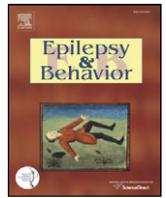




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Foramen ovale electrodes in the evaluation of epilepsy surgery: Conventional and unconventional uses

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ABSTRACT

Foramen ovale (FO) electrodes have been used in the evaluation of epilepsy surgery for more than 25 years. Their traditional application was in patients with mesial temporal lobe epilepsy. Due in part to advances in neuroimaging, their use has declined. We describe our cumulative experience with FO electrodes and use examples to illustrate a range of indications for FO recordings that extend beyond their conventional utility for mesial temporal lobe cases. We also summarize the pros and cons of FO electrodes implantation and attempt to reestablish their utility in presurgical evaluation.

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1. Introduction

Correct identification of the epileptogenic zone is paramount in surgical treatment for epilepsy. Although this can be often achieved with noninvasive tools, invasive EEG monitoring is occasionally required. Foramen ovale (FO) electrodes were developed in Zurich in the 1980s primarily for the presurgical evaluation of patients for selective amygdalohippocampotomy [1,2]. FO electrodes are four- to six-contact wire electrodes placed bilaterally through the foramen ovale into the ambient cistern. In this position, the electrodes come to be located intracranially but extracerebrally. Although FO electrodes were proven to correctly lateralize and localize the epileptogenic zone in mesial temporal lobe cases, the advent of more advanced imaging modalities, particularly in the MRI domain, has reduced their use [3]. We describe through illustrative cases our experience with the use of these electrodes and extend their utility beyond pure mesial temporal lobe cases.

2. Illustrative cases

2.1. Case I: Bilateral mesial temporal onset

A 65-year-old left-handed man with history of lupus was admitted for evaluation of epilepsy of 7 years' duration. Seizures were characterized by sudden onset without warning of disconnection from the environment, with preserved but incoherent speech along

with manual and oral automatisms. Despite multiple antiepileptic medications, his seizure frequency had increased to twice per week over the previous year, causing increasing disability. Examination showed only mild cognitive impairment. Brain MRI revealed subcortical white matter changes and generalized and bilateral hippocampal atrophy. [¹⁸F]Fluorodeoxyglucose positron emission tomography (FDG-PET) failed to identify asymmetries. Scalp video/EEG recording revealed bilateral independent temporal interictal discharges and seizure onsets with very rapid propagation to the contralateral side, suggesting multifocality or rapid spread from a unilateral mesial temporal focus to the contralateral side. To address this question, FO electrodes were implanted "on the fly" (i.e., during the admission as an unscheduled procedure) and confirmed independent bilateral seizure onsets (Fig. 1). The patient was deemed multifocal and no surgical treatment was offered.

2.2. Case II: Nonlateralizing and discordant mesial temporal onset

A 44-year-old right-handed man with a 14-year history of epilepsy was admitted for presurgical evaluation. Seizures consisted of loss of awareness without clear warning followed by postictal aphasia. They occurred on a weekly basis and generalized every 6–8 weeks, leading to status epilepticus on several occasions. There was a history of perinatal asphyxia. His seizures were resistant to eight antiepileptic medications and was eager for a surgical cure of his disease. Neurological examination revealed significant verbal memory deficits and moderate depression. Prior evaluation with MRI suggested left mesial temporal sclerosis, and a PET scan revealed left temporal hypometabolism. Interictal discharges were concordant with the presumed hypothesis of left mesial temporal lobe epilepsy, similar to

