NREM sleep parasomnias as disorders of sleep-state dissociation

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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.

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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 adults[3]. 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

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 DOAs[10], 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 entities[13]. 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 terrors[14], 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 point[1]. 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 terror[15].

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 amnesia[18]. 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 events[1].

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 narcolepsy[27], pontine and medullary lesions[28], Machado–Joseph disease[29] and Creutzfeldt–Jakob disease[30]. 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 ICSD-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 DOAs[1] (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 recall[42]. 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 adults[43].

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 stages[12], 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 DOAs[50]. 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 sexsomnia 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-occur[16]. Sleep-related abnormal sexual behaviours often emerge from SWS[59,60], and a case–control study showed that individuals with sexsomnia have similar rates of awakening from SWS as sleepwalkers[17].

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 fluctuations[61]. 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 controls[9]. 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 (≥150 μV) delta waves occurring during NREM sleep, was the first EEG marker to be described in relation to sleepwalking[7] (FIGS. 1,2). Irrespective of behavioural episodes, sleepwalkers have significantly more HSD activity than controls[64]. 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 breathing[67]. 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. Sleepwalking[a]: 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

[a]Includes subtypes with sleep-related eating or sleep-related abnormal sexual behaviour.

arousals revealed the existence of three different post-arousal EEG patterns[52]: 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 deprivation[68]. 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 episodes[68].

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 movements[69].

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 behaviours[58]. 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%.

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

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 resistance[70], 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 terror[52]. 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 activity[71].

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 process[53].

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 regions[73]. Source localization pointed mainly to involvement of the motor, premotor and cingulate areas[73]. 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 episodes[74].

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 sleepwalkers[76]. 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 episodes[77]. 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.

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.

