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Review article

Alzheimer's disease: Neurotransmitters of the sleep-wake cycle

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ABSTRACT

With aging, our sleeping pattern alters. Elderly often wake unrested because their sleep time and sleep efficacy is reduced. In Alzheimer's disease (AD) patients, these alterations are even more pronounced and may further aggravate cognitive decline. Therefore, sleep disturbances greatly impact self-care ability, caregiver exhaustion and institutionalization rate. Reestablishing an effective sleep-wake cycle in these patients still remains an unresolved challenge, partly because sleep physiology is quite complex and multiple neurotransmitter systems contribute to a single process. Gaining a better understanding of sleep physiology will be crucial for further research. Conjointly, animal models, along with a multidisciplinary approach, will be of great value to establish a common ground between AD and sleep disturbances and work towards a potential therapeutic application.

1. Introduction

For long, we have considered the sleep process to be a waste of precious time and an ineffective mechanism of our body to recover from daily activity. Only recently, we have started to realize the importance of sleep and discover its true underlying functions. Yet, considering all the neurotransmitters in our brain, there is still a lot of ambiguity about how exactly these molecules and their receptors contribute to the physiology of sleep. Moreover, these same neurotransmitter systems are affected in many brain diseases including Alzheimer's disease (AD), and often underlie their symptomatology (Francis, 2005; Lanari et al., 2006). In AD, disruptions of cholinergic and monoaminergic systems have been profusely described (Ferreira-Vieira et al., 2016; Simic et al., 2017; Vermeiren et al., 2016). Since these neurotransmitters are also majorly involved in sleep physiology, it is no wonder that severe sleep disturbances arise in this disease. Nevertheless, which neurotransmitter system truly underlies each specific sleep pathology, often remains disputable. In this review we aim to identify and name the underlying neurotransmitter systems involved in the sleep-wake cycle and how they are affected in AD. We also thoroughly summarize the current animal-based evidence of sleep-wake alterations in different transgenic models to demonstrate their contribution to our current knowledge. Other reviews have extensively described the relation between sleep and AD, focusing on symptomatology and treatment (Brzecka et al., 2018; Peter-Derex et al., 2015), mechanisms underlying the relation between sleep disruptions and AD (Cedernaes et al., 2017), and the influence of tau (Holth et al., 2017a), but none have combined knowledge about neurotransmitter disturbances and evidence from transgenic mouse models.

2. Organization of sleep-wake behavior

Many mammalian behavioral and physiological processes oscillate within a 24 -h period, including hormone levels, body temperature and the sleep-wake cycle. In humans, the sleep-wake cycle is biphasic and is roughly comprised of 8 h of nocturnal sleep and 16 h of daytime wakefulness (Boivin, 2005; Daan et al., 1984). Transitions between these two states occur infrequently and are almost instantaneous. Only 1–2% of the day is spent in this transitional state. Such observations led to the proposal of a 'flip-flop' system as a model for the regulation of state

Abbreviations: ACh, Acetylcholine; AChE, Acetylcholinesterase; AChEI, Acetylcholinesterase inhibitor; AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APOE, Apolipoprotein E; APP, Amyloid precursor protein; ATP, Adenosine triphosphate; Aβ, Amyloid beta; BID, Bis in die; CaMKIIα, alpha-Ca2 + /calmodulin-dependent protein kinase II; cAMP, Cyclic adenosine monophosphate; CSF, Cerebrospinal fluid; DMH, Dorsomedial nucleus of the hypothalamus; EEG, Electroencephalography; ERK, Extracellular signal-regulated kinases; GABA, Gamma-aminobutyric acid; ISF, Interstitial fluid; LDT, Laterodorsal tegmental nucleus; MAPT, Microtubule-asssociated protein tau; NA, Noradrenaline; NB, Nucleus basalis; NMDA, N-methyl-D-aspartic acid; NREM, Non-rapid eye movement; PPT, Pedunculopontine tegmental nucleus; PrP, Prion protein; PSEN1, Presenilin 1; REM, Rapid eye movement; SCN, Suprachiasmatic nucleus; SPZ, Subparaventricular zone; SWS, Slow wave sleep; TMN, Tuberomammillary nucleus; TST, Total sleep time; VLPO, Ventrolateral preoptic nucleus