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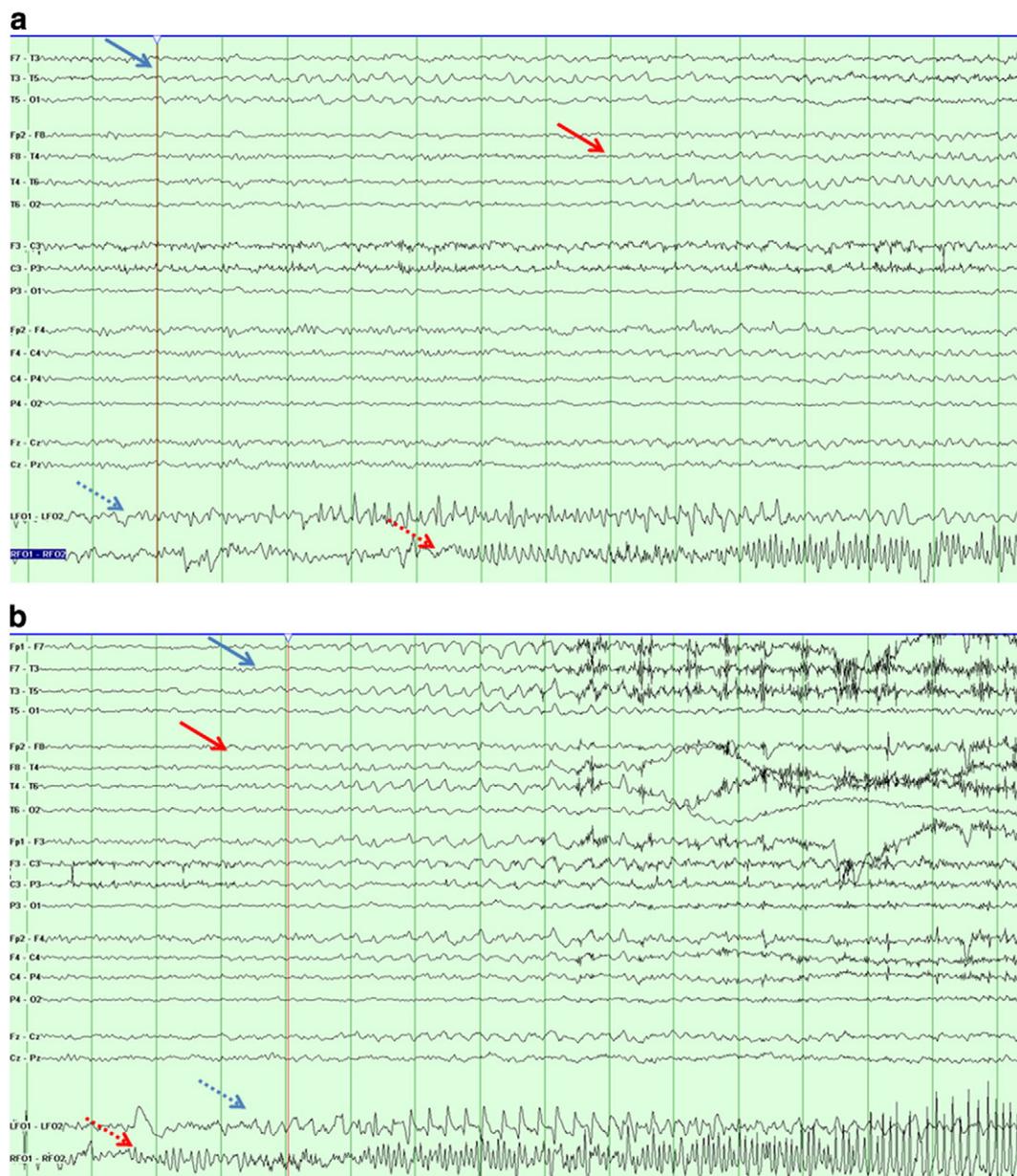


Fig. 1. Concurrent scalp and FO electrodes recordings show left (a) and right (b) mesial temporal seizure onsets with rapid propagation contralaterally. EEG settings for all figures: anteroposterior bipolar scalp and bilateral foramen ovale montage, high-pass filter 1 Hz, low-pass filter 70 Hz, sensitivity 7–10 μ V, speed 30 mm/second. Solid blue and solid red arrows depict areas of interest in the left and right scalp temporal chains, respectively. Dashed blue and dashed red arrows depict areas of interest in the left and right FO electrodes, respectively.

his neuropsychological profile. However, ictal EEG recordings had shown diffuse slowing obscured by muscle artifact with late lateralization to the contralateral, right mesial temporal region. Subsequent recordings with FO electrodes captured similar seizure onsets that were clearly localized to the left hippocampal region despite their diffuse scalp correlate prior to switching to the contralateral, right hippocampal region with their respective right frontotemporal correlate (Fig. 2). The patient underwent a left anterior temporal lobectomy. The pathology showed left hippocampal sclerosis. The patient has been seizure free since.

2.3. Case III: Mesial temporal versus lateral temporal onset

A 39-year-old right-handed woman with two decades of refractory epilepsy was admitted for presurgical evaluation. Initially she reported a single seizure type, consisting of daily gustatory and olfactory auras that would progress to loss of awareness at least twice a month and

to convulsions twice a year. There was a history of carbon monoxide poisoning in childhood. Because of increasing seizure frequency and progressive memory decline, depressed mood, and declining functionality, the patient was kept on undergoing surgery. Neuropsychological examination showed low Full Scale IQ and multidomain deficits with no clear lateralizing or localizing predominance. Neurological examination was unremarkable. MRI and PET scans of the brain failed to lateralize her disease. Scalp recordings showed predominantly right frontotemporal interictal discharges at a ratio of 10:1 (R:L) and six complex partial seizures with preserved speech arising from the right frontotemporal region, four of which spread to the contralateral side within 9–300 seconds. An electroclinical delay was noted in the ictal recordings, with behavioral manifestations preceding initial scalp EEG change by up to 40 seconds. On the basis of the electroclinical delay, the lack of anatomic abnormality, the presence of bilateral interictal discharges, and the rapid interhemispheric propagation of some events, FO electrodes were placed to better determine whether

