## Introduction

The insula, also referred to as the Island of Reil, is a cortical structure located deep in the lateral sulcus covered by temporal, parietal and frontal operculae.[1]

Seizure onset in the insular / opercular (I/O) cortex may easily be missed due to heterogeneous seizure manifestations reflecting the wide range of cortical functions in this area [2,3] and high connectivity with adjacent lobes facilitating rapid propagation of ictal epileptiform activity.[4] Thus, seizures originating in or spreading to the I/O display characteristics that overlap or mimic those originating in other lobes.[5] Failure to recognise involvement of the insula in temporal lobe epilepsy (TLE) is a major predictor for poor outcome after surgery.[6,7,8] Confusion of the role of these two structures was already proposed by Penfield in the early 1950's who noted the similarity of symptoms between spontaneous TLE and insula stimulation.[9,10]
Complementary I/O resection in temporal epilepsy surgery was initially abandoned because of the high morbidity and mortality rates due to the deep location of the insula and its close proximity to highly eloquent brain structures and blood vessels.[12] With advances in the understanding of physiological relationships, vascular anatomy, neuroimaging and surgical techniques, I/O surgery has become safer with encouraging postsurgical outcomes [13,14] after tailored I/O resection (seizure freedom in up to 69-83%).[14,1516–1819] This growing recognition of positive outcomes in I/O surgery has resulted in greater interest in effective approaches to the diagnosis of I/O epilepsy.

It is important to recognize I/O epilepsy early in children with pharmacoresistant focal epilepsy, as epilepsy surgery may not only lead to seizure control but may also have a positive impact on neurodevelopmental outcome.[20] However, typical I/O epilepsy manifestations, described in

adult surgical patients, are often subjective and difficult to identify in children who are often unable to report them.[2,20–22]

Non-invasive diagnostics often provide insufficient evidence for reliable I/O seizure localization.[7,23] Interictal epileptiform discharges on Scalp Electroencephalogram (EEG) are not always present and when seen, they often only allow lateralisation rather than localising information. [22,24–28] Findings on structural Magnetic Resonance Imaging (MRI) vary among studies [16,18,24,27,29–31] and are normal or non-specific in up to 72% of the patients.[18] There is currently insufficient evidence to comment on the utility of functional imaging techniques such as positron emission tomography (PET), magneto encephalography (MEG) and single-photon emission computed tomography (SPECT) in paediatric patients with I/O epilepsy.[5]

Stereo-EEG (sEEG), shown to be reliable and safe in children,[17,20] is increasingly applied to delineate the seizure onset zone especially in cases without a clear lesion in MRI.[5] However, there is limited information in the literature regarding I/O epilepsy in paediatric patients and the yield of sEEG implantations in this particular cortical area. Such information is vital since insufficient implantation of I/O may miss the seizure onset zone (SOZ) but unnecessary coverage might lead to needless complications and costs.

The aim of this study was to explore involvement of the I/O region in our paediatric sEEG cohort and to address the following questions: 1) How often is the I/O region involved in seizure onset or propagation? 2) Do semiology and non-invasive diagnostics reliably predict I/O epilepsy? 3) How high are complication rates of sEEG implantation and what are outcomes and complication rates of subsequent resective surgery within the I/O region?

**Methods**

We conducted a single-centre cohort study by including all consecutive paediatric patients with refractory focal epilepsy between November 2014 and January 2018 who underwent sEEG implantation (n = 53). We included those who had at least three contacts within the I/O region and an identified SOZ by sEEG.

We analysed the contacts within the I/O region during sEEG recordings and assessed whether these were involved in seizure onset or propagation excluding those with propagation to I/O contacts only at the time of evolution with bilateral convulsive manifestations. Based on these sEEG results we categorised our patients into three groups:

Group 1: The majority of recorded seizures originated within the I/O: 'I/O onset'
Group 2: Patients with onset extra I/O but with clear propagation to the I/O: 'I/O propagation'
Group 3: Patients with seizures not involving the I/O region: 'no I/O involvement'

For group 1 (I/O onset) a subgroup analysis was performed analysing differences between the anterior and posterior insula including adjacent operculae.

Findings of video-EEG telemetry (v-EEG), MRI and (where available) adjunctive investigations such as PET and MEG were used as part of the pre-surgical work-up. Their diagnostic value was assessed by relating their localisation with the SOZ identified with sEEG on a sub-lobar level. Electrophysiological patterns from telemetry were only used to assess lateralization, acknowledging that scalp EEG may be blind to deep sources and is therefore often of limited use in localising insula seizure onset.

As part of the standard practice at GOSH, PET analysis was conducted with visual analysis of co-registered PET and MRI complemented by statistical parametric mapping (SPM-8) based on voxel-wise statistics to identify areas of significant hypo-/hypermetabolism using a paediatric pseudocontrol group.[32] Areas of significant hypometabolism were compared with SOZ defined by sEEG on a sub-lobar level.

