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NREM sleep parasomnias as disorders of sleep-state dissociation

Anna Castelnovo^{1,2,6}, Régis Lopez^{3,6}, Paola Proserpio⁴, Lino Nobili^{4,5,6*} and Yves Dauvilliers^{3,6*}

Abstract | Non-rapid eye movement (NREM) sleep parasomnias (or NREM parasomnias) are fascinating disorders with mysterious neurobiological substrates. These conditions are common and often severe, with social, personal and forensic implications. The NREM parasomnias include sleepwalking, sleep terrors and confusional arousals — collectively termed disorders of arousal (DOAs) — as well as less well-known entities such as sleep-related sexual behaviours and eating disorders. Affected patients can exhibit waking behaviours arising abruptly out of NREM sleep. Although the individual remains largely unresponsive to the external environment, their EEG shows both typical sleep-like and wake-like features, and they occasionally report dreaming afterwards. Therefore, these disorders offer a unique natural model to explore the abnormal coexistence of local sleep and wake brain activity and the dissociation between behaviour and various aspects of consciousness. In this article, we critically review major findings and updates on DOAs, focusing on neurophysiological studies, and offer an overview of new clinical frontiers and promising future research areas. We advocate a joint effort to inform clinicians and the general public about the management and follow-up of these conditions. We also strongly encourage collaborative multicentre studies to add more objective polysomnographic criteria to the current official diagnostic definitions and to develop clinical practice guidelines, multidisciplinary research approaches and evidence-based medical care.

Non-rapid eye movement (NREM) sleep

Non-rapid eye movement sleep encompasses stages 1–3 of sleep and is characterized by distinct electrophysiological features from rapid eye movement sleep, such as the absence of phasic rapid eye movements and of muscle atonia.

Parasomnias

Sleep disorders defined as undesirable behavioural and physiological, autonomic or experiential events that accompany sleep.

Non-rapid eye movement (NREM) sleep parasomnias (hereafter referred to as NREM parasomnias) are a family of disorders that are thought to derive from incomplete arousal from NREM sleep (mainly slow-wave sleep (SWS)), which usually occurs during the first third of the major sleep period. NREM parasomnias consist of episodes of abnormal sleep-related complex movements and behaviours associated with various degrees of autonomic nervous system activation, inappropriate or scarce responsiveness to the external environment, limited or absent cognition or dream imagery, and partial to complete amnesia.

The classification of NREM parasomnia subtypes has changed over time and differs slightly between the various classification systems (BOXES 1, 2). The *International Classification of Sleep Disorders, Third Edition (ICSD-3)*¹ distinguishes two categories of NREM sleep parasomnias: disorders of arousal (DOAs), which include three main clinical presentations known as confusional arousals, sleep terrors and sleepwalking (also known as somnambulism), and sleep-related eating disorder (SRED), also known as sleep eating. Sleep-related abnormal sexual behaviour, also known as sexsomnia or sleep sex, is a subtype of confusional arousals and sleepwalking. In this

Review, we focus on DOAs, in particular, sleepwalking, sleep terrors and confusional arousals.

DOAs are poorly understood and underdiagnosed, leading to inadequate management and underestimation of the consequences. These common disorders are especially prevalent during childhood, with sleep terror reported in up to 34% of children at 1.5 years of age and sleepwalking in up to 13% of children at 10 years of age. DOAs often resolve by puberty; however, they are far more common in adults than is generally acknowledged, with a 2–4% prevalence of sleepwalking or sleep terror in both men and women^{2–4}. A US study found a 29% lifetime prevalence of DOAs, with two or more episodes per month reported by 1% of adults³. Adult-onset DOAs account for 17–27% of cases in clinical cohorts^{5,6}.

Currently, the diagnosis of a DOA is based solely on clinical criteria, in contrast to rapid eye movement (REM) sleep behaviour disorder (RBD), which requires objective criteria (namely, REM sleep without atonia). Many studies over the past few decades have attempted to characterize the macroarchitectural and microarchitectural features of sleep recordings in DOAs, with the aim of identifying EEG markers of the underlying

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Key points

- The non-rapid eye movement (NREM) sleep parasomnias (or NREM parasomnias) encompass disorders of arousal (DOAs) — namely, sleepwalking, sleep terrors and confusional arousals — and lesser-known entities such as sleep-related sexual behaviours and eating disorders.
- NREM parasomnias are common during both childhood and adulthood and can have adverse and frequently overlooked consequences, including unintentional self-harm, harm to others (with potential legal implications), daytime sleepiness and psychological distress.
- A key feature of NREM parasomnias is the dissociation between self-awareness and behaviour, as well as between wakefulness and sleep in different brain regions, as demonstrated by single-photon emission CT and stereo-EEG case reports.
- Neurophysiological and neuroimaging studies in people with DOAs have provided evidence of abnormal brain function not only during slow-wave sleep but also during REM sleep and wakefulness.
- Research in the field is currently hindered by the commonly held view of DOAs as benign conditions and by a lack of animal models, strong neurobiological hypotheses and clear pharmacological target symptoms.
- Collaborative networks need to be established to promote the development of objective diagnostic criteria and evidence-based clinical practice guidelines and to facilitate controlled pharmacological studies and multidisciplinary research.

Slow-wave sleep

(SWS). The deepest stage of non-rapid eye movement sleep, characterized by synchronized EEG activity producing high-amplitude slow waves with a frequency range of 0.5–4.0 Hz.

Local sleep

Refers to evidence that sleep can occur locally and asynchronously across brain regions, and that local sleep-like and wake-like activities can coexist in different brain areas at the same time.

pathophysiological alteration. Most — but not all — DOA episodes arise during the first 3 h of the night from sudden but incomplete arousal out of SWS (80% of cases) or stage 2 sleep (20% of cases)⁷. Although sleep macroarchitecture is largely preserved^{8,9}, DOAs are associated with subtle alterations of NREM sleep, which are evident at the microstructural level.

Confusional arousals, sleep terrors and sleepwalking have traditionally been classified as DOAs¹⁰, but recent conceptualizations indicate a crucial role for SWS and local sleep abnormalities in these conditions. Whether slow waves have a primary causal role in DOAs or whether they are part of a specific cortical reaction to abnormal arousal processes is still a matter of debate. Human sleep is considered to be a global process orchestrated by central specialized neuronal networks that modulate whole-brain activity; however, some studies point to local regulation of sleep, whereby features of sleep and wakefulness can exist simultaneously in different cerebral regions, especially during DOA manifestations^{11,12}. As we discuss in this Review, DOAs provide a good model to demonstrate that sleep and wakefulness are not mutually exclusive, that sleep is not necessarily a global brain phenomenon, and that dissociated (wake-like and sleep-like) electrophysiological behaviours coexist within the sleeping brain.

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Clinical features

Confusional arousal, sleepwalking and sleep terror are prototypical behavioural patterns of NREM parasomnias, and they probably represent a hierarchical continuum rather than distinct entities¹³. Although one of the patterns might predominate, most sleepwalkers also experience sleep terrors and confusional arousals^{5,13}, and considerable familial aggregation exists between sleepwalking and sleep terrors¹⁴, suggesting that they represent two different clinical manifestations of the same pathophysiological entity (FIG. 1).

Confusional arousal episodes occur when the patient is in bed. The individual often sits up in bed and looks around in a confused manner. Somniloquy (sleep-talking), with slow speech and blunted responses to questions, is frequently observed during confusional arousals. Sleepwalking typically begins as confusional arousal but can also start abruptly, and the patient might exhibit inappropriate behaviours, such as climbing out a window or urinating in a wastebasket, after leaving the bed. The ambulation may end spontaneously in an inappropriate place, or the individual might return to bed to continue sleeping without reaching conscious awareness at any point¹. Sleep terror episodes are accompanied by behavioural manifestations of intense fear, frightening screams and strong autonomic nervous system activation. The individual sits up in bed, unresponsive to external stimuli, with intense tachycardia, tachypnoea, mydriasis, increased muscular tone and sometimes incoherent vocalizations. In a clinical population, self-injurious and aggressive behaviours to others, with potential legal and forensic implications, were reported by almost half of patients with DOAs and were especially prevalent in men with sleep terror¹⁵.

Sleep-related sexual behaviours and SRED are two NREM parasomnia phenotypes that are frequently associated with confusional arousal, sleep terror and sleepwalking^{16,17}. Sexsomnia can include prolonged masturbation, sexual assaults and/or loud sexual vocalization during sleep, followed by amnesia¹⁸. SRED is defined as recurrent episodes of dysfunctional involuntary eating or drinking that occur after arousal during sleep. The individual exhibits diminished levels of consciousness and impaired recall of the events¹.

In rare cases, DOAs occur together with RBD in a parasomnia overlap disorder that complicates the final diagnosis^{19,20}. This condition has been reported to be associated with synucleinopathies^{21–26} but can be idiopathic, and is also observed in some rare conditions, such as narcolepsy²⁷, pontine and medullary lesions²⁸, Machado–Joseph disease²⁹ and Creutzfeldt–Jakob disease³⁰. Clinicians should be aware of the existence of parasomnia overlap disorder, and patients with REM or NREM parasomnia should be assessed for symptoms of other parasomnias.

During DOA episodes, the individual is disoriented in time and space, with diminished mentation, memory impairment and altered external perception. Awakening a person from a parasomnia episode is usually difficult and, once awakened, the individual often displays confusion and disorientation, frequently experiencing amnesia of the events. The ICS-3 and *Diagnostic and*

Box 1 | ICSD-3 criteria for NREM-related parasomnias

The *International Classification of Sleep Disorders, Third Edition*¹ (ICSD-3) describes two types of non-rapid eye movement (NREM) parasomnia: disorders of arousal (DOAs) and sleep-related eating disorder. The criteria for DOAs are as follows:

- Recurrent episodes of incomplete awakening from sleep
 - The events usually occur during the first third of the major sleep episode
 - The individual may continue to appear confused and disoriented for several minutes or longer following the episode
- Inappropriate or absent responsiveness to efforts of others to intervene or redirect the person during the episode
- Limited (for example, a single visual scene) or no associated cognition or dream imagery
- Partial or complete amnesia for the episode
- The disturbance is not better explained by another sleep disorder, mental disorder, medical condition, medication or substance abuse

Subtypes:

- Sleep terror
- Sleepwalking
- Confusional arousal

Sleep-related abnormal sexual behaviours is a clinical subtype of confusional arousals.

Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classifications^{1,31} consider amnesia to be a basic criterion for DOAs¹ (BOXES. 1,2). Early studies with small numbers of participants often reported complete amnesia after spontaneous awakening from the nocturnal episodes^{8,32} or the following morning^{33,34}. However, subsequent studies revealed that when patients were actively probed, they often reported vague recollections of — usually emotionally charged — actions, with mentation involving perceptual, cognitive and affective dimensions, at least after the most complex and agitated episodes of sleep terror and sleepwalking^{35–41}. The phenomena described by the patients seemed to be motivated by an intrinsic sense of emergency or underlying logic and corresponded to the observed behaviours, albeit with less aggressive content than in RBD^{35–37,40}.

Owing to their retrospective nature, these studies do not provide an accurate estimate of the incidence of recall⁴². Moreover, the available data refer almost exclusively to adult samples, and in clinical practice it is commonly acknowledged that the mental content of DOA episodes is less frequently reported by children than by adults. This phenomenon parallels the gradual development of dream imagery and cognitive abilities in children, and the less frequent reports of dreaming in young children than in adults⁴³.

Interestingly, a DOA subtype known as ‘violent somnambulism’ has been described, with ‘claustrophobic’ dream-like experiences and complex vehement dream enactments, in the absence of REM sleep without atonia on polysomnography^{44–46}. Taken together, the literature challenges the classic view of DOAs as amnesic, non-dreaming states. The observations support efforts to overturn the traditional view of rigidly demarcated global sleep stages¹², prompted partly by the discovery of high dream recall rates from awakenings out of NREM sleep, which suggests that localized areas of the brain behave as in ‘covert REM sleep’⁴⁷.

Cyclic alternating pattern (CAP). An EEG marker of arousal fluctuations of non-rapid eye movement sleep.

Slow-wave activity (SWA). A quantitative measure of non-rapid eye movement sleep intensity and dynamics that is based on spectral analysis of the slow waves.

Physiological measurements

Polysomnography. Video-polysomnography (vPSG) is currently considered to be of limited value in differentiating patients with DOAs from normal sleepers and is not indicated for the routine evaluation of NREM sleep parasomnia. At present, vPSG is performed only to rule out differential diagnoses, including RBD, sleep-related epilepsy and sleep-related dissociative (psychiatric) disorders, and to assess other potentially associated sleep disorders, such as obstructive sleep apnoea syndrome, which can also coexist with DOAs^{48,49}.

The overall sleep architecture is usually preserved in adults and children with DOAs⁵⁰. Case-control studies consistently found increased awakenings, arousals and/or microarousals from SWS in patients with DOAs compared with healthy controls^{16,39,51–58} (FIG. 1). Excessive SWS fragmentation might, therefore, represent a typical microstructural feature of NREM sleep in DOAs and could have a role in the triggering of abnormal motor episodes.

The literature regarding the polysomnographic characteristics of sexomnia and SRED is scarce. In many published cases of SRED, the eating episodes emerged from stage 2 NREM sleep instead of SWS. A systematic study of SRED and sleepwalking in adults suggested that these two parasomnias share several sleep architecture characteristics and frequently co-occur¹⁶. Sleep-related abnormal sexual behaviours often emerge from SWS^{59,60}, and a case-control study showed that individuals with sexomnia have similar rates of awakening from SWS as sleepwalkers¹⁷.

The cyclic alternating pattern (CAP) is a long-lasting periodic activity consisting of two alternating NREM sleep EEG patterns — A (phasic events, consisting of A1, A2 and A3 subtypes) and B (background rhythm) — that are related to arousal-level fluctuations⁶¹. CAP sequences reflect both the entire NREM sleep maintenance process and the fragmentation of NREM sleep. In a seminal study, patients who experienced sleepwalking or sleep terror showed an increased CAP rate, shorter B phases, a lower mean power of A phases and an increased percentage of A1 phases compared with controls⁹. An increase in CAP rate was also observed in pre-pubertal chronic sleepwalkers, with or without sleep-related respiratory disturbances, even on nights without sleepwalking episodes^{62,63}. These results suggested that a distinctive feature of DOAs is the abrupt and more frequent intrusion of the brief A phases of CAP during B phases, disrupting the homeostatic process that would be mediated by slow-wave activity (SWA).

The presence of hypersynchronous delta wave (HSD) activity, defined as several continuous high-voltage ($\geq 150 \mu\text{V}$) delta waves occurring during NREM sleep, was the first EEG marker to be described in relation to sleepwalking⁷ (FIGS. 1,2). Irrespective of behavioural episodes, sleepwalkers have significantly more HSD activity than controls⁶⁴. However, HSDs have relatively low specificity for the diagnosis of DOA as they have also been found in healthy controls, especially after sleep deprivation^{51,53,64–66}, and in individuals with sleep-disordered breathing⁶⁷. A systematic analysis of the electrophysiological events surrounding behavioural and non-behavioural SWS

Box 2 | DSM-5 criteria for NREM sleep arousal disorders

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*³¹ (DSM-5) defines non-rapid eye movement (NREM) sleep arousal disorders as follows:

- Recurrent episodes of incomplete awakening from sleep, usually occurring during the first third of the major sleep episode, accompanied by either one of the following:
 - 1. Sleepwalking³: repeated episodes of rising from bed during sleep and walking about. While sleeping, the individual has a blank, staring face, is relatively unresponsive to the efforts of others to communicate with him or her, and can be awakened only with great difficulty
 - 2. Sleep terrors: recurrent episodes of abrupt terror arousals from sleep, usually beginning with a panicky scream. There is intense fear and signs of autonomic arousal, such as mydriasis, tachycardia, rapid breathing, and sweating, during each episode. There is relative unresponsiveness to efforts of others to comfort the individual during the episodes
- No or little (for example, only a single visual scene) dream imagery is recalled
- Amnesia for the episodes is present
- The episodes cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- The disturbance is not attributable to the physiological effects of a substance (for example, a drug of abuse, or a medication)
- Coexisting mental and medical disorders do not explain the episodes of sleepwalking or sleep terrors

³Includes subtypes with sleep-related eating or sleep-related abnormal sexual behaviour.

arousals revealed the existence of three different post-arousal EEG patterns⁵²: diffuse, rhythmic delta activity; diffuse delta and theta activity intermixed with alpha and beta activity; and prominent alpha and beta activity. This pattern analysis was subsequently confirmed by a study that specifically addressed behavioural arousals, either spontaneous or induced by sleep deprivation⁶⁸. Slow delta activity was detected in almost 50% of all episodes that arose from SWS and in approximately 20% of episodes that arose from stage 2 NREM. Furthermore, the slow EEG activity was more likely to accompany simple than complex parasomnia episodes⁶⁸.

Some studies have attempted to provide a better video-based characterization and definition of parasomnia episodes during routine polysomnography. The severity of episodes was evaluated according to the different motor patterns^{55,68}. Episodes were classified as simple (for example, resting or turning on one's hands), complex behaviours (for example, attempting to leave the bed), and ambulation. Another study proposed an alternative classification based on three motor patterns — simple arousal movements, arising arousal movements and complex arousal movements — but unfortunately did not provide a clear definition that distinguished parasomnia episodes from normal sleep-related movements⁶⁹.

A recent paper has proposed the first vPSG-based criteria for the diagnosis of DOA in adults, based on quantification of the SWS interruptions (SWS fragmentation index (SWSFI)), the post-arousal EEG pattern (fast and slow/mixed arousal indices) and the nature of the associated motor behaviours⁵⁸. This study identified cut-offs for the SWSFI and slow/mixed arousal index, leading to correct classification rates of 73.3–85.3%, with sensitivity up to 94% and specificity up to 100%. The inclusion of parasomnia episodes recorded by vPSG increased the classification rate to 91.3%.

Autonomic activity. Although arousal fluctuations are well known to be disrupted in DOAs, the autonomic nervous system has been poorly investigated in this context. A study published in 1974 found that sleep terror episodes were associated with intense autonomic discharge, with rapid doubling or even tripling of the heart rate and a large increase in respiratory amplitude, along with a marked decrease in skin resistance⁷⁰, with, in the words of the authors, “no gradual build-up”. Another study assessed heart rate before and after behavioural and non-behavioural arousals from SWS in patients with sleepwalking and sleep terror⁵². The authors noted that heart rate acceleration emerged abruptly with SWS arousals, and mean pre-arousal and post-arousal heart rates differed significantly. Spectral analysis of heart rate variability revealed an increase in total power during the 5 min preceding sleepwalking episodes, indicating a shift in the sympathovagal balance in favour of sympathetic activity⁷¹.

Quantitative EEG. Abnormalities in SWA have been repeatedly reported in DOAs. These abnormalities consist of a decrease in SWA power over the central leads, mainly confined to the first cycle, as well as an abnormal temporal course of SWA^{53,72}. An exponential decay in SWA was observed in both patients and controls, but the time constant of the curve was significantly slower in patients than in controls. A significant decrease in the number of sleep spindles during the first cycle of sleep, especially in SWS, was found in sleepwalkers compared with controls, possibly reflecting alterations in the sleep maintenance process⁵³.

A study employing high-density EEG, which allows accurate assessment of the topographical distribution of EEG activity and waveforms across the entire scalp, revealed that the decrease in SWA power was not global and was localized over the centroparietal regions⁷³. Source localization pointed mainly to involvement of the motor, premotor and cingulate areas⁷³. The same study showed that these changes in SWA topography were also present during REM sleep and wakefulness. A low-density EEG study found an increase in the beta frequency range (24–30 Hz) in Brodmann areas 33 and 24 (pregenual and ventral anterior cingulate cortex) during the 4 s preceding the onset of sleepwalking episodes⁷⁴.

An increase in SWA before complex behavioural arousal has often been reported, although the timing of the SWA increase is open to debate^{53,66,75}. Increases in SWA and slow oscillation density were found in the run-up to sleepwalking episodes compared with non-behavioural awakenings in the same group of sleepwalkers⁷⁶. A spectral analysis study confirmed the coexistence of arousal and deep sleep in the 20 s immediately preceding the onset of behavioural episodes as compared with a 20 s period 2 min before the episodes⁷⁷. Using 19 EEG scalp electrodes, the researchers observed decreased functional local connectivity for lower-frequency bands (delta) in parietal and occipital regions, together with increased connectivity for higher-frequency bands (alpha and beta) in the large-scale frontoparietal networks, in the 20 s preceding a sleepwalking episode.

