

Electroclinical features of lateral and medial orbitofrontal epilepsy: a case series

Yiou Liu, Siyu Wang, Bo Hong, Haixiang Wang, Jiuluan Lin, Jie Shi, Tong Zhao, Jianjun Bai, Jia Li, Wenjing Zhou

IN **EPILEPTIC DISORDERS** 2020/6 Vol 22 , PAGES 759 TO 767

PUBLISHER **JLE**

ISSN 1294-9361

DOI 10.1684/epd.2020.1230

Uploaded: 09/16/2024

Article available online at

<https://stm.cairn.info/revue-epileptic-disorders-2020-6-page-759?lang=en>



Discover the contents of this issue, follow the journal by email, subscribe...
Scan this QR code to access the page for this issue on Cairn.info.



Electronic distribution Cairn.info for JLE.

You are authorized to reproduce this article within the limits of the terms of use of Cairn.info or, where applicable, the terms and conditions of the license subscribed to by your institution. Details and conditions can be found at cairn.info/copyright.

Unless otherwise provided by law, the digital use of these resources for educational purposes is subject to authorization by the Publisher or, where applicable, by the collective management organization authorized for this purpose. This is particularly the case in France with the CFC, which is the approved organization in this area.

Electroclinical features of lateral and medial orbitofrontal epilepsy: a case series

Yiou Liu¹, Siyu Wang¹, Bo Hong², Haixiang Wang¹, Jiuluan Lin¹, Jie Shi¹, Tong Zhao², Jianjun Bai¹, Jia Li¹, Wenjing Zhou

¹ Department of Epilepsy Center, Tsinghua University Yuquan Hospital, Beijing, China

² Department of Biomedical Engineering, School of Medicine, Tsinghua University, Beijing, China

Received May 14, 2020; Accepted August 14, 2020

ABSTRACT – *Aims.* To better understand the electroclinical features and epileptic network of lateral and medial orbitofrontal epilepsy (OFE). *Methods.* We evaluated four patients who had undergone epilepsy surgery. Epileptic foci in two patients originated from the lateral orbitofrontal cortex, and those in the other two originated from the medial orbitofrontal cortex, which was confirmed by stereoelectroencephalography (SEEG). Time-frequency spectrograms were also provided for assistance, and the change in high-frequency energy was superimposed on the 3D reconstructed brain with a colour code in order to more intuitively show the transfer of high-frequency energy as the seizure evolves. All patients underwent SEEG-guided radiofrequency thermocoagulation (RF-TC) or focal resection and achieved satisfactory results. *Results.* Lateral OFE and medial OFE were relatively independent with regards to clinical symptoms and epileptic network, however, lateral OFE was likely to propagate to the dorsolateral frontal lobe, whereas medial OFE (gyrus rectus) was more likely to propagate to the medial temporal lobe or insular lobe with long duration. There were significant differences in duration (21.17 ± 11.5 vs. 127.22 ± 235.05) and early propagation time (7.92 ± 4.44 vs. 29.0 ± 33.47) between the two origins. *Conclusion.* A better understanding of the electroclinical features of lateral and medial OFE is helpful to understand their epileptic networks and perform accurate resections in order to protect the cognitive and behavioural functions of patients.

Key words: lateral orbitofrontal epilepsy, medial orbitofrontal epilepsy, high-frequency energy, radiofrequency thermocoagulation (RF-TC), surgery

Correspondence:

Wenjing Zhou
Department of Epilepsy Center,
Tsinghua University Yuquan Hospital,
No.5, Shijingshan Road,
Shijingshan District,
Beijing, 100049, China
<liuyiou1125@126.com>
<closejeo@hotmail.com>

The orbitofrontal cortex (OFC), which rests on the roof of the orbit, is one of the least explored regions of the cerebral cortex (Geier *et al.*, 1977; Chauvel *et al.*, 1995; Niedermeyer *et al.*, 1998; Bartolomei *et al.*, 2000).

Epileptic seizures starting from the OFC have been less characterized in comparison with other types of epilepsy. The main reasons for the rare studies of medial OFE and lateral orbitofrontal epilepsy (OFE) may be the complexity of

anatomical partition, rare cases, inaccessibility of this region to surface electrodes and the resulting need for invasive recordings. In a previous review reporting the largest number of OFE, only 32 cases could be established as OFE, which was based on the criteria of a lesion localized in the OFC or the patient being seizure-free after surgical removal of the OFC in cases of non-lesional OFE; these diagnostic criteria could be disputed. Chibane *et al.* also pointed out that further study is required to identify discriminative features between medial and lateral OFE (Chibane *et al.*, 2017). OFC has vast bidirectional connectivity to a distributed network involving the frontal lobe, the temporal lobe, and the limbic system (Wang *et al.*, 2013). Kriegel *et al.* reported that OFE presents with either frontal lobe type seizures or temporal lobe type seizures depending on the spread pattern (Kriegel *et al.*, 2012), however, no specific area, representative of where these symptoms occur, was described. In humans, indeed in all primates, the posterior part of the OFC is connected with the anterior part of the insula (Cavada *et al.*, 2000). Smith *et al.* verified this by stimulating 13 posterior orbitofrontal sites and inducing a variety of sensations, which were mainly body tingling (Smith *et al.*, 2004). Rostrally placed OFC blends into the dorsolateral part of the prefrontal cortex. However, no study has identified the discriminative features and connection between medial and lateral OFE. Moreover, outcomes of surgery in patients with epilepsy originating solely from the medial or lateral OFC remain uncertain. Lesions or damage to the OFC have been associated with significant changes in emotion, personality, behaviour, and social conduct. The most recent reports indicate that prefrontal seizures, particularly ventromedial seizures, are correlated with strong emotionality and vocalization with bilateral and symmetrical hyperkinetic movements, and the dorsolateral part may manifest as stereotyped hyperkinetic movements with moderate vegetative signs, speed, and vocalization (Fayerstein, 2020). Marseille's cluster analysis study elaborated on the symptomatology and related localization of frontal lobe seizures. Although the symptomatology of each representative region of the OFC was not presented, the study showed that the lateral orbitofrontal area (BA 47/12) may be associated with relatively integrated movement, such as distal stereotypies or manipulative behaviour, and the medial orbitofrontal area (BA 14, BA11) may be associated with feelings of fear/anxiety/rage and negative emotional expression (Bonini *et al.*, 2014). This is possibly due to the interaction between the prefrontal lobe and temporal lobe, in particular, the ventromesial cortex such as the hippocampus and anterior cingulate region (Alberto, 2005; Fayerstein, 2020). A better understanding of the electroclinical features of medial and lateral OFE is therefore helpful for us to understand

