Original article

Auditory aura in frontal opercular epilepsy: sounds from afar

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ABSTRACT – Auditory auras are typically considered to localize to the temporal neocortex. Herein, we present two cases of frontal operculum/perisylvian epilepsy with auditory auras. Following a non-invasive evaluation, including ictal SPECT and magnetoencephalography, implicating the frontal operculum, these cases were evaluated with invasive monitoring, using stereoelectroencephalography and subdural (plus depth) electrodes, respectively. Spontaneous and electrically-induced seizures showed an ictal onset involving the frontal operculum in both cases. A typical auditory aura was triggered by stimulation of the frontal operculum in one. Resection of the frontal operculum and subjacent insula rendered one case seizure- (and aura-) free. From a hodological (network) perspective, we discuss these findings with consideration of the perisylvian and insular network(s) interconnecting the frontal and temporal lobes, and revisit the non-invasive data, specifically that of ictal SPECT.

Key words: auditory aura, frontal operculum, perisylvian epilepsy, ictal SPECT, magnetoencephalography

Epileptic aura, the subjective manifestation of a clinical seizure, has localizing significance in focal epilepsies (Palmini and Gloor, 1992). Though it is acknowledged that seizures may arise in functionally "silent" cortex, the symptomatogenic zone producing the aura is generally assumed to be in closest proximity to the ictal onset zone. However, there is no fundamental reason why the symptomatogenic cortex should be near the ictal onset zone. Examples of "propagated auras" are well recognized in temporal lobe epilepsy, though these auras are usually complex or experiential (Gloor, 1990). Elementary auras suggest activation of primary cortex (Palmini and Gloor, 1992).

Auditory auras localize to the temporal neocortex (Florindo *et al.*, 2006), specifically to primary auditory cortex or to surrounding auditory association cortex. These cortices are also implicated in musicogenic seizures (Wieser *et al.*, 1997; Tezer *et al.*, 2014; Diekmann and Hoppner, 2014).

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Herein, we present two patients who had auditory illusions as aura, with ictal onset originating from the frontal operculum and subjacent insula. We interpret the data as evidence of a "propagated aura" within an epileptogenic network.

Case 1

We present a 26-year-old, right-handed man with pharmacoresistant epilepsy with adolescent onset. Typical seizures began with a non-lateralized auditory aura, described as a distortion of sounds ("things sound weird"), accompanied by a feeling of anxiety. These could be triggered by music, and specifically by a sudden change in musical rhythm, a situation often experienced while practising with his amateur rock band. Auras also occurred spontaneously. The subsequent seizures were of a complex motor semiology, with early proximal stereotypies (kicking movements) and manual automatisms, in addition to prominent axial stiffening, facial flushing, and apnoea. Partial responsiveness and recollection were maintained. Postictal examination showed transient oromotor dysfunction (inability to speak). In rare generalized seizures, a phase of tonic contraction of the left face and leftward eye deviation occurred, with an initial extension of the left arm (sign of four) upon generalization. Seizures occurred daily and were frequent during sleep.

Interictal scalp EEG showed rare sharp waves over the vertex and the right fronto-central region. Ictal scalp EEG showed diffuse changes, maximal over the same region, but marred by muscle artefact. Magnetoencephalography (MEG) failed to demonstrate interictal discharges, however, a clinical seizure was produced upon exposure to musical stimuli (short extracts of rock music). Movement artefact prevented localization of the seizure by MEG.

High-resolution epilepsy-protocol MRI was unremarkable. FDG-PET showed a subtle hypometabolism in the right frontal operculum (*figure 1C*).

Ictal SPECT (SISCOM) of a typical seizure demonstrated hyperaemia bilaterally, maximal in the left frontal operculum/insula and anterior cingulum (*figure 1D*).

With this data, an hypothesis of right perisylvian epilepsy was proposed. Given the motor semiology, investigation of the mesial frontoparietal and cingulate cortices was also necessary. An intracranial evaluation with stereotactically-implanted depth electrodes (stereoelectroencephalography; SEEG) was designed to sample the right frontoparietal operculum, insula, mesial frontal and parietal regions, cingulum, and the superior temporal gyrus, including Heschl's gyrus (*figure 1A*; right-sided electrodes). Two sentinel electrodes were also placed, targeting the anterior and posterior cingulate gyrus in the left hemisphere (not shown).

