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What's behind drawing for an artist with left temporal lobe epilepsy? A multimodal neurophysiological study

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ABSTRACT

There are few studies in literature reporting drawing as a strong trigger of praxis-induced focal seizures.

The aim of the present case report was describing a case of focal epilepsy with praxis induced EEG activation, due to a cavernoma, in the left middle anterior temporal lobe by using a multimodal approach. We combined video-EEG, showing that drawing increased a sustained monomorphic delta activity localized on left anterior temporal region (F7-T1a), diffusing to the vertex (Fz) and the fronto-polar electrodes (F3), with DTI data, showing that the left uncinate fasciculus, connecting the temporal pole to the orbitofrontal cortex, significantly differed from controls. fMRI confirmed that drawing increased activation in these areas.

The congruence between findings supports the role of the left uncinated fasciculus linking the temporal lobe to the orbitofrontal cortex in the present focal epilepsy mainly facilitated by drawing.

1. Introduction

Reflex epilepsy refers to cases when seizures are triggered by specific stimuli such as music, reading, talking and praxis [49,29]. Praxis induction (PI) is defined as induction of seizures and/or epileptiform EEG activity by cognition-guided tasks [5]. There are reports of single patients or small groups of patients presenting with seizures or interictal epileptiform discharges (EDs) after specific tasks like playing chess, cards, writing and drawing. Seizures facilitated by complex motor tasks have been described in juvenile myoclonic epilepsy (JME) [28,28]. Reflex seizures occur in response to well-defined stimuli. H HBackspace However, even in other forms of the epilepsies, cognitive tasks may facilitate the occurrence of seizures. Thus, understanding how specific cognitive processes can play a role in ictogenesis might help to define the so-called tipping point, when normal physiological activities lead to neuronal hyperactivity and hypersynchrony [12].

In the present study, we report the case of an artist affected by focal epilepsy due to a cavernoma in the left middle anterior temporal lobe presenting with a peculiar EEG activation during drawing.

2. Materials and methods

2.1. Case report

We described the case of a 44-year-old right-handed [17] woman with 13 years of education. She attended an institute for the arts. S She is presently a professional artist, mainly interested in drawing, using different techniques.

Her medical history includes lymphoblastic leukemia at the age of 10 years, treated with chemotherapy and radiotherapy. No family history of epilepsy or other neurological diseases. In 2011, she experienced for the first time a seizure, which was clinically characterized by confusion and aphasia. She remembers that she was trying to speak to her daughter, but she could not utter any words and tried to express herself by gestures. During the seizure, she

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could only repeat one word: "*absolutely*". The seizure occurred after 2 months of intense drawing. She was immediately referred to an outpatient clinic. A brain MRI identified a cavernoma (3.83 cm^3 on the MRI T2-image) in the left middle and anterior temporal lobe (see Fig. 4D).

Electroencephalographic (EEG) recording showed discontinuous delta activity in the left medio-temporal region and sporadic inter-ictal spikes during drowsiness. She was started on lamotrigine and increased to 100 mg/day, with partial clinical benefit. Yet, in 2013 she discontinued lamotrigine because she developed severe depression, excessive daytime sleepiness and mental slowing. MRI follow-ups were performed every year. From 2013 until today, the patient has been experiencing clusters of focal impaired awareness seizures every 15–21 days. Seizures begin with a sudden overflow of personal memories and a brief impairment of awareness, followed by aphasia and use of passe-partout words. She does not experience post-ictal confusion but speech impairment may continue for several minutes. Most of the times, she can recognize the onset of seizures. Isolated focal to bilateral tonic-clonic seizures, preceded by right head and gaze deviation, occur especially after prolonged drawing. She experienced six focal to bilateral tonic-clonic seizures in all her history of epilepsy.

She was started on levetiracetam 1000 mg/day, which affected only focal to bilateral tonic-clonic seizures. A Aphasic seizures were unmodified in frequency and semiology. The patient experienced mental slowing and was not willing to increase the dose of the drug. She was therefore referred to our inpatient clinic for pre-surgical work up. Her neurological assessment was unremarkable. Blood samples including routine blood count, kidney and liver function tests, serum lipids, glucose level, serum lactate, lactic acid dehydrogenase, serum immunoglobulin, thyroid hormones and levetiracetam l blood levels were all normal. The neuropsychological assessment was performed on the same day as the patient underwent fMRI (see Supplementary Table 1).

