

Insights from studying human sleep disorders

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Problems with sleep are one of the commonest reasons for seeking medical attention. Knowledge gained from basic research into sleep in animals has led to marked advances in the understanding of human sleep, with important diagnostic and therapeutic implications. At the same time, research guided by human sleep disorders is leading to important basic sleep concepts. For example, sleep may not be a global, but rather a local, brain phenomenon. Furthermore, contrary to common assumptions, wakefulness, rapid eye movement (REM) and non-REM sleep are not mutually exclusive states. This striking realization explains a fascinating range of clinical phenomena.

Wake/sleep complaints are second only to complaints of pain as a cause to seek medical attention. Undiagnosed and untreated wake/sleep complaints exact an enormous toll at the personal level in terms of misery and at the societal level in socioeconomic consequences. Knowledge of sleep and sleep disorders has markedly increased over the past half-century, spearheaded by the discovery that sleep is far more than the passive absence of wakefulness. Not only is sleep an active brain process, but it actually represents two completely different states of being: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. These states are as different from each other as each is from wakefulness.

Most parts of the brain are active during all three states of being — wakefulness, NREM sleep and REM sleep — but active in a different mode, reflecting a striking reorganization of brain activity and function during these different states. Knowledge gained from basic research on sleep in animals has led to amazing advances in the understanding of human sleep, with important diagnostic and effective therapeutic implications. In addition, research guided by human sleep disorders is leading to important basic sleep concepts. These include the ideas that sleep may not be a global, but rather a local, brain phenomenon, and that wakefulness, NREM sleep and REM sleep are not mutually exclusive states: state dissociation or admixture might explain fascinating clinical phenomena. In Fig. 1, a period of 'ambiguous' sleep, with the simultaneous appearance of elements of both REM and NREM sleep, can be seen.

Although there are nearly 100 identified sleep/wake disorders, most sleep complaints conveniently fall into four categories: hypersomnia (excessive daytime sleepiness without obvious explanation), insomnia (trouble falling or staying asleep), circadian rhythm (biological clock) disorders, and parasomnias (complex behaviours arising from the sleep period). This review will focus on key disorders in each category that have provided important and exciting insights to our understanding of the wake/sleep process.

Hypersomnia

Hypersomnia should be taken very seriously, as sleepiness from any cause results in impaired sustained attention, with adverse, occasion-

ally disastrous, socioeconomic consequences in the classroom, workplace or on the highways. For instance, it is likely that more than 100,000 motor vehicle crashes annually in the United States are caused by driving while drowsy. Major disasters such as Three Mile Island, *Exxon Valdez*, Bhopal and *Challenger* were all officially attributed to sleepiness-related impaired judgement in the workplace¹. The most common cause of hypersomnia is volitional sleep deprivation for social or economic reasons (we get 20% less sleep than previous generations, and there is no evidence that earlier generations required more sleep, or that ours needs less). Sleepiness not explained by volitional sleep deprivation is almost always due to an underlying sleep disorder, most commonly obstructive sleep apnoea or narcolepsy.

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is the most common medical disorder causing hypersomnia, affecting over 2% of adult women and 4% of adult men. It is seen primarily in people who are loud snorers and is characterized by collapse of the upper airway during sleep. This upper airway collapse may be associated with a fall in the blood oxygen level and results in repetitive arousals (up to 100 per hour of sleep) to re-establish upper airway airflow. These brief arousals are not perceived by the individual but result in excessive daytime sleepiness. Important insights into OSA have been that, contrary to initial reports, OSA is not confined to middle-aged, overweight males but may be seen in children (3% of all children), women and thin individuals. The fact that OSA is a risk factor for hypertension and has been associated with heart disease and type 2 diabetes is of particular concern given the high prevalence of OSA and that obesity (currently an epidemic in many countries) is one risk factor for the development of OSA².

