Diagnostic and therapeutic approaches in refractory insular epilepsy

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Abstract
Due to heterogenous seizure semiology and poor contribution of scalp electroencephalography (EEG) signals, insular epilepsy requires use of the appropriate diagnostic tools for its diagnosis and characterization. The deep location of the insula also presents surgical challenges. The aim of this article is to review the current diagnostic and therapeutic tools and their contribution to the management of insular epilepsy. Magnetic resonance imaging (MRI), isotopic imaging, neurophysiological imaging, and genetic testing should be used and interpreted with caution. Isotopic imaging and scalp EEG have demonstrated a lower value in epilepsy from insular compared to temporal origin, which increases the interest of functional MRI and magnetoencephalography. Intracranial recording with stereoelectroencephalography (SEEG) is often required. The insular cortex, being highly connected and deeply located under highly functional areas, is difficult to reach, and its ablative surgery raises functional issues. Tailored resection based on SEEG or alternative curative treatments, such as radiofrequency thermocoagulation, laser interstitial thermal therapy, or stereotactic radiosurgery, have produced encouraging results. The management of insular epilepsy has benefited from major advances in the last years. Perspectives for diagnostic and therapeutic procedures will contribute to better management of this complex form of epilepsy.

KEYWORDS
epilepsy surgery, insula, neuroimaging, neurophysiology, refractory epilepsy
INTRODUCTION

The insula – also named Island of Reil – is located in the depths of three cerebral lobes. Its localization confers to this island some mystery. Neuroscientists embarking on an exploration of this deep region should equip themselves with the best instruments that modern medical imaging has brought.1 Because insular gyri are covered and highly connected with the frontal, parietal, and temporal lobes, epileptologists may be confused by its ictal semiology. Indeed, ictal manifestations of insular epilepsy often include clinical signs that classically characterize seizures originating from frontal, parietal, or temporal lobes, which are better known and mapped.2

To add to the complexity, the insula is not a single entity. It is anatomically divided into two parts by the central insular sulcus (Figure 1)3,4 and histologically into three parts.5 Moreover, the insula develops many brain connections with various brain structures and is both involved in simple (e.g., gustation) and more elaborate (e.g., pain, interoception) sensory functions, as well as in complex functions (e.g., emotions).6 This brain area is, therefore, a crossroad for highly functional connections between cortical structures.6 The high vascular density from middle cerebral artery and sylvian veins covering the insula imposes extreme caution in its surgical approach.6 Subtle variations in the ictal semiology depend on the parts of the insula that contain the epileptogenic zone (EZ),7 and direct electrical stimulation may help to better distinguish them.8 Insular epilepsy is rare but probably underestimated due to diagnostic difficulties.9

METHODOLOGY

The purpose of this review is certainly not to gather the entire literature covering insular epilepsy and its treatment into an exhaustive review. Our goal is to dig up novel information on the matter, and to provide a comprehensive view on the renewed approach to insular epilepsy that has recently emerged.

English-language articles related to human insular epilepsy were identified by a search in PubMed (1961–June 2022) using the following keywords: “insular epilepsy”, or the combination of “insula” and “epilepsy”. Due to the large number of articles and reviews published in the last years about the semiology of insular epilepsy and its electroclinical features, this review focuses only on diagnostic and therapeutic methods. The section entitled Summary of insular epilepsy provides a brief description of its epidemiology, semiology, and etiology to set the basis of the present review. The references in the selected papers were also included if relevant.

SUMMARY OF INSULAR EPILEPSY

3.1 Epidemiology

The exact prevalence and incidence are unknown due to underdiagnosis; still insular epilepsy remains probably rare.10

Key points

- Scalp electroencephalography (EEG) is less accurate for diagnosis of insular epilepsy than for other focal epilepsies.
- Functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and stereo-EEG (SEEG) should be more widely used to diagnose insular epilepsy.
- Insular resection is the gold standard for treatment of refractory insular epilepsy, although some alternatives are showing encouraging results.