their characteristics and perform accurate resection, in order to protect the cognitive and behavioural functions of patients (Pereira *et al.*, 2015). In this study, we selected cases in which seizures originated solely from medial or lateral OFC in order to explore electroclinical differences. In addition, epileptogenicity index and high-frequency oscillations (HFOs) were selected as the bio-electrical markers to demonstrate the seizure onset zone (SOz) and early propagation region.

Methods

Four patients who had undergone epilepsy surgery were enrolled at the Epilepsy Center of Yuquan Hospital Tsinghua University in Beijing. The epileptic foci in two patients originated from the lateral OFC and those in the other two from the medial OFC, which was confirmed by SEEG. We defined the lateral OFC as situated lateral to the lateral orbital sulcus and joined to the pars orbitalis of the inferior frontal gyrus, and defined the medial OFC as located within the medial orbital sulcus (Pereira *et al.*, 2015). The gyrus rectus, which lies along the medial margin of the orbital lobe, was also classified as the medial part. Tailored resection or RF-TC guided by SEEG was performed on all patients. The patients underwent a comprehensive presurgical evaluation, including MRI, long-term video-EEG (VEEG), positron emission tomography (PET), and a neuropsychological test. MRI scans of three-dimensional (3D) T1-weighted 1.0-mm-thick contiguous slices, fluid-attenuated inversion recovery (FLAIR) sequences, double inversion recovery (DIR) sequences, and T2-weighted (2D, axial, and coronal) and FLAIR sequences (2D, axial and coronal) were obtained. SEEG was proposed to identify the EZ and better define a possible surgical resection limit. Between 6 and 16 electrodes with multiple contacts (10–15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) were implanted per patient depending on the suspected origins in stereotactic conditions. Anatomical locations of the electrode leads were checked by the fusion of post-implantation CT with the reconstruction of the 3D image based on a preoperative T1-weighted MRI (Liu *et al.*, 2019; Bai *et al.*, 2019). Intracerebral recordings were performed using a video EEG system (Nihon-Kohden, Tokyo, Japan) with a sampling rate of 2,000 Hz. All seizures were reviewed by two independent reviewers.

Time-frequency spectrograms were also provided for assistance, which were calculated automatically by built-in software from Nihon Kohden. We used this measure to characterize epileptogenic activity and energy transfer. The presence of rapid discharges can be quantified after the transformation of raw SEEG signals (using a Morlet wavelet transform [MWT]) into

the time-frequency plane around seizure onset; the baseline is automatically set to the beginning of the waveforms. Temporal spectral evolution (TSE) on a colour scale shows the amplitude and power change in each frequency band for each time period (Quyen *et al.*, 2001). In order to visualize the high-frequency energy changes, we used Brainstorm to calculate the epileptogenicity index and presented high-frequency energy on the 3D brain (David, 2011; Tadel *et al.*, 2011). The notion of the “epileptogenicity index” was first introduced by Bartolomei and was applied to SEEG signals to perform quantified studies of different types of seizures (Bartolomei *et al.*, 2008). Our approach to the epileptogenic index is a modification of the methodology, but retaining the same philosophy.

We generated MWTs on a logarithmic scale, from 1 to 150 Hz, using the “flattening” option to amplify the higher frequencies and produce a more visually appealing image. A baseline of at least 20 s was chosen within the 2 min preceding the seizure, which needed to be void of any artifact. The baseline MWTs were used to normalize the seizure data of MWTs (Grinenko *et al.*, 2018). We also superimposed the change in high-frequency energy on the 3D reconstructed brain with a colour code in order to more intuitively show the transfer of high-frequency energy as the seizure evolves. When several seizures were recorded in the same patient, all corresponding data could be pooled together to complete data analysis.

After the SEEG evaluation, patients underwent a tailored resection, or RF-TC of the identified epileptogenic zone. Postoperative MRI was acquired at least six months after surgery. Seizure outcomes were assessed by neurosurgeons according to the Engel scale.

Results

The clinical and SEEG data of four patients are displayed in *table 1*. A total of 21 predominantly sleep-related seizures were recorded.