Narcolepsy

Narcolepsy is a relatively rare neurological disorder affecting 1 in 2,000 individuals. It is characterized by the tendency to fall asleep inappropriately during the daytime, particularly during sedentary or non-stimulating activities, despite having obtained an adequate amount of sleep the preceding night. Narcolepsy is the only known disorder representing abnormalities of the wake/sleep generators. Other symptoms

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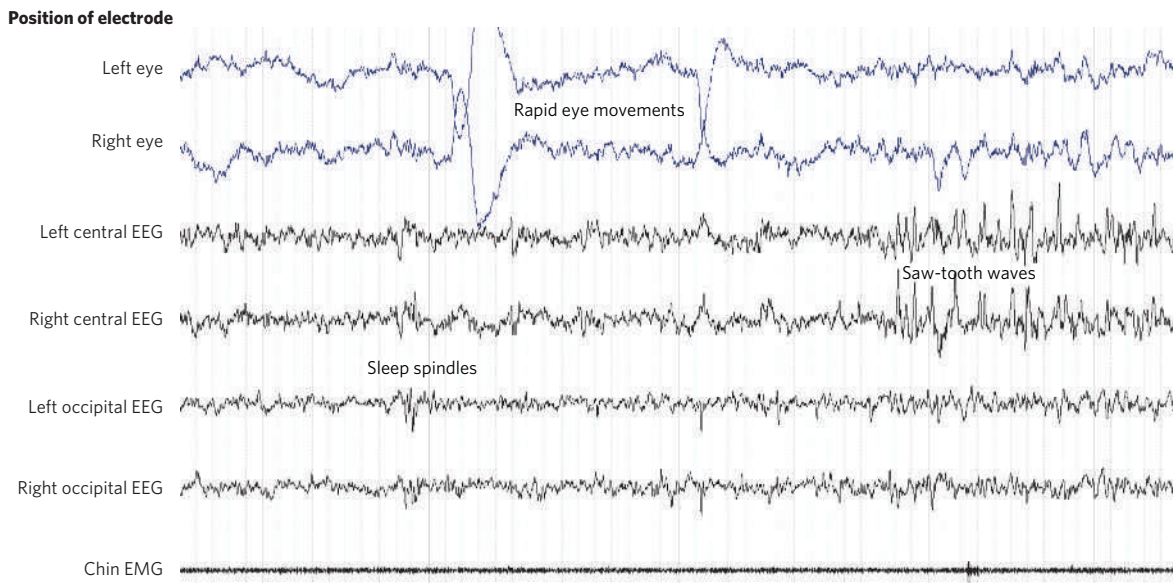


Figure 1 | Ambiguous sleep in a patient with narcolepsy. Note the simultaneous occurrence of elements of NREM sleep (sleep spindles) and REM sleep (rapid eye movements, saw-tooth waves and muscle atonia). EEG, electroencephalogram; EMG, electromyogram.

of narcolepsy include: first, cataplexy (sudden brief spells of muscle weakness), often triggered by emotionally laden events; second, hypnagogic (occurring at sleep onset) or hypnopompic (occurring at sleep offset) hallucinations; third, sleep paralysis (awakening to find the entire body paralyzed, with the exception of being able to breathe and move the eyes); fourth, automatic behaviour; and last, disrupted night-time sleep³.

The study of narcolepsy has been instrumental in promoting the concept of state dissociation: wakefulness and sleep are not necessarily mutually exclusive states, and furthermore, elements of one state of being may intrude inappropriately into another, often with striking consequences. Importantly, people with narcolepsy do not sleep more per 24 hours than non-narcoleptics; they are unable to keep the normal boundaries of wakefulness, NREM sleep and REM sleep⁴. The automatic behaviour (driving past the desired freeway exit, putting clothing into the refrigerator) represents an admixture of wakefulness and NREM sleep. There is enough wakefulness to perform complex behaviour but not enough for conscious awareness of the behaviours.

Sleep paralysis and cataplexy represent the simultaneous occurrence of REM sleep-related muscle paralysis and wakefulness. If the paralysis intrudes into wakefulness, the result is cataplexy. If it persists into wakefulness from a period of REM sleep, sleep paralysis results. The waking hallucinations represent the release of sleep-related dreaming into wakefulness, and the disrupted night-time sleep is a manifestation of the 'state-boundary dyscontrol' aspect of narcolepsy. Sleep paralysis and hypnagogic/hypnopompic hallucinations, but not cataplexy, are often experienced by people who do not have narcolepsy, particularly in the setting of sleep deprivation.

There was a time when narcolepsy was felt to be a psychiatric condition. There were somewhat plausible psychodynamic explanations (primarily as avoidance behaviours) for the symptoms of sleepiness, cataplexy and sleep paralysis. But narcolepsy is clearly caused by abnormalities of the central nervous system.

