Intercital regional slow activity in temporal lobe epilepsy correlates with lateral temporal hypometabolism as imaged with $^{18}$FDG PET: neurophysiological and metabolic implications

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Abstract

Objectives—The phenomenon of interictal regional slow activity (IRSA) in temporal lobe epilepsy and its relation with cerebral glucose metabolism, clinical data, MRI, and histopathological findings was studied.

Methods—Interictal $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG PET) was performed under continuous scalp EEG monitoring in 28 patients with temporal lobe epilepsy not associated with intracranial foreign tissue lesions, all of whom subsequently underwent resective surgery. Regions of interest (ROIs) were drawn according to a standard template. IRSA was considered lateralised when showing a 4:1 or greater ratio of predominance on one side.

Results—Sixteen patients (57%) had lateralised IRSA which was always ipsilateral to the resection and of maximal amplitude over the temporal areas. Its presence was significantly related to the presence of hypometabolism in the lateral temporal neocortex ($p=0.0009$). Logistic regression of the asymmetry indices for all measured cerebral regions confirmed a strong association between IRSA and decreased metabolism of the posterior lateral temporal neocortex only ($p=0.009$). No significant relation could be shown between slow activity and age at onset, duration of the epilepsy, seizure frequency, and MRI evidence for hippocampal atrophy. Furthermore, IRSA was not specifically related to mesial temporal sclerosis or any other pathology.

Conclusions—Intercital regional slowing in patients with temporal lobe epilepsy not associated with a mass lesion is topographically related to the epileptogenic area and therefore has a reliable lateralising, and possibly localising, value. Its presence is irrelevant to the severity or chronicity of the epilepsy as well as to lateral deactivation secondary to neuronal loss in the mesial temporal structures. Although slow EEG activity is generally considered as a non-specific sign of functional disturbance, interictal regional slowing in temporal lobe epilepsy should be conceptualised as a distinct electrographic phenomenon which is directly related to the epileptogenic abnormality. The strong correlation between interictal slowing and lateral temporal hypometabolism suggests in turn that the second may delineate a field of reduced neuronal inhibition which can receive interictal and ictal propagation.

Regional delta activity, either continuous and polymorphic or intermittent and rhythmic, is the most common EEG abnormality caused by underlying mass lesions, $^1$ is usually associated with white matter and thalamic locations, and is thought to reflect a deafferentiation of the overlying cortex. $^2$ Intercital regional slow activity (IRSA) is often seen in patients with partial epileptic seizures, and in this context it may be considered a reliable lateralising sign when adequately supported by ipsilateral epileptiform discharges. However, little attention has been focused on IRSA and the few relevant studies have dealt only with its lateralising value.$^4$ The conditions required for the appearance of IRSA in partial epilepsy, its inherent characteristics, and the underlying pathophysiological mechanisms remain largely obscure.

Functional brain imaging with $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG PET) in partial epilepsy has proved to be the most reliable test for identifying the functional deficit zone in the form of regional hypometabolism which usually includes the ictal onset zone.$^6$ In temporal lobe epilepsy reduced interictal metabolism of the epileptogenic temporal lobe occurs in 70%–95% of patients$^{6-13}$ and typically is much larger than the histopathological lesion$^{14}$ but the pathophysiological determinants of its extent are still unclear.

In a previous report on the association between interictal cerebral glucose metabolism and EEG changes in patients with partial seizures, Engel et al$^{15}$ found no quantitative relation between the degree of focal hypometabolism and the frequency of interictal EEG spikes, but their results regarding non-epileptiform electrophysiological abnormalities were less clear. In the present study, we investigated the
Temporal hypometabolism and slow wave activity

phenomenon of IRSA and its relation with cerebral metabolism in patients with temporal lobe epilepsy who underwent FDG PET during concurrent scalp EEG monitoring. As our aim was to study a pure culture of IRSA it was imperative to eliminate any significant deafferentation effects; therefore patients with intracranial mass lesions were excluded.

Patients and methods

Patients were consecutively selected from a large series of surgical candidates with medically intractable partial seizures, referred for brain FDG PET in St Thomas' Clinical PET Centre. Inclusion criteria were (a) a single temporal epileptogenic focus demonstrated by EEG recordings, and (b) no evidence of intra-axial foreign tissue lesion on brain MRI. No patient had any neurological condition other than epilepsy, nor any acute or chronic medical illness at the time of the PET study.

