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Disease and degeneration of aging neural systems that integrate sleep drive and circadian oscillations

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Sleep/wake and circadian rest-activity rhythms become irregular with age. Typical outcomes include fragmented sleep during the night, advanced sleep phase syndrome and increased daytime sleepiness. These changes lead to a reduction in the quality of life due to cognitive impairments and emotional stress. More importantly, severely disrupted sleep and circadian rhythms have been associated with an increase in disease susceptibility. Additionally, many of the same brain areas affected by neurodegenerative diseases include the sleep and wake promoting systems. Any advances in our knowledge of these sleep/wake and circadian networks are necessary to target neural areas or connections for therapy. This review will discuss research that uses molecular, behavioral, genetic and anatomical methods to further our understanding of the interaction of these systems.

Keywords: aging, neurodegenerative, sleep, wake, circadian, disease

Studies have shown that sleep and circadian activity rhythms become irregular with age (Morin, 1993; Valentinuzzi et al., 1997; Kendall et al., 2001). Sleep becomes fragmented during the night and daytime sleepiness increases (Carskadon et al., 1982; Huang et al., 2002). The quantity of REM sleep and slow wave sleep (SWS) decreases as well and the normal circadian amplitude of the sleep/wake cycle is dampened and shortened (van Gool et al., 1987; Turek et al., 1995). These changes lead to a reduction in the quality of life due to cognitive impairments and emotional stress. More importantly, severely disrupted sleep and circadian rhythms have been associated with an increase in disease susceptibility (Hastings et al., 2003; Gibson et al., 2009).

The mechanisms responsible for the development of fragmented sleep are not completely understood. However, examining the functional interaction between circadian oscillators and sleep/wake areas has aided in these efforts (Dijk and von Schantz, 2005). With increasing age, circadian and sleep/wake neural areas or connections within the network may compensate for initial dysfunctions (Van Someren et al., 2002). For example, the degeneration of one network component may be deleterious on the systems as a whole, while other components may be more resistant to age-associated degeneration (Naidoo et al., 2011). Discerning how systems change with age is important to understand how they contribute to normal and dysfunctional sleep and wake. Many of the same brain areas in the sleep and wake promoting systems are affected by neurodegenerative diseases. Any advances in our knowledge of these sleep/wake and circadian networks may aid in designing therapies targeting these neural areas or connections. This review will discuss research that uses molecular, behavioral, genetic and anatomical methods to further our understanding of the interaction of these systems.

AGING CIRCADIAN SYSTEMS

The desynchronization of central and peripheral circadian systems contributes to the decline in optimal functioning of bodily systems. This includes changes in neuroendocrine circadian rhythms, insulin sensitivity, altered thermoregulation and acceleration of tumor growth (Cincotta et al., 1993; Touitou and Haus, 2000; Hastings et al., 2003; Straub and Mocchegiani, 2004; Cretenet et al., 2010; Heller et al., 2011). These are complex interactions and dysfunction can be due to targeted disruption of neurons, neurotransmitter or neuropeptide production, transport or secretion. It is reasonable to expect that the neuronal activity or expression of circadian clock genes be reduced or rhythms phase shifted (Kolker et al., 2003). Additionally, the connections between central and peripheral oscillators may be degraded or less functional (Morales et al., 1987). Any one or a combination of these abnormalities may result in the decoupling of the circadian oscillators and the ensuing pathologies.

The master central pacemaker is the suprachiasmatic nucleus (SCN) which controls circadian rhythmicity. Rhythmicity can dampen and/or elongate/shift with age but the number or cell size of neurons in the SCN does not change. However, the oscillating activity of these neurons does deteriorate (Satinoff et al., 1993; Madeira et al., 1995). Additionally, glucose uptake decreases in the SCN in aged animals (Wise et al., 1988) and the expression of neuropeptides also diminishes. Vasoactive intestinal polypeptide (VIP) expressing neurons of the SCN are retinorecipient and vasopressin (AVP) expressing neurons of the SCN modulate rhythmicity (Wu et al., 2007). In aged male humans, the number of SCN neurons that express VIP decreases and in aged female rats the expression becomes arrhythmic (Zhou et al., 1995; Krajnak et al., 1998). Both genders also express less AVP protein, less mRNA

(Roozendaal et al., 1987; Zhou et al., 1995) and the normal daytime peak of AVP is reduced (Hofman and Swaab, 1994; Liu et al., 2000). Decreases in the neuroendocrine output of the SCN may directly or indirectly affect the coupling of central and peripheral oscillators.

