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RESEARCH ARTICLE

Dynamics of seizure-induced behavioral and autonomic arousal

Emilia Toth[1] · Ganne Chaitanya[2] · Michael Pogwizd[3] · Diana Pizarro[1] · Adeel Ilyas[5] · Steven Pogwizd[4] · Sandipan Pati[1]

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Abstract

Purpose Arousal is the most primitive, powerful instinct with survival benefit present in all vertebrates. Even though the arousal systems are classically viewed as "ascending" brainstem phenomena, there is a "descending" cortical feedback system that maintains consciousness. In this study, we provide electrophysiological confirmation that seizures localized to the anterior cingulum can behaviorally manifest as paroxysms of arousal from sleep.

Methods Temporal dynamics of arousal induced by anterior cingulate seizures were analyzed by using multiple modalities including stereoelectroencephalography (phase lag index and phase amplitude coupling), lead-1 ECG (point-process heart rate variability analysis) and diffusion tractography (DTI).

Results The ictal arousal was associated with an increase in synchronization in the alpha band and an increase in local theta or alpha-gamma phase-amplitude coupling. In comparison to seizures that lacked clinical manifestations, ictal arousal was associated with an increase in heart rate but not heart rate variability. Finally, DTI demonstrated degeneration in white fiber tracts passing between the anterior cingulum and anterior thalamus ipsilateral to the epileptogenic cortex. The patient underwent resection of the anterior cingulum, and histopathology confirmed focal cortical dysplasia type II.

Conclusion Anterior cingulate seizures inducing behavioral arousal have identifiable autonomic and EEG signatures.

Keywords Arousal · Hypnopompic seizure · Anterior cingulate · Phase lag index · Phase-amplitude coupling · Heart rate variability

Introduction

Sleep is a dynamic process in which spontaneous brain activity transitions through stages such as slow wave sleep (SWS), non-rapid and rapid eye movement sleep (NREM, REM). The relationship between sleep and epilepsy is complex and bi-directional, and sleep stages can influence the prevalence of epileptiform activities [1]. The term "arousal" indicates a temporary intrusion of wakefulness into sleep and is measured by a sudden increase in EEG alpha and theta activity with a frequency greater than 16 Hz (but not sleep spindles) lasting 3–15 s [2]. Arousal lasting for few seconds as the only clinical manifestation following the onset of a seizure is uncommon, and this phenomenon is termed as a "hypnopompic seizure" [3]. Literature related to the localization of these hypnopompic seizures is lacking, although an ictal SPECT study has localized seizures manifesting as arousal in the anterior cingulate gyrus [4]. The mechanism underlying ictal arousal is unknown; one prevailing hypothesis is that the seizure induces downstream activation of the reticular

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✉ Sandipan Pati
spati@uabmc.edu

[1] Department of Neurology, University of Alabama at Birmingham, 1719, 6th Avenue South, Birmingham, AL 35294-3410, USA

[2] Department of Clinical Neurosciences, National Institute of Mental Health and Neurosciences, Bangalore, India

[3] Department of Mathematics, University of Alabama at Birmingham, Birmingham, AL, USA

[4] Division of Cardiovascular Diseases, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

[5] Department of Neurosurgery, University of Alabama at Birmingham, Birmingham, AL, USA

activating system which regulates the transition from sleep to arousal.

In this case study, we provide electrophysiological confirmation that seizures arising from the anterior cingulum can behaviorally manifest as paroxysms of short-lasting arousal from sleep. We explored the temporal dynamics of arousal induced by cingulate seizures by analyzing (a) stereoelectroencephalography (sEEG) for neural synchrony (phase-lag index-PLI) and cross-frequency phase-amplitude coupling (PAC), (b) heart rate variability (HRV). We determined, (1) the spectral signatures of arousal following the onset of seizures, (2) the cardiac autonomic response to arousal, and (3) the temporal dynamics associated with ictal arousal. The anterior cingulate cortex is associated with regulation of autonomic processes (particularly in the sympathetic system), emotion and arousal. Based on this, we hypothesize that seizure-induced behavioral arousal localized to the anterior cingulate will be accompanied by an increased heart rate (autonomic arousal) and EEG features of arousal (alpha and theta oscillations).