In this article, we review the current and novel diagnostic tools, which have improved the investigation and diagnosis of insular epilepsy. We also review novel therapeutic strategies and tools implemented to ablate an insular EZ, leaving intact the precious adjacent cortices and tracts.
3.2 | Semiology

A great number of ictal symptoms and signs have been reported in insular epilepsy, including viscerosensory, somatosensory, olfactory, gustatory and auditory auras, autonomic disturbances, motor and hypermotor behaviors, tonic or clonic movements, language disorders, reflex or gelastic seizures, and ecstatic auras.12

Insular seizures may mimic temporal lobe seizures due to viscerosensory symptoms, parietal lobe seizures due to somatosensory symptoms, or frontal lobe seizures due to hypermotor behaviors.12 Nevertheless, the aura is generally described as suffocation, or painful or gustatory sensations.11 Awareness is commonly preserved.7 Brief operculo-insular symptoms can occur such as hypersalivation, clonic facial contractions, tachycardia, and strong laryngeal constriction (unpleasant sensation to strangulation).7 Somatosensory symptoms are generally unpleasant (e.g., electrical/warm sensation), focused on the intra/peri-oral area or distributed to large cutaneous areas, without the somatotopic jacksonian march, and not restricted to the contralateral hemibody (as for somatomotor symptoms).7 Painful seizures are suggestive of an insular involvement, especially if the pain is intense, spatially extended, and spreads without following the somatotopic distribution.13

Most of somatosensory functions and pain perception are restricted to the posterior insula, whereas visceral sensitivity and visceromotor functions are restricted to the anterior insula.8 Among this variety of symptoms, strong laryngeal constriction and unpleasant/painful/warm sensations with large or peri-oral territory as first symptoms of the seizure should suggest an insular onset.7

3.3 | Etiology

Most cases of insular epilepsy are magnetic resonance imaging (MRI) negative.11 Pathological examination of resected insular tissue reveals focal cortical dysplasia (FCD) in up to 68.5% of cases,14,15 and a variety of other lesions such as gangliogliomas, gliomas, cavernomas, or dysembryoplastic neuroepithelial tumors in both adults16 and children.17 The incidence of MRI-negative insular epilepsy is unknown.18

4 | DIAGNOSTIC METHODS IN INSULAR EPILEPSY

4.1 | Magnetic resonance imaging

4.1.1 | Structural MRI

Localization of the EZ requires a structural cerebral MRI following some specific protocols and an examination by an experienced radiologist in neuroimaging of epilepsy.19 The International League Against Epilepsy neuroimaging task force has set up a harmonized neuroimaging protocol of epilepsy structural sequences (HARNESS), generalizable regardless of the clinical setting and useful regardless of the presumed EZ localization.19 Structural MRI has an important place because identification of a lesion facilitates the diagnosis of insular epilepsy.11 As in other lobes, insular cortical malformations can be highlighted by structural MRI.18 Because a high proportion of FCD is reported by postoperative pathological examination,14,15 subtle signal changes suggestive of FCD should be searched for carefully.12 MRI studies have shown an insular and diffuse extra-insular atrophy in patients with operculo-insular epilepsy, including in adjacent opercula, orbitofrontal, mesiotemporal, lateral temporal cortices, and peri-rolandic region, without a clear diagnostic value.20 Reformatting of MRI slices in oblique reference planes may also help to highlight subtle insular lesions.21

To detect subtle lesions, such as FCD, additional sequences can be used (e.g., fluid and white matter suppression [FLAIR], edge-enhancing gradient echo [EDGE] imaging) as well as advanced image processing (e.g., voxel-based analysis using a morphometric analysis program on T1-derived contrasts, fluid-attenuated inversion recovery [FLAIR], and double inversion recovery images) and multimodality imaging.18 Increased MRI fields of view improve the lesion-detection rate. In particular, 7T MRI may help in the identification of FCD, even in the presence of nonlesional 3T MRI data.18 Although a FLAIR acquisition remains the best way to demonstrate FCD lesions, T2*-weighted gradient-echo images may show a black line within the gray matter as the hallmark of a type IIB FCD, the magnetization-prepared two rapid acquisition gradient-echo sequence (MP2RAGE) shows a better delineation of lesions due to a high contrast between white and gray matter, and susceptibility-weighted imaging (SWI) shows imaging signs associated with the angioarchitectural organization.