Narcolepsy has a clear genetic component, with over 90% of individuals with narcolepsy carrying the *HLA-DR2/DQ1* (under current nomenclature *HLA-DR15* and *HLA-DQ6*) gene (found in less than 30% of the general population). It is currently felt that DQ6, which corresponds at the genomic level to the subregions DQB1*0602 and DQA1*0102 on chromosome 6, is one of the more reliable markers for narcolepsy across ethnic groups⁵. This association is present in the different ethnic populations to varying degrees and represents the highest disease-HLA linkage known in medicine. Despite a genetic

component, the risk of a first-degree relative developing narcolepsy is only 1–2%, but that represents a 10–40-fold increase compared with the general population⁶. Clearly, there is a genetic component. However, that component is neither necessary nor sufficient to cause narcolepsy.

One of the most important and exciting discoveries in the field of sleep medicine resulted from animal experiments into narcolepsy and was the identification of the relationship between hypocretin-1 (also known as orexin) and narcolepsy. Hypocretin-1 is a neuropeptide confined to a small number of cells in the hypothalamus. It seems that patients with narcolepsy have lost these hypocretin-producing cells, possibly through an immune-mediated mechanism⁷. Undetectable levels of hypocretin-1 in the cerebrospinal fluid (CSF) are very specific for patients with narcolepsy who have cataplexy and who are HLA DQB1*0602 positive. Absent CSF hypocretin-1 levels have not been found in any other conditions that could be confused clinically with narcolepsy, and this suggests that CSF hypocretin determinations may be of value in the diagnosis of narcolepsy in difficult cases⁸.

There are numerous effective treatments for narcolepsy such as stimulant medications. Discovery of the role of hypocretin deficiency in narcolepsy will undoubtedly lead to more specific targeted treatments for narcolepsy and will teach much about wake/sleep function in general. It has already been shown that systemic administration of hypocretin-1 in narcoleptic dogs reduced cataplexy and normalized sleep and waking durations⁹.

Insomnia

Insomnia is the most prevalent sleep complaint in the general population. It is not defined by total sleep time, but, rather, by the inability to obtain sleep that is sufficiently long or 'good enough' to result in feeling rested or restored the following day. Although insomnia may be due to many underlying medical, psychiatric or psychological conditions, there is growing evidence that some insomnia is constitutional in nature. Many people with insomnia do not have any identifiable psychiatric or psychological problems. Furthermore, there is evidence that untreated insomnia is a risk factor for the development of psychiatric problems such as depression or substance abuse. Importantly, the relationship between insomnia and psychiatric conditions is bi-directional: depression may cause insomnia, and insomnia may cause depression.

There is convincing evidence that insomniacs may be in a constant state of hyperarousal. Many are actually less sleepy during the day than

non-insomniacs as measured by objective daytime nap studies. And they also have an increase in metabolic rate across the 24-hour period¹⁰. It has been proposed that chronic insomniacs may suffer from a more general disorder of hyperarousal that may be responsible for both the daytime symptoms and poor nocturnal sleep¹¹. Insomniacs experience an overall increase of adrenocorticotrophic hormone (ACTH) and cortisol secretion¹². The increased arousal level shown in electroencephalogram (EEG) power-spectra studies could help explain the impairment of the perception of having slept experienced by many insomniacs¹³. Neuroimaging studies in insomnia lend further support to underlying physiological abnormalities¹⁴.

Behavioural treatment for insomnia can be quite effective but can be time-consuming. Numerous pharmacological treatments are available. Over-the-counter sleep aids are of very questionable benefit¹⁵. Commonly, medications used to treat depression are prescribed to treat insomnia, although there is very little evidence that antidepressant medications are effective in the treatment of insomnia that is not associated with depression¹⁶. There are two classes of medication approved for the treatment of insomnia: the benzodiazepines and the newer, non-benzodiazepines. The risks of tolerance, abuse and dependency associated with chronic benzodiazepine administration for patients with well-documented sleep disorders have been greatly overrated¹⁷. Combined behavioural and pharmacological treatments are often effective¹⁸. Benzodiazepines may be safely and effectively administered for longer than three weeks¹⁹.