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Written informed consent was obtained for clinical MRI measurements. Considering that the study was retrospective, written consent to participate in the study was not applicable.

2.2. EEG and VEEG recordings

Video-EEG recording was carried out for four days and four nights, under pharmacological washout, with a 32-channel machine (Micromed System plus®). Electrodes were placed on patient's scalp according to the 10-20 International System with additional anterior-temporal electrodes (T1 and T2) including a single channel of ECG with Fz as reference. The low frequency filter was set at 0.3 Hz, the high frequency filter at 70 Hz and the sensitivity was 70 microV/mm. A video was recorded for the entire length of the monitoring activity. Video-EEG recordings were analyzed and scored by two independent expert neurophysiologists (A. N. and G. P.). Pathological EEG activity was quantitatively measured by calculating the spiking rate, defined as the number of spikes appearing during a trial divided by the trial duration. We

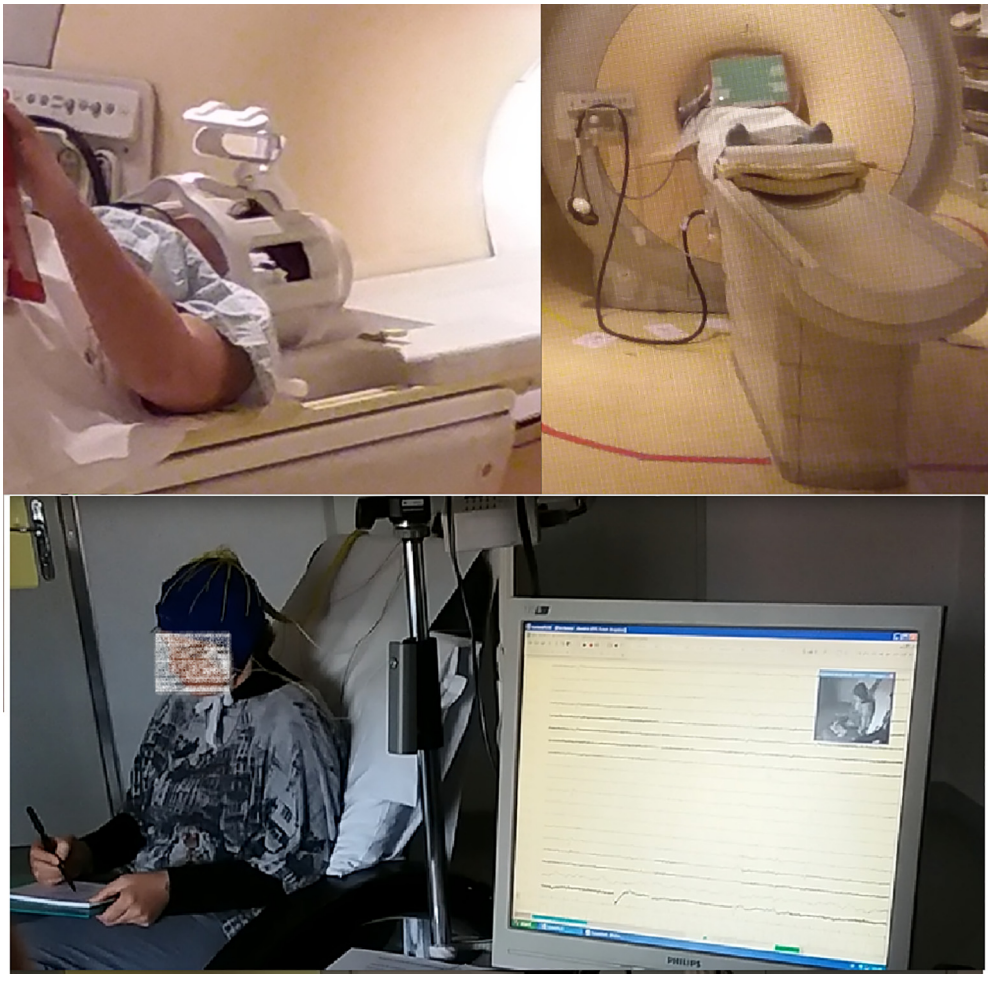

Fig. 1. fMRI set-up for the Creative Drawing and Square Drawing Tasks and the EEG experiment set-up on the lower panel.

divided each recording into six different settings: quiet wakefulness; routine wakefulness activity (talking, eating, drinking, getting dressed and so on); specific cognitive tasks (typing on the phone, listening to music, reading); art performing (freehand drawing with no time restriction); non-rapid eye movement (NREM) sleep; REM sleep.