In the SCN, clock genes constitute the core clock mechanism of the mammalian timekeeping system. Though the system is fairly complex, for brevity the simplest model is described. BMAL1 and CLOCK proteins dimerize and induce the transcription of *Period* (*Per*) and *Cryptochrome* (*Cry*) genes. In a negative feedback loop, levels of PER and CRY proteins increase and at a certain threshold form heterodimers which turn off the CLOCK BMAL1 regulated transcription of *Per* and *Cry* genes. This process takes roughly 24 h (Ko and Takahashi, 2006).

In aged animals the expression of certain clock genes changes in the SCN. *Per1*, *Per2*, and *Cry1* expression does not change significantly with age, but the normal photic stimulation of *Per1* expression is reduced (Asai et al., 2001; Kolker et al., 2003). Additionally, the free-running period of *Per1–luc* rhythmicity is shortened in aged animals (Yamazaki et al., 2002) and the amplitude of *Clock* and *Bmal1* expression is decreased (Kolker et al., 2003). Changes in clock gene expression in peripheral tissues do not always reflect what is seen in the SCN (Yamazaki et al., 2000), and may result from a disruption of signals to these tissues or the tissues themselves, which are more susceptible to the aging process.

Furthermore, projections to and from the SCN including peripheral oscillators may change with age. In motoneurons, aging results in a shortening in delay of spike potentials between axon and soma, as well as decreases in axon conduction velocity and increases in input resistance (Morales et al., 1987; Engelhardt et al., 1989). Similar changes may be seen in these circadian projections. Light, food and temperature cues also input to the SCN. The output from circadian and peripheral oscillators do not only influence the sleep/wake cycle, but regulates metabolism and reproduction. Studies indicate that some tissues retain the ability to oscillate, even if connections from the master pacemaker have been degraded. Peripheral tissues *in vitro* that have become arrhythmic can be chemically induced to oscillate (Yamazaki et al., 2002). However, in aged animals exhibiting a decreased photic response, retinal projections to the SCN are not degraded and must be related to either the retina or SCN clock functions (Zhang et al., 1998). It is increasingly evident that determining the source of age-related sleep/wake or circadian dysfunctions is rather complex.

SLEEP/WAKE SYSTEMS AGE

Another source of sleep/wake changes can likely be attributed to age-related neuronal dysfunction in the arousal and sleep promoting areas of the brain. The SCN directly or indirectly communicates with the sleep and wake promoting systems (Abrahamson et al., 2001; Aston-Jones et al., 2001; Chou et al., 2002). Orexinergic (or hypocretinergic) neurons are known to stabilize or maintain wake (Saper et al., 2001, 2005). These cells receive input from the SCN via the dorsomedial hypothalamus (DMH) and are localized in the perifornical and lateral hypothalamus (LH). There are two forms of the neuropeptide orexin/hypocretin (A and B) and two receptors. Though the neurons are limited to a discrete area, both orexinergic fibers and receptors are widely distributed throughout the brain. In diurnal and nocturnal rodents, orexinergic neurons are most active during the active phase (Martinez et al., 2002). Hypothalamic microdialysate analysis shows orexin-1 levels increase during wake and REM in adult animals (Kiyashchenko et al., 2002).

Mammals with no orexin or dysfunctional orexin/hypocretin receptors have disrupted sleep/wake cycles and narcoleptic symptoms. When orexin is decreased, the circadian rhythm of the sleep/wake cycle is disrupted. The flip–flop model of sleep/wake control suggests that there is a mutual inhibition between the areas that control sleep and the areas that control the wake state (Saper et al., 2001). In short, the ventrolateral preoptic area (VLPO) controls sleep and the brainstem cholinergic and monoaminergic systems control waking. Flipping weight between these areas controls the wake and sleep states. One input that stabilizes this switch is from the orexin neurons. Blocking or destroying these neurons or the orexin receptor 2 may flip the animal's state quickly from waking to sleep and vice versa, such as what occurs in narcoleptic individuals, orexin knockout mice, and canine narcolepsy (Chemelli et al., 1999; Lin et al., 1999; Peyron et al., 2000; Thannickal et al., 2000).

