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Insular interictal PET hypometabolism in patients with ictal asystole

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SUMMARY

We aimed to explore brain area(s) involved in the generation of ictal asystole (IA) by analysing the interictal PET metabolism of patients with IA recorded by video-EEG or video-SEEG.

We identified in our cohort of focal epilepsy patients who had undergone pre-surgical evaluation, those who had a recorded period of IA of more than three seconds. We investigated the anatomo-metabolic changes (interictal ^{18}F -FDG PET) of these patients in comparison with 1/ healthy subjects with similar age and sex distribution (n=19) using whole-brain voxel-based analysis (p-voxel<0.001, p-cluster<0.05, uncorrected), 2/ patients without IA with similar age and seizure onset zone (n=55).

We found 12 patients with IA. Epilepsy was mainly temporal (four right temporal mesial, four bi-temporal, two left temporal lateral, one right temporal lateral and one right temporal “plus”). Seven patients had negative-MRI. Whole-brain statistical analysis of PET imaging was performed at the voxel-level, showing that in comparison to healthy subjects and to epileptic patients without IA, a hypometabolism in the right posterior insula characterized epileptic patients with IA.

Our study suggests involvement of the right posterior insula - a part of the central autonomic network - in the pathophysiological mechanism of IA.

Key Words: Epilepsy, Seizure, Asystole, PET, Insula

INTRODUCTION

Ictal asystole (IA) is characterized by a sinus arrest triggered by an epileptic seizure,¹ and is thought to be a dramatic manifestation of changes induced within cardiovascular central autonomic control. It has been reported in between 0.2-0.4% of patients with epilepsy evaluated by long-term video-EEG^{2,3}, mostly occurring without pre-existing cardiac conditions. IA occurs during focal epileptic seizures on average starting 30 s after seizure onset³, and can be observed at the beginning of epilepsy or after many years of evolution^{2,3}. It has been mostly observed during temporal lobe seizures (about 80%), also some reports of extratemporal seizure origin exist^{2,3}. The lateralization is variable across studies³, with a possible predominance of left-sided seizures².

The potential pathophysiology of IA could be linked to alterations within the central autonomic network^{3,4} induced by seizures. Notably, insular, cingulate, orbito-frontal and temporal anterior direct cortical stimulation may induce cardiac rhythm changes⁵⁻⁷. Moreover, a stereo-EEG (SEEG) study suggests the implication of insular structures⁸ but the underlying pathophysiology remains largely unknown. The occurrence of IA in seizures originating from different seizure onset zones also challenges the ability to make anatomico-clinical correlation.

The study of interictal brain metabolism by ¹⁸F-FDG PET can reveal hypometabolism within specific brain networks occurring in patients with a particular ictal semiology, which may improve our understanding of mechanisms involved in the generation of these ictal manifestations⁹. Here, we have studied the interictal metabolism of patients who presented with IA during video-EEG or SEEG recordings and suffering from different

anatomo-clinical forms of epilepsy, in comparison to healthy subjects and epileptic patients without IA.

METHODS

From a database of patients who had continuous video-scalp-EEG or video-SEEG recordings, for presurgical evaluation of drug-resistant epilepsy in our department since 2005, we identified patients reported to have had IA. IA was defined as a cardiac pause longer than three seconds³, associated with clinical signs and EEG changes evocative of syncope. The putative seizure onset zone was defined using non-invasive data (clinical signs, EEG ictal onset, MRI data) and when available invasive SEEG recordings or/and surgical data (resection zone). We used whole-brain voxel-based analysis to compare cerebral metabolism in ¹⁸F-FDG PET between 12 epileptic patients with ictal asystole, and two different controls: 1) a group of healthy subjects similar for age and sex acquired in the same centre with the same protocol (NCT00484523) and 2) a group of patients with drug-resistant epilepsy but without ictal asystole similar for age and putative seizure onset zone (from all available patients explored during the same time period, and with a clear seizure onset zone demonstrated by SEEG or with seizure free outcome following resective surgery).

Healthy controls

Healthy subjects, without neurological/psychiatric symptoms or antecedent diagnosis, and with normal brain MRI, who underwent an ¹⁸F-FDG brain PET in our department, were

selected from a previous study including 60 subjects (NCT00484523) with similar distribution of age and sex compared to epileptic patients.

