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Letter to the Editor

LETTER TO THE EDITOR

A high-density polysomnographic picture of disorders of arousal

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Dear Editor,

We read with great interest the article of Flamand et al. "Confusional arousals during NREM sleep: evidence from intracerebral recordings" [1]. This work gives an outlook on the pathophysiology of cognitive features of non-rapid eye movement (NREM) parasomnias (disorders of arousal, DOA) and reinforces emerging concept of behavioral and cognitive manifestations of DOA to depend on widespread functional modifications of brain circuits' dynamics rather than simply on simultaneous co-occurrence of deep sleep and arousal in different brain regions [2]. In fact, previous studies have shown that DOA episodes are preceded by increased in slow wave activity (0.25–2.0 Hz) [3], in low delta power [4] or in slow oscillations (<1 Hz) [5] and changes in brain connectivity [6].

We would like to provide additional evidence to this hypothesis and to the comprehension of DOA pathophysiology. We recorded 14 NREM parasomnia episodes during two video-poly-somnographies (one with 10-channel electroencephalography [EEG], one with 256-channel high-density EEG) in a non-medicated, otherwise healthy 22-year-old male with history of recurrent nocturnal behaviors ranging from sleepwalking, sleep talking or unconscious eating to "minor" behaviors like eyes opening, head and trunk raising and looking around. The patient had familiar history of NREM parasomnia and no history of epilepsy or febrile seizures. All the 14 episodes recorded featured chin electromyographic activation, predominantly anterior high-voltage hypersynchronous delta activity (HSDA) of around 1.5 Hz (Supplementary Figure S1B) and non-stereotyped behaviors with typical semeiologic features of DOA-associated movements of motor pattern I and II [7]: abrupt rising of his head and eyes opening, gentle head turning and looking around, nose touching, incomprehensible speech and body position changes, in variable combinations. The patient appeared confused, rapidly fell asleep again and had no morning recall of the events. Mean duration of the episodes was of 70 ± 46 seconds.

For each episode, we performed a two-step time-frequency analysis (Morlet's Wavelet Transform of normalized EEG amplitude according to a baseline; frequency range: 1–30 Hz; frequency resolution: 0.05 Hz; time range: –90 seconds to 10 seconds; time resolution: 50 ms) on the EEG extract starting 120 seconds before each event's onset (defined as an abrupt, at least-twofold amplitude increase of chin electromyography accompanied by EEG arousal): first, on all the events recorded in both nights, on nine EEG channels; then, on the events recorded in the second night, on the averaged signals from 256 EEG derivations. Time-frequency analysis showed an increase in the low and high delta frequency bands (around 1.5 and 3.5 Hz, respectively), starting 5 seconds before the events' onset (Supplementary Figure S2). Source analysis (low-resolution brain electromagnetic tomography, LORETA) was then performed on the events recorded during the 256-channel-EEG video-polysomnography (PSG) (one-second epochs, with 500 ms overlap). 3D cortical distribution of the electric neuronal generators was computed for each epoch, for each frequency band (δ, ϑ, α1, α2, β1, β2, β3, γ). Delta (δ) band was subdivided in low delta (0.5–2.0 Hz) and high delta (2.0–4.0 Hz) based on the results

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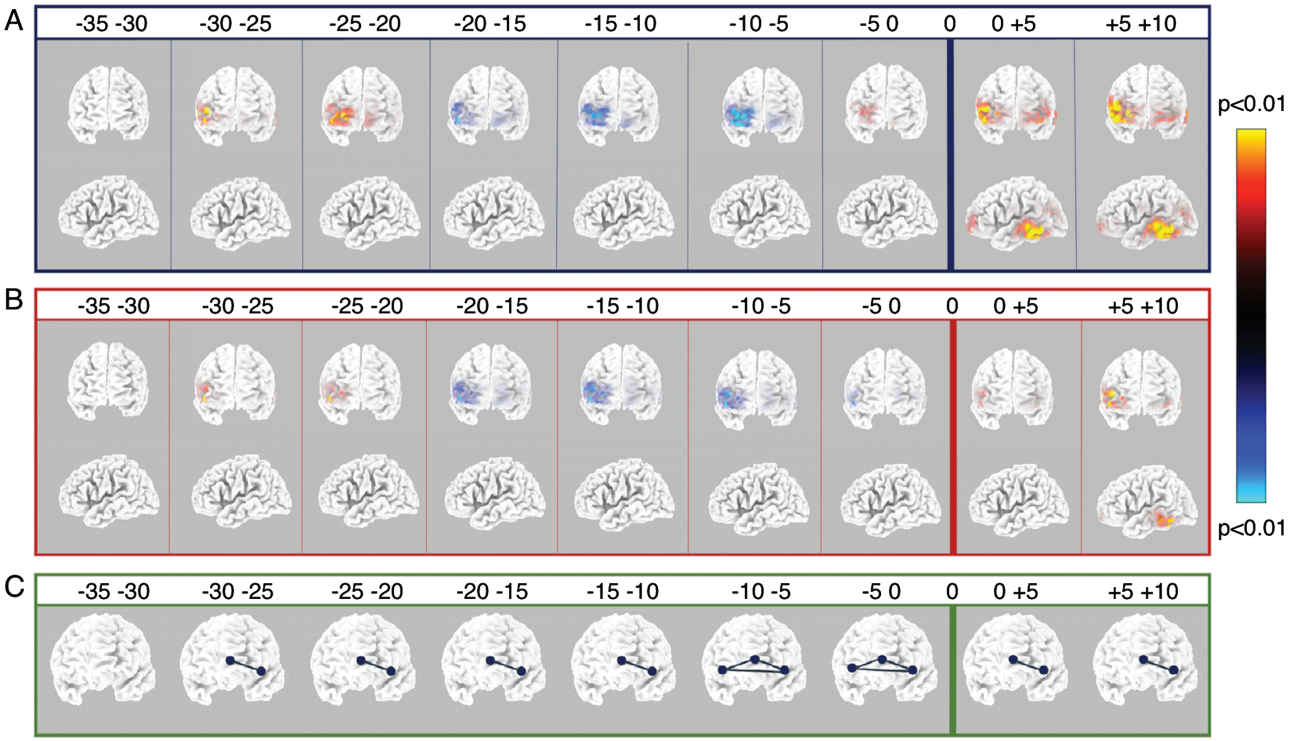

