]. However, little has been published on the patterns of hyperaemia found with ictal SPECT in suspected insula lobe cases. The current study aimed to outline our centre's experience with ictal SPECT in proven ILE and review the literature to see if common perfusion patterns occur. We aimed to determine if ictal SPECT is a reliable adjunctive test in insula cases and to explore its role in the tailoring of intracranial strategies.

2. Methods

2.1. Patients

The study retrospectively analysed patients from our centre with definite insular lobe epilepsy proven via stereo-EEG assessment and post-surgical seizure freedom. Patients were included from the beginning of our SEEG program in December, 2012 to December, 2016, to ensure adequate follow up after epilepsy surgery. Prior to intracranial assessment, all patients had long-term VEEG monitoring, and MRI and PET imaging. Additionally, in all patients progressing to intracranial assessment, ictal SPECT was performed in order to further refine the implantation strategy. The SPECT perfusion patterns in patients with SEEG proven ILE were examined for the purposes of our study. Given ictal SPECT scans are arguably dependant on timing of the injection with respect to seizure onset, only rapid ictal injections were accepted for analysis, with a cut off injection time of less than 20 s from clinical seizure onset.

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2.2. Non-invasive assessment

VEEG was performed with scalp electrodes placed according to the 10/20 International System with additional electrodes over the frontotemporal region (10/10 International System). During monitoring, medication was stopped or reduced in order to provoke seizures and recording lasted 5–7 days.

MRI studies included 3 T volumetric T1, T2 and FLAIR sequences. FDG-PET studies, following administration of 400 MBq of FDG-PET tracer were captured on an ECAT 951R PET scanner (CTI/Siemens, Knoxville, TN, U.S.A.).

2.3. SISCOM

Bedside ictal injection of SPECT tracer was performed by an experienced epilepsy nurse (MB). Patients were administered approximately 800 MBq of ^{99m}Tc-ECD (one case) or ^{99m}Tc-HMPAO (four cases). The interictal acquisition was performed a minimum of 24 h after last EEG documented seizure activity. Images were captured using a Siemens ECAM (Siemens Medical Solutions USA Inc., Hoffman Estates, IL. USA) dual headed gamma camera with a low-energy high-resolution collimator. The images were reconstructed using an iterative reconstruction algorithm, attenuation correction and post-reconstruction Gaussian filter applied. Subtraction ictal and interictal SPECT were processed according to a previously described method [7]. We considered significant a peri-ictal perfusion change of more than 1.5 standard deviations above the baseline. Seizure onset was defined as the earliest sign of clinical or electrical activity seen, and seizure cessation when activity was no longer present on the EEG, or in cases were no ictal EEG could be seen, when the clinical seizure stopped.

2.4. Intracranial EEG

Intracranial EEG was performed with stereotactic implantation of multiple intracranial electrodes (SEEG) (Microdeep intracerebral electrodes, Dixi Medical), in accordance with a predetermined hypothesis. Electrode placement was confirmed with a post implantation MRI and patients were monitored for 11–20 days. Major areas of hyperperfusion on the SISCOM were targeted with the SEEG electrodes. Seizure outcome after epilepsy surgery was reported in accordance with the Engel classification, Engel I considered seizure free, Engel II-IV not seizure free [8].

2.5. Literature review

The patterns of ictal SPECT hyperperfusion in our cohort were compared with those in the literature. To identify studies reporting the use of SPECT in insula lobe epilepsy we performed a systematic literature search in PubMed from January 2000 until March 2017. The year 2000 was selected as this was year in which two seminal papers refocused the epilepsy community to the possibility of seizures arising from the insula [9,10]. The search strategy included the keywords: insula, epilepsy, seizure, SPECT and SISCOM. The reference lists of all identified studies were examined for additional material. Papers identified by the search and reference lists were independently assessed by two authors, JS and MF. Only articles or reports where both authors concluded there was evidence to support definite insula lobe epilepsy were selected and data regarding both non-invasive and invasive assessments were extracted for comparison.

3. Results

3.1. Patient population

Between December 2012 to 2016, our centre performed 51 intracranial EEG assessments with SEEG. Within this group, six patients were documented to have seizures arising from the insula, five of whom were subsequently included for analysis. The sixth patient was excluded as the SPECT injection time was greater than 20 s and thus late in the seizure.