4.1.2 | Diffusion-Weighted MRI

Diffusion-weighted MRI helps to lateralize and to localize the EZ.22 A diffusion-weighted MRI study in extra-temporal lobe epilepsy (ETLE) demonstrated the usefulness of diffusion tensor imaging (DTI) to localize the EZ when coupled with positron emission tomography (PET) using 18Fluor-labeled fluorodeoxyglucose (18F-FDG-PET). Nevertheless, no significant results were detected in the single case of insular epilepsy.23 New diffusion sequences give more specific indicators of lesional changes; however, they have not been tested specifically in insular epilepsy.
4.1.3 | Magnetic resonance spectroscopy

There are currently no data supporting the usefulness of magnetic resonance spectroscopy in insular epilepsy, as N-acetyl-aspartate concentration correctly lateralized the insular focus in only 16.7% and N-acetyl-aspartate to creatinine ratio in 0% of patients with insular epilepsy.

4.1.4 | Perfusion MRI

Arterial spin labeling (ASL) can assess brain perfusion and detect blood flow changes around the EZ during the interictal period. Nevertheless, there is no detailed description of ASL application in insular epilepsy.

4.1.5 | Functional MRI

Functional MRI combined with electroencephalography (EEG-fMRI) could help to characterize the changes in blood oxygen level–dependent (BOLD) signal associated with interictal epileptiform discharges (IEDs) recorded during fMRI data acquisition. EEG-fMRI is able to highlight insular irritative zones (IZs) and to delineate the IZ inside the peri-sylvian area, even though BOLD signal changes may be more widespread than the actual IZ due to propagation of epileptic discharges. The increased synaptic activity due to IEDs induces increase in BOLD signal, IED-induced γ-aminobutyric acid (GABA)–mediated inhibition may induce decreased BOLD signal in brain areas surrounding or remote from the IZ.

4.2 | Isotopic imaging

4.2.1 | Positron emission tomography

Overall, FDG-PET can be useful for delineating the IZ. PET using 11Carbon-labeled flumazenil (11C-FMZ-PET) and PET using 18F-labeled flumazenil (18F-FMZ-PET) can be useful as well, although they are used less frequently.

Various hypometabolic patterns can be found, sometimes including insula, even when unique stereotyped seizures are present. Intercitically, 18F-FDG-PET in insulo-opercular epilepsy shows an extended hypometabolism including the insula, operculum, supplementary motor area, middle cingulate cortex, and basal ganglia. As for other types of epilepsies, the added-value of 18F-FDG-PET is rather unclear due to its relatively low spatial specificity. 18F-FDG-PET is also demonstrating insular hypometabolism in patients with temporal lobe epilepsy (TLE), without correlation with the postoperative outcome after an anterior temporal lobectomy. The results are similar for 11C-FMZ-PET. Such diffuse decreased binding may be related to the extended brain connections of the insular cortex. For instance, insular hypometabolism in 18F-FDG-PET and reduced binding in 11C-FMZ-PET do not predict surgical outcome in mesio-TLE (MTLE). 18F-FDG-PET and 11C-FMZ-PET do not always detect an operculo-insular EZ. Their sensitivity is indeed low (17%) as well as the specificity (53%).

Nevertheless, hypometabolism of the right posterior insula in 18F-FDG-PET has been detected in several cases of insular epilepsy related with ictal asystole.

No other PET tracer has been tested for the diagnosis of insular epilepsy.

4.2.2 | Single-photon emission computed tomography

Seizures are typically associated with an increased cerebral blood flow at the seizure-onset zone. This ictal hyperperfusion can be detected using single-photon emission computed tomography (SPECT) if the tracer such as 99mTc-HMPAO is injected as early as possible after the seizure onset. The accuracy of ictal SPECT is increased when ictal brain perfusion is compared with its interictal counterpart, that is, subtraction ictal SPECT co-registered to MRI (SISCOM). Delayed injection of the radiotracer, more than 45 s after seizure onset, or the selection of a non-optimal statistical threshold, can lead to wrong or inconclusive SISCOM results. Ictal SPECT may be non-contributive in the case of brief seizures with a rapid propagation to remote areas, which can occur in ETLE. It will often reveal multiple meaningless increases in regional cerebral blood flow, including in the insula. Still, it has been advocated that operculo-insular EZ can be evidenced by SPECT with a more intense increase in perfusion than in propagation areas. Nevertheless, the delay before tracer injection is frequently too long, due to the latency of EEG modifications. This can lead to false lateralization in the case of rapid propagation to the contralateral insula. Overall, SPECT sensitivity is low (23%) as well as specificity (48%) in insular epilepsy.