Lateral OFE: Patients 1 and 2

Patients 1 and 2 had negative MRI images. Interictal discharges were limited to the anterior head. Hypometabolism on PET was found in the frontal area for one patient, and the other had no significant change; no hypometabolism in the temporal lobe was found in either patient. According to the scalp EEG, seizures arose from one side of the anterior head (Patient 1) or SOZ was unclear (Patient 2). Clinically, Patient 1 and Patient 2 had no symptoms at the beginning of the seizures, and then hypermotor symptoms appeared. When discharges propagated to the lateral part of the frontal lobe, the clinical manifestations of

the two patients were extremely similar, beginning with pelvic thrusting, pedalling or raising of the legs; the manifestations were mild in Patient 1 and severe in Patient 2. Neither patient had a generalized tonic clonic seizure. There were no significant vegetative neurological symptoms. Based on the SEEG, 12 clinical seizures from two patients were recorded with an average duration of 21.17 ± 11.5 s; both seizures started in the lateral OFC with low-voltage fast activities, then propagated to the lateral part of the frontal lobe accompanied by hypermotor symptoms. The average duration of early propagation was 7.92 ± 4.44 s.

A time-frequency plane confirmed that high-frequency energy started earlier in the lateral OFC, followed by the lateral part of the frontal lobe, with Patient 1 propagating to the superior frontal sulcus and inferior frontal gyrus and Patient 2 propagating to the pars opercularis, middle frontal gyrus, and pars triangularis. This process was accompanied by delays or a decrease in frequency energy power. There was no high-frequency response in the temporal lobe (*figure 1C, 2C*). Epileptogenicity index analysis confirmed that the highest epileptogenicity index values for Patients 1 and 2 were in the lateral OFC (*figure 1F, 2F*). For Patient 1, dynamic high-frequency energy analysis of the 3D image showed early involvement of the lateral part of the OFC, followed by activation of the lateral part of the frontal lobe (2-3 s), after which energy increased when symptoms appeared (5-6 s) (*figure 1D*). For Patient 2, high-frequency oscillations originated from the lateral orbital gyrus, followed by the activation of the lateral part of the frontal lobe (12 s) and an increase of energy power in these areas (*figure 2D*).

RF-TC was performed for Patient 1 in the lateral OFC, and she had one simple partial seizure after 14 months. RF-TC was initially performed for Patient 2, and he was seizure-free for 12 months; when seizures recurred, he had right orbitofrontal lobe resection and had no seizures after six months of follow-up.

Medial OFE: Patients 3 and 4

The two patients had negative MRI images. Interictal discharges arose from one side or bilateral sides of the anterior head. Hypometabolism on FDG-PET was found in the frontotemporal lobe for one patient and in the temporal lobe for the other. Seizure onset was characterized by a slow wave or sharp discharges from one side of the anterior head. No specific aura was found. No symptoms were found at the beginning of the seizures. Symptoms appeared when discharges propagated to eloquent areas. Both patients showed the symptoms of medial temporal lobe epilepsy, including oral-facial and manual automatism, impaired awareness, and vegetative nervous symptoms such as

Table 1. Clinical and SEEG features of studied patients

	Lateral orbitofrontal		Medial orbitofrontal	
	Patient 1	Patient 2	Patient 3	Patient 4
Age at onset (y)	6	8	2	11
Age at SEEG (y)	7	34	3	17
Main semiology	Pelvic thrusting, pedalling, awareness	Pelvic thrusting, pedalling, awareness	Palpitations, manual and oral-facial automatism, impaired awareness	Attention impairment, manual and oral-facial automatism
MRI	normal	normal	normal	normal
PET (hypometabolism)	R-frontal	normal	L-frontotemporal	L-temporal
Interictal (scalp)	R-frontotemporal	R-anterior head	L-anterior head	Bil-anterior head
Onset (scalp)	R-frontal slow	none	anterior head Slow wave	L-temporal Sharp wave
No. electrodes (contacts)	6 (94) right	14 (200) 4 left, 10 right	9 (140) left	16 (236) 9 left, 7 right
Total seizure	5	7	2	7
Mean duration (s)	21.17±11.5 *		127.22±235.05	
Onset (SEEG visually)	LatOrG (R)	LatOrG (R)	Rectus gyus (L)	Rectus gyus (L)
epileptogenicity index positive zone (SEEG)	LatOrG (R)	LatOrG (R)	Rectus gyus (L)	Rectus gyus (L)
Early propagation area (SEEG)	SFS, IFG	MFG and trIFG	InsP, AM	InsP, TP, Hi,
Early propagation duration (s)	7.92±4.44 *		29.0±33.47	
Surgery/thermocoagulation	RF-TC of LatOrG (R)	RF-TC of LatOrG (R)→OFG (R) resection	Part resection of OFG (L) →rectus (L)	RF-TC of rectus (L)
Histopathology	NA	FCD IIb	FCD IIb	NA
Outcome (Engel)/FU (months)	Class IB (14)	Class IA (6)	Class IA (10)	Class IA (14)

L: left; R: right; InsP: insular pole; AM: amygdala nuclei; OFG: orbitofrontal gyrus; Bil: bilateral; InsP: insular pole; TP: temporal pole; Hi: hippocampus; NA: not applicable; LatOrG: lateral orbital gyrus; SFS: superior frontal sulcus; IFG: inferior frontal gyrus; MFG: middle frontal gyrus; trIFG: pars triangularis; RF-TC: radiofrequency thermocoagulation. * $p < 0.05$ (lateral orbitofrontal vs medial orbitofrontal).

palpitations and hyperventilation. Intracranial monitoring recorded nine clinical seizures with an average duration of 127.22 ± 235.05 s. SEEG indicated that both seizures started in the rectus gyus with low-voltage fast activities, then propagated to the medial structure of the temporal lobe or insular lobe and showed

symptoms associated with the limbic system (figure 3C, 4C). The average duration of early propagation was 29.0 ± 33.47 s. We defined the ipsilateral propagation time as the time elapsed from electrographic seizure onset to initial spread to an adjacent ipsilateral lobe.