There has been much interest in using melatonin as a sleep-inducing agent. Melatonin is secreted by the pineal gland, and its secretion is controlled by the light–dark cycle. Although often thought of as a ‘sleep’ hormone, it is actually a ‘darkness’ hormone, being secreted at night in both day-active and night-active species. Its effect on sleep is variable. Melatonin may prove useful in certain specific conditions. For example, melatonin is effective in improving sleep in a subgroup of elderly patients with insomnia who have low melatonin levels. Melatonin is clearly ineffective in a sizable number of those suffering from insomnia, and its use in the general treatment of insomnia remains to be clarified²⁰. Melatonin agonists are being evaluated as sleep-inducing agents.

Awareness of the neurophysiological factors that predispose to insomnia and the mechanism of action of sedative-hypnotic agents are important elements in the diagnosis and successful management of insomnia. Further study of insomnia in neurological conditions will expand our understanding of sleep/wake patterns and brain function. If some patients with insomnia are physiologically hyperaroused, a case may be made for chronic administration of sedative-hypnotic agents. The recent identification of a number of sleep/wake-related neurotransmitters and neuropeptides will lead to the development of newer and more selective sleep-promoting agents.

Restless legs syndrome

Restless legs syndrome (RLS) is one of the most common causes of severe insomnia. It is a neurological sensory/movement disorder affecting 5–15% of the general population²¹. RLS is characterized primarily by a vague and difficult-to-describe unpleasant sensation in the legs. This discomfort appears primarily during periods of inactivity, particularly during the transition from wake to sleep in the evening. Patients often have difficulty in describing the unpleasant sensations; they rarely use conventional terms of discomfort such as ‘numbness, tingling or pain’, but rather bizarre terms such as ‘pulling, searing, drawing, crawling, shimmering or boring’, suggesting that RLS sensations are unlike any experienced by unaffected individuals. These distressing sensations are typically relieved only by movement or stimulation of the legs. Many different techniques have been found by patients: walking about, stomping the feet, rubbing, squeezing or stroking the legs, taking hot showers or baths, or applying ointment, hot packs or wraps to the legs. Although these treatments are effective while they are being performed, the discomfort usually returns as soon as the individual becomes inactive or returns to bed to try to sleep. The

Box 1 | How much sleep do you need?

- The total sleep requirement is genetically determined on an individual basis.
- Although the average is 7.5–8 hours per night, the range is between 4 hours and 10–11 hours.
- One is sleep-deprived if:
 - One uses an alarm clock to be awakened in the morning (otherwise, the brain would have awakened before the alarm went off when it had accumulated as much sleep as it needs).
 - One tends to fall asleep during periods of reduced environmental stimulation. Boring lectures, dimly lit rooms, heavy meals or long automobiles drives do not cause sleepiness, they simply unmask it.
- The best way to determine one’s constitutional sleep requirement is to recall (or speculate as to) what one’s would be if one were in an environment where the wake-sleep pattern was completely free of external demands or constraints from work, family, school, social or meals.

motor restlessness often appears to follow a circadian pattern, peaking between midnight and 04:00 (ref. 22). The higher prevalence of depression and anxiety found associated with RLS is felt to be secondary to the RLS²³.

Recent studies suggest there may be a susceptibility gene locus, which would explain why RLS is often familial²⁴. RLS is commonly seen in pregnancy, haemodialysis or peritoneal dialysis for renal failure and iron-deficiency anaemia. Its relationship with iron metabolism abnormalities has led to studies indicating that RLS is associated with abnormal iron metabolism within the central nervous system²⁵. Recent elegant functional neuroimaging studies have identified thalamic, red nucleus and brainstem involvement in the generation of periodic limb movements in patients with RLS²⁶. One PET study found reduced dopamine 2 binding in the caudate and putamen²⁷. A subcortical origin of RLS is supported by transcranial magnetic stimulation studies²⁸.

Demonstration of a continuous hypersensitivity to pin-prick, but not to light touch, confirms a sensory component to RLS²⁹ and may explain the efficacy of opiate medications in RLS³⁰.

Most cases of RLS respond gratifyingly to medical treatment including anti-parkinsonian agents, benzodiazepines, opiates and anti-convulsant medication. The dopaminergic anti-parkinsonian medications are particularly effective²⁴. Further study of the relationship between dopamine and central nervous system iron metabolism will be of great interest and value to neurophysiologists, neurochemists, neuropharmacologists and, of course, patients.

