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SCIENCE AND SOCIETY

The rhythm of rest and excess

Russell G. Foster and Katharina Wulff

Abstract | There is a stark contrast between our attitudes to sleep and those of the pre-industrial age. In Shakespeare's *Julius Cæsar* we are told to "Enjoy the honey-heavy dew of slumber". There seems little chance of this today, as we crave more, work more and expect more, and, in the process, abandon sleep. Our occupation of the night is having unanticipated costs for both our physical and mental health, which, if continued, might condemn whole sectors of our society to a dismal future.

For centuries, sleep has been regarded as a simple suspension of activity; today we appreciate that it is a complex and highly organized series of physiological and behavioural states. On average, we spend 30% of our lives asleep, and we have little idea why. This ignorance is probably the main reason why our society has such little regard for sleep. At best we tolerate the fact that we need to sleep, and at worst we think of sleep as an illness that needs a cure. This attitude is not only dangerous but unsustainable. Our immune defence, cognitive performance and mental health are all affected by sleep and our circadian rhythms. Disruption of the sleep–wake axis results in a broad range of interconnected pathologies, including poor vigilance and memory, reduced mental and physical reaction times, reduced motivation, depression, insomnia, metabolic abnormalities, obesity, immune impairment and even a greater risk of cancer. There is an intimate connection between these pathologies and the way in which we have organized our society in recent years[1].

The introduction of artificial lighting and the re-structuring of working hours has progressively detached our species from the 24-hour cycle of light and dark. Our working culture of long hours and shift work, and the 24-hour availability of almost everything have conspired to demote sleep in our priorities. In our 24/7 society, we have established a new benchmark for wakefulness, in which many employers expect their staff to work to the beat of an artificial rhythm and to perform with equal efficiency throughout the 24 hours of a day. This imposed structure conflicts with our basic biology and is suboptimal for our health. In an attempt to cope with tiredness, we have fallen into a stimulant–sedation loop, in which stimulants, such as caffeine and nicotine, are used for wakefulness during the day and sedatives, such as hypnotics and alcohol, are used at night to induce sleep. The following morning, stimulants are needed once again to override the sedatives and impaired sleep. In addition, many drugs have been developed to modify sleep and alertness, to beat jet lag and to create 'metabolically dominant soldiers' — warriors who can fight 24 hours a day for 7 days without rest.

In this perspective, we consider some of the causes and consequences of sleep and circadian rhythm disruption. In the space available, this article cannot be all encompassing, but our aim is to highlight the importance of this topic, illustrate how many agents of sleep disruption are interconnected, and promote discussion about how we might use this information to adjust the way we organize our lives. The relationships between our health, performance, sleep, circadian timing system, and some of the agents and conditions that modulate sleep are shown in FIG. 1. This figure provides the outline for the discussion below, and frames our central question: can society use the emerging knowledge about the impact of sleep and circadian rhythms on health to achieve a better balance between our opposing biological drives for rest and excess?

The basic biology of sleep

Sleep is a highly complex state that shows alternating patterns of neurological activity. These have been classified into rapid eye movement (REM) and non-REM (NREM) sleep stages[2]. On the initiation of sleep, an individual will pass down slowly through stages 1–4 NREM sleep, and then rapidly ascend these stages into REM sleep, which is accompanied by considerable body muscle paralysis (motor atonia). Following REM, an individual will descend once again through stages 1–4 of NREM sleep. This cycling of NREM and REM sleep lasts ~70–90 min, and in an average night we might experience five of these NREM–REM sleep cycles. Unless disturbed by an alarm clock, we usually wake naturally from REM sleep[2,3].