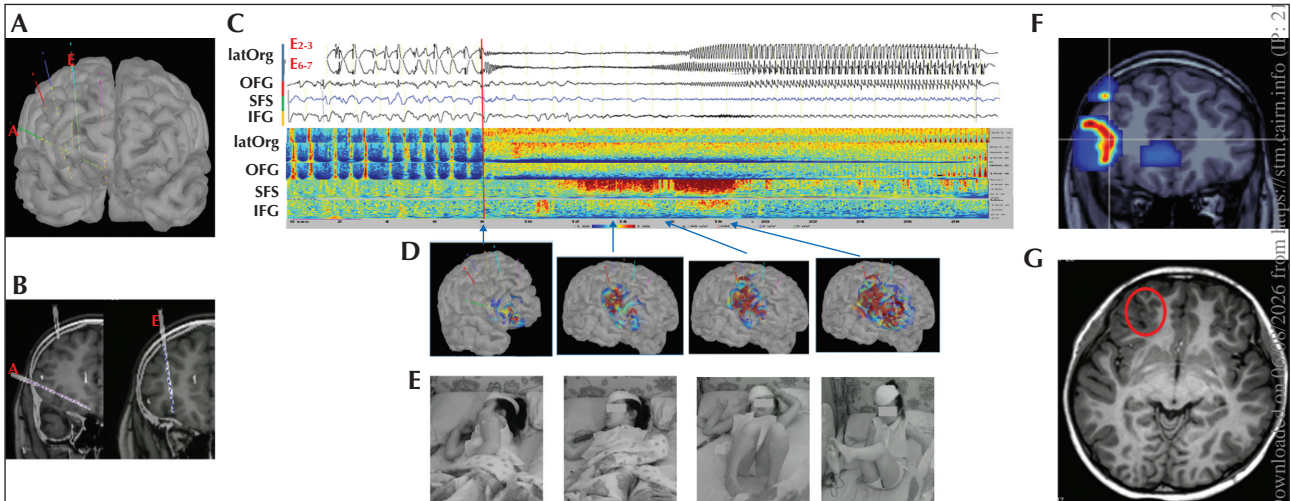


Figure 1. SEEG recordings of Patient 1. (A) Three-dimensional MRI reconstruction of the depth electrodes. The electrodes explored the medial and lateral part of the right frontal lobe. The middle part of electrode A (latOrG) and internal contact of electrode E (from MFG to latOrG) captured the seizure onset. (B) The actual placement of electrodes A and E shown on a 3D MRI image. (C) Seizures started with low-voltage fast activities in the latOrG (vertical bar indicates seizure onset), then propagated to SFS and IFG. SEEG power in the time-frequency plane (below): SOZ is characterized by early rapid discharges and high-frequency energy in latOrG, followed by SFS and IFG. (D) The high-frequency signal was superimposed on the 3D reconstruction image, showing early involvement of the latOrG and transfer of high-frequency energy from the latOrG (0 s) to the lateral part of the frontal lobe (2–3 s), then energy increased when symptoms appeared (5–6 s). (E) The patient had no symptoms at the beginning of the seizure; when propagating to the lateral part of the frontal lobe, the patient woke up with pelvic thrusting, pedaling or raising of the legs. (F) Epileptogenicity index values are shown as a colour scale overlying the MRI; the highest epileptogenicity index value was confined to latOrG. (G) Illustration showing sites of thermocoagulation in the latOrG (in red circle); the patient had a simple partial seizure after 14 months. LatOrG: lateral orbital gyrus; OFG: orbitofrontal gyri; SFS: superior frontal sulcus; IFG: inferior frontal gyrus; SOZ: seizure onset zone.

High-frequency energy started earlier from the gyrus rectus, followed by the medial part of the temporal lobe, and in Patient 3 propagated to the amygdala nuclei and hippocampus, and Patient 4 to the insular pole, temporal pole, and hippocampus, as shown in the time-frequency plane (figure 3C, 4C). This process was accompanied by delays or a decrease in frequency energy power. There was no high-frequency response in the lateral part of the frontal lobe. Epileptogenicity index analysis confirmed that the highest epileptogenicity index value was in the rectus gyrus (figure 3E, 4E). High-frequency energy superimposed on the 3D image was highly successful in reconstructing high-frequency energy transfer, which showed early involvement of the medial orbitofrontal lobe, followed by energy activation of the medial temporal lobe (20 s) for Patient 3 and activation of the insular pole and temporal pole (60 s) for Patient 4 (figure 3D, 4D).

Patient 3 underwent two surgical resections. Part of the rectus was missed in the first resection, and he still had frequent seizures. The missed part was then removed in the second resective surgery, and he was seizure-free after 10 months, which confirmed the epileptic origin of the posterior gyrus rectus. RF-TC was performed on the left rectus gyrus of Patient 2, who was seizure-free after 14 months of follow-up.

