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Case Report

EEG–fMRI findings in late seizure recurrence following temporal lobectomy: A possible contribution of area tempestas ☆

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ABSTRACT

Late seizure relapses following temporal lobectomy for drug-resistant temporal lobe epilepsy occur in 18–30% of operated-on cases, and recent evidence suggests that a significant proportion of them are due to maturation and activation of proepileptic tissue having defied initial resection and located at the vicinity of or at a short distance from its borders, usually over the posterior medial, basal temporal-occipital, and lateral temporal regions. Experimental studies in animals and functional imaging studies in humans suggest that the area tempestas, a particular region of the basal-frontal piriform cortex, is critical for kindling and initiation and propagation of seizure activity arising from different cortical foci, especially limbic ones. This case report of a patient with late seizure relapse, three years following an initially successful right temporal lobectomy for ipsilateral medial temporal sclerosis, is the first one in the literature to demonstrate interictal EEG–fMRI evidence of significant BOLD signal changes over the inferior, basal and lateral temporal and temporooccipital cortices posterior to the resection margin, plus a significant BOLD signal change over the ipsilateral basal frontal region, closely corresponding to the piriform cortex/area tempestas. Our case study provides further functional imaging evidence in support of maturation/activation of proepileptic tissue located at the vicinity of the initial temporal lobe resection in cases of late seizure relapses and suggests, in addition, a possible role for the piriform cortex/area tempestas in the relapsing process.

1. Introduction

Late seizure recurrences following temporal lobectomy for intractable epilepsy occur in 18–30% of operated-on patients [1–4]. It has been suggested that these late relapses are due to maturation of proepileptic tissue having defied initial resection and being located usually at the vicinity of it [4,5]. The term proepileptic can be used to characterize tissue which is not yet epileptogenic but encompasses the potential to become epileptogenic following a maturation time interval and under certain circumstances (such as facilitatory long-term influences from nearby epileptogenic structures and networks) [5]. According to a recent report from the Cleveland clinic group [4], posterior medial/basal and lateral temporal and occipital areas are the most likely regions harboring this type of proepileptic tissue whose late maturation is held responsible for seizure reappearance. On the contrary, early recurrences are associated with incorrect localization and resection of the epileptogenic zone or with partial/incomplete resections only.

Experimental studies have shown that the area tempestas (AT), a particular region lying within the primary olfactory cortex (OC), is critical for controlling the initiation and propagation of either generalized or focal seizure activity [6–8]. In humans, relevant evidence has been recently described in an interictal EEG–fMRI and flumazenil-PET (FMZ-PET) group analysis of patients with partial-onset epilepsies of various locations [9]; EEG–fMRI revealed significant BOLD signal changes associated with interictal sharp wave activity to ipsilateral basal frontal-OC, corresponding to a presumed AT location, as well as concordant significant increases in FMZ-PET volume of distribution (FMZ-VT), compared to healthy subjects.

In this study, we present interictal EEG–fMRI evidence of AT involvement in a well-documented case of mesial temporal sclerosis (MTS) having a satisfactory seizure outcome following an ipsilateral temporal lobectomy for the first three years since the procedure and relapsing subsequently during antiepileptic drug tapering.

2. Materials and methods

2.1. Case preoperative history

This 25-year-old right-handed man presented with a history of drug-resistant partial-onset seizures since age 10 years. He had no personal or family risk factors for epilepsy. Seizure semiology consisted of a rising epigastric sensation, a fearful feeling, clouding of consciousness, and oral and hand automatisms. He had no history of secondary generalizations. By the time of the presurgical evaluation, the patient's seizures had failed to improve after repeated trials with almost all