The five patients included 4 women and 1 male, aged between 13 and 41 with a median age of 30 and seizure onset ages between 8 months and 10 years (median 8 years old). Ictal semiology was variable among patients; however, all reported a focal sensory seizure with preserved awareness (3 somatosensory, 1 gustatory, 1 throat constriction) followed by bilateral motor seizures with impaired awareness. One patient with Tuberous Sclerosis Complex (TSC) had a left temporal resection during childhood without altering the pattern of seizures or the semiology.

3.2. Semiology

All patients were admitted for VEEG recording, and detailed seizure semiology was analysed and recorded for each patient. Specifically, seizures consisted of a tightening sensation in the throat, progressing to drooling, right face and arm clonic jerking (patient 1); an electrical or numb feeling in the left or bilateral feet and a sense of fear, progressing to prominent flailing of right arm and leg, left arm posturing, facial grimace end eventually a bilateral tonic clonic seizure (patient 2); left hand tingling or numbness, spreading to left arm, face, trunk and leg, occasionally progressing to bilateral tonic clonic seizures (patient 3); burning sensation over right face, followed by a noise in the right ear and a sensation of jerking on the right side of body, and evolving into truncal posturing, bilateral asymmetric shoulder abduction and neck flexion (patient 4); bad taste in mouth followed drooling, oral automatisms, restlessness and shuffling movements in the bed (patient 5)

3.3. Non-invasive assessment

The inter-ictal EEG showed multiregional epileptiform discharges (n = 1), bilateral (n = 2) or ipsilateral (n = 1) fronto-temporal discharges and no discharges (n = 1) (Table 1). The scalp recorded ictal onset was non-localisable in all seizures across all patients.

The MRI was non-lesional in 4 patients, but the fifth patient with TSC had multiple tubers throughout both hemispheres that included both insula. FDG-PET did not demonstrate definite hypometabolism of the insula across all patients. Definite hypometabolism of both temporal lobes was seen in 2 patients, possible reduction of the ipsilateral hemisphere in the patient with TSC and normal in the remaining 2 patients.

3.4. SISCOM

SPECT tracer was injected at a median time of 7 s (range 3–17 s) following clinical seizure onset, in seizures with duration from 11 to 85 ss (median 42 s). The injection times for each patient and seizure semiology at the time of injection is shown in Table 1.

SISCOM analysis showed significant insular hyperperfusion in four patients (Fig. 1, Pt 1–3, Pt 5). Of these four patients all demonstrated bilateral insula activation, with the region of greatest hyperperfusion actually occurring in the insula lobe contralateral to the proven SEEG onset in two of these cases (Pt 1 and 2, Fig. 1). Apart from the insula, the basal ganglia were involved in four patients; in two cases the activation was bilateral, with one being ipsilateral to the side of seizure onset and the other being contralateral. In the patient with TSC the SISCOM demonstrated hyperaemia of the ipsilateral thalamus and contralateral temporal neocortex.

3.5. Intracranial assessment

All patients showed a posterior insula onset to their seizures with SEEG. In one of these cases, the seizure onset zone also included the

Table 1
Patient's baseline characteristics and explorations.

Gender, Age (Age at seizure onset)	Semiology	Interictal EEG	Ictal EEG	SISCOM	SPECT time	MRI (Histopath)	SEEG onset (electrodes implanted)	Months follow up post-op & outcome
Pt 1 Female, 30 yo (8 yo)	Throat sensory to right face and arm clonic	Bilateral fronto-temporal	Non-localising	Left BG/right > left insula	5 sec injection/ 70 sec seizure	Normal (FCD 2b)	Left posterior insula (17)	21 (Engel 1a)
Pt 2 Female, 41 yo (2 yo)	Sensory seizure to complex motor/ bilateral tonic clonic	Multiregional	Non-localising	Bilateral insular, left > right	10 sec injection/ 42 sec seizure	Normal (FCD 2a)	Right posterior insula (14)	40 (Engel 1b)
Pt 3 Male, 31 y0 (10 yo)	Left hemisensory seizure to bilateral tonic clonic	Right fronto-temporal	Non-localising	Bilateral BG, Right > left insula	7 sec injection/ 85 sec seizure	Normal (FCD 1a)	Right posterior insula (14)	36 (Engel 1a)
Pt 4 Female, 21 yo (8 months old)	Right face sensory seizure to bilateral asymmetric tonic seizure	Bilateral fronto-temporal	Non-localising	Right temporal/left BG	3 s injection/11 sec seizure	Tuberous sclerosis (FCD 2b)	Left posterior insula (11)	50 (Engel 1a)
Pt 5 Female, 13 yo (8 yo)	Sensory seizure (gustatory) to complex motor seizure	Normal	Non-localising	Bilateral insula, right > left	17 s injection/36 sec seizure	Normal (FCD 2a)	Left posterior insula (13)	36 (Engel 1a)