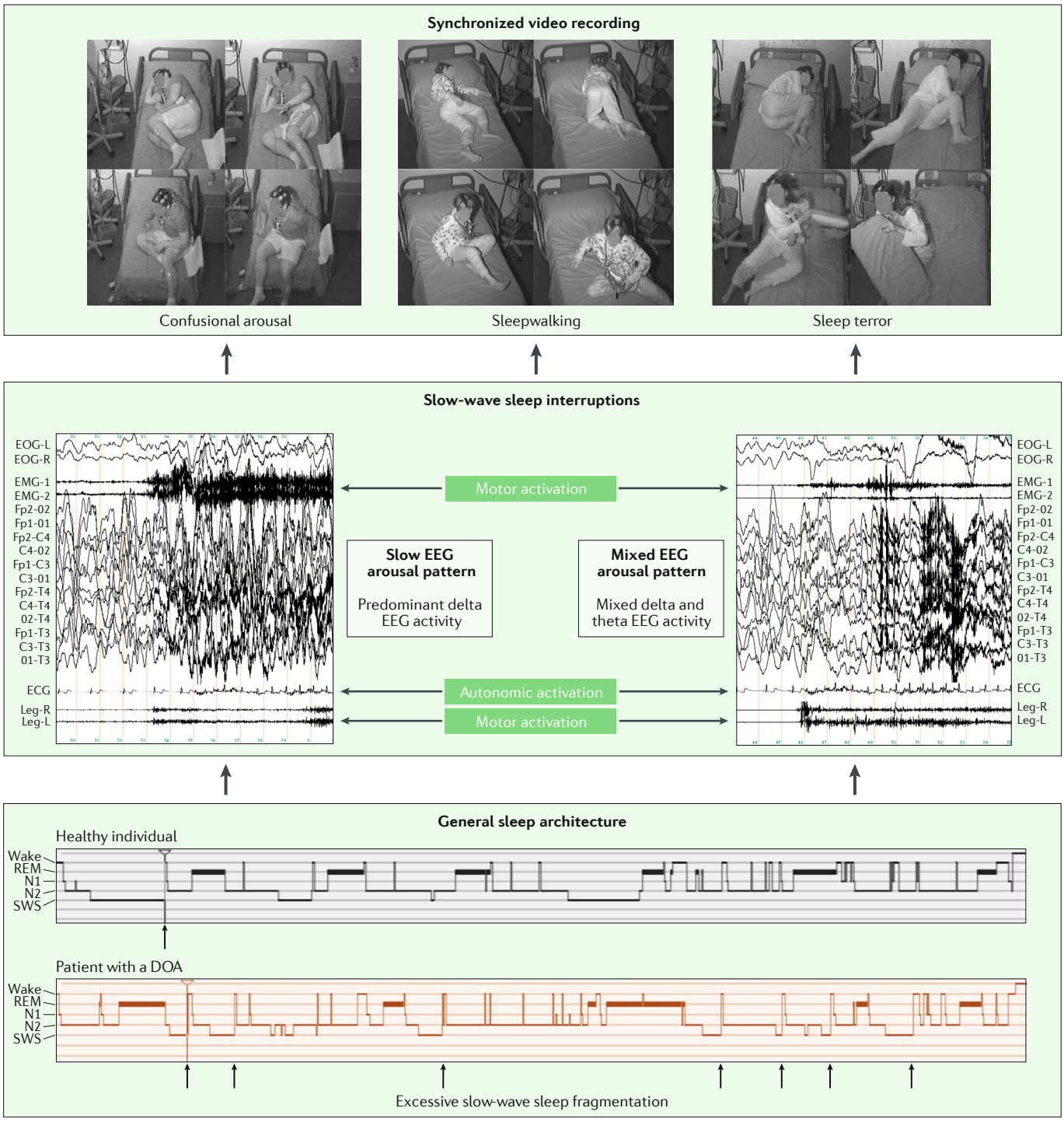

Fig. 1 | **Video-polysomnographic characteristics of disorders of arousal.** The sleep macroarchitecture in disorders of arousal (DOAs) reveals excessive slow-wave sleep (SWS) fragmentation (SWS interruptions are indicated by arrows in the bottom box). The frequent arousals from SWS are often associated 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.

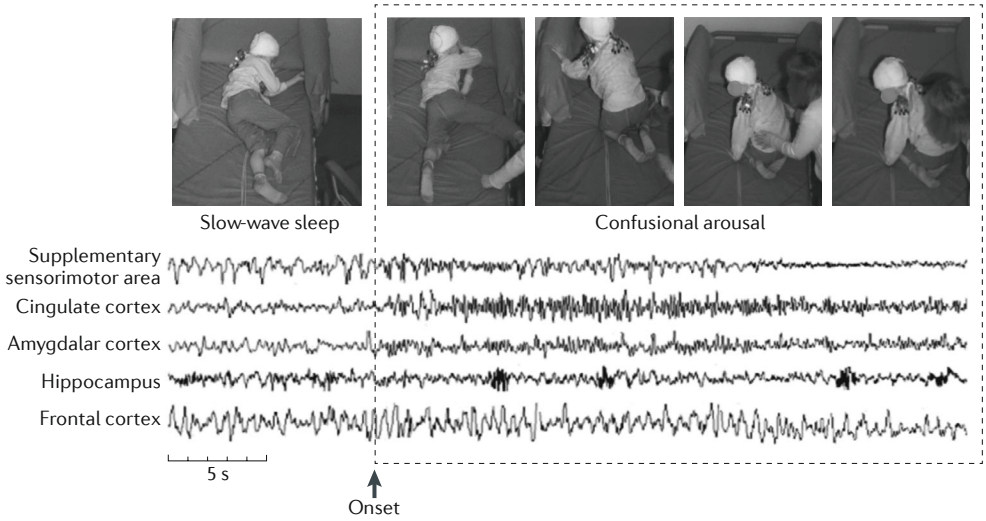

Fig. 2 | **Stereo-EEG recording in a disorder of arousal.** Coexistence of local non-rapid eye movement (NREM) sleep-like and wake-like patterns captured by stereo-EEG during a confusional arousal (only the first 30 s are represented). During the episode, the individual sits up in bed, utters unintelligible 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, temporopolar 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 wakefulness[80].

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 above[78], 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 sleep[11]. 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 experience[82].

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 group[83]. 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 episode[84]. 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.

