LATENCY TO N3 INTERRUPTION IN AROUSAL DISORDERS

Perretti C[1,2], Gales A[1], Leu-Semenescu S[1,4], Dodet P [1,3,4], Bianquis C[1], Groos E[1], Puligheddu M[2], Maranci JB[1,3,4], Arnulf I[1,3,4]

[1]Sleep Clinic, Pitie-Salpetriere Hospital, APHP-Sorbonne, Paris, France; [2]Sleep Disorder Research Center, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; [3]Sorbonne University, Paris, France; [4]Paris Brain Institute (ICM), INSERM, CNRS, Paris, France;

Institution at which the work was performed: Sleep Clinic, Pitié-Salpêtrière Hospital, Paris, France.

Corresponding author

Pr. Isabelle Arnulf, Service des pathologies du sommeil, Hôpital Pitié-Salpêtrière

83 boulevard de l'hôpital, 75013 Paris

Phone: 33 1 42 16 77 03/04 ; Fax: 33 1 42 16 77 00

E-mail: isabelle.arnulf@aphp.fr

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ABSTRACT

Study objectives: To help expert witnesses in criminal cases using the "sleepwalking defense", we studied the time of first and last interruptions from stage N3 in patients with arousal disorders, including sexsomnia, as well as their determinants.

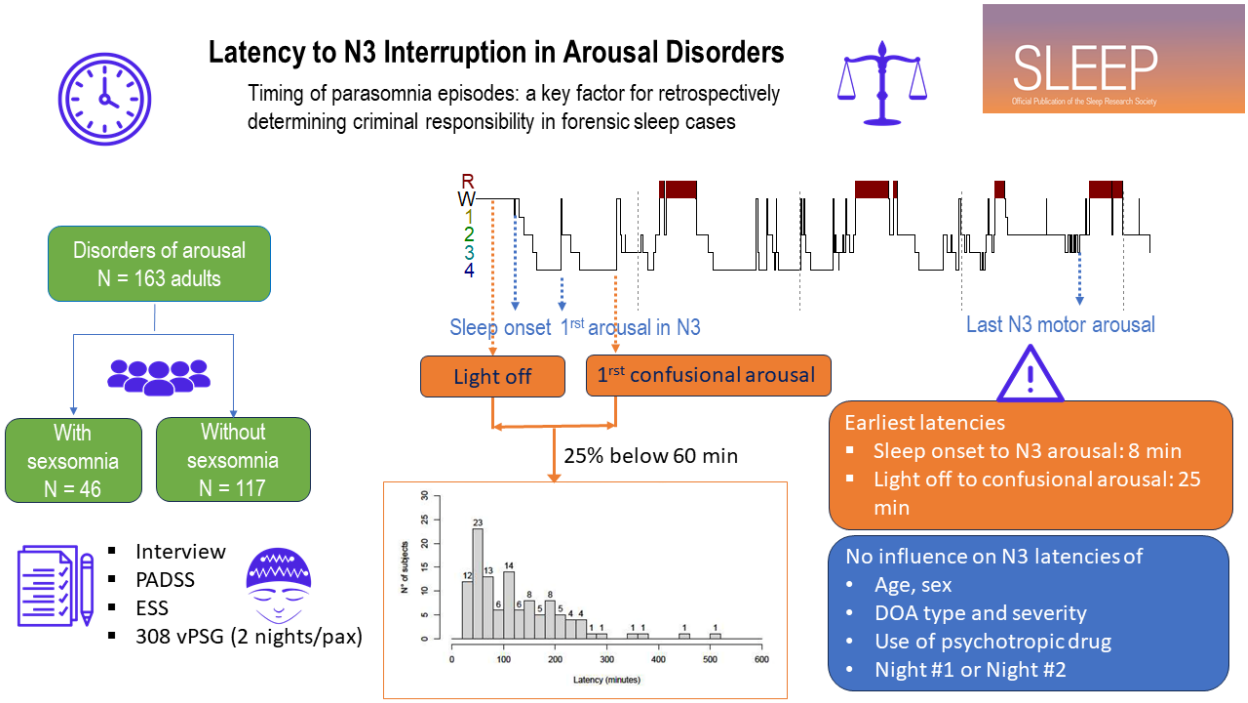
Methods: The epochs of lights off, sleep onset, first N3 interruption (with and without behaviors), and last N3 interruption were determined by videopolysomnography on two consecutive nights in 163 adults with disorders of arousal, including 46 with and 117 without sexsomnia.

Results: The first N3 interruption (independently of concomitant behavior) occurred as early as 8 minutes after sleep onset and within 100 minutes of falling asleep in 95% of cases. The first motor arousal from N3 occurred as early as 25 min after lights off time, a timing more variable between participants (between 30 and 60 minutes after lights off time in 25% of participants and within 60 minutes of falling asleep in 50%). These latencies did not differ between the groups with and without sexsomnia. No correlation was found between these latencies and the young age, sex or clinical severity. The latency of motor arousals was shorter when they were associated with a fast-wave EEG profile and were not preceded by another type of N3 arousal.