The spiking rate was calculated visually. Finally, a polygraphic EEG recording, with the same location and number of electrodes, was obtained while the patient was performing the same cognitive tasks she had carried out during the fMRI session (see Fig. 1).

2.3. fMRI and DTI study

A Philips Achieva 3-T (Best, Netherlands) whole-body scanner was used to acquire DTI, anatomical and functional images, using a SENSE-Head-8 channel head coil and a custom-built head restrainer to minimize head movements. 7 blocks of a creative drawing task and 7 blocks of a square drawing task, each lasting 30 s, were presented in a counterbalanced order, alternating with a 15 s resting baseline. Each block included an audio instruction (3 s) asking the patient to perform creative drawing or alternatively to draw squares. Synchronization was controlled by Presentation (Neurobehavioral Systems). Stimuli were presented using an audio system (Resonance Technology). A homemade MRI compatible portable desktop lectern was placed above the waist of the patient and adjusted to her arm's length (see Fig. 1). Cushions positioned under her right upper arm restricted excessive arm movements during drawing. A booklet was fixed on the lectern. The patient viewed the booklet and her hand via a double-mirror system attached to the head coil about 10 cm above the eyes. Spontaneous 9-minute patient-selected drawing with restricted right arm movement was performed.

Functional images and diffusion tensor data were acquired as previously reported (e.g., [24]). All calculations were performed on UNIX workstations (Ubuntu 8.04 LTS, i386) using MATLAB r2018a (The Mathworks Inc., Natick, MA/USA) and SPM12 (Statistical Parametric Mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK http://www.fil.ion.ucl.ac.uk/spm). DTI data were analyzed using DTIStudio (version 3.0.3).

3. Results

3.1. Neuropsychological assessment

Fluid intelligence was normal [1]. Her forward and backward digit span was within the normal range. She showed neither ideomotor nor oral apraxia. Language was unimpaired, as evidenced by the Token Test [7], phonological and semantic fluency [16], oral picture naming of nouns and verbs, auditory and visual noun and verb comprehensions, phonemic discrimination, reading sentences and sentence and syntagm repetition [15]. Semantic associations [9] and object decisions [19] were normal as well as reading and repetition of words and pseudowords (Ripamonti et al., [30]), and on writing words and pseudowords from dictation (Luzzatti et al., [31]) (see Supplementary Table 1).

3.2. EEG recordings

Video-EEG recordings were carried out for a total of 91 hours and 25 minutes. Mean duration of wakefulness was 1108 minutes, including wakefulness after sleep onset (see Table 1 for the specific setting durations).

We recorded four seizures, clinically characterized by speech arrest, slight head and gaze deviation to the right, oral (chewing) and right-hand automatisms (rubbing the surface of objects) and left-hand dystonic posture. All seizures occurred during wakefulness. Awareness was not fully impaired. In fact, after the seizure ceased, she could name the objects that the technician showed her during the ictal phase. Seizures lasted 2 minutes. The patient presented speech impairment for several minutes after they ended. Three seizures out of four occurred while the patient was drawing. The fourth happened while she was talking with the nurse, just after a drawing session. On the EEG, seizures were characterized by abrupt onset of low voltage ictal fast activity evolving to bihemispheric theta activity for 20 seconds, with post-ictal slowing (see Supplementary Fig. 1).

Interictal epileptiform activity was characterized by spikes and spike-and-wave complexes on T3 and T5, with distribution to fronto-polar and temporal anterior electrodes. This activity could be recorded mainly during sleep, whereas it was poorly represented during quiet and active wakefulness (see Fig. 2), being the spiking rate 0.4 and 0 respectively. During slow waves sleep (SWS), spiking rate increased, while epileptiform activity became rare during REM sleep (see Table 1A).