Circadian rhythm disorders

Most living creatures follow a relentless and pervasive daily rhythm of activity and rest that is ultimately linked to the geophysical light–dark cycle. Plants, animals, even unicellular organisms, show daily variations in metabolic activity, locomotion, feeding and many other functions³¹. The importance of the light–dark cycle upon the human biological clock is underscored by the fact that in totally blind humans, only one-third will be entrained to the environment. One-third will have a cycle that is 24 hours but out of phase with the environment, with the remaining third experiencing a free-running pattern longer than 24 hours³².

The primary symptom of circadian rhythm disorders is the inability to sleep during the desired sleep time. Once asleep, there is no abnormality of sleep, only an abnormality of the timing of sleep. The cause of all circadian rhythm disorders is an inability of the individual’s biological clock to adjust to the demands of the geophysical environment. Wake–sleep schedule disorders fall into two categories: primary (malfunction of the biologic clock *per se*) and secondary (resulting from environmental effects upon the underlying clock). The secondary disorders (such as jet-lag and shift work) are usually immediately apparent upon simple questioning of the patient. The primary disorders may be much more difficult to diagnose, as they typically masquerade as other sleep, medical or psychiatric disorders such as hypersomnia, insomnia, substance (sedative-hypnotic or stimulant)



Figure 2 | A sleepwalking episode. A 23-year-old female demonstrates a very rapid progression from lying in her bed in deep sleep (slow-wave NREM sleep) to have a precipitous arousal with immediate standing up and sleepwalking that culminates with her tripping and nearly falling out of bed.

abuse or psychiatric conditions.

Until recently, the circadian rhythm disorders were only of academic interest, as no effective treatments existed. Fortunately, this has changed, and many patients with these often incapacitating disorders will benefit from accurate diagnosis and appropriate treatment. The mainstays of treatment are chronotherapy and phototherapy. In addition, there are promising new pharmacological treatments on the horizon³³.

In chronotherapy, the desirable total sleep time is determined by sleep logs during a 'free-running' period. The patient then delays or advances sleep onset, by a few hours every day and sleeping only the predetermined number of hours until the sleep onset time is at the desired time, at which time the patient attempts to maintain that time³⁴. This method requires several days of free time and can be difficult if sleeping quarters cannot be kept dark and quiet when sleep will be occurring during the daytime.

Phototherapy (exposure to bright light) has a potent effect upon the biological clock, and exposure at strategic times of the wake/sleep cycle results in a change in the underlying rhythm. This has afforded an opportunity to treat circadian dysrhythmias effectively. The timing and duration of the phototherapy depend upon diagnosis and individual response. The patient sits at a prescribed distance from a bright light producing 2,500 lux at the point where it reaches the patient. The effect of light upon human rhythms varies with intensity, wavelength, timing and duration of exposure. Once the desired sleep period time has been achieved, continued light exposure must be maintained. Much remains to be learned regarding these variables and the effectiveness of phototherapy in the clinical setting³⁵.

Delayed sleep syndrome

In delayed sleep-phase syndrome (DSPS), the patient falls asleep late and rises late. There is a striking inability to fall asleep at an earlier, more desirable time. This may present itself as either sleep-onset insomnia or daytime hypersomnia (particularly in the morning). DSPS is the most common of the primary circadian dysrhythmias, and may, in part, be the consequence of societal increases in night-time activities³⁶. For example, a college student is habitually unable to fall asleep until 02:00, and has great difficulty getting up in time for her 08:00 classes from Monday to Friday. She finds herself dozing off during morning classes. On Saturday and Sunday she sleeps in until about 10:00, and feels rested upon arising, with no episodes of dozing during the day. Combinations of chronotherapy, phototherapy and medications may be effective in 'resetting' the clock. Unfortunately, the treatment regimen must be maintained, or the clock will again become delayed.

Advanced sleep-phase syndrome

Individuals suffering from advanced sleep-phase syndrome (ASPS) fall asleep early and awaken earlier than desired. They are unable to remain awake until the desired time, falling asleep in the early evening and awakening in the very early hours of the morning. This may present as hypersomnia (particularly in the evening) or sleep-mainte-

nance insomnia. Patients complain of interruption of evening activities by their sleepiness. They may avoid evening social activities, fearing the intrusive sleepiness. The undesirable early morning awakenings in this condition may lead to a misdiagnosis of depression. Bright light exposure in the evening may delay the clock to a more acceptable pattern.

Other, less common, circadian dysrhythmias beyond the scope of this review include a 'non-24-hour wake-sleep pattern' and 'irregular wake-sleep pattern'.