Conclusion: The first motor arousal may occur early in the night in patients with arousal disorders, with or without sexsomnia, suggesting that abnormal behaviors occurring as early as 25 min after lights off time in clinical and criminal cases can be a parasomnia manifestation.

Key words: arousal disorders, NREM parasomnia, video polysomnography, behavior, forensic

Graphical abstract



STATEMENT OF SIGNIFICANCE

The timing of episodes of parasomnia is one of determining factor for criminal responsibility in the context of forensic sleep medicine. However, current literature provides only general (and not scientifically determined) estimates of this measure. We aimed to describe the latencies of first and last N3 interruptions from different sleep stages in patients with classic arousal disorders and sexsomnia according to motor behaviors specific for NREM parasomnia. Arousals from N3 stage were extremely precocious in a large proportion, although those associated with eye opening and other complex motor behaviors showed marked interpatient-variability. Timing of arousals from N3 stage was independent from clinical and demographic characteristics.

INTRODUCTION

Disorders of arousal (DOA) are NREM parasomnias including sleepwalking, night terrors and confusional arousals. They are undesirable physical events or experiences occurring during sleep as a result of incomplete arousal from stage N3.[1] They consist of inappropriate behavior, with altered responsiveness and partial or complete amnesia, which may include screaming, sitting up, looking around, walking and manipulating objects.[2] DOA are relatively common during childhood (up to 17% between 2 and 18 years) but are also reported in 2-6% of adults.[3] "Sleep-related abnormal sexual behavior", also called sexsomnia, is a recently described DOA considered as a specific subtype of confusional arousal. It manifests as masturbation, spontaneous orgasms, fondling, initiation and realization of sexual intercourse, sexual molestation and assaults, and loud sexual vocalizations.[4]

DOA can negatively affect the quality of life, as patients often report greater sleep instability, as well as higher levels of anxiety and sleepiness in comparison to healthy controls.[5] However, the most dangerous consequence of these conditions is the potential occurrence of violent behaviors in sleep resulting in harm to self or others, even leading to legal consequences. They can be associated to various degrees of injury to the bed partner or other people (exceptionally culminating in murder), whereas patients affected by sexsomnia may engage in sexual fondling or any kind of sexual penetration with a non-consensual individual or a minor. In such criminal cases, the defendant may claim the innocence of the accused subject based on the premise of reduced or absent level of awareness during the episode, a procedure known as "sleepwalking defense". This type of defense confronts the sleep clinician with the challenging task of providing evidence whether a criminal act could be the result of a parasomnia or not. Evaluation in this context typically relies on retrospective data, including history of any motor or

vocal behavior during sleep reported from the victim and other witnesses, and information about the crime collected in the forensic file.[6] Video-polysomnography (v-PSG) is performed to rule out triggering factors (sleep apnea, restless leg syndrome) and other sleep disorders associated with nocturnal movements (including REM behavior disorder and sleep hypermotor epilepsy). Several experts, however, question its utility, claiming that a normal exam cannot rule out a DOA and that the occurrence of parasomnia during v-PSG does not prove that a criminal act was perpetrated while asleep. Some recent studies, nonetheless, have identified markers sensible and specific for differentiating normal subjects from DOA patients. In a series of 160 adult patients and 50 aged-matched controls an index of arousal from N3 $\geq$ 6.8/h was 79% sensitive and 82% specific, and an index of slow/mixed arousal > 6/h was 100% specific for discriminating patients with DOA from controls.[7] Another case-control study evaluated behavioral criteria supporting the diagnosis of sleepwalking/sleep terror in 52 DOA patients and 52 matched controls.[8] A cutoff of two or more N3 interruptions containing eye opening was 94% sensitive and 77% specific for a diagnosis of DOA. Only DOA patients displayed expressions of fear/surprise, sat, screamed, or stood up during N3 interruptions, making these features highly specific. These EEG and behavioral criteria were later confirmed in patients with sexsomnia, although showing a lower degree of sensitivity by comparison to classical DOA.[9]

One main aspect of forensic evaluation is to demonstrate that the timing of the criminal act is compatible with the occurrence of a parasomnia episode. Medical literature reports only approximately the actual timing of DOA episodes, including “first third of the night”[10] or “within one to three hours from sleep onset”.[11] Since most behavioral episodes happen during N3 sleep, defense experts often use the latency to N3 onset as a proxy measure. However, measures often derive from normal subjects. Recent studies showed that the earliest latency to N3 stage onset

could be as short as 10.6 min in normal subjects and 5.5 min in a large series of patients with DOA.[12,13] These measures, however, reflect only a propensity for DOA occurrence, without giving information about the timing between sleep onset and the actual parasomnia event.