Discussion

There have been few studies on the electroclinical characteristics of OFE due to the rarity of cases and difficult diagnosis. Description of the anatomical features of the OFC in humans is limited in the literature except for some functional studies involving the general area. A recent anatomical study in humans concluded that five gyri of OFC, namely the gyrus rectus, orbital medial gyrus, orbital anterior gyrus, orbital lateral gyrus, and orbital posterior gyrus, were delimited by four main sulci (Pereira *et al.*, 2015). In most cases, however, the OFC is divided into the lateral, medial, and intermediate cortex by two longitudinal orbital sulci (orbital medial sulcus and orbital lateral sulcus). Therefore, the latter anatomical definition was used in the present study to differentiate the medial part of the OFC from the lateral part of the OFC. The gyrus rectus, which lies along the medial margin of the orbital lobe, is defined as the medial OFC (Jean *et al.*, 2006). Both medial OFE and lateral OFE lack specificity in terms of scalp EEG. In general, interictal or ictal scalp EEG studies are not very helpful in identifying epileptogenic foci residing in the basal frontal lobe because of the hidden location of this part. Orbital discharges may have a regional distribution or appear generalized. In our four patients, the interictal discharges were confined to the

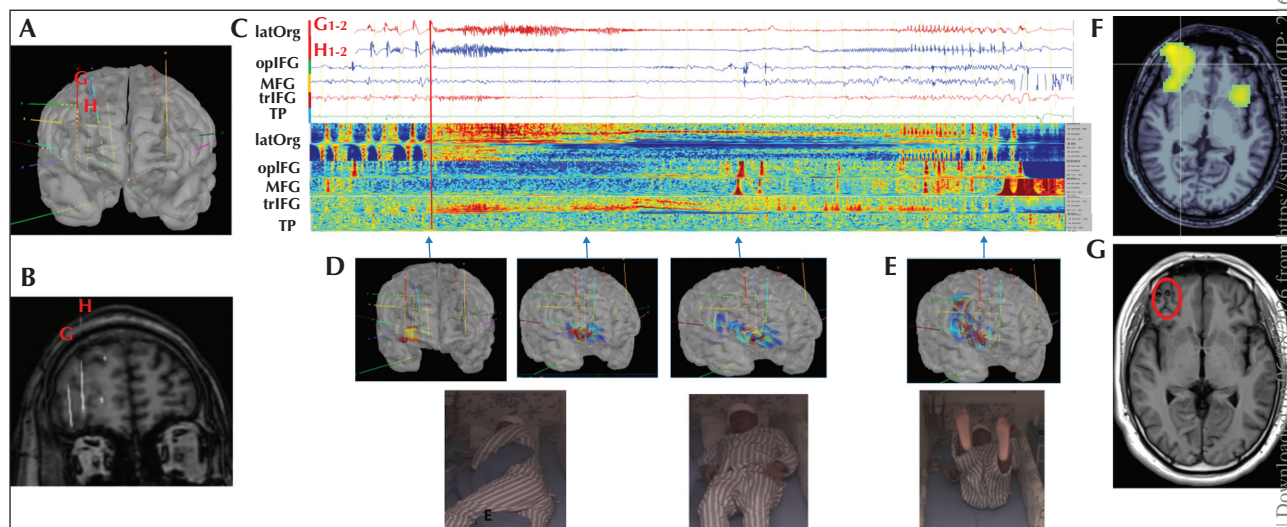


Figure 2. SEEG recordings of Patient 2. (A) Three-dimensional MRI reconstruction of the depth electrodes. The electrodes explored the medial and lateral part of the bilateral frontal lobe, mainly on the right. Electrodes G (from MFG to LatOrG) and H (from MFG to LatOrG, almost parallel to G and more inside) captured the seizure onset. (B) The actual placement of electrodes G and H shown on the 3D MRI image. (C) Seizures started with low-voltage fast activities in the latOrG, then propagated to the MFG and trIFG. SEEG power in the time-frequency plane: SOZ with early rapid discharges and high-frequency energy in latOrG, followed by opIFG, MFG, and trIFG. There was no high-frequency response in the temporal lobe. (D) The high-frequency signal on the 3D reconstruction image showing early involvement of the latOrG (0 s), followed by the activation of the lateral part of the frontal lobe (12 s). (E) The patient had no symptoms at the beginning of the seizure; when propagating to the lateral part of the frontal lobe, he presented with the same symptoms as Patient 1. (F) Based on epileptogenicity index analysis, the seizure onset of the patient was confined to latOrG. (G) Illustration showing sites of thermocoagulation in the latOrG. The patient was seizure-free for 12 months, then seizures recurred; he had right orbitofrontal lobe resection after which no seizures occurred. opIFG: pars opercularis; MFG: middle frontal gyrus; trIFG: pars triangularis.