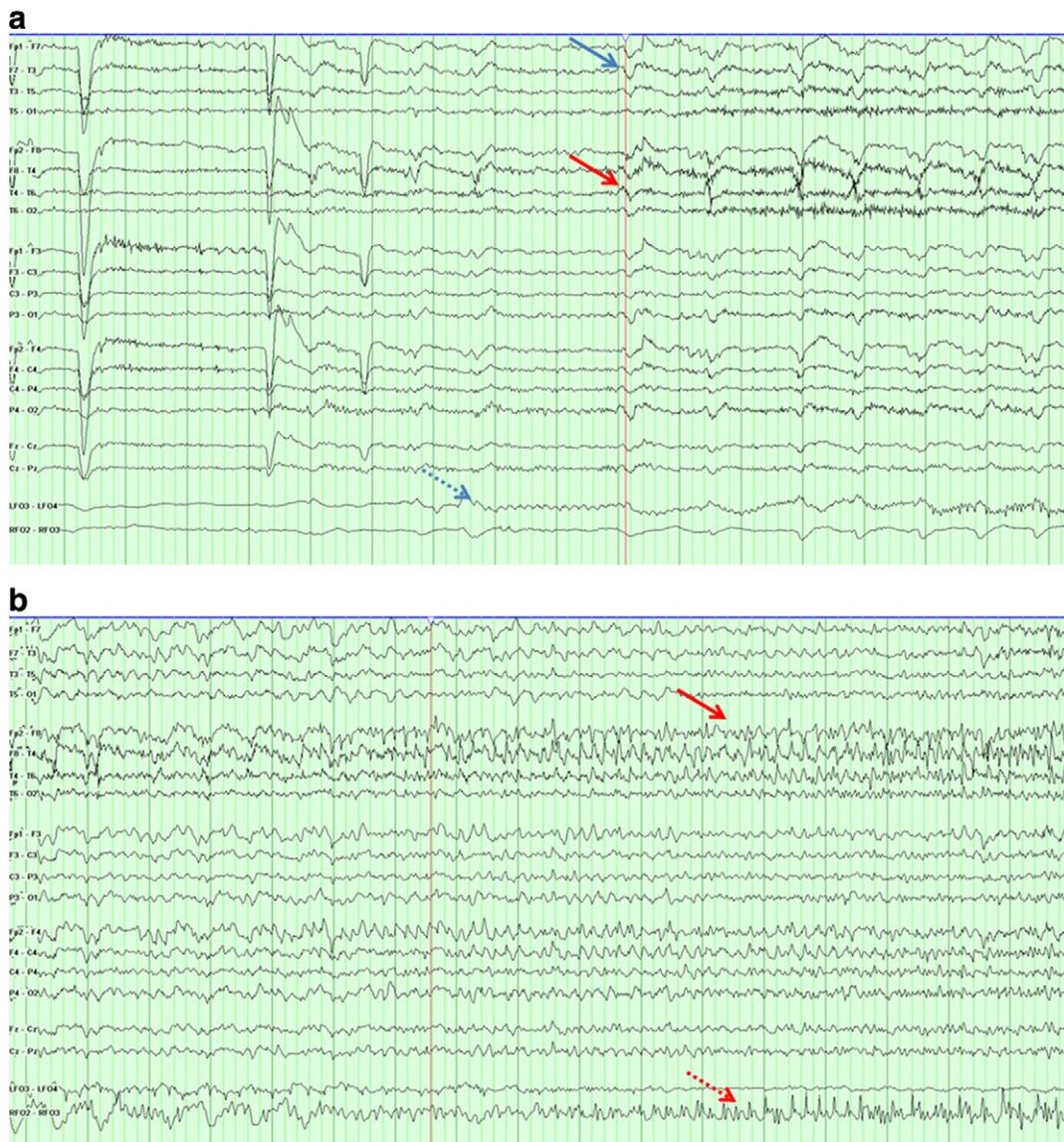


Fig. 2. Concurrent scalp and FO electrode recordings show a clear left FO onset with a nonlateralizing scalp correlate (a) that transferred to the right FO electrode 60 seconds later correlating with a clear right frontotemporal scalp lateralization (b).

there was a single epileptic focus in the right temporal lobe. FO recordings revealed four seizures, two of which were of right mesial temporal origin, with a clinico-electrographic signature similar to that observed in the previous scalp investigation. The remaining two events were characterized by a novel semiology including ictal aphasia and demonstrated onset and involvement of the left temporal neocortex without spread to the ipsilateral FO electrode (Fig. 3). Given her strong enthusiasm for surgery and the fact that the most frequent, disabling, and medication-refractory seizures were of right mesial temporal origin, the patient was offered a palliative right anterior temporal lobectomy. Pathology showed mesial temporal sclerosis. Postoperatively, the patient has experienced a significant reduction of her seizures with an Engel class II outcome. Her residual seizures manifest with auditory hallucinations and ictal aphasia, presumably reflecting the left lateral neocortical temporal focus identified by ictal FO recording.

2.4. Case IV: Mesial temporal versus pseudotemporal

A 33-year-old right-handed woman with a history of depression and postpartum psychosis was admitted for presurgical evaluation of

27 years of medically refractory epilepsy. Her seizures consisted of an aura of fear, followed by brief loss of consciousness accompanied by whole-body stiffening, grimacing, and humming with quick recovery. Occasionally the seizures generalized. Because of the impact of her disease on her mood and cognition and the risk it posed to the care of her children, she sought surgical treatment. Neuropsychological evaluation showed low average IQ and widespread left hemispheric dysfunction. Verbal memory was preserved. Brain MRI revealed subtle increased T2 signal in the left mesial temporal structures. FDG-PET revealed mild hypometabolism in the same region. Scalp recording captured numerous, brief, habitual seizures characterized by diffuse amplitude attenuation with overriding paroxysmal fast activity of maximal amplitude in the left frontotemporal area. Scarce left frontotemporal interictal activity was recorded. Based on the discrepancy between the radiographic studies suggesting a mesial temporal focus and the behavioral and electrophysiological data suggesting a frontal focus, FO electrodes were implanted as a minimally invasive means to differentiate between these two possibilities prior to embarking on a riskier phase II investigation with subdural electrodes. Multiple seizures recorded with FO electrodes in place demonstrated only late involvement of the mesial structures, occurring on average