To shed lights in this forensic area, which often lacks of objective measures, we decided to measure the latency (from lights off and from sleep onset) to the first and last N3 interruptions, with and without specific behavioral features in a large clinical population of adults with classical DOA, as well as in a group of adults with sexsomnia. We wanted to determine if a parasomniac behavior could occur rapidly after light off (which is a measure that can be recalled by the defendant and the victim) and after sleep onset (although sleep onset time is harder to estimate than lights off time, due to amnesia at sleep onset). Conversely, although parasomniac behaviors predominate in the beginning of the night, some patients may have episodes late in night. We therefore determine the time of the last N3 interruption, with and without behavior. We examined whether these latencies would shorten with younger age, gender, clinical characteristics of the parasomnia (and especially whether there were differences between DOA patients with and without sexsomnia, as this last parasomnia is more often associated with forensic cases) and medications.

METHODS

Participants

In this retrospective study, we selected two groups (classical DOA and sexsomnia) of participants among the patients referred to the adult sleep disorder clinic of the Pitié-Salpêtrière University Hospital for abnormal behaviors during sleep. For the classical DOA group, we enrolled all patients referred during one year, from January 2021, 2nd to December 2021, 23rd in the sleep clinic, in whom a diagnosis of NREM parasomnia had been confirmed. Because

sexsomnia was rarer than other DOA, we extended the inclusion of sexsomnia patients to those referred from September 2015 to December 2022 for amnestic sexual behavior during sleep with a confirmed diagnosis of sexsomnia.

All participants had to meet the general criteria for DOA,[1] which include: (i) recurrent episodes of incomplete awakening from sleep; (ii) inappropriate or absent responsiveness to efforts of others to intervene or redirect the person during the episode; (iii) limited or no associated cognition or dream imagery; (iv) partial or complete amnesia for the episode; and (iv) the disturbance was not better explained by another sleep disorder, mental disorder, medical condition, medication, or substance use. In addition, DOA were classified as sleepwalking (the arousals are associated with ambulation and other complex behavior out of bed), confusional arousal (the episodes are characterized by mental confusion or confused behavior that occurs while the patient is in bed and there is an absence of terror or ambulation outside of the bed), sleep terror (the arousals are characterized by episodes of abrupt terror, typically beginning with an alarming vocalization such as a frightening scream and there is intense fear and signs of autonomic arousal, including mydriasis, tachycardia, tachypnea, and diaphoresis during an episode), or sexsomnia (abnormal sexual behaviors during disordered arousals including prolonged or violent masturbation, sexual molestation and assaults, initiation of sexual intercourse, and loud sexual vocalizations during sleep—followed by morning amnesia). Around half of patients with sexsomnia had been already included in a previous published study.[9] When two to four different types of DOA were associated in single participants, we classified them within the main category for which they were medically referred.

In order to better represent classical adults referred to a sleep laboratory for suspected DOA, we chose to keep in the patients with comorbid neurologic conditions (including epilepsy,

provided that the parasomnia episodes were unrelated to the epilepsy as checked on history, interview and extended EEG during v-PSG), mental disorders (anxiety, depression and attention deficit/hyperactivity disorder) and mild sleep disorders (including mild obstructive sleep apnea defined by an apnea-hypopnea index lower than 15, and mild restless leg syndrome, defined as requiring no treatment). We included patients treated with psychotropic drugs, including neuroleptics, benzodiazepines, antidepressants and epileptic drugs. In contrast, subjects referred for forensic purposes were not included in this study, because DOA was a matter of defense and the interviews could be biased to avoid conviction. To avoid a possible influence of sleep deprivation on sleep latencies, participants who had slept less than an average of 6 hours in the week prior to the sleep tests were not included.

Ethics

Because this study was a retrospective collection of clinical and polysomnographic measures from chart review, the local ethics committee waived written consent from the patients, provided they had given their oral consent for their data to be anonymously collected (non-opposition procedure), which was the case here. This non-opposition was stipulated in the medical report and consigned in the medical file. The sleep clinic has the authorization MR003 N°#2008449 to collect the measures as well as ensure anonymization, following the general regulation on the protection of personal data.

Clinical Measures

The clinical characteristics of the patients were collected in the files (the number with such information is indicated), and included time at symptoms onset (childhood, teenage, adulthood), characteristics of episodes (sleepwalking, sleep terrors, confusional arousal, sexsomnia, sleep-related eating disorder), comorbidities (medical, neurological and mental and

sleep disorders) and current treatment (antidepressant, benzodiazepine, neuroleptic, antihistaminic, others). They had been collected during the medical interview with a sleep physician from the sleep unit in the visit preceding the v-PSG. The presence of violent behaviors during episodes, defined as harm toward self or to others, was also assessed. The scores at the Epworth Sleepiness Scale (ESS) and at the Paris Arousal Disorders Severity Scale (PADSS) were collected. The Paris Arousal Disorders Severity Scale (PADSS) is composed of three parts[2]. The PADSS-A is an inventory of 17 abnormal amnestic behaviors scored as never (0), sometimes (1), and often (2), and yields a maximum score of 26; PADSS-B evaluates the frequency of behavioral episodes from 0 (never) to 6 (several times per night); PADSS-C evaluates the general consequences of the disorder, including injury to oneself (0–2) or to others (0–2), disturbance of others' sleep (0–2), morning tiredness (0–2), and psychological (shame, anxiety) consequences (0–2), yielding a maximum of 10. The total of the scale is 50 and a score greater than 9 has a good sensitivity and specificity for separating patients with DOA from healthy controls.