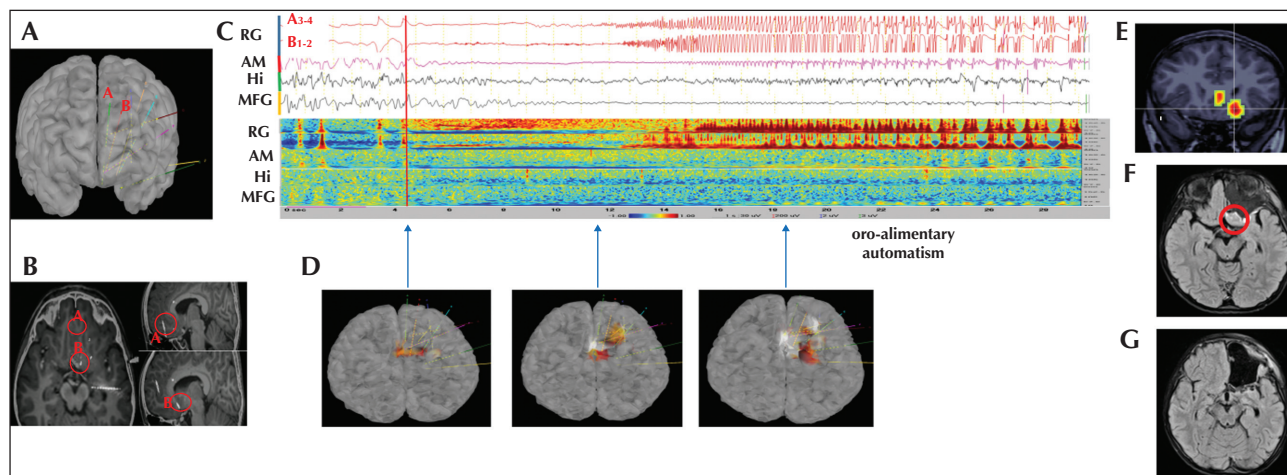


Figure 3. SEEG recordings of Patient 3. (A) The electrodes mainly explored the medial and lateral part of the left frontal lobe. Electrodes A (from SFG to anterior RG) and B (from SFG to posterior RG) captured the seizure onset. (B) The actual placement of electrodes A and B shown on a 3D MRI image. (C) Seizures started with low-voltage fast activities in the RG (internal leads of electrodes A and B), then propagated to AM and Hi, and the patient showed oro-alimentary automatism. There was no high-frequency response in the lateral part of the frontal lobe (MFG). (D) The high-frequency signal on the 3D reconstruction image showing early involvement of the RG (0 s), followed by the activation of the mesial temporal lobe (20 s). (E) Based on epileptogenicity index analysis, the seizure onset of the patient was confined to RG. (F, G) The patient underwent two surgical resections. Part of the RG was missed in the first resection (in red circle), and he still had seizures; the missed part was then removed, and he was seizure-free after 10 months of follow-up. RG: rectus gyrus; postOrG: posterior orbital gyrus; InsP: insular pole; AM: amygdala nuclei; SFG: superior frontal gyrus.

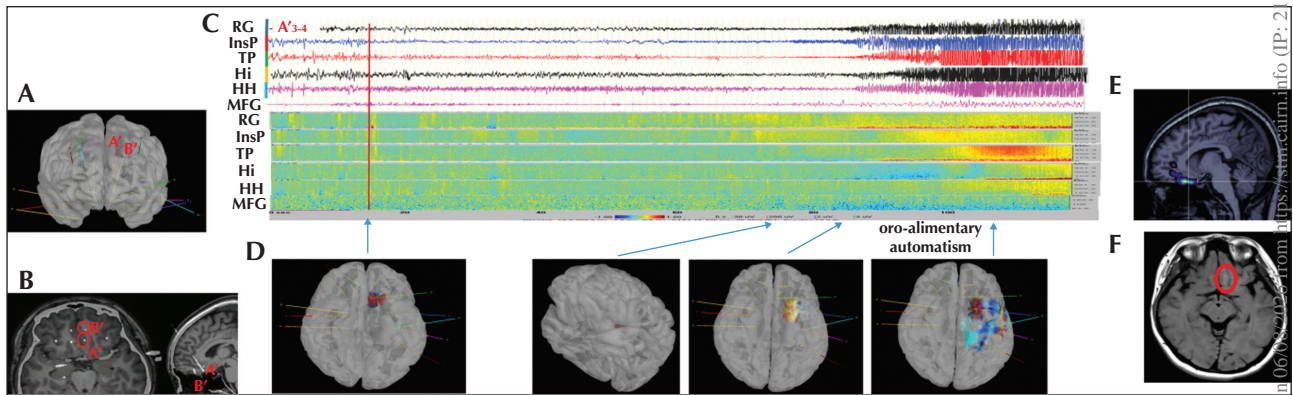


Figure 4. SEEG recordings of Patient 4. (A) The electrodes explored the bilateral medial and lateral part of the frontal and temporal lobe. Electrodes A' (from SFG to posterior RG) and B' (from SFG to anterior RG) captured the seizure onset. (B) The actual placement of electrodes A' and B' (internal contact of electrode) is shown on the MRI image. (C) Seizures started with low-voltage fast activities in the RG (internal leads of electrodes A' and B') then propagated to the insular pole and temporal pole and hippocampus; the patient showed symptoms of oro-alimentary and hand automatism when these areas were involved. (D) The high-frequency signal on the 3D reconstruction image showing early involvement of the RG (0 s), followed by the activation of the insular pole, temporal pole (60 s), and mesial temporal lobe (70-80 s). (E) Based on epileptogenicity index analysis, the seizure onset of the patient was confined to RG. (F) RF-TC was performed in the left rectus gyrus, and the patient became seizure-free after 14 months of follow-up; sites of thermocoagulation in the RG are depicted on the MRI image.

SFG: superior frontal gyrus; RG: rectus gyrus; InsP: insular pole; TP: temporal pole; Hi: hippocampus; HH: head of hippocampus.

anterior head, and the EEG changes at the onset could also be manifested in various forms. Interictal epileptiform discharges always allowed lateralization but not precise localization. Ictal scalp EEG recordings of OFE may provide poor localizing value, since false localization to the temporal region is not uncommon in patients with OFE, such as in Patient 4, whose scalp EEG showed temporal lobe origin, which may lead to false localization. PET identified hypometabolism extending outside the OFC. The medial temporal lobe structure showed low PET metabolism in medial OFE, which may be associated with propagation to the limbic system. However, PET hypometabolism was negative in the lateral OFE group or was confined to the frontal region without involving the medial temporal lobe, explaining the independent network of medial and lateral OFE. The prefrontal cortex may be clinically silent, and seizures usually give rise to ictal manifestations by virtue of propagation to eloquent areas of the cortex. We observed this by using intracranial electrodes; when the seizure started from the OFC, there were no clinical symptoms. In addition, no secondary generalized seizures were found in either lateral OFE or medial OFE, indicating that OFE is less likely to cause GTCS. Frequent features of OFE include predominantly sleep-related seizure occurrence, lack of aura, and hypermotor manifestations such as automatisms and thrashing movements, which is consistent with our report. Some case series have reported sudden motion arrest and unresponsiveness at the beginning (Talairach, 1992; Munari, 1992). Previous literature has indicated that if discharges propagated rapidly from

