

# EEG Activation Does Not Differ in Simple and Complex Episodes of Disorders of Arousal: A Spectral Analysis Study

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**Purpose:** Disorders of arousal (DoA) are characterized by incomplete awakening from NREM sleep, with the admixture of both deep sleep and wake EEG activity. Previous observations suggested that changes in EEG activity could be detected in the seconds preceding DoA episodes. The aims of this work were to characterize the topography of EEG spectral changes prior to DoA episodes and to investigate whether or not behavioral complexity could be predicted by changes in EEG immediately preceding behavioral onsets.

**Patients and Methods:** We collected 103 consecutive video-polysomnographic recordings of 53 DoA adult patients and classified all episodes as simple, rising and complex arousal movements. For each episode, a 5-second window preceding its motor onset (“pre-event”) and a 60-second window from 2 to 3 minutes before the episodes (“baseline”) were compared. Subsequently, a between-group comparison was performed for the pre-event of simpler versus the more complex episodes.

**Results:** Spectral analysis over 325 DoA episodes showed an absolute significant increase prior to DoA episodes in all frequency bands excluding sigma, which displayed the opposite effect. In normalized maps, the increase was relatively higher over the central/anterior areas for both slow and fast frequency bands. No significant differences emerged from the comparison between simpler and more complex episodes.

**Conclusion:** Taken together, these results show that deep sleep and wake-like EEG rhythms coexist over overlapping areas before DoA episodes, suggesting an alteration of local sleep mechanisms. Episodes of different complexity are preceded by a similar EEG activation, implying that they possibly share a similar pathophysiology.

**Keywords:** parasomnia, disorders of arousal, neurophysiology, spectral EEG

## Introduction

Disorders of arousal (DoA) are currently included in the group of NREM sleep parasomnias as undesired events characterized by incomplete awakening from NREM sleep.<sup>1</sup> They are characterized by inappropriate judgement of the environment, absent or inadequate responsiveness, limited or absent mental content and partial amnesia of the event. DoA encompass 3 main clinical entities, namely, confusional arousal, sleep terrors and sleepwalking.<sup>1</sup> Only a few studies have systematically assessed DoA semiology,<sup>2-6</sup> but a conclusive agreement is still lacking. A recent video-polysomnographic (VPSG) analysis of 184 episodes attempted to classify DoA motor episodes, identifying three specific patterns of increasing complexity.<sup>7</sup> These motor patterns went from simple arousal movements (SAMs), involving head with or without limb/trunk elevation, to rising arousal movements (RAMs), in which patients sit up in bed, to complex

arousal movements (CAMs), implicating getting out of bed and sleepwalking.<sup>7</sup> In comparison to RAMs and CAMs, SAMs are more difficult to differentiate from physiological arousal-related phenomena and represent the real challenge for sleep experts. In a given subject, SAMs are often an initial small fragment of a more complex episode, but appear more frequently as isolated events across the night sleep of the patient. This finding led to the speculation of a possible common neurophysiologic background for the different motor manifestations.<sup>7</sup>

Since the first electroencephalographic (EEG) description,<sup>8</sup> it became clear that most DoA episodes arise from N3 stage of NREM sleep,<sup>9–11</sup> the deeper stage of sleep, characterized by a reduced response to external stimuli as well as decreased awareness of the environment.<sup>12</sup> Capturing an in vivo episode of sleepwalking, a SPECT study disclosed a “dissociation” between more activated areas, such as posterior cingulate cortex and anterior cerebellum, and areas with decreased blood flow, such as fronto-parietal associative cortices, suggesting the selective activation of thalamo-cingulate networks with persistent inhibition of other thalamo-cortical pathways.<sup>13</sup> Since then, some pre-surgical stereo-EEG studies in patients with refractory epilepsy recorded by chance DoA episodes.<sup>14–17</sup> The picture resulting from these studies indicates the persistence of deep sleep rhythms over anterior, fronto-parietal associative cortices and hippocampi, responsible for the unawareness and frequent amnesia during DoA episodes, together with fast EEG rhythms more typical of wakefulness over the cingulate cortices, motor areas, amygdala, and thalami, which in turn account for the motor and emotional activation during the episodes.<sup>11,16</sup> Moreover, both slow and fast EEG activities have been recorded even in the same brain areas, adding further complexity to DoA neurophysiology.<sup>17</sup> These local wake/sleep phenomena account for the dissociation of the arousal process, for which NREM parasomnias are currently under the name of DoA.<sup>9,10,18</sup> In addition, DoA are also considered to have a dysfunctional N3 stage, characterized by an inability to maintain slow wave sleep (SWS), an increased fragmentation of this stage and an abnormal response to sleep deprivation, which facilitates the occurrence of more complex episodes.<sup>6,9</sup> Stereo-EEG studies offer excellent temporal and spatial resolution but, albeit providing impressive results, they are usually performed in other clinical entities and the subset of explored cerebral areas is strictly dependent on the epileptic focus localization. In addition, even if all these studies carefully rejected arousals with a possible seizure activity, the involvement of epilepsy in their observation cannot be completely ruled out.<sup>17</sup> Over the last years, some EEG studies specifically targeting subjects with DoA tried to characterize the neurophysiologic activity preceding DoA episodes<sup>19–29</sup> by means of visual, spectral power or connectivity analysis. Overall, most studies focused on slow wave activity, analyzed on fronto-central leads. A common finding across the studies is the increase in delta power, especially in frontal areas, in the seconds immediately preceding an episode, with variability in the chosen time window (Table 1).<sup>20,22,24–27</sup> The main limitations of these works include different methodological designs, involving nights after a sleep deprivation protocol or not homogeneous criteria for EEG frequency bands.<sup>27</sup> In addition, these studies mostly included small samples of patients and number of episodes analyzed. The events taken into account were often the most complex behavioral episodes available in their recordings and a comparison with less elaborate behaviors was not performed.