Sleep measures

All participants underwent one or two consecutive nights with v-PSG recording in the clinic. Electroencephalography included ten EEG leads (A1; A2; F3; C3; T3; O1; F2; C4; T4, O2) acquired in a monopolar referential montage. Monitoring included two electro-oculograms, three surface electromyography (levator menti, right and left tibialis anterior muscles), naso-oral thermistor, nasal pressure through a cannula, tracheal sounds, thoracic and abdominal movements measured through plethysmography belts, electrocardiography, pulse oximetry, EEG-synchronized infrared video monitoring and sound recording in the room. The patients were recommended to keep regular sleep–wake schedules with no sleep deprivation during the

week preceding the sleep monitoring, although they did not complete any sleep log. However, the absence of previous sleep debt was assessed during a clinical interview with a sleep physician, which included a careful report of sleep time, sleep schedule and daytime naps during previous weekdays and weekends. Patients arrived between 4 pm and 7 pm, were hooked, and had diner in the unit. Sleep was monitored from lights off (ad libitum) to lights on (ad libitum) during both nights. Patients stayed in the unit between Night #1 and Night #2, performing quiet activities including answering physician interviews, examination, and questionnaires, reading, phoning, working on their computer, or walking in the hospital garden, but were not allowed to sleep, as checked by the nurses from the recording room via cameras.

The scoring of the sleep stages and events (respiratory events, including apnea, hypopnea, and flow limitation, defined as a plateau on nasal pressure lasting at least ten seconds and followed by an arousal; periodic leg movements, arousals) was performed by trained neurologists according to standard criteria.[14] In line with previous studies,[7,8,9,15] the analysis of v-PSG included all N3 interruptions, defined by: (i) the occurrence of abrupt EEG frequency shifts with a combination of theta and alpha waves, and/or frequencies > 16Hz and lasting at least 3 seconds; or (ii) the occurrence of increased muscle activity with persisting delta activity on EEG leads lasting for at least 3 seconds. N3 interruptions were then characterized based on EEG activity and motor behavior. EEG activity was classified as: (i) fast, i.e., prevalence of alpha or beta activity and < 20% of theta/delta activity; (ii) mixed/slow, defined as theta/delta activity > 20%, with or without alpha/beta activity. Motor behavior during N3 interruptions was classified into simple (no movement or comfort, auto-centered gesture like turning in bed, scratching nose or changing position, as routinely observed during spontaneous arousals in normal subjects)[16] or complex (eyes opening, sudden movements usually accompanied by eyes opening like raising

head or trunk, looking around in a confused way, making complex gesture, speaking or shouting).[8] Lastly, we divided N3 interruptions into spontaneous or provoked, if a respiratory event, a leg movement or an external stimulus (noise, nurse contact) occurred within the 5 second preceding their onset. We identified and reported the epoch of: (i) lights off; (ii) sleep onset; (iii) N3 onset; (iv) first N3 interruption; (v) first N3 interruption with complex behavior, and (v) last N3 interruption. The latencies between these epochs were calculated.

Statistical Analysis

Clinical and polysomnographic measures were shown as numbers and percentage or means and standard deviations. Comparisons between DOA and sexsomnia subgroups were performed using t-test or Mann-Whitney test for quantitative measures and chi-square test or Fisher's exact test for qualitative measures. Latencies were described using histogram, median, interquartile in general and compared between DOA subgroups with sleepwalking, sleep terrors, confusional arousals and sexsomnia using analysis of variance. The demographic and clinical associations of these latencies were measured using Pearson correlations for quantitative measures, and Student t test for categorial measures. A p-value lower than 0.05 was considered as significant. Statistical analysis was performed using R software, version 4.3.1[17].