Sleep spindles

Short bursts of neural oscillatory activity that are generated by thalamic nuclei during stage 2 non-rapid eye movement sleep.

Stereo-EEG. Stereo-EEG has provided valuable information on the areas involved during DOA episodes^{78–81}. However, the data were derived from case reports in patients with epilepsy who were candidates for surgery, and the number and placement of electrodes were

constrained by the localization of the epileptogenic focus. In contrast to other techniques such as PET, single-photon emission CT (SPECT) and MRI, EEG offers a unique opportunity to image the brain with exquisite temporal resolution throughout the sleep period.

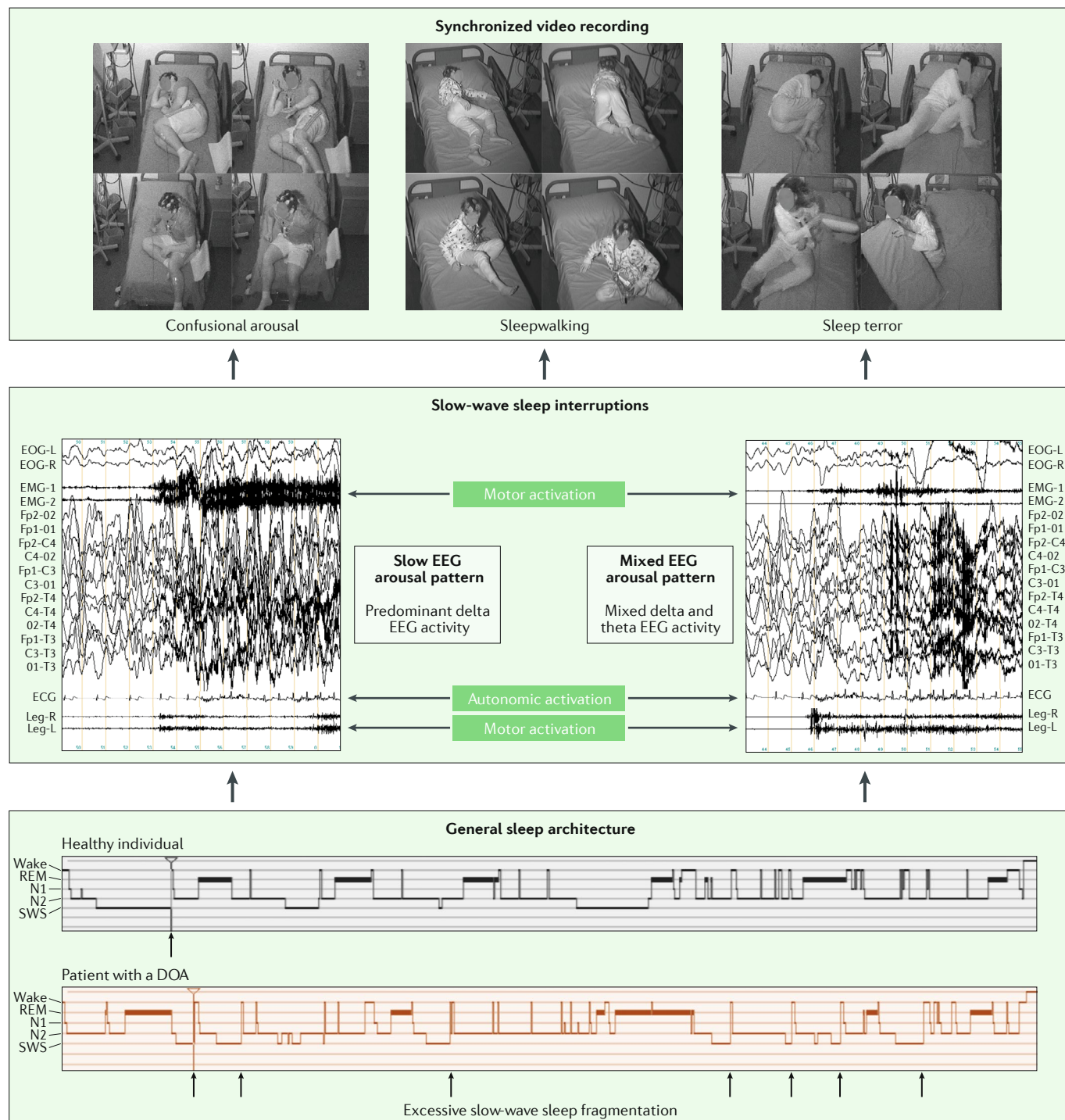


Fig. 1 | Video-polysomnographic characteristics of disorders of arousal. The sleep macroarchitecture in disorders of arousal (DOAs) reveals excessive slow-wave sleep (SWS) fragmentation (SWS interruptions are indicated by arrows in the bottom box). The frequent arousals from SWS are often associated with persistent slow or mixed sleep EEG activity with motor and autonomic activations, as shown in the middle box. These SWS interruptions can be accompanied by complex behavioural manifestations, defined as sleepwalking, confusional arousal and sleep terror episodes, as illustrated in the top box. ECG, electrocardiogram; EMG, electromyogram; EOG, electro-oculogram; N1, stage 1 NREM sleep; N2, stage 2 NREM sleep; NREM, non-rapid eye movement; REM, rapid eye movement.

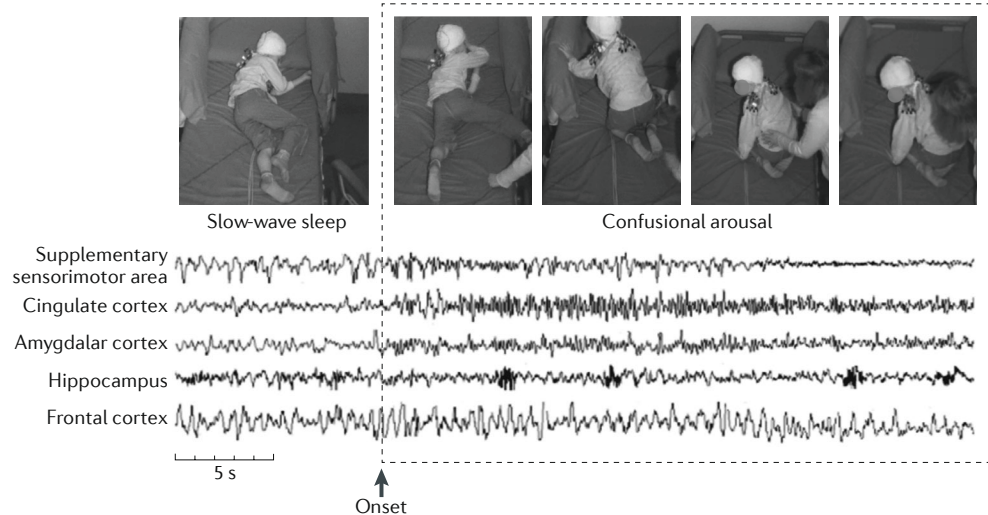


Fig. 2 | **Stereo-EEG recording in a disorder of arousal.** Coexistence of local non-rapid eye movement (NREM) sleep-like and wake-like patterns captured by stereo-EEG during a confusional arousal (only the first 30 s are represented). During the episode, the individual sits up in bed, utters unintelligible words, is confused and fails to answer questions posed by his mother and a technician. The EEG activity suddenly changes at the onset of the confusional arousal from typical NREM sleep activity to wake-like activity in the supplementary sensorimotor area and the cingulate and amygdalar cortices. By contrast, during the confusional arousal, the EEG activity recorded from the hippocampus and the frontal cortex remains identical to the activity observed in slow-wave sleep. Figure adapted with permission from REF.⁷⁸, John Wiley & Sons.

Stereo-EEG case studies of two children and one young adult (aged 7, 17 and 20 years)^{78–80} showed the coexistence of sleep-like patterns — for example, increased or persistent bursts of sleep-like delta waves over frontoparietal associative networks and spindles in the hippocampus — and wake-like patterns characterized by low-voltage fast activity over the motor cortex and limbic structures, such as the cingulate cortex (frontal and central cingulate gyrus), insular cortex, temporo-parietal cortices and amygdala (FIGS. 2,3). The frequent emotional activation and amnesia for parasomnias could derive, respectively, from the activation of the limbic system disengaged from the prefrontal cortex and the parallel deactivation of the frontal associative and hippocampal cortices during sleepwalking episodes. During a DOA episode, EEG activity within the ventromedial portion of the thalamus showed a slight decrease in delta power and a clear-cut emergence of beta activity, similar in frequency and amplitude to the thalamic activity recorded during wakefulness⁸⁰.

Although the general pattern of sleep-like and wake-like EEG activity — over frontal and limbic regions, respectively — is similar across DOA episodes, individual episodes with diverse clinical features are likely to involve slightly different sets of brain areas. In one of the cases mentioned above⁷⁸, a dissociated EEG pattern similar to the one observed during a nocturnal clinical episode frequently occurred in the absence of any detectable clinical manifestations. It remains unclear whether these phenomena differ from the local NREM sleep activations in the motor cortex with persistence of deep-sleep EEG patterns in the prefrontal cortex that have been observed during normal sleep¹¹. If the local dissociated electrophysiological state is actually an intrinsic feature of NREM sleep, DOAs might represent

an exaggeration of the natural tendency of these local networks to exhibit a reduced arousal threshold^{11,12}.

These physiological dissociated states during sleep could imply an adaptive role for this phenomenon. For instance, the coexistence of wake-like and sleep-like EEG patterns allows birds and dolphins to continue flying or swimming during sleep. In humans, a reduced arousal threshold in the motor cortex during NREM sleep might have been selected during evolution because it enables a prompt motor response in life-threatening situations. This state-dissociation hypothesis may also help us to interpret the alteration of consciousness during DOA episodes. Similar to sleep and wakefulness, consciousness has fluid boundaries, and the fluctuations in the level of consciousness that are observed during DOA episodes could relate to abnormalities of the spatial and temporal connectivity within different cortical areas that normally results in a united conscious experience⁸².