¹⁸F-FDG PET imaging and processing

¹⁸F-FDG brain PET scans were acquired in the same centre using an acquisition protocol conforming to European guidelines, at resting-state, in subjects fasting for at least 4h with a controlled, normal glycaemic level, using an integrated PET/CT General Electric camera (Waukesha, WI), after an intravenous administration of 150 MBq per 15-min acquisition at 30min post-injection. Images were reconstructed on a 192×192 matrix using the ordered subsets expectation maximization algorithm and corrected for attenuation using a CT transmission scan. All PET imaging were performed during the hospital admission for phase 1 of presurgical evaluation as part of the non-invasive video-scalp-EEG and neuroimaging evaluation. There was no EEG monitoring during PET scans. The interictal nature of PET scans was established by clinical observation 15 min prior to FDG administration and during the uptake period of 30 min, and also retrospectively by the visual interpretation of each exam (no focal hypermetabolism or global hypometabolism in patients with or without IA).

Whole-brain statistical analysis was performed at the voxel-level using SPM8 software (Wellcome Department of Cognitive Neurology, University College, London, UK) to compare patients to healthy subjects with consideration of their age and sex as covariables, and to identify cluster(s) of hypometabolism in these patients.

The PET images were spatially normalized onto the Montreal Neurological Institute (MNI) atlas. The dimensions of the resulting voxels were 2×2×2 mm. The images were then smoothed with a Gaussian filter (8 mm full-width at half-maximum) to blur individual

variations in the gyral anatomy and to increase the signal-to-noise ratio. Proportional scaling was performed to give the same global metabolic value to each PET examination.

The SPM(T) PET maps were obtained at an uncorrected height threshold (voxel-level significance) of $p < 0.001$ (corresponding to a T-value of 3.42), and an uncorrected p-value for the cluster of $p < 0.05$. Moreover, individual analysis of patients with IA was performed comparing PET brain metabolism of each patient to the group of healthy subjects using this same T-value threshold to take into account of the difference of sample size ($T > 3.42$).

Finally, metabolic differences between epileptic patients with IA vs without IA were tested: 1/ at whole-brain voxel-based level using the same previous statistical threshold (p -voxel < 0.001 and p -cluster < 0.05 , uncorrected), and 2/ at cluster level after extraction of mean metabolic values of the cluster(s) previously found between patients with IA and healthy subjects ($p < 0.05$, t-test). This last extraction was done using Marsbar (<http://marsbar.sourceforge.net/>).

Standardized Protocol Approvals, Registrations, and Patient Consents

The institutional review board of the French Institute of Health (IRB15226) approved this study and written patient consent was obtained.

RESULTS

We report the data from 12 patients with drug-resistant focal epilepsy and ictal asystole (nine women, mean age = 31.3, age range = 17 – 50; details in Table 1). The mean duration of ictal asystole was 20.4 seconds (min-max= 5-30 seconds) and the mean monthly seizure frequency was 2.3 (min-max=0.33-12). The seizure onset zone was defined using video-SEEG

recordings for three patients and video-scalp-EEG recordings for the remaining nine patients. Of the three patients explored with video-SEEG, only one patient had ictal asystole during SEEG recording. In this patient, ictal asystole appeared 40 seconds after a left mesio-temporal seizure onset with secondary contralateral seizure spread including right mesio-temporal and mid insular regions (third *gyrus brevis*; notably the left insula was not sampled). The seizure onset zone was defined as follows: four right temporal mesial, four bi-temporal, two left temporal lateral, one right temporal lateral and one right temporal “plus” (temporo-fronto-parietal). MRI showed an epileptogenic lesion in five patients with two right temporal mesial cavernoma, one bilateral periventricular nodular heterotopia, one perinatal stroke and one with sequelae of left anterior temporal lobectomy (previously mild malformation of cortical development, mMCD). Only one patient had a lesion involving the right insular cortex (perinatal stroke). At the end of presurgical evaluation, three patients were operated (two right and one left anterior temporal lobectomy) with two becoming seizure-free.

We compared the patients with IA to 55 patients with drug-resistant focal epilepsy without IA (28 women, mean age = 36.1, age range = 14-60, 16 with bitemporal, 16 with right temporal mesial, eight with right temporal lateral epilepsy, seven with right temporal “plus”, and six with left temporal lateral epilepsy).