RESULTS

Demographic and Clinical Characteristics of Participants

Among the 163 participants meeting the inclusion criteria and having been included, 117 had a DOA without predominant sexsomnia (a group named here "nsDOA") and 46 had a predominant sexsomnia (Table 1). Age was similar between groups. There were more male

participants in the sexsomnia than in the nsDOA group. Participants with sexsomnia had less often a history of DOA than those with nsDOA. More participants with nsDOA than sexsomnia had a history of any DOA subtype in childhood. There were no between-group differences in terms of history of isolated sleep talking. The current DOA subtype had more often started in childhood in the nsDOA group and in adulthood in the sexsomnia group. In the present clinical symptoms, combinations of several types of DOA were frequent in the nsDOA group, including confusional arousals in all patients, sleep terrors in 65%, sleepwalking in 67.5%, and rare episodes of amnestic sexual behaviors in 9%. Conversely, participants with sexsomnia had less frequently sleepwalking episodes, sleep terrors and confusional arousals. More participants in the nsDOA group had injured a bed partner or themselves than those with sexsomnia (but forensic cases of sexsomnia had been excluded). Participants with nsDOA were sleepier than those with sexsomnia, as indicated by a higher mean score at the ESS and a higher prevalence of participants with an ESS greater than 10. The PADSS-A (inventory of behavior), PADSS-B (frequency of parasomnia) and PADSS-total scores were higher in nsDOA group than in the sexsomnia group, whereas PADSS-C score (consequences of the parasomnia) was not different between groups. More patients in the nsDOA group than in the sexsomnia group had an abnormal (greater than 9) PADSS-total score. There was no difference in the proportion of participants reporting use of psychotropic medications in the nsDOA group (20.5%) and sexsomnia group (10.9%). Pharmacological classes included neuroleptics (n = 6), antiepileptics (n = 9), antidepressants (n = 18), benzodiazepines (n = 3), antihistaminic drug s (n = 3) and stimulants (n = 1), and 8 participants took combination of drugs of different classes.

Polysomnographic Sleep Measures

In the total group, 153/163 (93.8%) patients underwent two consecutive nights of v-PSG and 10/163 (6.1%) underwent a single night v-PSG. Among the 316 v-PSG collected, 8 were excluded from the analysis because they were not accessible or had acquisition problems rendering latencies non interpretable (e.g., v-PSG segmented in several bouts), leading to a total of 308 v-PSG analyzed here. As indicated in the Supplementary Table S1, they were no difference in the latencies to sleep onset and to REM sleep, sleep continuity (wakefulness after sleep onset, sleep efficiency), sleep architecture (% of N1, N2, N3 and REM sleep) and sleep fragmentation (arousal index, apnea/hypopnea index and periodic leg movements index) between nsDOA and sexsomnia groups during Night#1 and Night #2, except that total sleep time was shorter in the nsDOA group than in the sexsomnia group on Night#1 only (not found in Night#2).

Latency to the Various Types of N3 Interruptions

All participants presented at least two N3 interruption during each v-PSG. N3 interruptions associated with complex behaviors were identified in 92/117 (79.7%) participants in the nsDOA group and 22/46 (47.9%) patients in the sexsomnia group during Night#1 ($P < 0.001$ for a between group difference), as well as in 80/100 (80%) participants in the nsDOA group and in 23/45 (51.2%) participants in the sexsomnia group during Night#2 ($P < 0.001$). As shown in Table 2, the latencies from light off or sleep onset to first and last N3 interruptions, as well as to first N3 interruption associated with a complex behavior (motor arousal) were not different between the nsDOA group and the sexsomnia group during Night #1 and Night #2.

Comparing the same latencies between Night#1 and Night#2 in both groups showed no difference too (Supplementary Table S2).

The latency to first N3 interruption associated with a complex behavior was on average longer than the latency to first N3 interruption, whether in the nsDOA or in the sexsomnia group ($P<0.001$ for all comparisons). The first N3 interruption contained a complex behavior in 46/163 participants (28.2%), whereas the complex behavior occurred several minutes after the first N3 interruption with simple behavior in Night #1 in 68/163 (41.7%) participants. In Night#2, the first N3 interruption already contained a complex behavior in 27/145 (18.6%) participants, whereas the complex behavior occurred several minutes after the first N3 interruption with simple behavior in 76/145 (52.4%) participants. As indicated in Figure 1, the latency to first N3 interruption followed a semi Gaussian curve centered around 35 min from light off and 25 min from sleep onset. Latency from N3 onset to first N3 interruption followed a logarithmic distribution with a peak of frequencies in the first 10 minutes. In contrast, latency to the first parasomnia behavior from light off was more variable, including no obvious peak, and timing for behavioral arousals staggered from 25 to over 280 min after lights off. When considering the latency from sleep onset to first parasomnia behavior, a more obvious peak emerged around 20-40 min.

Latency from sleep onset to last N3 interruption followed a Gaussian distribution on both nights with median value around 400 minutes for both groups and an interquartile range around 130 minutes. Last N3 interruption generally coincided with the end of last stage N3. In Night#1, 15.9% (26/163) of last N3 interruptions and in Night#2, 18.6% (27/145) were associated with a complex behavior. The frequency of complex motor behaviors were not different between the

nsDOA group and the sexsomnia group in Night#1 (18.8% vs 8.6%) and Night#2 (21% vs 13.3%).