Interestingly, a sustained slow activity was recorded during active wakefulness, which was expressed mainly during freehand drawing, painting and typing on the phone (see the spiking rate reported in Table 1A). It was a continuous monomorphic sharp delta activity with mean amplitude of 30 microV (range 19.5–62 microV, the latter during drawing) and 2 Hz frequency, localized

Table 1
Spiking rate data.

Daily moments	Minutes (mean)	Spiking Rate (n°/min) Monomorphic Delta Activity	Spiking Rate (n°/min) Interictal Epileptiform Activity
A) Spiking rate in wakefulness and sleep during video-EEG monitoring			
Quiet wakefulness	270	10.30	0.4
Routinely wakefulness activity	330	20.10	0.0
Specific cognitive activity	188	52.17	0.0
Typing on the phone	86	56.79	0.0
Listening to music	38	50.75	0.0
Reading	64	45.64	0.0
Art performance (drawing/painting)	320	88.71	0.0
NREM sleep	273	7.77	31.7
N1 stage	7	23.7	11.2
N2 stage	167	9.8	29.5
N3 stage (SWS)	99	0.0	35.0
REM sleep	64	35.33	19.35
B) Spiking rate during motor, cognitive and creative tasks			
Task performance	Minutes (mean)	Spiking Rate (n°/min) Monomorphic Delta Activity	Spiking Rate (n°/min) Interictal Epileptiform Activity
Quiet wakefulness	23.6	14.7	0.3
Word Listening	2.7	28.1	22.5
Tongue Movements	2.0	25.0	0.0
Drawing	9.0	37.1	0.7
Creative	5.3	37.5	0.9
Squares	4.0	36.2	0.5
Naming	4.0	30.7	0.0
Verb	2.7	25.9	0.0
Object	1.3	40.5	0.0
Comprehension	2.7	35.6	7.5
Reading	3.0	31.0	1.3
Words	2.0	32.5	1.5
Pseudo-words	1.0	28.0	1.0

on anterior temporal region (F7-T1a), which diffused to the vertex (Fz) and the fronto-polar electrodes (F3) (see Fig. 3). It was an interictal finding and without evidence of evolution. This activity resembled TIRDA (temporal intermittent rhythmic delta activity) but unlike TIRDA, it decreased during drowsiness and NREM sleep whereas it was expressed mainly during active wakefulness. An enhancement of the slow activity during REM sleep was detected, with 3 Hz frequency and 32 microV amplitude (see Fig. 3C). Furthermore, it was not organized in short trains and it could last as long as the patient was drawing.

EEG recordings were then carried out asking the patient to reproduce the same cognitive tasks she had performed during fMRI session. The slow activity observed during structured and time-dependent tasks was irregular in morphology, with lower frequency (1–2 Hz) and lower amplitude as compared to free creative processes. It is worthwhile to note that only two tasks required the use of the hand (drawing geometrical figures and freehand drawing). The spiking rate was lower: 30 for geometrical drawing and 37.5 for freehand drawing (see Table 1B).

4. fMRI and DTI results

fMRI activations related to both creative and square drawing included similar areas (for a list of coordinates see Supplementary Table 2), namely the fusiform gyrus, the inferior temporal gyrus, the temporal pole, the amygdala, the post- and the pre-central gyrus, the middle frontal gyrus and the orbital gyrus, with a widespread activation for the former (Fig. 4A) as compared to square drawing (Fig. 4B).

DTI analysis showed that the patient significantly differed from healthy controls in terms of the left uncinate fasciculus (lower number of fibers, $Z = -3.87$, $p < .05$ and FA, $Z = -2.37$, $p < .05$), which connects the temporal pole with the orbitofrontal cortex, where increased monomorphic delta activity was recorded during drawing. fMRI data confirmed that these areas were involved in drawing, as increased activation was triggered by both tasks with a similar signal intensity (See Fig. 4).

Fig. 4F shows that activations related to creative drawing vs square drawing were found in the i) fusiform gyrus bilaterally, ii) right precuneus, iii) left middle occipital gyrus, and iv) left inferior temporal gyrus, and were localized along the ventral pathway involving the ILF and the IFOF, which were contiguous to the cavernoma.