Figure 1. (A) Low delta (0.5–2.0 Hz) nonparametric voxel-wise comparison map, showing increased activity in the right rPFC (BA 10) in the (–30/–25 seconds) and (–25/–20 seconds) time windows ($p = 0.01$ and $p < 0.05$, respectively), followed by reduced activity at (–20/–15 seconds), (–15/–10 seconds), and (–10/–5 seconds) ($p = 0.01$) and new increase just before the event onset (–5/0 seconds) (n.s.). A higher increase is observed since (0/+5 seconds) at the right rPFC, left rPFC, and left temporal cortex (BA 10, 11, 45, 46, 47, 37, 20, 21, 22) ($p = 0.01$). (B) High delta (2.0–4.0 Hz) nonparametric voxel-wise comparison map, documenting increased activity in the right rPFC (BA 10) at (–30/–25 seconds) and (–25/–20 seconds) ($p < 0.05$), followed by reduced activity in (–20/–15 seconds), (–15/–10 seconds), (–10/–5 seconds), and (–5/0 seconds) time windows ($p = 0.01$, $p < 0.05$, $p = 0.01$, n.s.) and a new increase starting just after events' onset (0/+5 seconds) ($p < 0.05$). Besides at the right rPFC, high delta activity also increases in the left rostral prefrontal and temporal cortices since (+5/+10) seconds in BA 10, 11, 45, 46, 47, 37, 20, 21, 22 ($p < 0.01$). (C) Connectivity analysis (Granger's causality estimation) showing increased bidirectional connectivity ($p < 0.05$) between the left rostral prefrontal and temporal cortices between (–30/–25) seconds and (–15/–10) seconds, then among bilateral prefrontal and left temporal cortices between (–10/–5) seconds and (–5/0) seconds, then again between the left rostral prefrontal and temporal cortices ([0/+5] seconds to [+5/+10] seconds). 0 indicates DOA events' onset.

of time-frequency analysis showing increased power at 1.5 and 3.5 Hz. Statistical nonparametric mapping on reconstructed source activities showed marked variations over time in delta power: (1) an increase in low delta (0.5–2.0 Hz) power in right prefrontal cortex (Brodmann's areas [BA] 10 and 11) and then of high delta (2.0–4.0 Hz) power at BA 10 starting 30 seconds before the events' onset; (2) a reduction in both frequency bands from 20 seconds to 5 seconds before the events' onset over BA 10; (3) a subsequent increase of low delta power in the 5 seconds before the events' onset in the same regions; and (4) during the events, delta activity increased and spread over right and left prefrontal and left temporal cortices (BA 10, 11, 45, 46, 47, 37, 20, 21, 22) (Figure 1, A and B).

Granger's causality estimation (5-second consecutive time series from the three involved regions) suggested bilateral interactions (1) between the left rostral prefrontal cortex (rPFC) and the homolateral temporal cortex starting from 30 seconds before and continuing after the events' onset; (2) among bilateral rPFC and left temporal cortex during the 10 seconds preceding the events' onset (Figure 1C).

Our findings are in line with and add complementary information to the ones of Flamand et al. First, we recorded NREM parasomnia events in a non-epileptic patient with a clear-cut history of DOA, advocating that functional impairment of a widespread network underlying these events might not be necessarily related to epilepsy. Moreover, differently from Flamand et al., we studied a wider temporal frame preceding DOA events and found that functional network modifications start as early as 30 seconds before each event's onset. Finally, by means of 256-channel-EEG video-PSG we obtained better spatial resolution and wide-ranging overview of the brain regions involved in DOA. In particular, we highlighted a putative role of right rPFC and prefronto-temporal circuit in DOA. During wakefulness, right rPFC acts as a gateway orienting attention shift towards internal or external stimuli [8] and is involved in motor inhibition [9], while left prefronto-temporal circuit is implicated in stimulus-independent reasoning (brain-to-brain mentation) [10]. We interpret DOA events to be triggered by simultaneous occurrence of increased brain-to-brain mentation (connectivity in left prefronto-temporal circuit), together with functional inhibition of the right rPFC (due to increased high delta activity), driven by a permissive window represented by low delta activity. Subsequent decrease of low and high delta activity in right rPFC together with increased connectivity between the right rPFC and the left prefronto-temporal circuit might represent an "attempt" by the brain to limit delta activity to diffuse. Failure of this "protective measure" might let delta burst spread to the contralateral prefrontal area, releasing parasomnia behaviors from their tonic inhibition from rPFCs (now inhibited by low delta activity). Meanwhile, simultaneous impairment of prefrontal cortices and left prefronto-temporal circuit might result in defective

integration of sensory inputs (coming from the outer environment upon arousals) with brain-to-brain mentation, altering awareness and events' recall.

Although replication in larger patients' series is needed, these new findings might help explaining both motor and cognitive correlates of DOA episodes.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Conflict of interest statement. None declared.

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