J Neurol (2010) 257:882–897
DOI 10.1007/s00415-010-5517-4

REVIEW

How vital is sleep in Huntington's disease?

Anna O. G. Goodman · Roger A. Barker

Received: 10 November 2009 / Revised: 15 February 2010 / Accepted: 25 February 2010 / Published online: 24 March 2010

Abstract Huntington's disease (HD) is a fatal neurodegenerative disease caused by an abnormal expansion of a CAG repeat in exon 1 of the HD gene on chromosome 4. The disease runs a debilitating and progressive course with an average survival of 15–25 years after disease onset. HD patients classically develop involuntary movements including chorea, as well as progressive cognitive and psychiatric disturbances, although a number of other features have also been reported, including changes in sleep and circadian rhythms; it is this latter area that forms the focus of this review.

Keywords Huntington's disease · Sleep · Circadian rhythms · Quality of life · Polysomnography · Actigraphy

Introduction

Huntington's disease (HD) is a progressive, fatal neurodegenerative disease caused by an abnormal expansion of a CAG repeat in exon 1 of the huntingtin gene (Huntington's Disease Collaborative Research Group, 1993). The disease affects approximately 4–8 individuals per 100,000 [64] and typically presents between 35 and 45 years of age, with an average survival of 15–25 years after disease onset (Bates et al. 2002).

HD neuropathology shows a loss of up to 30% of brain weight resulting from neuronal cell death, with a direct correlation between brain atrophy and duration and severity of the disease [174]. Despite the widespread location of the mutant huntingtin, the primary atrophy of HD is located within the central nervous system. Whilst the basal ganglia have been shown to be preferentially affected with up to 60% loss of mass in the caudate nucleus, putamen, and globus pallidus [174], neurodegeneration is more widespread, probably from disease onset [140, 141], and includes a range of cortical and subcortical structures.

The classical description of HD is of involuntary choreiform movements involving the limbs and face, which reverts to bradykinesia, rigidity, postural instability, as well as axial posturing, or dystonia with disease progression [79]. HD patients also develop progressive cognitive [57, 91, 102] and psychiatric disturbances [58, 119, 120, 142, 155]. However, a number of other features have also been reported, including weight loss [6, 31, 59, 139] and changes in sleep [3, 123, 172]. Figure 1 highlights the brain regions affected in HD that are also involved in sleep.

Stages of sleep

Sleep is defined by different stages that occur in a characteristic, sequential order with specific electrophysiological patterns on electroencephalography (EEG) linked to electromyography (EMG) and electrooculography (EOG), collectively known as polysomnography (PSG) [138]. Sleep typically consists of a non-rapid eye movement phase (NREM), in which an increasing depth of sleep is seen from Stages 1–2 ('light sleep') to 3–4 ['deep sleep' or 'slow wave sleep' (SWS)]. The entire sequence from Stage 1–4 takes approximately 60–90 min in normal subjects, followed by rapid eye movement (REM) sleep. After approximately 10 min of REM sleep, the brain typically cycles back through the NREM sleep stages. This cyclical pattern repeats four to five times a night (see Fig. 2). Early

A. O. G. Goodman (✉) · R. A. Barker
Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, UK
e-mail: aogr2@cam.ac.uk

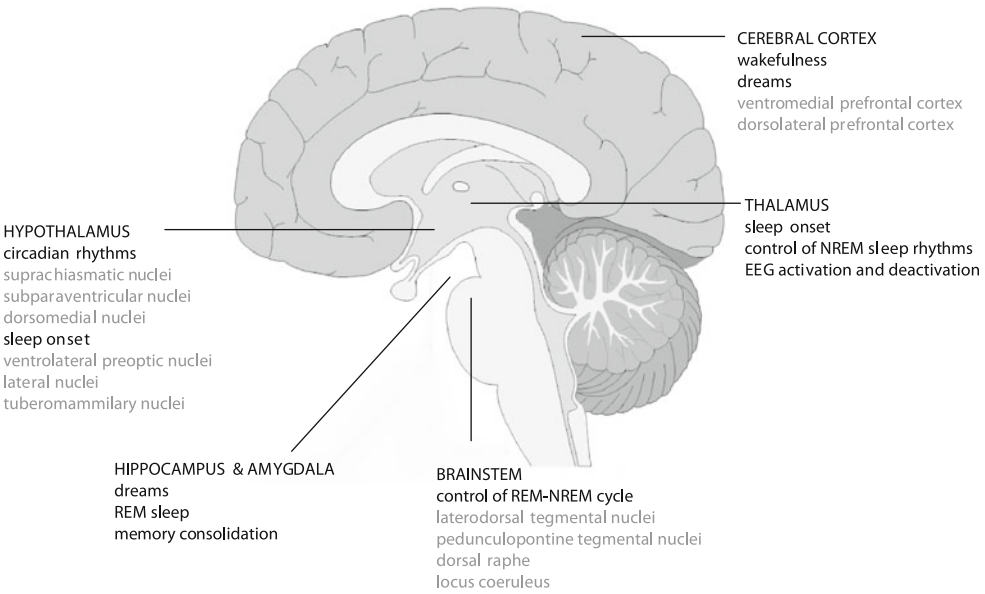


Fig. 1 Areas of the brain that experience pathology in HD that are also involved with sleep and circadian rhythms. Schematic diagram showing the various brain regions that experience pathology as part of the course of the disease which are also involved with the regulation of sleep and circadian rhythms

	Brain regions affected in HD (with references)	Involved in sleep
Amygdala	Rosas et al., 2003	✓
Brainstem	Rosas et al., 2003	✓
Cerebellum	Vonsattel et al., 1985; Rosas et al., 2003	
Cerebral Cortex	de la Monte et al., 1988; Rosas et al., 2003; Rosas et al., 2008	✓
Cerebrum	Rosas et al., 2003	
Hippocampus	Rosas et al., 2003	✓
Hypothalamus	Kremer et al., 1990; Kassubek et al., 2004; Petersen et al., 2005; Politis et al., 2008	✓
Striatum	Vonsattel et al., 1985; Rosas et al., 2003; Kassubek et al., 2004; Muhlau et al., 2007	
Substantia Nigra	Oyanagi et al., 1989	
Thalamus	Dom et al., 1976; Jernigan et al., 1991; Muhlau et al., 2007	✓
White matter	Rosas et al., 2003	

in the night, NREM sleep is usually deeper and occupies a disproportionately large amount of time, especially in the first cycle, whilst REM sleep might be short or aborted. Later in the night, NREM sleep is lighter whereas a higher proportion of each cycle is made up of REM sleep [4], this effect is known as the polarity of REM sleep and is caused by a combination of circadian and sleep-dependant factors.

Neurophysiology of sleep

Regional regulation of sleep

Traditionally, sleep has been considered to be a property of the whole organism, resulting in either an awake, drowsy or sleep state. This 'whole-organism sleep' was understood to be initiated and regulated centrally by interactions between specialized sleep and wake-promoting neuronal networks [78, 104, 146, 161]. More recently, a new theory has emerged suggesting that sleep is local and activity- or use-dependent, and is then consolidated by these central mechanisms. The primary units that transition between the sleeping and waking states are 'cortical columns', tightly connected neurons located in the cortex [82–84]. Therefore, sleep at this level of organization is auto-regulatory in that prior and ongoing activity in the network determines the probability of the network entering the sleep-like state, at least at the cortical level.

Central regulation of sleep

Once sleep is initiated locally as a consequence of previous activity, it is then consolidated by central mechanisms [84].

Wakefulness

Centrally, several distinct neuronal populations mediate arousal and the cortical desynchrony of wakefulness via

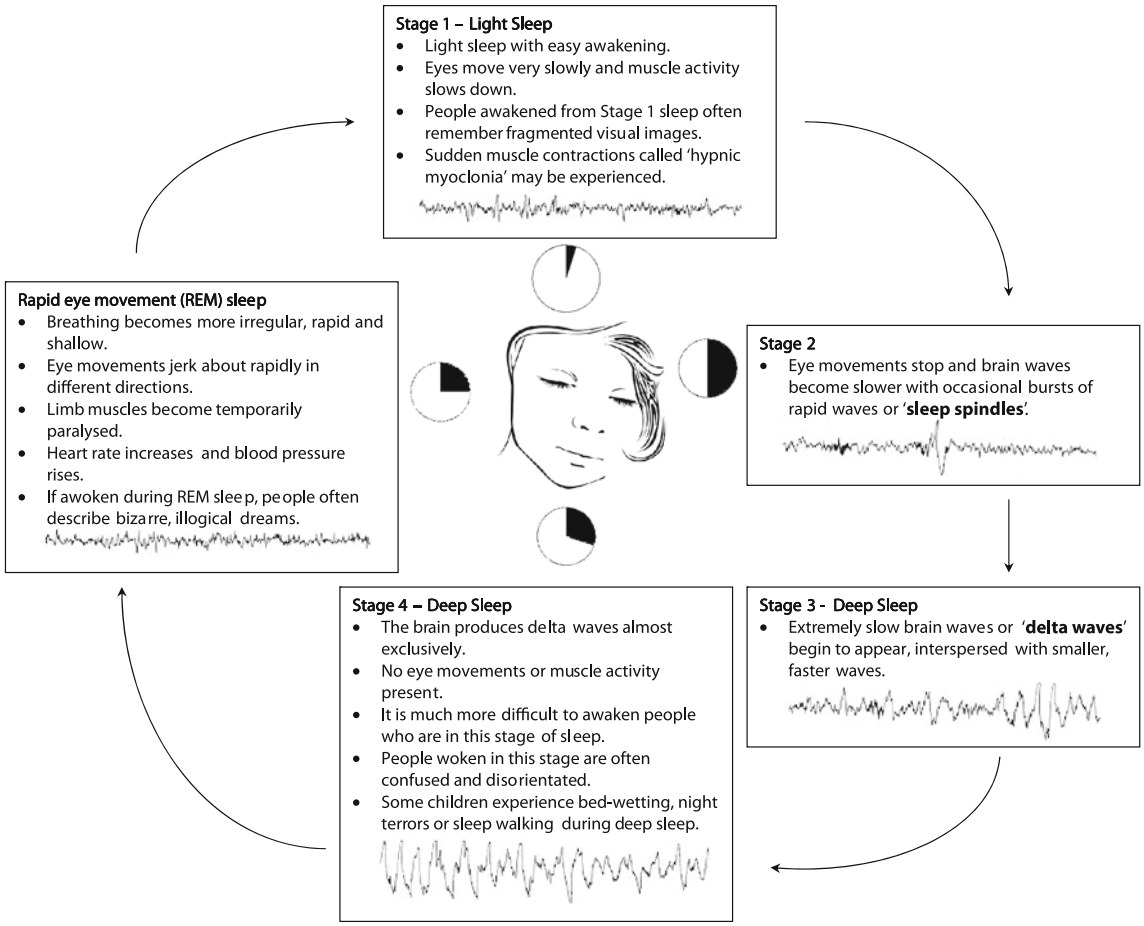


Fig. 2 Different stages of sleep in a healthy young adult. Stages of sleep progress in a cycle from Stage 1 to REM sleep. *Shaded circles* represent percentage of time spent in the various stages of sleep. Adult humans spend approximately 5% in Stage 1 sleep, 50% in Stage 2 sleep, 20% in Stages 3 and 4 (SWS) and 25% in REM sleep. In contrast, infants spend about 50% of their time in REM sleep. An increase in age normally results in decreased metabolic rate and physical activity and thus a decrease in energy demands and the need to conserve energy. As a consequence, SWS and total sleep normally decreases while Stage 1 sleep increases [9, 123]. Stage 2 and REM sleep, however, remain unchanged until very old age [29, 66], although Stage 2 sleep spindles and K complexes become less well formed, less numerous, lower in frequency (spindles) and amplitude (K-complexes), and are accompanied by more awakenings during the night [123]