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appropriate antiepileptic drugs in monotherapeutic and combination schemes, and he had been experiencing mainly diurnal seizures in clusters of 3–4 within 48 h, 2–3 times per month. Presurgical long-term video-EEG monitoring revealed the presence of strictly right hemispheric interictal sharp-wave activity, most of it showing an anterior-inferior temporal max (F8/F10 and T4/T10) and, less frequently, an anterior-frontal one (Fp2/F4). Typical seizures were recorded with a broadly distributed ictal rhythm consisting at onset of repetitive 2- to 3-Hz sharp-wave activity over the right frontotemporal region spreading subsequently to the ipsilateral centroparietal region and in a less well-organized manner to the contralateral side as well. MRI revealed findings strongly suggestive of right-sided MTS. There were no MRI findings suggesting right frontal lobe pathology. The patient finally underwent an ipsilateral anteromedial temporal lobectomy. Acute preresection electrocorticography through subdural strips confirmed robust spiking from the temporal pole and medial-basal temporal region. The lateral-inferior frontal cortex was explored revealing infrequent spikes. The hippocampus was resected up to 2.5 cm along its length. Biopsy confirmed the presence of severe hippocampal sclerosis.

2.2. Case postoperative history

At 3, 12, and 24 months postoperation, the patient was continuously seizure-free and had had normal routine EEGs. Until the 24th month, the patient has been constantly on his preoperative antiepileptic regime, consisting of levetiracetam 2000 mg/day and oxcarbazepine 1200 mg/day. By that time, gradual oxcarbazepine withdrawal was undertaken, removing 300 mg from the total daily dosage every 3 months. About one month following complete oxcarbazepine withdrawal and under conditions of intense emotional stress, the patient relapsed. He would report again the same aura of rising epigastric sensation and fearful feeling, along with the same preoperative semiology of oral and manual automatisms, albeit with less clouding of awareness, shorter seizure duration, and rapid recovery. He experienced about 10 isolated events within the next 3 months until he was subjected to a new video-EEG study. The study revealed strictly unilateral, right-sided interictal sharp wave activity localized over the frontotemporal region (Fp2/F4/F8) (Fig. 1A). Several typical seizures were recorded with semiology similar to his preoperative ones and an ictal EEG correlate consisting of semirhythmic 2- to 3-Hz repetitive sharp waves evolving to 3- to 4-Hz sharply contoured waves, with a broad right anterior quadrant distribution closely resembling the preoperative ictal EEG (Fig. 1B). A new MRI scan demonstrated the cavity of the initial anteromedial temporal lobectomy and no evidence of new pathology.

Oxcarbazepine was reintroduced to his antiepileptic regime and titrated to prelapse dosage (1200 mg/24 h). Since then, the patient has reportedly returned to being seizure-free again.

3. Results

The patient underwent a 30-min EEG–fMRI study in the MR scanner, during which he remained in relaxed awareness with eyes closed. Eighteen spike–wave discharges of right frontal/frontotemporal distribution (Fig. 1A) were identified and analyzed. The technical details of the EEG–fMRI procedure and analysis can be found in a previous study [10].

The interictal analysis revealed areas of statistically significant BOLD signal change as follows:

- decreased BOLD signal clusters over the right inferior/basal temporal (close to the lateral resection borders), inferior lateral temporooccipital, and posterior mesial/basal occipital regions (at a distance from the posterior resection margin) (Fig. 2B, C, and D, respectively);
- increased BOLD signal over the right posterior lateral temporal neocortex (Fig. 2A) and over the right basal frontal/piriform cortex (PC) and inferior basal-ganglionic region (corresponding to AT) (Fig. 2A).

4. Discussion

Besides afferent inputs from the olfactory bulb and basal forebrain, the PC and AT receive inputs from several subcortical structures, including the hypothalamus, raphe nuclei, ventral tegmental area, locus ceruleus, etc., and provide dense efferent connections to the ventrolateral orbital and lateral orbital cortex, amygdala, entorhinal cortex and subiculum, insular neocortex, mediodorsal thalamus, and hypothalamus as well [6,7]. Experimental evidence exists that PC/AT may serve as a site from which seizures and kindling may be evoked and may also be involved in the propagation and amplification of epileptic discharges elicited from other brain areas, especially limbic ones [6,8].