4.3 | Genetic tests

There are no specific genes known for insular epilepsy. However, some case reports have identified mutations in genes including CHRNA4, DEPDC5, and SYN1 in patients with insular epilepsy.
are commonly related to sleep-related hypermotor epilepsy with an autosomal dominant mode of inheritance.\textsuperscript{38} \textit{DEPDC5} mutations cause various types of focal epilepsy. Mutations of these genes were detected in a few patients with insular epilepsy.\textsuperscript{10} SYN1 is abundant in the limbic system and neocortex, and its mutations are leading to impaired synaptic function.\textsuperscript{39} Investigation of the SYN1 Q555X mutation in a family with reflex seizures implied large tempo-ri-insular networks.\textsuperscript{39}

4.4 | Neurophysiologic imaging

4.4.1 | Electroencephalography and electrical source imaging

Scalp EEG is rather insensitive to insular sources\textsuperscript{2} as they are located far from scalp electrodes and are masked by opercular electrical activity.\textsuperscript{40} IEDs and ictal discharges originating from the insular cortex can project over the frontal or temporal electrodes.\textsuperscript{2,11} This leads to the misdiagnosis of insular seizures as temporal, parietal, or frontal seizures.\textsuperscript{36} In insular epilepsies, scalp EEG allows, at most, the lateralization of the EZ rather than its localization,\textsuperscript{11} and suggests a deep source in the case of a rhythmic slow-wave ictal pattern.\textsuperscript{41}

As an estimation of the brain source of an electrical potential field, electrical source imaging (ESI) based on high-density EEG can help to correctly localize ictal or interictal insular discharges,\textsuperscript{42} as well as interictal ESI based on low-density EEG.\textsuperscript{43} Frequent discharges are more commonly found with FCD, which is the most common lesion at the origin of insular epilepsy.\textsuperscript{14}

4.4.2 | Magnetoencephalography and magnetic source imaging

Magnetoencephalography (MEG) seems to be more effective than EEG, PET, or SPECT for the detection of insular epilepsies,\textsuperscript{40} as MEG sensors can record radial magnetic fields generated by tangential sources from sulcal cortex and these neuromagnetic fields are not influenced by cortical layers that they pass through (e.g. opercular cortex in case of insular epilepsy). Single equivalent current dipole modeling (sECD) can highlight an insular MEG dipole cluster, correlated with insular IEDs during intracranial recordings.\textsuperscript{33,44} MEG has a diagnostic utility in patients with suspected insular epilepsy, even after ineffective epilepsy surgery\textsuperscript{45} or negative results from other non-invasive assessment techniques (Figure 2)\textsuperscript{12,46} despite the deep-seated location of the insular cortex.\textsuperscript{33} The resection of the whole cluster of dipoles correlates with a better surgical outcome (Figure 2).\textsuperscript{12}

MEG can distinguish various patterns in insular epilepsy: anterior, posterior, or diffuse peri-sylvian.\textsuperscript{11,12} Because anterior and posterior insular regions are involved in distinct functional networks, IEDs originating from these regions will have distinct propagation patterns.\textsuperscript{47} Insular IEDs indicate insular involvement in the IZ rather than in the actual EZ.\textsuperscript{45} Nevertheless, interictal MEG can help to highlight subtle MRI lesions not previously detected, as shown in a case of FCD involving the posterior insula.\textsuperscript{48}

MEG is also able to detect high-frequency oscillations (HFOs in the ripples band, 80–250 Hz) and distributed source modeling is able to localize them in the insular cortex, more focally than sECD.\textsuperscript{49}

4.4.3 | Stereo-electroencephalography

The insular cortex is frequently explored with depth electrodes of stereo-electroencephalography (or SEEG),\textsuperscript{2,41,50} as electrocorticography (ECoG) is less reliable in this type of epilepsy.\textsuperscript{36} and subdural electrodes (strips and grids) have an elevated risk of complications\textsuperscript{11} due to the vicinity of the middle cerebral artery and collaterals and the depth localization covered by opercula. SEEG helps to delineate the EZ, often restricted to one or two insular gyri, particularly in the case of MRI-negative insular epilepsy.\textsuperscript{2}