A disruption in orexin function or a reduction in orexin levels leads to less stable sleep/wake cycles such as that seen in many elderly patients with sleep disorders (Porkka-Heiskanen, 2003). Additionally, decreases in excitatory orexin innervation to the noradrenergic locus coeruleus (LC) is thought to be a contributing factor of poor sleep/wake quality in aged cats (Zhang et al., 2002). Orexin B immunoreactive (-ir) axon density was determined to be significantly lower in the LC of aged macaques than that observed in the young or adult animals (43 and 35% decrease respectively; Downs et al., 2007). Real time PCR studies showed that *prepro-hypocretin* mRNA does not change in the aged hypothalamus (Terao et al., 2002) but *in situ* hybridization studies show that at the single cell level, preproorexin gene expression does decrease in cell count and optical density (Porkka-Heiskanen et al., 2004). Furthermore, orexin A and B protein expression as measured by radioimmunoassay was decreased in the LH (Porkka-Heiskanen et al., 2004). The number of orexinergic-ir neurons as well as the optical density of respective fibers in the LH is reduced in aged animals (Brownell and Conti, 2010; Sawai et al., 2010). It is interesting to note that orexinergic innervation of the cholinergic basal forebrain, which modulates wake and REM sleep, is reduced in aged guinea pigs (Zhang et al., 2005). Orexin/hypocretin receptor mRNA expression is also decreased in aged animals. Hypocretin receptor 1 mRNA is reduced in the hippocampus and hypocretin receptor 2 mRNA is significantly reduced in thalamic areas, hippocampus, and the brainstem (Terao et al., 2002). Neural activity measured by c-fos immunoreactivity is reduced in orexinergic neurons of mice at 24 months (Naidoo et al., 2011).

Changes are also seen in the cholinergic and monoaminergic wake active areas of aged animals. Nicotinic and muscarinic receptors of the acetylcholinergic system decrease in the SCN with age (van der Zee et al., 1991). In young animals, the noradrenergic neurons of the LC are important in wake promotion, receive direct input from the SCN and follow a circadian pattern of activation (Aston-Jones et al., 2001). In aged rats, LC projections to the frontal cortex and dentate gyrus decrease but axonal branching

increases depending on the target and age. This is suggested to be a compensatory mechanism (Shirokawa et al., 2000). In the ventral periaqueductal gray (vPAG) the wake active dopaminergic neurons have recently been identified (Lu et al., 2006). We have recently reported a reduction in the neural activity of these dopaminergic neurons of the vPAG and the noradrenergic neurons of the LC in aged mice (Naidoo et al., 2009, 2011).

The wake active histaminergic system originates in the tuberomammillary nucleus (TMN) and sends widespread projections to areas that include the cortex, thalamus and brainstem. Histamine levels were found to be increased in middle aged rats when compared to young, and the level of histamine methyl transferase was decreased (Mazurkiewicz-Kwilecki and Prell, 1984). The histamine receptor mRNA levels also change with age. There are four types of histaminergic receptors located throughout the brain and body. Histamine H1, H2 and H3 receptor mRNA is decreased in the aging brain (Terao et al., 2004). Given these changes in the aging wake promoting neurotransmitter systems as well as wake maintaining systems, it is clear that therapies to alleviate or attenuate these changes need to be developed.

Sleep promoting areas may show a reduction in function with age. The VLPO neurons are active during SWS (Sherin et al., 1996; Szymusiak et al., 1998) and when lesioned results in insomnia (Lu et al., 2000). GABAergic and galaninergic inhibitory neurons from this area project to wake active histaminergic neurons (Sherin et al., 1996). Interestingly, the number of activated VLPO neurons during sleep does not change in old rats (Shiromani et al., 2000) although connections between these areas may become dysfunctional or degraded with age. The SCN has a minor input into the VLPO, but substantial direct and indirect inputs to the DMH (Novak and Nunez, 2000; Chou et al., 2002). The DMH heavily inputs the VLPO and it would be beneficial if these pathways were examined during aging.

Age-associated changes in the serotonergic system affect the function of respiratory motor output during sleep. Serotonergic input to the hypoglossal nucleus decreases, which is thought to lead to a decline in upper airway muscle performance (Behan and Brownfield, 1999). In aged rhesus monkeys, serotonin receptor 2 density reduces in the occipital and parietal cortex including the deep layers of the motor cortex (Wenk et al., 1989; Bigham and Lidow, 1995). Serotonin levels also decrease in the occipital areas but do not change in the cingulate cortex in aged monkeys (Beal et al., 1991). It is likely with normal aging that changes in any neurotransmitter system affecting sleep vary across the brain. This presents a difficult task to fully determine the interaction of aging and sleep.