Clinical case description

A 25-year-old left-handed male was referred to our level-IV epilepsy center for the management of drug-resistant epilepsy (DRE). Seizures started at 8y of age. By 20y of age, he failed therapy with three appropriate anti-seizure medications (lacosamide, topiramate, eslicarbazepine). Hence, comprehensive presurgical evaluation of epilepsy was initiated with phase I and II investigations. Based on the localization results from 3T structural MRI, fluoro-2-deoxyglucose-PET (FDG-PET), scalp EEG and magnetic source imaging (MSI), a robot-assisted SEEG implantation (ROSA® Robot, Medtech) targeting bilateral anterior and mid-cingulate gyri, amygdala, anteroposterior hippocampus, lateral temporal, orbitofrontal and prefrontal regions was performed. Overall, seven focal seizures originating from the right anterior cingulate gyrus (R_AntCingG) were recorded with the clinical accompaniment of waking up from sleep, staring, and chewing automatism associated with event amnesia, lasting between 20 and 180 s. The patient also had five electrographic seizures during sleep, with similar EEG signature at the onset but lacking the clinical manifestations. The patient underwent resection of the R_AntCingG, with histopathology confirming focal cortical dysplasia type II. The patient was seizure free 7 months after surgery (Engel class-I outcome). This study was approved by the institutional review board (UAB, Birmingham), which waived the requirement for a written consent.

Data acquisition and analysis

Stereo-electroencephalography (SEEG) acquisition and analysis

SEEG with simultaneous Lead-1 ECG was monitored using Natus Xltek® (details in supplementary methods). Seizures with behavioral arousal (*A*+) and without arousal/awakening (*A*−) were identified. Based on clinically and electrographically defined seizure onset (right anterior cingulate gyrus), we defined three time windows for the purpose of analysis: (1) pre-seizure (PreSz), (2) electrographic onset to behavioral manifestation of arousal called the 'arousal time-corresponding-window' (TCW; average length of TCW of *A*+ seizures was used as the corresponding window for A- seizures which lacked clinical arousals) and (3) 'postarousal-through-seizure-termination' (AfterTCW) window. To characterize the spectral signatures of ictal arousal (and not the electrographic ictal changes per se), we performed the analysis on a cortical SEEG channel that (a) lacked any ictal epileptiform discharges as determined by visual inspection, and (b) showed reactivity (increased amplitude and frequency from the background) with wakefulness. Such an electrode was isolated to the contralateral (left) lateral temporal neocortex. Summary of the electrodes used for analyses was as follows: (a) seizure onset channels in R_AntCingG; (b) PLI was performed on all recorded intracranial EEG channels; and (c) PAC was performed with a channel in the left lateral temporal neocortex.

We used phase lag index (PLI) and phase-amplitude coupling (PAC) to establish the electrophysiological markers of arousal:

Initially, we estimated the PLI across all the SEEG channels, as a measure of the overall frequency-specific-synchronization changes across the three windows, to help us establish the major frequencies in which we noticed the seizure-related changes [5]. The data were dynamically sampled at 2 s non-overlapping windows length and were filtered to delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (13–30 Hz), gamma (30–80 Hz) bandwidths after correcting for any 60 Hz line artifacts. Interchannel asymmetry of phase difference distribution was calculated using a Hilbert transform for every frequency band across the three time windows. The PLI was calculated as the average PLI across a constant length of 4*2 s for PreSz and AfterTCW windows. The PLI in TCW depended on the length of arousal behavior. Secondly, we wanted to test PAC as a marker of the arousal phenomenon by measuring the modulation index (amplitude of higher frequency oscillations modulated by the phase of lower frequency activity) [6]. Wavelet-based dynamic PAC [6]

was calculated for every possible frequency pair between 3 and 60 Hz in 3 s non-overlapping segments within ± 30 s window around the seizure onset in the left lateral temporal SEEG channel. We estimated significant PAC peaks if the modulation index (MI) was greater by 2SD in the given window compared to the seizure onset window (Fig. 1d).