projections to the thalamus and basal forebrain [107, 146]. Circuits regulating NREM sleep include the preoptic anterior hypothalamus, which contains the ventrolateral preoptic (VLPO) area, the median preoptic area and the basal forebrain. REM sleep and the alternation between NREM and REM sleep are also under central control, with the pedunculopontine tegmental nucleus (PPT) and the laterodorsal tegmental (LDT) nuclei being especially important in this process. Multiple wake-promoting networks also exist, including the orexin system in the lateral hypothalamus. This is summarised in Fig. 3, and shows that the ascending arousal system (AAS) has two major elements to it: the ascending pathway to the thalamus which activates the thalamic relay neurons which are important for transmitting information to the cerebral cortex, and a second pathway which activates the cerebral cortex to facilitate the processing of thalamic input.

Sleep

The VLPO of the anterior hypothalamus is a critical region involved in inhibiting the arousal circuits during sleep [152]. Neurons in the VLPO send outputs to all of the major cell groups in the brainstem and hypothalamus involved with arousal [152]. VLPO neurons are active during sleep, therefore specific VLPO neuronal loss produces profound insomnia and sleep fragmentation [94]. It has been shown that the sleep-promoting anterior regions directly interact with the wake-promoting posterior regions of the hypothalamus in a mutually inhibitory manner [152]; as a result, these pathways function like a classic 'flip–flop' switch which produces sharp transitions in state, but is relatively unstable [52, 99, 145]. The addition of the LH orexin neurons, which are located outside the flip–flop switch, stabilizes it, thereby reducing transitions during both sleep and

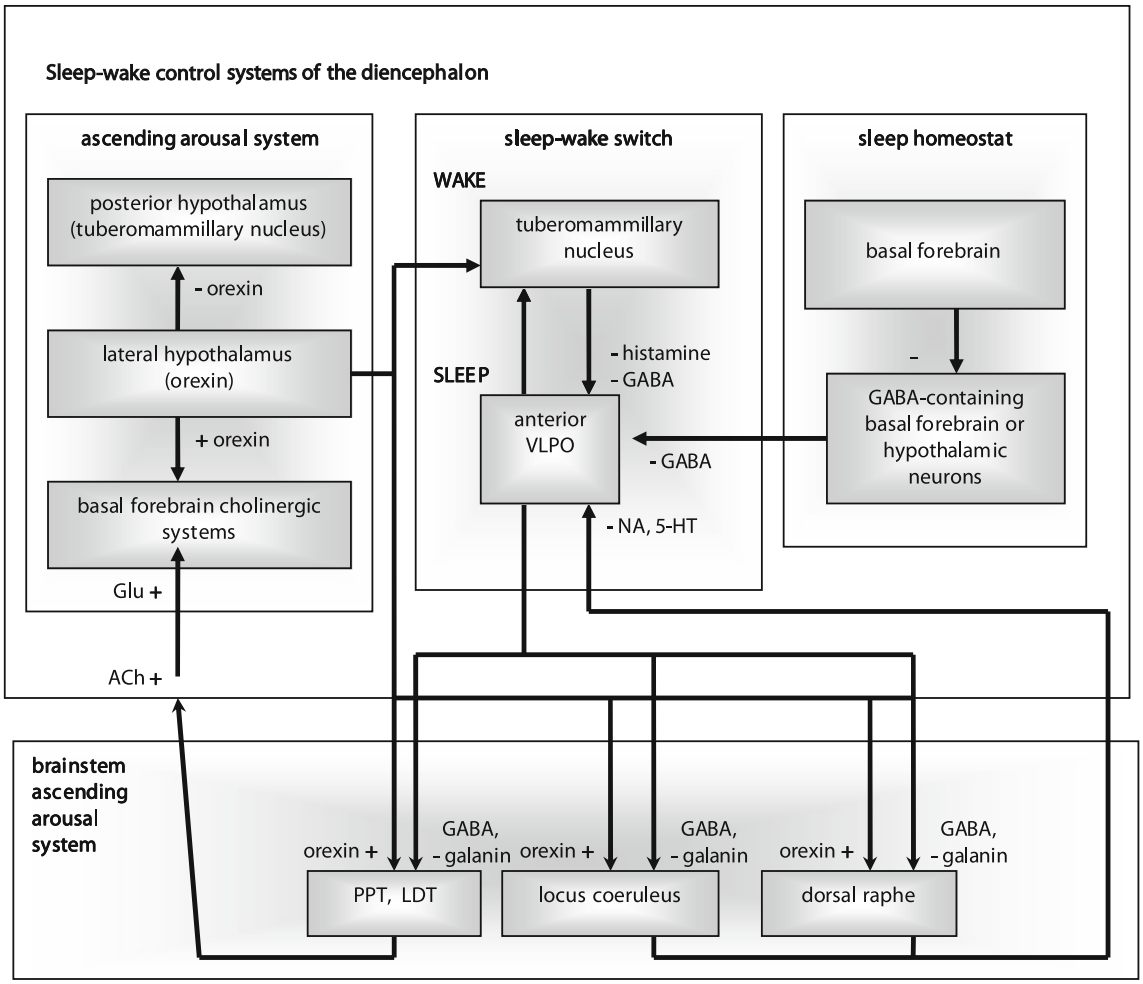


Fig. 3 Sleep–wake control systems of the subthalamic diencephalon and associated links to input from the circadian clock and to ascending arousal systems of the brainstem. Primary interactions include disinhibition of the sleep-promoting ventrolateral pre-optic area (VLPO) neurons by adenosinergic inhibition of GABA (γ-aminobutyric acid)-containing basal forebrain neurons [163]; VLPO GABA-mediated inhibition of brainstem and diencephalic ascending arousal systems [152]; reciprocal inhibition of VLPO cells by noradrenergic and serotonergic input from ascending brainstem arousal systems [160], and by GABA-containing cells of the tuberomammillary nucleus that are co-localized with histaminergic neurons [52, 145]; wake-related orexinergic stabilization of these same ascending arousal systems [145]; and brainstem cholinergic facilitation of wake-related basal forebrain cholinergic activity through a glutamatergic intermediary. *5-HT* 5-hydroxytryptamine (serotonin), *ACh* acetylcholine, *Glu* glutamate, *LDT* laterodorsal tegmental nucleus, *NA* noradrenaline, *NREM* non rapid eye movement, *PGO* Ponto-geniculo-occipital, *PPT* pedunculopontine tegmental nucleus, *REM* rapid eye movement. *VLPO* ventrolateral preoptic area. Diagram was modified from [115]

wakefulness. Thus, narcoleptic humans who lack orexin have increased transitions between these two states [145].

Sleep regulatory substances

Many substances have been implicated in sleep regulation. Sleep regulatory substances (SRS) act on subcortical sleep-regulatory circuits [111]. It is generally agreed that nitric oxide (NO), adenosine, prostaglandin D_2, interleukin-1 (IL1), tumour-necrosis factor (TNF), and growth-hormone-releasing hormone (GHRH) are all involved in the regulation of the duration and intensity of NREM sleep [111]. These substances work in the biochemical cascades that form the NREM sleep homeostat and act on the basal forebrain neurons [7], the hypothalamic preoptic neurons [111], the locus coeruleus [28] or the serotonergic neurons of the raphe to promote NREM sleep [96]. REM sleep-promoting substances include vasoactive intestinal polypeptide, while prolactin and wake-promoting substances include orexin (mentioned previously), ghrelin, adrenocorticotrophin hormone and corticotrophin-releasing hormone (Tables 1, 2).

Table 1 Neural activity of neurotransmitter systems during sleep and wakefulness

Brainstem nuclei involved	Neurotransmitter	Activity state of relevant brainstem neurons
Wakefulness		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Active
Locus coeruleus	Noradrenaline	Active
Raphe nuclei	Serotonin	Active
NREM sleep		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Low activity
Locus coeruleus	Noradrenaline	Low activity
Raphe nuclei	Serotonin	Low activity
REM sleep on		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Active (PGO waves)
Locus coeruleus	Noradrenaline	Very low activity
Raphe nuclei	Serotonin	Very low activity
REM sleep off		
Locus coeruleus	Noradrenaline	Active

Table 2 Results from past HD-related sleep studies

First author	Year	Subjects (*n*)		Methods	Results
		HD patients	Control subjects		
Videnovic	2009	30	0	Questionnaires Interview	1. 77% had abnormal sleep 2. Poor nocturnal sleep was associated with longer disease duration 3. 80% Nocturnal or early morning awakening 4. 50% Excessive daytime sleepiness 5. 20% Symptoms suggestive of REM behaviour disorder
Arnulf	2008	25	50	PSG MSLT	1. 12% REM behaviour disorder 2. Lower sleep efficiency 3. Increased Stage 1 sleep 4. Reduced REM with no narcolepsy 5. Periodic limb movements 6. Insomnia 7. Earlier sleep onset
Morton	2005	8	3	Actigraphy Sleep diary	Altered sleep–wake activity pattern
Wiegand	1991	16	16	PSG	1. Increased sleep onset latency 2. Reduced sleep efficiency 3. Reduced SWS 4. Frequent nocturnal awakenings 5. No differences reported between medicated versus non-medicated patients.
Emser	1988	10	22 (12 with PD)	PSG	HD, Increased sleep spindle density (PD, Reduced sleep spindle density and SWS)
Hansotia	1985	7	6	PSG	Advanced HD 1. Reduced sleep efficiency 2. Increased sleep onset latency 3. Increased interspersed wakefulness

HD Huntington's disease, *PD* Parkinson's disease, *PSG* polysomnography, *MSLT* multiple sleep latency tests, *REM* rapid eye movement, *SWS* slow wave sleep

SRSs, therefore, act locally in the cortex to enhance sleep phenotypes by causing changes to the electrical and chemical outputs of a network, thereby altering their responsiveness to inputs [1, 21, 154].