the OFC to the mesial temporal structures, *déjà-vu* feelings and oral-facial and manual automatisms were most prominent. Hence, OFE is electroclinically indistinguishable from temporal lobe seizures given the widespread connections between the limbic system and the OFC (Shihabuddin, 2001; Rheims *et al.*, 2005). If it spreads to the dorsolateral frontal regions, hyperactive automatisms with frenetic, agitated movements prevail (Kriegel *et al.*, 2012). We observed, through intracranial electrodes, that medial OFE propagated to the medial temporal lobe and insular lobe. The close relationship between the OFC and the limbic system has been well known; the uncinate fasciculus and the so-called ventral and dorsal limbic pathways are the main bidirectional association pathways linking the OFC with the temporal lobe, which explains the close connection between the two. In this study, the lateral part of the OFC propagated to the dorsolateral frontal lobe, and the symptoms were more rigid and movement was integrated. This appears to be more in line with Group 3 of the symptomatology identified by Bonini *et al.* (2014). At the same time, our intracranial electrode also confirmed that this specific manifestation occurred when the discharge propagated to the dorsolateral frontal lobe. Anatomically speaking, the anterior orbital gyrus and the rostral part of the lateral orbital gyrus are considered part of the middle frontal gyrus, which could explain the propagation from the lateral OFC to the dorsolateral part of the frontal lobe. It should be emphasized that this hyperkinetic behaviour is not necessarily limited to the dorsolateral frontal part. The repetitive nature of

some hyperkinetic behaviour suggests the possibility of a similar mechanism which may occur in other clinical conditions. In this study, lateral OFE was shown to be more prone to this relatively integrated and unique movement, without frightened facial expression or screaming. This is more “cortical-dependent” than “subcortical-dependent”, since identical hyperkinetic behaviour could emerge from two distinct independent cortical networks (Bartolomei *et al.*, 2005; Vaugier *et al.*, 2009; Guedj *et al.*, 2012; Vaugier *et al.*, 2017).

In general, seizures arising from the frontal lobe may start and end abruptly and tend to have a shorter duration. Some investigators have observed that “orbitofrontal seizures” propagate more slowly, with a period ranging from 12.5 to 85 s, compared to seizures arising from other frontal regions (Munari *et al.*, 1995). However, our study found that the duration of propagation of OFE depends on where the seizure started. The exact mechanism is unclear.

Two-dimensional (2D) and three-dimensional (3D) epileptogenicity maps, quantifying high-frequency oscillations (HFOs) at seizure onset, demonstrate good reproducibility and sensitivity and have proven helpful for better understanding the epileptogenic brain networks subserving different kinds of focal seizures (Coubes *et al.*, 1993; Bartolomei *et al.*, 2008; Blauwblomme *et al.*, 2011; David *et al.*, 2011; Job *et al.*, 2014).

In ideal circumstances, the orbitofrontal origin of the epilepsy is deduced postoperatively on the basis of a surgical resection restricted to the OFC, leading to long-term cessation of seizures after surgery. Many of the reported cases of OFE were combined OFE and temporal lobe epilepsy cases, for which both regions were resected. Resection of the OFC alone is rare, let alone the distinction between medial and lateral OFE. Additionally, the inclusion criteria for OFE are controversial (Ludwig *et al.*, 1975; Munari *et al.*, 1995). All patients in our group underwent RF-TC or focal resection and achieved satisfactory results, which further supported the focal onset of seizure solely from the medial OFC and lateral OFC.

Limitations

We acknowledge that the number of cases in this study was small due to the restricted criteria. In addition, the medial OFE only covered the gyrus rectus, and did not include other structures medial to the orbital medial sulcus. In addition, the anterior orbital gyrus and posterior orbital gyrus should also be investigated, which requires more detailed research in this area.

Conclusion

In this study, we sought to obtain a better understanding of OFE, in particular, to distinguish the electrical electroclinical features and network between lateral orbitofrontal and medial OFE. The results show that medial OFE and lateral OFE are relatively independent with regards to clinical symptoms and epileptic networks. Moreover, scalp EEG and imaging are not specific, which could be misleading for surgery, therefore intracranial electrodes are needed to further clarify the seizure onset and define a precise resection area in order to protect the cognitive and behavioural functions of patients. □

Disclosures.

None of the authors have any conflict of interest to declare.