The primary objective of this study was to characterize the EEG activity preceding DoA episodes by means of a whole scalp and broad-band EEG spectral analysis in a large population of DoA patients. The secondary aim was to compare the EEG activity prior to different types of motor episodes, in order to test our hypothesis that minor DoA episodes might be fragments of the major ones.

## Materials and Methods

### Study Sample

All patients included in the study had been consecutively referred to the Sleep Center of the Department of Biomedical and NeuroMotor Sciences, University of Bologna, and IRCCS Istituto delle Scienze Neurologiche di Bologna, in a time period ranging from 2007 to 2021 and evaluated by a sleep disorder specialist (FP). All patients included had a clinical diagnosis of DoA according to the ICSD – III criteria confirmed by VPSG recording of at least one DoA episode.<sup>7</sup> Exclusion criteria were the presence of neurological or psychiatric disorders, the presence of psychotropic therapy and/or the presence of other sleep disorders. Clinical data including age, sex, family history of parasomnia, age of onset and frequency of episodes at the observation, and principal type of nocturnal manifestation, were collected. Patients

**Table 1** EEG Quantitative Studies in DoA Analyzing the Pre-Episode Period

First Author/ Year	Study Sample	Number of Nights and Design	Study Type	Channels Analysed	Number of Episodes	Time Window Before the Episodes	Results
<b>Zadra and Nielsen (1998)<sup>21</sup></b>	1 pt with ST and 10 controls	3 undisturbed nights for the pt; 2 for the controls	Spectral EEG analysis -Delta (0.75–3.75 Hz) -Theta (4.00–7.75 Hz) -Alpha (8.00–12.75 Hz) -Beta (13.00–20.25 Hz) -Beta2 (20.50–31.00 Hz)	Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6, Fz, Cz, Pz	3	0–60 s of pre-episode vs 60 s of continuous sleep in controls.	Higher delta activity related to the intensity of the episodes.
<b>Espa et al (2000)<sup>19</sup></b>	11 pts with SW and 11 controls	2 undisturbed nights	Spectral EEG analysis -SWA (0.75–4.50 Hz)	C3, C4	15	2 min of stable N3 sleep vs 2 min in the 10 min before the event vs 2 min before the event; same analysis for non-behavioral events and arousals in controls.	Progressive ↑ of SWA before the episodes (maximum over the 2 min before); higher SWA before the episodes vs both non-behavioral events and awakenings in controls.
<b>Guilleminault et al (2001)<sup>20</sup></b>	12 pts with SW and 12 controls	1 undisturbed night	Spectral EEG analysis -Low delta (0.75–2.00 Hz) -High Delta (2.25–4.00 Hz)	C4	21	4–12 s vs 28–32	Higher low delta power over the 4–12 s before the episodes.
<b>Jaar et al (2010)<sup>22</sup></b>	22 pts with SW/ST	1 baseline and 1 recovery night after 25 h of sleep deprivation	Spectral EEG analysis + Slow Wave oscillation -SWA (0.50–4.00 Hz) -Delta (1.00–4.00 Hz) -Slow delta (0.50–1.00 Hz)	Fz, Cz, Pz	22	-0–200 s -0–32 s -0–180 s vs 0–20 s (mean SWA and SWO values)	↑ SWA over 32 s before the episodes > on Cz, Pz; Higher SWA over 20 s before the episodes rather than previous 180 > on Fz; ↑ SWO density over 32 s Higher SWO density over 20 s vs 180 >Fz, Cz.
<b>Perrault et al (2014)<sup>25</sup></b>	12 pts with SW	1 undisturbed night	Spectral EEG analysis + Slow Wave oscillation -SWA (0.50–4.00 Hz) -Delta (1.00–4.00 Hz) -Slow delta (0.50–1.00 Hz)	C3	12	-0–32 s -32 s–1 min -1 min–2 min -2 min–3 min	Higher SWA over all time windows in episodes vs non-behavioral events; no significant ↑ SWA over a specific time window before the episodes; higher SWO density before episodes rather than non-behavioral events.

(Continued)

Table I (Continued).

First Author/ Year	Study Sample	Number of Nights and Design	Study Type	Channels Analysed	Number of Episodes	Time Window Before the Episodes	Results
Januszko et al (2016) <sup>23</sup>	15 pts with SW/ST	2 undisturbed nights	Spectral EEG analysis + source localization (eLORETA) -SWA (0.50–4.00 Hz) -Delta (0.50–3.50 Hz) -Theta (3.50–7.50 Hz) -Alpha (7.50–12.50 Hz) -Beta1 (12.50–18.00 Hz) -Beta2 (18.00–24.00 Hz) -Beta3 (24.00–30.00 Hz)	Spectrum: C3; eLORETA: 23 scalp electrodes	26	-0–4 s -4–8 s	↑ in beta 3 over the 0–4 s before the episodes in Brodmann motor areas 24 and 33.
Desjardins et al (2017) <sup>24</sup>	27 pts with SW	1 undisturbed night	Spectral EEG analysis -Delta (0.50–4.00 Hz) -Theta (4.00–8.00 Hz) -Alpha (8.00–12.00 Hz) -Sigma (12.00–14.00 Hz) -Beta1 (14.00–22.00 Hz) -Beta2 (22.00–32.00 Hz) - EEG functional connectivity: -Msc -ICoh	Spectrum: Fz, Cz, Pz; connectivity: Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, O2	27	-0–20 s -120–140 s	Higher delta and theta over the 20 s before the episode; ↓ connectivity in low delta in parieto-occipital areas, ↑ connectivity in alpha and beta in fronto-parietal and inter-hemispheric networks.
Ratti et al (2018) <sup>26</sup>	1 pt with DoA	2 undisturbed nights	Spectral EEG analysis -Low delta (0.5–2.00 Hz) -High delta (2.00–4.00 Hz) -Other bands: range NS -EEG functional connectivity: -Granger's causality estimation	HD-EEG, 256 electrodes	14	-0–120 s	30 s before the event: higher low delta in Brodmann areas 10 and 11 and high delta in Brodmann area 10; 20–5 s: ↓ of the same bands; 5–0 s: ↑ in delta activity in Brodmann area 10; altered connectivity in prefronto-temporal networks.