An orthogonal implantation offers optimal control of the trajectories with respect to the peri-sylvian arteries\textsuperscript{2} through frontal, parietal, and temporal opercula,\textsuperscript{11} which can be implicated in insular epilepsy.\textsuperscript{51} This method allows the implantation of up to eight electrodes, including at least one electrode in each short gyrus and two electrodes in each long gyrus for a maximal spatial sampling.\textsuperscript{2} Still, only a couple of electrode contacts are localized inside the insular cortex.\textsuperscript{52} The exploration of insular cortex with depth electrodes seems to be a safe procedure with this orthogonal implantation.\textsuperscript{53} Nevertheless, due to the high vascular density from the middle cerebral artery and sylvian veins covering the insular surface, orthogonal implantation can lead to risks of vascular injury.\textsuperscript{54} The inferior part of the insula can be difficult to reach, and, therefore, undersampled.\textsuperscript{41} The opercular region is crucial for language in the dominant side and can be affected during implantation.\textsuperscript{55}

An oblique implantation, based on stereotactic MRI,\textsuperscript{55} avoids this vascular risk with parasagittal trajectories within a plane parallel to that of the insula\textsuperscript{2,53} through the frontal and parietal lobes.\textsuperscript{11} This method allows the implantation of up to five electrodes, each of them could have from six to eight electrode contacts inside the insular
cortex. Robot-assisted implantations are safe and efficient, whereas frameless oblique implantation bears the risk of inaccuracy at the target point in the insular cortex compared with other cerebral lobes. An increased electrode length leads to increased inaccuracy due to lateral deviation at the target point. This inaccuracy can be corrected by a combination of frame-based stereotaxy with new generation planning software.
Oblique and orthogonal implantations can be combined during the same SEEG investigation to optimize the spatial sampling of the whole operculo-insular region. Insular depth electrodes will be combined with the implantation of adjacent regions (frontal, parietal, or temporal) depending on the electro-clinical hypothesis about EZ. In some rare cases, depth electrodes are combined with strips or grids to investigate both insular and opercular cortices. Some cases require a bilateral insular implantation, mostly in the case of MRI-negative epilepsy when an insular onset is suspected based on ictal semiology. Insular ictal discharges may have an early contralateral propagation or may start simultaneously in both hemispheres leading to a risk of false lateralization.

Parasagittal transinsular apex depth electrode placement is an alternative to orthogonal or oblique implantations if unilateral insulo-opercular involvement is suspected.

SEEG recordings allow differentiation of insular involvement at the onset of seizures or in the propagation of ictal discharges. Ictal patterns consist mostly of low-voltage fast recruiting activity (Figure 3), followed by rhythmic high-frequency spikes, usually limited to a small part of the insular cortex. Propagation to other parts of the insula may occur within a few seconds to some minutes, and then to opercular, frontal, cingulate, or mesial temporal cortex (Figure 3).

An insular involvement is also frequent in children with refractory focal epilepsy (RFE) (64% of implication at the onset or in the propagation of seizures), whose seizure semiology is less specific than in adults, leading to high impact of SEEG and subsequent good surgical outcome.

Electrical stimulations during SEEG help to localize ictal symptoms when the triggered clinical symptomatology is concordant with spontaneous seizures, and to delimitate the functionally eloquent cortices. Direct electrical insular stimulation may trigger somatosensory, visceral sensations, auditory sensations, vestibular sensations, speech disturbances, olfacto-gustatory sensations, and motor responses.

The main limitation of SEEG remains the spatial sampling bias. SEEG recording may fail to highlight insular EZ in the case of a clinical hypothesis not considering this area at the origin of the seizures.

Quantitative analysis may complement the visual analysis performed by epileptologists (e.g., the epileptogenicity index, i.e., the quantitative method based on spectral and temporal content of ictal pattern, is able to detect pure insular-onset epilepsy including a distinction between the anterior and posterior insular seizures).

### 4.4.4 Simultaneous recordings

Simultaneous MEG and EEG recordings can be useful to detect insular IEDs and to determine the propagation network, even when both isolated EEG and MEG were negative.

