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A 16-year-old girl with focal seizures and impaired awareness: divergent non-invasive data related to a diffuse epileptogenic network

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ABSTRACT – We describe a patient with medically refractory focal epilepsy who presented with divergent non-invasive data, with MRI revealing hippocampal sclerosis and EEG indicating involvement of the occipital lobe. A localized corticectomy over the occipital convexity was performed based on intracranial EEG recording. The patient was seizure-free after four years of follow-up. Electroclinical hypotheses and challenges of defining the epileptogenic network are discussed.

Key words: hippocampal sclerosis, epilepsy surgery, intractable epilepsy, occipital resection, atypical epileptogenic network

Patient details

A 16-year-old, right handed female presented with medically uncontrolled epilepsy that began at age 6 years. The initial seizure presentation consisted of generalized convulsions accompanied by bowel and bladder incontinence. During childhood and adolescence, she developed a more defined seizure pattern with episodes that were preceded by an olfactory aura of smelling gas, immediately followed by a feeling of pressure in her head and loss of vision in her left visual field, accompanied by dots of light in the right visual field. The variably following motor convulsive phase was characterized by left head version, followed by generalized convulsive movements, incontinence, and postictal lethargy. Her seizures occurred once or twice monthly and always lasted less than three minutes. Motor convulsions were often associated with medical non-compliance.

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She was currently being treated with levetiracetam, at 1,000 mg BID; previous medication included sodium valproate.

Her past medical history was significant for non-specific migraine headaches and attention deficit hyperactivity disorder, but more recently her headaches localized to the right posterior head region and lasted several hours. She had developed normally but struggled in school, obtaining generally poor grades. The family history was negative for seizures. Her general and neurological examinations were normal.

Video/EEG monitoring revealed normal background activity with superimposed medium- to high-amplitude rhythmic slowing over the right frontal region (*figure 1A*). Multiple clinical seizures were captured that revealed an onset characterized by low-amplitude fast frequencies over the right temporo-occipital region, followed by a build-up of spike-wave discharges and subsequent generalized discharges (*figure 1B*).

Hypothesis 1

Although the presence of an olfactory aura strongly implicated seizure onset within mesial temporal structures, possibly the uncus, the scalp EEG revealed temporo-occipital discharges which implicated possible seizure origin in the occipital lobe. The patient's well-defined visual aura and right posterior headaches also favoured an occipital seizure origin.

Non-invasive investigations

The scalp EEG revealed interictal spikes arising independently over the right frontal, posterior temporal, and occipital regions.

Ictal onset was, however, consistently focal over the right posterior temporal occipital region. 3-D electrical source imaging utilizing Curry software localized electrographic seizure onset to the infero-lateral occipital cortex in proximity to the pole (*figure 1D*).