Neuroimaging

The literature on neuroimaging in DOAs is limited. A morphometric study revealed a significant decrease in grey matter volume in the left dorsal posterior cingulate and midcingulate cortices in patients with DOAs compared with a control group⁸³. A landmark SPECT case study found local changes in brain activity during a behavioural episode, with the highest increase in regional cerebral blood flow being observed in the anterior cerebellum and posterior cingulate cortex during sleepwalking, in comparison with quiet SWS preceding the episode⁸⁴. By contrast, large areas of frontal and parietal association cortices remained deactivated compared with data obtained from 24 normal volunteers during wakefulness. This result is consistent with the dissociated pattern, characterized by simultaneous existence of

Stereo-EEG

The practice of recording EEG signals via invasive electrodes surgically implanted into the brain tissue in presurgical, treatment-resistant patients with epilepsy.

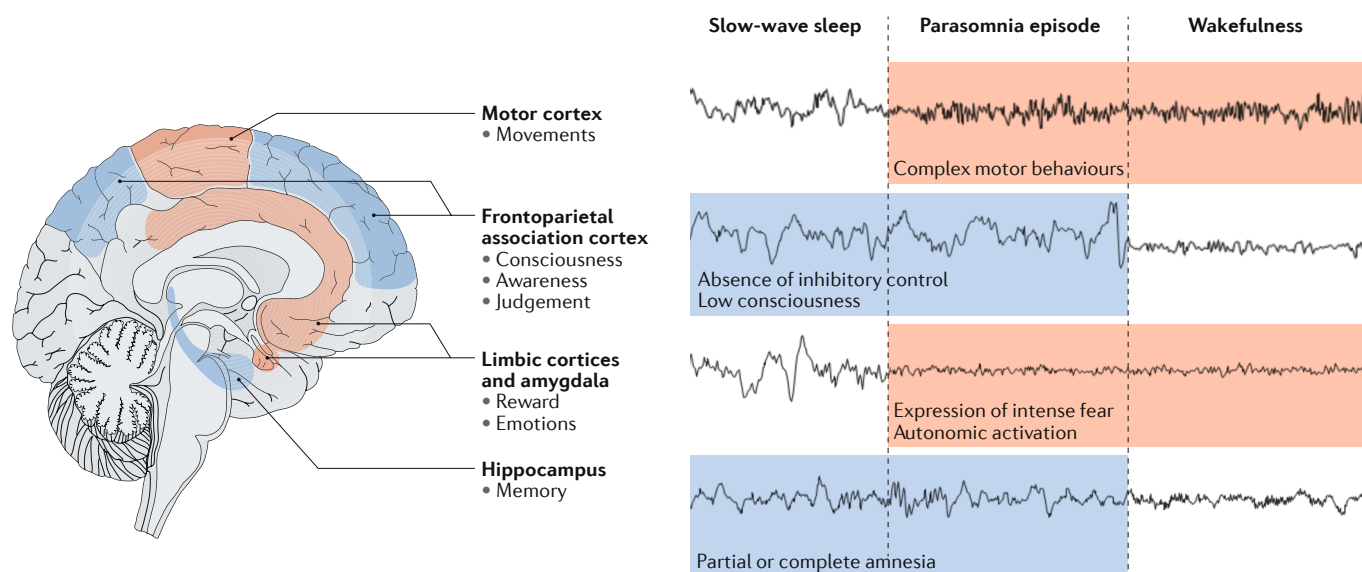


Fig. 3 | **Sleep-wake dissociation in disorders of arousal.** The coexistence of non-rapid eye movement sleep-like patterns in the frontoparietal associative cortices and hippocampus (blue shading) and wake-like patterns in the motor cortex and limbic structures (red shading) might underlie behavioural and cognitive dissociation during parasomnia episodes.

sleep-like and wake-like activities over targeted regions, that was observed in stereo-EEG studies. However, the correlations between brain activity and the range of the different behaviours shown by individuals during sleepwalking episodes remain unknown.

A recent study showed reduced cerebral blood flow in prefrontal and insular regions during SWS after recovery from 24 h sleep deprivation in sleepwalkers compared with controls⁸⁵. Another SPECT study showed a change in metabolism in the inferior temporal cortex bilaterally after sleep deprivation, but not at baseline, in sleepwalkers compared with controls⁸⁶.

Daytime functioning

Despite the well-known SWS instability in DOAs, relatively little attention has been devoted to the potential consequences of these parasomnias on daytime functioning. A series of studies supports the notion that around 40% of individuals with DOAs have excessive daytime sleepiness (EDS)^{3,5,39,56,73,87–90}. Objective EDS was found in one small study of 10 sleepwalkers, which used the Multiple Sleep Latency Test (MSLT)⁸⁷, but this result was not replicated in a subsequent larger study on a sample of 30 patients with sleepwalking and sleep terror⁵⁶. The latter study did, however, find reduced sleep latencies in the first two of five MSLT trials. To our knowledge, no study has assessed subjective or objective EDS in children with DOAs. The EDS reported by adult sleepwalkers does not seem to be explained by the presence of concomitant sleep disorders, SWS fragmentation or the frequency of episodes^{5,56,73,88}. Together, these findings suggest that EDS is an intrinsic feature of the DOA phenotype.

Few studies have investigated cognitive performance in individuals with DOAs. In a large case-control study⁵, patients with DOAs reported increased levels of cognitive fatigue, and preliminary findings suggest that

individuals with these conditions exhibit impairments in visuospatial working memory and selective visual attention⁹¹. By contrast, no deficits in executive functioning or verbal memory consolidation were detected in patients with DOAs in two other controlled studies^{57,89}. Furthermore, neuropsychological performance did not correlate with measures of subjective daytime sleepiness or sleep fragmentation^{57,89}. In sleepwalkers, significant impairments in executive functions related to inhibitory control were found after 25 h of sleep deprivation^{57,89}.

DOAs were initially linked to psychiatric disorders⁴, as supported by epidemiological studies⁹². A history of depression and anxiety might be more frequent in adults with DOAs than in controls, but no direct relationship seems to exist between the conditions⁵. The cause-consequence relationship between psychiatric disorders and DOA is still being debated. Severe and injurious parasomnias can cause substantial distress, thereby predisposing the individual to depressive or anxiety disorders. In turn, such psychiatric disorders can cause severe sleep-onset insomnia and sleep fragmentation and, as a consequence, chronic sleep deprivation. These events, combined with the need for psychotropic medications, represent potential priming factors for DOAs. However, treatments for comorbid psychiatric disorders do not seem to influence the clinical presentation and frequency of DOA episodes⁹³.

Neurobiology

The field of basic research in DOAs is extremely sparse owing to a lack of available animal models and strong neurobiological hypotheses. Some experts have proposed that NREM sleep parasomnias are exclusive to humans, as no spontaneous episodes have been reported in animals, even nonhuman primates⁹⁴. However, one experimental study revealed that microinjections of serotonin into the cholinergic basal ganglia neurons of rats

LOD score

The LOD score is a statistical test often used for genetic linkage analyses. It compares the likelihood of two loci actually being linked against the likelihood of observing this result purely by chance.

during sleep resulted in a behavioural awake state associated with high EEG delta activity — a dissociated state that resembled sleepwalking⁹⁵. Several clinical findings implicate serotonergic pathways in the pathophysiology of DOAs⁹⁶. A high frequency of sleepwalking was found among patients with migraine, a condition that is associated with altered serotonergic regulation^{97–101}. Conversely, sleepwalking was associated with an increased risk of migraine¹⁵. The use of serotonergic medications such as paroxetine, olanzapine or lithium might trigger sleepwalking episodes^{102–106}.

A transcranial magnetic stimulation study in sleepwalkers during wakefulness found reduced efficiency of inhibitory circuits at the level of the motor cortex, indicating that GABAergic transmission is impaired in DOAs¹⁰⁷. GABA is a good candidate to explain the potential impaired efficiency of inhibitory subcortical circuits during parasomnia as it constitutes an important inhibitory neurotransmitter with key roles in NREM sleep processing^{108,109} and regulation of nociception^{110,111}. Of interest, one study suggested a relationship between dissociated brain activity in sleepwalking and nociceptive dysregulation, with a high frequency of chronic pain during wakefulness together with frequent analgesia during severe parasomnia episodes¹⁵. Furthermore, the GABA_B agonist sodium oxybate is known to strongly increase SWS and to frequently induce parasomnia episodes in patients with narcolepsy^{112,113}.

A familial basis for DOAs is recognized in up to 60% of cases, although the mode of transmission is unclear^{1,5,33}. The probability of childhood sleepwalking increases with the number of affected parents, with incidences of 22% when both parents are unaffected, 45% when one parent has a DOA and 60% when both parents are affected¹⁴. Twin studies have shown a five-fold higher concordance for sleepwalking in monozygotic than in dizygotic twins¹¹⁴. However, only a few studies have been conducted to identify genes that predispose individuals to DOA. A high frequency of the *HLA-DQB1*05:01* allele was found in a clinical sample of 60 adult and child sleepwalkers¹¹⁵. Furthermore, excessive transmission of *HLA-DQB1*05* and

*HLA-DQB1*04* was observed in familial cases. These results were recently confirmed, with an increased frequency of *HLA-DQB1*05:01* in adults with sleepwalking and sleep terror¹¹⁶. A pangenomic study was conducted in a four-generation family in which DOAs segregated as a dominant condition with low penetrance¹¹⁷. The study included 22 members of the family, 9 of whom had DOAs. Linkage analysis for the DOA phenotype revealed a maximum LOD score for a chromosome 20q locus, but no coding gene mutations were identified in this multiplex family.

A pathophysiological model

DOAs seem to result from the co-occurrence of various predisposing, priming and precipitating factors — the so-called ‘3-P model’¹¹⁸(Fig. 4). DOAs are unlikely to occur in the absence of these factors; however, the model cannot account for fluctuations in parasomnia occurrence.

The predisposing factor is likely to relate to the genetic background. As detailed above, the familial aggregation of DOAs is thought to be explained by genetic susceptibility. The genetic contribution might be especially important in individuals in whom DOAs persist beyond adulthood.