**Abbreviations:** Pt, patient; ST, sleep terror; s, seconds; SW, sleepwalking; SWA, slow wave activity; min, minutes; h, hours; SWO, slow wave oscillations; eLORETA, exact low resolution electromagnetic tomography; Msc, magnitude-squared coherence; ICoh, imaginary part of the coherence; NS, not specified; HD, high density.

underwent at least two nocturnal home-VPSGs (XLTEK Trex HD, Natus Medical Incorporated<sup>®</sup>, video-camera Handycam HDR-CX700, Sony, 12.3 Megapixel resolution). All patients were instructed to keep their habitual sleep routine in the week preceding the exam. None of them underwent a sleep deprivation schedule.

Video-polysomnographic recordings were performed using standard bipolar EEG (according to the International 10–20 system) and included 19 electrodes (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, and O2), electrocardiogram, electro-oculogram, chin and both anterior tibialis electromyography, thoracoabdominal plethysmography bands, and synchronized audio-video recording.

Sleep stages were scored in 30s epochs according to the AASM criteria.<sup>30</sup> Nocturnal sleep data were collected for all patients.

The study was approved by our local Ethical Committee “Comitato Etico Interaziendale Bologna-Imola, CE-BI”, code 17176/2017. All subjects gave written informed consent to the study protocols, in agreement with the Convention of Helsinki.

## Episodes Analysis

All full-night VPSG recordings were independently reviewed by two sleep specialists (GM, GL) who checked for the global quality of the recordings, including artifacts, technical issues and presence of disturbing noises and/or lights. For the aim of the study, only episodes with clear visibility on the video recordings were included. Each DoA episode was subclassified according to Loddo et al motor classification<sup>7</sup> as:

- SAMs or pattern I, when movements implied head flexion/extension (IA) alone or in conjunction with limbs flexion/extension (IB) and partial trunk flexion/extension (IC);
- RAMs or pattern II, involving complete trunk flexion/extension and sitting up in bed;
- CAMs or pattern III, characterized by getting up, leaving the bed and walking.

Inter-observer discordances on the classification of episodes were sorted out by a third observer, a sleep specialist with expertise in nocturnal motor episodes semeiology (FP).

The beginning of each episode was time marked with either the first electromyographic activation or the first visible movement (including eye opening) on the video analysis. The end of the episode was set as the last visible movement on the video review. Collected features for each episode included the arising sleep stage, the sleep cycle and the duration.

## EEG Analysis

All recordings were conducted on a 32-channel polygraph, using vertex referencing and digitized at a sampling rate of 256 Hz. Recordings were acquired with DC filter set up to filter out drift and slow components.

All data were converted in a European Data Format (EDF) file and subsequently imported in MATLAB (MathWorks Inc., Natick, MA, 2020a). For each episode, 6-minute segments preceding the episode onset were extracted. Each segment was visually inspected with the support of a user graphical interface (<https://github.com/CSC-UW/csc-eeeg-tools>), in order to mark noisy channels and epochs. Additional spectral-based and topographic procedures were used to identify individual channels with distinctly greater power relative to neighboring channels or epochs with clearly deviant spectra or topographies. Each segment was then band-pass filtered (zero-phase digital low-pass and high-pass filter with reflection, 0.5–45 Hz, using the “filtfilt” function of the signal-processing toolbox). Channels marked as bad were interpolated using spherical interpolation, while epochs marked as bad were discarded. The filtered signal was re-referenced to the average of the scalp voltage and divided into consecutive 5-second epochs. Spectral analysis was conducted on clean 5-second epochs (for a total of 360 seconds preceding each episode) using the Fast Fourier Transform (Welch averaged modified periodogram with a Hamming window, 50% overlap). For topographic analysis, spectral density was averaged in 6 frequency ranges (slow wave activity or delta: 0.5–4 Hz; theta: 4–8 Hz; alpha: 8–12 Hz; sigma: 12–16 Hz; beta: 15–25 Hz; and low gamma: 25–45 Hz), in accordance with previous studies.<sup>31</sup> Topographic maps of both absolute averages referenced data and subject-normalized data (z-score across channels) were examined.

For the purpose of this study, we compared the time window of 5 seconds before each episode, considered as the “pre-episode” time, with a time frame of 60 seconds from 2 to 3 minutes before the episodes (“baseline” stable N3 sleep

without arousal or micro-arousal). The same procedure was applied for episodes arising from N2 sleep. We chose this time window in accordance with other studies, which disclosed an abrupt shift of EEG frequencies in this time frame.<sup>15,23</sup>

## Statistical Analysis

Comparisons of scalp power maps were performed separately for each frequency band. At the scalp level, multiple comparison adjustment was performed using a non-parametric cluster-based permutation test,<sup>32</sup> as described in previous works.<sup>31,33,34</sup> Specifically, for each performed test, a null distribution was generated by randomly shuffling the group-label of each subject for comparisons. At each iteration of the permutation procedure, the test-statistics was computed for each electrode and the size of the largest significant electrode-cluster (uncorrected  $p < 0.05$ ) was stored in a frequency table. Finally, the 95th percentile (5% significance level) was used as the critical cluster-size distribution threshold. Although this test faithfully addresses the problem of multiple comparisons across an image, it should also be noted that we did not attempt to strictly correct for the issue of multiple testing across different comparisons (for example, across bands and stages) given the exploratory nature of this study.