Analysis of heart rate

Arousal can be a short lasting event and, hence, to compute the instantaneous heart-rate (HR: bpm), and heart rate variability (HRV: σHR-bpm), we used the Point-Process model with adaptive filtering across 3 windows: (1) 30 s before onset, (2) TCW and (3) AfterTCW (30 s) [7].

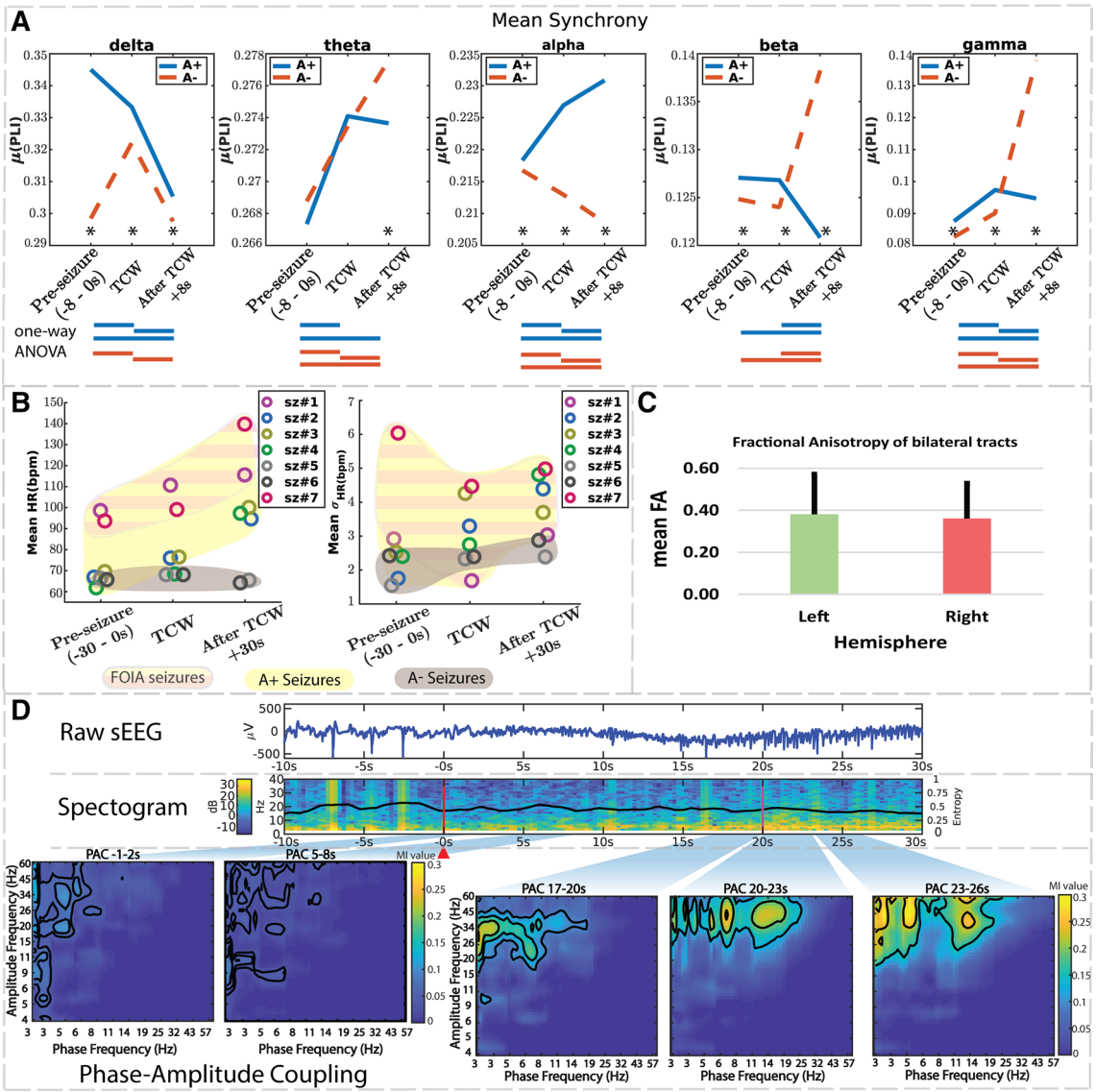

Fig. 1 Phase-lag index (PLI), heart rate (HR), heart rate variability (HRV), Diffusion Tractography and Phase-amplitude coupling (PAC) results: **a** average PLI (μPLI) is higher in TCW in all frequency bandwidths with ictal arousal (A^+, blue line) except theta band (* $p < 0.017$, t test with Bonferroni correction) (* The significance of the rmANOVA model, blue lines- significance of post hoc analysis of $A+$seizures, red lines—significance of post hoc analysis of $A-$ seizures), **b** Left panel contains average HR (bpm), right shows average HRV (σHR-bpm) from all the seizures. Ictal tachycardia was evident with arousal ($A+$seizures), but not with electrographic seizures ($A-$, grey circles). **c** Mean fractional anisotropy (meanFA) was lower ipsilateral to seizure onset (right) compared to the contralateral side (left). **d** Phase-amplitude coupling representations with overlaid thresholds (outer threshold line: mean + 1SD, middle threshold line: mean + 2SD, inner threshold line: mean + 3SD). The window around the arousal shows increased MI (yellow blobs) theta-gamma, and alpha-gamma coupling

Tractography to map tracts between median raphae and the epileptogenic zone

Diffusion tractography image (DTI) acquired in 3T Achieva Philips® scanner (Netherlands) was preprocessed for subject motion and EPI correction; data quality was assured in ExploreDTI [9]. After this, the DTI images were analyzed. Bilateral tracts were estimated in DSI studio (http://dsi-studio.labsolver.org), by seeding the dorsal and the median raphae, and terminating in the R_AntCingG and L_AntCingG, respectively, while passing through corresponding anterior thalamic nuclei.

Results