Two types of priming factors have been identified. First, factors that deepen sleep, such as sleep deprivation^{5,39,115} and various substances, including Z-drugs^{119–122}, lithium^{102,103} and sodium oxybate^{123,124}, are frequently recognized by the patients themselves to increase the frequency of their episodes. Sleep deprivation also increases the complexity of the sleepwalking events observed in the laboratory so that they more closely resemble the episodes experienced in the home environment^{38,55,64,125,126}. Second, factors that are known to induce or increase sleep fragmentation might promote or trigger sleepwalking episodes. These factors include comorbid conditions (for example, obstructive sleep apnoeas, periodic leg movements, chronic pain, brain lesions or narcolepsy)^{8,32,70}, fever¹²⁷, late physical activity, strong positive emotions before sleep, stress, and anxiety⁵. Although many clinicians believe that stress and

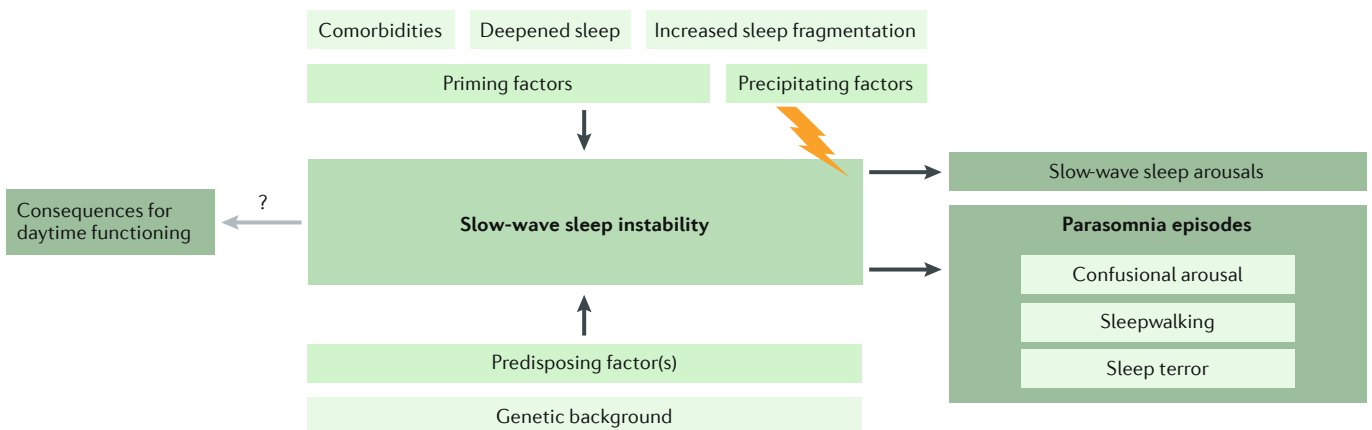


Fig. 4 | A pathophysiological model of disorders of arousal. A combination of predisposing and priming factors leads to increased slow-wave sleep instability that promotes the occurrence of disorder of arousal episodes, potentially triggered by precipitating factors.

anxiety promote NREM sleep parasomnias, the literature is scarce^{128–130}, and no study to date has systematically explored the relationship between perceived subjective stress and anxiety and the intensity and frequency of episodes of NREM sleep parasomnias. Alcohol has traditionally been considered as a priming factor, but controlled studies are lacking^{42,118}. Antidepressants have been associated with an increased risk of RBD in controlled studies, but evidence for a link with NREM sleep parasomnias is limited to case reports and case series¹³¹, and some antidepressants have even been proposed as therapies for specific subtypes of other parasomnias, such as nocturnal enuresis.

The precipitating factors are less recognized as they show considerable interindividual and intraindividual diversity. Sleepwalkers often report that they experience more frequent episodes when sleeping in unfamiliar places or during travel, suggesting a role for arousing external stimuli, such as noise or physical contact, in triggering parasomnia⁴². The role of external stimuli in triggering DOA episodes has been corroborated by laboratory studies^{8,32,41}. Some studies also suggested a role for internal stimuli such as subtle respiratory events or leg movements in triggering SWS interruptions^{53,93} and parasomnia episodes. However, the frequency of sleep apnoea syndrome or restless legs syndrome was not increased in a large clinic-based population of patients with DOAs as their primary complaint¹³². One study found that in a selected population of adults with non-comorbid DOA (that is, without frequent restless legs syndrome or severe apnoea–hypopnoea syndrome), most SWS interruptions were spontaneous, and they were triggered by respiratory events or movement in <2.5% of cases⁵⁸.

Experimental attempts to induce sleepwalking episodes with a combination of 25 h of sleep deprivation and forced arousals with auditory stimuli during SWS revealed that this procedure could induce parasomniac events in a substantial proportion of predisposed adults but not in controls³⁸.

Management

Though often benign, DOAs can place both the affected individual and people around them in great danger given the absence of conscious control, awareness and perceived pain during nocturnal behavioural episodes. Harmful consequences can ensue unexpectedly and with no forewarning in individuals with usually benign and nonviolent DOAs. As the number of DOA cases observed in specialized centres is low compared with the prevalence observed in epidemiological studies, an effort must be made to alert the general population and general practitioners to the need for adequate education, treatment and follow-up of these conditions.

First-line interventions include avoidance of priming factors (for example, sleep deprivation, sedative drug intake or emotional stimulation before sleep onset), environmental safety measures such as the use of door alarms, and advising the patient's sleeping partner to provide quiet guidance to get them back into bed^{133,134}. Therapeutic interventions are required when the DOA is associated with potential or documented violent

and injurious behaviours or substantial functional impairment such as daytime sleepiness, fatigue and distress. However, the management of DOA is poorly codified, and no controlled studies have been conducted to evaluate the efficacy of behavioural or pharmacological interventions¹³³. Application of scheduled awakenings showed positive results in child sleepwalkers in two case series^{135,136}. Scheduled awakening involves quietly waking the child ~0.5 h before they are most likely to experience a parasomnia episode. Parents are instructed to record their child's episodes using a sleep diary before, during and after the behavioural intervention. No data are available on the use of this method in adults with DOAs. Other non-pharmacological interventions such as hypnosis, relaxation and psychotherapy have been proposed for the treatment of DOAs^{137–141}, with controversial results¹⁴².

Benzodiazepines, in particular clonazepam, are frequently recommended as effective treatments for DOAs. Despite the widespread use of clonazepam as a first-line pharmacological agent in DOAs, only low-level evidence for its efficacy is available. In chart review studies, low doses of clonazepam (0.5–1.0 mg daily) alleviated DOA in 74–86% of adult patients^{4,143,144}. The use of various psychotropic drugs, including paroxetine, diazepam, carbamazepine, melatonin and melatonin agonists, has been reported in several case reports^{65,142,145–148}. As evidence is lacking for off-label use of pharmacological agents, clinicians might wish to ensure that patients are fully informed about all therapeutic options.

Conclusions and future perspectives

Until the past few years, clinical research in the context of DOAs was scarce. However, recent discoveries have added new dimensions to the concept of local sleep regulation and opened up new perspectives in the interpretation of the substrates that underlie abnormal behavioural states of vigilance, such as those that characterize DOAs¹⁴⁹. The general pattern of local sleep-like and wake-like activities over frontal and limbic regions, respectively, seems to be the hallmark of DOAs, although literature on the topic is still limited. We believe that a joint effort is now required to promote the creation of collaborative networks within the scientific community so as to facilitate the establishment of large databases and multidisciplinary research approaches.

The research will first need to add evidence to the intriguing local dissociated electrophysiological state model that we have described in this Review. The combination of provocative sleep-deprivation and/or sleep-fragmentation paradigms and new technological advances, such as high-density EEG and combined high-density EEG–MRI techniques, which can provide exquisite spatial and temporal resolution, is likely to contribute substantially to this effort. Further case–control studies to evaluate the sympathetic–parasympathetic balance during wakefulness and sleep should be conducted in both adults and children. Mental correlates and self-awareness during episodes will also need to be assessed in parallel, given the unique window that DOAs open to the study of consciousness and the clear forensic implications of this line of research.

Another important step is to investigate the mechanisms underlying DOAs in both children and adults. The natural course of DOAs is still unknown, and we cannot yet predict whether a DOA in any given child will resolve in adulthood or whether it will persist or even reappear after many asymptomatic years. Genome-wide association or exome-sequencing studies, using a case-control design or involving large multiplex families, need to be conducted to identify common genetic variants that are associated with DOAs. DOAs should be amenable to these approaches given their high frequency in both children and adults. In addition, some genes implicated in sleep homeostasis and SWS are potential candidates for targeted analyses.

The lack of objective and quantitative diagnostic criteria for DOAs is a major issue that impedes the development of collaborative clinical and research studies with good quality standards. A recent proposal for a

new polysomnography-based scoring method offers a potential opportunity to identify relevant DOA biomarkers⁵⁸. For this scoring method to be included in the next revision of the ICSID, further studies will be needed to determine its efficiency for discriminating DOAs from other sleep-related abnormal behaviours.

The development of valid and objective criteria could also be important in the context of forensic sleep medicine. However, experts must keep in mind that such criteria would identify individuals at high risk of DOAs but should not be used to establish or refute the occurrence of a parasomnia episode at the time of a criminal act^{150–152}. Finally, controlled treatment trials are required to improve clinical management, especially for complex and severe cases, to enable the formulation and implementation of evidence-based guidelines for clinical practice.