Determinants of N3 interruptions latencies

Because no type of N3 latencies differed between DOA groups and nights, groups were merged. We conducted a bivariate analysis on latencies from sleep onset to first N3 interruptions and to first N3 interruptions with complex behaviors in all participants in both nights, using linear regression for quantitative variables and analysis of variance (ANOVA) for categorical variables (Supplementary Tables S3 and S4). No significant correlation was found between any latency and continuous measures including age, and scores at the Epworth sleepiness scale or at the PADSS (total and subscales). The analysis of variance in Night#1 and Night#2 showed that categorical measures, including history of previous DOA, clinical phenotype or presence of comorbidities, did not impact the latency to first N3 interruption, except that the presence of violent behavior was associated to longer latency to first N3 interruption with complex behavior ($F = 9.64$, $p = 0.002$) in Night#1 but not in Night#2. In Night#1 (but not in Night #2), the intake of psychotropic medication yielded a longer latency to first N3 interruption with complex motor behavior ($F = 7.36$, $p = 0.007$) than no drug use. The interaction between violent behaviors and use of psychotropic drugs was not significant.

We performed additional group comparison considering the characteristics of different N3 interruptions. The majority of N3 interruptions, independently of motor pattern, were spontaneous. Comparison between different causes of arousal (hypopnea, noise, leg movement) yielded no difference in latencies from sleep onset in both nights. N3 interruptions with fast EEG activity occurred with a shorter latency from sleep onset in Night#1 ($p < 0.001$) and Night#2 ($p =$

0.002) than those with a slow/mixed activity. This association was confirmed considering the first N3 interruptions with complex behavior (Night#1, $p = 0.02$; Night#2, $p < 0.001$). Additionally, the first N3 interruption with complex motor behavior occurred earlier when it was not preceded by an arousal with simple motor behavior in both Night#1 and Night#2 ($p < 0.001$ for both nights). Use of psychotropic medication was not associated with a specific EEG pattern for N3 interruption in either night, independently from motor behavior.

DISCUSSION

In this retrospective study, the latencies of N3 arousals were described and compared between different NREM parasomnias. Latency comparison between nsDOA and sexsomnia groups showed no significant difference on either nights, thought participants in the sexsomnia group had a lower rate of N3 interruption with complex behavior during recordings. These findings correlate with previous evidence suggesting that sexsomnia represents a "milder variant" of DOA in terms of polysomnographic findings,[9] exhibiting lower rate of eye opening and less frequent confusional behavior in comparison to classical sleepwalking/sleep terror, although equally disabling for the patient as confirmed by similarity between PADSS score C in both groups.

Numerous studies have demonstrated that patients with DOA exhibit a high number of arousals from N3 stage, which represent a distinguishing feature from healthy subjects.[18,19] We showed that N3 interruptions can be precocious in DOA patients, occurring earlier than what has been suggested in recent criminal trials.[12] First N3 interruptions, regardless of motor behaviors, could appear as early as 8 minutes after sleep onset and less than 1 minute after the onset of N3 stage. The timeframe was relatively restricted in both nights, as less than 5% of N3 interruptions

occur after 100 minutes from sleep onset and only 25% and 5% respectively occur after 20 and 50 minutes from N3 onset. In contrast, first N3 interruptions with complex behaviors showed marked between-patient variability, occurring from the earlier to the latest part of the night, although more than 85% of the episodes took place in the classic 3 first hours of the night reported in standard literature. However, the minimal latency from sleep onset was below 15 minutes in both nights, and half of participants presented a first episode of parasomnia behavior within the first 60 minutes after sleep onset in both Night#1 and Night#2.

As determining the exact time of sleep onset can be challenging in the context of forensic medicine, the latency from light off time was studied too, since it represents a measure easier to recall for witnesses than sleep onset time. In this context, we showed that complex motor arousals can occur between 30 and 60 minutes from the moment of attempting to sleep in up to 25% of participants, with minimal latencies being 27,5 minutes in Night#1 and 25 minutes in Night#2. Previous research has shown that complex motor arousals including head raising and look of surprise/fear are specific of parasomnia and not observed in normal subjects. The time intervals found here represents a reliable reference for predicting the timeframe in which a potential harmful parasomnia episode could take place. Longitudinal collections of video-polysomnography in the same patients could help confirm the reliability of our measures. The use of home videos could help in this direction[20]. There were no difference in any latency between Night#1 and Night#2, which implies that a possible "first night effect" held minimal influence on the timing of N3 interruptions, suggesting that these measures could also apply in a real life setting. We did not consider episodes of parasomnia occurring during N2 stage here, since the majority of episodes occur out of N3 stage.[21] As the latency to N3 sleep was short, it is unlikely that our findings were significantly influenced by this decision.