The human equivalent of AT has been demonstrated by Laufs et al. [9] in their EEG–fMRI and FMZ-PET group analysis of patients with partial-onset epilepsy; the activated area in our case closely corresponds to the position indicated in that study (the reader is referred to [9] for a direct comparison). So far, EEG–fMRI evidence of AT involvement has been shown in this study and in group analysis only. To the best of our knowledge, this is the first report demonstrating interictal EEG–fMRI evidence of AT involvement following late seizure recurrence after temporal lobectomy at the single-case level. Certainly, we do not have preoperative EEG–fMRI data to compare and determine whether AT involvement was evident preoperatively or its involvement began at some point in time following the operation. In this last case, a more direct facilitatory influence of AT in the recurrence process might be inferred. Even though we do not possess information about the preoperative status of AT, our data still provide evidence supporting a facilitatory influence of this region in epileptogenesis.

An alternative explanation would be that it is not the AT, per se, which is involved due to its unique seizure-inducing properties but an independent occult epileptogenic pathology coincidentally located at the same region. We certainly cannot definitely rule out this hypothesis, given that we did not have direct electrocorticographic explorations of this area nor any tissue resected from it available for analysis. We think, however, that such an interpretation is very unlikely for the reasons that follow. First, as already commented on, late seizure relapses after temporal lobectomy are most likely related to the maturation of proepileptic tissue located close to, or at some distance from, the original epileptogenic zone. Posterior lateral, basal, and inferior temporal and temporooccipital areas are commonly implicated in this regard [4,5], and in our case, BOLD signal changes in EEG–fMRI were definitely detected over these areas, suggesting their involvement. Second, seizure semiology remained the same as preoperatively, consistent with spread over the same symptomatogenic zone. Symptoms and signs were strongly suggestive of temporolimbic network involvement, and hyperkinetic features consistent with basal frontal recruitment [11] were never reported or observed. In addition, detailed questioning did not elicit any recollection of olfactory hallucinations, typical for seizures arising from the OC [12]. Third, preoperative MRI suggested and histopathology confirmed the presence of severe hippocampal sclerosis, and there was no MRI abnormality over the basal frontal region. Certainly, the absence of an abnormality on MRI does not necessarily rule out the presence of a subtle developmental lesion. However, in most double pathology temporal lobe epilepsy cases (MTS plus malformations of cortical development/focal cortical dysplasia), both pathologies colocalize into the same temporal lobe [13,14]. It is important to note that at the time of the operation, the inferolateral frontal cortex was explored through acute preresection electrocorticography, and only sparse spikes were recorded from it, in sharp contrast to very frequent spiking from the anteropolar and mediobasal temporal regions.

All of the above considered, we think that the scenario of an MRI-occult, independent epileptogenic lesion over the basal/OC frontal region is very weak, and a precise colocalization of such a hypothetical lesion with AT should be an extremely coincidental event. Instead, we believe that the recurrence is due to activation of proepileptic tissue located over the temporal/occipital areas close to or at a short distance from the