Simultaneous MEG and SEEG recordings may help to assess the EZ and to reach seizure freedom, as these recording combinations overcome the limited spatial sampling associated with SEEG.

### 4.5 New promising diagnostic tools in insular epilepsy

#### 4.5.1 Optically pumped magnetometers

Optically pumped magnetometers (OPMs) are novel cryogenic-free MEG sensors that can be placed directly on the scalp (by opposition with cryogenic MEG sensors that must be buried in a one-size-fits-all rigid helmet) leading to reduced brain-to-sensor distance. They have shown their ability to detect IEDs in patients with ETLE with a higher amplitude and a higher signal-to-noise ratio than MEG. Magnetic source imaging (MSI) based on OPMs can localize IEDs with localization potential similar to that of MEG and record ictal discharges from multiple neocortical areas. OPMs are user-friendly and comfortable for patients. This new technology could have a particular value in insular epilepsy due to the low efficiency of EEG and the high added value of MEG.
PET using \(^{11}\)C-labeled \(\alpha\)-methyl-L-tryptophan (\(^{11}\)C-AMT-PET) can help to localize some specific lesions such as epileptogenic tubers and certain types of epileptogenic cortical malformations.\(^{35}\) PET using \(^{11}\)C-labeled choline can help localize an insular EZ in patients with structural insular epilepsy, probably due to the involvement of choline with the synthesis of cell membrane during the process of astrogliosis.\(^{69}\) PET using 18-kDa translocator protein tracers (TSPO-PET) is used to detect neuroinflammation in cases of TLE. It can involve various TSPO radioligands,\(^{70}\) such as \(^{11}\)C-PBR28-PET and \(^{11}\)C-DPA713 PET, able to lateralize the EZ, contrary to \(^{11}\)C-PK11195.\(^{70}\) In cases of ETLE, \(^{11}\)C-DPA713 PET is able to detect an increased tracer uptake in nonlesional EZ, still lower than in lesional EZ.\(^{70}\) \(^{18}\)F-DPA714 PET could be the most promising method for clinical use due to its good signal-to-noise ratio and its longer half-time than \(^{11}\)C-labeled radioligands.\(^{70}\)

Studies in mice models of MTLE have shown increased tau and amyloid levels both during epileptogenesis and after long-term spontaneous seizures.\(^{71}\) These modifications were found mostly in the EZ and then in the propagation network.\(^{71}\) This suggests that tau-PET and amyloid-PET could be investigated as diagnostic tools in epilepsy.

The use of such new radiotracers is promising in insular epilepsy, in which \(^{18}\)F-FDG-PET has a low performance.

## 5 | THERAPEUTIC APPROACHES TO INSULAR EPILEPSY

### 5.1 | Curative methods

#### 5.1.1 | Insular resection

An insular resection tailored within the insular cortex,\(^{11}\) based on SEEG recording data, allows attainment of Engel class I seizure outcome (Figure 4)\(^{15-17,41,72}\) in 60%–80% cases.\(^{16,72,73}\) The surgical outcome remained good (Engel class I or II in seven or nine patients) in a small case series of insular resection following a first surgical failure.\(^{74}\) Due to the proximity of the middle cerebral artery and the thickness of opercula, it can be difficult to reach the targeted area by conventional neurosurgery or stereotactic methods.\(^{11,75}\) Historically, insular open surgery procedures bore high morbidity and mortality.\(^{11}\) Currently, depth electrodes can be used as landmarks to tailor the resection\(^{76}\) and lead to reduced morbidity and mortality.\(^{11}\) Nevertheless, a learning curve is observed for the neurosurgeon performing the resection, and postoperative permanent neurological deficits are less frequent with experienced surgical teams.\(^{44}\) In the case of complete resection of the EZ, the surgical outcome is as good as epilepsy surgeries in other brain areas.\(^{77}\) A meta-analysis of the surgical procedures applied indicates that resection of the anterior insular region has been more frequent than complete insular cortectomy.\(^{14}\)