On SEEG, frequent spiking was observed in the right frontal operculum/insula (electrode Q) and planum temporale (electrode U). Five typical seizures were recorded which showed onset in the right frontal operculum/insula (Q1,2). Ictal spread was next to the right planum temporale (U6,7) and mid-superior insula (R1,2), with variable latency (*figure 1B*). The first clinical sign only appeared when the seizure discharge had involved these three areas and motor signs began when the motor regions, sampled by electrodes M and N, were involved. Typical auditory aura was reported in one seizure during wakefulness but only after the seizure was over, and the patient thought it was triggered by music during a film he was watching. Upon cortical stimulation, his auditory aura was reproduced by low-amplitude (1-2 mA; 0.3 msec pulse width; 25 Hz biphasic) bipolar stimulation of contacts within (U3-4) and anterior to (T3-4) Heschl's gyrus. Stimulation of the contacts in the lateral surface of the right frontal operculum (R5-6) produced a negative motor response of the tongue, reminiscent of his postictal deficit. A typical seizure (without auditory aura) was reproduced with low-amplitude (1 mA; 0.3 msec pulse width; 25 Hz biphasic) electrical stimulation of Q1-2, the contacts of ictal onset for spontaneous seizures. Finally, cortico-cortical evoked potentials (CCEPs; using the protocol of Matsumoto *et al.* [2004]) demonstrated a robust unidirectional connection between the right frontal operculum/insula (Q1-2) and right planum temporale (U6-7).

Based upon these findings, the patient underwent resection of the right frontal operculum and subjacent insula. Despite unremarkable histopathology, he has remained seizure-free and without aura at last contact, 18 months after surgery.

Case 2

We next present a 46-year-old, left-handed man with pharmacoresistant epilepsy of childhood onset. Starting at the age of 5 years, he was reported to have seizures, predominantly nocturnal, characterized by contraction of the face on one side. From adolescence onwards, seizures began with a non-lateralized stereotyped auditory aura, as if his hearing was "muffled", associated with an indescribable feeling of an impending seizure. He would then make sniffing sounds and become unresponsive, with later tonic contraction of the right face and salivation. Varied hyperkinetic motor movements and vocalization would follow. Postictally, he was aphasic for 1-2 minutes.