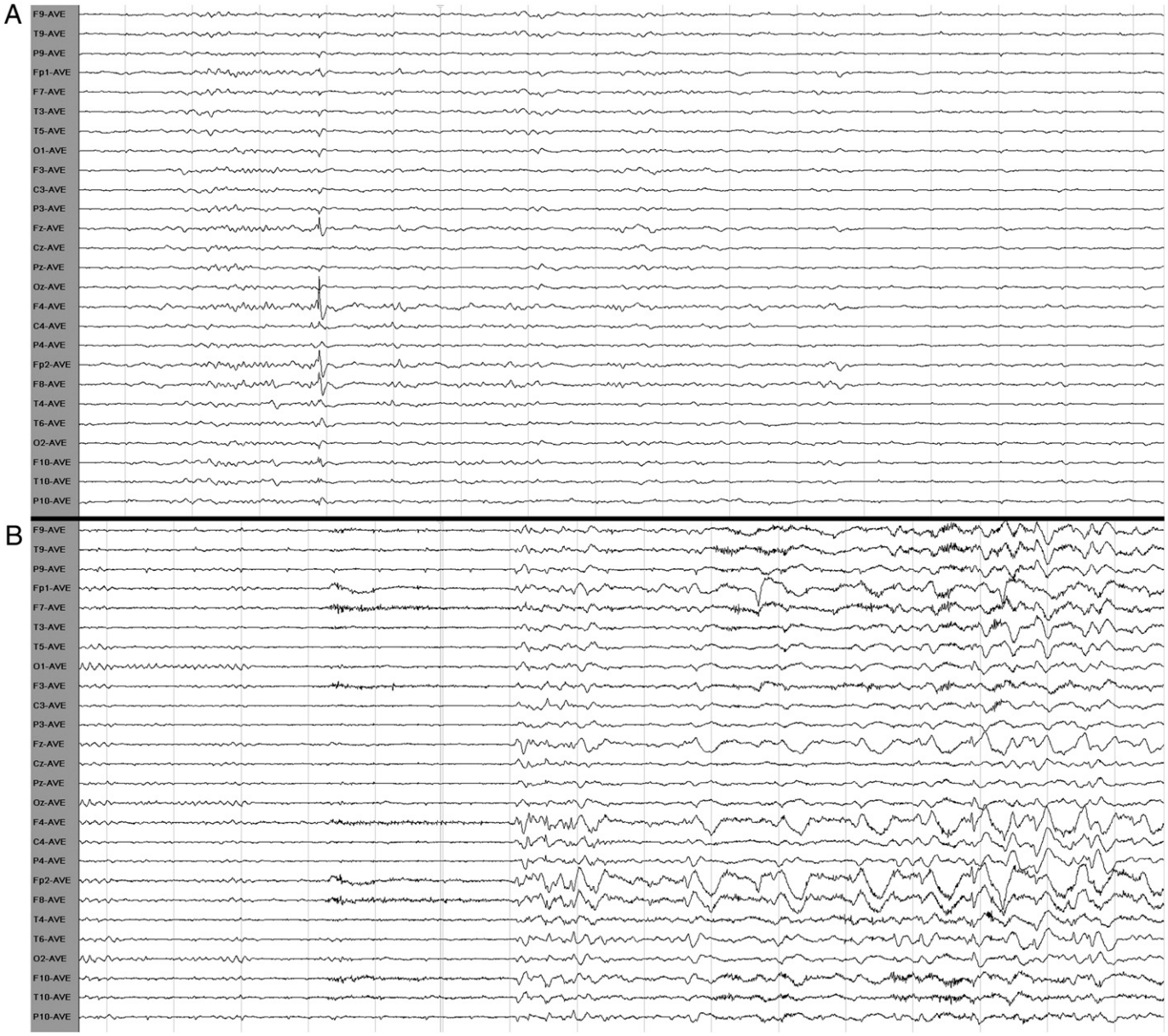

Fig. 1. A) Interictal EEG of our patient showing a typical discharge of right frontal/frontotemporal distribution. B) Ictal EEG with right frontal/frontotemporal onset.