Underscoring the inherent nature of these conditions, human genetic studies have identified specific genes associated with both advanced and delayed sleep-phase syndromes³⁷⁻³⁹.

Drugs that shift biological rhythms are called chronobiotics. One promising pharmacological treatment is melatonin. Melatonin is secreted by the pineal gland, and its secretion is coupled to the wake-sleep cycle and to the circadian cortisol rhythm. It is a valuable marker of the underlying wake-sleep period. It is likely that melatonin plays an important role in biological rhythms. There is evidence that administration of exogenous melatonin may alter the biological rhythm in certain conditions^{33,40}.

Circadian dysrhythmias are common, and may be disabling in terms of academic, employment or family consequences, and so the sleep medicine field is eagerly awaiting the development of effective chronobiotics.

Parasomnias

Parasomnias are defined as unpleasant or undesirable behavioural or experiential phenomena that occur predominantly or exclusively during sleep. They were initially thought to be a single phenomenon, often attributed to psychiatric disease. It is now clear that parasomnias are not a unitary phenomenon but rather are the manifestation of a wide variety of completely different conditions, most of which are diagnosable and treatable. The common parasomnias are another example of 'dissociated sleep states', representing the simultaneous admixture of wakefulness and either NREM sleep (disorders of arousal such as sleepwalking or sleep terrors) or wakefulness and REM sleep (REM sleep behaviour disorder). Parasomnias may result in striking clinical phenomena, which appear as the brain becomes reorganized across states, and are therefore apt to occur during the transition from one state to another.

In view of the large number of neural networks, neurotransmitters and other state-determining substances that must be recruited synchronously for full state declaration and the frequent transitions among states during the wake-sleep cycle, it is surprising that errors in state declaration do not occur more frequently than they do⁴¹. In addition to the phenomenon of state dissociation, in which two states of being overlap or occur simultaneously, there are probably additional underlying physiological phenomena that contribute to the appearance of complex motor behaviours during sleep. These include: activation of locomotor centres during sleep, sleep inertia (a period of confusion or disorientation during the transition from sleep to wakefulness) upon arousal and sleep state instability (oscillation between



Figure 3 | The rapid evolution of a sleep terror episode. A 24-year-old male patient has a long and increasingly severe history of violent sleep terrors. In the video prints shown here, the patient emerged precipitously from slow-wave NREM sleep, without any physiological or motor forewarning. This is typical of sleep terrors (see the text for more details).

wakefulness and sleep)⁴².

The parasomnias, which are usually due to admixtures of states of being, along with narcolepsy, support the concept that wake and sleep are not mutually exclusive states, and that sleep is not necessarily a global brain phenomenon.

NREM parasomnias

The disorders of arousal are the most impressive and most common of the NREM sleep parasomnias. These share common features. They tend to arise from slow-wave sleep (stages 3 and 4 of NREM sleep) and therefore usually occur during the first third of the sleep cycle (and rarely during naps). They are common in childhood, usually decreasing in frequency with increasing age^{43,44}.

Disorders of arousal may be triggered by febrile illness, alcohol, previous sleep deprivation, physical activity, emotional stress or medications. Such precipitants should be thought of as triggering events in susceptible individuals and not the cause. Persistence of these behaviours beyond childhood or their development in adulthood has erroneously been taken as an indication of underlying psychopathology. Careful clinical evaluations of patients with disorders of arousal have dispelled the myth that these conditions are the manifestation of significant underlying psychiatric or psychological problems⁴⁵⁻⁴⁷.

Disorders of arousal occur on a broad spectrum ranging from confusional arousals, through somnambulism (sleep walking) to sleep terrors. Some take the form of 'specialized' behaviours such as sleep-related eating and sleep-related sexual activity⁴⁸⁻⁵¹.

Confusional arousals

These are often seen in children and are characterized by movements in bed, occasionally thrashing about or inconsolable crying⁵². 'Sleep drunkenness' is probably a variation on this theme⁵³. The prevalence of confusional arousals in adults is approximately 4% (ref. 54).

Sleepwalking

Sleepwalking is prevalent in childhood (1-17%), peaking at 11-12

years of age, and is far more common in adults (nearly 4%) than generally acknowledged^{54,55}. Sleepwalking may be either calm or agitated, with varying degrees of complexity and duration (Fig. 2).