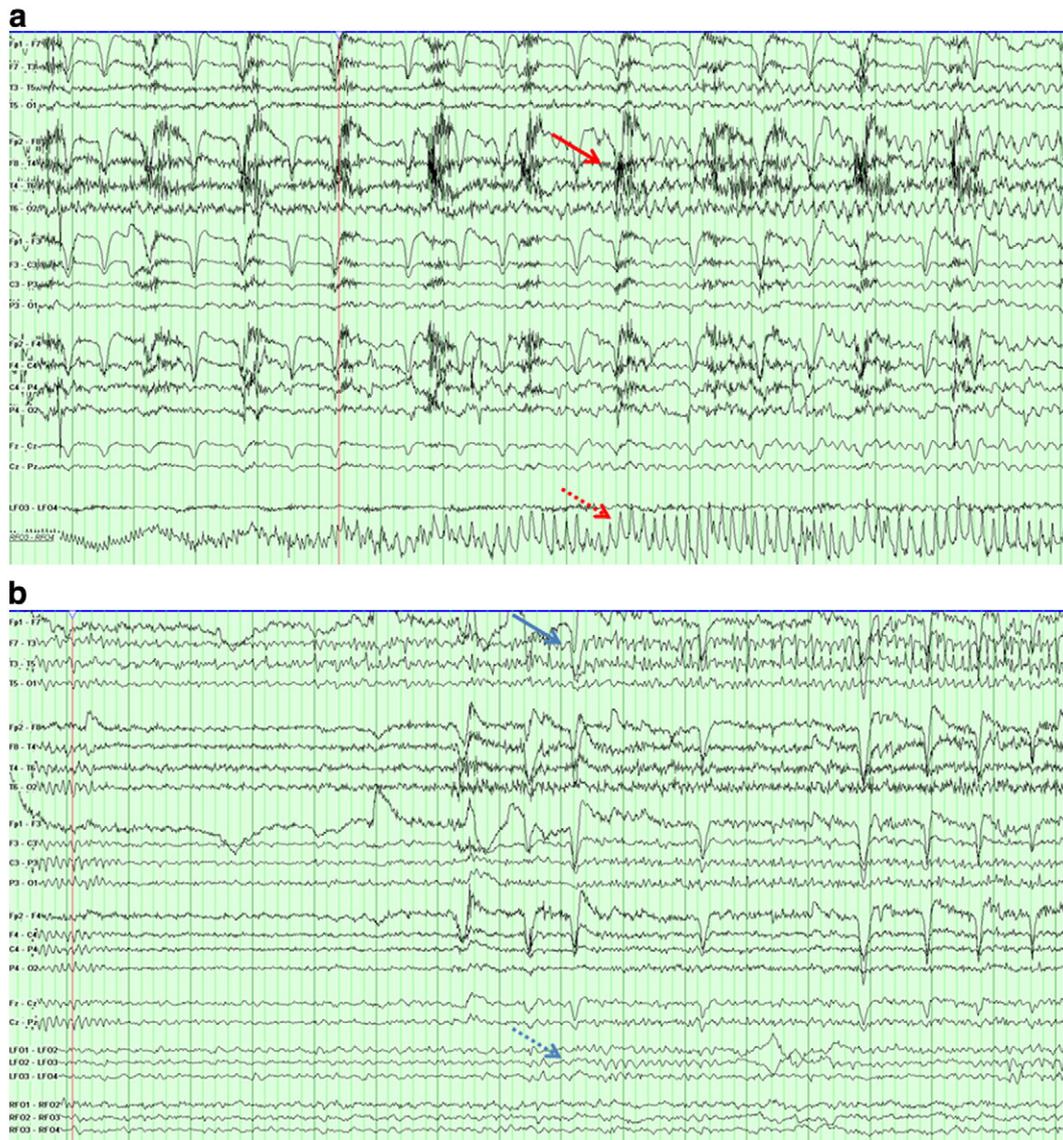


Fig. 3. Concurrent scalp and FO electrodes recordings show a right scalp mesial temporal seizure onset with right FO electrode involvement (a) and a left scalp lateral temporal seizure onset without left FO electrode involvement (b).

20 seconds after the clinical and scalp onset (Fig. 4). Subsequent investigation with grid electrodes confirmed the presence of a frontal epileptogenic zone.