The time of first N3 interruption was not influenced by age, sex, and clinical parameters like sleepiness, severity of parasomnia, history of DOA or DOA subtypes. Our results could be due to the limits of classification of NREM parasomnia. Patients with DOA represent a heterogeneous population when a common neurophysiological mechanism leads to multiple symptomatic manifestations arising in variable proportions in different patients. The absence of differences between the nsDOA group and the sexsomnia group suggests also that the time of the first N3 interruption is independent from the clinical phenotype of the parasomnia.

Participants with a history of harm to themselves or others showed a longer latency to first complex motor N3 arousal in Night#1, but this finding was not confirmed on Night#2. Violent behaviors indicate an important motor component during parasomniac episodes, generally in the context of sleepwalking, but are also influenced by the specific features of the sleep environment and the presence of a bed partner. Sexsomnia patients generally refer to sleep centers for personal distress over amnestic sexual activity, whether rare cases of forced sexual behavior usually had legal implications, which we intentionally decided to exclude.

Latency of N3 interruptions was shorter, independently from the presence of complex motor behavior, when the EEG pattern during arousal prevalently contained rapid (alpha and beta) rather than slow (delta and theta) frequencies. Previous researches[22,23] have shown that slow wave activity is reduced in DOA patients during the first NREM period compared to healthy subjects, leading also to a lower decline of slow wave activity across the night. It is possible that when arousals occur soon after the beginning of N3 stage, the amount of delta wave activity on the scalp is still insufficient to generate a dissociated pattern, leaving faster rhythms as the predominant frequencies on EEG, Conversely, as N3 stage progresses, increasing theta

and delta frequencies would allow for a more hybrid alpha/delta EEG pattern to appear during arousals.

The relationship between psychotropic drugs and DOA is controversial, as different classes of drugs has been employed in the treatment of these conditions,[24] while at the same time some molecules has been associated with the appearance of sleepwalking.[25] Most of the evidence derive from case-reports or small cohort studies, therefore cause-effect correlation remain a matter of debate. Moreover, prospective studies on DOA tend to exclude subjects treated with psychotropic drugs, as to limiting confounding factors, resulting in insufficient data on effects of these medications on parasomnia episodes. As we aimed to obtain results applicable in a real life setting, we included participants under different pharmacological treatments. Zolpidem is the only drugs for which a consistent association with parasomnia triggering has been reported[26–28] and none of our participants was treated with it. Latency to first N3 interruption with complex motor behavior was found to be longer in Night#1 (but not in Night#2) in participants under psychotropic drugs, but no other differences were found in latencies and behaviors here between participants taking or not psychotropic drugs. Further research is needed to confirm this preliminary finding and evaluate possible differences on timing of arousal between drug treatments.

Our study present several limitations inherent to its retrospective nature. Two-nights v-PSG recordings were not universally available and Epworth and PADSS scales were not completed by all participants. Nonetheless, the large number of participants enrolled in the study allowed for a robust statistical analysis on all variables. Participants did not complete a sleep diary prior to recording, but sleep deprivation (which can influence sleep latencies) was ruled out by interview. Participants were, also, studied in a laboratory setting without their usual bed

partner, which prevented us from evaluating the effect of physical contact as a potential triggering factor[29]. This may have proved significant especially for patients with sexsomnia[30], who often report contact and proximity to a person in bed as a provocative factor, potentially contributing to the lower rate of episodes with complex behavior in that group. Other known precipitating factors that were not evaluated in this study were alcohol consumption and sleep deprivation. The latter in particular can increase the likelihood of parasomnia episodes by increasing homeostatic sleep pressure and has been successfully employed in an experimental protocol for inducing somnambulistic episodes in sleepwalkers[31]. Future research could investigate the possible effect of these conditions on the timing of arousal from N3 sleep in DOA patients.

This study provide a first estimate of the range of latencies to first arousal in N3 sleep in a large population of patients with arousal disorders, which could represent a reference in forensic cases. As recommendations for forensic cases, one may note that a history of DOA and other parameters scored by PADSS apparently do not have an impact on N3 fragmentation or latencies. Based on these findings, we suggest that the expert witness should ask about the presence of arousal prior to the criminal act and the exact timing of lights out and sleep onset.

CONCLUSION

Arousals can occur early during N3 stage in patients with DOA and up to 25% can present an episode with motor behavior compatible with parasomnia between 30 and 60 minutes from the light off time. Time of N3 interruptions is independent of clinical phenotype, while an EEG pattern dominated by frequencies in the alpha/beta range and the absence of previous arousal is associated with shorter latency.

DISCLOSURE STATEMENT

Financial disclosure statement: None. This was not an industry-supported study.

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

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Figure 1: Distribution of latency to first N3 interruption (top row) and first N3 interruption with complex behavior (bottom row) in all participants during Night#1.

Table 1. Demographic and clinical characteristics of participants with disorders of arousal and sexsomnia.