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1. American Academy of Sleep Medicine. *The International Classification of Sleep Disorders — Third Edition* (American Academy of Sleep Medicine, 2014).
2. Stallman, H. M. & Kohler, M. Prevalence of sleepwalking: a systematic review and meta-analysis. *PLoS ONE* **11**, e0164769 (2016).
3. Ohayon, M. M., Mahowald, M. W., Dauvilliers, Y., Krystal, A. D. & Léger, D. Prevalence and comorbidity of nocturnal wandering in the U. S. adult general population. *Neurology* **78**, 1583–1589 (2012).
4. Schenck, C. H., Milner, D. M., Hurwitz, T. D., Bundlie, S. R. & Mahowald, M. W. A polysomnographic and clinical report on sleep-related injury in 100 adult patients. *Am. J. Psychiatry* **146**, 1166–1173 (1989).
5. Lopez, R. et al. Functional impairment in adult sleepwalkers: a case-control study. *Sleep* **36**, 345–351 (2013).
This large case-control study on the functional consequences of sleepwalking shows a high frequency of fatigue, sleepiness and altered quality of life in individuals with this condition.
6. Bargiotas, P. et al. Demographic, clinical and polysomnographic characteristics of childhood- and adult-onset sleepwalking in adults. *Eur. Neurol.* **78**, 307–311 (2017).
7. Jacobson, A., Kales, A., Lehmann, D. & Zweizig, J. R. Somnambulism: all-night electroencephalographic studies. *Science* **148**, 975–977 (1965).
This milestone study was the first to describe the EEG characteristics of sleepwalking.
8. Jacobson, A. & Kales, A. Somnambulism: all-night EEG and related studies. *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* **45**, 424–455 (1967).
9. Zucconi, M., Oldani, A., Ferini-Strambi, L. & Smirne, S. Arousal fluctuations in non-rapid eye movement parasomnias: the role of cyclic alternating pattern as a measure of sleep instability. *J. Clin. Neurophysiol.* **12**, 147–154 (1995).
10. Broughton, R. J. Sleep disorders: disorders of arousal? Enuresis, somnambulism, and nightmares occur in confusional states of arousal, not in “dreaming sleep”. *Science* **159**, 1070–1078 (1968).
11. Nobili, L. et al. Dissociated wake-like and sleep-like electro-cortical activity during sleep. *Neuroimage* **58**, 612–619 (2011).
12. Nobili, L. et al. Local aspects of sleep: observations from intracerebral recordings in humans. *Prog. Brain Res.* **199**, 219–232 (2012).
13. Derry, C. P., Harvey, A. S., Walker, M. C., Duncan, J. S. & Berkovic, S. F. NREM arousal parasomnias and their distinction from nocturnal frontal lobe epilepsy: a video EEG analysis. *Sleep* **32**, 1637–1644 (2009).
14. Petit, D. et al. Childhood sleepwalking and sleep terrors: a longitudinal study of prevalence and familial aggregation. *JAMA Pediatr.* **169**, 653–658 (2015).
This large epidemiological study confirms the high prevalence of DOAs during childhood and the strong familial aggregation of sleepwalking and sleep terrors.
15. Lopez, R., Jausse, I. & Dauvilliers, Y. Pain in sleepwalking: a clinical enigma. *Sleep* **38**, 1693–1698 (2015).
16. Brion, A. et al. Sleep-related eating disorder versus sleepwalking: a controlled study. *Sleep Med.* **13**, 1094–1101 (2012).
17. Dubessy, A. L., Leu-Semenescu, S., Attali, V., Maranci, J. B. & Arnulf, I. Sexsomnia: a specialized non-REM parasomnia? *Sleep* **40**, zsw043 (2017).
18. Schenck, C. H., Arnulf, I. & Mahowald, M. W. Sleep and sex: what can go wrong? A review of the literature on sleep related disorders and abnormal sexual behaviors and experiences. *Sleep* **30**, 683–702 (2007).
19. Schenck, C. H., Boyd, J. L. & Mahowald, M. W. A parasomnia overlap disorder involving sleepwalking, sleep terrors, and REM sleep behavior disorder in 33 polysomnographically confirmed cases. *Sleep* **20**, 972–981 (1997).
20. Dumitrascu, O., Schenck, C. H., Applebee, G. & Attarian, H. Parasomnia overlap disorder: a distinct pathophysiologic entity or a variant of rapid eye movement sleep behavior disorder? A case series. *Sleep Med.* **14**, 1217–1220 (2013).
21. Comella, C. L., Nardine, T. M., Diederich, N. J. & Stebbins, G. T. Sleep-related violence, injury, and REM sleep behavior disorder in Parkinson’s disease. *Neurology* **51**, 526–529 (1998).
22. Ondo, W. G. et al. Daytime sleepiness and other sleep disorders in Parkinson’s disease. *Neurology* **57**, 1392–1396 (2001).
23. Tan, E. K. et al. Evaluation of somnolence in Parkinson’s disease: comparison with age- and sex-matched controls. *Neurology* **58**, 465–468 (2002).
24. Poryazova, R., Waldvogel, D. & Bassetti, C. L. Sleepwalking in patients with Parkinson disease. *Arch. Neurol.* **64**, 1524–1527 (2007).
25. Oberholzer, M., Poryazova, R. & Bassetti, C. L. Sleepwalking in Parkinson’s disease: a questionnaire-based survey. *J. Neurol.* **258**, 1261–1267 (2011).
26. Di Fabio, N., Poryazova, R., Oberholzer, M., Baumann, C. R. & Bassetti, C. L. Sleepwalking, REM sleep behaviour disorder and overlap parasomnia in patients with Parkinson’s disease. *Eur. Neurol.* **70**, 297–303 (2013).
27. Dauvilliers, Y., Arnulf, I. & Mignot, E. Narcolepsy with cataplexy. *Lancet* **369**, 499–511 (2007).
28. Limousin, N. et al. A brainstem inflammatory lesion causing REM sleep behavior disorder and sleepwalking (parasomnia overlap disorder). *Sleep Med.* **10**, 1059–1062 (2009).
29. Kushida, C. A., Clerk, A. A., Kirsch, C. M., Hotson, J. R. & Guilleminault, C. Prolonged confusion with nocturnal wandering arising from NREM and REM sleep: a case report. *Sleep* **18**, 757–764 (1995).
30. Puligheddu, M. et al. Overlap parasomnia disorder in a case of Creutzfeldt–Jakob disease. *Sleep Med.* **36**, 75–77 (2017).
31. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 5th edn (American Psychiatric Association, 2013).
32. Kales, A., Jacobson, A., Paulson, M. J., Kales, J. D. & Walter, R. D. Somnambulism: psychophysiological correlates. I. All-night EEG studies. *Arch. Gen. Psychiatry* **14**, 586–594 (1966).
33. Kales, A. et al. Somnambulism. Clinical characteristics and personality patterns. *Arch. Gen. Psychiatry* **37**, 1406–1410 (1980).
34. Kales, J. D. et al. Night terrors. Clinical characteristics and personality patterns. *Arch. Gen. Psychiatry* **37**, 1413–1417 (1980).
35. Guilleminault, C., Moscovitch, A. & Leger, D. Forensic sleep medicine: nocturnal wandering and violence. *Sleep* **18**, 740–748 (1995).
36. Oswald, I. & Evans, J. On serious violence during sleepwalking. *Br. J. Psychiatry* **147**, 688–691 (1985).
37. Pillmann, F. Complex dream-enacting behavior in sleepwalking. *Psychosom. Med.* **71**, 231–234 (2009).
38. Pilon, M., Montplaisir, J. & Zadra, A. Precipitating factors of somnambulism: impact of sleep deprivation and forced arousals. *Neurology* **70**, 2284–2290 (2008).
This study describes an experimental procedure to induce sleepwalking episodes in individuals with DOAs, using sleep deprivation and forced arousals with auditory stimuli during SWS.
39. Oudiette, D. et al. Dreamlike mentations during sleepwalking and sleep terrors in adults. *Sleep* **32**, 1621–1627 (2009).
40. Uguccioni, G. et al. Fight or flight? Dream content during sleepwalking/sleep terrors versus rapid eye movement sleep behavior disorder. *Sleep Med.* **14**, 391–398 (2013).
41. Fisher, C., Kahn, E., Edwards, A. & Davis, D. M. A psychophysiological study of nightmares and night terrors. I. Physiological aspects of the stage 4 night terror. *J. Nerv. Ment. Dis.* **157**, 75–98 (1973).
42. Pressman, M. R. Sleepwalking, amnesia, comorbid conditions and triggers: effects of recall and other methodological biases. *Sleep* **36**, 1757–1758 (2013).
43. Foulkes, D. *Children’s Dreaming and the Development of Consciousness* (Harvard Univ. Press, 1999).
44. Szu’cs, A. et al. Violent somnambulism: a parasomnia of young men with stereotyped dream-like experiences. *Med. Hypotheses* **83**, 47–52 (2014).
45. Bonkalo, A. Impulsive acts and confusional states during incomplete arousal from sleep: criminological and forensic implications. *Psychiatr. Q.* **48**, 400–409 (1974).
46. Mahowald, M. W., Schenck, C. H., Goldner, M., Bachelder, V. & Cramer-Bornemann, M. Parasomnia pseudo-suicide. *J. Forensic Sci.* **48**, 1158–1162 (2003).
47. Nielsen, T. A. A review of mentation in REM and NREM sleep: ‘covert’ REM sleep as a possible reconciliation of two opposing models. *Behav. Brain Sci.* **23**, 851–866 (2000).
48. Fois, C., Wright, M. A., Sechi, G., Walker, M. C. & Eriksson, S. H. The utility of polysomnography for the diagnosis of NREM parasomnias: an observational study over 4 years of clinical practice. *J. Neurol.* **262**, 385–393 (2015).
49. Aurora, R. N. et al. Practice parameters for the non-respiratory indications for polysomnography and multiple sleep latency testing for children. *Sleep* **35**, 1467–1473 (2012).