AGE-ASSOCIATED NEURODEGENERATIVE DISEASES AND SLEEP

In many patients afflicted with neurodegenerative diseases the physical and mental consequences lead to sleep disorders (**Table 1**). For example, sleep fragmentation can occur if the patient cannot move well or insomnia may develop due to depression or feelings of helplessness. Medications used to alleviate some of the motor or cognitive symptoms such as levodopa in Parkinson's disease (PD) can also contribute to disruptions in normal sleep/wake behaviors. Sleep disorders may occur secondarily or due to concurrent or related neurodegenerative pathologies. However, some research indicates that sleep disturbances may predict manifestation of neurodegenerative diseases (Postuma and Montplaisir, 2009). Sleep disturbance or loss also affects metabolic and immune function (Krueger et al., 1998; Knutson et al., 2007). Chronic sleep loss could lead to neuronal damage resulting in altered hypothalamic pituitary adrenal axis function, cognitive deficits and memory loss. Increases in the number of patients with neurodegenerative diseases may be related to or the result of a society that does not sleep.

In Alzheimer's disease (AD), sleep disturbances increase with the severity of the disease. Initially there is an increase in nighttime arousals and a decrease in SWS (Vitiello et al., 1991). In the later stages, circadian disruption, severe daytime wakefulness and a reduction in REM sleep occurs, likely due to a reduction in acetylcholine (Dykierek et al., 1998). Circadian rhythm dysfunction has been proposed to be due to changes in SCN and pineal functions (Wu et al., 2007). Degeneration of cholinergic input from the nucleus basalis of Meynert to the cortex may be responsible for some of the sleep/wake changes (Montplaisir et al., 1995). Neurofibrillary tangles found in the histaminergic TMN of AD patients and amyloid-β peptide (Aβ) aggregation also contributes to the AD pathology. Normally in the interstitial fluid Aβ has a diurnal fluctuation with low levels during sleep and peak levels during wake. Recently one study showed that prolonged wake and/or orexin administration increased levels of the Aβ in the interstitial fluid of the brain in mice (Kang et al., 2009). Administration of an orexin antagonist reduced amyloid deposits in several brain areas suggesting that manipulating sleep or the orexin system in AD patients could improve symptoms (Kang et al., 2009). Although the research is sparse, melatonin, phototherapy and exercise have all had positive effects in the treatment of circadian and sleep/wake disorders of AD patients (Wu and Swaab, 2007). As one in three Americans develops AD, there is a crucial need for more research in these therapies.

REM sleep behavior disorder (RBD) has been associated with PD and thought to be an early manifestation (Schenck et al., 1996; Boeve et al., 2003; Postuma and Montplaisir, 2009). Sleep attacks and excessive daytime sleepiness (EDS) are also commonly seen in patients with PD (Factor et al., 1990; Diederich et al., 2005). The degeneration begins at the brainstem and progresses rostrally, although degeneration of the dopaminergic neurons of the substantia nigra pars compacta is the main contributor to PD characteristics (Braak et al., 2004). RBD results from pedunculopontine dysfunction and likely explains RBD manifesting previous to PD (Rye, 1997; Boeve et al., 2007). Some studies have successfully seen bright light therapy or sleep modifications reduce the symptoms of PD (Hogl et al., 1998; Willis and Turner, 2007).

Huntington's disease (HD) is a genetic disorder characterized by a polyglutamine (CAG) repeat (Scherzinger et al., 1999). Neurodegeneration is extensive throughout the brain, affecting cortical and subcortical areas but primarily affects the basal ganglia (Vonsattel et al., 1985). Sleep and wake regions of the brain including the brainstem, thalamus, hypothalamus and cortex are also affected in HD (Kremer et al., 1991). The SCN pacemaker is functional in mouse models of HD, so a dysfunction of the circadian circuitry is proposed to contribute to circadian abnormalities (Pallier et al.,

Table 1 | Common sleep and wake characteristics of neurodegenerative diseases.