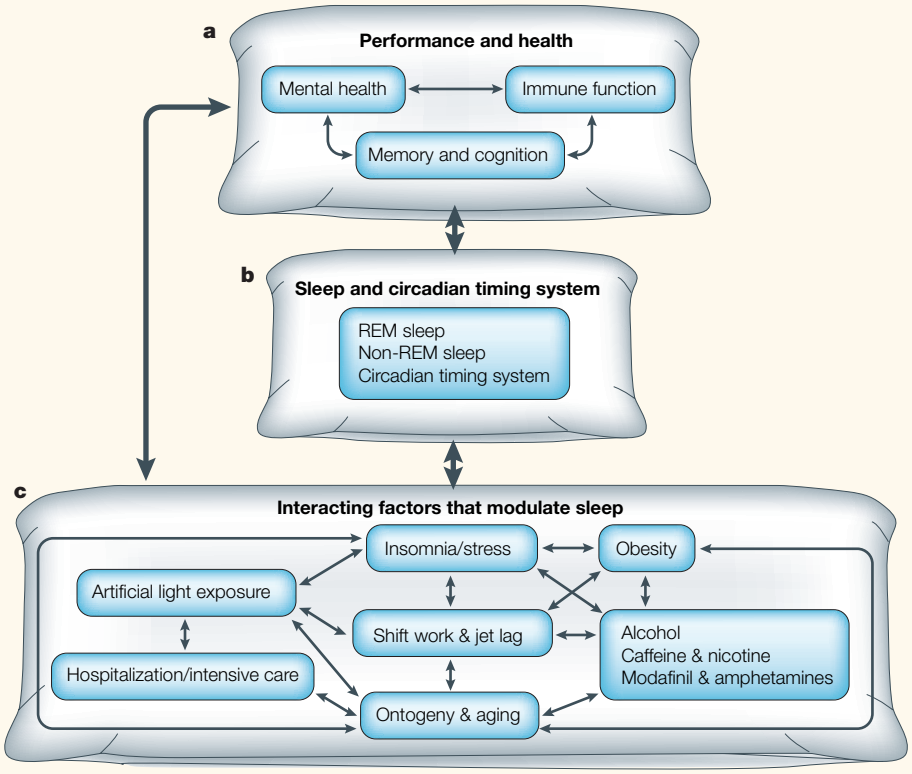

Figure 1 | **Interactions that modulate sleep, health and performance. a** | The interactions between mental health, memory, cognition and immune function that contribute to our performance and health. Mental health problems, for example, are often associated with impaired cognition and decreased immunity [45,118]. **b** | The circadian system is crucial in consolidating and aligning the phases of sleep, and REM and NREM sleep interact to produce a series of sleep stages throughout the night[119]. **c** | The complex interactions between a range of superficially independent agents and conditions. For example, artificial light exposure in shift workers can increase stress, which can, in turn, promote metabolic imbalances that lead to obesity[62]. Stress also encourages the use of alcohol, which, in turn, can lead to obesity and insomnia. Obesity produces further stress and insomnia, promoting the use of sedatives at night and stimulants during the day[110,112]. These interactions are all modulated by age[120], and increasing age promotes the likelihood of hospitalization. Hospitalization is often accompanied by abnormal light exposure, which promotes insomnia or stress[121,122]. Each of these three sets of factors (**a**–**c**) modulates each other, either directly or indirectly (through the sleep and circadian timing system). For example, immune responses (**a**) have a direct effect on sleep arousal states (**b**), which, in turn, influence many of the components in **c**. Changes in **c** have feedback effects on both **a** and **b**.

Sleep seems to be generated by two broadly opposing mechanisms: the homeostatic drive for sleep and the circadian system that regulates wakefulness. The circadian clock adjusts almost every aspect of our physiology, including sleep. Under normal conditions we experience a 24-hour pattern of light and dark, and our circadian system uses the dawn–dusk transition to align biological time to environmental time. The circadian system is then used to anticipate the differing demands of the 24-hour day and to 'fine-tune' physiology and behaviour in advance of the changing conditions. In anticipation of sleep, body temperature drops, blood pressure decreases and sleep propensity increases. Then, before dawn, our metabolism is geared-up in anticipation of increased activity when we wake. The coordinating centre that generates these circadian rhythms resides in a paired cluster of ~20,000 neurons called the suprachiasmatic nuclei (SCN) of the anterior hypothalamus[4]. Together, the circadian and homeostatic processes interact to consolidate sleep.

The homeostatic drive describes an intuitive process, whereby the drive for sleep increases with the length of time that an individual has been awake. This involves mutually inhibitory interactions between sleep-promoting and arousal-promoting systems. Sleep-promoting neurons localized in the ventrolateral preoptic area (VLPO) and median preoptic nucleus (MnPn) exert GABA (γ-aminobutyric acid)-mediated and galaninergic inhibitory control over putative arousal-promoting cell groups that are found in multiple arousal centres in the upper brainstem and diencephalon[5,6]. NREM sleep occurs as a consequence of the activation of VLPO neurons and the progressive decrease in the firing rate of aminergic and cholinergic arousal-promoting neurons, which results from increased GABA release. Both the activation of VLPO neurons and the release of GABA increase proportionally with growing sleep depth. After an adequate amount of sleep, we wake at a circadian time during the transition from night to day. It is the circadian system that determines the timing of sleep propensity and wakefulness, and it is often defined as the wake-promoting system[7,8]. In the absence of the circadian component (for example, after a SCN lesion), sleep still occurs, but becomes highly fragmented and is expressed as a continuous series of relatively short sleep episodes that are promoted by the homeostatic drive alone[9].