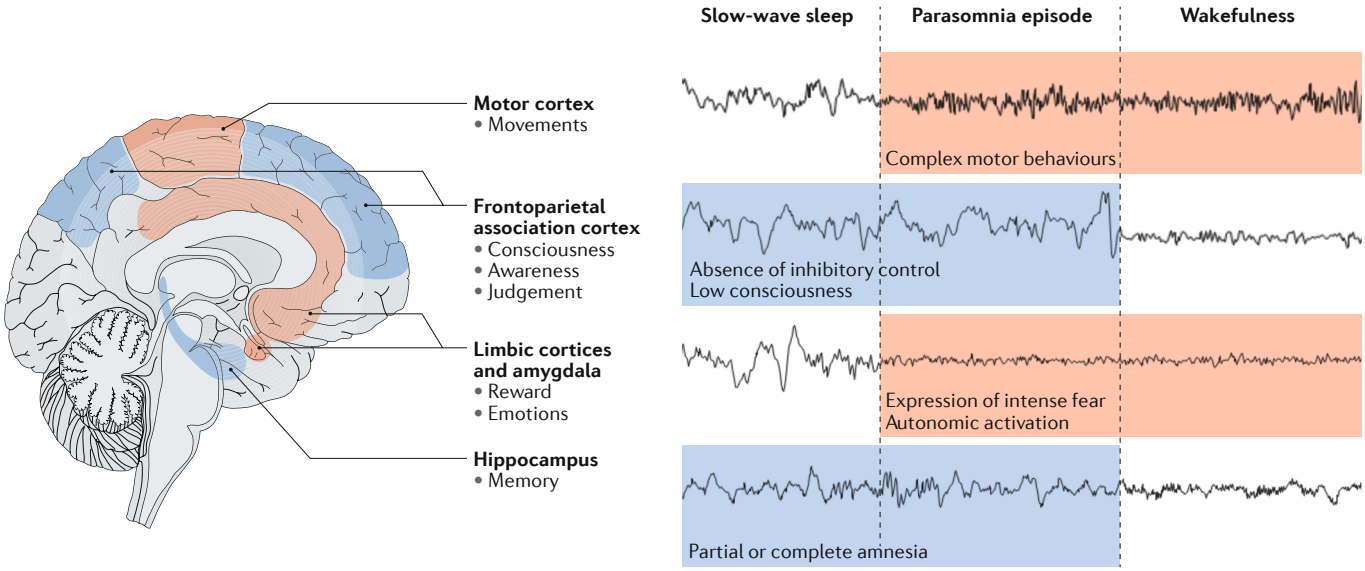

Fig. 3 | **Sleep–wake dissociation in disorders of arousal.** The coexistence of non-rapid eye movement sleep-like patterns in the frontoparietal associative cortices and hippocampus (blue shading) and wake-like patterns in the motor cortex and limbic structures (red shading) might underlie behavioural 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 controls[85]. 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 controls[86].

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 terror[56]. 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 study[5], 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 attention[91]. 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 disorders[4], as supported by epidemiological studies[92]. 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 conditions[5]. 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 episodes[93].

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 primates[94]. However, one experimental study revealed that microinjections of serotonin into the cholinergic basalis 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 sleepwalking[95]. Several clinical findings implicate serotonergic pathways in the pathophysiology of DOAs[96]. 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 migraine[15]. 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 DOAs[107]. 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 episodes[15]. 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 affected[14]. Twin studies have shown a fivefold higher concordance for sleepwalking in monozygotic than in dizygotic twins[114]. 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 sleepwalkers[115]. 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 terror[116]. A pangenomic study was conducted in a four-generation family in which DOAs segregated as a dominant condition with low penetrance[117]. 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], fever[127], late physical activity, strong positive emotions before sleep, stress, and anxiety[5]. Although many clinicians believe that stress and

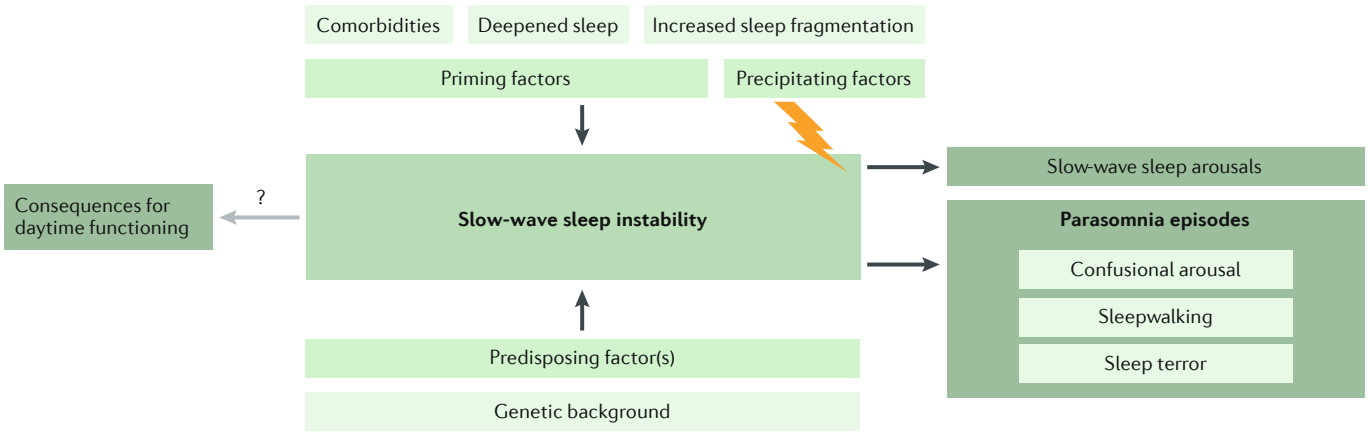

Fig. 4 | **A pathophysiological model of disorders of arousal.** A combination of predisposing and priming factors leads to increased slow-wave sleep instability that promotes the occurrence of disorder of arousal episodes, potentially triggered by precipitating factors.

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 series[131], 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 parasomnia[42]. 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 complaint[132]. 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 cases[58].

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 controls[38].

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 interventions[133]. 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 results[142].

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 DOAs[149]. 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 biomarkers[58]. For this scoring method to be included in the next revision of the ICSD, 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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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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