## Results

### Sample and Episode Features

A total of 53 patients (25 males, mean age  $32.1 \pm 15.4$  years) were involved in this study. In all, 103 VPSGs were performed: one in 18 patients, two in 26 patients, three in 4 patients, four in 4 patients and five in 1 patient. Clinical features of the sample are summarized in Table 2. Two patients were on levothyroxine and antihypertensive medications, two on levothyroxine alone, one on antihypertensive therapy alone, one was taking a proton pump inhibitor, 2 were on asthma medication spray, and 4 females were on estroprogestinic therapy. Thirty-six percent of patients reported occasional alcohol intake while 9% reported habitual intake (a glass of wine twice per day). Thirty-two percent of

**Table 2** Clinical Features of DoA Patients

	DoA	Male	Female
<b>Subjects</b>	53	25 (47.2)	28 (52.8)
<b>Age at VPSG recording (years, mean <math>\pm</math> SD)</b>	$32.1 \pm 15.4$	$33.1 \pm 17.9$	$31.1 \pm 13.4$
<b>Age at first diagnosis (years, mean <math>\pm</math> SD)</b>	$30.7 \pm 15.1$	$32.0 \pm 17.5$	$29.6 \pm 12.7$
<b>Body mass index (Kg/m<sup>2</sup>)</b>	$23.1 \pm 4.3$	$23.9 \pm 3.5$	$22.3 \pm 4.9$
<b>Therapies*</b>	12 (22.6)	2 (8.0)	10 (35.7)
<b>Positive family history of DoA</b>			
Yes	23 (43.4)	13 (52.0)	10 (35.7)
No	23 (43.4)	8 (32.0)	15 (53.6)
Unknown	7 (13.2)	4 (16.0)	3 (10.7)
<b>Onset of DoA</b>			
Infancy	32 (60.4)	18 (72.0)	14 (50.0)
Puberty/adolescence	17 (32.1)	5 (20.0)	12 (42.9)
Adulthood	4 (7.5)	2 (8.0)	2 (7.1)
<b>Clinical manifestations</b>			
Confusional arousal	6 (11.3)	3 (12.0)	3 (10.7)
Sleep terror	5 (9.4)	4 (16.0)	1 (3.6)
Sleepwalking	11 (20.8)	6 (24.0)	5 (17.8)
More than one DoA type	31 (58.5)	12 (48.0)	19 (67.9)
<b>Frequency of episodes at first clinical investigation</b>			
< than 1 per month	5 (9.4)	1 (4.0)	4 (14.3)
Monthly	9 (17.0)	5 (20.0)	4 (14.3)
Weekly/daily	39 (73.6)	19 (76.0)	20 (71.4)

**Notes:** Results are expressed as mean  $\pm$  standard deviation or number (%). \*Antihypertensive drugs, proton pump inhibitor, levothyroxine, asthma medication spray, estroprogestinic therapy.

**Abbreviation:** SD, standard deviation.

patients drank from 1 to 2 coffees per day while 18% drank 3 or more per day. With reference to smoking, 20% were previous smokers, 6% were occasional smokers and 17% were habitual smokers (mean of 8.5 cigarettes per day). Sleep features of the sample are shown in Table 3. The overall number of recorded DoA episodes was 325, 270 SAMs (51 with a pattern IA; 123 with a pattern IB; 96 with a pattern IC), 41 RAMs and 14 CAMs. Episode mean duration, sleep stage and sleep cycle at onset of SAMs, RAMs and CAMs are described in Table 4. A mean of 3.2 episodes per night was recorded. Overall, 88% of episodes arose from N3 stage.

## Episodes versus Baseline

In spectral analysis, we observed an absolute significant increase in all frequency bands with the exception of sigma (Figure 1). In normalized maps, a clear-cut dissociation between anterior and posterior areas was observed for theta band, with a relative increase in power over the anterior areas and a relative decrease over the posterior ones. A similar pattern was observed for delta frequency, with the exception of a relative decrease over a small anterior area that included fronto-polar

**Table 3** Sleep Features

	VPSG
<b>Number</b>	103
<b>Sleep data</b>	
TST (min)	428.3 ± 101.7
SL (min)	9.3 ± 8.9
SE (%)	88.3 ± 7.8
WASO (min)	53.2 ± 35.4
N1 (%)	6.6 ± 4.3
N2 (%)	43.8 ± 10.1
N3 (%)	27.9 ± 9.0
REM (%)	21.6 ± 5.6
N1 stage (min)	28.3 ± 20.0
N2 stage (min)	186.4 ± 57.5
N3 stage (min)	118.9 ± 47.9
REM stage (min)	95.1 ± 38.4