Children were referred to Aston University Birmingham or the Free University of Brussels for MEG investigations. MEG contained a 306-channel whole-head ElektraTriux MEG system. Source analysis was performed using Signal Aperture Magnetometry (SAM-g2) and single equivalent dipole model of interictal epileptiform discharges. The localisations of single spikes were used and the cluster of the most frequent source was considered. Results were co-registered with the T1 of the patient's MRI. Results were compared with SOZ defined by sEEG on a sub-lobar level.

During our multidisciplinary epilepsy surgery meeting (including paediatric neurologists, neurosurgeons, neuroradiologists and clinical neurophysiologists) the primary hypothesis of the location of the epileptogenic zone (EZ) was documented based on semiology and non-invasive diagnostics. We compared this 'pre-sEEG' hypothesis with results from sEEG to assess I/O recognition in our practice.

For analysis of seizure semiology we conducted a seizure-based analysis: seizures from patients with several seizure types were categorised - in analogy to the classification of patients- into three different groups defined by SEEG: onset in I/O (group 1), propagation to I/O (group 2), no I/O involvement (group 3). Seizure semiology of each seizure type was categorised according to 27 features, including symptoms described in adult literature specific for I/O seizures (table 3). For each seizure the first three subsequent semiological features were included.

We recorded complications of the sEEG depth electrode implantations and for patients with subsequent surgery details of resection, thermocoagulation when performed and postoperative outcome using the Engel classification[33]. Post-operative neurological deficit was defined as new neurological deficit lasting at least 48 hours after surgery, permanent if patient failed to return to baseline within 6 months.

All sEEG electrode implantations were robot-assisted (Renishaw Neuromate) and involved both lateral orthogonal and combined anterior and posterior parasagittal oblique approaches. Post-operative CT was conducted in all patients to exclude post-implant haemorrhages and confirm electrode location.

The data were analysed using IBM SPSS Statistics version 24. Descriptive statistics were used for all variables and frequencies for categorical variables. Significance between categorical groups was calculated using the Freeman-Halton extension of the Fisher exact probability test and significance between mean ranks was calculated with the Mann-Whitney U test.[34] The results were corrected for multiple comparisons using the Bonferroni correction.[35]

**Results**

Between November 2014 and January 2018, a total of 53 paediatric patients with medically refractory epilepsy underwent sEEG electrode implantation (figure 1), of whom 52 underwent sEEG recording (1 patient had a subdural haemorrhage necessitating removal of electrodes prior to ictal recording (n = 1)). A further 23 were excluded from further analysis for the following reasons: less than three contacts within the I/O region implanted (n = 11) or SOZ not identified on sEEG (n = 12).

Of 53 patients with SEEG implantation I/O involvement (onset or spread) was noted in 64% (34 patients: 12 of group 1, 11 of group 2 and 11 patients with undefined SOZ).

The cohort of 29 patients undergoing further analysis comprised 13 males (45%) and 16 females (55%). Age range was 1 - 20 years (mean = 10.6 years) with 28 (90%) children under the age of 18 at time of implantation. In twenty-three (79%) of the patients I/O was involved in seizure onset or propagation and were categorised as group 1 or 2 (table 1). In group 1 (n=12) SEEG identified the SOZ in the anterior insula region in 4 patients (33%) and the posterior insula in 8 (67%) patients (supplementary table). SEEG identified SOZ in group 2 and 3 from the temporal (15% and 33% respectively), parietal (15% and 0%), frontal (39% and 33%) or adjacent lobes (e.g. temporo-parietal, 31% and 33%).

Three patients in group 1 (SOZ in I/O) also showed a second seizure type with extra I/O onset and early propagation to I/O (type 2 seizures). These were atypical seizures during a seizure cluster following anti-epileptic medication withdrawal in one patient, who became seizure free after stereotactic laser ablation in posterior insula. Two other patients had extensive lesions with one seizure type arising from the I/O, however also a different seizure type with onset outside the I/O and early spread to I/O was seen. One patient underwent surgery with poor postoperative outcome (Engel 4), the other patient did not wish to proceed to surgery due the risk of a motor deficit. Two patients in group 2 presented also with a second seizure type without I/O involvement (type 3 seizures). Group 3 patients solely presented with seizures with 'no I/O involvement'.

***Comparison between non-invasive diagnostics, semiology and SEEG results***

V-EEG and MRI was conducted in all patients (table 2). **V-EEG** correctly lateralized in all patients in group 1, 91% in group 2 and 83% in group 3. No clear difference was seen in scalp EEG patterns (interictal or ictal) between patients with SOZ in the anterior and or posterior insula. EEG changes were most commonly found over the central region (interictal: 75%, ictal 83%) although often involving a wider field (supplementary table).

The SOZ on sEEG was concordant with MRI lesions in 50% of patients in group 1, 45% in group 2 and 50% in group 3. There were fewer children with non-lesional MRI in group 1 and 2 compared with group 3 (17% and 27% vs. 50% respectively). In group 1 and 2 subtle MRI findings were described, which subsequently proved to be discordant with sEEG findings (i.e. false positive) in 33% (group 1) and 27% (group 2) vs 0% group 3.