	Brain areas, neurons damaged	General	Putative predictive factors	Circadian	NREM	REM	Wake	Therapeutic interventions
Age-associated degeneration	Basal forebrain, LC, cerebral cortex; DA, orexin[1,2,3]; cholinergic receptors[4]	Phase advanced, fragmented sleep and wake, EDS[5,6]	Disrupted melatonin system[7,8]	Altered circadian rest-activity rhythms[9,10]; altered peripheral resynchronization[11]	Decreased SWS[12]	Decreased REM[12,13,14]	Fragmented wake, increased napping, EDS[6,10]	Phototherapy[15]
Alzheimer's disease	Basal forebrain; cerebral cortex; ACh[16,17]	Decreased total sleep time[18]	REM density[13]	Disrupted core-body temperature rhythm[19]; disrupted melatonin system[20]	Decreased SWS[18]; decreased sleep spindles[21]	Decreased REM[13]; increased iNOS during REM[22]	Fragmented wake, increased napping[23]	Phototherapy, exercise[24]; orexin/hypocretin antagonist in mice[25]
Parkinson's disease	Substantia nigra pars compacta; DA[26]; Orexin[27]	Sleep fragmentation[28]; RBD[29]	REM behavior disorder[29,30]	Decreased diurnal variation of cortisol[31]; altered circadian rest-activity rhythms[9]	Decreased SWS, decreased sleep spindles[32]	RBD[29]; intrusion of REM into NREM[33]	EDS[34]	Phototherapy[35]
Huntington's disease	Basal ganglia; DA[36,37]	Fragmented sleep and wake, decreased REM[38]	Increased sleep spindles[32]	Disruption associated with increased nocturnal activity[39]; delayed sleep phase[42]	Chorea during stage 1[40]; increased stage 1[38]; increased sleep spindles[32,41]	Decreased REM, increased latency to REM[38]	Wake is impaired but reports that are different from age-matched controls are not consistent [41,42]	Food entrainment[43]; alprazolam to restore circadian rhythms slows cognitive decline[44]
Amyotrophic lateral sclerosis	Motor neurons of the motor cortex, brainstem, and spinal cord; progressive degeneration of 5HT neurons contributes to decreased motoneuron activity[45]	SDB, insomnia[46,47]; reduced quality of sleep correlated with the severity of the disease[48]; degeneration leads to muscle weakness and SDB[46]	SDB (predictive of early respiratory failure)[46]	Disrupted cortisol circadian rhythm[49]	Decreased SWS[48]	Decreased and fragmented REM sleep[48]; sleep disordered breathing[46]	EDS[48,50]	CPAP[50, 51]; BiPAP[52]; melatonin supplementation[53]

DA, dopamine; iNOS, inducible nitric oxide synthase.

[1]Sturrock and Rao (1985), [2]Zhang et al. (2005), [3]Naidoo et al. (2011), [4]van der Zee et al. (1991), [5]Carskadon et al. (1982), [6]Foley et al. (2007), [7]Magri et al. (1997), [8]Touitou (1995), [9]Whitehead et al. (2008), [10]Huang et al. (2002), [11]Davidson et al. (2008), [12]Turek et al. (1995), [13]Dykierek et al. (1998), [14]Feinberg et al. (1967), [15]Myers and Badia (1995), [16]Brun and Englund (1981), [17]Teipel et al. (2005), [18]Vitiello et al. (1991), [19]Satlin et al. (1995), [20]Wu et al. (2007), [21]Montplaisir et al. (1995), [22]Tseng et al. (2010), [23]Bonanni et al. (2005), [24]Wu and Swaab (2007), [25]Kang et al. (2009), [26]Braak et al. (2004), [27]Thannickal et al. (2007), [28]Factor et al. (1990), [29]Schenck et al. (1996), [30]Postuma and Montplaisir (2009), [31]Hartmann et al. (1997), [32]Emser et al. (1988), [33]Mouret (1975), [34]Diederich et al. (2005), [35]Willis and Turner (2007), [36]Vonsattel et al. (1985), [37]Kremer et al. (1991), [38]Arnulf et al. (2008), [39]Morton et al. (2005), [40]Fish et al. (1991), [41]Wiegand et al. (1991), [42]Aziz et al. (2010), [43]Maywood et al. (2010), [44]Pallier et al. (2007), [45]Sandyk (2006), [46]Kimura et al. (1999), [47]Atalaia et al. (2007), [48]Lo Coco et al. (2011), [49]Patacchioli et al. (2003), [50]Barthlen and Lange (2000), [51]Howard et al. (1989), [52]David et al. (1997), [53]Weishaupt et al. (2006).

2007). Central and peripheral clock gene expression is altered as well (Morton et al., 2005; Maywood et al., 2010). The sleep/wake cycle is disrupted in HD patients characterized by self-reported EDS, sleep fragmentation at night, and delayed sleep phase (Arnulf et al., 2008; Videnovic et al., 2009; Aziz et al., 2010). Sleep is lighter with an increase in Stage 1 and a decrease in REM sleep (Arnulf et al., 2008). Disruptions in the circadian and sleep/wake cycles of these patients exacerbate symptoms, increasing depression, cognitive deficits and metabolic dysfunctions (Aziz et al., 2010). It is important to note that pharmacological and behavioral manipulation of sleep and wake reduces disease progression and improves cognitive function and circadian gene expression in a mouse model of HD (Hockly et al., 2002; Pallier et al., 2007; Pallier and Morton, 2009; Maywood et al., 2010).