Sleep terrors

The sleep terror is the most dramatic disorder of arousal, frequently initiated by a loud, blood-curdling scream associated with extreme panic, followed by prominent motor activity such as hitting the wall, running around or out of the bedroom, even out of the house, resulting in bodily injury or property damage. A universal feature is inconsolability, and attempts at consolation are fruitless and may serve only to prolong or even intensify the confusional state. Complete amnesia for the activity is typical, but may be incomplete⁵⁶. The intense endogenous arousal and exogenous unarousability constitute a curious paradox. As with sleepwalking, sleep terrors are much more prevalent in adults than generally acknowledged (up to 3%) (ref. 54). Although usually benign, these behaviours may be violent (Fig. 3), resulting in considerable injury to the victim or others or damage to the environment, occasionally with forensic implications⁵⁷. Treatment options include reassurance, behavioural or pharmacological approaches⁵⁸.

REM sleep parasomnias

The most common and best-studied REM sleep parasomnia is the REM sleep behaviour disorder (RBD). In patients with RBD, somatic muscle atonia, one of the defining features of REM sleep, is absent, permitting the acting out of dream mentation, often with violent or injurious results (Fig. 4). Figure 5 demonstrates the striking release of motor activity during REM sleep in a patient with RBD.

The cases so far reported indicate strikingly similar clinical features⁵⁹. The presenting complaint is that of vigorous sleep behaviours usually accompanying vivid dreams. These behaviours may result in repeated injury, including ecchymoses, lacerations and fractures. Some of the self-protection measures taken by the patients (tethering themselves to the bed, using sleeping bags or pillow barricades, or sleeping on a mattress in an empty room) reveal the recurrent and serious



Figure 4 | REM sleep behaviour disorder. Pictures taken from a video in a sleep laboratory of older men who have RBD. These men throw punches while dreaming of fighting during REM sleep.