**PET** was performed in 22 patients (76%). PET changes were concordant with the SOZ defined by SEEG in 50% of group 1, 44% of group 2, and 20% of group3 3. From group 1 (I/O onset) significant PET hypometabolism was found within the I/O in 4 patients (50%). In 4 patients with I/O onset in whom PET was considered non concordant, PET hypometabolism was found in areas of secondary spread in 3 patients (38%) and was non-concordant with onset or spread in one patient (13%). Patients with spread to the I/O region (group 2) or without I/O involvement (group 3) did not show I/O PET abnormalities.

**MEG** was performed in 9 patients (31%) with concordant findings to sEEG in 2 out of 5 in group 1, in 2 out of 3 patients in group 2 and in the only patient who underwent MEG in group 3. One group 2 patient (I/O spread) presented with a cluster of sources within the right insular region and was therefore false-positive.

***SEEG outcome and primary hypothesis***

SOZ in I/O was the primary hypothesis for 15 of 29 patients (52%) and this was confirmed by sEEG in 9/15 cases (60%, figure 2). Despite the fact that the I/O region was not the primary hypothesis in 14 patients (48%), sEEG recordings subsequently found onset within this region in 3/14 cases (21%).

Tonic (67% vs 25%, p = 0.019) and hypermotor (33% vs 0%, p = 0.023) features were more common with insula involvement (group 1 and 2 vs. group 3, table 3). Automatisms (50% vs 6%, p = 0.002) and emotional (42% vs 9%, p = 0.022) features were more common in seizures with no insula involvement (group 3 vs. group 1 and 2). When excluding group 3 from the analysis the only feature differentiating group 1 from group 2 were hypermotor features (57 vs 16%, p = 0,036). None of these observations reached statistical significance when correcting for multiple comparisons with Bonferroni corrections (all p values = > 0.05). Insula associated symptoms (marked with asterisk in table) described in the adult literature were present in 50% of our I/O onset cohort (group 1), 53% of our I/O secondary propagation cohort (group 2) and 36% of our I/O not involved cohort (group 3, p = 0.491).

***Invasive: depth electrode implantations***

Table 4 summarizes the details of implantation and surgery. A total of 346 (median 11 per patient) electrodes were implanted. The electrodes had 8-18 recording contacts per electrode. Patients in group 1 had more contacts in the I/O region than patients in group 2 or 3 (median 25 vs. 11 contacts vs. 6 respectively, p = 0.069). All patients from group 1 had one or two oblique electrodes implanted compared to only 36% of group 2 and 50% in group 3. Significantly more contacts within the I/O region were seen in group 1 compared to patients with unidentified SOZ (median 25 vs. 12 contacts respectively, p = 0.046). Overall similar numbers of contacts were found in the anterior versus posterior I/O region for the three groups and statistical comparison (Wilcoxon Signed-rank test) between anterior and posterior I/O

contacts did not reach significance (group1: 11 anterior, 14 posterior, p=0.054, group 2: 7 anterior 6 posterior, p=0.823 group 3: 2 anterior, 5 posterior, p=0.293).

There were two sEEG complications; a subdural haemorrhage for which electrodes were removed, resulting in no sEEG recording and a small subdural haematoma on electrode removal following radio frequency thermocoagulation resulting in a mild left hemiparesis, which completely resolved within one month.

***Surgery***

Resection, thermocoagulation or no treatment was offered depending on results of sEEG (table 4). No surgical treatment was offered in one (8%) group 1 patient due to low expectation of achieved seizure freedom with an extensive area including eloquent cortex involved in the SOZ. Two patients (in group 2) were offered surgery but the families declined due to spontaneous reduction in seizure frequency or concern around surgical risk.

**Radio frequency Thermocoagulation (RFTC)** was performed in 3 (25%) patients in group 1 (one anterior and two posterior insula) and none in group 2 or group 3. Of these, both patients in group 1 with posterior insula onset remain seizure free (Engel 1). One of these patients had seizure recurrence just after one year post thermocoagulation, subsequently underwent laser interstitial thermal therapy to the posterior insula and has remained seizure free since (currently 10 months). The third patient from group 1 (with anterior insula onset) showed no appreciable change after thermocoagulation (Engel 4). No complications or new neurological deficit occurred after thermocoagulation in these patients.

**Resection** (23 patients) was performed in 67% patients of group 1, 82% patients of group 2 and all patients of group 3. In the whole group, initial post-operative neurological deficit was

observed in 15 patients (65%) after resection. Deficit type included motor weakness (87%), speech disturbances (13%) and visual field deficit (13%). Resection in group 2 and 3 included the temporal (47%), parietal (14%) or frontal (47%) lobes. One group 2 patient had part of the insula resected due to rapid insular spread from the basal-frontal region.

Insula resections (n = 8, 35%) were conducted through a trans-frontal (38%), -parietal (25%) or combined -parietotemporal/frontotemporal (38%) approach and included opercular cortex resection from the adjacent frontal, parietal or temporal lobe in all cases. There was one post-surgical intracerebral infection after resection of the left insula and frontal operculum (group 1). Six out of the 8 patients undergoing partial insulectomies (anterior and posterior insula seizure onset 50% respectively 50%) experienced initial neurological deficit. Deficit type was motor weakness in all with additional speech disturbance in one. The neurological deficits were transient (completely resolved between 48 hrs and 6 months post operatively) in all but one patient (83%). One patient (17%) had initial left sided hemiparesis which almost completely resolved but continued to have some fine finger incoordination at last follow up. All patients underwent post-operative MRI and no areas of white matter infarction were identified.