PET-EEG studies

Continuous scalp EEG monitoring, starting about 5 minutes before the tracer injection and lasting for 35–40 minutes, is routinely practised in St Thomas' Clinical PET Centre to confirm the interictal state of the patient or assist in scan interpretation when a seizure occurs. Thus, eye opening and closing manoeuvres, and activation methods such as intermittent photic stimulation and hyperventilation are not often used. Electrodes are placed according to the international 10–20 system and patients are continuously observed for ictal clinical manifestations. Patients with traces containing too much artifact were excluded from the study. Preadolescent patients were also excluded as asymmetric temporal slow activity mainly over the posterior areas is often seen as a physiological variant. The seizure type and recency and the number of seizures reported within the past 24 hours were noted to exclude patients with postictal recordings. Because the exact duration of postictal slowing has not been investigated, we reviewed the postictal EEG tracings in 12 habitual seizures (six complex partial seizures (CPS) and six secondary generalised tonic-clonic seizures (GTCS)), recorded in eight of our patients who underwent prolonged preoperative video telemetry. EEG was transcribed on to paper, continuously for the first hour after the seizure, and intermittently thereafter in spike free sections of 20–30 seconds about every 5 minutes, and tracings were visually assessed for any persistent focal slowing. Continuous slow activity was visually identifiable up to 23 minutes at the most after a CPS, and up to 2 hours after a secondary GTCS. These time limits are well outlasted by those set by Panet-Raymont and Gotman who considered the EEG postictal when recorded within one hour of a CPS and eight hours of a GTCS; therefore analysis of additional postictal EEG tracings was not deemed necessary for the purpose of this study. Twenty eight patients (20 men and eight women) with seizure recency at the time of PET ranging from 8 hours to 3 weeks (median 5 days) with less than 12 hours in only three patients with CPS, had clearly interictal recordings and fulfilled all inclusion criteria. PET-EEGs were visually identified by two independent electroencephalographers who were blind to PET results and patient identity. None of these recordings contained any electrographic seizure. Epileptiform abnormalities and focal or regional slowing showing a 4:1 (75%) or greater ratio of predominance (in terms of spike frequency and time of appearance respectively) on one side were considered lateralised. Findings were compared with those of the previous scalp EEGs for each patient to evaluate consistency. Seizure recency in the previous recordings ranged from 6 hours to 3 weeks (median 3 days) with three missing values.

FURTHER EEG STUDIES

All patients had standard and sleep activated interictal scalp EEG studies. Twenty three patients had in addition ictal recordings obtained with video telemetry, of whom there were 17 with foramen ovale, two with subdural strip, one with subdural mat and strip, and three with scalp electrodes. All intracranial recordings were performed after the PET studies. In the remaining five patients, ictal studies were not considered necessary as typical anterior temporal spike discharges were strongly lateralised and concordant with the other investigations.

PET studies

All patients underwent interictal brain PET using 18F-FDG. Scans were performed after a 6 hour fast using an ECAT 951R whole body scanner (Siemens CTI/Knoxville TN). Patients were injected intravenously with 250 MBq 18FFDG, with eyes closed in a quiet room adjacent to the scanner. Any unnecessary communication during the tracer uptake period was discouraged. Patients were positioned supine within the field of view of the camera and images from skull base to vertex were acquired over a period of 30 minutes commencing 30 minutes after tracer injection. Thirty one slices were produced over a 10.6 cm axial field of view with six sequential static scans of five minutes duration acquired. Frames were then summed to produce high quality images, with those showing excessive movement rejected. Attenuation correction was performed using the method of Bergstrom et al16 and the complete set of image planes was reconstructed and smoothed to obtain an image data set with a spatial resolution of 8.5 mm in all three orthogonal directions. The scans were visually interpreted by two nuclear medicine physicians, blind to patient identity, with any differences resolved by consensus. Semiquantitative analysis of transaxial slices (cut parallel to the long temporal axis) was performed by positioning under visual guidance multiple 7 mm circular regions of interest (ROIs) over fixed sites in the brain using a template designed for the purpose (fig 1). Counts (cts) within these regions were averaged to provide 10 anatomical paired regions

Counts (cts) within these regions were averaged to provide 10 anatomical paired regions
for which asymmetry indices (AIs) were calculated as follows:

\[ AI = \frac{c_{\text{left ROI}} - c_{\text{right ROI}}}{\text{sum of } c_{\text{both ROIs}}} \times 200\% \]

All patients were taking anticonvulsive medication at the time of PET imaging.