As with the first case, scalp EEG showed sharp waves in the fronto-central region, in this case on the left. Ictal
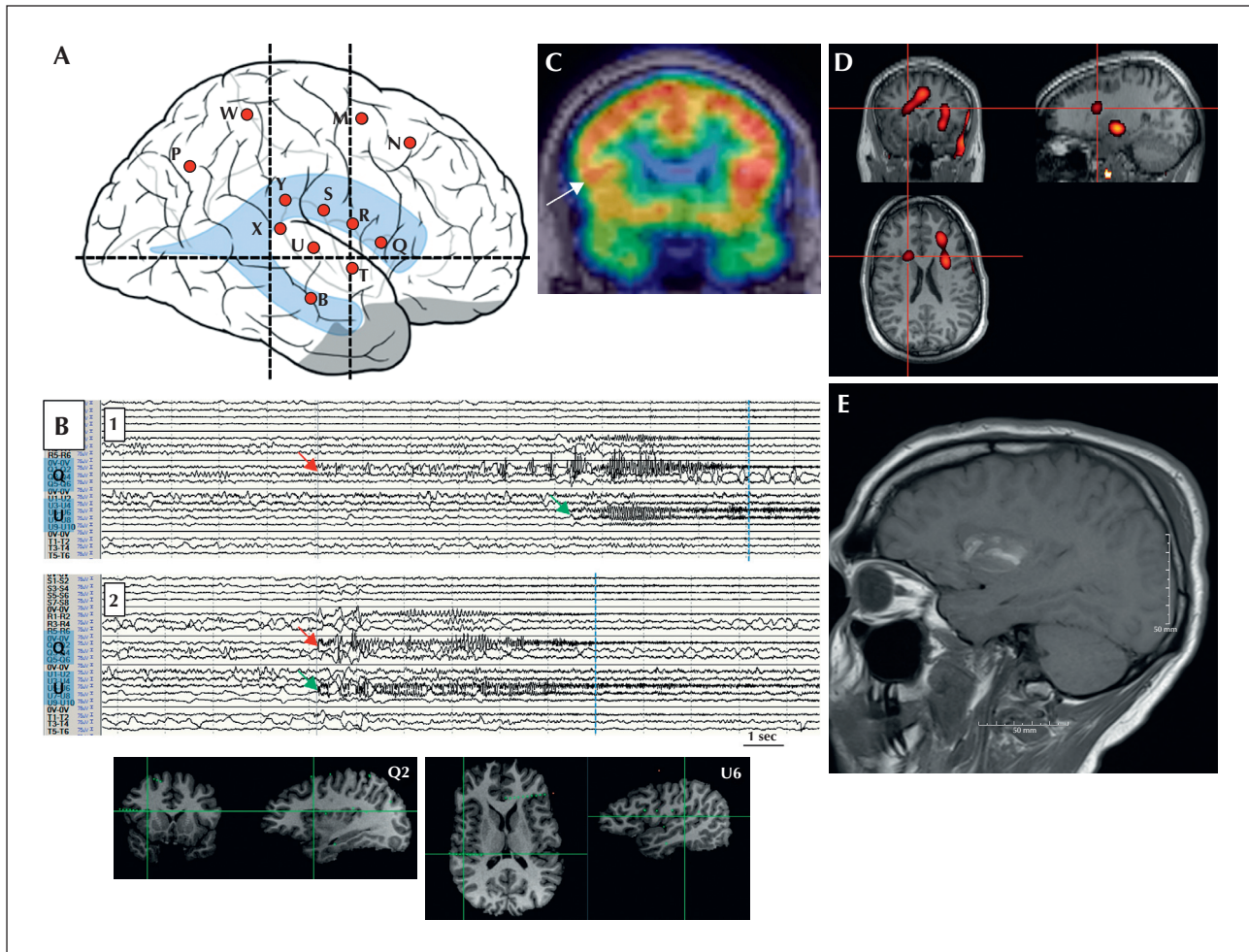
Figure 1. (A) Right-sided SEEG schema with 12 depth electrodes exploring the anterior and posterior perisylvian region (electrodes Q-T) and mesial frontal region/supplementary motor area (SMA; electrodes M and N). (B) Two representative seizures showing onset at contacts Q1,2 (frontal operculum/insula; red arrow) and U6,7 (planum temporal; green arrow) on a 15-second page (band pass: 5.3-300 Hz). The onset at these contacts was simultaneous in the second example, though in the first example the ictal discharge at U5,6 was delayed relative to that at Q1,2. These seizures occurred during sleep without report of aura. Clinical onset is denoted by the blue line. In other seizures, including the one with reported auditory aura, a build-up of spiking occurred in contacts Q1,2 for tens of seconds prior to ictal onset. Prominent early involvement was also noted in the mesial contacts of M and N (SMA; not shown), in addition to neighbouring perisylvian contacts. (C) Interictal FDG-PET showing hypometabolism in the right frontal operculum (arrow). (D) Ictal SPECT (Z=2) of a typical seizure recorded prior to SEEG evaluation. Injection was performed at nine seconds from clinical onset. There was a dominant focus in the left frontal operculum/insula and anterior cingulum. A lesser degree of hyperaemia was seen in the right insular region (crosshairs). Semiology of this seizure involved left face tonic contraction, suggestive of right opercular activation. (E) Post-resection MRI showing defect in the right frontal operculum and subjacent insula.

EEG was poorly localizing, with subtle rhythms seen in the same region. On MEG, several unique polyspikes were detected, which localized, by single equivalent current dipole modelling, to a cluster centred on the left inferior frontal sulcus (*figure 2E*).

On MRI, subtle T2-weighted signal intensity was apparent involving the left inferior frontal sulcus, with features suggestive of a transmantle cortical dysplasia (*figure 2C*). There was a corresponding region of hypometabolism on FDG-PET (*figure 2D*). Ictal SPECT demonstrated a dominant focus of hyperaemia extending from the left frontal opercular region to the superior temporal gyrus (*figure 2F*). Intracarotid methohexital (Wada) testing confirmed left hemisphere language dominance.