**Histological results** were obtained from resection specimens and are summarised in table 4. Focal cortical dysplasia (all type 2) was present in 44% of all resections. FCD was more often present in the I/O involved than the I/O not involved group but this did not reach significance (53 vs 17%, p = 0.179). Nature of histology was not correlated with seizure freedom after surgery.

The median time of **follow-up** was 17 months (interquartile range 12.5-21.5), which was similar among groups. Resection in group 1 led to seizure freedom (Engel 1) in 63% with an additional 26% achieving seizure reduction, comparable to group 2 with seizure freedom in 56% and an additional 11% achieving seizure reduction. In group 3 resections led to seizure freedom in 67% and seizure reduction in an additional 34%. Within group 1, patients undergoing resection

of the posterior part of the insula seemed to have better results (Engel 1 and 2: 100%) than those undergoing resection of the anterior part of the insula (Engel 1 and 2: 33%). This however did not reach significance (p = 0.107).

## Discussion

Our series demonstrates that the I/O region is commonly involved in seizure onset or propagation in children with pharmacoresistant focal epilepsy undergoing sEEG. In those included in our study, 81% of the patients show onset or propagation to the I/O region. Even when taking all implantations into account at least 64% (34 out of 53 patients) were found to have I/O involvement. This percentage is possibly even higher, as I/O involvement cannot be excluded in those patients without sufficient I/O exploration.

### *Comparison between non-invasive diagnostics and SEEG results*

Presence of semiological features and other non-invasive investigations **suggesting** seizure onset in the I/O region were subsequently only confirmed in approximately half of the cases by the sEEG (figure 2). Moreover I/O region **not** being involved in the hypothesis based on semiology and non-invasive tests was refuted by sEEG showing I/O onset in 21%. Our pre-surgical non-invasive investigation could therefore not reliably distinguish between seizure onset in I/O and propagation to I/O. These numbers confirm the importance of sEEG exploration in paediatric patients with difficult to localize epilepsy, especially when

involvement of the I/O region is suspected. Comparable studies are limited: Dylgjeri and colleagues presented data from 10 patients with I/O epilepsy explored by sEEG and mention that further 73 patients underwent I/O implantation but did not show SOZ from the I/O region.[17] However, the study does not mention in how many of these patients spread to I/O was noted. Tomycz and colleagues reported I/O implantation in 49 paediatric patients and found I/O onset in 65%, again it remains unclear in how many of the cases without I/O onset, I/O spread was seen.[3217,20,36] The difficulty in distinguishing between I/O onset and propagation can be explained by the high connectivity to adjacent lobes of the insular cortex. The orbitofrontal and inferior frontal regions show strong connectivity with the anterior portion of the insula and the Rolandic cortex with the transitional (between the anterior and posterior portion) insular area.[4] Extensive connections with the rostro-caudal part of the insula have been described with the cingulate, parahippocampal, supramarginal and angular gyri and the precuneus and occipital regions.[37] Therefore seizure onset in any of these structures can easily propagate from and towards the I/O region. This high connectivity plays a pivotal role in the semiology that is observed during a seizure resulting in difficulty distinguishing insula onset seizures from seizures in adjacent or connected regions on semiology and ictal EEG data alone.

Hypermotor manifestations such as repetitive bipedal movements or rocking and tonic posturing were commonly seen in our I/O onset group. These features are explained by rapid frontal involvement through strong connections between the antero superior portion of the insula and the mesial frontal and cingulate regions. [4,17,20,2638] Our findings show that these semiologies in children, typically suggestive of seizure onset in the frontal lobe, should also raise the possibility of seizure onset within the I/O area. [39] Viscerosensory semiology, such as thoracic heaviness and abdominal sensations, peri-oral paresthesia, heart rate changes and pain are highly suggestive of I/O epilepsy in adult series. [40,4120,2242,43] These symptoms occurred in

50% of our I/O involved cohort and notably were not more common compared with the no I/O involvement group (36%), in line with other paediatric studies (i.e. 29-31%). [17,20] These manifestations are subjective which may be challenging in children, many of whom do not have the language skills to describe their symptoms.

Cortico-cortical evoked potentials show that the right and left insula are closely connected. Therefore, insular seizures may propagate very quickly to the contralateral insula.[408] Despite this, lateralisation of v-EEG findings were confirmed by SEEG findings in all our patients with I/O onset. This might have implications for sEEG planning in this patient group suggesting that routine bilateral I/O implantation may not be required in children even in cases without clear MRI lesion. However this conclusion is limited by the lack of bilateral I/O implantation, in particular in the group of patients who did not become seizure free. Larger case studies with bilateral implantations are needed to answer this question.