5. Discussion

Drawing triggered a sustained monomorphic delta rhythm localized in left temporal pole, inferior frontal gyrus and frontopolar areas, which decreased during other control tasks. DTI analyses showed that these areas are connected through the uncinate fasciculus, which was significantly affected by the cavernoma in terms of decreased number of fibers and FA. Our results are consistent with the literature reporting that cavernomas can cause both displacement and disruption of fibers [8]. The uncinate fasciculus connects the temporal lobe with portions of the frontal lobe such as the orbitofrontal cortex. The task that provoked patient's increased delta activity significantly increased activation in the temporal pole, and the orbitofrontal cortex, among other areas involved in the network sustaining drawing. These areas have been previously related to artistic production and appreciation. The orbitoftrontal cortex is involved in processing the affective significance of aesthetic appreciation [10], and the temporal pole has been shown to be activated by recognition and meaning attribution involved in aesthetic appreciation [6,13]. In healthy participants, who were asked to draw a dog, horse or face from memory, it has been shown that low-frequency rTMS to the left anterior temporal lobe triggered a major change in the drawings style in 4 out of 11 subjects [22]. Other authors [21] reported the case of a patient who underwent left temporal lobectomy because of a ganglioglioma in the

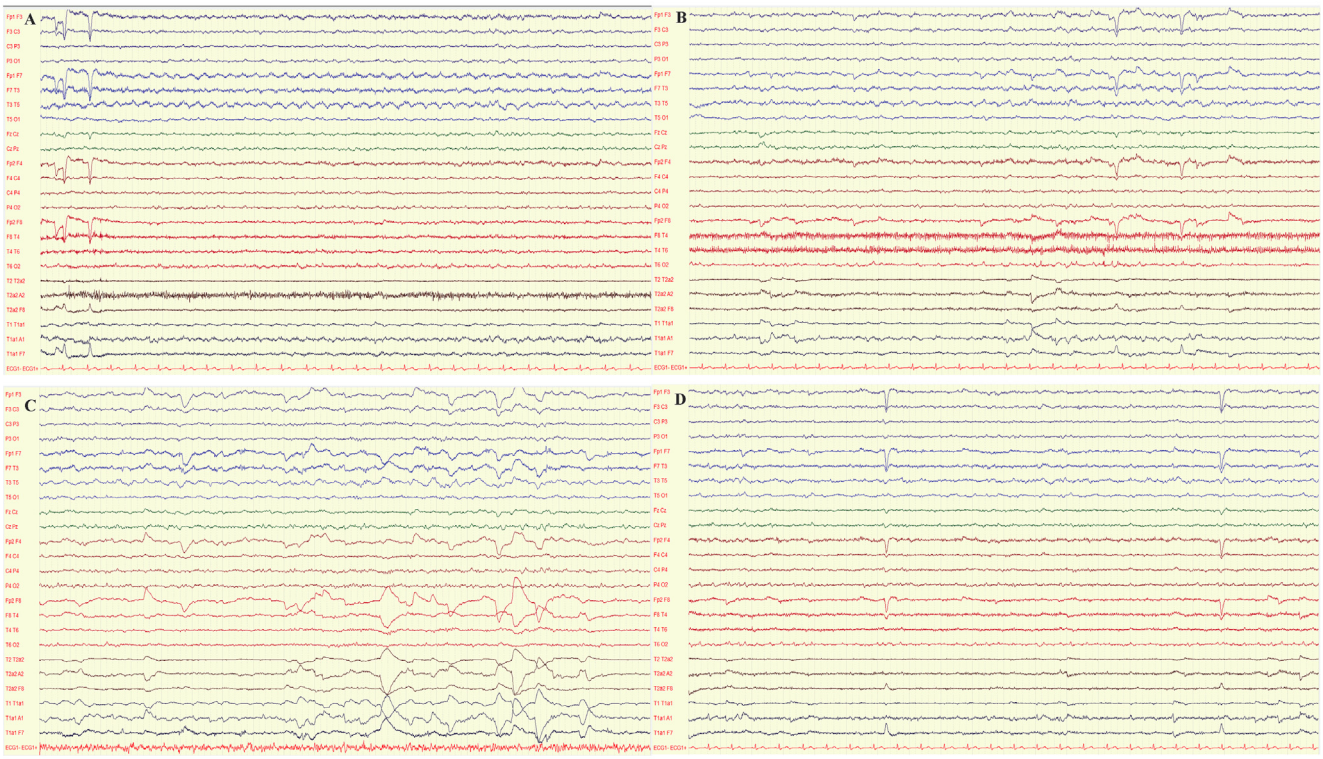

Fig. 2. Interictal epileptiform activity characterized by spikes and spike-and-wave complexes at T3 and T5 during drowsiness (A) and slow wave sleep (B).