**Note:** Results are expressed as mean ± standard deviation.

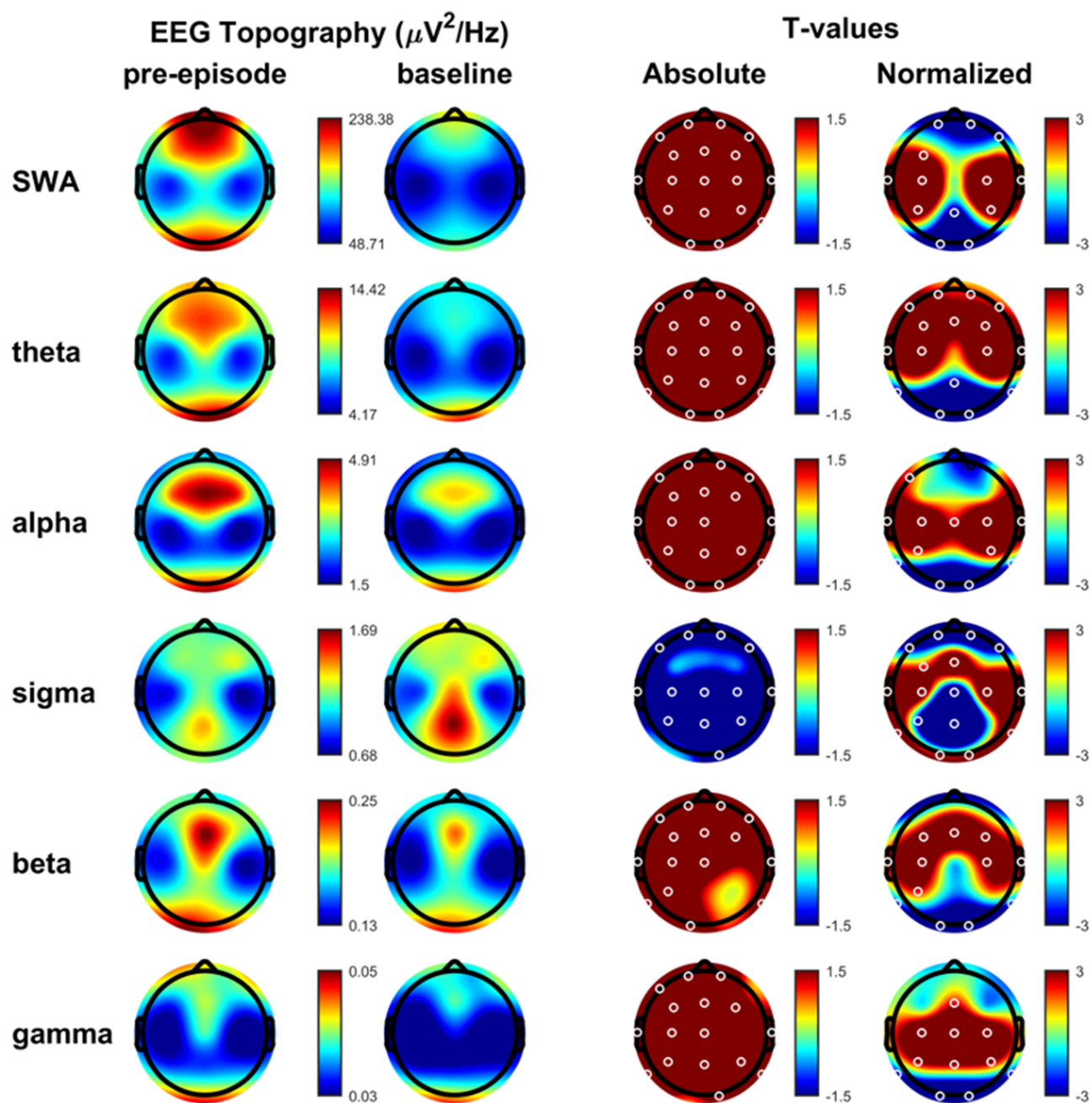
**Abbreviations:** VPSG, video-polysomnography; TST, total sleep time; min, minutes; SL, sleep latency; SE, sleep efficiency; WASO, wake after sleep onset.

**Table 4** Features of SAMs, RAMs and CAMs

	Total	SAMs	RAMs	CAMs
<b>Number</b>	325	270	41	14
<b>Mean duration (s)</b>	42.0 ± 43.0	33.6 ± 33.9	65.4 ± 42.6	134.6 ± 64.8
<b>Sleep stage</b>				
N2	40 (12.3)	35 (13.0)	5 (12.2)	0 (0)
N3	285 (87.7)	235 (87.0)	36 (87.8)	14 (100)
<b>Sleep cycle</b>				
I cycle	108 (33.2)	89 (33.0)	14 (34.2)	5 (35.7)
II cycle	109 (33.5)	87 (32.2)	16 (39.0)	6 (42.9)
III cycle	62 (19.1)	53 (19.6)	7 (17.1)	2 (14.3)
IV cycle	19 (5.9)	18 (6.7)	1 (2.4)	0 (0)
V cycle or more	27 (8.3)	23 (8.5)	3 (7.3)	1 (7.1)

**Note:** Results are expressed as mean ± standard deviation or number (%).

**Abbreviations:** SAMs, simple arousal movements; RAMs, rising arousal movements; CAMs, complex arousal movements; s, seconds.