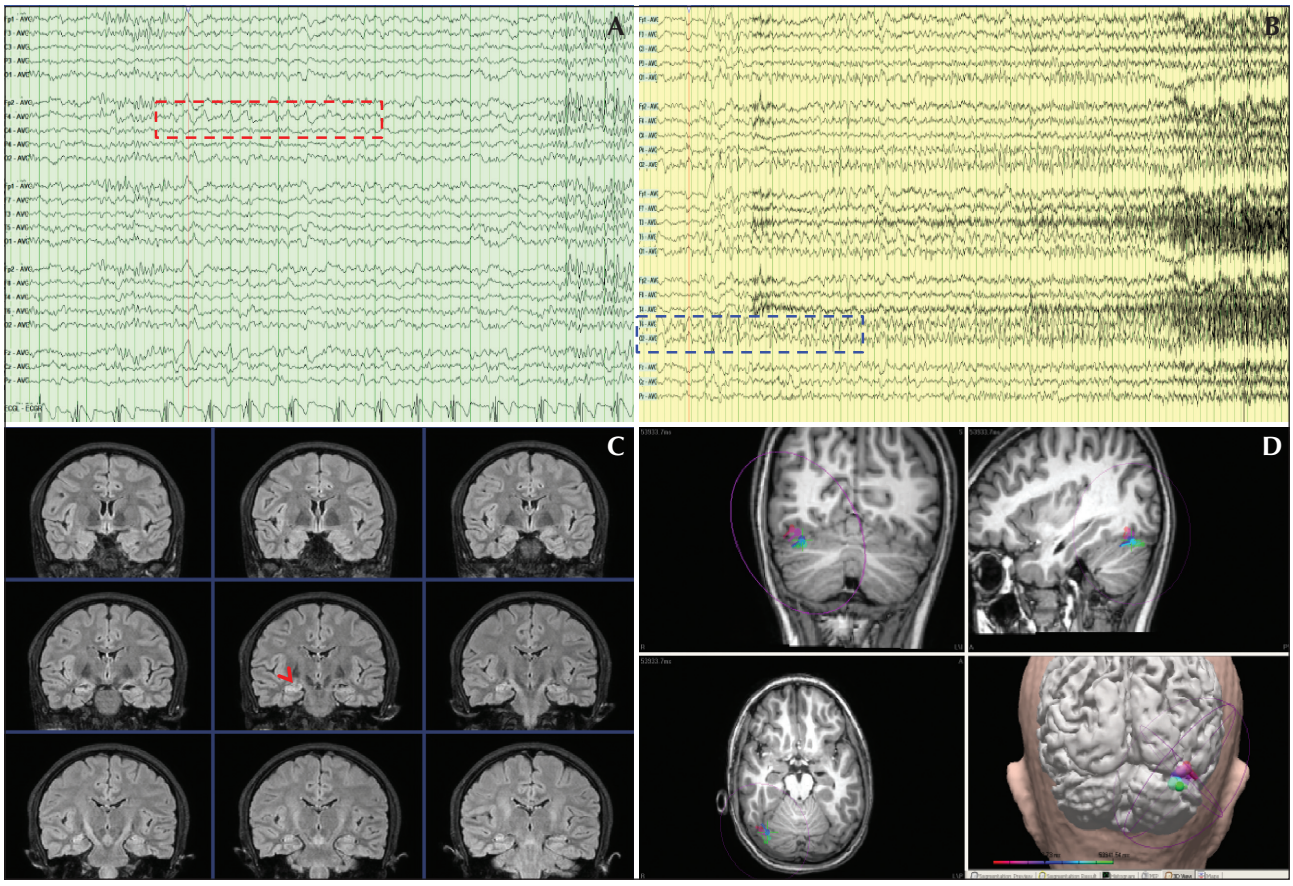

Figure 1. (A) and (B): Video-EEG recording during the waking state. (A): Normal background activity with superimposed medium to high amplitude rhythmic slowing over the right frontal region (red rectangle). (B): Seizure onset characterized by low to medium amplitude fast frequencies over the right temporo-occipital region (blue rectangle) followed by a build-up of spike-wave discharges and subsequent generalized discharges. (C): Brain MRI 3D Coronal FLAIR. Increased signal in the body of the right hippocampus consistent with hippocampal sclerosis (red arrow). (D): NeuroScan Curry 7 software (Rotating Dipole model). Quantitative EEG morphology of the spikes are well formed and indicate ictal spike activity in the right occipital cortex.