Circadian rhythms

In mammals, the 'master' internal circadian clock is located in the suprachiasmatic nuclei (SCN) of the anterior

hypothalamus and is vital for establishing the circadian rhythm of sleep–wake, Fig. 4.

The primary environmental synchronizer of mammalian circadian rhythms is the daily light–dark cycle. A class of intrinsically photosensitive retinal ganglion cells that express the photopigment melanopsin integrates photic information for entrainment within the retina and projects to the SCN core via the retinohypothalamic tract [11, 60]. The mechanism behind the circadian clock in mammals involves a cell autonomous transcription–translation negative-feedback loop consisting of a highly conserved set of core genes; *Clock*, *Bmal1*, period homologue 1 (*Per1*), *Per2*, Cryptochrome 1 (*Cry1*) and *Cry2* [8, 93, 167], see Fig. 5a.

Despite a recognized role for the SCN in governing the timing of sleep, the SCN has no monosynaptic outputs at all to the brainstem arousal sites and only minimal outputs to sleep-regulatory centers such as the LH and VLPO.

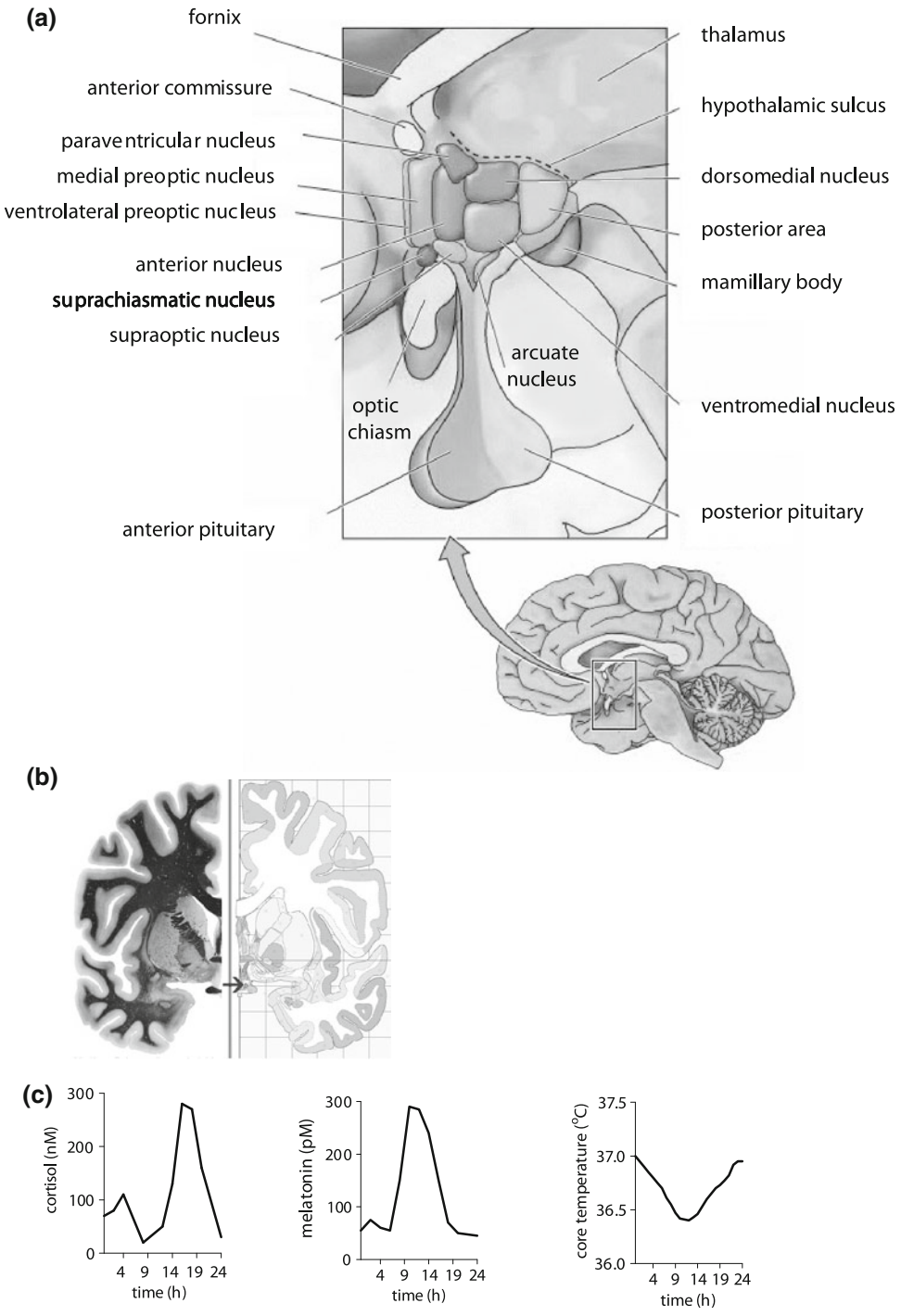


Fig. 4 The suprachiasmatic nucleus. **a** A schematic diagram showing a cross-section of the hypothalamus highlighting (in *bold*) the location of the suprachiasmatic nucleus (SCN), the body's 'clock' in relation to other hypothalamic nuclei. Reproduced with permission from Sinauer Associates. **b** Cross-section of the human brain highlighting the location of the SCN (*arrow*). Reproduced with permission from J. Mai, Atlas of the Human Brain, Elsevier 2007. **c** Circadian rhythms of cortisol, melatonin and core body temperature

The circadian regulation of sleep behavior is therefore thought to be mediated by multisynaptic projections from the SCN to sleep–wake centers of the brain [30, 146] via the ventral subparaventricular zone (SPZ) [175], followed by a secondary projection to the dorsomedial hypothalamic nucleus (DMH). The DMH sends an excitatory dense glutamatergic projection to the lateral hypothalamus and an inhibitory GABAergic projection to the VLPO [20], and is critical in the circadian regulation of sleep–wake cycles, see Fig. 5b.

The SCN clockwork also has active local "clock" systems in peripheral, non-neural tissues such as the lung, liver, pancreas, spleen, thymus and the skin [65]. These local clockworks are tuned into each other, and to solar time, by metabolic and neuroendocrine cues that depend on the SCN. Output pathways from the SCN, therefore, are not limited to the control of sleep–wake cycles and have been shown to mediate a diverse number of physiological functions both in the brain and the periphery, including the timing of hormone release, feeding behaviour and body-temperature fluctuations [2, 146].

In conclusion, even though there are central global coordinators of the sleep–wake states, such as the clock mechanisms of the SCN, the global co-ordination of NREM sleep is likely to reflect an emergent property of loosely coupled local processes. Sleep-regulatory circuits, therefore, integrate information that is related to locally induced cortical column states with information that is important for the determination of whether an animal is ultimately awake or asleep, for example the time of day, mental activity, sensory input and emotion and disease related information.

Purpose of sleep

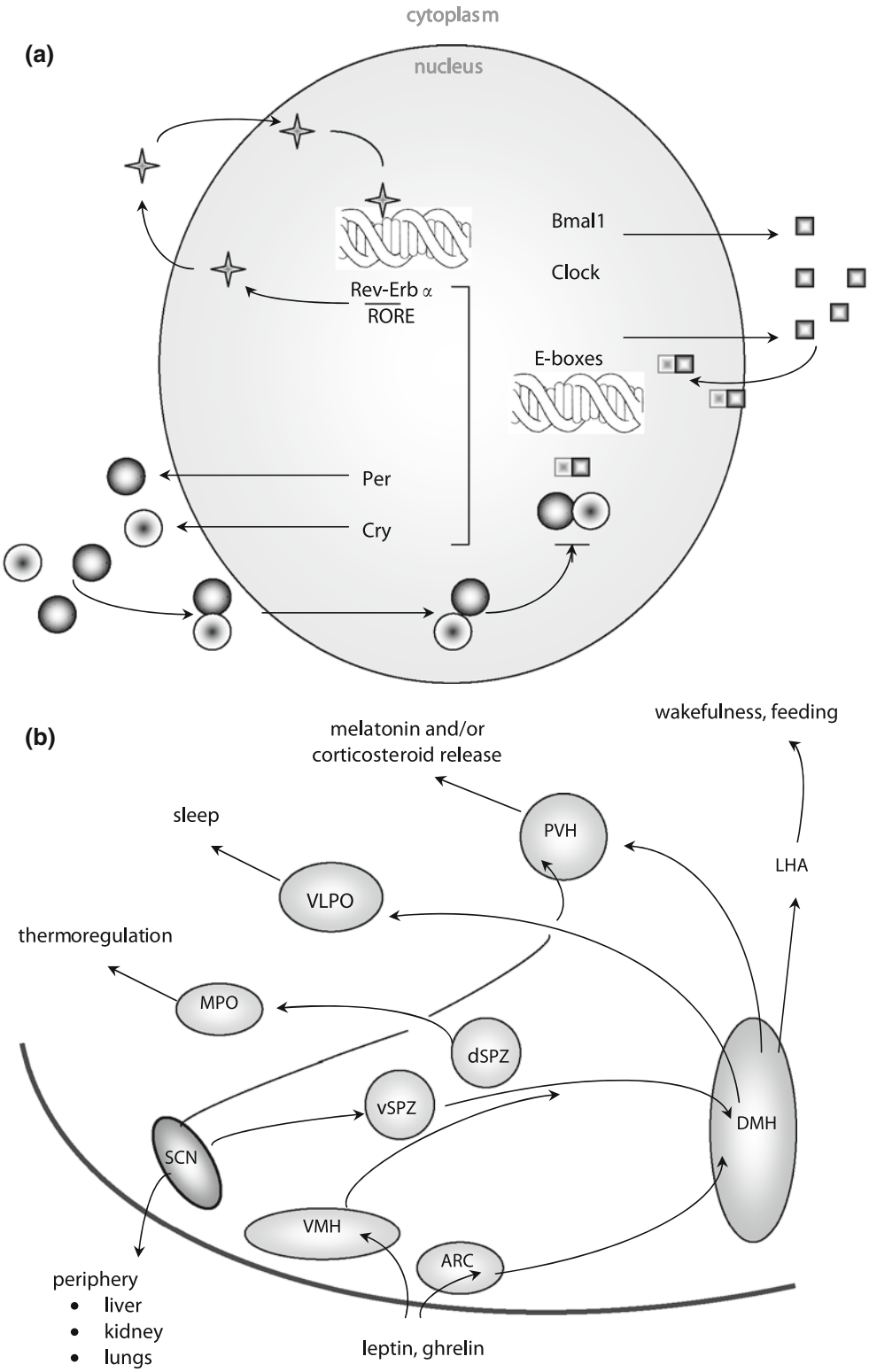
Despite many proposed theories, the precise purpose and function of sleep remains unknown, although recently it has been suggested that sleep should be viewed as a state that increases the efficiency of behaviour by reducing energy use when activity is not beneficial. Thus sleep is a state of adaptive inactivity, rather than being considered to be a maladaptive and vulnerable state, persisting only because it contains some unknown adaptive physiological function [156].