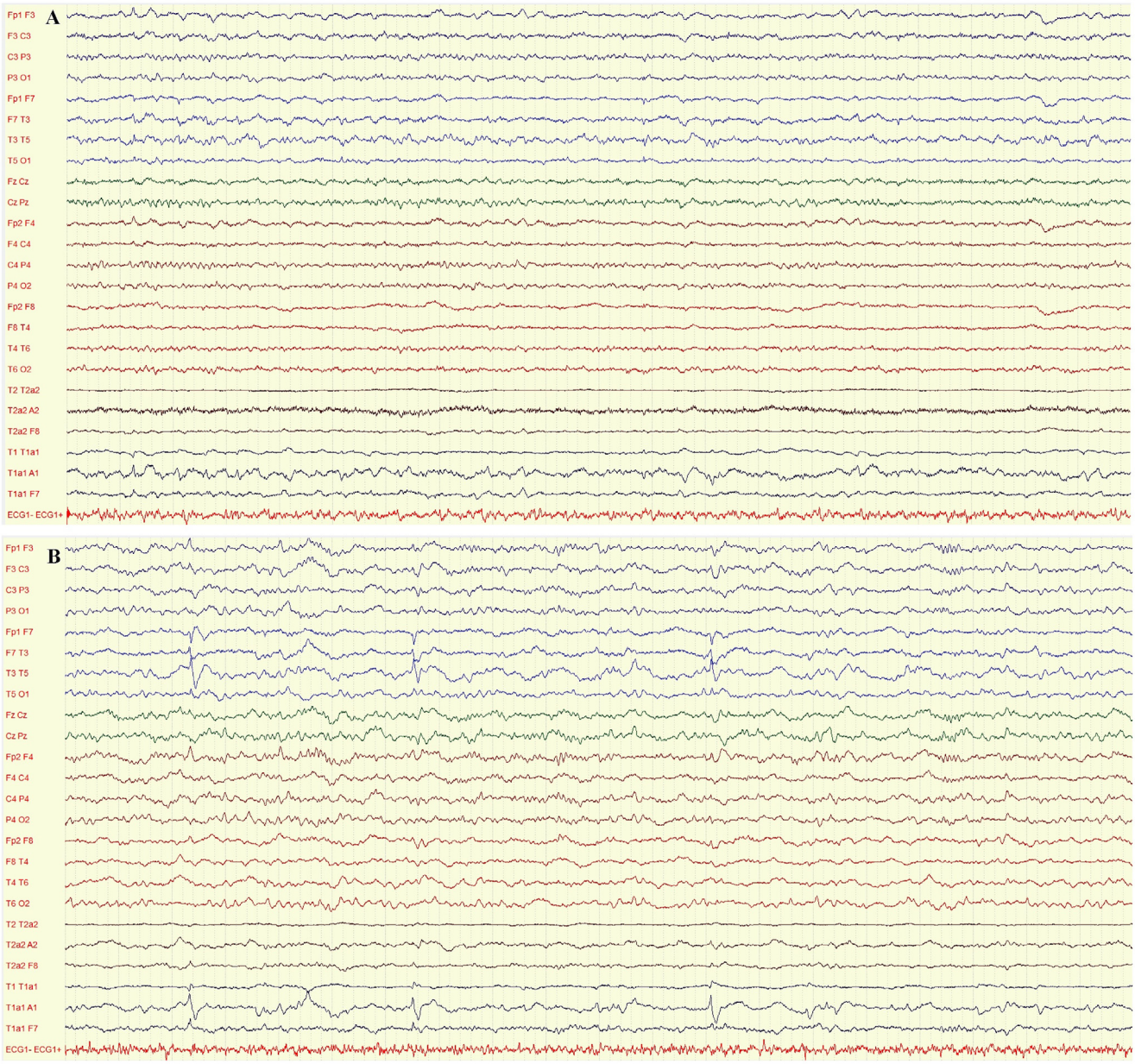

Fig. 3. Modulated manifestation of the monomorphic delta activity localized on left anterior temporal (F7-T1a1) and frontal regions (F3) at different times: free drawing (A), typing on the phone (B) and REM sleep (C). The activity is well represented during drawing and cognitive tasks, it is absent during quiet wakefulness (D).