Because of the insula cortices deep location in the Sylvian fissure the EEG may be of limited value for localisation in insula epilepsies. [44] [45] [46] While EEG findings in insula epilepsy are non-specific, they may show distinct topographical spike patterns in the adjoining superficial cortex: mainly frontopolar and frontotemporal patterns from the anterior insula and temporal or central lead patterns from the posterior site of the insula.[23] In our study however, such a topographical difference between scalp EEG changes arising from the anterior versus posterior insula described in adult patients was not apparent with most common discharges or slowing over the central region (interictal: 75%, ictal 83%). A possibly explanation might be that children may show broader propagation patterns.

**MRI:** Variable results have been published on the proportion of insula epilepsy cases without MRI detectable lesion (lesion negative MRI in 8 to 72%).[4016–18,20,47] In paediatric patients, the proportion of MRI lesion negative insula epilepsy cases are more consistent (20-30%)[17,20] and are in agreement with our findings (17%). Subtle MRI findings which proved to be discordant

with sEEG findings were found in 33% of the patients. This highlights difficulties in detecting I/O abnormalities and may be explained by insular/subinsular bright spots commonly seen in both healthy participants and refractory noninsular epileptic patients.[31]

**PET** showed focal localized hypometabolism in patients with I/O onset in 50% of the patients which is in line with other paediatric and adult insula studies showing sEEG concordant PET abnormalities in 40-53%.[5,17,20]. Patients with spread to the I/O region (group 2) or without I/O involvement (group 3) did not show I/O PET abnormalities. The results in our small sample size suggest that although the sensitivity for I/O hypometabolism in patients with I/O is only 50%, the specificity is high (100%). **MEG** in adult case series of insula epilepsy showed promising results with concordant tight clusters in 64% and additional diffuse perisylvian spikes in 29%.[48] Concordant interictal dipoles were seen in 50% of our paediatric patients with I/O onset or spread undergoing MEG. MEG clusters within the I/O were also observed in patients with onset from the amygdala and hippocampus (group 2). Our results on PET and MEG are limited by the sample size and therefore we cannot make firm conclusion on the diagnostic performance. Moreover, comparisons of diagnostic value of PET or MEG cannot be made in our study since these additional tests were only conducted in more complex cases leading to potential bias.

***Sampling of the insula***

The posterior part of the insula was more often involved in our IO onset group, which is in line with literature. [17,20,23] No significant differences between numbers of contacts within the anterior versus the posterior insula suggest that more common involvement of the posterior

insula cannot be attributed to different sampling of these regions. More comprehensive sampling in the anterior and posterior region was conducted in the I/O onset group compared to the unidentified SOZ (11/12 with I/O spread) group. Hence, we cannot exclude that we might have missed IO onset due to under sampling of this region. Moreover, the I/O region was more extensively sampled in the I/O onset group (both anterior and posterior insula) compared to the I/O propagation group (I/O contacts 25 vs 11, p = 0.069). This might raise the possibility that insula onset might have been missed by under sampling in patients who did not become seizure free after surgery.

***Depth electrode implantations and surgery***

We would advocate a robot assisted approach both orthogonal, through the frontoparietal and temporal operculum, and oblique, through the frontal and parietal cortices. This approach has been recommended by others and has led to low rates of complications despite comprehensive coverage of the I/O region.[40] Safety of sEEG implantation in the I/O region has been demonstrated in several other adult [3,15,49–52] and paediatric [17,20] studies reporting no sEEG related complications following electrode implantation or removal.

No isolated insulectomies were performed but were combined with resection of adjacent lobes and operculae. This is in keeping with previous literature in children demonstrating that pure I/O surgery is rare. [17,32] Partial insulectomies were included in one third of all our resections, led to seizure freedom or significant improvement (Engel 1 and 2) in up to 75% in agreement with other studies. [20] [17] Posterior insula surgery was equally safe to surgery in the anterior insula (50% of those with neurological deficit) and led to better outcomes compared to surgery of the anterior insula but this did not reach significance due to low sample numbers.

Insula surgery carries a risk of damage to perforating middle cerebral artery vessels supplying the internal capsule thus causing ischaemic deficits.[53] This fear for neurological complications has historically caused reluctance among neurosurgeons to operate in this region. Ischemic lesions after insula surgery in the corona radiata are reported in between 41 – 67% with rates of neurological deficit between 45 – 55%. [54,55] While we report a high rate of neurological deficit in our cohort (75%), the deficits were transient in all but one patient. This remaining patient had mild residual fine finger incoordination at 6 months post-operatively. As no ischemic lesions were seen in any of the postoperative MRI scans we hypothesize that our increased rates of transient neurological deficit compared to adult literature might be explained by the increased chance of oedema and postoperative swelling. We have used ultrasonic aspiration around the insula, suggested to be a risk factor for oedema due to thermal injury, which might have contributed to the oedema. [56] More recently in our series, we have routinely used continuous subcortical stimulation and would advocate this approach since it has been a useful adjunct to reduce rates of neurological deficit. [57] Transient neurological deficit may also relate to resection of eloquent overlying fronto-parietal operculae. In conclusion, the transient nature of the neurological deficits in this cohort and the fact that no children suffered dense hemiparesis confirms that insula surgery can be conducted safely in children. Nevertheless the incidence of transient neurological deficit is high. Patients and their families need to be counselled appropriately and post-operative physiotherapy is likely to be required.