Postoperative neurological complications are reported in 30%–60% of the cases, but they remain transient in 75% of them.\(^{75}\) Permanent morbidity in 5%–10% of the patients includes 5% of permanent motor deficit.\(^{75}\) Autonomic function changes are also reported after insular resection, including changes in heart rate variability.\(^{78}\) Self-reported decreased appetite is described after insular resection, probably in relation to dysfunctional autonomic and gustatory functions, which is concordant with implication of the insular cortex in feeding behaviors.\(^{79}\) Cognitive impairment remains rare after insular resection,\(^{80}\) even in the case of children with previously impaired development.\(^{81}\) Nevertheless, subtle deficits in specific cognitive functions can be expected (e.g., impairment of processes associated with the oro-motor function)\(^{80}\) Impaired emotional processing after insular resection\(^{82,83}\) could be related to the insular involvement in the salience network.\(^{82}\) Such impairment may lead to personality changes.\(^{84}\) Alteration of this network may lead to attention deficiency\(^{85}\) and impaired autobiographical memory.\(^{83}\)

Surgical opening of the sylvian valley carries the risk of injury or spasm of the trunk or branches of the middle cerebral artery.\(^{75}\) Some perforating branches of the middle cerebral artery provide terminal vascularization to the caudal part of the corona radiata.\(^{11,75}\) Lesions of these...
branches may occur following resection of the posterior insula and parietal operculum, leading to permanent motor deficiency up to hemiparesis, which can be avoided by sparing of a small piece of gray matter at the bottom of the peri-insular sulcus. Because the lenticulostriate arteries run along the limen insulae, deep hemostasis leads to risk of ischemia in the internal capsule. Ischemic lesions are detected in 60% of patients, leading to only few or transient clinical consequences. Insular surgery requires retraction or removal of a part of the operculum. In the case of the temporal operculum, the functional risk remains moderate. In the case of the frontoparietal operculum, a hemifacial sensory-motor deficit, generally transient, may occur. If the lesion affects the dominant hemisphere, a language deficit may occur, which is temporary in most cases. Putamen and internal capsule are close to the posterior insula and intraoperative electrical stimulation is useful to search for a motor response in this area. Nevertheless, a transoperative subpial dissection respecting the arachnoidal-pial layer without opening the sylvian fissure and avoiding vessel coagulations is possible. The risk of these postoperative complications is lower in the case of microsurgical technique, when the resection involves an operculum included in the EZ, and when the resection is performed by an experienced neurosurgeon. Moreover, awake surgery should be considered to monitor neurological status, allowing more extended resection without increased impairment.

Seizure freedom after tailored insular resection is similar to the result obtained in patients with TLE (60%–85%). Thus resection remains the gold standard.

### 5.1.2 SEEG-guided radiofrequency thermocoagulations

Radiofrequency thermocoagulations may be performed at the end of the SEEG recording as a safe alternative to surgical resection (Figure 4). The progressive temperature rise between determined intracranial contacts leads to cell death and focal lesions from 5 to 7 mm with low side effects. Because insular EZ are usually restricted to one or two insular gyri, radiofrequency thermocoagulations via an oblique electrode implanted in the long axis of a gyrus will lead to a complete destruction of the gyrus. The technique is well tolerated with no added morbidity.
Seizure-freedom rate is lower (53%) than for insular resection (60%–85%).\textsuperscript{10} In some cases, seizures reappear rapidly with the same intensity and frequency.\textsuperscript{15} Seizure freedom is more likely in the presence of FCD, well-localized EZ, low-radiofrequency thermolesion volume, low number of radiofrequency thermocoagulation, and low ratio volume/number.\textsuperscript{92} The best efficacy/safety compromise is obtained with a radiofrequency thermolesion volume of about 2 cm\textsuperscript{3}.\textsuperscript{92} One case of insular epilepsy treated with radiofrequency thermocoagulations guided by MEG was described and the patient reached seizure freedom.\textsuperscript{93}