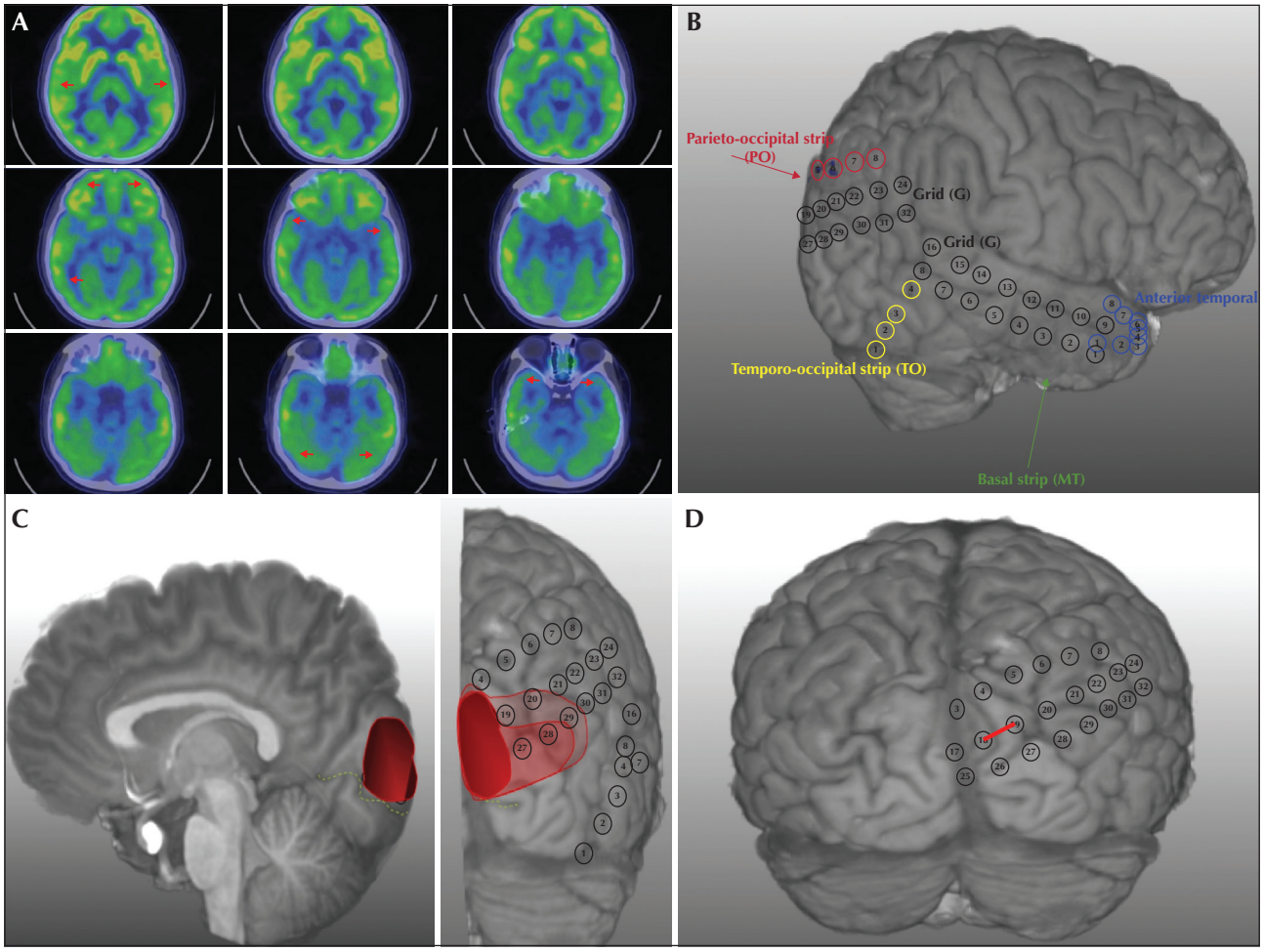

Figure 2. (A): Brain FDG-PET Axial. Bilateral frontal-parietal hypometabolism is more extensive in the left cerebral hemisphere. (B): Subdural electrodes implanted over the right cerebral hemisphere. See text for description of electrode placement. (C): Highly circumscribed zone of seizure onset (intense red area) is restricted to two adjacent contacts over the occipital pole. Medium red indicates field of some of the discharges seen at contacts 26/18. Lightest red area is a region of interictal slowing. (D): Functional mapping data revealing an area in the occipital lobe (red line) that triggered a typical olfactory aura.

Anatomical MRI revealed increased signal in the body of the right hippocampus, consistent with hippocampal sclerosis (HS) (*figure 1C*). Diffusion tensor imaging revealed an expected asymmetric decrease in the size of the right arcuate fasciculus. Functional MRI revealed lateralization of receptive and expressive language to the left hemisphere and appropriate contralateral representation of left and right sensorimotor functionality. There was bilateral and symmetric activation of visual cortex.

FDG PET revealed bilateral frontal-parietal hypometabolism that was more extensive in the left cerebral hemisphere (*figure 2A*). Ictal SPECT revealed a subtle increase in the accumulation of radiopharmaceutical in the right frontal-parietal region with left cerebellar hyperperfusion.

Neuropsychological investigations revealed a level of cognitive function within the borderline range, with a FSIQ of 75. Her verbal abilities were significantly better developed than non-verbal abilities. Both her verbal skills and verbal memory were stronger compared to non-verbal capacities. She also evidenced significant difficulty on measures of constructional praxis and visual-perceptual discrimination.