***Limitations***

Our study has several limitations: our results should be replicated in larger cohorts from other centres to better distinguish patients with I/O onset and I/O spread. Insufficient sampling (including lack of bilateral implantations) of the I/O region cannot be excluded for patients who did not become seizure free after surgery and for patients in whom the SOZ was not identified.

The analysis of seizure semiology in our study was based on the first three symptoms observed but did not include a detailed analysis of timing between each manifestation and the ictal changes seen over involved sEEG contacts. Such analysis may help to distinguish better between I/O onset and propagation. Furthermore longer follow up data after surgery would be desirable to test the predictive value of sEEG in the I/O region.

## Conclusion

Insula and operculae regions are often involved in paediatric patients with difficult to localize refractory epilepsy yet it is difficult to distinguish between I/O onset and propagation on non-invasive investigation alone. Focal tonic seizures with hypermotor features, whilst not specific are often seen in children with I/O involvement. Viscerosensory or non-somatotopic signs are less specific in children compared to adult patients but non-specific semiology should not preclude I/O exploration if other non-invasive diagnostics are in keeping with I/O onset.

SEEG is a safe investigation in children, even with high numbers of electrodes in the I/O region. I/O surgery based on sEEG in selected paediatric patients is safe, and leads to high rates of seizure freedom but with high rates of transient neurological deficits.

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**Table 1 Baseline**

| Groups | Group 1<br>I/O SOZ | Group 2<br>I/O spread | Group 3<br>No I/O involvement |
|---|---|---|---|
| Number of patients | 12 | 11 | 6 |
| Age at implantation (years)[1] | 8.6 | 10.8 | 13.9 |
| Rate of female | 6 (50%) | 6 (55%) | 4 (67%) |
| Number of seizures | 17 | 19 | 10 |
| Seizure type 1 (I/O onset) | 14 | None | none |
| Seizure type 2 (I/O spread) | 3 | 16 | none |
| Seizure type 3 (no I/O involvement) | none | 2 | 10 |

|**Baseline table of all 29 included patients divided in three groups. Some patients presented with several seizure of different types.1. Mean age at sEEG implantation in years*|

**Table 2 Performance of non-invasive diagnostics***

| | I/O SOZ (n = 12) | I/O spread (n = 11) | No I/O involvement (n = 6) |
|---|---|---|---|
| EEG | | | |
| Lateralizing concordant | 12 (100%) | 10 (91%) | 5 (83%) |
| Lateralizing discordant | 0 (0%) | 1 (9%) | 1 (17%) |
| MRI | | | |
| True positive | 6 (50%) | 5 (45%) | 3 (50%) |
| False positive | 4 (33%) | 3 (27%) | 0 (0%) |
| Non-lesional | 2 (17%) | 3 (27%) | 3 (50%) |
| PET | | | |
| Performed | 8 | 9 | 5 |
| True positive | 4 (50%) | 4 (44%) | 1 (20%) |
| False positive | 4 (50%) | 4 (44%) | 4 (80%) |
| Negative | 0 (0%) | 1 (11%) | 0 (0%) |
| MEG | | | |
| Performed | 5 | 3 | 1 |
| True positive | 2 (40%) | 2 (67%) | 1 (100%) |
| False positive | 1 (20%) | 1 (33%) | 0 (0%) |
| Negative | 2 (40%) | 0 (0%) | 0 (0%) |

|**Diagnostic performance of non-invasive diagnostics.* |

**Table 3: semiology vs seizure type: a seizure based analysis.**

| Groups | I/O SOZ | | I/O spread | | No I/O involvement | |
|---|---|---|---|---|---|---|
| **Seizures** | 14 | | 19 | | 12 | |
| **Features** | | | | | | |
| Tonic | 11 | (79%) | 11 | (58%) | 3 | (25%) |
| Clonic | 1 | (7%) | 1 | (5%) | 2 | (17%) |
| Atonic | 0 | (0%) | 0 | (0%) | 0 | (0%) |
| Negative motor | 0 | (0%) | 2 | (11%) | 0 | (0%) |
| Hypermotor | 8 | (57%) | 3 | (16%) | 0 | (0%) |
| Complex motor | 1 | (7%) | 0 | (0%) | 0 | (0%) |
| Spasms | 0 | (0%) | 1 | (5%) | 0 | (0%) |
| Myoclonic | 1 | (7%) | 4 | (21%) | 1 | (8%) |
| Facial motor*[1] | 1 | (7%) | 5 | (26%) | 2 | (17%) |
| Chapeau | 2 | (14%) | 1 | (5%) | 0 | (0%) |
| Smile (behavioural) | 0 | (0%) | 1 | (5%) | 1 | (8%) |
| Manual automatisms | 0 | (0%) | 0 | (0%) | 3 | (25%) |
| Orofacial automatisms | 1 | (7%) | 2 | (11%) | 6 | (50%) |
| Vocalisation | 2 | (14%) | 3 | (16%) | 0 | (0%) |
| Viscerosensory*[2] | 4 | (29%) | 2 | (11%) | 0 | (0%) |
| Autonomic*[3] | 1 | (7%) | 2 | (11%) | 2 | (17%) |
| Somatotopic | 0 | (0%) | 1 | (5%) | 0 | (0%) |
| Non somatotopic*[4] | 1 | (7%) | 0 | (0%) | 0 | (0%) |
| Pain* | 1 | (7%) | 0 | (0%) | 0 | (0%) |
| Impaired awareness | 0 | (0%) | 0 | (0%) | 1 | (8%) |
| Auditory | 0 | (0%) | 0 | (0%) | 0 | (0%) |
| Gustatory* | 0 | (0%) | 0 | (0%) | 0 | (0%) |
| Emotional*[5] | 1 | (7%) | 2 | (11%) | 5 | (42%) |
| Impaired speech | 0 | (0%) | 1 | (5%) | 0 | (0%) |
| Behavioural arrest | 2 | (14%) | 7 | (37%) | 1 | (8%) |
| Gelastic* | 0 | (0%) | 0 | (0%) | 0 | (0%) |
| Reflex* | 0 | (0%) | 0 | (0%) | 0 | (0%) |