left third temporal gyrus, causing seizures. Following surgery, the patient significantly changed his artistic preferences for music, literature and painting. As far painting was concerned, the patient newly developed interest in realistic works. By contrast, his preference for other categories (e.g., food, dress, and faces) was unchanged.

The network sustaining creative drawing recruited also other areas along the ventral visual stream. This was also reported in healthy subjects, so the task elicited a normal pattern of fMRI activations in our patient, including the fusiform gyrus, an area known to be activated during active drawing compared to passive viewing [39,26]. Activation involved the right precuneus, which is an area found to be related to artistic abilities [7,6,23,26], and the left posterior inferior temporal gyrus [20] and in line with the role of this area in object recognition along the ventral pathway of the visual system [25].

As regards seizures, we observed that three seizures occurred during drawing and the fourth just after drawing. Furthermore, unexpected feature, consisting in sustained monomorphic delta activity, appeared during spontaneous freehand drawing and persisted throughout the drawing sessions. Slow delta activity was triggered by action involving the use of the hand. Considering the occurrence of seizures and the onset of monomorphic delta activity mainly during drawing session, drawing emerged as a strong trigger for seizures in this patient, presenting similarities observed with activation in reflex epilepsies. A previous report describes the case of a 17-year-old patient with myoclonic seizures often triggered by drawing [2]. Another case of a 19-year old male was reported with myoclonic jerks selectively induced by drawing [11]. In a large series of unselected patients suffering from different types of epilepsy, a neuropsychological activation protocol (NPA) provoked epileptiform discharges mainly in patients with genetic