2.5. Case V: Cryptic mesial temporal onset versus nonepileptic seizures

A 34-year-old right-handed man with 9 years of intractable epilepsy complicated by depression with suicidality was emergently admitted for presurgical evaluation. His seizures consisted of an aura of déjà vu followed by loss of awareness and rare secondary generalization. They were inextricably interwoven with a pharmacoresistant depressive disorder that led to a suicide attempt. Examination and neuroimaging (PET and MRI brain) were negative. Neuropsychological evaluation showed preserved verbal memory. EEG recordings in an outside facility showed ictal onsets obscured by chewing artifact. Repeat recordings in our institution, this time with FO electrodes, showed abundant and exclusively left mesial temporal interictal discharges, mostly without scalp correlate. All recorded seizures emanated from the left mesial temporal structures in the FO electrodes while simultaneous scalp EEG was obscured by muscle artifact (Fig. 5a). In view of the patient's life-threatening affective disorder with preserved verbal memory, a limited left anterior temporal lobectomy was performed without

a Wada investigation. Pathology revealed nonspecific gliosis. The patient returned 1 year later with a new suicide attempt and worsening depression. Despite the lack of convulsive or well-documented complex partial events, he complained of daily "auras" that were nonspecific but differed from prior auras and did not involve his preoperative warning of déjà vu. Scalp recordings captured several of these events without clear correlate. Rare left temporal interictal epileptiform discharges were recorded. Given the incongruity of the patient's preoperative scalp and FO interictal activity, in the setting of a limited mesial resection, the decision to extend the recordings with implantation of FO electrodes "on the fly" was undertaken. The goal of this implantation was to determine whether his subjective experiences represented cryptic ictal discharges arising from residual mesial temporal structures. Medication was withheld and the patient was recorded for 9 days during which he experienced frequent sensations that he interpreted as auras. Recordings demonstrated no clear electrographic correlate (Fig. 5b). Eventually he sustained two left temporal lobe seizures arising from the posterior neocortical resection margin with late involvement of residual mesial structures. FO recordings confirmed the lack of objective evidence for the patient's complaints and no further surgery was advocated. Instead, the patient was discharged with antiepileptic and psychiatric treatment.

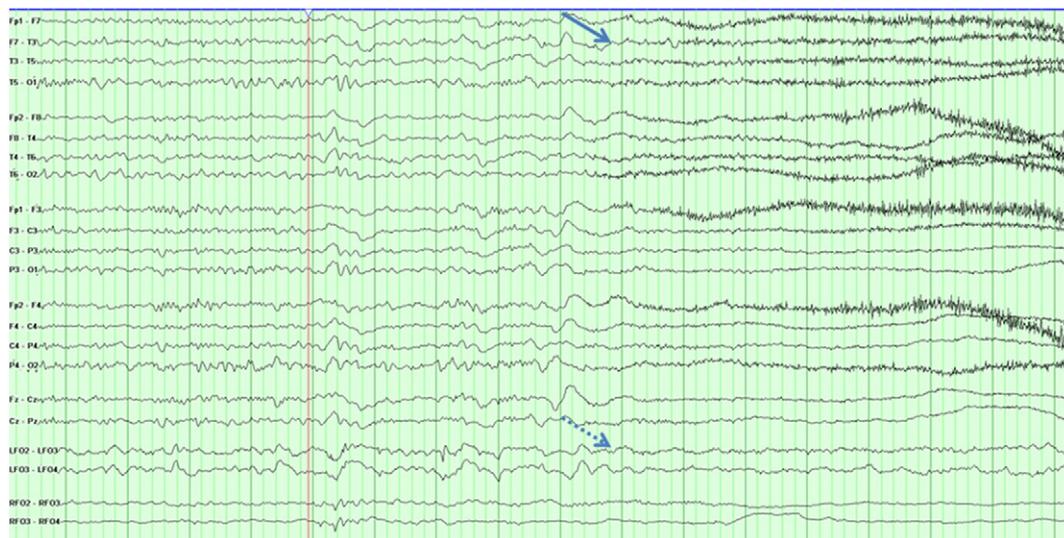


Fig. 4. Concurrent scalp and FO electrodes recordings show a frontal lobe seizure characterized by generalized decrement with overriding paroxysmal fast activity, of maximal amplitude in the left hemisphere, without left FO electrode involvement.

3. Discussion

Mesial temporal lobe onset seizures may propagate to the ipsilateral temporal neocortex, contralateral hippocampus, or both of these structures simultaneously [4]. Mesial onsets are often blurred on scalp EEG by chewing, muscle, or movement artifacts, simultaneous appearance in the two hemispheres, or rapid contralateral propagation, suggesting lateralization to the discordant side. Each of these scenarios raises the question of whether the patient has purely unilateral disease or independent bitemporal foci. Even in bitemporal cases, when the issue is determining whether there is a predominant side of onset that might permit a palliative operation, it is important to be able to carefully quantitate the ratio of onsets on one side versus the other. Finally, there is the question of whether behavioral events are caused by a localized, but inaccessible (with respect to scalp EEG) site of onset. FO electrodes have conventionally been used as an important tool for addressing these questions. For example, in our first case FO electrodes allowed us to demonstrate independent bitemporal onsets with rapid contralateral propagation, and our second case demonstrated focal FO onset in a patient with nonlateralizing scalp ictal onset. Similar findings were reported by Alarcon et al. in their meticulous review of 314 seizures studied with FO electrodes. Sixty-seven percent began with symmetric or asymmetric bilateral scalp EEG changes, whereas only 28% had bilateral initial involvement of FO electrodes. Moreover, 4.1% of seizures were obscured by artifact on scalp EEG, whereas only 1.3% were obscured on FO recordings [5]. On the basis of these data, because a large proportion of unilateral-onset seizures have bilateral scalp involvement or are obscured by artifact, FO electrodes should be considered prior to terminating the presurgical evaluation of these patients.