MRI STUDIES

Standard qualitative brain MRI studies were performed in all patients and included T1 and T2 weighted images. For 25 patients MR images were obtained on a 1.5T General Electric Signa Advantage scanner (GE Medical Systems, Milwaukee) using a 3-D coronal volumetric spoiled gradient echo sequence (SPGR) with a flip angle of 35°, TR33, and TE5. One hundred and twenty four 1.5 mm contiguous slices were obtained using a 22 cm field of view and a matrix size of 256×192 to cover the whole cerebral. When no abnormality could be ascertained on visual analysis, hippocampal volume measurements were undertaken. Hippocampal volumetry was not possible in three qualitatively normal scans performed in other centres.

RESECTIVE SURGERY AND HISTOPATHOLOGY

Twenty seven patients subsequently underwent standard anterior temporal lobectomy (11 right, 16 left) and one left sided selective amygdalohippocampectomy. Histopathology confirmed mesial temporal sclerosis in 24 patients and additional cortical dysplasia in two of them, cortical dysplasia alone in the parahippocampal gyrus in one, and non-specific gliotic changes in three. The postoperative follow up period exceeded one year in only 20 patients, therefore correlation of the different variables with the outcome was not attempted.

STATISTICAL ANALYSIS

Statistical analysis included Student’s t test with unequal variances, χ² with Yates’ correction, and logistic regression.

Results

CLINICAL DATA

The median age at PET examination was 23 years (range 14 to 52 years). The median age at seizure onset was 6 years (range 6 months to 28 years), and the median duration of the disease before PET examination was 16 years (range 6 to 44 years). All patients had CPS with frequency at the period of the investigation ranging from 0.07 to three a day (median 0.33). Secondarily generalised seizures occurred in 18 patients (64 %) with an estimated frequency ranging from three a year to nine a

Table 1  FDG PET, interictal EEG, MRI, and histopathological findings in 28 patients with temporal lobe epilepsy

<table>
<thead>
<tr>
<th>PET</th>
<th>Interictal temporal spikes</th>
<th>Interictal slow activity</th>
<th>MRI</th>
<th>Histopathology</th>
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<td>28</td>
<td>19</td>
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*Indicative of mesial temporal pathology.
†Hypometabolism extended in extratemporal areas in 10 patients.
‡Volumetric studies were not performed in one patient.
CD=cortical dysplasia; ns=non-specific changes.
month. Fourteen patients had a history of prolonged, complicated, or multiple febrile convulsions. Neurological examination was invariably normal.

MRI STUDIES
Evidence of unilateral mesial temporal pathology on brain MRI in the form of hippocampal formation atrophy, increased hippocampal signal on T2 weighted images, or lateralising volume, was present in 21 patients (75%), in all ipsilateral to the side of the resection (table 1). Hippocampal volumetry was normal in four patients in whom visual analysis failed to provide lateralising information. No other abnormality was noted in any of the scans.

FDG-PET STUDIES
Qualitative visual analysis of PET images disclosed one or more zones of hypometabolism in 24 patients (85.7%) and normal metabolic patterns in the remaining four. Regional hypometabolism was unilateral and concordant with the other investigations in 23 patients and bilateral in one (table 1). In this patient metabolism was equally depressed in the lateral temporal areas on both sides (AI=6.1%) but clearly more in the right mesial temporal area than the left (AI=16.9%). Reduced metabolism of the lateral temporal neocortex was seen in 19 patients and was not associated with any of the clinical variables tested or the MRI findings. Although metabolic depression involving both mesial and lateral temporal areas was found in most patients with medial temporal sclerosis, or cortical displasia, or both, one patient with extensive unilateral hypometabolism more pronounced in the lateral temporal neocortex had mild, non-specific changes whereas two others with typical medial temporal sclerosis had entirely normal metabolism (table 1).