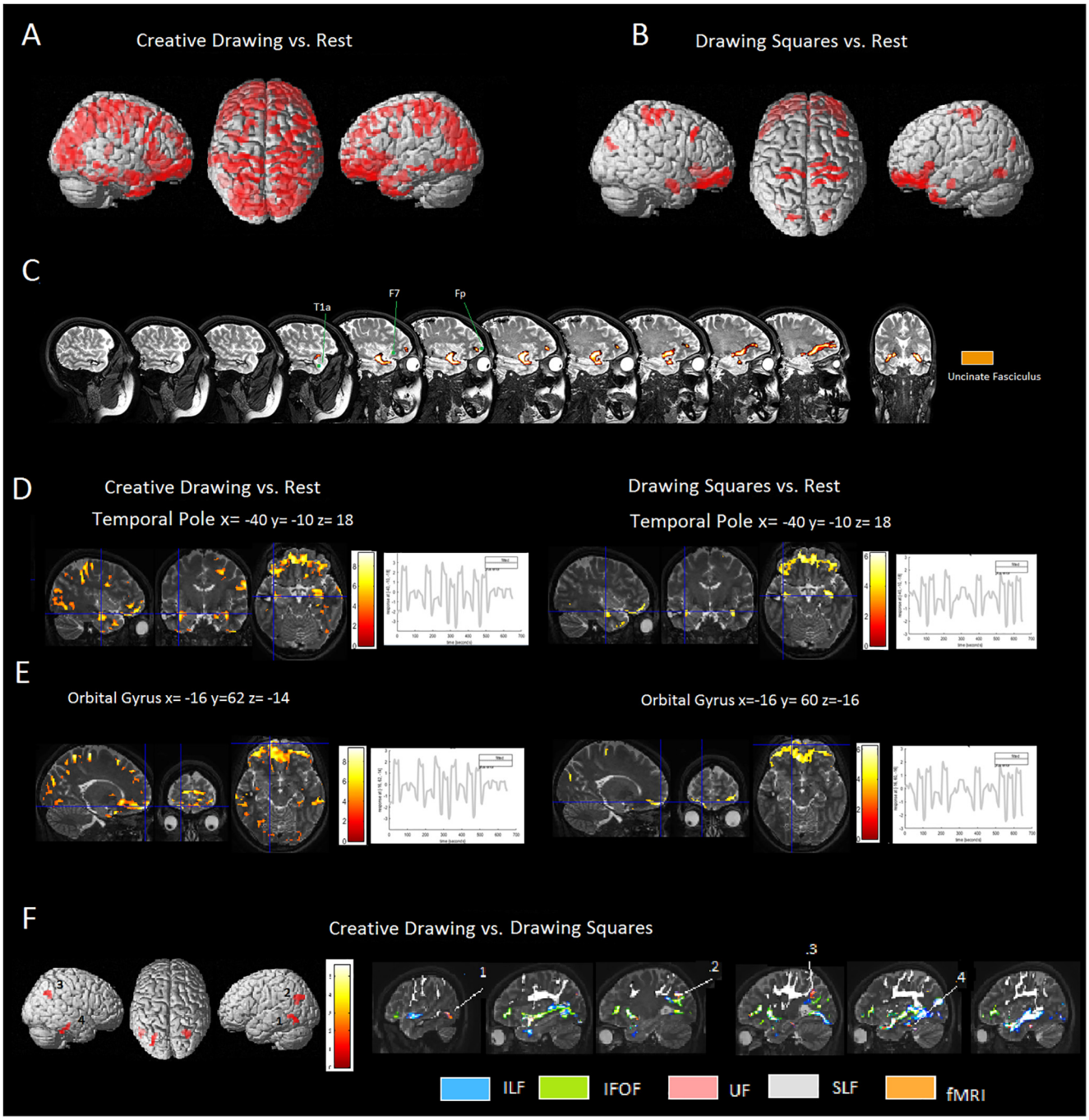

Fig. 4. Patient's fMRI maps during the creative drawing task vs. rest (A) and drawing squaressw task vs. rest (B). The uncinate fasciculus superimposed on the patient's T2 MRI image showing the position of the T1a, F7 and Fp electrodes, where the monomorphic delta activity was recorded during drawing (C), along with the fMRI activation found during the two drawing tasks in the temporal pole (D) and in the orbital gyrus (E). creative drawing vs. drawing squares (F) activations superimposed on the patient's sagittal MRI images. UNC = uncinate fasciculus, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFOF = inferior fronto-occipital fasciculus.

generalized epilepsies, especially JME, but also patients with temporal lobe epilepsy [14].

Currently, we do not know what the sustained delta activity really represents. It is not a clear epileptiform pattern even if observed with the limit of scalp EEG recoding. It cannot be classified as pure lesional slowing, because it widely changes with cognitive activity and behavioral states. This activity presents many similarities with TIRDA, which is known to be associated with temporal lobe epilepsy. However, TIRDA is known to occur mainly during drowsiness and light sleep, while in our patient the monomorphic delta activity was recorded during active wakefulness and was progressively suppressed by NREM sleep. Moreover, unlike TIRDA, this activity was not organized in rhythmic intermittent short trains. It could be recorded for long periods, during drawing session.

We hypothesize that this delta activity may reflect deeper EDs in the mesial temporal lobe or represent a pathological response to activation of networks involving the use of hand and cognitive complex tasks. In fact, pathological mechanism supposed for praxis-induced seizures is an up-regulation of a complex cognitive network serving physiological functions as proprioception and motor activity [48,28]. Furthermore, among neurological disorders

associated with creative complex motor task, there are focal task specific dystonias, a group of focal dystonias affecting an isolated body part, triggered by a specific action, more often found in the musicians, whose pathophysiology has been linked to abnormalities in inhibition [18].

There are several limitations of our study. The most important one is based on the retrospective nature of the investigation. In addition, the study reports a single case of a lesional epilepsy and is therefore not generalizable to a larger patient population.

6. Conclusions

We describe praxis-induced electrophysiologic changes on EEG associated with creative drawing.

Functional MRI performed independently associated this interictal feature to drawing and to the left uncinate fasciculus, linking the temporal lobe to the orbitofrontal cortex. Further non-lesional connectivity analyses performed with simultaneous EEG-fMRI may be helpful in identifying various networks for patients with focal epilepsy and artistic creativity.

Ethical Statement

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Written informed consent was obtained for clinical MRI measurements. Considering that the study was retrospective, written consent to participate in the study was not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2020.100418.

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