Pt= Patient, yo= years old, BG= basal ganglia, FCD= focal cortical dysplasia, SISCOM= Subtraction of Ictal SPECT Coregistered to MRI; " > " = greater hyperaemia on SISCOM.

superior bank of the Sylvian fissure extending towards the frontal operculum (Pt 1, Fig. 1). In two cases, the combination of clinical semiology and non-invasive assessments were truly non-lateralised and a bilateral implantation was performed (Pt 1 and 5). In these patients, inter-ictal discharges were seen to propagate to the contralateral insula between 20–30 msec, and the ictal pattern crossed to the other side in 200–800 msec. The intracranial propagation pattern was dependant on the clinical semiology, with the seizures seen to readily engage the anterior insula, as well as, broad networks through the recorded frontal and temporal lobes. The planning for each patient is shown in Fig. 1.

3.6. Surgical outcomes

All patients underwent a tailored open resection following the result of the SEEG and all have gone from having multiple daily to weekly seizures to achieve seizure freedom (Engel 1a four patients, one patient Engel 1b), with a follow up of 21–50 months. Histopathology showed cortical dysplasia type 1a (n = 2), type 2a (n = 2) and type 2b in the patient with TSC, in keeping with a tuber. Fig. 1 shows the extent of surgical resections for each patient.

3.7. Review of literature

A PubMed search of predetermined terms revealed 28 case reports, series and articles with a further 20 identified from the reference lists. On careful independent consideration by two authors, only 9 articles reached consensus for the documentation of SPECT/SISCOM in the context of definite insula lobe epilepsy [3,5,11–17]. Given the previously discussed uncertainty regarding non-invasive assessment in insula lobe epilepsy all selected articles included a component of intracranial EEG to reach the definite inclusion status, with onsets limited to the insula. A summary of the SPECTs in these articles have been presented in Table 2.

None of the previous articles published the timing of their SPECT tracer injections in relation to the seizure onset. The articles did not report rapid ictal injections as part of their methodology, although all injections are ictal. Fifteen cases were identified: of those, in terms of localisation, only one case (6%) is reported as having hyperperfusion in the insula; in 7 cases (46%) the hyperperfusion is reported in insula and other structures, and in 7 cases (46%), the hyperperfusion was outside the insula, was multifocal or no significant hyperperfusion was seen. In terms of lateralisation, eight (53%) of the studies the ipsilateral hemisphere shows hyperperfusion in the ictal scan. The published SPECT data supports our findings at the time of injection the ictal hyperperfusion was often falsely localised to regions outside the insula, and there are few cases where ictal injections have demonstrated insula hyper-perfusion at all.

4. Discussion

Our experience shows in patients with ILE, rapid ictal SPECT injections can provide some supportive evidence of insula involvement, which in itself may be sufficient to support progressing to intracranial EEG recording. The main finding of the study however, was even though all included SPECT injections were rapid, SISCOM had some localising value but it was poorly lateralising. These findings were well supported by both the anatomical connectivity of the insula and the published descriptions of similar cases in the literature that have shown the reliability of SISCOM to accurately determine the seizure onset zone in ILE is somewhat diminished [5,17].

A critical feature when interpreting the finding is of course time scale. Injection of SPECT tracer has been approximated to take 30 s to reach the brain, where its uptake was dependent on a pattern of ictal perfusion remaining present for between 1–2 min, and around 70% of the ligand is taken up [18]. Consider this in the context of seizures arising from the insular lobe, where it has been well documented close