Studies in rodents have helped to provide insight into the role of sleep; total sleep deprivation in rats produces a reliable syndrome that includes skin lesions, increased food intake, weight loss, increased energy expenditure, decreased body temperature and death [137]. Selective REM and SWS deprivation result in similar findings [87]. The effect on humans is not as striking as in other animals, however sleep deprivation or a disturbance of the sleep–wake axis has revealed a broad range of interconnected pathologies [17, 48], including, amongst other things, impaired memory and learning [15, 48], reduced mental and physical reaction times [74, 169], reduced motivation, depression [44, 48] elevated cortisol levels [92], increased susceptibility to illness [25, 149, 151] and metabolic abnormalities [148, 159]. A disturbance of sleep can therefore have a substantial impact upon an individual's health and quality of life, which may be even more significant in disease states such as HD.

Fig. 5 Gene expression in circadian timing. **a** E-boxes are regulatory DNA sequences that enhance transcription by providing a target for transcription factors. Circadian timing is sustained by three connected streams of rhythmic gene expression. The first stream involves the E-box-mediated activation of genes (including *Per* and *Cry*) by *Clock*/*Bmal* heterodimers in early circadian day. This activation is inhibited in the late circadian day by accumulation of *Per*/*Cry* complex in the nucleus, resulting in the closure of an oscillatory negative feedback loop. When *Per*/*Cry* levels decline, the circadian cycle of expression is initiated. The rate of expression is sensitive to the phosphorylation status of Per. *Rev-erbα* is expressed in phase with *Per* and *Cry* and acts as a negative regulator of *Bmal1*. Through disinhibition, *Rev-erbα* establishes a positive feedforward loop in part of the second stream of gene expression. This loop drives expression of *Bmal1* in antiphase to the negative factors and helps to initiate the new cycle of gene expression, as well as to enhance core oscillation by segregating the intervals of peak *Clock*/*Bmal* transcription and peak *Per*/*Cry* negative feedback. *Bmal* brain and muscle aryl hydrocarbon receptor nuclear translocator (ARNT)-like, *Cry* Cryptochrome; *Per* Period. Diagram modified from [65]. **b** Schematic diagram showing SCN connectivity. The body's biological clock has only a small number of outputs to sleep-regulatory systems. The majority of these outputs go to the area which includes the dorsal and ventral subparaventricular zone (vSPZ and dSPZ, respectively), and the hypothalamic dorsomedial nucleus (DMH). vSPZ neurons transmit information required for the organization of daily sleep–wake cycles, while the neurons of the dSPZ are vital for body temperature cycles. SPZ outputs are integrated in the DMH with other inputs. DMH neurons thus drive the circadian cycles of sleep, feeding, activity and corticosteroid secretion. Rhythms of body temperature are maintained by dSPZ projections back to the medial preoptic area (MPO), whereas the DMH is the original source of projections to the VLPO for sleep cycles, to the neurons of the paraventricular nucleus (PVH) containing corticotropin-releasing hormone (CRH) for corticosteroid cycles, and to the orexin and melanin-concentrating hormone neurons of the lateral hypothalamus (LHA) for wakefulness and feeding cycles. The connectivity of the SPZ and DMH allows circadian rhythms to adapt to environmental stimuli, such as food availability, as well emotional inputs from the limbic system, visceral sensory inputs and finally cognitive influences from the prefrontal cortex. *ARC* arcuate nucleus, *DMH* dorsomedial nucleus, *LHA* lateral hypothalamus, *MPO* medial preoptic area, *PVH* paraventricular nucleus, *SCN* suprachiasmatic nucleus, *SPZ* subparaventricular zone, *VLPO* ventrolateral preoptic nucleus, *VMH* ventromedial nucleus. Diagram modified from [146] ▶

Aging and neurodegenerative disease

Predictable changes in sleep take place as part of the normal aging process in humans. Aging is usually associated with decreased metabolic rate and physical activity, and thus with a decrease in energy demands and the need to conserve energy. The resulting sleep-related changes include a decreased amount of total sleep time, sleep efficiency and



percentages of SWS and REM sleep, with increases in sleep latency and Stages 1 and 2 [112]. Sleep therefore appears to become more fragmented and 'lighter' with age.

Patients with neurodegenerative diseases such as Parkinson's and Alzheimer's disease often have sleep disturbances [103, 133], which creates problems not only for the patient but also for their family and carers [86, 171]. For example, REM sleep behavior disorder (RBD) is characterized by a loss of the normal muscle atonia that accompanies REM sleep, allowing the person to "act out"

his or her dreams, which can often involve harmful or violent behaviour. There is a high prevalence of RBD in neurodegenerative disease ranging from ~33 to 60% in PD [22, 51], 50 to 80% in Lewy body dementia [13] and 80 to 95% in Multiple Systems Atrophy [126, 165].

Although the nature of the sleep-related impairments differs to some extent in a disease specific fashion, some common abnormalities have been observed in neurodegenerative disorders of the central nervous system. Sleep becomes progressively fragmented with disease duration and is associated with increased awakenings and overall time spent awake [103, 123]. SWS and REM sleep are often reduced and polygraphic features (spindles and K complexes) become less well defined and numerous [103, 123, 176]. This often results in poor quality sleep and excessive daytime sleepiness that can lead to, or exacerbate, cognitive impairment, mood disorders and increase the risk for accidents [62, 63, 101].

Unfortunately, PD-related treatments such as dopamine agonists, (e.g. pramipexole, and ropinirole) have all been suggested as further contributing towards the sleep problems of PD in some patients by causing 'sleep attacks' [49, 113, 147]. Whilst the aetiology of this is unknown, it has been suggested that dopamine agonists cause a desynchronizing effect on the EEG that is reflected in a disruption of sleep continuity [16].

Polysomnography in Huntington's disease

Although the majority of studies investigating sleep in HD were initially carried out ~20 years ago, interest in this aspect of the disease has recently resurfaced [3, 172].

To date, sleep studies in HD patients provide evidence of a progressively worsening sleep disorder [123], which appears to be independent of CAG repeat length [3, 61]. Mild stage patients reportedly have no clinical sleep disturbance, but do have mild PSG abnormalities, with increased interspersed wakefulness and a longer time to first REM episode [3, 61]. We have also seen something similar in unpublished data from eight patients in the early stages of the disease. In addition, we found an overall loss of form and definition in the patients' rest-activity actograms suggesting deterioration of circadian timing (Goodman AOG, unpublished data), which is consistent with previous findings [106]. However, none of the patients complained of sleep disturbance or showed excessive daytime sleepiness using standard questionnaires such as the Epworth Sleepiness Scale and the Functional Outcomes of Sleep Questionnaire, although self-reporting questionnaires designed to look at sleep in HD patients may not always provide an accurate assessment of the situation since HD patients can lack insight [68]. Nevertheless, it has been reported that up to 87.8% of patients acknowledge having sleep problems, which were rated by 61.7% as either 'very' or 'moderately' important factors contributing towards the patient's overall problems [168].

As HD progresses, it has been reported that awake EEGs exhibit a gradual slowing and diminution of amplitude [150, 158, 177]. Patients with moderate disease also experience increased time in Stages 1 and 2 of sleep [61] and reduced SWS and REM sleep [61, 157, 177]. REM sleep percentages have been shown to decrease with disease severity [3] and, in contrast to other neurodegenerative diseases, HD patients show a higher density of sleep spindles compared to healthy control subjects [36, 157, 177]. Moderately severe HD patients experience impaired initiation of sleep with increased sleep onset latency [177], as well as impaired maintenance of sleep with increased nocturnal awakenings or arousals and a high percentage of wakefulness after sleep onset [61, 157, 177]. Thus, HD patients experience reduced sleep efficiency [19, 61, 100, 157, 177]. A well known cause of excessive daytime sleepiness is sleep disordered breathing or sleep apnoea. However to date, no significant difference has been found between HD patients and controls in terms of sleep apnoea [14]. Issues of cataplexy, hypnagogic hallucinations or sleep paralysis have not been identified as problems in HD patients [3].

Brain-derived neurotrophic factor (BDNF), a neurotrophin that increases the resistance of neurons to metabolic, excitotoxic and oxidative insults [18, 33], has also been associated with slow-wave activity, with reports showing that a decrease in BDNF leads to a decrease in slow-wave activity [40]. As decreased production of brain-derived neurotrophic factor has been identified in HD patients [46, 179], it is therefore possible that this decrease contributes towards the decreases in SWS observed in HD patients [157, 177].

Sleep related movement disorders in Huntington's disease

A range of different parasomnias have been described, of which the most common is Restless Legs Syndrome (RLS). Although a genetic association between RLS and HD has been suggested [37], RLS has not been reported to be significantly increased in the HD population.

Periodic limb movement (PLM) disorder (PLMD) is characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep. Studies have found that HD patients have more frequent periodic leg movements compared to controls [3, 61], although there is debate as to how accurately the defined PLM criteria can distinguish between true PLMD in patients compared to those who simply experience chorea as part of their movement disorder.

Parasomnias in Huntington's disease

Rapid eye movement sleep behaviour disorder (RBD) is a parasomnia characterised by vivid, often frightening dreams associated with simple or complex motor behaviour during REM sleep. Patients appear to act out their dreams, in which the exhibited behaviours mirror the content of the dreams and have been heavily linked to α-synucleinopathies. The risk for example of developing neurodegenerative disease in idiopathic REM sleep behaviour disorder is substantial (12-year risk of 52.4%), with the majority of patients developing Parkinson's disease or Lewy body dementia [131]. The most recent polysomnography paper to publish on RBD in HD reported a 12% prevalence (three out of 25 HD patients) [3].

Possible causes of sleep disturbance in HD

Sleep and circadian systems are distinct, although they interact in a variety of different ways; not all sleep disorders result from a problem of circadian rhythmicity, but all circadian disorders produce sleep disturbances. Do patients with HD therefore experience a 'pure' sleep disorder, a circadian disturbance, or a combination of both? This is an important question to address, since a sleep disorder without an associated circadian abnormality can be treated as a 'pure' sleep disorder.

Transgenic mouse models of HD have shown that improving circadian and sleep patterns using Alprazolam can actually improve cognitive function and survival in R6/2 mice [116, 117]. Another recent study has shown that arrhythmic hamsters fail to perform in a hippocampal-dependant learning task and that learning can be restored using a GABA antagonist [143]. Therefore, if in patients there is circadian involvement, the impact on the disease could potentially be more widespread, since by treating the sleep and circadian disorder (with, for example, melatonin, chronotherapy or light therapy), one could potentially affect other aspects of the disease, including the cognitive deficits that are a core element of HD and which are a major problem for many patients and their families.