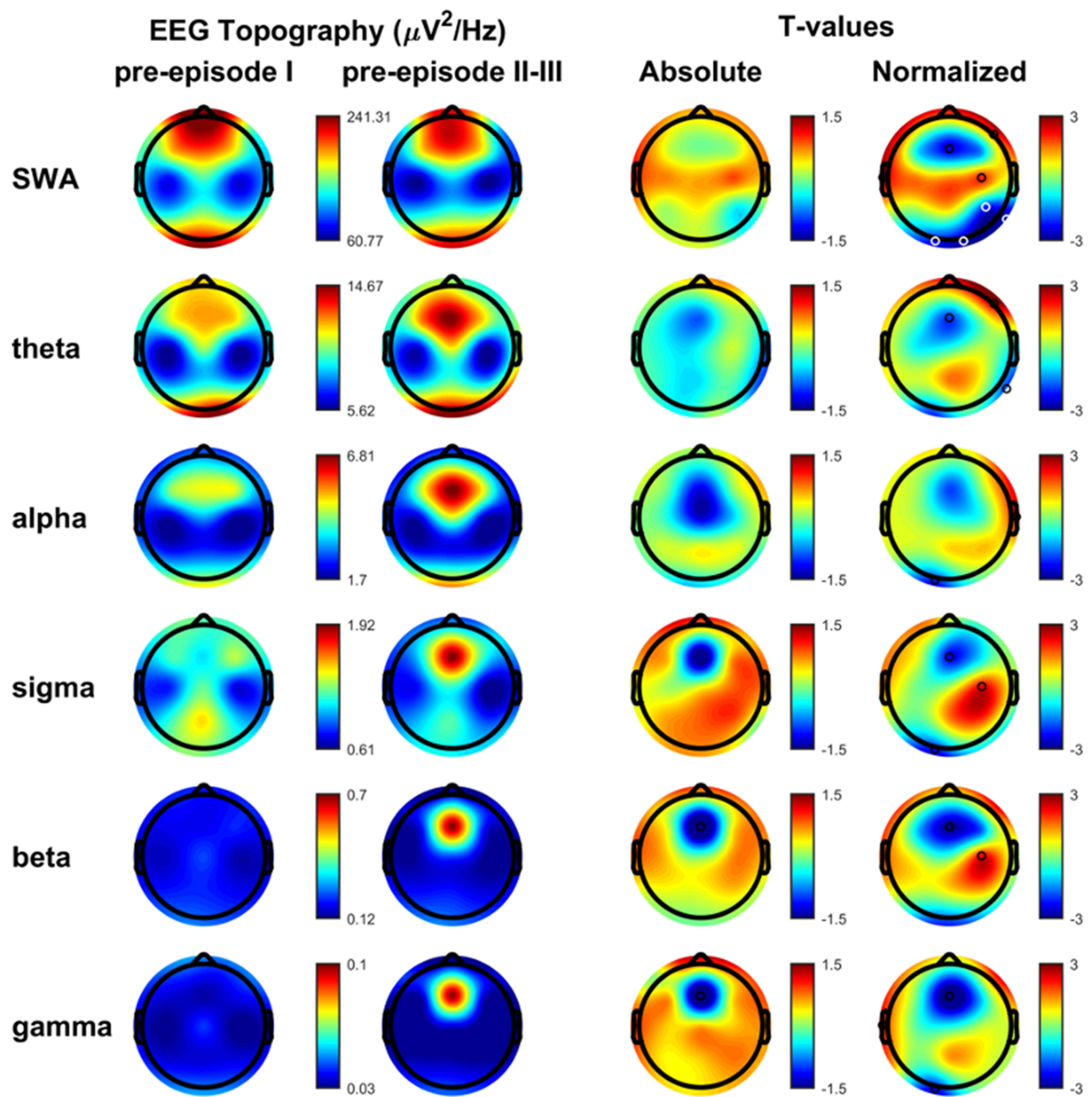


**Figure 1** Pre-episode versus baseline. Spectral bands of all DoA episodes analyzed, for each band frequency: slow wave activity or delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–16 Hz), beta (15–25 Hz), and low gamma (25–45 Hz). First column: average NREM sleep EEG topographies across frequency bands during pre-episode. Second column: topographic averages during stable NREM sleep, two to three minutes before the episode. Third column: map showing the individual electrode t-value (two-tailed, paired) maps for the comparison between pre-episode and baseline sleep in terms of absolute power. Red values represent an increase in absolute EEG power and blue values represent a decrease. Fourth column: same as third column except that each subject was spatially normalized using the z-score across electrodes before creating the t-value comparison. White dots belong to significant clusters ( $P < 0.05$ ) using statistical non-parametric mapping for multi-comparison correction. **Abbreviations:**  $\mu\text{V}$ , microvolts; Hz, Hertz.

derivations (Fp1 and Fp2) and F8. In addition, also beta band showed a distribution very similar to slow frequencies, prominent over both central and anterior areas. Alpha and gamma bands displayed a similar pattern, being relatively higher over the central areas. Finally, only sigma band showed a significant absolute decrease before the episodes, which showed a distribution typical of sleep spindles in normalized maps, with a relative increase over the vertex and central areas.

These results were not influenced by episodes arising from N2 sleep ([Figure S1](#), [Supplemental materials](#)).





**Figure 2** SAMs versus RAMs/CAMs. Spectral bands of simple and more complex DoA episodes for each band frequency: slow wave activity or delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–16 Hz), beta (15–25 Hz), and low gamma (25–45 Hz). First column: average NREM sleep EEG topographies across frequency bands during pre-episode in SAMs. Second column: average NREM sleep EEG topographies across frequency bands during pre-episode in RAMs/CAMs. Third column: map showing the individual electrode t-value (two-tailed, unpaired) maps for the comparison between SAMs and RAMs/CAMs in terms of absolute power. Red values represent an increase in absolute EEG power and blue values represent a decrease. Fourth column: same as third column except that each subject was spatially normalized using the z-score across electrodes before creating the t-value comparison. White dots belong to significant clusters ( $P < 0.05$ ) using statistical non-parametric mapping for multi-comparison correction. Black dots indicate individual channels with  $P < 0.05$  (uncorrected).

**Abbreviations:**  $\mu\text{V}$ , microvolts; Hz, Hertz.

## Inter-Episode Differences

As illustrated in [Figure 2](#), no differences were detected in the absolute values in any of the EEG frequency bands between SAMs and the major episodes (RAMs and CAMs). In normalized maps, only a significant micro-cluster (Occipital O1, O2 and Pz derivations) was detected over posterior areas in the delta band, decreased in the simpler episodes.

## Discussion

### Coexistence of Wake/Sleep EEG Rhythms Before DoA Episodes

In the present work we analyzed the EEG spectral activation preceding behavioral episodes in a large sample of DoA patients, collecting over 300 events, further classified and distinguished on the basis of different motor complexity.<sup>7</sup> To our knowledge, this is the largest sample of DoA episodes analyzed by means of spectral EEG. In contrast with several previous studies, our analysis was not restricted to some specific EEG leads but involved the whole EEG scalp and the whole EEG band spectrum. Our work demonstrates an absolute increase in power of all frequency bands with the exception of sigma before the motor onset of the DoA episodes.