Characterization of the temporal and spatial evolution of seizures may yield prognostic information [6] along with hints about the underlying pathology. In particular, data derived from FO recordings suggest that seizures with direct propagation to the contralateral FO electrode are more likely than those with direct propagation to the contralateral scalp to be associated with radiological evidence of mesial temporal lobe sclerosis and favorable surgical outcome [7]. Additionally, interhemispheric propagation times greater than 20 seconds (on depth electrode recordings) were suggestive of underlying hippocampal sclerosis [8]. Thus, FO electrodes may not only clarify the site of seizure onset in mesial temporal lobe epilepsy, but may also provide insight into the underlying pathology along with more accurate prognostic information. Our second case demonstrated

an average FO propagation time to the contralateral FO electrode of 60–70 seconds, had mesial temporal sclerosis on the left based on MRI and surgical pathology, and has had an Engel Class I epilepsy surgery outcome.

In addition to the conventional uses of FO electrodes discussed above, we have identified several novel or nonconventional settings in which these electrodes have provided important information. Seizure onsets outside the mesial temporal lobes may masquerade as mesial onset seizures, clinically and electrographically on scalp recordings. In particular, frontal lobe seizures often propagate to the ipsilateral temporal lobe, causing problems with localization clinically [9] and electrographically [10]. For example, using intracranial recordings, Lee et al. identified 3 of 20 patients with apparent anterior temporal scalp ictal onset who had frontal lobe epilepsy [11]. Another 3 of these patients had extratemporal seizure onsets in the parietal, occipital, and temporoparietal regions, respectively. The frequencies of scalp ictal rhythms at onset varied between the temporal and the extratemporal cases [11]. Moreover, in some series, up to 75% of seizures with a midtemporal onset (T3/T4) had a mesial temporal onset with FO recordings, despite being traditionally considered as lateral temporal or extratemporal [5]. These reports raise concern about the potentially misleading nature of surface temporal interictal and ictal epileptogenic discharges in differentiating mesial from lateral temporal epilepsy and in distinguishing true temporal lobe epilepsy from “pseudotemporal epilepsy” [12]. Additionally, imaging may also be misleading, as mesial temporal sclerosis may be seen as a secondary phenomenon from a primary ictal source. In some cases, such as the third and fourth examples described above, FO electrodes may function as an intermediate step to confirm or refute the involvement of mesial temporal structures in clinical or scalp EEG ictal onsets and, thus, guide or prevent further invasive investigation.

Many epileptiform discharges identified with FO electrodes are not visible extracranially [13]. Studies have shown that the spiking rate can range from 2 to 10 times higher in FO electrodes compared with scalp recordings [14]. These results corroborate our personal experience with the use of FO electrodes. It is therefore conceivable that patients with underlying mesial temporal lobe epilepsy may have seemingly normal scalp recordings. Patients with complex partial seizures may present with evolving or fluctuating memory dysfunction without other apparent clinical signs, either as discrete amnesic episodes or more insidiously, mimicking dementia [15]. In such individuals, when the index of suspicion is high, FO electrode recordings may facilitate the diagnosis of an epileptic pseudodementia.