Amyotrophic lateral sclerosis (ALS) is considered an age-associated neurodegenerative disease with the age of onset ranging from 40 to 70. Although onset can occur in children this is rare. Most ALS cases are sporadic and about 10% are familial. Also called Lou Gehrig's or motor neuron disease (Boillee et al., 2006), both upper and lower motor neurons are affected. Motor neurons of the motor cortex, brainstem and spinal cord gradually degenerate leading to muscle weakness, sleep disordered breathing (SDB) and paralysis (Kimura et al., 1999). Additionally, sleep is reduced in both REM and SWS stages with resulting EDS (Barthlen and Lange, 2000; Lo Coco et al., 2011). Some patients find relief using assisted breathing such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP; Howard et al., 1989; David et al., 1997; Barthlen and Lange, 2000).

Amyotrophic lateral sclerosis is a complex disease of many subtypes with various genetic and environmental contributing factors. One such factor is glutamate toxicity which is decreased using the drug Riluzole (Shaw and Ince, 1997). Alternative therapies are also being considered including the regulation of the serotonin system. Levels of serotonin are decreased in ALS patients and compensatory increases in glutamate lead to excitotoxicity. It has been suggested that motor neurons with a high density of serotonergic innervation are more susceptible to degeneration (Sandyk, 2006). Serotonin is the precursor to melatonin, which is also likely to be decreased. As melatonin has antioxidant properties and inhibits glutamate release, this reduction would further exacerbate degeneration. Indeed, melatonin supplements slowed disease progression when given to a mouse model of familial ALS (Weishaupt et al., 2006).

PLASTICITY AND COMPENSATION

Normally the SCN is coupled to peripheral oscillators, although studies have shown that SCN control is not necessary for sustaining oscillatory activity. If signals from central oscillators reduce in strength due to age or neurodegeneration, other cues may entrain the peripheral oscillators (Weinert, 2005). Unmasking mechanisms within sleep/wake systems is difficult due to the many checks and balances that ensure homeostasis. Although compensation and plasticity occurs to a lesser extent in older animals, a relatively high degree is preserved (Van Someren et al., 2002). This may not always be advantageous as epigenetic methylation of circadian genes has been associated with dementia (Liu et al., 2008). Understanding how the aging brain can compensate and remain plastic will be beneficial to focus on more effective treatments for sleep/wake and neurodegenerative disorders.

DISCUSSION

Many neurodegenerative diseases result from targeted destruction of neurotransmitter systems. The co-morbidity of sleep disorders with neurodegenerative diseases suggests that changes in many of these neural areas manifests in sleep/wake and circadian dysfunction. Effects on the sleep/wake and circadian systems may result from, or contribute to, the increasing pathology. Some research has shown the benefit of pharmacologically or behaviorally restoring rhythms and sleep/wake for delaying pathologies (**Table 1**). This is important to understand in a society where sleep is not considered a priority. A few points worth considering are as follows: Sleep is a basic need that is made secondary to work schedules and some leisure activities for many adults. In developing children and adolescents, early school start times and late night extracurricular meetings contribute to a culture of sleep deprived, cognitively unhealthy Americans. If restoring our circadian and sleep/wake cycles can ward off the deterioration of the brain, it is imperative to educate the public about the very real damage of abnormal sleep/wake cycles not only in aging individuals but at every age.

The fragmented sleep/wake pattern seen in aging individuals can be due to the degeneration or dysfunction of the circadian and sleep/wake networks. Uncoupling of the central and peripheral oscillators may exacerbate dysfunction via altered feedback signals or signaling pathways. It is likely that several brain regions are affected and that there are individual differences in how the sleep/wake and circadian networks degrade. Additionally there may be differential plasticity and compensation in the integration of these neural systems, making the identification of applicable therapies very difficult. However, if mechanisms contributing to the normal aging process of these networks are identified, this may elucidate a general therapy for restoring sleep/wake and circadian homeostasis. Ultimately this could also reduce the onset or improve the symptoms of neurodegenerative diseases. It is crucial that we immediately invest our energies and resources in understanding these mechanisms as well as in the dissemination and implementation of current knowledge and therapies to the public.

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