|*Up to three features per seizure were noted and therefore exceeds the number of seizures.* ***Key symptoms described in adult literature for insular derived epilepsy. Note that the majority of these key symptoms involve subjective features.|1. Facial grimace or other motoric features of the face. Not Chapeau de Gendarme or behavioural smile.| 2. Thoracic heaviness, chest/throat tightness, choking, suffocation, retching or abdominal sensations.| 3. Eructations, borborygms, gagging, vomiting, hypersalivation, heart rate changes, piloerection or flushing. |4. Large cutaneous areas, bilateral, perioral.|5. Psychic symptoms as anxiety, panic, fear or ecstatic feeling of well-being.|*

**Table 4 Invasive: implants and surgery**

| | I/O SOZ (n = 12) | I/O spread (n = 11) | No I/O involvement (n = 6) |
|---|---|---|---|
| ***Implantation*** | | | |
| Median electrodes in total (range) | 12 (8 – 17) | 13 (9 – 16) | 10 (8 – 11) |
| Median electrodes in I/O (range) | 5 (2 – 8) | 3 (1 – 6) | 2 (1 – 3) |
| Median contacts I/O (range) | 25 (7 – 41) | 11 (3 – 43) | 6 (3 – 13) |
| Median contacts I/O anterior (range) | 11 (2 – 19) | 7 (2 – 20) | 2 (0 – 5) |
| Median contacts I/O posterior (range) | 14 (2 – 26) | 6 (0 – 23) | 5 (0 – 13) |
| Complications due sEEG | 0 (0%) | 1 (5%) | 0 (0%) |
| | | | |
| ***Surgery*** | | | |
| Surgery offered | | | |
| Resection | 8 (67%) | 9 (82%) | 6 (100%) |
| Thermocoagulation | 3 (25%) | 0 (0%) | 0 (0%) |
| No surgery | 1 (8%) | 0 (0%) | 0 (0%) |
| Resection performed | 8 | 9[1] | 6 |
| Type of resection | | | |
| Insula + operculum | 3 (38%) | 0 (0%) | 0 (0%) |
| Insula + operculum + adjacent structures | 4 (50%) | 1 (11%) | 0 (0%) |
| Operculum + adjacent structures | 1 (13%) | 1 (11%) | 0 (0%) |
| Only adjacent structures | 0 (0%) | 7 (78%) | 6 (100%) |
| | | | |
| Surgical complications | 1 (13%) | 0 (0%) | 0 (0%) |
| Neurological deficit after surgery | 6 (75%) | 5 (56%) | 4 (67%) |
| Temporary[2] | 5 | 3 | 3 |
| Permanent | 1 | 2 | 1 |
| Histology | | | |
| Non-specific[3] | 3 (38%) | 5 (56%) | 3 (50%) |
| Focal cortical dysplasia | 5 (62%) | 4 (44%) | 1 (17%) |
| Hippocampal sclerosis | 0 (0%) | 0 (0%) | 1 (17%) |
| Tubers | 0 (0%) | 0 (0%) | 1 (17%) |
| Outcome | | | |
| Engel 1 | 5 (63%) | 5 (56%) | 4 (67%) |
| Engel 2 | 1 (13%) | 1 (11%) | 1 (17%) |
| Engel 3 | 1 (13%) | 0 (0%) | 1 (17%) |
| Engel 4 | 1 (13%) | 3 (33%) | 0 (0%) |

*[1] Resection offered but declined by parents [2] Neurological deficit lasting at least 48 hours but with recovery within 6 months [3] Non-specific included: gliosis, damage, non-diagnostic*