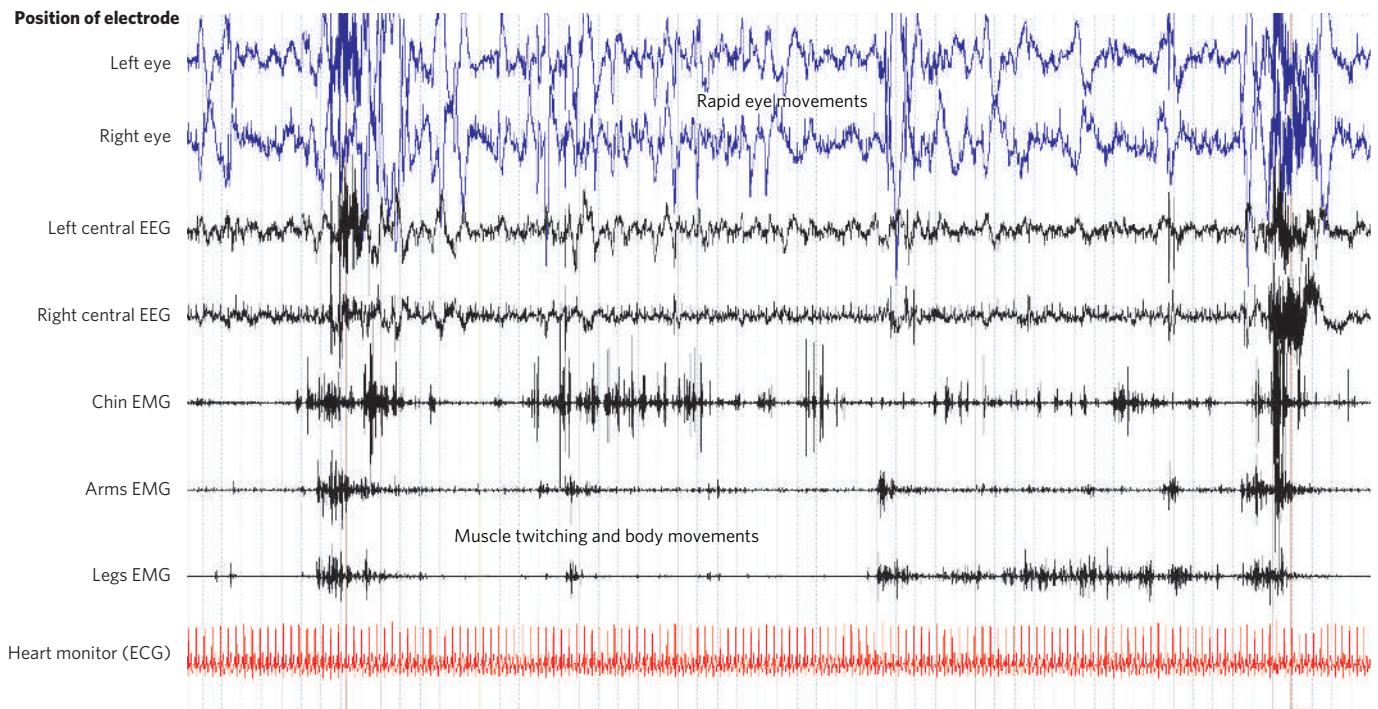


Figure 5 | REM sleep without atonia in a patient with REM sleep behaviour disorder. Note the prominent muscle activity and body movements during REM sleep, which is normally accompanied by active muscle paralysis. EEG, electroencephalogram; EMG, electromyogram.

nature of these episodes. The potential for injury to self or a bed partner raises interesting and difficult forensic medicine issues. Two striking demographic characteristics of RBD are that it predominantly affects males (about 90%) and usually begins after the age of 50 years. Chronic RBD may be preceded by a lengthy prodrome. RBD in humans occurs in both an acute and chronic form. The acute form is often due to undesirable side-effects of prescribed medications, most commonly antidepressant medications, particularly the serotonin-specific reuptake inhibitors (SSRIs)⁶⁰.

The chronic form of RBD is usually either idiopathic or associated with neurological disorders. One of the most interesting implications of chronic RBD is its growing association with neurodegenerative disorders, particularly the synucleinopathies (Parkinson's disease, multiple system atrophy or dementia with Lewy body disease). RBD may be the first manifestation of these conditions, and may precede any other manifestation of the underlying neurodegenerative process by more than 10 years⁶¹. As patients with RBD are followed over time, it is becoming clear that more are developing neurodegenerative disorders. This has led to the suggestion that the term 'idiopathic' RBD be replaced by 'cryptogenic' RBD. The striking relationship between RBD and neurodegenerative disorders has led to fascinating neuroimaging and cerebral blood flow studies in patients with RBD⁶²⁻⁶⁸. Such clinical/neuroimaging studies in a variety of neurological conditions will undoubtedly reveal much about brain function and sleep/wakefulness. The fact that RBD may be a very early harbinger of Parkinson's disease will become very important when a neuroprotective pharmacological agent is developed for Parkinson's disease. In keeping with the fact that both narcolepsy and RBD represent state boundary dyscontrol conditions, it should be no surprise that there is a higher incidence of RBD in patients with narcolepsy. Adding to the likelihood that RBD will occur in patients with narcolepsy, medications prescribed to treat cataplexy associated with narcolepsy (tricyclic antidepressants, SSRIs and monoamine oxidase inhibitors) can trigger or exacerbate RBD⁶⁹.

Fortunately, the benzodiazepine clonazepam is a highly effective treatment for RBD⁷⁰. The mechanism of action of clonazepam in RBD is unknown.

Isolated, often bizarre, sleep-related events may be experienced by perfectly normal people, and most do not warrant further extensive or

expensive evaluation. Serious attention should be made to complaints of sleep-related behaviours that are potentially violent or injurious. Forensic issues may result from such behaviours⁵⁷.

Future directions

Progress in basic science sleep physiology and clinical sleep medicine is rapid at the moment. Knowledge gained from sleep research in insects and animals will undoubtedly lead to even more effective treatments for the myriad human sleep disorders. Identification of sleep and circadian abnormalities in transgenic mouse models of Alzheimer's disease and Huntington's disease are just two examples⁷¹⁻⁷³. The evolving relationship between RBD and neurodegenerative disorders and sleep in the prion diseases (Creutzfeldt-Jakob, fatal familial insomnia and bovine encephalopathy) is another. Many aspects of sleep and wakefulness are genetically influenced⁷⁴. Increasingly, studies in *Drosophila* are providing important information regarding genetic influences in sleep patterns (duration and timing of sleep)⁷⁵⁻⁷⁷. In addition, questions raised by human sleep disorders will help direct basic science research. Close collaboration between basic science sleep researchers and sleep medicine clinicians will continue to result in great discovery. ■

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