Given the proximity of the visible lesion to putative language cortex (Broca's area), necessitating the need for language mapping, this patient was investigated using a combination of subdural and depth electrodes (*figure 2A*). This was aimed at sampling the left perisylvian region, with depth electrodes targeting the lesional frontal cortex (electrode L') and the superior temporal gyrus (T' and U'), the latter placed in an attempt to explain the auditory aura.
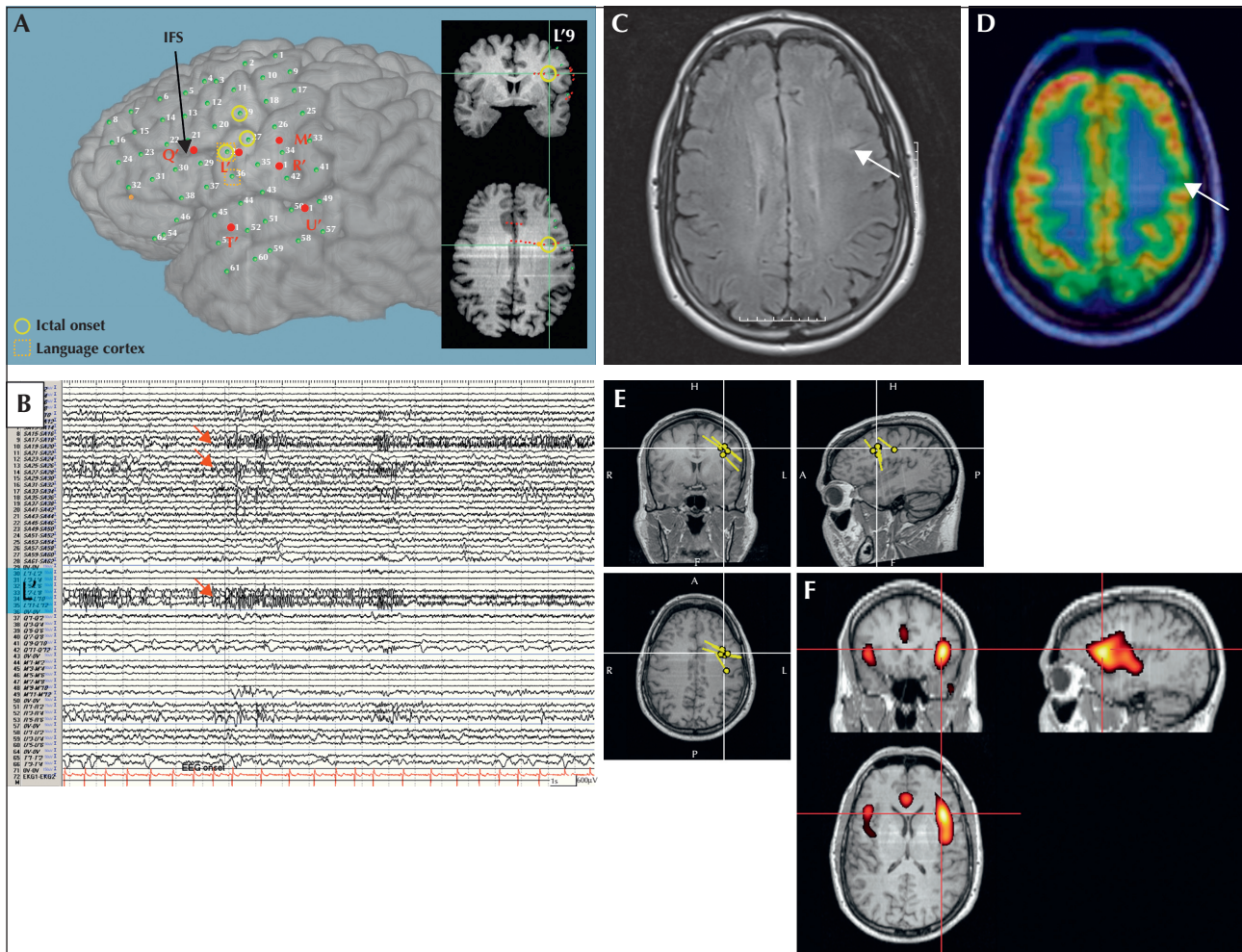
Figure 2. (A) Left-sided perisylvian subdural and depth electrode implantation with electrodes targeting the suspected lesion in the inferior frontal sulcus (L'). The inferior frontal sulcus (IFS) is indicated. (B) Ictal onset with tonic fast activity, most prominent in L'9 (see inset in [A]) and overlying subdural contacts (SA19, 27, 28; denoted as yellow circles in [A]) on a 20-second page (band pass: 5.3-120 Hz). Clinical onset occurred approximately 20 seconds later (not shown). The ictal onset zone overlapped with language cortex, as determined by cortical stimulation (boxed; contacts 28 and 36). (C) Axial FLAIR showing subtle T2 hyperintensity suggestive of focal cortical dysplasia. (D) Interictal FDG-PET showing hypometabolism of the left frontal operculum. (E) Single equivalent dipole model of MEG-unique epileptiform activity. Dipoles were clustered in the region of the right inferior frontal sulcus. (F) Ictal SPECT (Z=2) in a typical seizure recorded prior to SEEG evaluation. Injection was performed at 14 seconds from onset. A dominant focus of hyperaemia is seen extending from the left frontal to the left temporal operculum.