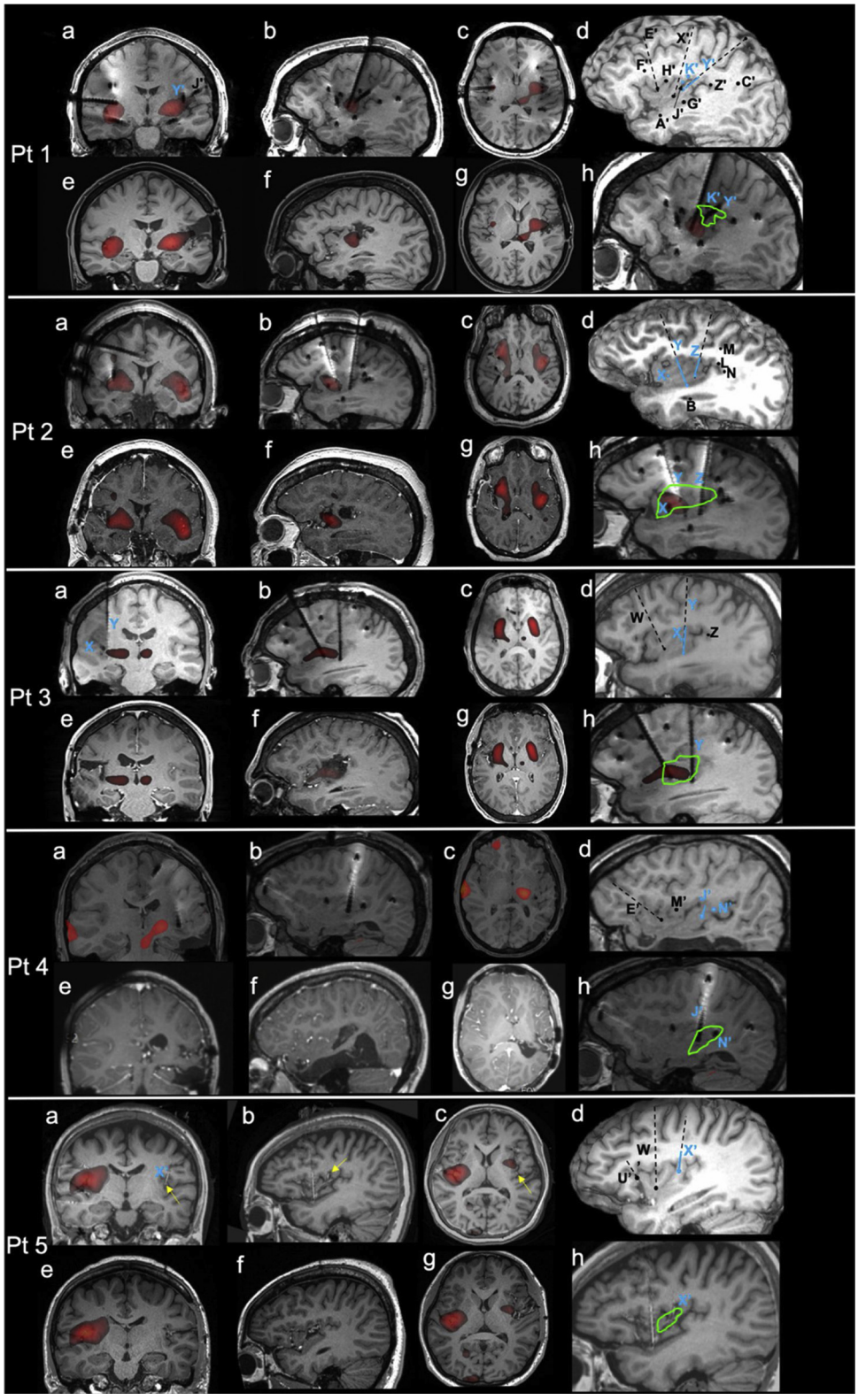

Fig. 1. a–c: Post SEEG implantation MRI overlay with SISCOM SPECT (red blob) showing an hyperperfusion > 1.5 SD. d: All SEEG electrode trajectories into the insula. Each electrode is labelled accordingly. Electrodes showing ictal onset are colored blue. e-g: Post-resection MRI overlay with SISCOM SPECT (red blob). h: Green represented resection margin. Pt 5 had CT brain after SEEG instead of MRI. Post implantation CT are overlaid onto preop MRI to demonstrate electrode positions (yellow arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

connectivity to the contralateral insula [19], as well as, frontal and temporal networks proceeds an order of magnitude more rapid than this [20,21]. This finding was confirmed in our cases with bilateral insula implantation, which demonstrated ictal engagement of the contralateral insula in less than 1 s. It was therefore not surprising the SISCOM in this context demonstrated bilateral or even predominantly contralateral hyper-perfusion. This was exemplified by our patients having injections during the aura before evolution into a seizure, where

Table 2
Previous reports of ictal SPECT in ILE. The examinations are always ictal SPECTs, unless specified. Cases were selected when the ictal onset was limited to the insula.