5.1.3 | MRI-guided laser interstitial thermal therapy

Laser interstitial thermal therapy (LITT) ablation is an alternative to surgical resection leading to seizure freedom without complications.\textsuperscript{11,61,94} LITT uses stereotactic implanted thermal source leading to a local EZ heating ablation.\textsuperscript{10} Lesions from 5 to 20 mm in diameter are induced and are visually controlled by MRI during the procedure. Because LITT is associated with a good seizure outcome in deep EZ locations,\textsuperscript{10} it is not surprising that a seizure reduction similar to open surgical resection is achieved in insular epilepsy.\textsuperscript{95,96} The ablation of a higher proportion of the insular cortex and a larger insular volume is correlated with a good seizure outcome,\textsuperscript{97} including Engel class I.\textsuperscript{98} Twenty-nine percent of LITT procedures are associated with transient adverse effects including mild hemiparesis (25%) and aphasia (4%).\textsuperscript{99} Transient aphasia is reported as a perioperative morbidity,\textsuperscript{100} which can be avoided with the help of DTI tractography if white matter tracts are visualized during insular LITT ablation.\textsuperscript{101}

5.1.4 | Stereotactic radiosurgery (Gamma Knife)

Radiosurgery, with the Leksell Gamma Knife is efficient for the ablation of a small EZ, which is frequently occurring in insular epilepsy.\textsuperscript{102} Removal of insular focus by this technique is reported to reduce seizure frequency, but this is not yet supported by results in large series.\textsuperscript{103} Nonetheless, larger studies focusing on MTLE have shown a lower seizure-freedom rate in the case of stereotactic radiosurgery, compared with surgical resection, and a similar rate of neurocognitive deficits, leading to the conclusion that stereotactic surgery should be offered to patients with surgical contraindications or who are opposed to open surgery.\textsuperscript{104}

5.2 | Palliative methods

5.2.1 | Responsive neurostimulation, deep brain stimulation, and vagus nerve stimulation

Stimulation methods provide a partial reduction of insular seizures, but seizure freedom is rare.\textsuperscript{10,11} Postoperative complications of insular responsive neurostimulation (RNS), during both electrode placement and stimulation, have not been reported, and some patients have demonstrated a good seizure outcome despite the low rate of seizure freedom.\textsuperscript{105} RNS is related to a higher seizure reduction (70%) than vagus nerve stimulation (~40%) and deep brain stimulation (~40%).\textsuperscript{11}

5.3 | New therapeutic perspectives in insular epilepsy

5.3.1 | Focused ultrasound

Low- and high-intensity focused ultrasound (HIFU) could be effective as treatment of RFE.\textsuperscript{106} Low-intensity focused ultrasound (LIFU) is able to modulate the epileptic focus, whereas HIFU will ablate the epileptic focus as a non-invasive alternative to surgical resection.\textsuperscript{106} Both LIFU and HIFU have been tested mostly in animal models of epilepsy and only in some cases of epileptic patients.\textsuperscript{106} FUS has been tested for treatment of RFE in a phase 1 pilot study including a patient in whom the EZ, defined on SEEG, included the anterior part of the insular cortex.\textsuperscript{107} A neuromodulation effect is suggested by changes in neural activities without structural brain lesions.\textsuperscript{107}

5.3.2 | Deep transcranial magnetic stimulation

Deep transcranial magnetic stimulation (TMS) using H-coil has demonstrated its ability to target the insula in a study that aimed at treating addiction by modulating drug reward and addictive processes.\textsuperscript{108} Because TMS delivered into the EZ has demonstrated a significant seizure and IED reduction in patients with RFE,\textsuperscript{109} deep TMS could be tested as a treatment for refractory insular epilepsy.

6 | CONCLUSION

Due to heterogeneous semiology and deep localization of the EZ, insular epilepsy remains a clinical and therapeutic challenge. Several diagnostic tools can be used to detect insular involvement in seizure generation, including
structural and functional MRI, MEG, and SEEG. Diffusion-weighted MRI and some recent PET tracers have not been tested specifically in insular epilepsy and should be better investigated.

The gold standard in curative therapy of insular epilepsy remains a tailored insular resection. Other curative methods (i.e., radiofrequency thermocoagulation, LITT, Gamma Knife) should be considered as alternatives. Their value should be tested in larger samples of patients before they may be proposed as first-line treatments.

Research on the insula, the mysterious island, is still ongoing. To help in its exploration, new diagnostic tools are anticipated in the near future. They should enhance our knowledge of the pathophysiological processes involved in insular epilepsy. In addition, the emergence of new therapeutical strategies will advance the treatment of insular epilepsy.

A U T H O R  C O N T R I B U T I O N S
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R E F E R E N C E S