Neural pathway disruption

As a consequence of the widespread neurodegeneration in HD, areas directly or indirectly involved in sleep and circadian rhythms are likely to be affected, see Fig. 1. This includes the striatum as, although it is not considered to be a key part of the sleep–wake process (see above), studies involving striatal lesions have nevertheless suggested a possible involvement with sleep [23, 100, 173]. This effect may be mediated through the outflow of the basal ganglia to critical thalamic nuclei and the PPT [56, 77].

Significant volume reductions in the brainstem, a key structure involved in the regulation of sleep, have been reported in HD patients [140], with some evidence of such reductions worsening with disease severity and increasing UHDRS motor score [72]. This brainstem atrophy in HD has been described to precede even caudate atrophy [98] and thus, like PD, it may be that disturbances of sleep could precede the motor aspects of HD and could be a core feature of this disorder.

The hypothalamus, particularly the lateral hypothalamus, is crucial for the regulation of sleep and metabolism [164]. Neurons containing orexin found in the lateral hypothalamus [27, 124] have been reported to be abnormal in HD. Significant atrophy and loss of orexin neurons in the lateral hypothalamus of HD patients' brains have been identified [5, 81, 122]; a subsequent neuroimaging study identified hypothalamic atrophy in patients, even in the early stages of the disease [76]. However cerebrospinal fluid samples have not always found evidence for a loss of this peptide [53].

The anterior, ventral region of the hypothalamus contains the SCN [125]. Abnormalities within it have been described in neurodegenerative diseases [65] with a loss of circadian synchrony in both the central nervous system and peripheral tissues and cells [125]. In HD, the reported sleep disturbance may reflect a more fundamental problem in circadian rhythms and their central and peripheral regulation; indirect evidence seems to support this. The primary symptom of a circadian rhythm disorder is the inability to sleep during the desired sleep time. HD patients reportedly lie sleepless at night with insomnia and have a tendency towards increased daytime somnolence and sleep episodes [172] with naps at unpredictable hours [3, 61]. Second, studies using actigraphy have found that HD patients make significantly more movements and have increased activity during sleep compared with controls [71]. This apparent reversal of the day–night pattern of sleep seems to support the suggestion of a disturbance in circadian rhythm [61]. Third, a disturbed circadian rhythmicity of hormones, such as prolactin, has been identified [45]. Finally, findings of increased REM latency in HD [3] are consistent with a phase-delayed circadian rhythm, further suggesting a problem with an internal misalignment of the body clock and sleep–wake cycle. Although a thorough and comprehensive study investigating circadian disturbance in HD patients has not been undertaken to date, this is not the case experimentally, where the R6/2 transgenic mouse model of the disease has been systematically investigated [39, 106]. So for example, Morton et al. reported that R6/2 transgenic mice had disturbed night-day activity that worsened with disease progression. These abnormalities were also accompanied by a marked disruption of expression of the

circadian clock genes *mPer2* and *mBmal1* in the SCN, as well as in the motor cortex and striatum.

Other causes of disordered sleep in HD

Depression has been associated with difficulty falling asleep, frequent nocturnal awakenings, early morning awakening, decreased total sleep and non restorative sleep. In HD, affective symptoms such as depression and anxiety are common even before disease onset [24, 34]. Furthermore, commonly prescribed medications for HD patients, such as antidepressants, neuroleptics, dopamine antagonists and tetrabenazine, can impact on sleep and wakefulness by causing, for example, insomnia and increased drowsiness.

Silvestri et al. [157] reported that existing chorea decreases and may even disappear during sleep. Other studies report that both normal semi-purposeful sleep movements and dyskinesias are markedly suppressed during the deeper phases of sleep, yet reappear after EEG evidence of arousal, following a shift to a lighter sleep stage [19, 47]. Therefore, although chorea during sleep arousals is likely to affect sleep [97] it has, however, been discounted as the principal cause of the sleep disturbance in HD [47].

The presence of dystonia and age-related problems such as dementia, nocturia, body pain and other physical or mental health conditions [123], in addition to environmental factors, all may contribute to sleep abnormalities. For example, as the disease progresses, patients may choose to retire from their daytime jobs, resulting in an unstructured lifestyle, which may result in irregular sleep–wake behaviour and circadian rhythms (disturbed entrainment).

The consequences of disturbed sleep in HD

Considerable circumstantial evidence exists to suggest a link between the HD-related symptoms and sleep deprivation. HD has a characteristic cluster of symptoms that may include several of the following: a loss of motor control [79], changes in mood [75], memory [70] and cognitive impairment [102]. Sleep deprivation has also been implicated in many of the same repertoire of symptoms and signs, including profound effects on cognitive and motor function [35, 48, 90] and memory. For example, SWS is involved in hippocampus-dependent declarative memory consolidation [121, 127]. Evidence suggests that a loss of circadian timing reduces the ability of the hippocampus to encode learned information [143]. This may be relevant in HD, since impaired declarative memory has been found in HD patients, including presymptomatic gene carriers [54]. It is possible, therefore, that the memory deficits found in HD are related in part to a reduction in SWS and/or circadian disturbances. Perturbations in clock genes, both in humans and other animals, have also been associated with psychiatric conditions [89], addiction [95], and metabolic syndromes [150], all of which occur frequently in HD.

Metabolic consequences

Epidemiological and clinical data indicate that voluntary sleep curtailment [118, 166] and disorders that impair sleep architecture, such as narcolepsy [88] and sleep apnoea [134], are associated with an increased incidence of disrupted metabolic regulation. In rats, chronic total sleep deprivation leads to pronounced changes in energy regulation, glucose metabolism [148], plasma ghrelin and leptin concentrations [12, 109], increased food intake, progressive weight loss and hyperthermia [10, 38]. Indeed, HD patients experience hyperphagia, weight loss [42, 43, 80, 105, 132, 144, 162], increased 24 h energy expenditure [50, 55, 132] and glucose metabolism [41, 128] and altered leptin and ghrelin concentrations [130, 132] which could be related to changes in sleep. Furthermore, recent data have emerged to suggest that circadian processes are also critically involved in energy homeostasis [170].

HD patients with longer CAG repeats have been found to have a lower body weight, which the authors attribute to be the result of a hypermetabolic state [6]. A disturbance in sleep in this already vulnerable group is therefore likely to exacerbate any existing difficulty in maintaining weight.

The significance of disturbed sleep in HD

The question that therefore remains is which symptoms exist first in HD? Do sleep disturbances in HD not only exacerbate other pre-existing symptoms, but actually cause others? These are both relevant and important questions, since in an already vulnerable population, a disturbance of sleep would increase vulnerability. It is highly likely that in HD many of the symptoms experienced by patients are adversely affected by disturbances of sleep, especially since these problems can be found even in the early stages of the disease. The connection between abnormalities in sleep and circadian rhythms in relation to other signs and symptoms of the disease may be critically important. A decline in quality of life can directly result from disturbed circadian-regulated sleep, and changes such as this can have a profound impact on both patient and carer [136]. Defining the abnormalities of sleep that exist in HD and understanding their influence on other disease related features is important for enabling clinicians to initiate appropriate investigations and to instigate treatments that could dramatically improve quality of life in both patients

and their families/carers; this may even have an effect on the natural history of the condition. Indeed, in this respect it has been shown that modification of sleep patterns using Alprazolam can actually improve cognitive function and survival in the R6/2 transgenic mouse model of HD [116, 117]. However, Alprazolam has been shown to cause circadian shifts in rodents but not in humans and, in fact, reduces restorative SWS and REM sleep [67], the key aspects of sleep that are already jeopardised in HD. Nevertheless, this study does highlight the point that modifying/correcting sleep abnormalities may improve a whole range of other abnormalities in HD, including cognition.

One study in PD involving 391 patients found that the clinical factors that showed the highest predictive value for worsening health-related quality of life were non-motor symptoms, such as sleep disorders [135]. Defining the extent and nature of sleep-related abnormalities in HD more thoroughly is not only critical in improving the quality of life in both patients and carers, but also in revealing additional clinically relevant information about the disease itself. If sleep abnormalities were predictive of HD, as they may be for PD [131], it may be possible to intervene to treat the sleep problem and consequentially reduce symptom severity. This may involve not just drug therapies, as in transgenic mouse models of HD; environmental enrichment has been shown to slow disease progression [69]. It is possible that lifestyle modifications such as a program of regular exercise may be a useful therapy in the treatment of patients with sleep disorders, since it has been shown that there is an association of regular exercise or physical activity with a lower prevalence of symptoms of disturbed sleep [153]. Indeed, a number of studies in healthy subjects have documented that both acute and long term exercise increase slow-wave sleep and total sleep time [85, 110, 178].

Conclusion

In conclusion, sleep sustains cognitive and physical performance, health, well-being and productivity and even mild sleep deprivation degrades performance over a few days. Widespread pathology is observed in HD, including regions that are involved in both sleep regulation and circadian rhythms. Evidence suggests that HD patients may experience disturbance in both of these processes, which in turn may have effects on a wide range of other essential functions, such as metabolism. Abnormalities in sleep and circadian rhythms also have negative impacts upon cognitive and psychiatric function as well as memory, all of which are problems that lie at the heart of HD. Treating these disturbances as part of the general care of the patient has the potential to dramatically improve quality of life, as well as potentially reducing the severity of other symptoms and could even affect disease progression.

Acknowledgments Our own work in this area has been supported by the High Q/CHDI organization and an NIHR Medical Research Centre award to the University of Cambridge/Addenbrooke's Hospital.