	Semiology	Ictal SPECT	SEEG
Ryvlin et al. [11]	SS/psychic aura to hypermotor Sz	Lt frontostriatal	Lt anterior insula/frontal operculum
Nguyen et al. [3]	SS aura to simple motor Sz	Lt frontoparietal, insula and cingulate (SISCOM)	Lt insula (Grids)
Nguyen et al. [3]	SS aura to hypermotor Sz	Multiple, non-localising (SISCOM)	Lt insula (depth electrodes)
Dobesberger et al. [12]	Abdominal aura to hypermotor Sz	Rt anterior insula, frontal operculum and thalamus	Rt anterior insula
Heers et al. [15]	Burning paraesthesia of palate and face to bilateral tonic to hypermotor Sz	Lt frontoopercular and parietal (SISCOM)	Lt insula (depth electrodes)
Kakisaka et al. [16]	Lt arm SS aura to BATS	Rt insula – Lt lateral frontal	Rt insula
Desai et al. [14]	Dysgeusia to automatisms	Lt insula	Lt insula
Xiao et al. [17]	Rt hemibody SS aura to Rt tonic Sz	Multifocal including Lt insula	Lt posterior insula
Xiao et al. [17]	Rt face SS aura to hypermotor Sz	Multifocal	Lt opercular, temporo-parietal-insula
Mohamed et al. [5]	Auditory aura to complex motor Sz	Lt F3, temporal pole, anterior insula	Lt anterior insula → F3, F2
Mohamed et al. [5]	Dysgeusia, drooling, LUE SS aura	No activation	Rt anterior insula → posterior insula
Mohamed et al. [5]	Dyscognitive Sz to bilateral tonic clonic Sz	Lt frontotemporal	Lt anterior insula → temporal orbitofrontal
Mohamed et al. [5]	Face SS aura to complex motor Sz	Multifocal	Lt posterior insula → parietal, operculum, F3
Mohamed et al. [5]	Rt SS aura to hypermotor Sz	Multifocal – bilateral insulae	Lt posterior insula – anterior insula → frontal
Malak et al. [13]	Rt painful paraesthesia aura	Lt posterior insula, Lt cingulate	Lt posterior insula

SS = somatosensory, Sz = seizure Rt = right, Lt = left, BATS = bilateral asymmetric tonic seizure, LUE= Left Upper Extremity, SISCOM= Subtraction of Ictal SPECT Coregistered to MRI"→" represents early spread on SEEG.

bilateral insula hyperperfusion was already evident. Furthermore, we also analyzed the data using the common SISCOM threshold of 2 and 2.5 standard deviation and found significant hyperperfusion only in contralateral insula. It is known that SISCOM foci with lesser ictal hyperperfusion can provide some clues of the "actual" ictal onset [7,22], and this was observed in our series. SISCOM threshold lesser than 1.5 standard deviation produced widespread and larger hyperperfused regions that is difficult to interpret.

Arguably, among the non-invasive investigations, the one with a great capacity for being able to identify the epileptogenic network has been ictal SPECT/SISCOM [23]. In a study comparing hyperperfusion sites on SISCOM with SEEG connectivity analysis, Tousseyn et al. [24] found a strong correlation between ictal onset zone and hyperperfusion, and how this correlation decreases as connectivity to ictal onset zone is less strong. This evidence suggests that in certain types of epilepsy, probably those originating in areas with widespread connectivity as ILE, the SISCOM must be interpreted as an hyperperfused network.

According to our data, the network beneath ILE may have certain hyperperfusion patterns. In our series, three patients were injected at the time of developing bilateral tonic semiology. These patients showed hyper-perfusion of either bilateral insula with bilateral basal ganglia or even ipsilateral basal ganglia with contralateral temporal neocortex. Wong et al. [25] demonstrated that ictal SPECT injection had different patterns of perfusion depending on the clinical semiology at the time of injection. In cases with bilateral asymmetric tonic components, the sites of hyper-perfusion were the ipsilateral supplementary sensorimotor area (SSMA), bilateral basal ganglia and contralateral cerebellar hemisphere, finding also reported in the literature, and mostly related to frontal lobe epilepsy [26,27]. Despite sharing the semiology, none of our patients demonstrated ictal hyper-perfusion of the SSMA, which was previously a reliable finding of the bilateral tonic seizure type. Thus, this interpretation of the SISCOM in ILE may provide valuable, but indirect, information the seizure is arising from the insula rather than the frontal lobe. Apart from the insula, the other region commonly demonstrated to show hyperperfusion was the basal ganglia and this was also noted in case series from the literature [11,12]. The anatomical connectivity of the insula to the BG has been well described in both animals and humans [28–30]. This, at least theoretically, provides means for early and more frequent involvement of the BG as opposed to seizures originating from more distant generators, however our study was not designed to answer such a question. SPECT hyperperfusion of the BG is by no means specific for insula lobe epilepsy, however early ictal or bilateral BG hyperperfusion may provide an additional clue to suggest the insula is part of the epileptic network [25,31].