50. Zadra, A., Desautels, A., Petit, D. & Montplaisir, J. Somnambulism: clinical aspects and pathophysiological hypotheses. *Lancet Neurol.* **12**, 285–294 (2013).
This review addresses pathophysiological hypotheses and promising research perspectives in the field of DOAs.
51. Blatt, I., Peled, R., Gadoth, N. & Lavie, P. The value of sleep recording in evaluating somnambulism in young adults. *Electroencephalogr. Clin. Neurophysiol.* **78**, 407–412 (1991).
52. Schenck, C. H., Pareja, J. A., Patterson, A. L. & Mahowald, M. W. Analysis of polysomnographic events surrounding 252 slow-wave sleep arousals in thirty-eight adults with injurious sleepwalking and sleep terrors. *J. Clin. Neurophysiol.* **15**, 159–166 (1998).
This study provides the first EEG-based classification of SWS arousals and parasomnia episodes in DOAs.
53. Espá, F., Ondze, B., Deglise, P., Billiard, M. & Besset, A. Sleep architecture, slow wave activity, and sleep spindles in adult patients with sleepwalking and sleep terrors. *Clin. Neurophysiol.* **111**, 929–939 (2000).
54. Espá, F., Dauvilliers, Y., Ondze, B., Billiard, M. & Besset, A. Arousal reactions in sleepwalking and night terrors in adults: the role of respiratory events. *Sleep* **25**, 871–875 (2002).
55. Joncas, S., Zadra, A., Paquet, J. & Montplaisir, J. The value of sleep deprivation as a diagnostic tool in adult sleepwalkers. *Neurology* **58**, 936–940 (2002).
56. Lopez, R., Jaussent, I. & Dauvilliers, Y. Objective daytime sleepiness in patients with somnambulism or sleep terrors. *Neurology* **83**, 2070–2076 (2014).
57. Uguccioni, G., Pallanca, O., Golmard, J. L., Leu-Semenescu, S. & Arnulf, I. Is sleep-related verbal memory consolidation impaired in sleepwalkers? *J. Sleep Res.* **24**, 197–205 (2015).
58. Lopez, R. et al. Diagnostic criteria for disorders of arousal: a video-polysomnographic assessment. *Ann. Neurol.* **83**, 341–351 (2018).
This study provides the first vPSG-based diagnostic criteria for DOAs in adults.
59. Cicolin, A. et al. Sexual behaviors during sleep associated with polysomnographically confirmed parasomnia overlap disorder. *Sleep Med.* **12**, 523–528 (2011).
60. Yeh, S. B. & Schenck, C. H. Sexomnia: a case of sleep masturbation documented by video-polysomnography in a young adult male with sleepwalking. *Sleep Sci.* **9**, 65–68 (2016).
61. Parrino, L., Ferri, R., Bruni, O. & Terzano, M. G. Cyclic alternating pattern (CAP): the marker of sleep instability. *Sleep Med. Rev.* **16**, 27–45 (2012).
62. Bruni, O. et al. NREM sleep instability in children with sleep terrors: the role of slow wave activity interruptions. *Clin. Neurophysiol.* **119**, 985–992 (2008).
63. Guilleminault, C., Palombini, L., Pelayo, R. & Chervin, R. D. Sleepwalking and sleep terrors in prepubertal children: what triggers them? *Pediatrics* **111**, e17–e25 (2003).
64. Pilon, M., Zadra, A., Joncas, S. & Montplaisir, J. Hypersynchronous delta waves and somnambulism: brain topography and effect of sleep deprivation. *Sleep* **29**, 77–84 (2006).
65. Kavey, N. B., Whyte, J., Resor, S. R. & Gidro-Frank, S. Somnambulism in adults. *Neurology* **40**, 749–752 (1990).
66. Guilleminault, C., Poyares, D., Aftab, F. A., Palombini, L. & Abat, F. Sleep and wakefulness in somnambulism: a spectral analysis study. *J. Psychosom. Res.* **51**, 411–416 (2001).
67. Pressman, M. R. Hypersynchronous delta sleep EEG activity and sudden arousals from slow-wave sleep in adults without a history of parasomnias: clinical and forensic implications. *Sleep* **27**, 706–710 (2004).
68. Zadra, A., Pilon, M., Joncas, S., Rompré, S. & Montplaisir, J. Analysis of postarousal EEG activity during somnambulistic episodes. *J. Sleep Res.* **13**, 279–284 (2004).
69. Loddó, G. et al. Specific motor patterns of arousal disorders in adults: a video-polysomnographic analysis of 184 episodes. *Sleep Med.* **41**, 102–109 (2018).
70. Fisher, C., Kahn, E., Edwards, A., Davis, D. M. & Fine, J. A psychophysiological study of nightmares and night terrors. 3. Mental content and recall of stage 4 night terrors. *J. Nerv. Ment. Dis.* **158**, 174–188 (1974).
71. Busek, P. et al. Spectral analysis of the variations in heart rate and cardiac activation on waking up in sleepwalking [Spanish]. *Rev. Neurol.* **41**, 338–343 (2005).
72. Gaudreau, H., Joncas, S., Zadra, A. & Montplaisir, J. Dynamics of slow-wave activity during the NREM sleep of sleepwalkers and control subjects. *Sleep* **23**, 755–760 (2000).
73. Castelnovo, A. et al. Scalp and source power topography in sleepwalking and sleep terrors: a high-density EEG study. *Sleep* **39**, 1815–1825 (2016).
This first high-density EEG study conducted in individuals with DOAs reveals regional differences in the distribution of SWA during NREM and REM sleep and during wakefulness.
74. Januszko, P. et al. Sleepwalking episodes are preceded by arousal-related activation in the cingulate motor area: EEG current density imaging. *Clin. Neurophysiol.* **127**, 530–536 (2016).
75. Jaar, O., Pilon, M., Carrier, J., Montplaisir, J. & Zadra, A. Analysis of slow-wave activity and slow-wave oscillations prior to somnambulism. *Sleep* **33**, 1511–1516 (2010).
76. Perrault, R., Carrier, J., Desautels, A., Montplaisir, J. & Zadra, A. Electroencephalographic slow waves prior to sleepwalking episodes. *Sleep Med.* **15**, 1468–1472 (2014).
77. Desjardins, M. E. et al. EEG functional connectivity prior to sleepwalking: evidence of interplay between sleep and wakefulness. *Sleep* **40**, zsx024 (2017).
78. Terzaghi, M. et al. Dissociated local arousal states underlying essential clinical features of non-rapid eye movement arousal parasomnia: an intracerebral stereo-electroencephalographic study. *J. Sleep Res.* **21**, 502–506 (2012).
79. Terzaghi, M. et al. Evidence of dissociated arousal states during NREM parasomnia from an intracerebral neurophysiological study. *Sleep* **32**, 409–412 (2009).
80. Sarasso, S. et al. Fluid boundaries between wake and sleep: experimental evidence from stereo-EEG recordings. *Arch. Ital. Biol.* **152**, 169–177 (2014).
This article presents the third and most recently published stereo-EEG case report in an individual with a DOA, which captured thalamic wake-like activity during a nocturnal behavioural episode.
81. Gibbs, S. A. et al. Sleep-related epileptic behaviors and non-REM-related parasomnias: insights from stereo-EEG. *Sleep Med. Rev.* **25**, 4–20 (2016).
82. Mahowald, M. W., Cramer Bornemann, M. A. & Schenck, C. H. State dissociation, human behavior, and consciousness. *Curr. Top. Med. Chem.* **11**, 2392–2402 (2011).
83. Heidbreder, A. et al. Gray matter abnormalities of the dorsal posterior cingulate in sleep walking. *Sleep Med.* **36**, 152–155 (2017).
84. Bassetti, C., Vella, S., Donati, F., Wielepp, P. & Weder, B. SPECT during sleepwalking. *Lancet* **356**, 484–485 (2000).
This paper presents the only functional imagery study performed during a parasomnia episode, showing increased regional cerebral blood flow in the anterior cerebellum and posterior cingulate cortex together with persistence of sleep-related deactivation of the frontal and parietal association cortices.
85. Desjardins, M. E. et al. Altered brain perfusion patterns in wakefulness and slow-wave sleep in sleepwalkers. *Sleep* <https://doi.org/10.1093/sleep/zsy039> (2018).
86. Dang-Vu, T. T. et al. Sleep deprivation reveals altered brain perfusion patterns in somnambulism. *PLoS ONE* **10**, e0133474 (2015).
87. Montplaisir, J., Petit, D., Pilon, M., Mongrain, V. & Zadra, A. Does sleepwalking impair daytime vigilance? *J. Clin. Sleep Med.* **7**, 219 (2011).
88. Desautels, A. et al. Daytime somnolence in adult sleepwalkers. *Sleep Med.* **14**, 1187–1191 (2013).
89. Labelle, M. A. et al. Sleep deprivation impairs inhibitory control during wakefulness in adult sleepwalkers. *J. Sleep Res.* **24**, 658–665 (2015).
90. Carrillo-Solano, M., Leu-Semenescu, S., Golmard, J. L., Groos, E. & Arnulf, I. Sleepiness in sleepwalking and sleep terrors: a higher sleep pressure? *Sleep Med.* **26**, 54–59 (2016).
This article presents the largest study to assess subjective sleepiness in DOAs.
91. Ferini-Strambi, L., Galbiati, A., Marelli, S. & Zucconi, M. Disorders of arousal: evaluation of neurocognitive function in 69 consecutive patients. *Sleep* **40**, A274–A274 (2017).
92. Ohayon, M. M., Guilleminault, C. & Priest, R. G. Night terrors, sleepwalking, and confusional arousals in the general population: their frequency and relationship to other sleep and mental disorders. *J. Clin. Psychiatry* **60**, 268–276 (1999).
93. Guilleminault, C. et al. Adult chronic sleepwalking and its treatment based on polysomnography. *Brain* **128**, 1062–1069 (2005).
94. Kantha, S. S. Is somnambulism a distinct disorder of humans and not seen in non-human primates? *Med. Hypotheses* **61**, 517–518 (2003).
95. Cape, E. G. & Jones, B. E. Differential modulation of high-frequency gamma-electroencephalogram activity and sleep-wake state by noradrenaline and serotonin microinjections into the region of cholinergic basal ganglia neurons. *J. Neurosci.* **18**, 2653–2666 (1998).
96. Juszczak, G. R. & Swiergiel, A. H. Serotonergic hypothesis of sleepwalking. *Med. Hypotheses* **64**, 28–32 (2005).
97. Barabas, G., Ferrari, M. & Matthews, W. S. Childhood migraine and somnambulism. *Neurology* **33**, 948–949 (1983).
98. Casez, O., Dananctet, Y. & Besson, G. Migraine and somnambulism. *Neurology* **65**, 1334–1335 (2005).
99. Giroud, M., d'Athis, P., Guard, O. & Dumas, R. Migraine and somnambulism. A survey of 122 migraine patients [French]. *Rev. Neurol. (Paris)* **142**, 42–46 (1986).
100. Miller, V. A., Palermo, T. M., Powers, S. W., Scher, M. S. & Hershey, A. D. Migraine headaches and sleep disturbances in children. *Headache* **43**, 362–368 (2003).
101. Pradalier, A., Giroud, M. & Dry, J. Somnambulism, migraine and propranolol. *Headache* **27**, 143–145 (1987).
102. Charney, D. S., Kales, A., Soldatos, C. R. & Nelson, J. C. Somnambulistic-like episodes secondary to combined lithium-neuroleptic treatment. *Br. J. Psychiatry* **135**, 418–424 (1979).
103. Landry, P., Warnes, H., Nielsen, T. & Montplaisir, J. Somnambulistic-like behaviour in patients attending althium clinic. *Int. Clin. Psychopharmacol.* **14**, 173–175 (1999).
104. Kawashima, T. & Yamada, S. Paroxetine-induced somnambulism. *J. Clin. Psychiatry* **64**, 483 (2003).
105. Kolivakis, T. T., Margolese, H. C., Beauclair, L. & Chouinard, G. Olanzapine-induced somnambulism. *Am. J. Psychiatry* **158**, 1158 (2001).
106. Faridhosseini, F. & Zamani, A. A case report of somnambulism associated with olanzapine. *Iran. J. Psychiatry Behav. Sci.* **6**, 72–74 (2012).
107. Oliviero, A. et al. Functional involvement of cerebral cortex in adult sleepwalking. *J. Neurol.* **254**, 1066–1072 (2007).
108. Gallopini, T. et al. Identification of sleep-promoting neurons in vitro. *Nature* **404**, 992–995 (2000).
109. Steriade, M. The GABAergic reticular nucleus: a preferential target of corticothalamic projections. *Proc. Natl. Acad. Sci. USA* **98**, 3625–3627 (2001).
110. Jasmin, L., Rabkin, S. D., Granato, A., Boudah, A. & Ohara, P. T. Analgesia and hyperalgesia from GABA-mediated modulation of the cerebral cortex. *Nature* **424**, 316–320 (2003).
111. Enna, S. J. & McCarron, K. E. The role of GABA in the mediation and perception of pain. *Adv. Pharmacol.* **54**, 1–27 (2006).
112. Boscolo-Berto, R. et al. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. *Sleep Med. Rev.* **16**, 431–443 (2012).
113. Lopez, R., Arnulf, I., Drouot, X., Lecendreux, M. & Dauvilliers, Y. French consensus. Management of patients with hypersomnia: which strategy? *Rev. Neurol. (Paris)* **173**, 8–18 (2017).
114. Hublin, C., Kaprio, J., Partinen, M., Heikkilä, K. & Koskenvuo, M. Prevalence and genetics of sleepwalking a population-based twin study. *Neurology* **48**, 177–181 (1997).
This epidemiological study provides robust information about the prevalence of sleepwalking across ages and shows a fivefold higher concordance in monozygotic than in dizygotic twins.
115. Lecendreux, M. et al. HLA and genetic susceptibility to sleepwalking. *Mol. Psychiatry* **8**, 114–117 (2003).
This case-control study demonstrates an increased frequency of the HLA-DQB1*05:01 allele in sleepwalkers and an excess of HLA-DQB1*05 and HLA-DQB1*04 transmission in familial cases.
116. Heidbreder, A. et al. Not only sleepwalking but NREM parasomnia irrespective of the type is associated with HLA DQB1*05:01. *J. Clin. Sleep Med.* **12**, 565–570 (2016).
117. Licitis, A. K., Desruisseau, D. M., Yamada, K. A., Duntley, S. P. & Gunnert, C. A. Novel genetic findings in an extended family pedigree with sleepwalking. *Neurology* **76**, 49–52 (2011).