Invasive recordings demonstrated frequent spiking in the left inferior frontal gyrus/sulcus. During the period of invasive recording, five typical seizures occurred during sleep (without reported aura), with ictal EEG onset and prominent evolution in this same region (*figure 2B*). Electrical stimulation demonstrated an overlap of language cortex with the ictal onset zone in the inferior frontal gyrus (pars opercularis; contacts 28 and 36). In addition to producing speech arrest, a typical auditory aura was triggered with stimulation (5 mA; 0.3 msec pulse width; 25 Hz biphasic) of the left inferior frontal gyrus/sulcus (L'8-9), without the elicitation of afterdischarges. Contacts in the superior temporal gyrus were not stimulated. Given the demonstrated overlap between the ictal onset zone and language cortex, a surgical resection was not performed.

Discussion

Auditory auras are generally assumed to be highly indicative of lateral neocortical temporal lobe epilepsy, with rare exceptions reported (Clarke *et al.*, 2008). Our two patients described auditory aura as their earliest clinical symptom despite their epilepsy localizing to the frontal operculum (right and left, respectively), and subjacent insula in the first case. In addition, a

musicogenic reflex component was present in Case 1. These data must be interpreted from a hodological (network) perspective.

The ventrolateral prefrontal (opercular) cortex, receiving projections from the auditory parabelt region (superior temporal gyrus) and temporal visual association cortex, functions to integrate audio-visual information, specifically with respect to verbal communication (Romanski, 2007). This region is also implicated in the inhibition of resultant motor responses to auditory stimuli (Brunetti *et al*., 2008). In this regard, it should be noted that the auditory auras described by our patients were not elementary sound hallucinations. Rather, the auras here belong to the category of auditory perceptual distortion or illusion, and may therefore reflect disturbance of higher order auditory processing. Thus, we speculate that the auras in these cases result from a disturbance of this extended auditory processing network, both producing a perceptual alteration, and interrupting the operculum from its normal inhibitory influence on motor responses to auditory stimuli. This may explain the semiology in Case 1, where auditory stimuli resulted in reflex seizures with prominent motor and autonomic semiology.

Interposed between the frontal operculum and temporal lobe is the insula. This structure receives afferent projections from a diverse number of brain regions, in particular from auditory cortex. Of direct relevance to our cases, Isnard *et al*. (2008) reported on the elicitation of auditory symptoms by insular stimulation. In order to distinguish seizures in this region from those of temporal lobe epilepsy proper, the concept of "perisylvian epilepsy" has been introduced. Both of our patients manifested with initial auditory auras followed by prominent autonomic and hemifacial motor semiology, and are arguably best understood as examples of this syndrome.

One unexpected feature common to these two cases is their ictal SPECT. Both studies showed bilateral opercular/insular hyperaemia, with dominant hyperperfusion ipsilateral to the epileptogenic focus in Case 2, but contralateral in Case 1. This apparent false lateralization in Case 1 was understood to be a consequence of rapid propagation to contralateral homologous regions, a finding we have observed in other patients with operculo-insular epilepsy. Beyond simply indicating the ictal onset zone, recent publications have suggested that ictal hyperaemia instead tracks the anatomical structures or networks involved in seizure propagation (Wong *et al*., 2010). In both cases, hyperaemia was bilateral, as would be expected in an epileptogenic network that involves bilateral perisylvian cortex (Brunetti *et al*., 2008).

Another method for establishing functional connectivity is the methodology of cortico-cortical evoked responses (CCEPs) introduced by Matsumoto

et al. (2004). CCEPs in Case 1 showed a prominent response in the right planum temporale following stimulation of the right frontal operculum/insula. The opposite response did not occur. Whether this apparently unidirectional connection is normal or pathological cannot be determined. It has been suggested that regions of ictal propagation exhibit enhanced CCEP responses (Enatsu *et al*., 2012), however, it must be emphasized that the physiological CCEP connectivity in the non-dominant perisylvian region has not been established.

Taken together, these cases demonstrate the occurrence of auditory aura in seizures originating outside the temporal lobe, and in particular, arising from the frontal operculum. The exact mechanism for this is unclear, but we suggest that this observation should be understood on the basis of the underlying network(s) within perisylvian and insular cortex interconnecting the frontal and temporal lobes, and specifically, the extended auditory processing network. These cases also highlight the importance of sampling these cortices in patients with auditory aura. □

Supplementary Data.

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

Disclosures.

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TEST YOURSELF

(1) What is the localization and lateralization of musicogenic seizures?

(2) Where is Broca's area located anatomically?

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".