CONTINUOUS SURFACE EEG MONITORING
The EEG findings and their relation to PET, MRI, and histopathology are shown in table 1. Interictal epileptiform discharges were noted in 25 patients and were lateralised in 20 (in 19 patients to the side of the resection, and in one to the other side). In the five patients with non-lateralising epileptiform abnormalities, bitemporal independent focal or regional spiking was noted in three, and mainly generalised discharges in two patients.

Lateralised slowing was noted in 16 patients (57%), in all ipsilateral to the side of the resection. In 14 of these it was recorded from the temporal lobe exhibiting lateralised spiking, whereas in the other two no clear epileptiform abnormalities were noted. Its distribution was relatively focal involving the anterior, mid, and the posterior temporal electrodes in 11 patients (fig 2), and more widespread, extending to frontal or central areas in five. Slow activity was mainly polymorphic and appeared most often in runs of variable duration. The predominant frequency was at 1.5–3 Hz, often admixed with frequencies of up to 4.5 Hz, and the amplitude was invariably greater over the temporal areas. IRSA showed clear evidence of reactivity in eight patients; eye opening resulted in elimination of slow waves in five and in significant attenuation in three. The effect was reproducible and lasted for as long as the eyes remained open. However, closing the eyes did not result in an immediate reappearance of the abnormality. No adequate information could be obtained for the remaining eight patients as recordings were performed mainly during the “eyes closed” condition. However, IRSA invariably attenuated or disappeared during the period around the radiotracer injection, when the eyes were open, presumably with associated visual fixation and enhanced mental alertness.

Comparison with the previous interictal scalp EEGs showed that the occurrence or not of IRSA was consistent for every patient.

RELATION BETWEEN IRSA AND PATTERN OF INTERICTAL CEREBRAL METABOLISM
The presence of IRSA was significantly related to the presence of hypometabolism in the lateral temporal neocortex (p=0.0009) on visual analysis. This metabolic pattern was evident in all patients with IRSA except one who had qualitatively and quantitatively normal metabolism. On the other hand, three out of 18
In bivariate logistic regression the effect of each region in turn was adjusted for the strongest predictor (posterior lateral temporal area).

patients with unilateral hypometabolism involving the lateral temporal neocortex had no lateralised IRSA, whereas the single patient with extensive bilateral hypometabolism had bilateral slowing. Univariate logistic regression of the asymmetry indices for all measured cerebral regions disclosed that the appearance of IRSA was strongly associated with decreased metabolism of the posterior lateral temporal neocortex. Although a similar but less significant relation seemed to exist between IRSA and hypometabolism in parietal-occipital cortical areas, bivariate analysis after adjusting for posterior temporal neocortex asymmetry index showed that no other area was significantly linked to the appearance of IRSA (table 2).

Using a cut off limit of 10% for the AI of the posterior lateral temporal area, 12 of the 16 patients with IRSA were above, and 10 of the 12 patients without IRSA were below this limit (sensitivity 75%, specificity 83%).

The presence of correctly lateralised interictal temporal spiking did not correlate with the presence of a hypometabolic zone (p=0.141), but showed a trend towards correlation with the presence of lateral temporal hypometabolism without reaching the 5% level (p=0.07).

**Relation between IRSA and clinical, MRI, and histopathology data**

No significant relation could be shown between IRSA and either the MRI results, or any of the clinical indices tested although the duration of the disease showed an unexpected trend (mean duration in patients with IRSA 15 (SD 8.67) years; mean duration in patients without IRSA 22.75 (SD 11.7) years; p=0.071). Fourteen out of 16 patients with lateralised IRSA had mesial temporal sclerosis, one had cortical dysplasia alone, and one had mild non-specific changes. Of the 12 patients without IRSA, two had non-specific pathology, and 10 had mesial temporal sclerosis (two with additional cortical dysplasia).