Slow frequencies exhibited, in normalized maps, a relative increase over anterior areas (with the exception of an anterior micro-cluster for delta band) and a consequent relative decrease posteriorly. As shown in [Table 1](#), previous spectral EEG studies disclosed an absolute increase of delta power before DoA episodes mainly over the fronto-central derivations, using different time windows and methodology.<sup>20,22,24,25,27</sup> Our whole scalp map representation depicts a relatively higher slow wave activity (SWA) over a wide fronto-parietal network, considered to account for the unawareness and the lack of inhibition typical of DoA episodes.<sup>9,16</sup> Interestingly, the relative posterior decrease of delta power encountered in our maps reminds of the parieto-occipital “hot zone” considered as a neural signature of dreaming.<sup>35</sup> It is well known by now that DoA episodes might be linked to dreamlike mentation, usually more rudimentary, shorter and less elaborate and enriched in details than REM dream content.<sup>36–38</sup> From this perspective, we might speculate that the relative posterior decrease of delta band disclosed in our study before the episodes might advocate the presence of dreaming mental content preceding and potentially triggering the episodes of DoA. In our study, along with a significant increase in slow frequencies, we disclosed before DoA episodes the concurrent presence of faster EEG rhythms, such as alpha, beta and gamma, over central and anterior areas (mostly for beta band), in a distribution approximately tracing motor and pre-motor areas. The admixture of sleep and wake activity in DoA, even in the same brain areas in some cases, has been demonstrated in stereo-EEG studies during the motor episode.<sup>14–17,39</sup> In particular, the presence of fast EEG rhythms over motor, cingulate and limbic structures has been related to the motor activation and emotional behaviors of DoA.<sup>16</sup> Our findings show a pattern characterized by wake-like EEG frequencies within sleep rhythms prior to the onset of the episode, suggesting that the shift toward a partial awakening,<sup>24</sup> as well as the preparation for a motor activation,<sup>23</sup> precedes the motor event itself. Beta band oscillations have been demonstrated to play a key role in motor control both for pyramidal and extra-pyramidal networks.<sup>40</sup> Modifications of beta spectrum might thus suggest the imminent activation of the motor cortex and consequent motor behaviors of DoA. In addition, we found an increase in gamma band power before the episodes, a finding not clearly described in other studies with the only exception of a partial overlap with beta spectrum disclosed in some studies.<sup>23,24</sup> Gamma band has been related to active waking processes involving attention<sup>41</sup> or oneiric content in REM sleep and has been suggested to underlie dreaming content also in SWS.<sup>42</sup> These aspects, however, remain controversial since increases in gamma bands have been disclosed also in states of reduced consciousness such as anesthesia or epileptic seizures.<sup>43,44</sup>

The only band that showed a significant decrease before the episodes was the sigma one, normally representing the expression of sleep spindles. This finding is shared by physiological arousal in healthy control subjects from N3 sleep, where a blockade of spindles has been demonstrated.<sup>45</sup> In addition, sleep spindles have an inverse relationship with slow wave activity and periods with reduced spindle density are correlated with higher arousability.<sup>46</sup> Sleep spindles, in fact, are considered to have a protective role for sleep continuity and to be an expression of the thalamic stimuli filtering, disentangling the brain from acoustic and sensory stimulation and ensuring the stability of sleep.<sup>46,47</sup> As a consequence, the transitory disappearance of spindles before an arousal has been hypothesized to reflect a time frame in which sensorial transmission improves through the thalamic relay, preparing for a brain state apt to information processing.<sup>24,47</sup> As a future direction, to further characterize thalamocortical dysfunction which may contribute to the onset of DoA episodes, the study of K-complexes and sleep spindles may be worth specific attention in these patients.

### The Arousal Process in DoA: Where Does It Differ from Physiological Arousal?

The findings from our study delineate a complex interplay between the different EEG bands, confirming their coexistence in different brain areas and the concept that different states of being, exemplified in this case by

NREM sleep and wakefulness, may co-occur and become clinically evident in sleep parasomnias.<sup>18</sup> The existence of local sleep phenomena, however, has been highlighted also in physiological arousals, with evidence from different stereo-EEG studies of the coexistence of different patterns and EEG rhythms, together with frequent activation of the motor cortex concurrently with an arousal.<sup>45,48–51</sup> In addition, a reduction of delta rate during N2 and N3 has been recorded in precentral gyrus in human sleep, independently of arousals,<sup>52</sup> suggesting that motor areas are persistently more active during sleep even in normal subjects. The greater activation in motor areas, in fact, is believed to play a key role in providing an adequate response to arousal.<sup>48</sup> A spectral analysis focusing on the pre-arousal period in normal subjects, performed on a single channel, revealed an increase and the coexistence of slow (delta, theta) and fast (alpha, beta) EEG frequencies<sup>53</sup> in the seconds immediately before the arousal, similar to our results in DoA. Overall, several research studies from the last 30 years on the arousal process recognized the heterogeneity of possible manifestations, going from an autonomic/subcortical level, characterized by heart or respiration changes, to cortical modifications, represented by a “synchronized” or a “desynchronized” response, respectively reflected by slower or faster EEG frequencies.<sup>47,53–57</sup> Moreover, recent studies highlighted topographic variability in cortical activation/deactivation patterns during normal arousals,<sup>45,58</sup> suggesting that this heterogeneity may depend on several factors comprising the sleep stage, the sleep depth, and internal or external triggers.<sup>45,47</sup> In turn, this heterogeneity reflects the double nature of the arousal process, preserving the continuity of sleep, on the one hand, and ensuring a prompt response to a stimulus, on the other.<sup>45,47,48,54,58</sup> The clinical result is that one may either keep sleeping or awaken in response to a perturbing stimulus. DoA patients, conversely, appear mentally sleeping but physically awake, a response which embodies at the same time the double nature of the arousal.<sup>59</sup> Among studies focused on the pre-arousal activity in DoA (Table 1), only few included controls and showed a higher spectral power in delta band before DoA episodes,<sup>19–21</sup> suggesting a greater difficulty in fully awakening in DoA. However, homogeneous studies directly comparing DoA and healthy subjects are lacking and potential differences in the pre-arousal period should be searched in the presence of topographic distribution, different power of EEG bands, along with differences in connectivity pathways. Some studies comparing DoA and healthy subjects discovered slight functional and even structural alterations in DoA during wakefulness or normal sleep, independently of episodes, pointing to increased excitability of motor and cingulate areas,<sup>31</sup> impaired inhibitory mechanisms within the motor cortex,<sup>60</sup> potentially underpinned by a volumetric reduction of midcingulate cortex.<sup>61</sup> These alterations suggest that subthreshold triggers might be sufficient to activate motor responses in these predisposed patients during NREM sleep, leading to increased and dysfunctional arousability. This “dissociated” response, from an evolutionary perspective, has been regarded as a dysfunctional survival reflex, with a prompt motor and emotional activation in response to sudden external threats, together with the persistence of sleep need over other brain areas,<sup>16,62</sup> leading to potential traumatic injuries during DoA episodes.