References

1. Alam MN, McGinty D, Bashir T, Kumar S, Imeri L, Opp MR, Szymusiak R (2004) Interleukin-1beta modulates state-dependent discharge activity of preoptic area and basal forebrain neurons: role in sleep regulation. Eur J Neurosci 20:207–216
2. Antle MC, Silver R (2005) Orchestrating time: arrangements of the brain circadian clock. Trends Neurosci 28:145–151
3. Arnulf I, Nielsen J, Lohmann E, Schieffer J, Wild E, Jennum P, Konofal E, Walker M, Oudiette D, Tabrizi S, Durr A (2008) Rapid eye movement sleep disturbances in Huntington disease. Arch Neurol 65:482–488
4. Aserinsky E (1996) The discovery of REM sleep. J Hist Neurosci 5:213–227
5. Aziz A, Fronczek R, Maat-Schieman M, Unmehopa U, Roelandse F, Overeem S, van DS, Lammers GJ, Swaab D, Roos R (2008) Hypocretin and melanin-concentrating hormone in patients with Huntington disease. Brain Pathol 18:474–483
6. Aziz NA, van der Burg JM, Landwehrmeyer GB, Brundin P, Stijnen T, EHDI Study Group, Roos RA (2008) Weight loss in Huntington disease increases with higher CAG repeat number. Neurology 71:1506–1513
7. Basheer R, Strecker RE, Thakkar MM, McCarley RW (2004) Adenosine and sleep–wake regulation. Prog Neurobiol 73:379–396
8. Bell-Pedersen D, Cassone VM, Earnest DJ, Golden SS, Hardin PE, Thomas TL, Zoran MJ (2005) Circadian rhythms from multiple oscillators: lessons from diverse organisms. Nat Rev Genet 6:544–556
9. Berger RJ (1975) Bioenergetic functions of sleep and activity rhythms and their possible relevance to aging. Fed Proc 34:97–102
10. Bergmann BM, Everson CA, Kushida CA, Fang VS, Leitch CA, Schoeller DA, Refetoff S, Rechtschaffen A (1989) Sleep deprivation in the rat: V. Energy use and mediation. Sleep 12:31–41
11. Berson DM (2007) Phototransduction in ganglion-cell photoreceptors. Pflugers Arch 454:849–855
12. Bodosi B, Gardi J, Hajdu I, Szentirmai E, Obal F Jr, Krueger JM (2004) Rhythms of ghrelin, leptin, and sleep in rats: effects of the normal diurnal cycle, restricted feeding, and sleep deprivation. Am J Physiol Regul Integr Comp Physiol 287:R1071–R1079
13. Boeve BF, Silber MH, Ferman TJ (2004) REM sleep behavior disorder in Parkinson's disease and dementia with Lewy bodies. J Geriatr Psychiatry Neurol 17:146–157
14. Bollen EL, Den Heijer JC, Ponsioen C, Kramer C, Van der Velde EA, van Dijk JG, Roos RA, Kamphuisen HA, Buruma OJ (1988) Respiration during sleep in Huntington's chorea. J Neurol Sci 84:63–68
15. Born J, Wagner U (2004) Awareness in memory: being explicit about the role of sleep. Trends Cogn Sci 8:242–244
16. Brunner H, Wetter TC, Hogl B, Yassouridis A, Trenkwalder C, Friess E (2002) Microstructure of the non-rapid eye movement sleep electroencephalogram in patients with newly diagnosed

Parkinson's disease: effects of dopaminergic treatment. Mov Disord 17:928–933
17. Carskadon MA (2004) Sleep deprivation: health consequences and societal impact. Med Clin North Am 88:767–776
18. Cheng B, Mattson MP (1994) NT-3 and BDNF protect CNS neurons against metabolic/excitotoxic insults. Brain Res 640:56–67
19. Chokroverty S (1996) Sleep and degenerative neurologic disorders. Neurol Clin 14:807–826
20. Chou TC, Scammell TE, Gooley JJ, Gaus SE, Saper CB, Lu J (2003) Critical role of dorsomedial hypothalamic nucleus in a wide range of behavioral circadian rhythms. J Neurosci 23:10691–10702
21. Churchill L, Rector DM, Yasuda K, Fix C, Rojas MJ, Yasuda T, Krueger JM (2008) Tumor necrosis factor alpha: activity dependent expression and promotion of cortical column sleep in rats. Neuroscience 156:71–80
22. Comella CL, Nardine TM, Diederich NJ, Stebbins GT (1998) Sleep-related violence, injury, and REM sleep behavior disorder in Parkinson's disease. Neurology 51:526–529
23. Corsi-Cabrera M, Grinberg-Zylberbaum J, Arditti LS (1975) Caudate nucleus lesion selectively increases paradoxical sleep episodes in the rat. Physiol Behav 14:7–11
24. Craufurd D, Thompson JC, Snowden JS (2001) Behavioral changes in Huntington Disease. Neuropsychiatry Neuropsychol Behav Neurol 14:219–226
25. Davis KL, Davis BM, Greenwald BS, Mohs RC, Mathe AA, Johns CA, Horvath TB (1986) Cortisol and Alzheimer's disease, I: basal studies. Am J Psychiatry 143:300–305
26. de la Monte SM, Vonsattel JP, Richardson E P Jr (1988) Morphometric demonstration of atrophic changes in the cerebral cortex, white matter, and neostriatum in Huntington's disease. J Neuropathol Exp Neurol 47:516–525
27. de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, Fukuhara C, Battenberg EL, Gautvik VT, Bartlett FS, Frankel WN, van den Pol AN, Bloom FE, Gautvik KM, Sutcliffe JG (1998) The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA 95:322–327
28. De SG, Gareri P, Sinopoli VA, David E, Rotiroti D (1997) Comparative, behavioural and electrocortical effects of tumor necrosis factor-alpha and interleukin-1 microinjected into the locus coeruleus of rat. Life Sci 60:555–564
29. Dement WC, Miles LE, Carskadon MA (1982) 'White paper' on sleep and aging. J Am Geriatr Soc 30:25–50
30. Deurveilher S, Semba K (2005) Indirect projections from the suprachiasmatic nucleus to major arousal-promoting cell groups in rat: implications for the circadian control of behavioural state. Neuroscience 130:165–183
31. Djousse L, Knowlton B, Cupples LA, Marder K, Shoulson I, Myers RH (2002) Weight loss in early stage of Huntington's disease. Neurology 59:1325–1330
32. Dom R, Malfroid M, Baro F (1976) Neuropathology of Huntington's chorea. Studies of the ventrobasal complex of the thalamus. Neurology 26:64–68
33. Duan W, Guo Z, Mattson MP (2001) Brain-derived neurotrophic factor mediates an excitoprotective effect of dietary restriction in mice. J Neurochem 76:619–626
34. Duff K, Paulsen JS, Beglinger LJ, Langbehn DR, Stout JC (2007) Psychiatric symptoms in Huntington's disease before diagnosis: the predict-HD study. Biol Psychiatry 62:1341–1346
35. Ellenbogen JM (2005) Cognitive benefits of sleep and their loss due to sleep deprivation. Neurology 64:E25–E27
36. Emser W, Brenner M, Stober T, Schimrigk K (1988) Changes in nocturnal sleep in Huntington's and Parkinson's disease. J Neurol 235:177–179
37. Evers S, Stogbauer F (2003) Genetic association of Huntington's disease and restless legs syndrome? A family report. Mov Disord 18:225–227
38. Everson CA (1995) Functional consequences of sustained sleep deprivation in the rat. Behav Brain Res 69:43–54
39. Fahrenkrug J, Popovic N, Georg B, Brundin P, Hannibal J (2007) Decreased VIP and VPAC2 receptor expression in the biological clock of the R6/2 Huntington's disease mouse. J Mol Neurosci 31:139–148
40. Faraguna U, Vyazovskiy VV, Nelson AB, Tononi G, Cirelli C (2008) A causal role for brain-derived neurotrophic factor in the homeostatic regulation of sleep. J Neurosci 28:4088–4095
41. Farrer LA (1985) Diabetes mellitus in Huntington disease. Clin Genet 27:62–67
42. Farrer LA, Meaney FJ (1985) An anthropometric assessment of Huntington's disease patients and families. Am J Phys Anthropol 67:185–194
43. Farrer LA, Yu PL (1985) Anthropometric discrimination among affected, at-risk, and not-at-risk individuals in families with Huntington disease. Am J Med Genet 21:307–316
44. Fava M (2004) Daytime sleepiness and insomnia as correlates of depression. J Clin Psychiatry 65 Suppl 16:27–32
45. Ferrari E, Nappi G, Vailati A, Martignoni E, Bossolo PA, Polleri A (1979) Circadian periodicity of plasma prolactin in some neurological diseases. Int J Chronobiol 6:231–242
46. Ferrer I, Goutan E, Marin C, Rey MJ, Ribalta T (2000) Brain-derived neurotrophic factor in Huntington disease. Brain Res 866:257–261
47. Fish DR, Sawyers D, Allen PJ, Blackie JD, Lees AJ, Marsden CD (1991) The effect of sleep on the dyskinetic movements of Parkinson's disease, Gilles de la Tourette syndrome, Huntington's disease, and torsion dystonia. Arch Neurol 48:210–214
48. Foster RG, Wulff K (2005) The rhythm of rest and excess. Nat Rev Neurosci 6:407–414
49. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S (1999) Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 52:1908–1910
50. Gaba AM, Zhang K, Marder K, Moskowitz CB, Werner P, Boozer CN (2005) Energy balance in early-stage Huntington disease. Am J Clin Nutr 81:1335–1341
51. Gagnon JF, Bedard MA, Fantini ML, Petit D, Panisset M, Rompre S, Carrier J, Montplaisir J (2002) REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 59:585–589
52. Gallopin T, Fort P, Eggermann E, Cauli B, Luppi PH, Rossier J, Audinat E, Muhlethaler M, Serafin M (2000) Identification of sleep-promoting neurons in vitro. Nature 404:992–995
53. Gaus SE, Lin L, Mignot E (2005) CSF hypocretin levels are normal in Huntington's disease patients. Sleep 28:1607–1608
54. Ghilardi MF, Silvestri G, Feigin A, Mattis P, Zgaljardic D, Moisello C, Crupi D, Marinelli L, Dirocco A, Eidelberg D (2008) Implicit and explicit aspects of sequence learning in pre-symptomatic Huntington's disease. Parkinsonism Relat Disord 14:457–464
55. Goodman AO, Murgatroyd PR, Medina-Gomez G, Wood NI, Finer N, Vidal-Puig AJ, Morton AJ, Barker RA (2008) The metabolic profile of early Huntington's disease—a combined human and transgenic mouse study. Exp Neurol 210:691–698
56. Grofova I, Zhou M (1998) Nigral innervation of cholinergic and glutamatergic cells in the rat mesopontine tegmentum: light and electron microscopic anterograde tracing and immunohistochemical studies. J Comp Neurol 395:359–379
57. Hahn-Barma V, Deweer B, Durr A, Dode C, Feingold J, Pillon B, Agid Y, Brice A, Dubois B (1998) Are cognitive changes the first symptoms of Huntington's disease? A study of gene carriers. J Neurol Neurosurg Psychiatry 64:172–177