References

- Alberto Tassinari C, Tassi L, Calandra-Buonaura G, *et al.* Biting behavior, aggression, and seizures. *Epilepsia* 2005; 46: 654-63.
- Bai J, Zhou W, Wang H, *et al.* Value of stereoelectroencephalography (SEEG)-guided radiofrequency thermocoagulation in treating drug-resistant focal epilepsy. *Brain Sci Adv* 2019; 5(3): 189-202.
- Bartolomei F, Chauvel P. Seizure symptoms and cerebral localisation: frontal lobe and rolandic seizures. In: Oxbury JM, Polkey CE, Duchowny M. *Intractable Focal Epilepsy*. WB Saunders, London, 2000; 55-62.
- Bartolomei F, Chauvel P, Wendling F. Epileptogenicity of brain structures in human temporal lobe epilepsy: a quantified study from intracerebral EEG. *Brain* 2008; 131(7): 1818-30.
- Bartolomei F, Trébuchon A, Gavaret M, Régis J, Wendling F, Chauvel P. Acute alteration of emotional behaviour in epileptic seizures is related to transient desynchrony in emotion-regulation networks. *Clin Neurophysiol* 2005; 116(10): 2473-9.
- Blauwblomme T, Kahane P, Minotti L, *et al.* Multimodal imaging reveals the role of activity in eating-reflex seizures. *J Neurol* 2011; 82(10): 1171-3.
- Bonini F, Mcgonigal A, Trébuchon A, *et al.* Frontal lobe seizures: from clinical semiology to localization. *Epilepsia* 2014; 55(2): 264-77.
- Cavada C. The anatomical connections of the macaque monkey orbitofrontal cortex. A review. *Cerebral Cortex* 2000; 10(3): 220-42.
- Chauvel P, Kliemann F, Vignal JP, *et al.* The clinical signs and symptoms of frontal lobe seizures. Phenomenology and classification. *Adv Neurol* 1995; 66(1): 115-25.
- Chibane IS, Boucher O, Dubeau F, *et al.* Orbitofrontal epilepsy: case series and review of literature. *Epilepsy Behav* 2017; S1525505017305334.
- Coubes P, Awad LA, Antar M, *et al.* Comparison and spacial correlation of interictal HMPAO-SPECT and FDG-

- PET in intractable temporal lobe epilepsy. *Neurol Res* 1993; 15(3): 160-8.
- David O, Blauwblomme T, Job AS, *et al.* Imaging the seizure onset zone with tereo-electroencephalography. *Brain* 2011; 134(10): 2898-911.
- Fayerstein J, McGonigal A, Pizzo F, *et al.* Quantitative analysis of hyperkinetic seizures and correlation with seizure onset zone. *Epilepsia* 2020; 61(5): 1019-26.
- Geier S, Bancaud J, Talairach J, *et al.* The seizures of frontal lobe epilepsy. A study of clinical manifestations. *Neurology* 1977; 27(10): 951-8.
- Grinenko O, Li J, Mosher JC, *et al.* A fingerprint of the epileptogenic zone in human epilepsies. *Brain* 2018; 141(1): 117-31.
- Guedj E, McGonigal A, Vaugier L, Mundler O, Bartolomei F. Metabolic brain PET pattern underlying hyperkinetic seizures. *Epilepsy Res* 2012; 101(3): 237-45.
- Job AS, De Palma L, Principe A, *et al.* The pivotal role of the supplementary motor area in startle epilepsy as demonstrated by SEEG epileptogenicity maps. *Epilepsia* 2014; 55(8): e85-8.
- Kriegel MF, Roberts DW, Jobst BC. Orbitofrontal and Insular Epilepsy. *J Clin Neurophysiol* 2012; 29(5): 385-91.
- Ludwig B. Cerebral seizures of probable orbitofrontal origin. *Epilepsia* 1975; 16(1): 141-58.
- Munari C. Electroclinical symptomatology of partial seizures of orbital frontal origin. *Adv Neurol* 1992; 57(2): 257-65.
- Munari C, Tassi L, Di LM, *et al.* Video-stereo-electroencephalographic investigation of orbitofrontal cortex. Ictal electroclinical patterns. *Adv Neurol* 1995; 66: 273.
- Niedermeyer E. Frontal lobe epilepsy: the next frontier. *Clin Electroencephalogr* 1998; 29.
- Pereira RT, Silva RMA, Paz Daniel de Araújo RMA, *et al.* Orbitofrontal sulcal and gyrus pattern in human: an anatomical study. *Arq Neuropsiquiatr* 2015; 73(5): 431-44.
- Quyen MLV, Foucher J, Lachaux JP, *et al.* Comparison of Hilbert transform and wavelet methods for the analysis of neuronal synchrony. *J Neurosci Methods* 2001; 111(2): 83-98.
- Rheims S, Demarquay G, Isnard J, *et al.* Ipsilateral head deviation in frontal lobe seizures. *Epilepsia* 2005; 46(11): 1750-3.
- Shihabuddin B, Abou-Khalil B, Delbeke D, *et al.* Orbitofrontal epilepsy masquerading as temporal lobe epilepsy: a case report. *Seizure* 2001; 10(2): 134-8.
- Smith JR, Sillay K, Winkler P, King DK, Loring DW. Orbitofrontal epilepsy: electroclinical analysis of surgical cases and literature review. *Stereotact Funct Neurosurg* 2004; 82(1): 20-5.
- Tadel F, Baillet S, Mosher JC, John C, *et al.* Brainstorm: a user-friendly application for MEG/EEG analysis. *Comput Intell Neurosci* 2011: 1-13.
- Talairach J, Bancaud J, Bonis A, *et al.* Surgical therapy for frontal epilepsies. *Adv Neurol* 1992; 57: 707-32.
- Vaugier L, Aubert S, McGonigal A, *et al.* Neural networks underlying hyperkinetic seizures of "temporal lobe" origin. *Epilepsy Res* 2009; 86(2-3): 200-8.
- Vaugier L, McGonigal A, Lagarde S, *et al.* Hyperkinetic motor seizures: a common semiology generated by two different cortical seizure origins. *Epileptic Disord* 2017; 19(3): 362-6.
- Wang ZI, Ristic AJ, Wong CH, *et al.* Neuroimaging characteristics of MRI-negative orbitofrontal epilepsy with focus on voxel-based morphometric MRI post-processing. *Epilepsia* 2013; 54: 12.
- Liu Y, Zhou W. Clinical features and surgical treatment of epilepsy after viral encephalitis. *Brain Sci Adv* 2019; 5(1): 41-50.