Nineteen healthy subjects were selected to have similar distribution of age and sex with epileptic patients (31.33yrs \pm 10.44 for patients vs 31.58yrs \pm 6.74 for healthy subjects; 75.0% female patients vs 73.7% female for healthy subjects; $p>0.67$).

Whole-brain PET imaging statistical analysis, in comparison to healthy subjects, showed that patients with IA had a significant cluster of brain hypometabolism in the right posterior

superior insula / opercular region (p -voxel <0.001 ; p -cluster = 0.05; k = 225 voxels; T-voxel max = 4.98; MNI coordinates of voxel max: 40 0 18; Figure 1). Individual Z-scores of all patients within the cluster, in comparison to healthy subjects, were all <-6 . There was no other brain area with statistically significant hypometabolism at the group-level. Individual maps of significantly hypometabolic voxels of each patient with IA in comparison to healthy subjects is shown in the *Supporting Information*.

At voxel-level using SPM, no significant whole-brain difference was found between patients with or without IA at the previous fixed statistical threshold (p -voxel <0.001 , uncorrected).

At cluster-level after Marsbar extraction, the cluster of hypometabolism in the right posterior superior insula / opercular region found between patients with IA and healthy subjects was hypometabolic in patients with IA in comparison to patients without IA (difference in mean metabolic cluster values: $p<0.001$, t-test).

DISCUSSION

In this study, we found that the right posterior insular opercular region interictal metabolism was significantly lower in patients with temporal lobe epilepsy and ictal asystole compared to healthy subjects and also in epileptic patients with similar seizure onset but without IA. This region could therefore be involved in the genesis of IA, during the propagation of epileptic seizures from the temporal lobe structures.

While the exact relationships between interictal brain hypometabolism and the spatial organisation of seizures are complex, previous studies have indicated that interictal hypometabolism is related to the location of the seizure onset zone and the regions that are

the sites of early propagation¹⁰⁻¹². For instance, studies have correlated interictal hypometabolism in motor networks in patients with hyperkinetic seizure semiology^{13,14} and para-hippocampal gyrus hypometabolism is present in patients with *déjà-vu*⁹, in agreement with the suspected ictal pathophysiology. Our findings, in this cohort, suggest a probable alteration of the right insula, which is part of the central autonomic network, in focal seizures leading to ictal asystole. The usual delay of several seconds before the appearance of ictal asystole after the seizure onset² also suggests a mechanism triggered by seizure spread. Indeed, seizures were thought to have temporal rather than insular onset; however, the insula is extensively connected to temporal and other extratemporal structures and thus is a frequent part of the propagation network for seizures originating from other lobes. Clearly, the seizure spread will also not be limited just to the right insula in our patients, but our data suggests that right insula may be involved by seizures with ictal asystole. This hypothesis is consistent with the fact that cardiac rhythm is under the control of central autonomic centres including insula, ventromedial prefrontal cortex, cingulum and amygdala⁴. These cortical structures are directly and indirectly connected through thalamic nuclei and/or hypothalamus with autonomic centres located in the medulla oblongata⁴. It is therefore possible that a cortically mediated transient excessive vagal tone during focal seizures involving these structures leads to ictal asystole, although the exact pathophysiology is still not well elucidated³. Consistent with this hypothesis, an animal experimental study has found synchronization between chemically induced epileptic activity and cardiac vagal neural discharges¹⁵. The exact location (and potential lateralisation) of the insula cardiac autonomic control remains debated. The posterior (and central) insula region, located on the border of chemosensory and somato-motor insular functional subdivisions, has been implicated in multiple neuroimaging studies in the processing of painful, somato-

and viscerosensory and interoceptive stimuli, including associations with heart rate and heart rate variability¹⁶. Intracerebral electrical stimulations also provide interesting findings about the brain regions that cause changes in cardiac rhythm. In one study, intraoperative insular stimulation during a temporal lobectomy was able to produce bradycardia (more often on the left side) without leading to an ictal asystole⁵. Of note, the posterior insula was not accessible to stimulation with this technique and the high current intensities used make it possible that there may have been activation of other adjacent areas. Two recent SEEG studies, showed that stimulation of the posterior insula could induce bradycardia, without predominance on the side^{6,17}. Specifically, bradycardia was induced by stimulation of the posterior insula just behind the central sulcus and in the superior half⁶. Our results from FDG-PET analysis, demonstrating a hypometabolism of the posterior part of the insula is in agreement with these stimulation data. One study was able to induce IA by stimulating the anterior cingulum⁷. Moreover, a SEEG recording of an ictal asystole demonstrated a seizure spread within the posterior insula at the time of the ictal asystole⁸. Ictal asystole has been also recorded during intracranial EEG recordings of bitemporal mesial and right frontotemporal seizures^{7,18}, but these older studies did not include insular sampling.