The seizures and their different characteristics are depicted in Table 1. All seizures were noted in nonrapid eye movement (NREM) stage 2 of sleep. Among the seizures, three distinct semiological variations were noted: (1) arousal seizures ($A+$) that were limited to brief periods of behavioral arousal only (FOA); (2) seizures that progressed beyond arousal to oro-motor automatism, staring around the room (classified as focal onset seizures with impaired awareness-FOIA); and (3) electrographic seizures without arousal ($A-$) from sleep. Our results were confined to only $A+$ and $A-$ seizures.

It was found that seizures both with and without arousal ($A+$ and $A-$) had low gamma synchronization (PLIγ) before the start of the seizure (mean PLIγ: preSz: $A+ = 0.088$, $A-0.082$). An increase in gamma synchronization was noted from PreSz to TCW (mean PLIγ: $A+ = 0.096$, $A- = 0.09$). Alpha synchronization (PLIα) showed an increase from the PreSz to TCW, in $A+$ seizures compared to A-seizures (mean PLIα: PreSz: $A+$:0.22, $A-$:0.217, TCW: $A+ = 0.228$, $A- = 0.212$) (Fig. 1a). $A+$ seizures showed a peak PAC pattern of theta-gamma ($\theta-\gamma$) and alpha-gamma ($\alpha-\gamma$) coupling ($>$ mean + 2SD) which was not seen in $A-$ seizures. These results are in concordance with the frequency bands, with the PLI synchronization as noted (Fig. 1d).

$A+$ seizures had a distinctly higher heart rate through the TCW and after, when compared to A^- seizures (Fig. 1b). Among the arousal seizures, the mean HR was highest for the seizures that progressed to automatism and wakefulness. However, we did not notice any discernible difference in HRV between $A+$ and $A-$ seizures. Analysis of the DTI showed the tracts lateralized to the seizure onset side had lower mean FA values compared to the contralateral hemisphere, implying the disorganization of the white matter ipsilateral to the seizure onset (FA: Left: 0.38 ± 0.19; Right: 0.36 ± 0.17) (Fig. 1c).

Discussion

In summary, this report confirms that seizures arising from the neocortex (anterior cingulum) can induce arousals from sleep (hypnopompic seizures) that are accompanied by (a) EEG features of arousal- peak $\alpha-\gamma$ and $\theta-\gamma$ coupling, increased phase synchronization in theta, alpha and gamma bands; and (b) increased heart rate.