58. Hamilton JM, Salmon DP, Corey-Bloom J, Gamst A, Paulsen JS, Jerkins S, Jacobson MW, Peavy G (2003) Behavioural abnormalities contribute to functional decline in Huntington's disease. J Neurol Neurosurg Psychiatry 74:120–122
59. Hamilton JM, Wolfson T, Peavy GM, Jacobson MW, Corey-Bloom J (2004) Rate and correlates of weight change in Huntington's disease. J Neurol Neurosurg Psychiatry 75:209–212
60. Hankins MW, Peirson SN, Foster RG (2008) Melanopsin: an exciting photopigment. Trends Neurosci 31:27–36
61. Hansotia P, Wall R, Berendes J (1985) Sleep disturbances and severity of Huntington's disease. Neurology 35:1672–1674
62. Happe S (2003) Excessive daytime sleepiness and sleep disturbances in patients with neurological diseases: epidemiology and management. Drugs 63:2725–2737
63. Happe S, Berger K (2001) The association of dopamine agonists with daytime sleepiness, sleep problems and quality of life in patients with Parkinson's disease—a prospective study. J Neurol 248:1062–1067
64. Harper PS (1992) The epidemiology of Huntington's disease. Hum Genet 89:365–376
65. Hastings MH, Reddy AB, Maywood ES (2003) A clockwork web: circadian timing in brain and periphery, in health and disease. Nat Rev Neurosci 4:649–661
66. Hayashi Y (1979) The all-night polygraphies for healthy aged persons (1st report)—with special reference to sleep characteristics of the aged persons (author's transl). Rinsho Shinkeigaku 19:653–660
67. Hindmarch I, Dawson J, Stanley N (2005) A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep 28:187–193
68. Ho AK, Robbins AO, Barker RA (2006) Huntington's disease patients have selective problems with insight. Mov Disord 21:385–389
69. Hockly E, Cordery PM, Woodman B, Mahal A, van Dellen A, Blakemore C, Lewis CM, Hannan AJ, Bates GP (2002) Environmental enrichment slows disease progression in R6/2 Huntington's disease mice. Ann Neurol 51:235–242
70. Hoth KF, Paulsen JS, Moser DJ, Tranel D, Clark LA, Bechara A (2007) Patients with Huntington's disease have impaired awareness of cognitive, emotional, and functional abilities. J Clin Exp Neuropsychol 29:365–376
71. Hurelbrink CB, Lewis SJ, Barker RA (2005) The use of the Actiwatch-Neurologica system to objectively assess the involuntary movements and sleep–wake activity in patients with mild-moderate Huntington's disease. J Neurol 252:642–647
72. Jech R, Klempir J, Vymazal J, Zidovska J, Klempirova O, Ruzicka E, Roth J (2007) Variation of selective gray and white matter atrophy in Huntington's disease. Mov Disord 22:1783–1789
73. Jernigan TL, Salmon DP, Butters N, Hesselink JR (1991) Cerebral structure on MRI, Part II: specific changes in Alzheimer's and Huntington's diseases. Biol Psychiatry 29:68–81
74. Jewett ME, Dijk DJ, Kronauer RE, Dinges DF (1999) Dose–response relationship between sleep duration and human psychomotor vigilance and subjective alertness. Sleep 22:171–179
75. Julien CL, Thompson JC, Wild S, Yardumian P, Snowden JS, Turner G, Craufurd D (2007) Psychiatric disorders in preclinical Huntington's disease. J Neurol Neurosurg Psychiatry 78:939–943
76. Kassubek J, Juengling FD, Kioschies T, Henkel K, Karitzky J, Kramer B, Ecker D, Andrich J, Saft C, Kraus P, Aschoff AJ, Ludolph AC, Landwehrmeyer GB (2004) Topography of cerebral atrophy in early Huntington's disease: a voxel based morphometric MRI study. J Neurol Neurosurg Psychiatry 75:213–220
77. Kodama T, Honda Y (1999) Acetylcholine and glutamate release during sleep–wakefulness in the pedunculopontine tegmental nucleus and norepinephrine changes regulated by nitric oxide. Psychiatry Clin Neurosci 53:109–111
78. Koella WP (1984) The organization and regulation of sleep. A review of the experimental evidence and a novel integrated model of the organizing and regulating apparatus. Experientia 40:309–338
79. Kremer B, Weber B, Hayden MR (1992) New insights into the clinical features, pathogenesis and molecular genetics of Huntington disease. Brain Pathol 2:321–335
80. Kremer HP, Roos RA (1992) Weight loss in Huntington's disease. Arch Neurol 49:349
81. Kremer HP, Roos RA, Dingjan G, Marani E, Bots GT (1990) Atrophy of the hypothalamic lateral tuberal nucleus in Huntington's disease. J Neuropathol Exp Neurol 49:371–382
82. Krueger JM, Obal F (1993) A neuronal group theory of sleep function. J Sleep Res 2:63–69
83. Krueger JM, Obal F Jr (2003) Sleep function. Front Biosci 8:d511–d519
84. Krueger JM, Rector DM, Roy S, Van Dongen HP, Belenky G, Panksepp J (2008) Sleep as a fundamental property of neuronal assemblies. Nat Rev Neurosci 9:910–919
85. Kubitz KA, Landers DM, Petruzzello SJ, Han M (1996) The effects of acute and chronic exercise on sleep. A meta-analytic review. Sports Med 21:277–291
86. Kumar S, Bhatia M, Behari M (2002) Sleep disorders in Parkinson's disease. Mov Disord 17:775–781
87. Kushida CA, Bergmann BM, Rechtschaffen A (1989) Sleep deprivation in the rat: IV. Paradoxical sleep deprivation. Sleep 12:22–30
88. Kwok EH, Dun NJ (2002) Orexin/hypocretin system: obesity, narcolepsy and beyond. Drug News Perspect 15:166–174
89. Lamont EW, James FO, Boivin DB, Cermakian N (2007) From circadian clock gene expression to pathologies. Sleep Med 8:547–556
90. Laureys S, Peigneux P, Perrin F, Maquet P (2002) Sleep and motor skill learning. Neuron 35:5–7
91. Lemiere J, Decruyenaere M, Evers-Kiebooms G, Vandenbussche E, Dom R (2004) Cognitive changes in patients with Huntington's disease (HD) and asymptomatic carriers of the HD mutation—a longitudinal follow-up study. J.Neurol 251:935–942
92. Leproult R, Copinschi G, Buxton O, Van Cauter E (1997) Sleep loss results in an elevation of cortisol levels the next evening. Sleep 20:865–870
93. Lowrey PL, Takahashi JS (2004) Mammalian circadian biology: elucidating genome-wide levels of temporal organization. Annu Rev Genomics Hum Genet 5:407–441
94. Lu J, Greco MA, Shiromani P, Saper CB (2000) Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. J Neurosci 20:3830–3842
95. Lynch WJ, Girgenti MJ, Breslin FJ, Newton SS, Taylor JR (2008) Gene profiling the response to repeated cocaine self-administration in dorsal striatum: a focus on circadian genes. Brain Res 1213:166–177
96. Manfridi A, Brambilla D, Bianchi S, Mariotti M, Opp MR, Imeri L (2003) Interleukin-1beta enhances non-rapid eye movement sleep when microinjected into the dorsal raphe nucleus and inhibits serotonergic neurons in vitro. Eur J Neurosci 18:1041–1049
97. Mano T, Shiozawa Z, Sobue I (1982) Extrapyramidal involuntary movements during sleep. Electroencephalogr Clin Neurophysiol Suppl 431–442
98. Masucci EF, Borts FT, Kurtzke JF (1990) CT brainstem abnormalities in the differential diagnosis of Huntington's disease. Comput Med Imaging Graph 14:205–212

99. McGinty D, Szymusiak R (2000) The sleep–wake switch: a neuronal alarm clock. Nat Med 6:510–511
100. Mena-Segovia J, Cintra L, Prospero-Garcia O, Giordano M (2002) Changes in sleep-waking cycle after striatal excitotoxic lesions. Behav Brain Res 136:475–481
101. Mitler MM, Carskadon MA, Czeisler CA, Dement WC, Dinges DF, Graeber RC (1988) Catastrophes, sleep, and public policy: consensus report. Sleep 11:100–109
102. Montoya A, Price BH, Menear M, Lepage M (2006) Brain imaging and cognitive dysfunctions in Huntington's disease. J Psychiatry Neurosci 31:21–29
103. Montplaisir J, Petit D, Lorrain D, Gauthier S, Nielsen T (1995) Sleep in Alzheimer's disease: further considerations on the role of brainstem and forebrain cholinergic populations in sleep–wake mechanisms. Sleep 18:145–148
104. Moore RY (2007) Suprachiasmatic nucleus in sleep–wake regulation. Sleep Med 8 Suppl 3:27–33
105. Morales LM, Estevez J, Suarez H, Villalobos R, Chacin d B, Bonilla E (1989) Nutritional evaluation of Huntington disease patients. Am J Clin Nutr 50:145–150
106. Morton AJ, Wood NI, Hastings MH, Hurelbrink C, Barker RA, Maywood ES (2005) Disintegration of the sleep–wake cycle and circadian timing in Huntington's disease. J Neurosci 25:157–163
107. Moruzzi G, Magoun HW (1995) Brain stem reticular formation and activation of the EEG. 1949. J Neuropsychiatry Clin Neurosci 7:251–267
108. Muhlau M, Weindl A, Wohlschlager AM, Gaser C, Stadtler M, Valet M, Zimmer C, Kassubek J, Peinemann A (2007) Voxel-based morphometry indicates relative preservation of the limbic prefrontal cortex in early Huntington disease. J Neural Transm 114:367–372
109. Mullington JM, Chan JL, Van Dongen HP, Szuba MP, Samaras J, Price NJ, Meier-Ewert HK, Dinges DF, Mantzoros CS (2003) Sleep loss reduces diurnal rhythm amplitude of leptin in healthy men. J Neuroendocrinol 15:851–854
110. O'Connor PJ, Youngstedt SD (1995) Influence of exercise on human sleep. Exerc Sport Sci Rev 23:105–134
111. Obal F Jr, Krueger JM (2003) Biochemical regulation of non-rapid-eye-movement sleep. Front Biosci 8:d520–d550
112. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV (2004) Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 27:1255–1273
113. Ondo WG, Dat VK, Khan H, Atassi F, Kwak C, Jankovic J (2001) Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology 57:1392–1396
114. Oyanagi K, Takeda S, Takahashi H, Ohama E, Ikuta F (1989) A quantitative investigation of the substantia nigra in Huntington's disease. Ann Neurol 26:13–19
115. Pace-Schott EF, Hobson JA (2002) The neurobiology of sleep: genetics, cellular physiology and subcortical networks. Nat Rev Neurosci 3:591–605
116. Pallier PN, Maywood ES, Zheng Z, Chesham JE, Inyushkin AN, Dyball R, Hastings MH, Morton AJ (2007) Pharmacological imposition of sleep slows cognitive decline and reverses dysregulation of circadian gene expression in a transgenic mouse model of Huntington's disease. J Neurosci 27:7869–7878
117. Pallier PN, Morton AJ (2009) Management of sleep/wake cycles improves cognitive function in a transgenic mouse model of Huntington's disease. Brain Res 1279:90–98
118. Patel SR, Redline S (2004) Two epidemics: are we getting fatter as we sleep less? Sleep 27:602–603
119. Paulsen JS, Nehl C, Hoth KF, Kanz JE, Benjamin M, Conybeare R, McDowell B, Turner B (2005) Depression and stages of Huntington's disease. J Neuropsychiatry Clin Neurosci 17:496–502
120. Paulsen JS, Ready RE, Hamilton JM, Mega MS, Cummings JL (2001) Neuropsychiatric aspects of Huntington's disease. J Neurol Neurosurg Psychiatry 71:310–314
121. Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, Phillips C, Degueldre C, Del FG, Aerts J, Luxen A, Maquet P (2004) Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron 44:535–545
122. Petersen A, Gil J, Maat-Schieman ML, Bjorkqvist M, Tanila H, Araujo IM, Smith R, Popovic N, Wierup N, Norlen P, Li JY, Roos RA, Sundler F, Mulder H, Brundin P (2005) Orexin loss in Huntington's disease. Hum Mol Genet 14:39–47
123. Petit D, Gagnon JF, Fantini ML, Ferini-Strambi L, Montplaisir J (2004) Sleep and quantitative EEG in neurodegenerative disorders. J Psychosom Res 56:487–496
124. Peyron C, Tighe DK, van den Pol AN, de LL, Heller HC, Sutcliffe JG Kilduff TS (1998) Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci 18:9996–10015
125. Piggins HD, Loudon A (2005) Circadian biology: clocks within clocks. Curr Biol 15:R455–R457
126. Plazzi G, Corsini R, Provini F, Pierangeli G, Martinelli P, Montagna P, Lugaresi E, Cortelli P (1997) REM sleep behavior disorders in multiple system atrophy. Neurology 48:1094–1097
127. Plihal W, Born J (1999) Effects of early and late nocturnal sleep on priming and spatial memory. Psychophysiology 36:571–582
128. Podolsky S, Leopold NA, Sax DS (1972) Increased frequency of diabetes mellitus in patients with Huntington's chorea. Lancet 1:1356–1358
129. Politis M, Pavese N, Tai YF, Tabrizi SJ, Barker RA, Piccini P (2008) Hypothalamic involvement in Huntington's disease: an in vivo PET study. Brain 131:2860–2869
130. Popovic V, Svetel M, Djurovic M, Petrovic S, Doknic M, Pekic S, Miljic D, Milic N, Glodic J, Dieguez C, Casanueva FF, Kostic V (2004) Circulating and cerebrospinal fluid ghrelin and leptin: potential role in altered body weight in Huntington's disease. Eur J Endocrinol 151:451–455
131. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J (2009) Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology 72:1296–1300
132. Pratley RE, Salbe AD, Ravussin E, Caviness JN (2000) Higher sedentary energy expenditure in patients with Huntington's disease. Ann Neurol 47:64–70
133. Prinz PN, Vitaliano PP, Vitiello MV, Bokan J, Raskind M, Peskind E, Gerber C (1982) Sleep, EEG and mental function changes in senile dementia of the Alzheimer's type. Neurobiol Aging 3:361–370
134. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE (2004) Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol 160:521–530
135. Qin Z, Zhang L, Sun F, Fang X, Meng C, Tanner C, Chan P (2009) Health related quality of life in early Parkinson's disease: impact of motor and non-motor symptoms, results from Chinese levodopa exposed cohort. Parkinsonism Relat Disord 15:767–771
136. Ready RE, Mathews M, Leserman A, Paulsen JS (2008) Patient and caregiver quality of life in Huntington's disease. Mov Disord 23:721–726
137. Rechtschaffen A, Bergmann BM, Everson CA, Kushida CA, Gilliland MA (2002) Sleep deprivation in the rat: X. Integration and discussion of the findings. 1989. Sleep 25:68–87
138. Rechtschaffen A, Kales A (1968) A manual of standardized terminology, technique and scoring system for sleep stages of human sleep. Brain Information Service, Los Angeles
139. Robbins AO, Ho AK, Barker RA (2006) Weight changes in Huntington's disease. Eur J Neurol 13:e7