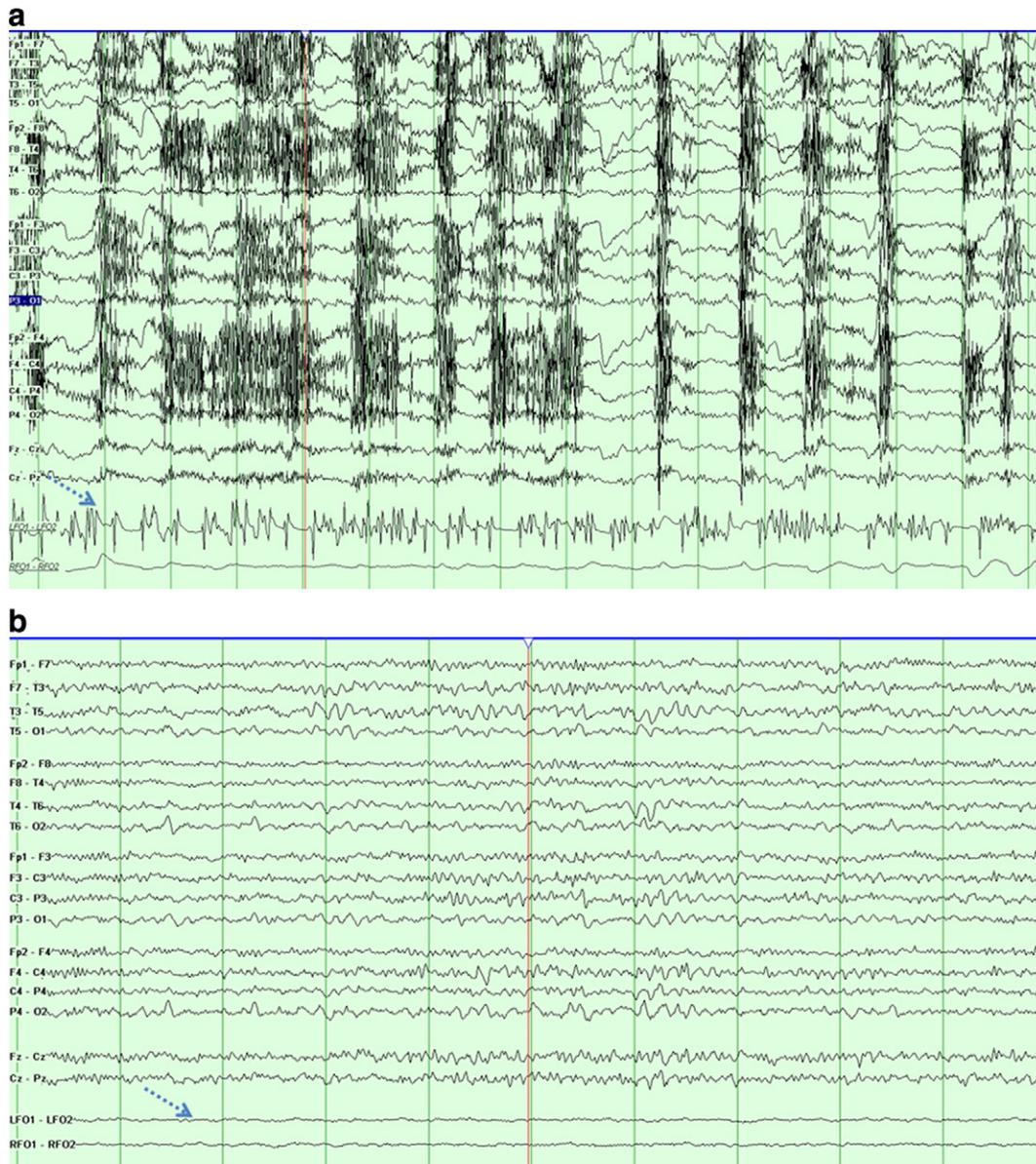


Fig. 5. Concurrent scalp and FO electrodes recordings show a left mesial temporal seizure onset in the FO electrode obscured by chewing artifact on the scalp EEG associated with a frank seizure aura preoperatively (a) and lack of scalp and FO abnormalities during a subjective "seizure aura" in the repeated recording 1 year postoperatively (b). The asymmetry in (b) is due to the neurosurgical breach.

Similarly, scalp recordings have significant limitations in the reliable diagnosis of nonepileptic seizures. Scalp electrodes sample only one-third of the cortex, rendering discharges arising from sulci or interhemispheric regions undetectable [16]. Epileptiform activity generated by buried cortex, such as the amygdala and hippocampus, may not be captured on scalp recordings [17]. Therefore, in selected cases, such as case V, where a significant amount of ambiguity exists and exact diagnosis is critical, FO electrode recordings may provide additional assistance. Table 1 summarizes the aforementioned conventional and unconventional uses of FO electrodes.

In our institution, 21 patients have been implanted with FO electrodes in the past 5 years (July 2005–September 2010) for a total of 22 implantations. Twelve were male and nine female. The mean age at the time of implantation was 40.6 years (range: 19–65). The mean age at the onset of epilepsy was 18.2 years (range: 1–60). The mean duration of their disease at the time of FO implantation was 21 years (range: 2–52). The indications for the implantation were: bilateral independent mesial temporal ictal onsets (8 patients), nonlateralizing ictal onsets (3), ictal onsets obscured by artifact (2), delayed or absent

scalp EEG changes (5), and discordant data (4). The FO recordings showed that 19 of these patients had unilateral or bilateral independent mesial temporal ictal onsets. In the other 3 implantations, 2 patients had seizures without or with only late involvement of the FO electrodes and 1 had nonepileptic events. On the basis of the results obtained with FO recordings, anterior temporal lobectomy was recommended for 12 patients. The other 7 patients were felt to be poor surgical candidates because of either bilateral mesial temporal

Table 1
Conventional and unconventional uses of FO electrodes.

Conventional uses	Unconventional uses
Mesial temporal lobe epilepsy:	Mesial vs lateral temporal lobe onset
Obscured or nonlateralizing onset	Mesial temporal vs pseudotemporal onset
Bitemporal or cross-over onset	Cryptic mesial temporal lobe epilepsy vs nonepileptic seizures
Discordant onset	Cryptic mesial temporal lobe epilepsy vs dementia

Table 2
Experience with FO electrodes at our institution from July 2005 to September 2010.

Total number of implantations	22
Gender (female)	9
Age at time of implantation	40.6 (19–65) ^a
Age at onset of disease	18.2 (1–60) ^a
Duration of disease (years)	21 (2–52) ^a
Indications for implantation	
Bilateral independent mesial temporal ictal onsets	8
Nonlateralizing ictal onset	3
Ictal onset obscured by artifact	2
Delayed or absent scalp EEG changes	5
Discordant data	4
Findings from FO recordings	
Unilateral or bilateral independent mesial temporal ictal onsets	19
Seizures without or with late involvement of the FO electrodes	2
Nonepileptic events	1
Course of action based on FO recordings	
Anterior temporal lobectomy	12
Further invasive investigation	2
No surgical intervention ^b	8
Complications	
Small subarachnoid hemorrhage	1
Post-implantation jaw pain	1

^a Mean (range).^b Bilateral mesial temporal ictal onsets with evenly distributed burden of disease and high risk of postsurgical amnesia or nonepileptic seizures.

ictal onsets with evenly distributed burden of disease, high risk of postsurgical amnesia, or nonepileptic events. One patient suffered a small subarachnoid hemorrhage as a complication of FO electrode removal and one patient complained of post-implantation jaw pain. Table 2 summarizes our experience with FO electrodes.