In humans and other diurnal mammals, core body temperature and/or melatonin (the principal hormone of the pineal gland) levels might also be important in the consolidation of sleep. A circadian rhythm in melatonin synthesis is regulated by a multi-synaptic pathway that originates in the SCN. The rhythm in pineal melatonin is aligned to the 24-hour day so that melatonin is always released at night. The level of released melatonin rises shortly after dusk and falls in anticipation of dawn. Melatonin synthesis is also acutely inhibited by light. In humans, sleep is normally initiated during the rising phase of melatonin release and the falling phase of core body temperature[10,11]. Attempts to sleep during the declining phase of melatonin and the rising phase of core body temperature, as in night-shift workers (see below), usually result in a shorter and less well consolidated sleep episode[12]. If exogenous melatonin is taken during the day it can induce sleepiness and produce impairments in cognitive performance. Many experiments have shown that people can become sleepy 30–120 min after taking melatonin (0.5–5.0 mg), although not everyone is similarly affected. And, unsurprisingly, it does not have a hypnotic effect in nocturnal rodents. Melatonin can be used to shift the human circadian clock and so to blunt some of the problems associated with jet lag[10,13]. In this context, it is worth noting that the SCN contains high concentrations of melatonin receptors, and that melatonin is particularly effective in suppressing the electrical activity of the SCN around dawn and dusk[14], whereas other neuropeptides, such as pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP), are effective in

modulating the neuronal activity of the SCN at other times of the day through their PAC_1 and $VPAC_2$ receptors[15].

The necessity for sleep

All mammals show patterns of REM and NREM sleep, including the egg-laying platypus and echidna[16,17]. Therefore, the broad nature of our sleep pattern is likely to be at least 120 million years old, and probably much older[18]. Explanations proposed so far for why we sleep are varied and have yet to be fully resolved[19]. This paucity of knowledge has, without doubt, fuelled society's disregard for sleep, and it can only be hoped that this attitude will change as our understanding about the function of sleep increases.

Sleep and cognitive function. Evidence from both animal and human studies indicates that there is a strong link between sleep and what has been termed 'sleep-dependent memory processing'. In many animal studies, sleep deprivation after learning tasks has been shown to impair performance in subsequent tests. Early experiments in this area did not use adequate controls for sleep deprivation, which made it difficult to exclude reduced alertness as the reason for a lowered performance. However, recent studies used the appropriate controls and have made strong and unambiguous associations between sleep and memory consolidation. In humans, the learning of various tasks improves significantly following a night of sleep[20,21]. Furthermore, the selective disruption of REM, but not NREM, sleep abolishes this performance gain[22]. More detailed studies selectively deprived individuals of slow wave sleep (SWS) — stages 3 and 4 of NREM — and REM sleep and concluded that memory consolidation was initiated in SWS and then enhanced during REM sleep[23]. If the sleep-dependent memory processing hypothesis is correct — and not all agree[24] — then it will depend on structural and functional changes in neurons in the CNS[25]. This allows us to conclude, although tentatively, that one aspect of sleep disruption will be impairment of the mechanisms of brain plasticity that are associated with memory and learning.

Sleep duration in humans shows a bell shaped distribution, with an average sleeping duration of 7.0–7.9 h[26–28]. However, some individuals sleep for significantly less time. When people are sleep restricted to 3 or 5 h per day over 7 consecutive days, there is a dose-dependent decline in vigilance and performance[29]. Similarly, when the length of sleep periods is gradually increased after cumulative sleep restriction, performance improves. Interestingly, the first few hours of sleep seem to be particularly important for recovery[30]. This might help to explain why sleep naps of as little as 10 min have been shown to improve subjective alertness[31,32], and how a nap of 60–90 min, which contains both REM and SWS, enhances performance to levels that are equivalent to those seen after a full night of sleep[33]. However, the presumption that the brain can adapt to protracted periods of only a few hours of sleep each night has been contradicted by studying the effect of systematic chronic sleep restriction on cognitive performance. In these experiments, sleep loss caused a marked decline in waking performance, and, significantly, these individuals were largely unaware of this deficit[34,35]. So, sleep impaired individuals are unable to assess the extent of their deficit.

> In humans, the learning of various tasks improves significantly following a night of sleep

Sleep and immune function. The impairment in cognitive performance is an obvious feature of sleep disruption, but this might be the tip of the iceberg in terms of the consequences for our health. Evidence is increasing that there is a complex and important interaction between sleep and the immune system: disrupted or reduced sleep seems to impair the immune system, and immune responses triggered by infection can alter sleep patterns. Sleep-deprived rats readily die of septicaemia[36], and in humans the activity of natural killer cells can be lowered by as much as 28% after only one night without sleep[37]. Loss of sleep also impairs many other aspects of the immune system, including circulating immune complexes, secondary antibody responses and antigen uptake[38,39]. Interestingly, proinflammatory cytokines have been shown to enhance SWS, whereas anti-inflammatory cytokines inhibit NREM sleep. These cytokines are thought to act on NREM sleep through an interaction with growth hormone-releasing hormone, prolactin and VIP[40].