140. Rosas HD, Koroshetz WJ, Chen YI, Skeuse C, Vangel M, Cudkowicz ME, Caplan K, Marek K, Seidman LJ, Makris N, Jenkins BG, Goldstein JM (2003) Evidence for more widespread cerebral pathology in early HD: an MRI-based morphometric analysis. Neurology 60:1615–1620
141. Rosas HD, Salat DH, Lee SY, Zaleta AK, Pappu V, Fischl B, Greve D, Hevelone N, Hersch SM (2008) Cerebral cortex and the clinical expression of Huntington's disease: complexity and heterogeneity. Brain 131:1057–1068
142. Rosenblatt A (2007) Neuropsychiatry of Huntington's disease. Dialogues Clin Neurosci 9:191–197
143. Ruby NF, Hwang CE, Wessells C, Fernandez F, Zhang P, Sapolsky R, Heller HC (2008) Hippocampal-dependent learning requires a functional circadian system. Proc Natl Acad Sci USA 105:15593–15598
144. Sanberg PR, Fibiger HC, Mark RF (1981) Body weight and dietary factors in Huntington's disease patients compared with matched controls. Med J Aust 1:407–409
145. Saper CB, Chou TC, Scammell TE (2001) The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci 24:726–731
146. Saper CB, Scammell TE, Lu J (2005) Hypothalamic regulation of sleep and circadian rhythms. Nature 437:1257–1263
147. Schapira AH (2000) Sleep attacks (sleep episodes) with pergolide. Lancet 355:1332–1333
148. Scheen AJ, Van Cauter E (1998) The roles of time of day and sleep quality in modulating glucose regulation: clinical implications. Horm Res 49:191–201
149. Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, Fuchs CS, Colditz GA (2003) Night-shift work and risk of colorectal cancer in the nurses' health study. J Natl Cancer Inst 95:825–828
150. Scott DF, Heathfield KW, Toone B, Margerison JH (1972) The EEG in Huntington's chorea: a clinical and neuropathological study. J Neurol Neurosurg Psychiatry 35:97–102
151. Sephton S, Spiegel D (2003) Circadian disruption in cancer: a neuroendocrine–immune pathway from stress to disease? Brain Behav Immun 17:321–328
152. Sherin JE, Shiromani PJ, McCarley RW, Saper CB (1996) Activation of ventrolateral preoptic neurons during sleep. Science 271:216–219
153. Sherrill DL, Kotchou K, Quan SF (1998) Association of physical activity and human sleep disorders. Arch Intern Med 158:1894–1898
154. Shibata M (1990) Hypothalamic neuronal responses to cytokines. Yale J Biol Med 63:147–156
155. Shiwach R (1994) Psychopathology in Huntington's disease patients. Acta Psychiatr Scand 90:241–246
156. Siegel JM (2009) Sleep viewed as a state of adaptive inactivity. Nat Rev Neurosci 10:747–753
157. Silvestri R, Raffaele M, De Domenico P, Tisano A, Mento G, Casella C, Tripoli MC, Serra S, Di Perri R (1995) Sleep features in Tourette's syndrome, neuroacanthocytosis and Huntington's chorea. Neurophysiol Clin 25:66–77
158. Sishta SK, Troupe A, Marszalek KS, Kremer LM (1974) Huntington's chorea: an electroencephalographic and psychometric study. Electroencephalogr Clin Neurophysiol 36:387–393
159. Spiegel K, Leproult R, L'hermite-Baleriaux M, Copinschi G, Penev PD, Van Cauter E (2004) Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. J Clin Endocrinol Metab 89:5762–5771
160. Steininger TL, Gong H, McGinty D, Szymusiak R (2001) Subregional organization of preoptic area/anterior hypothalamic projections to arousal-related monoaminergic cell groups. J Comp Neurol 429:638–653
161. Steriade M (2003) The corticothalamic system in sleep. Front Biosci 8:d878–d899
162. Stoy N, McKay E (2000) Weight loss in Huntington's disease. Ann Neurol 48:130–131
163. Strecker RE, Morairty S, Thakkar MM, Porkka-Heiskanen T, Basheer R, Dauphin LJ, Rainnie DG, Portas CM, Greene RW, McCarley RW (2000) Adenosinergic modulation of basal forebrain and preoptic/anterior hypothalamic neuronal activity in the control of behavioral state. Behav Brain Res 115:183–204
164. Swaab DF, Hofman MA, Lucassen PJ, Purba JS, Raadsheer FC, Van de Nes JA (1993) Functional neuroanatomy and neuropathology of the human hypothalamus. Anat Embryol (Berl) 187:317–330
165. Tachibana N, Oka Y (2004) Longitudinal change in REM sleep components in a patient with multiple system atrophy associated with REM sleep behavior disorder: paradoxical improvement of nocturnal behaviors in a progressive neurodegenerative disease. Sleep Med 5:155–158
166. Taheri S, Lin L, Austin D, Young T, Mignot E (2004) Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 1:e62
167. Takahashi JS, Hong HK, Ko CH, McDearmon EL (2008) The genetics of mammalian circadian order and disorder: implications for physiology and disease. Nat Rev Genet 9:764–775
168. Taylor N, Bramble D (1997) Sleep disturbance and Huntingdon's disease. Br J Psychiatry 171:393
169. Tietzel AJ, Lack LC (2002) The recuperative value of brief and ultra-brief naps on alertness and cognitive performance. J Sleep Res 11:213–218
170. Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Losee-Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS, Bass J (2005) Obesity and metabolic syndrome in circadian Clock mutant mice. Science 308:1043–1045
171. Van Someren EJ (2000) Circadian and sleep disturbances in the elderly. Exp Gerontol 35:1229–1237
172. Videnovic A, Leurgans S, Fan W, Jaglin J, Shannon KM (2009) Daytime somnolence and nocturnal sleep disturbances in Huntington disease. Parkinsonism Relat Disord 15:471–474
173. Villablanca J (1972) Permanent reduction in sleep after removal of cerebral cortex and striatum in cats. Brain Res 36:463–468
174. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson E P Jr (1985) Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol 44:559–577
175. Watts AG, Swanson LW (1987) Efferent projections of the suprachiasmatic nucleus: II. Studies using retrograde transport of fluorescent dyes and simultaneous peptide immunohistochemistry in the rat. J Comp Neurol 258:230–252
176. Wetter TC, Collado-Seidel V, Pollmacher T, Yassouridis A, Trenkwalder C (2000) Sleep and periodic leg movement patterns in drug-free patients with Parkinson's disease and multiple system atrophy. Sleep 23:361–367
177. Wiegand M, Moller AA, Lauer CJ, Stolz S, Schreiber W, Dose M, Krieg JC (1991) Nocturnal sleep in Huntington's disease. J Neurol 238:203–208
178. Youngstedt SD, O'Connor PJ, Dishman RK (1997) The effects of acute exercise on sleep: a quantitative synthesis. Sleep 20:203–214
179. Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, MacDonald ME, Friedlander RM, Silani V, Hayden MR, Timmusk T, Sipione S, Cattaneo E (2001) Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science 293:493–498