Foramen ovale electrodes have several advantages. They lie next to the mesial temporal structures. Thus, they are capable of recording reliably from a concealed cortical region that is highly epileptogenic and therefore, commonly affected in epilepsy, while avoiding the problem of signal attenuation by the skull and associated muscle and electrode movement artifacts [6]. Their impedances remain stable through prolonged recorded sessions [6]. They are typically implanted under fluoroscopy and general anesthesia in a procedure lasting <1 hour and, therefore, can be implanted “on the fly” in patients admitted for routine scalp EEG monitoring. Therefore, in selected patients, FO electrodes may avoid re-admission for a “phase 2” investigation.

On the other hand, their use is not risk free. Their placement typically requires general anesthesia and special neurosurgical expertise. Therefore their placement cost is considerable, though still significantly lower than that for stereoelectroencephalography (SEEG) [18]. Although generally well tolerated, minor complications such as cheek dysesthesias, cheek bleeding, and electrode expulsion have been reported in 4.83% of cases [19]. In large series, severe complications (e.g., clotting or intracranial hemorrhage) were reported in approximately 1.8% of 331 patients implanted. This rate appears smaller than those reported with subdural grids and strips and similar to the range reported with stereotactically implanted depth electrodes [19]. Similar to other invasive recordings, replacement of malfunctioning electrodes is difficult [6]. Moreover, even though FO electrodes record closer to the mesial structures, closed fields, as may occur in the amygdala, may still be theoretically undersampled [17]. Their direct sampling radius is confined in the mesial structures, and therefore, in unselected cases, they may depict the propagation rather than the onset of the ictus and provide potentially misleading information. Table 3 summarizes the aforementioned advantages and disadvantages of these electrodes.

Although some epilepsy surgery centers were unable to demonstrate a significant benefit from the use of FO electrodes [20], many support their utility [21–26]. Recently, Beleza et al. reported their cumulative experience with combined epidural and FO electrodes investigations from the 1990s and identified a significant yield of additional information that either allowed resection or guided further investigation in all but 3 of 59 cases [27]. In another study of 192 FO telemetries, five patients were found with incorrect seizure onset lateralization on these recordings when compared with the gold standard of SEEG [17]. However, all these cases had clinical onsets before the first electrographic change and rapid cross-over that prompted the implantation with invasive electrodes subsequently [17]. Moreover, the same authors identified an overall incidence of false lateralization by subdural electrodes similar to the error rate with multipolar FO contacts [17]. Additionally, other authors have highlighted their utility also for the pediatric population [28].

Finally, it is important to highlight that the use of FO electrodes by no means represents a panacea. When used in unselected cases the information they provide may be not only meaningless, but also misleading. A clear hypothesis should exist. When compared with the clinical or scalp electrographic onset, the lack of involvement or delayed involvement of technically well-placed FO electrodes should

Table 3
Advantages and disadvantages of FO electrodes.

	Advantages	Disadvantages
Spatial resolution	Ideal sampling of mesial temporal lobe structures, superior to noninvasive (scalp T1/T2) and semi-invasive (sphenoidal) electrodes Seizure onset and seizure propagation patterns can be identified, providing useful diagnostic and prognostic information	Theoretically, they can still miss “closed loop” amygdalar discharges Limited spatial resolution bears risk of misleading information in unselected patients in whom clinical or scalp EEG onset precedes FO involvement
Interpretability	Improved signal-to-noise ratio Small number of channels facilitates rapid interpretation in comparison to subdural recordings	Superficial contacts are occasionally located extracranially and substitution of malfunctioning electrodes is difficult.
Implantation–explantation	Easier to implant than SEEG and even easier to explant at the bedside Can also be used when scarring of the dura prevents subdural electrode placement	Requires neurosurgical experience with the implantation technique
Scheduling	Can be implanted “on the fly,” contrary to SEEG	Typically requires arrangements for general anesthesia and fluoroscopy
Complications	Low rate of major complications	Rare cases of subarachnoid hemorrhage and brainstem damage have been reported
Tolerability	Overall well tolerated	Jaw pain and dysesthesia are not uncommon
Duration of recording	Can be extended longer than typical SEEG	Prolonged recordings have been associated with higher complication rates
Cost	Lower than SEEG.	Higher than alternative noninvasive (T1/T2) or semi-invasive (sphenoidal) techniques

be interpreted with caution and raise suspicion for a non-mesial temporal onset.

3.1. Conclusion

The purpose of FO recordings is not to mitigate the undisputable merits of SEEG in epilepsy surgery. In carefully selected patients, however, FO electrodes offer a safer, intermediate, and more readily available alternative to invasive recordings for the identification of the epileptic focus, and diminish the likelihood of ineffective surgery because of insufficient or misleading information. Despite the advent of advanced neuroimaging modalities, FO electrodes still have a role to play in individual cases in detecting the operable or inoperable epileptogenic zone(s) or assisting in further, invasive evaluation. In challenging, prudently chosen cases, they may also assist in the diagnosis of lateral temporal lobe epilepsy, extratemporal epilepsy, epileptic pseudodementia, and nonepileptic seizures.

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