Cortisol provides an important link between the immune system, sleep and psychological stress. Sleep disruption and sustained psychological stress increase cortisol concentrations in the blood. Indeed, one night of lost sleep can raise cortisol concentrations by almost 50% by the following evening[41]. High levels of cortisol suppress the immune system, so excessively tired people are more susceptible to illness. In this context, night-shift workers are at a higher risk of certain types of cancer, and there has been considerable speculation as to the cause[42–44]. In view of the considerable stress and sleep loss that are associated with night-shift work, immune system impairment seems to be the strongest candidate of those proposed for the higher risk of cancers in this group.

Sleep and mental health. Mental health problems are almost always associated with disturbances in sleep, although the causative mechanisms are not clear. Sleep-maintenance insomnia and early morning awakening are hallmarks of major depression, with a lifetime risk of ~20% in the population[45,46]. Of those patients considered to be 'full responders' to antidepressant medication, 44% continue to report sleep disturbances[47]. Furthermore, sleep disturbance is a strong predictor of a relapse into depression in medicated patients[48]. Depression is often accompanied by anxiety disorders, which are also closely related to chronically disturbed sleep. When we experience excessive anxiety, our sleep, work, sense of pleasure and relationships often suffer. Panic disorder, post-traumatic stress disorder, generalized anxiety disorder and social phobia are all anxiety-related disorders that are associated with sleep disruption and loss. A population study involving several European countries indicated that anxiety is related to insomnia in 47% of individuals who have a history of a psychiatric disorder[49].

Several neuropeptide systems have been identified that act broadly on sleep, depression and anxiety. For example, neuropeptide Y (NPY), which is abundantly expressed in many brain regions (including the locus coeruleus, hypothalamus, hippocampus, nucleus accumbens, amygdala and neocortex), is associated with a reduction in sleep latency, anxiety and depression[50]. Galanin (which is found in the hippocampus, amygdala and hypothalamus, with noradrenaline in locus coeruleus neurons, and with serotonin in dorsal raphe neurons) also seems to have sleep-promoting and anxiety-reducing effects[50,51]. By contrast, neuropeptide S (NPS) induces wakefulness but, paradoxically, reduces anxiety[52], and in this respect resembles nicotine[53]. These neuropeptides and/or their analogues provide potentially new pharmacological agents for the treatment of sleep and mental health abnormalities.

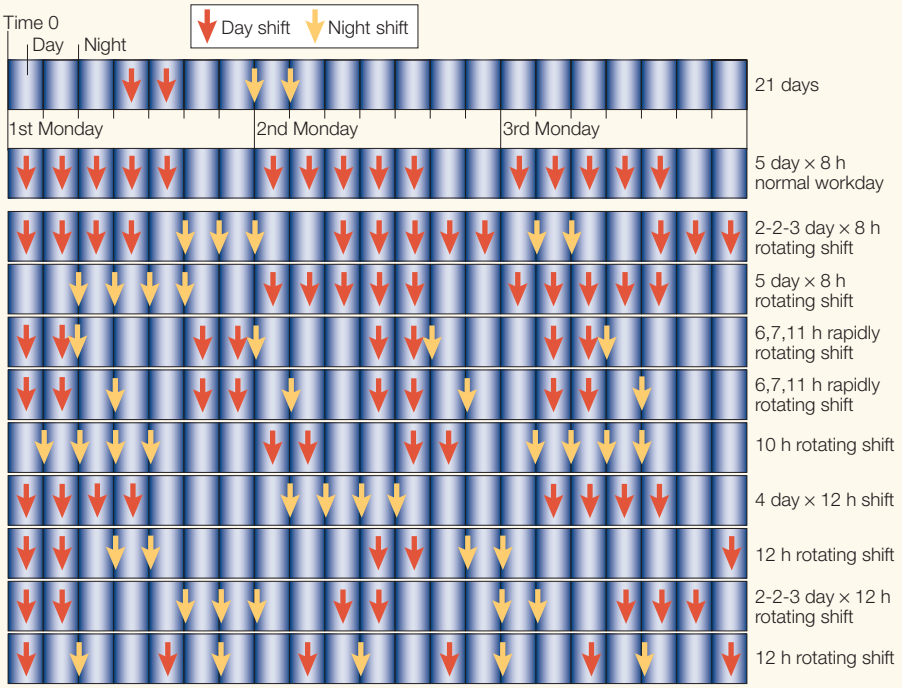

Figure 2 | **Shift-work schedules that have been used in Europe.** This figure illustrates the broad range of operating shift-work systems currently in use in Europe. There is no conclusive evidence to favour any particular shift-work schedule, although there is overwhelming evidence that extended workdays (9–12 h) and night work are harmful[84].The top line illustrates 21 days, with night and day indicated, and the arrows show either a day or night shift. The second line shows the traditional working schedule of 8 h day-time work for 5 days each week. Note that delaying shift schedules (for example, morning to afternoon to night) seems to allow more sleep than advancing schedules (for example, morning to night to afternoon), but still do not allow the circadian system to adapt. Lines 3–11 provide examples of different shift-work schedules, including rotating, rapid rotating and permanent systems[123–125].