**Discussion**

**Incidence and lateralising value of IRSA**

Focal, non-epileptiform abnormalities such as interictal slow activity, postictal changes, and deficits in fast frequencies, may provide useful lateralising information in the non-invasive stage of the preoperative evaluation process. Among them interictal focal slow activity remains generally unaffected by chronic antiepileptic drug therapy and is easier to study, as it requires neither ictal recordings nor barbiturate or benzodiazepine administration. However, the relevant studies are few with a reported incidence and lateralising value varying from 25% to 100%. Methodological differences (criteria for lateralisation, visual versus spectral analysis), and different patient selection criteria might explain these discrepant findings.

In the present study IRSA in the PET EEG was visually identified in 16 out of 28 patients (57%) and was correctly lateralising in all. In our patients the presence (or absence) of regional slowing in the previous interictal scalp EEG studies was consistent with the findings of the PET EEG, showing the same distribution when present. Gotman and Koffler also noted that regional slow activity in partial epilepsy is not subjected to significant day to day changes.

**On the nature of the IRSA in temporal lobe epilepsy**

**Relation with structural neuroimaging and pathological variables**

In this study IRSA was not associated with the presence of MRI evidence of hippocampal pathology, nor was it specifically related (and by implication aetologically linked) to medial temporal sclerosis or to any other pathology (cortical dysplasia, gliosis, or minor morphological changes). A practical implication from these findings is that the role of IRSA as a reliable indicator of the epileptogenic focus in temporal lobe epilepsy is not limited to cases in which the pathology is mesial temporal sclerosis as it was previously suggested. A theoretical implication may be that, in the absence of intracranial mass lesion, neocortical deafferentation secondary to hippocampal neuronal loss is not a determinant for the generation of interictal regional slowing.

**Relation with clinical variables**

In the present series statistical analysis showed that IRSA was not related to disease duration, age at onset, seizure frequency, and secondary generalisation; therefore it is unlikely to reflect merely a regional brain functional impairment secondary to chronic epileptogenesis.

**Topographic relation to epileptogenic zone**

In our patients IRSA was invariably recorded from the cortical areas overlying the epileptogenic focus confirming previous findings. Panet-Raymont and Gotman found a correlation between slow activity and interictal spikes.

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**Table 2** Logistic regression for indices of asymmetry in each region to predict interictal regional slow activity

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<th>Regions</th>
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on electrocorticogram (ECoG) and noted that the fact that maximum delta activity does not always correlate with the area of maximal spiking with respect to their spatial location does not necessarily contradict the hypothesis that both electrical phenomena originate from the same abnormal area.

A general understanding of diffuse or regional slow EEG activity is that it reflects in a non-specific manner, a functional disturbance of diverse aetiology,20 21 not necessarily linked to focal epileptogenesis. In patients with temporal lobe epilepsy not associated with intracranial mass lesions; however, our findings suggest that interictal regional slowing may be conceptualised as a distinct electrophographic phenomenon which is directly related to the primary epileptogenic abnormality (as irrelevant to neocortical deafferentation secondary to hippocampal neuronal loss, and chronic epileptogenesis), and has a reliable lateralising and possibly localising value.

**IRSA AND INTERICTAL CEREBRAL GLUCOSE METABOLISM**

The present study is not the first to explore the above relation. Engel et al15 investigated the relation between interictal cerebral glucose metabolism and EEG changes monitored by stereotactically implanted depth or scalp electrodes in a less homogenous group of patients, some of whom had demonstrable lesions on CT. Although some relation between slow waves and focal hypometabolism was seen, no significant correlation was found between the presence of focal non-epileptiform abnormalities and the presence of a hypometabolic zone or between the degree of focal hypometabolism and the frequency of interictal spikes. However, these investigators did not distinguish between mesial and lateral temporal hypometabolism (LTH). We were unable to show a relation between interictal spiking and the presence of a hypometabolic zone, or a specific metabolic pattern. We did show, however, in a semiquantitative analysis of FDG PET images, that the presence of IRSA which was consistently recorded from the anterior, posterior, and mid-temporal electrodes, was strongly related to depressed metabolism of the posterior lateral temporal neocortex. This pattern was evident in most but not all of our patients (for example, some of them had more intense hypometabolism in the anterior rather than the posterior lateral temporal neocortex), but was manifested by the group averages. Some discrepancy in the topography may be due to the low spatial resolution of both PET and EEG as well as to the fact that comparisons were based on the different groups of ROIs rather than the individual hypometabolic ROIs, as our aim was to evaluate possibly gross and not detailed relation between IRSA and cerebral metabolism. As in the case of IRSA, and in accordance with previous studies,12 22 25 LTH was not related to factors reflecting the severity or the chronicity of the epilepsy.