Invasive investigations

Based on the non-invasive investigation findings, we hypothesized that the seizure onset zone was likely to be a single epileptogenic hub that functioned within a more widespread right cerebral hemispheric network

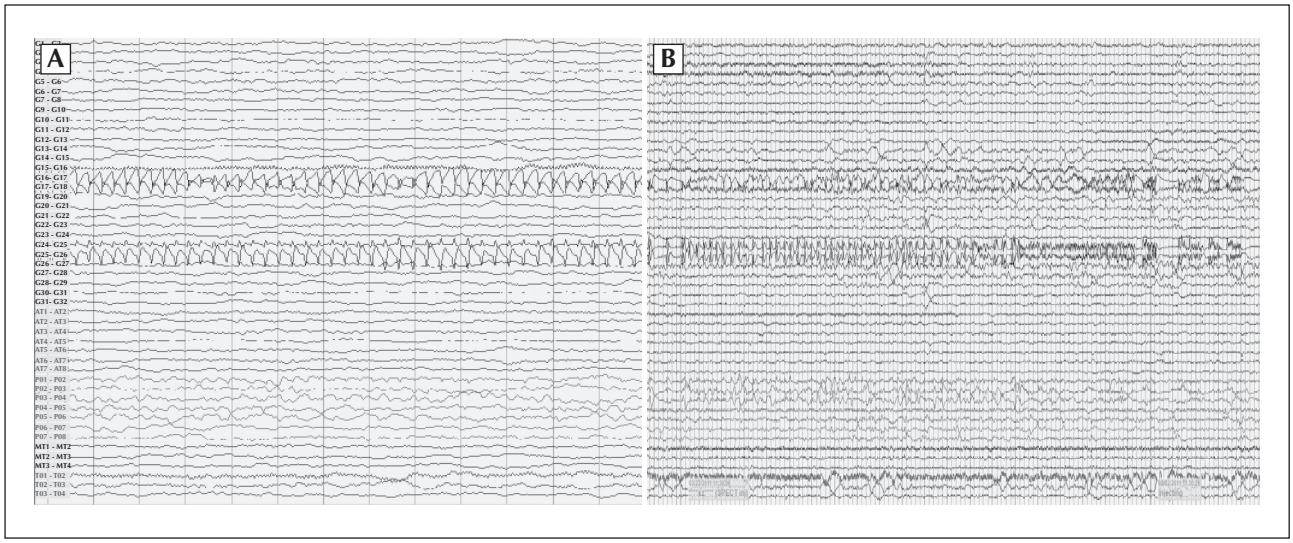

Figure 3. Subdural vEEG Monitoring. (A) Interictal activity was localized to grid contacts 18 and 26 in the occipital pole. Note the synchronous phase reversals of opposite polarity from a source between electrodes and lack of adjacent involvement and seizure propagation. (B) Subclinical seizures captured during recording which was preceded by a buildup of rhythmic spiking at contact 26 or both contacts 26 and 18. Field extension, when present, was seen at PO1-3. This was followed by onset of fast activity at 26 and 18 with field spread to PO1 and PO2.

connecting the temporal, frontal, and occipital lobes. The mesial temporal region and occipital pole were regions of primary interest given her highly specific sensory auras and the demonstration of hippocampal sclerosis. The frontal lobe was regarded to be secondarily activated and unlikely to be the primary seizure focus.

Based on the lack of specific anatomical localizing information from non-invasive investigations, a decision was made to chronically implant subdural electrodes over the right cerebral hemisphere. Broad coverage was elected. A 32-contact grid was placed over the temporo-occipital convexity. Multiple 8- and 4-contact strips were used to sample the anterior temporal and occipital lobes (*figure 2B*).

The intracranial interictal EEG revealed intermittent burst-suppression over the occipital pole in a region to the right of the midline. Multiple seizures were captured which revealed a highly circumscribed zone of seizure onset restricted to two adjacent contacts over the occipital pole (*figure 2C*). Discharges recorded from these contacts exhibited synchronous phase reversals of opposite polarity from a source between the contacts (*figure 3*). No other occipital or temporal electrode contacts participated in electrographic seizure onset and distant sites were only activated secondarily with seizure propagation. Stimulation of the primary electrode pair elicited an olfactory aura, but this finding could not be re-confirmed (*figure 2D*). There were no vision changes upon stimulation of multiple regional occipital contacts.

Hypothesis 2

The remarkably circumscribed and reliable anatomical localization of the seizure onset zone limited to two adjacent occipital pole contacts was unanticipated from the non-invasive investigations except for the 3-D source of the scalp ictal EEG. This finding suggested a highly restricted field of epileptogenicity and phase reversal between the electrodes further confirmed the precise location. Although interictal electrographic abnormalities had a more widespread field, they were regarded as indicating electrically dysfunctional, but not primarily epileptogenic, surrounding tissue. As no contact over the temporal lobe was activated at seizure onset, the temporal lobe was confirmed to be a secondary, rather than a primary, epileptogenic site.