The term hypnopompic, from pompe (the act of sending), was first used by Frederic W. H. Myers (1843–1901) to describe phenomena occurring during the transition between sleep and awakening [8]. Awad et al. coined the term "hypnopompic seizures" to describe ictal arousal from sleep as the main clinical manifestation of the seizure [3]. Here we report the temporal dynamics of hypnopompic seizures that are localized to the anterior cingulum. Increase in long-range synchronization in alpha and theta bands and an increase in local theta or alpha-gamma coupling supports that behavioral arousal can be induced by a seizure. Finally, ictal arousal is associated with higher heart rate but not heart rate variability. The intracranial EEG findings at onset

Table 1 The seizures and their characteristics

Seizure	Time of the day (24-h)	With or without arousal (A^+, A^-)	Semiology	Seizure duration (s)	Seizure onset to arousal corresponding time window TCW (s)
1	23:43	A^+	Arousal → FOIA	76	3
2	22:49	A^+	Sleep → arousal	52	4
3	00:26	A^+	Sleep → arousal	38	20
4	02:45	A^+	Sleep → arousal	47	16
5	06:03	A^-	Electrographic	21	14[a]
6	03:02	A^-	Electrographic	20	14[a]
7	03:36	A^+	Arousal → FOIA	86	26

$A+$ seizures with arousal behavior; $A-$ seizures without arousal from sleep (electrographic seizures); *FOIA* focal onset seizures with impaired awareness; *TCW* time corresponding window (in relation to arousal)

[a]Seizures without arousal, imitated arousal windows were calculated from the average TCW of the A + seizures

(rhythmic sharps followed by low voltage fast activity), improved surgical outcome and the presence of histopathological finding increases confidence in the localization of an otherwise MRI-negative nonlesional epilepsy. A previous study reported hyperperfusion with ictal SPECT in the right anterior cingulate following ictal paroxysmal arousal [4].

The anterior cingulate cortex is known to modulate emotion and autonomic arousal that includes preferential activation of the sympathetic system in the heart [9]. The increase in heart rate suggests the influence of sympathetic activation following arousal. HRV is an invasive indicator of autonomic nervous system activity, and the changes in HRV reflect the balance between changes in the sympathetic and parasympathetic systems. The lack of significant change in HRV suggests that the net effect of combined sympathetic and parasympathetic changes on the heart was negligible. Contemporary models of the wake-sleep regulatory system are based on the seminal research conducted by Moruzzi and Magoun, which hypothesized that the ascending reticular activating system (RAS) promotes arousal and wakefulness [10]. Subsequent studies have demonstrated the existence of an additional neuronal system within the forebrain that can support wakefulness even in the presence of a lesion in the brainstem arousal system [11, 12]. We have explored the white matter connectivity that demonstrated pathways between the anterior cingulate and the intralaminar thalamus that might offer one explanation of how seizures from the anterior cingulate can activate the arousal network. The cholinergic system is associated with arousal that innervates basal forebrain structures, including cingulum to the brainstem and intralaminar thalami [13]. The lack of arousal response in a few seizures originating in the anterior cingulum can be attributed to the variable spread of seizures, thereby not activating structures like the thalamus.

Conclusion

In this case study, we report that focal seizures localized to the right anterior cingulum can induce behavioral arousal from sleep that is accompanied by autonomic and EEG features of arousal. Spectral signatures of arousal consisted of increased theta and gamma oscillations. We speculate that the increase in local theta-gamma cross-frequency coupling and phase synchronization in alpha band underpins local and long-range circuit mechanisms for arousal.

Author Contributions SP was instrumental in the conception and design of the study, evaluation of the patient and EMU acquisition of data, contributed to data analysis and writing the manuscript. ET and GC performed analysis and interpretation of data and drafting the article or revising it critically for important intellectual content. MPo and SPo were instrumental in the analysis of HR and HRV. DP and AI helped in data collection, timely critical review of the results and concepts and in the revision of the manuscript. SP in the capacity of the corresponding author agrees to be accountable for all aspects of the work in ensuring the accuracy or integrity of any part of the work investigated and resolved.

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Compliance with Ethical Standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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