Group	All DOA	nsDOA	Sexsomnia	P
No of subjects	163	117	46	
Age, y	30.2 ± 8.3	30.8 ± 8.7	28.8 ± 7.0	0.12
Male sex, N (%)	94 (57.7)	49 (41.9)	45 (97.8)*	<0.001
History of DOA				
No history	28 (17.2)	10 (8.5)	18 (39.1)*	<0.001
Childhood	99 (60.7)	81 (69.2)*	18 (39.1)	<0.001
Adolescence	20 (12.3)	18 (15.4)	2 (4.3)	0.06
Isolated sleep talking	16 (9.8)	8 (6.8)	8 (17.4)	0.07
Onset of present parasomnia				
Childhood	84 (51.5)	79 (67.5)*	5 (10.9)	<0.001
Adolescence	22 (13.5)	18 (15.4)	4 (8.7)	0.31
Adulthood	57 (35.0)	20 (17.1)	37 (80.4)*	<0.001
Present clinical symptoms				
Somnambulism, N (%)	84 (51.5)	79 (67.5)*	5 (10,9)	<0.001
Sleep terror, N (%)	77 (47.2)	76 (65.0)*	1 (2,2)	<0.001
Confusional arousal, N (%)	129 (79.1)	117 (100)*	12 (26.1)	<0.001
Sexsomnia, N (%)	57 (35.0)	11 (9.4)	46 (100)*	<0.001
Harm to himself or others, N (%)	35 (21.5)	32 (27.4)*	3 (6.58)	0.002
Daytime sleepiness (Epworth Sleepiness Scale)				
N	161	116	45	
Score, 0-24	9.2 ± 4.7	9.8 ± 5.0*	7.7 ± 3.6	0.004
Score > 10, N (%)	58 (36.0)	50 (43.1)*	8 (17.8)	0.003
Severity of parasomnia (Paris Arousal Disorder Severity Scale)				
N	110	72	38	
Total score, 0-50	14.4 ± 5.5	16.2 ± 5.4*	11.1 ± 3.9	<0.001
A score, 0-34	6.3 ± 4.0	7.7 ± 4.0*	3.8 ± 2.5	<0.001
B score, 0-6	3.6 ± 1.2	3.8 ± 1.2*	3.1 ± 1.1	0.002
C score, 0-10	4.5 ± 1.7	4.7 ± 1.8	4.2 ± 1.6	0.08
Total score > 9, N (%)	91 (82.7)	67 (93.1)*	24 (63.2)	<0.001
Use of psychotropic drugs	29 (17.8)	24 (20.5)	5 (10.9)	0.17

Measures are mean ± SD or number (percentage). *Significant between group difference.

Table 2. Latency to first and last N3 interruptions and to first N3 interruption associated with complex behaviors during Night#1 and Night#2 in participants with classical arousal disorders (nsDOA) and with sexsomnia

Group	nsDOA	Sexsomnia	P
	Median (Q1-Q3)	Median (Q1-Q3)	
Night #1			
Latency to first N3 interruption, min			
From Light Off	59.0 (42.0 – 80.0)	60.3 (39.1 – 74.1)	0.91
From sleep onset	31.0 (21.5 – 44.0)	33.0 (22.6 – 55.9)	0.21
From N3 onset	9.5 (4.5 – 19.0)	11.3 (5.1 – 24.9)	0.45
Latency to first N3 interruption with complex behavior, min			
From Light Off	101.5 (56.8 – 170.9)	138.8 (51.0 – 174.9)	0.55
From sleep onset	56.0 (31.9 – 130.1)	73.5 (44.9 – 133.8)	0.37
From N3 onset	41.3 (14.4 – 105.1)	35.5 (16.8 – 94.9)	0.88
Latency to last N3 interruption, min			
From Light off	445.0 (365.5 – 510.0)	419.5 (361.8 – 496.1)	0.54
From sleep onset	413.0 (325.5 – 477.0)	399.0 (329.3 – 458.8)	0.64
Night #2			
Latency to first N3 interruption, min			
From Light Off	58.3 (39.3 – 77.6)	56.0 (36.5 – 85.5)	0.83
From sleep onset	26.0 (19.5 – 45.0)	27.0 (19.5 – 47.5)	0.99
From N3 onset	8.0 (4.0 – 15.5)	10.0 (4.0 – 23.0)	0.58
Latency to first N3interruption with complex behavior, min			
From Light Off	90.3 (66.9 – 160.8)	91.5 (67.3 – 153.5)	0.61
From sleep onset	57.0 (38.9 – 126.5)	64.0 (47.8 – 93.5)	0.51
From N3 onset	35.0 (18.3 – 88.3)	40.0 (27.0 – 81.5)	0.43
Latency to last N3 interruption, min			
From Light off	462.0 (386.0 – 517.4)	418.0 (355.5 – 491.5)	0.15
From sleep onset	424.5 (349.5 – 480.6)	387.5 (319.0 – 454.0)	0.16

Q1: first quartile, Q3: third quartile;

Figure 1