Although stimulation of the ictal onset electrode pair elicited an olfactory aura, we did not have depth electrode coverage of the amygdalo-hippocampal region and could not definitively prove an occipital origin of olfactory aura, rather than secondary propagation.

Action taken

Based on the results of the extracranial and intracranial investigations, a single occipital gyrus was targeted for resection and a very limited tissue excision was performed (*figure 4*). The surgical procedure was uncomplicated and the post-operative course was benign. Neuropathological examination of the excised

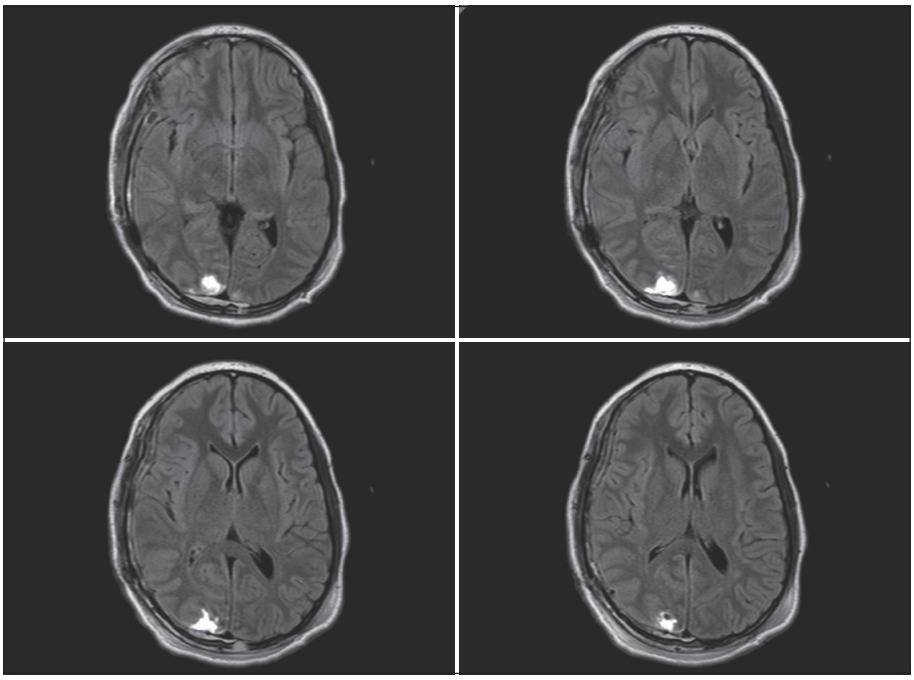

Figure 4. Post-operative brain MRI 3D Axial FLAIR. The surgical cavity is outlined by high signal denoting CSF in the right posterior occipital lobe with mild surrounding brain edema.

tissue specimen revealed fragmented cortex with focal minimal neuronal disorganization suggestive of low-grade focal cortical dysplasia.

Follow-up

The patient has been seizure-free for five years and off all medication for four years. She is attending college in Puerto Rico and living independently. She has not had follow-up neuropsychological testing.

Discussion

Mesial temporal lobe epilepsy (MTLE) is the most frequent form of drug-resistant epilepsy and is commonly associated with hippocampal sclerosis (Malmgren and Thom, 2012). Although the hippocampus is the primary epileptogenic area for most patients with TLE and HS, the epileptogenic network may extend beyond the hippocampus as evidenced by neuroimaging studies (Marsh *et al*., 1997; Briellmann *et al*., 1998; Bonilha *et al*., 2003; Wieser, 2004; McDonald *et al*., 2008; Santana *et al*., 2010; Labate *et al*., 2011), neuropsychological deficits (Oyegbile *et al*., 2004; Marques *et al*., 2007), and clinical data (Erickson *et al*., 2006; Rahal *et al*., 2006). In our patient, the mesial temporal region was likely be secondarily activated by ictal discharges propagated from the primary hub in the occipital lobe. We acknowledge that this interpretation remains inconclusive without direct hippocampal recording.