Sleep deprivation and shift work

The introduction of electricity and artificial lighting in the nineteenth century and the resultant re-structuring of work times has progressively detached us from the natural 24-hour cycles of light and temperature. We probably sleep less now than any other time in our history. Much has been written about the effects of sleep loss. In general terms, sustained excessive wakefulness will result in performance deficits, including increased errors, poor vigilance, poor memory, reduced mental and physical reaction times, and reduced motivation[2,34,54]. Overall, the impact of inadequate sleep is estimated to cost the US economy $150 billion a year in terms of increased stress and reduced work-place productivity, with women affected 1.5 times more often than men[55].

After 27 h wakefulness, the drop in our cognitive performance is greater than the impairment caused by a blood alcohol concentration of 0.085% — a level that is above the legal driving limit in many countries[56]. Sleep deprivation is also associated with a range of metabolic abnormalities[57], with glucose metabolism[58] and the leptin profile[59] being particularly sensitive. In one study, young men were permitted only 4 h sleep on 6 consecutive nights, and were then given a high-carbohydrate meal. It took 40% longer for the blood-glucose levels of these individuals to be regulated, while their blood insulin was at a level comparable to the levels seen in the early stages of diabetes. These abnormalities were reversed by 12 h sleep. The authors of this study suggested that long-term sleep deprivation might contribute to chronic conditions such as diabetes, obesity and hypertension[60–62]. Sleep loss and obesity could possibly be linked through the functions of body-fat regulating peptide hormones such as leptin and ghrelin[57,63]. Furthermore, obesity is strongly correlated with sleep apnoea and, therefore, additional sleep disturbance[64]. Under these circumstances, a dangerous positive feedback loop of obesity and sleep disturbance can often result.

A recent survey of sleep timing preferences across all ages documented a specific delay in sleep timing during adolescence that might be controlled by the circadian sleep–wake system[65]. However, it is unlikely that the circadian system functions alone. Increasing autonomy, social activities, greater access to evening entertainment (for example, television in the bedroom, computer game play and internet use) and studying for examinations all combine to drive delayed bed times and rise times. Consequently, many adolescents show a dramatically reduced sleep time, greater weekend sleeps and general oversleeping. The high levels of day-time sleepiness seen in such adolescents are comparable with the excessive sleepiness that is caused by sleep apnoea.

Like shift-workers, sleepy teenagers are more inclined to use stimulant drugs, nicotine or caffeine to overcome sleepiness (see below), and teenagers form the largest at-risk group for drowsy driving and 'fall-asleep' car accidents[66]. Despite a large body of literature documenting associations between delayed sleep and high levels of sleep deprivation with impaired attention and psychopathologies, these problems have been largely ignored in terms of the time structure imposed on teenagers. Several studies have provided further evidence supporting a change, showing that a later starting time for school greatly improves the alertness and daytime function of teenagers[67,68].

Sleep loss and disruption is most obvious in night-shift workers and individuals with insomnia. More than 20% of the population of employment age work for at least some time outside the 7.00 a.m.–7.00 p.m. day[69]. The introduction of modern daily work shifts in the 1970s reduced the working week from 42–38 or even 36 h per week, and this compression of working hours has increased the time available for work-free periods and leisure activities[70]. However, this has come at a considerable cost[71]. Josephine Arendt at the University of Surrey makes the point, "Because of their rapidly changing and conflicting light–dark exposure and activity–rest behavior, shift workers can have symptoms similar to those of jetlag. Although travelers normally adapt to the new time zone, shift workers usually live out of phase with local time cues". Even after 20 years of night-shift work, individuals do not normally show shifts in their circadian rhythms in response to the demands of working at night[72].