Our study has several limitations notably the relatively low number of subjects (ictal asystole being a rare event during video-EEG/SEEG) and the lack of intracerebral EEG recordings of the right insula in all our patients to confirm the ictal spread within this area. The lateralisation of interictal hypometabolism in the right insula, at the group level, could also be influenced by the higher proportion of right or bilateral compared to left temporal onset epilepsies in our cohort. In previous studies, IA has been more often (50-65%) observed in left seizure onset zones^{2,3}. However, in this study all patients even with left temporal epilepsy had significant hypometabolism within the right insula. Moreover, other factors

than ictal asystole could contribute to the observed interictal hypometabolism in our patients.

In conclusion, we have found an interictal significant hypometabolism in the right posterior insula in patients with focal seizures inducing ictal asystole. It suggests potentially a common alteration in the cerebral regulation of cardiac rhythm, involving the insula, independently of the seizure onset zone.

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DISCLOSURE

None of the authors has any conflict of interest to disclose

ETHICAL PUBLICATION STATEMENT

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

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Figure 1: Significant cluster of brain ¹⁸F-FDG PET hypometabolism at the group-level for the patients with ictal asystole.

In comparison to healthy subjects, patients with ictal asystole presented with significant brain hypometabolism of the right posterior insula/opercular region (p-voxel < 0.001, p-cluster < 0.05, uncorrected). Results are expressed as T-score.

Patient Number	Age at investigation (years)	Sex	Language Dominance	Duration IA (seconds)	Monthly Seizure Frequency (mean)	MRI lesion	Seizure Onset Zone	Ictal Activity at time of IA	IA recorded during	SEEG	Surgery (histology)	Post-surgical outcome (follow-up)
1	17	W	L	20	1	Bilateral periventricular heterotopia	Bitemporal	Bitemporal	EEG	Yes	No	NA
2	32	W	L	27	2	No	R temporal lateral	L temporal (anterior to posterior spread)	EEG	No	No	NA
3	22	W	L	30	3	No	R temporal mesial	R temporal	EEG	No	Yes (aspecific)	Seizure-free (3 month)
4	27	W	L	27	1	No	Bitemporal	R temporo-frontal + L temporal	EEG	No	No	NA
5	20	W	L	25	1	No	R temporal mesial	Bitemporal	EEG	No	No	NA
6	35	W	Bilateral*	15	12	No	Bitemporal	Bitemporal + R insula	SEEG	Yes	No	NA
7	41	W	L	20	2	No	Bitemporal	Bitemporal	EEG	No	No	NA
8	44	W	L	30	1	L anterior temporal lobectomy	L temporal lateral (after surgery)	L temporal	EEG	No	Yes (mMCD)	Not seizure-free (7 years)
9	34	W	L	19	1	No	R temporal lateral	R temporo-fronto-parietal	EEG	No	No	NA
10	34	M	L	5	0.33	R temporo-mesial cavernoma	R temporal mesial	R temporal	EEG	No	No	NA
11	50	M	L	5	2	R temporo-mesial cavernoma	R temporal mesial	R temporal	EEG	No	Yes (cavernoma)	Seizure-free (4 years)
12	20	M	L	22	1	R perisylvian perinatal stroke	R perisylvian (temporo-insulo-fronto-parietal)	R temporo-fronto-parietal	EEG	Yes	No	NA

Table 1: Clinical features of the 12 patients analysed

W: women / M: men / mMCD: mild malformation of cortical development / NA: not applicable / L: left / R: right

*Language dominance was evaluated using manual dominance, neuropsychological assessment, ictal semiology, fMRI (and effect of stimulation during SEEG recording for one patient). * (right-handed with history of left-handed persons in the family, SEEG stimulation with disturbance of language on both hemispheres)*