It is also well-recognized that occipital lobe epilepsy constitutes a major diagnostic challenge because of its propensity to rapidly spread to distant sites in the temporal and frontal lobes in up to 50% of cases (Salanova *et al*., 1992; Williamson *et al*., 1992). The well-established projection pathway from the occipital cortex to both ipsilateral and contralateral temporal structures often makes the distinction between occipital and temporal lobe seizure onset challenging. While visual auras are commonly regarded as relatively specific to the occipital lobe (Appel *et al*., 2015), they also occur in seizures of anteromedial temporal and occipito-temporal origin (Gupta *et al*., 1983; Fried *et al*., 1995; Bien *et al*., 2000).

The olfactory aura in our patient is also commonly observed in seizures arising in both the temporal and occipital lobes (Palmini and Gloor, 1992; Acharya *et al*., 1998). Thus temporal lobe-like auras, such as an olfactory sensation, with possible occipital lobe seizure origin, must be analysed with extreme caution (Palmini and Gloor, 1992). Our case also emphasizes the importance of interpreting auras in conjunction with other seizure features, especially if the aura is discordant with other localizing signs, as has been observed in patients with TLE who are evaluated for surgery (Gupta *et al*., 1983; Bien *et al*., 2000).

Furthermore, multiple auras can occur in different seizures or in the same seizure, either simultaneously or sequentially. Several authors showed multiple auras originating in a single epileptogenic zone, usually located in temporal or posterior quadrant foci, which appear to be experiences from sequential or simultaneous activation of multiple symptomatogenic zones (Widdess-Walsh *et al*., 2007). It is therefore possible that different single auras reflect different propagation pathways from the same focus. (Widdess-Walsh *et al*., 2007).

In our case, the scalp EEG revealed a discrete ictal onset over the right occipital region that was confirmed by 3D electrical source imaging. This was the only non-invasive data that helped guide the placement of subdural electrodes over the occipital cortex. Our functional imaging findings likely represented a propagation of the epileptogenic network, in fact, we know ictal SPECT and FDG-interictal PET are prone to effects of seizure propagation by expanding the epileptogenic zone (Guerrini *et al*., 2015). For this motive, we considered our ictal SPECT and FDG-interictal PET data unreliable to detect the epileptogenic zone. From a practical standpoint, during presurgical non-invasive evaluation to find the epileptogenic zone, one should consider the clinical semiology and interictal and ictal scalp EEG findings, such as the starting points from which to analyse first the non-invasive morphological and functional data and then, in the absence of concordant data, one should proceed with the invasive evaluation.

Limited resection proved sufficient to eliminate this patient's seizures. There is a growing consensus that large-scale networks subtend the core phenomena of epilepsy, including seizure generation, cognitive dysfunction, and response to treatment (Fahoum *et al*., 2012; Varotto *et al*., 2012; Centeno and Carmichael, 2014). Indeed, investigation of epileptic networks now serves as a key concept for a deeper understanding of the disease. (Laufs *et al*., 2007; Gotman, 2008; Richardson, 2012; Duchowny and Bhatia, 2014). Within this conceptual framework, however, the concept of the hub is of special importance for surgical therapy as it is likely that some brain regions are more responsible for seizure onset and propagation (hub), while others (nodes) are only remotely involved (Duchowny *et al*., 2000; Pittau *et al*., 2014). While epileptic activity could result from localized abnormal neuronal activity in connected network regions or abnormal regional interactions, seizure freedom is unlikely without removing the primary hub.

Although completeness of resection is an important correlate of seizure outcome, the definition of completeness remains elusive within the ill-defined framework of an epileptogenic network. It is also recognized that some patients are seizure-free after an incomplete resection (Perry *et al*., 2010) and the seizure freedom in these cases is still possible after complete ablation of the structural lesion, but not the seizure onset zone, or vice versa (Perry *et al*., 2010). The core relationships of extensive epileptogenic networks are still largely unknown. Whether network perturbations are capable of inducing independent nodal seizure onsets is also an important unresolved issue.

Conclusions

From a practical standpoint, our case demonstrates that the hippocampus was more likely only a non-pacemaker propagating node of the network, while the occipital lesion was the primary epileptogenic zone. Thus, since the invasive investigation showed an epileptogenic zone over the occipital lobe with inactivity of the hippocampal region, it was reasonable to perform a minimally invasive procedure despite the presence of HS, as reported by others previously (Bekelis *et al*., 2013). □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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

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TEST YOURSELF

(1) Which brain region is typically responsible for olfactory aura at seizure onset?

(2) Can multiple auras occur in different seizures or in the same seizure?

(3) Which part of the epileptic network is most critical for determining seizure onset?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".