This failure to adapt has provided a strong drive to develop a better 'shift system'. Despite the great variety and complexity of 'shift systems' that have been tried (FIG. 2), so far all attempts have failed to fully alleviate the circadian problems associated with shift work. Metabolism, along with alertness and performance, are still high during the day when the night-shift worker is trying to sleep, and low at night when the individual is trying to work. A misaligned physiology, along with poor sleep, in night-shift workers has been associated with increased cardiovascular

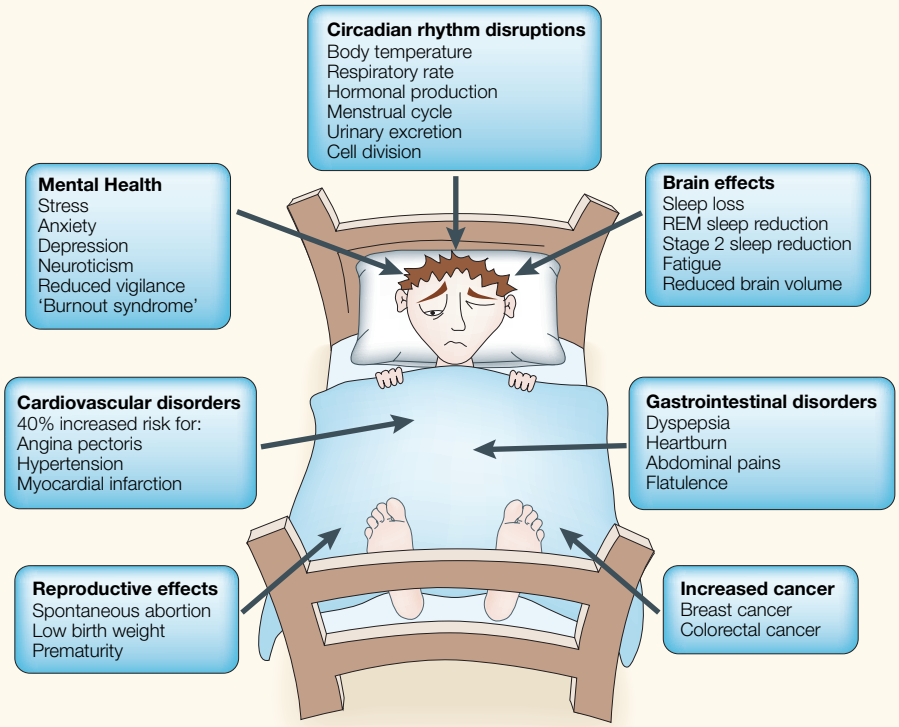

Figure 3 | **Health problems associated with shift work.** The figure illustrates the many physiological and mental health problems that could result from long-term shift work and the associated sleep disruption. REM, rapid eye movement. For further information, see REFS 43,72–75,126,127.

mortality, an eightfold increase in the incidence of peptic ulcers and a higher risk of some forms of cancer[72–75]. Other problems include a greater risk of accidents[76], chronic fatigue, excessive sleepiness, difficulty sleeping, higher rates of substance abuse and depression. Night-shift workers are also much more likely to view their jobs as extremely stressful[77] (FIG. 3).

So, why do the clocks of shift workers not shift in response to exposure to light at night in the work place? This is because the circadian system reseponds to bright natural sunlight as the 'day' in preference to the dim artificial lights commonly found in the workplace at night. Exposure to strong natural light on the journey to and from work, and perhaps during the day, normally prevents the night-shift worker from shifting. However, in the absence of any natural light the clock will eventually respond to man-made light. Theoretically, this information could be used to develop practical counter-measures to the problems of working at night. However, most night-shift workers prefer not to be adapted to a reversed sleep–wake cycle, as they like to spend their work-free time with family and friends at maximum alertness[70,78–80]. A possible compromise would be a partial adaptation to night shifts and daytime sleep[81], although not everybody is likely to adapt to this schedule in the same way. 'Evening types' have naturally better alertness in later hours and so make better night-shift workers, whereas 'morning types' are usually better at adapting to early morning shifts[82]. In the future, individuals involved in shift work could be asked about their sleep preferences, and work schedules could be allocated accordingly[82]. Given the restorative effect of a 60–90 min nap on cognitive performance, it is perhaps surprising that long naps have not been more regularly incorporated into shift-work schedules[33].

The alarming consequences of sleep deprivation have also been shown in several studies on American medical students in their first postgraduate year working in a hospital[83–85]. These students had weekly work schedules of ~70–80 h, and extended work shifts of ~32 h four times a month. Remarkably, this regime is currently approved by the Association of American Medical Colleges[84,86]. The students showed a 16.2% increased risk of a motor vehicle accident during their commute from work to home, and a large increase in attentional failures while working overnight in the intensive care unit. By reducing the number of work hours to 63, and with a maximum of 16 h per shift, the rate of attentional failures was less than half that observed for the 32-h shift. These examples illustrate the impact of long hours and long shifts on health and safety, and the obvious need for enforceable regulations relating to working hours in all sectors of the community, including public transportation and education[1]. Potential indicators for the detection of excessive sleepiness while driving include oculomotor impairments. For example, saccadic velocity slows significantly with partial sleep deprivation, and correlates with impaired driving performance[87].