These results beg the question as to the role of SISCOM in the context of ILE. ILE is a great mimicker of other types of epilepsy [32]. It is proposed that SISCOM interpretation in this context moves away from the classical approach. Classical utilisation and interpretation of ictal SPECT and SISCOM has been to highlight the seizure onset zone [33], especially in the case of temporal lobe epilepsy [34]. However, the SPECT in ILE cannot be reliably utilised in this fashion, primarily as the test lacks the required temporal and spatial resolution, as highlighted in our cases and the review of the literature. Therefore, the main role of non-invasive investigation arguably becomes providing some measurable support for progressing to intracranial assessment and to refine implantation strategies by identifying the epileptogenic network to be interrogated. Seeing the often bilateral network arising from our investigations, one of our proposals would be to foresee a bilateral implantation of the insular lobe, whenever SISCOM and semiology points to that lobe being the origin of the seizures.

This study has some concessions. The main one being the study was retrospective and only five patients from our centre were identified. However, SPECT is still a useful tool in many surgical centres, and the patterns of ictal SPECT hyper-perfusion were in keeping with those reviewed from the literature. Furthermore, no previous reports have defined the ictal injection times. All patients had SISCOM performed using paired ictal-interictal HMPAO SPECT except for one patient who had SISCOM performed on paired ictal-interictal ECD SPECT. To date, it remained unclear whether HMPAO or ECD was a better isotope for peri-ictal SPECT in extratemporal epilepsy [22,35,36]. Previous quantitative SPECT analysis showed no difference in the relative ictal increase in uptake between subtracted images of ECD or HMPAO SPECT studies [35].

As a result of the sample size being small there were several confounders. All five of the patients included in our study had a seizure onset zone in the posterior insula. The connectivity of the posterior insula differs from the anterior and it is not definitive from the current study that the results can be generalised to all regions of the insula. However, the patients from our centre did demonstrate the reported phenomena that seizures arising in the posterior insula rapidly engaged the three short anterior gyri, which then could have presumably recruited similar networks. Furthermore, only two patients had bilateral

SEEG implantations. Given the rapid spread between insulae an argument may be made that with unilateral implantations the seizure onset zone could be easily missed. This statement is true in general, but in our study the largest argument against this was the post resection outcome, where all five patients achieved an Engel 1 outcome. The surgical resections did include portions of the regional hyperaemia in each of the patients except Patient 4. The hyperaemia maps the seizure propagation and the resections were based upon the SEEG with regard to seizure onset, immediate propagation and stimulation evoked seizures. We would not expect to resect all the regions of hyperaemia.

Our patients had different pathologies, and this may have implications on the SISCOM pattern [22]. Specific pathologies are associated with different patterns of seizure onset and propagation [37]. In the limited published literature; SPECT ictal perfusion have differed when compared to pathology [38]. We do not have sufficient numbers of patients to quantify the relation between pathology and perfusion patterns. FCD 2b did not appear to have a more restricted or better-defined SPECT pattern of hyperaemia. Furthermore, one of our patients had TSC; where there has been some literature suggesting the connectivity of these patients is abnormal [39]. This discussion was outside the scope of the current study; however, the main finding still applies here where despite a 3 s injection, the SPECT did not localise to the insula.

5. Conclusion

Despite an increasing number of published cases, insular lobe epilepsy remains a challenge to localise with non-invasive assessment. The highly recognisable seizure semiology has often been the only clue to its existence and invasive EEG has been critical in determining surgical solutions. This study highlights the technical limitations of SPECT when attempting to assess seizures arising from the insula and confirms the overall finding from the literature; that ictal SPECT can help localisation, but may be falsely lateralising. Our work suggests ictal SPECT may have a role in determining the ictal network and its identification. The connectivity of the insula is complex and the authors encourage other groups to report on the patterns of hyper-perfusion in insula lobe epilepsy. This collective information would play a critical role in furthering our understanding of the functional connectivity of the insula and refining SEEG implantation strategies.

Disclosures

We confirm we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Neither of the authors has any conflict of interest to disclose.

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