118. Pressman, M. R. Factors that predispose, prime and precipitate NREM parasomnias in adults: clinical and forensic implications. *Sleep Med. Rev.* **11**, 5–30 (2007).
This extensive review provides a comprehensive pathophysiological model for DOAs based on predisposing, priming and precipitating factors.
119. Chen, Y. W., Tseng, P. T., Wu, C. K. & Chen, C. C. Zaleplon-induced anemic somnambulism with eating behaviors under once dose. *Acta Neurol. Taiwan.* **23**, 143–145 (2014).
120. Ferentinos, P. & Paparrigopoulos, T. Zopiclone and sleepwalking. *Int. J. Neuropsychopharmacol.* **12**, 141–142 (2009).
121. Liskow, B. & Pikalov, A. Zaleplon overdose associated with sleepwalking and complex behavior. *J. Am. Acad. Child Adolesc. Psychiatry* **43**, 927–928 (2004).
122. Pressman, M. R. Sleep driving: sleepwalking variant or misuse of z-drugs? *Sleep Med. Rev.* **15**, 285–292 (2011).
123. Lecendreux, M. et al. Tolerance and efficacy of sodium oxybate in childhood narcolepsy with cataplexy: a retrospective study. *Sleep* **35**, 709–711 (2012).
124. Wang, Y. G., Swick, T. J., Carter, L. P., Thorpy, M. J. & Benowitz, N. L. Safety overview of postmarketing and clinical experience of sodium oxybate (Xyrem): abuse, misuse, dependence, and diversion. *J. Clin. Sleep Med.* **5**, 365–371 (2009).
125. Mayer, G., Neissner, V., Schwarzmayr, P. & Meier-Ewert, K. Sleep deprivation in somnambulism. Effect of arousal, deep sleep and sleep stage changes [German]. *Nervenarzt* **69**, 495–501 (1998).
126. Zadra, A., Pilon, M. & Montplaisir, J. Polysomnographic diagnosis of sleepwalking: effects of sleep deprivation. *Ann. Neurol.* **63**, 513–519 (2008).
127. Kales, J. D., Kales, A., Soldatos, C. R., Chamberlin, K. & Martin, E. D. Sleepwalking and night terrors related to febrile illness. *Am. J. Psychiatry* **136**, 1214–1215 (1979).
128. Thaller, J. L., Rosen, G. & Saltzman, S. Study of the relationship of frustration and anxiety to bruxism. *J. Periodontol.* **38**, 193–197 (1967).
129. Gungormus, Z. & Erçiyas, K. Evaluation of the relationship between anxiety and depression and bruxism. *J. Int. Med. Res.* **37**, 547–550 (2009).
130. Sutin, A. R., Terracciano, A., Ferrucci, L. & Costa, P. T. Teeth grinding: is emotional stability related to bruxism? *J. Res. Pers.* **44**, 402–405 (2010).
131. Stallman, H. M., Kohler, M. & White, J. Medication induced sleepwalking: a systematic review. *Sleep Med. Rev.* **37**, 105–113 (2018).
132. Lopez, R. & Dauvilliers, Y. Is restless legs syndrome involved in ambulation related to sleepwalking? *Sleep* **39**, 955–956 (2016).
133. Harris, M. & Grunstein, R. R. Treatments for somnambulism in adults: assessing the evidence. *Sleep Med. Rev.* **13**, 295–297 (2009).
134. Galbiati, A., Rinaldi, F., Giora, E., Ferini-Strambi, L. & Marelli, S. Behavioural and cognitive-behavioural treatments of parasomnias. *Behav. Neurol.* **2015**, 786928 (2015).
135. Frank, N. C., Spirito, A., Stark, L. & Owens-Stively, J. The use of scheduled awakenings to eliminate childhood sleepwalking. *J. Pediatr. Psychol.* **22**, 345–353 (1997).
136. Tobin, J. D. Treatment of somnambulism with anticipatory awakening. *J. Pediatr.* **122**, 426–427 (1993).
137. Hauri, P. J., Silber, M. H. & Boeve, B. F. The treatment of parasomnias with hypnosis: a 5-year follow-up study. *J. Clin. Sleep Med.* **3**, 369–373 (2007).
138. Conway, S. G., Castro, L., Lopes-Conceição, M. C., Hachul, H. & Tufik, S. Psychological treatment for sleepwalking: two case reports. *Clinics (Sao Paulo)* **66**, 517–520 (2011).
139. Hurwitz, T. D., Mahowald, M. W., Schenck, C. H., Schluter, J. L. & Bundlie, S. R. A retrospective outcome study and review of hypnosis as treatment of adults with sleepwalking and sleep terror. *J. Nerv. Ment. Dis.* **179**, 228–233 (1991).
140. Kales, J. C., Cadieux, R. J., Soldatos, C. R. & Kales, A. Psychotherapy with night-terror patients. *Am. J. Psychother.* **36**, 399–407 (1982).
141. Kellerman, J. Behavioral treatment of night terrors in a child with acute leukemia. *J. Nerv. Ment. Dis.* **167**, 182–185 (1979).
142. Reid, W. H., Haffke, E. A. & Chu, C. C. Diazepam in intractable sleepwalking: a pilot study. *Hillside J. Clin. Psychiatry* **6**, 49–55 (1984).
143. Schenck, C. H. & Mahowald, M. W. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am. J. Med.* **100**, 333–337 (1996).
144. Attarian, H. & Zhu, L. Treatment options for disorders of arousal: a case series. *Int. J. Neurosci.* **123**, 623–625 (2013).
145. Lillywhite, A. R., Wilson, S. J. & Nutt, D. J. Successful treatment of night terrors and somnambulism with paroxetine. *Br. J. Psychiatry* **164**, 551–554 (1994).
146. Jan, J. E., Freeman, R. D., Wasdell, M. B. & Bomben, M. M. 'A child with severe night terrors and sleep-walking responds to melatonin therapy'. *Dev. Med. Child Neurol.* **46**, 789 (2004).
147. Özcan, Ö. & Dönmez, Y. E. Melatonin treatment for childhood sleep terror. *J. Child Adolesc. Psychopharmacol.* **24**, 528–529 (2014).
148. Sasayama, D., Washizuka, S. & Honda, H. Effective treatment of night terrors and sleepwalking with ramelteon. *J. Child Adolesc. Psychopharmacol.* **26**, 948–948 (2016).
149. Mahowald, M. W. & Schenck, C. H. Insights from studying human sleep disorders. *Nature* **437**, 1279–1285 (2005).
150. Morrison, I., Rumbold, J. M. & Riha, R. L. Medicolegal aspects of complex behaviours arising from the sleep period: a review and guide for the practising sleep physician. *Sleep Med. Rev.* **18**, 249–260 (2014).
151. Mahowald, M. W. & Schenck, C. H. Parasomnias: sleepwalking and the law. *Sleep Med. Rev.* **4**, 321–339 (2000).
152. Pressman, M. R. Disorders of arousal from sleep and violent behavior: the role of physical contact and proximity. *Sleep* **30**, 1039–1047 (2007).

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All authors researched data for the article, discussed the content, wrote the text, and reviewed and edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

Informed consent

The authors affirm that human research participants provided informed consent for publication of the images in FIGS. 1 and 2.

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Review criteria

Articles discussed in this Review were identified by PubMed searches using the search terms "parasomnias", "disorders of arousal", "sleepwalking", "somnambulism", "sleep terrors", "confusional arousals", "sleep-related eating disorder" and "sexsomnia", among others. The reference lists of identified papers were searched for further relevant articles, and related citations for identified papers as listed on the PubMed site were evaluated. The final selection of references was based on the relevance to the scope of this Review.

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