Insomnia occurs in ~20% of the general population, with rates at their highest in retired people, women, the unemployed and white-collar workers[88,89]. All of these individuals have difficulties in falling asleep (taking more than 45 min), show disrupted sleep, often waking early, and feel excessively sleepy during the following day. Although some of these individuals show objective sleep-stage disturbances in NREM and REM sleep, others who complain of poor sleep fail to show abnormal EEG sleep records[90]. For a long time insomnia was considered to be a symptom, but is now more often thought of as a syndrome, with various causes that lead to specific disorders. The most consistent impact of insomnia is a high risk of depression. The causes of insomnia are far from clear, but there is increasing evidence that both the sleep and waking systems of the brain are involved, and some form of 'hyperarousal' has been proposed as a possible mechanism. Individuals with insomnia show higher levels of metabolic activity in the brain during both wakefulness and NREM sleep, and their inability to fall asleep may be related to a failure of arousal mechanisms to decline in activity from waking to sleep states[91,92]. An objective analysis of the nature of sleep loss and behaviour has emerged in the form of brain imaging[93–96]. Neuroimaging of the brain in primary insomnia revealed unexpected results of transient hypometabolic rather than hypermetabolic activity[97], which indicates a homeostasis-related imbalance of sleep.

Social drugs that modulate sleep

All human societies — not just those of the advanced industrial nations — are awash with socially acceptable drugs that modify sleep and alertness. A daily cycle of drug-induced stimulation and sedation characterizes the typical day for billions of people, and in view of our lack of sleep this might not be too surprising[98]. Amphetamines and cocaine were popular stimulants all over the world until their dangerous addictive qualities were appreciated, and their use became proscribed during the 1950s. Today, the most frequently used stimulants are caffeine

Table 1 | **The caffeine content of various beverages, foods and drugs**

Beverages, foods and drugs	*Caffeine content (mg)
Sprite or Fanta (12 oz/360 ml)	0
Decaffeinated coffee (8 oz/240 ml)	1–5
Milk chocolate (1 oz/28 g)	6
Green tea (8 oz/240 ml)	15–20
Dark chocolate (1 oz/28 g)	20
Pepsi Cola (12 oz/360 ml)	38
Dr Pepper (12 oz/360 ml)	40
Coca-Cola (12 oz/360 ml)	46
Black tea (8 oz/240 ml)	40–60
Espresso (2 oz/60 ml)	50–120
Red Bull (8.2 oz/246 ml)	80
Instant coffee (8 oz/240 ml)	65–100
Brewed coffee (8 oz/240ml)	80–135
Drip coffee (8 oz/240ml)	115–175
Typical caffeine pill	200

*Values supplied by the US Food and Drug Administration.

and nicotine, with alcohol often consumed as a sedative to reverse the effects of these stimulants. Consumption of these drugs has never been higher, although drugs such as modafinil (Provigil; Cephalon) might conceivably replace these ancient stimulants in our search for a 'cure' for sleep.

A cup of coffee or tea represents the start of the day for hundreds of millions of people, and caffeinated drinks are used throughout the day as a stimulant by both adults and children. The caffeine content of these drinks is summarised in TABLE 1. The alerting effects of caffeine occur within 15–30 min. This stimulant modulates performance, learning and memory, and muscular strength, and reduces overall sleepiness. Caffeine seems to advance the time of REM sleep, produce an overall reduction in SWS and interrupt consolidated sleep. There is considerable individual variation in the speed at which caffeine is metabolized, having a half-life of between 3 h and 7 h, with an average of 4 h. So, an afternoon or evening cup of coffee can still result in a significant amount of caffeine in the body at bedtime, which will delay sleep. Caffeine might act by competitively binding to an adenosine receptor subtype, thereby blocking the mood-depressing and sleep-inducing effects of adenosine[99]. Although caffeine is only mildly addictive compared with nicotine, our dependence on this stimulant is illustrated by the fact that more than 6×10^8 kg of coffee beans are sold each year, which, after oil, constitutes the second most valuable commodity traded on the open market.

The frequent accompaniment to coffee is nicotine, another drug that came into common use with caffeine[100]. The use and sale of tobacco is accompanied by government health warnings and the common knowledge that this substance has caused countless deaths. One of the reasons that we remain addicted to this substance is that the nicotine in tobacco frequently has a marked improvement on cognitive performance by mimicking the action of acetylcholine[101]. Tobacco smoking is more prevalent in night-shift workers (for example, nurses[102]), probably because after sleep deprivation cognitive performance — in terms of alertness, hand-eye coordination, concentration, reaction times and short-term memory — is improved in smokers compared with non-smokers[103]. Furthermore, long-term memory and learning seem to be enhanced as a result of nicotine exposure[104]. Given these effects on arousal, it is perhaps not surprising that nicotine reduces both the duration and quality of sleep. Furthermore, smokers also tend to drink more caffeinated drinks[105,106].