**PET**

| Group 1 | | | |
|---|---|---|---|
| **PID** | **Conclusion PET** | **Conclusion sEEG** | **Concordant: onset/spread zone** |
| 3497 | Bilateral hypometabolism R>L, decreased uptake inferiorly in the right frontal lobe, just anterior to the sylvian fissure. Also evident more superiorly within the right frontal lobe. | Primary seizure focus right frontal operculum/insula with some spread to posterior insula alter. | No, only spread |
| 3935 | Marked focal reduction in the left hemisphere close to the central sulcus and likely to be in the anterior parietal lobe on the left. | L insula with rapid propagation to frontal cortex anterior to resection | No, fully discordant. |
| 4468 | Left parietal from insular cortex to the superior temporal gyrus | Left: lesion/ PET hypometabolism to posterior operculum to posterior insula with subsequent spreading to the mid insula, motor hand and subsequently angular gyrus, mid insula and posterior parietal | Yes, either onset and spread |
| 4668 | Appearances in keeping with known post-surgical cavity and further foci of hypometabolism in the right frontal love | Right fast posterior cingulate gyrus and parietal operculum/ posterior insula -> rhythmic slow , at times also ant insula | No, only spread |
| 5018 | Decreased tracer uptake related to the left insular cortex which extends up into the anterior parietal region, in the post central gyrus with likely involvement of the adjacent pre-central gyrus and left superior temporal gyrus. | LEFT posterior part of the insula (localised to C1-4, J1-2 and F8-9 which all lie in close proximity to one another | Yes, onset and spread |
| 5063 | Most significant left insular and left parietal operculum. | Left: From S1 extending up to the insula. Very extensive | Yes, either onset and spread |
| 5493 | Reduced tracer uptake left temporal extending to the left insular cortex and also affecting the left caudate head. | Left: Insular cortex, left frontal operculum, spread to lateral temporal lobe (post>ant) and hippocampus. | Yes, either onset and spread |
| 5980 | Assymetric hypometabolism within the right temporal lobe. | Right: Parietal and temporal operculum, anterior long gyrus of insula involved. | No, only spread |

| Group 2 | | | |
|---|---|---|---|
| **PID** | **Conclusion PET** | **Conclusion sEEG** | **Concordant/ SOZ or also spread zone** |
| 3155 | No evidence of an epileptogenic focus identified. | Lesion left middle frontal gyrus (under Les-preMotor, motor face and cingulum) towards left inferior frontal gyrus | PET negative |
| 3457 | Prior to surgery: widespread left hemisphere interictal hypoperfusion | Left: Basal frontal lobe and frontal operculum | Yes, spread only |
| 3487 | Right hemispheric onset, most marked abnormality seen within the right frontal and temporal lobes. | SOZ right mesial temproal especially in parahippocampal gyrus, amygdala and hippocampus | Yes, spread and onset |
| 4075 | Not marked but supportive of left hemispheric onset frontal temporal region | Left parieto-occipital region with rapid involvement of the fusiform gyrus and the lateral cortex of the MTG. | No, spread only |
| 4092 | Right superior parietal lobe. | Superior parietal with contacts 9-11 being most often involved in onset, with spread to S1 area, parietal operculum and insula but none of these were clearly involved in seizure onset | Yes, onset and spread |
| 4580 | Subtle minor reduction in the mesial right temporal lobe | Right SMA/Cingulate + M1 | No, discordant |
| 8133 | Focal area of significantly reduced tracer uptake in the right frontal region anteriorly, moderately reduced tracer uptake in the right posterior frontal and parietal lobes in comparison to the left is also seen. | Right SMA, but left SMA could not be excluded. She had thermocoagulation of electrode 2 (SMA) ,3 (prSMA) and 4 (PMFG) which resulted in 2 months seizure free. After that some sz recurred and therefore a right frontal resection was offered. | Yes, onset and spread |
| 8344 | Significantly decrease uptake within the left temporal lobe extending into the left inferior parietal lobe. | left anterior hippocampus, post hippocampus and amygdala, most prominent is ant hippocampus | Yes, concordant onset and spread |
| 8468 | Hypometabolism of fcd and also more diffuse hypometabolism in the left temporal lobe. | Rightsided: SOZ diffuse - main involvement superior occipital and inferior occipital with spread to MTG, Post ITG, post STG and frontal operculum | No, discordant |

| Group 3 | | | |
|---|---|---|---|
| **PID** | **Conclusion PET** | **Conclusion sEEG** | **Concordant/ SOZ or also spread zone** |
| 3454 | Two probable areas of hypometabolism in the right hemisphere - one in the mid-posterior central region frontally, another more posteriorly in the same hemisphere | Right Around the right superior frontal gyrus | No, spread only |
| 7694 | Marked reduction uptake in pole and antero lateral aspect right temporal lobe. Also reduction uptake left lateral frontal and posterior fronto-parietal regions. | Right amygdala | No, spread only |
| 8056 | Reduction left lateral temporo-parietal region | Left: Anterior hippocampus onset. Rapid spread to posterior hippocampus, amygdala, superior temporal gyrus, temporooccipital. | No, spread only |
| 8206 | Reduced uptake mesial right temporal lobe and lateral aspect of right temporal lobe | R amygdala | No, spread only |
| 8532 | Inferior right frontal lobe, medial and anterolateral aspects of the right temporal lobe. | Right frontal cortex posterior to prior resection cavity and temporal lobe incl mesial structures | Yes, onset and spread |

**Commented [PK1]:** Due to spread defined as discordant now. 4/5 discordant in group 3.