## A Common Mechanism Underlying Episodes of Different Complexity and Its Clinical Inference

Our work demonstrated no significant differences in the spectral EEG preceding simpler and more complex DoA episodes. In a previous paper from our group, SAMs were described as the simpler motor patterns often corresponding to a smaller fragment of the more complex RAMs and CAMs episodes in DoA patients.<sup>7</sup> This observation led to the speculation that a similar mechanism could underlie simple and elaborate episodes, and the higher complexity might reflect a greater impairment of the arousal process, responsible for the gating of different motor patterns.<sup>7</sup> EEG quantitative studies described in the literature have often focused on more elaborate episodes in smaller samples compared to ours (Table 1). One previous EEG study analyzing the distribution of hypersynchronous delta waves detected by visual EEG inspection did not disclose differences in simple and complex episodes,<sup>29</sup> classified according to the different behavioral manifestations.<sup>6</sup> Indeed, our results reveal that the overall activation preceding DoA episodes does not differ between simpler and more complex events, suggesting that SAMs share a similar pathophysiological ground with the more elaborate episodes. This finding has relevant clinical implications due to the higher occurrence and probability of recording SAMs during VPSG, hence providing good diagnostic accuracy even in the absence of complex

behaviors. Moreover, SAMs could also represent a stable long-life “trait” in DoA subjects, evolving into more complex manifestations when predisposing conditions or particular triggers occur.

In the normalized maps, a small but significant micro-cluster of decreased delta power over a small posterior area was detected in SAMs. Due to the low localizing power of standard EEG montage, this result is difficult to interpret and any consideration would be merely speculative. However, it might be hypothesized that lower posterior slow waves represent higher levels of arousal/activation and therefore a lower possibility of evolving into a longer and more complex episode. In addition, it must be kept in mind that the analysis of EEG spectrum is limited to the pre-episode period, since the episode itself is habitually covered with movement artifacts. Therefore, it is likely that reliable differences between simple and complex episodes have to be searched for in the analysis of the event itself. In this regard, stereo-EEG studies revealed that several brain areas might display both slow and fast EEG rhythms, suggesting that DoA episodes are underpinned by more than an exclusive pattern,<sup>17</sup> which might well explain the different complexity and/or the distinctive clinical manifestations. On the other hand, a large study sample is hard to obtain with stereo-EEG studies, hence a systematic analysis focused on the different complexity appears difficult to provide.

In summary, our work provides the identification of a similar pattern of EEG bands distribution in episodes of different complexity, in close proximity to the event, over a large number of DoA episodes. Of note, identifying specific sleep markers before parasomnias might also help differentiate between NREM parasomnias and other motor sleep disorders or sleep-related hypermotor epilepsy (SHE), whose differential diagnosis remains challenging in particular cases or in the presence of only minor events.<sup>63</sup> A recent work moved a step in this direction, providing an analysis of the periodic and aperiodic components of EEG power spectrum in DoA and SHE patients, in sleep segments free from episodes.<sup>64</sup> However, an analysis of the pre-episode might be helpful to identify distinctive patterns before the motor events, especially when only minor events are recorded, leaving diagnostic uncertainty. In addition, the identification of a specific episode before its occurrence might possibly be helpful, in future research, to develop closed loop techniques<sup>65</sup> in order to prevent it.

To date, our sample is the largest dataset of DoA episodes analyzed by means of spectral EEG technique. The study of EEG frequencies, especially SWA, might be influenced by inter-individual differences providing less reliable results, in case of small samples.<sup>22</sup> Therefore, collecting over 300 episodes might ensure a more normal distribution and flatten the inter-individual differences in the study of the EEG spectrum. In addition, the whole scalp and broad-band analysis provides some insight into the global dynamic of EEG frequencies before the episodes.

All our patients were recorded following their normal sleep habits in their habitual sleep setting in the absence of any sleep deprivation procedure. If, on the one hand, sleep deprivation elicits more complex episodes, the influence on sleep homeostasis could have altered the EEG spectral analysis, on the other. Moreover, home-based VPSGs minimize the “first night effect”<sup>66,67</sup> and provide a “natural” sleep environment possibly allowing for the collection of more events.

Our work has some limitations to disclose. First, the limited number of channels of standard EEG recording limits further and more accurate topographic investigations in our study. In addition, patients in our cohort were not directly questioned at the end of each episode. Therefore, a correlation between clinical parameters (orientation, awareness, recall of dream scenario) with EEG measures was not possible. This kind of approach is highly warranted in the study of NREM parasomnias, since they can be considered an ideal model to address different neurocognitive domains during sleep (memory, attention, oneiric content). Finally, we did not have a control group of healthy sleepers. Extending the analysis to physiological arousals of a control group is essential to deepen and help shed light on current understanding of these fascinating disorders.

## Conclusion

In conclusion, the activity preceding simpler and more complex episodes is not significantly different, suggesting a common neurophysiologic mechanism that leads to their occurrence, with possible implications for the management of these disorders and their natural history. The results of our work confirm the view of NREM parasomnias as a complex state, with intermingled features of both wakefulness and SWS. Sleep as a local phenomenon has been demonstrated also in normal subjects, reinforcing the consideration that DoA patients embody the ultimate deregulation of a dysfunctional arousal process, where the tip of the iceberg is the clinical motor episode,<sup>59</sup> with evidence of the coexistence of wake-like

and sleep-like activity even in the same areas.<sup>17</sup> The presence of broadband alterations with a specific local topographic distribution in the pre-episode disclosed in our study might provide diagnostic utility as well as a deeper understanding of DoA networks and pathophysiology.

Larger samples including a control group, homogeneous study designs and additional functional analysis techniques are needed to further elucidate DoA pathophysiology.

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## Disclosure

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