Alcohol is frequently used to help promote sleep. Its effects on the brain vary, but four neurotransmitter systems are generally affected: glutamate, GABA, dopamine and serotonin[107]. A study in the USA during the 1990s found that 13% of individuals had used alcohol to help induce sleep during the previous year compared with 18% who had used medications and 5% who had used both[108]. In societies with more relaxed drinking laws, such as Europe, this figure is probably higher. Although alcohol can promote sleep, it also disrupts certain aspects of sleep — in particular, it reduces the total duration of the sleep period and the amount of REM sleep experienced during the second half of the night. It also exacerbates daytime sleepiness. Regular alcohol consumption builds up a tolerance to sleep induction and so the same level of sedation requires increasing concentrations of alcohol over time. When alcohol consumption turns into abuse, insomnia is one of the most obvious side effects[109]. A recent study showed that 61% of alcoholics entering a treatment programme had suffered insomnia over the previous 6 months. Even after alcoholics have stopped drinking, their sleep patterns can be abnormal for as much as 2 years. Alcohol also acts to relax the muscles of the upper airway. This partial collapse of the upper airway restricts air flow and makes breathing more difficult, and in severe cases causes sleep apnoea and, therefore, yet more interrupted sleep[110].

The search is on to create the 'metabolically dominant soldier' — a warrior who can fight for 24 hours a day for 7 days without rest. Eliminating the need for sleep while maintaining a high level of mental and physical performance is considered to be the way forward in modern warfare. Soldiers, sailors and aircrew have to make instant decisions based on incomplete information. Even a slight drop in cognitive performance can make all the difference between life and death[4], which helps to explain why USAF aircrews have regularly used amphetamines[111]. However, a range of side effects are associated with amphetamine use, including agitation, irritability, nausea and impotence. Furthermore, when the drug wears off it can lead to a rebound effect that causes extreme fatigue or depression[112].

By contrast, modafinil is a so-called eugeroic ('good arousal') drug[111] that has been shown to increase both wakefulness and vigilance. The French government admitted that the Foreign Legion used modafinil during covert operations inside Iraq during the first Gulf War. There are great hopes for modafinil among the US military[113], with unpublished reports indicating that after more than 24 h sleep deprivation modafinil can produce a marked improvement in both subjective sleepiness and cognitive skills. However, this improvement is not equivalent to the effect of a full night of sleep (C. Czeisler, personal communication). At present, it is unclear how modafinil works[114,115], but it is also proving clinically useful in the treatment of a range of disorders that are associated with impaired

cognitive performance, including narcolepsy, Alzheimer's disease, depression and attention-deficit disorder[116,117]. Police, hospital staff, pilots, other groups who work all night and even students taking exams are among the tens of millions in our 24-hour society who might also be tempted to take modafinil. Caffeine and nicotine have been the dominant (legal) alerting drugs of the nineteenth and twentieth centuries, but modafinil and its analogues might be the stimulants of the twenty-first century.

Conclusions and perspectives

Because we are not conscious when we are asleep this important aspect of our lives fails to impinge on our consciousness much of the time. In short, we tend to ignore sleep. We have only the most rudimentary grasp of the function of sleep, and yet we seem driven to casually discard this aspect of our physiology. The discussion above has highlighted some of the problems we face if we ignore the role of sleep and circadian timing in our lives. Our biology and our society seem to be in serious opposition, and it is not clear which force will win. Although it is true that millions of years of natural selection have made us what we are, our problem is that we don't really understand what that is.

So, where do we go from here? Based on our increasing understanding of the mechanisms that generate circadian rhythms and sleep, it is not too far-fetched to imagine that in the next few years we will develop a range of drugs that could be used to manipulate these rhythms. We might develop a world in which we sleep for only 2 hours a night, and are active throughout the other 22 hours. This would have a profound impact on the structure of our society, the nature of work, the way we educate our children and even how we might care for an increasingly aged population. We could become the first species to dominate both day- and night-time. This last frontier has certainly been eroded, and we are now set for a full-scale invasion. We have to make some difficult choices. We could manage the continued development of the '24-hour society' and, if necessary, use pharmacological intervention to counteract the biological downside of working around the clock; or we could reject the trend and use what we know about the clock to embrace sleep and biological time, and thereby gain the advantages of millions of years of evolution.

But have we gone too far? Are we still truly free to make these choices? We cannot 'turn back the clock' and 'the 24/7 genie will not return to its bottle' have become the mantra of society, and, as a result, many believe that we have no alternative but to wage total war on the night. It seems likely that technology will help us to cope with 24/7. But is coping really living? In one sense it might not matter that much, as many of us will become so numb that we will no longer be able to appreciate the difference between existing and living. Surly the future can be made better than this?

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Competing interests statement

The authors declare no competing financial interests.

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