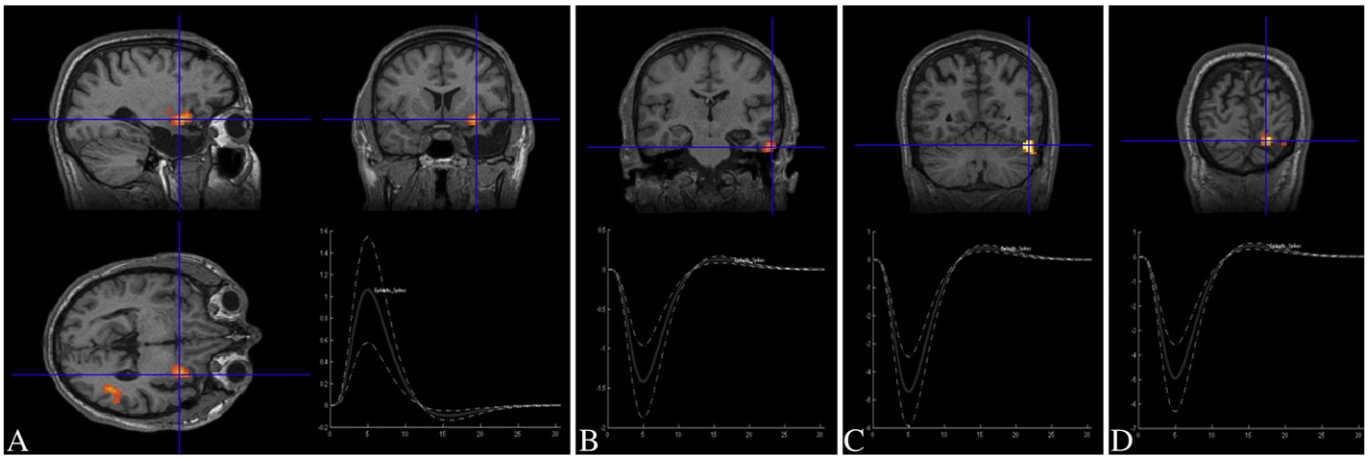

Fig. 2. EEG–fMRI results of our patient showing discharge-correlated BOLD changes in: A) the right AT ($z = 4.04$, BOLD$^+$) and the ipsilateral posterior lateral temporal neocortex ($z = 3.82$, BOLD$^+$); B) the right anterior inferior temporal gyrus ($z = 4.77$, BOLD$^-$), opposite to the posterior resection border; C) the right posterior inferior temporal gyrus ($z = 6.81$, BOLD$^-$); and D) the right mesiobasal occipital region ($z = 6.07$, BOLD$^-$).

original resection borders. This point could be criticized especially with regard to the areas showing decreased BOLD signal, given the overall ambiguity about the nature and specificity for epileptogenic focus localization of BOLD decreases [15]. Despite uncertainties in this regard, negative BOLD signal changes in the region of the spike field and epileptogenic zone are described in about 10% of EEG–fMRI studies in patients with focal epilepsies [16,17] and may be even more prevalent in pediatric cases [18]. In addition, the sites of decreased BOLD signal in our case were all located on the ipsilateral-to-the-operation temporal and occipital lobes close to or at some distance from resection borders and far away from the "default network" regions that typically show BOLD signal decreases and are related to transient alterations in cognition rather than to true epileptic activity originating from these sites [15,19,20].

5. Conclusions

We propose that proepileptic tissue at the vicinity of the initial resection and AT may facilitate each other, ending up in seizure recurrences. Proepileptic tissue may induce a subclinical kindling-like process, which, at some point in time, involves AT. By that moment and thanks to this area's anatomofunctional properties, more extensive brain areas and networks are possibly recruited, and clinical seizures emerge. In addition, alterations of subcortical inputs (due to physical/psychological stresses for example) may have an impact on AT function, leading under certain circumstances to an activation of its kindling properties upon susceptible brain regions as well. Either one or both mechanisms might be operative on a case-by-case basis with seizure recurrence as the final outcome.

Certainly, further EEG–fMRI studies of surgical cases are required in order to assess AT significance for surgical outcome prognosis: for example, activation of this area preoperatively might be a marker of already established facilitatory influences with a concomitant higher risk for postoperative seizure recurrence. It might also stress the need for targeted and region-specific pharmacologic interventions.

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