**IRSA AND POLYMORPHIC DELTA ACTIVITY ASSOCIATED WITH CEREBRAL MASS LESIONS**

Patients with destructive brain lesions show a similar neocortical slow activity which is closely associated with mainly deep white or subcortical grey matter locations.2 As experimental studies showed that purely cortical lesions affecting only the grey matter were not associated with delta activity it has been suggested that the latter results from some kind of cortical deafferentation and is generated by otherwise relatively normal cortical neurons.3 Delta activity in these cases may be continuous or episodic but typically does not block to visual attention and alerting procedures.26 By contrast, IRSA seems to be reactive and does not seem to depend primary on cortical deafferentiation.

**IMPLICATIONS FOR THE PATHOPHYSIOLOGICAL BASIS OF INTERICTAL CEREBRAL HYPOMETABOLISM**

Patients with mesial temporal lobe epilepsy documented on depth EEG grounds may have reduced metabolism in both medial and lateral temporal areas, whereas some of them even show extratemporal metabolic depression.12 25 Although some underestimation of the degree and overestimation of the extent of hypometabolism of mesial temporal structures is expected due to the increase of the partial volume averaging and decrease of the recovery coefficient,13 the involvement of the lateral neocortex in mesial temporal lobe epilepsy is still poorly understood.

It has been proposed that the metabolic depression of the lateral temporal neocortex may relate to its chronic deactivation due to the primary neuronal loss in the hippocampal formation and amygdala and the term “diachisis” has been used in this context.14 Pathological studies, however, have shown no relation between the degree of interictal temporal hypometabolism and the amount of hippocampal gliosis or cell loss,25 26 27 and no correlation was found between the magnitude of the hippocampal volume asymmetry and the degree of the lateral or mesial temporal hypometabolism by most of the studies.28 That LTH in temporal lobe epilepsy does not necessarily reflect lateral deactivation due to hippocampal cell loss is further supported by our present findings confirming previous observations that temporal hypometabolism can occur in the absence of any identifiable pathology;22 25 and that pathologically established mesial temporal sclerosis is not necessarily associated with abnormal interictal metabolism.8

An alternative hypothesis is that metabolic changes in temporal lobe epilepsy may, at least partially, relate to the mechanisms involved in the generation and propagation of epileptic activity. Leidermann et al29 found a relative increase in the metabolic rate of the epileptogenic temporal lobe after a partial seizure, that tends to persist more after a complex partial than after a simple partial seizure (48 and 24 hours respectively), indicating that postictal metabolic changes may be graded according to the magnitude of the preceding electrophysical...
event. Savic et al showed that the spatial pattern of interictal hypometabolism may be influenced by the electroclinical expression of the preceding partial seizure, being limited in patients with strictly limbic seizures and more extensive in those with subsequent limb posturing. Schlaug et al recently suggested that the hypometabolic pattern shows not only possible epileptogenic zones but also symptomatic brain regions.

It is possible that the hypometabolic pattern in temporal lobe epilepsy is multifactorially determined as none of the so far implicated factors (hippocampal neuronal loss, structural changes of the lateral temporal neocortex, electroclinical seizure pattern) has been shown to exert an exclusive causative effect on it. It is also uncertain to what extent regional hypometabolism reflects a degree of epileptogenicity. On the assumption that subclinical and ictal discharges propagate through neuronal pathways of the lowest inhibitory potential, and given the fact that neuronal inhibition is an active process associated with increased glucose metabolism, it is suggested that interictal regional hypometabolism in temporal lobe epilepsy delineates a field of reduced rather than increased inhibition with the reduction of the inhibitory synaptic activity accounting for the decrease of energy requirements. In this context, the postictal relative increase of the metabolic rate in the epileptogenic temporal lobe can be attributed to inhibitory mechanisms that are temporarily engaged to suppress subsequent ictal events. The fact that IRSA recorded on scalp EEG and interictal spiking in acute EcoG propagate through hypometabolic regions provides further support for this hypothesis.

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