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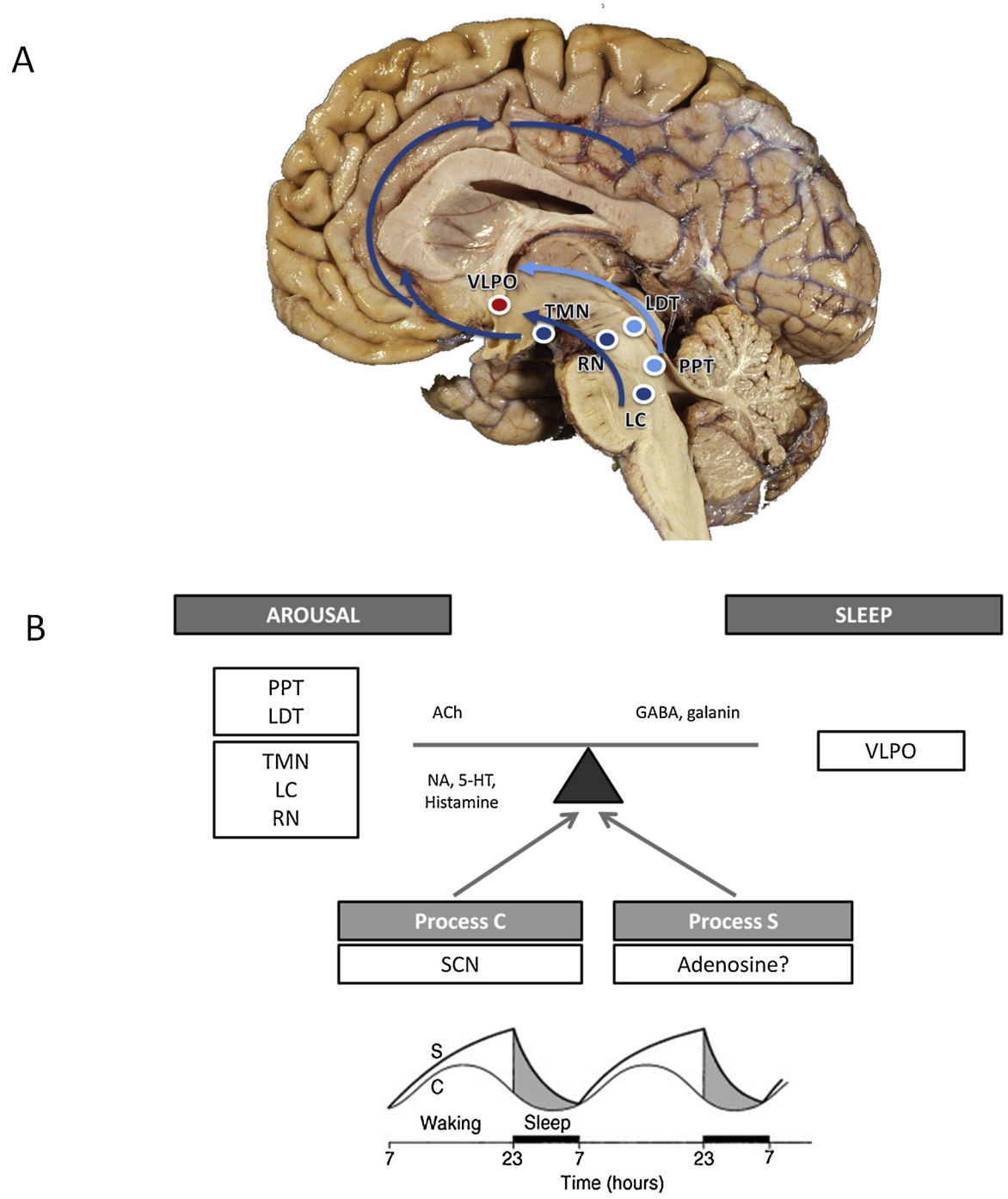

Fig. 1. *A.* Anatomical landmarks of all different main nuclei involved in sleep regulation. The ascending reticular activating system, which is responsible for maintaining wakefulness, is comprised of two branches. The first branch originates in the pedunculopontine nucleus (PPT) and laterodorsal tegmental nucleus (LDT) and is most active during wakefulness and REM. The second branch finds its origin in the tuberomammillary nucleus (TMN), locus coeruleus (LC) and raphe nuclei (RN). In contrast to the first branch, the second branch is not active during REM sleep. The ventrolateral preoptic nucleus (VLPO), the nucleus that maintains sleep by inactivating the arousal system, is located in the preoptic area. ***B.* The flip-flop switch and its two-process regulation.** The VLPO initiates sleep, while the PPT, LDT, TMN, LC and RN initiate arousal. The transitions between these states are organized in a flip-flop switch, which is controlled by a two-process model. Process C is the circadian factor that drives alertness and stands under control of the suprachiasmatic nucleus (SCN). Process S, the homeostatic drive for sleep, is regulated by adenosine. Process S builds up as the day progresses, while the circadian wake drive diminishes. The urge to sleep is greatest when the difference between the two processes is greatest (Borbely and Achermann, 1999). ACh, Acetylcholine; NA, Noradrenaline; 5-HT, Serotonin; GABA, *gamma*-aminobutyric acid.
Photo (A) is property of the IBB Biobank, Antwerp, Belgium, Scheme (B) is based on Saper et al. (2005) *(*Saper et al., 2005*) and* Byars and Amin (2008) *(*Byars and Amin, 2008*)*

stability (Saper et al., 2001, 2005). In this model, the arousal- and sleep-promoting systems are reciprocal inhibitory circuits, in which one system turns off the other as soon as either side obtains a small advantage over the other. The self-reinforcing flip-flop circuit creates a feedback loop that is bistable, hence avoiding transitional states. This evolutionary advantageous system prevents organisms to drift slowly back and forth between sleep and wakefulness, thereby aiding in the procurement of food and the avoidance of predation (Fig. 1).

2.1. Neurotransmitters involved in wakefulness

Wakefulness is maintained by the ascending reticular activating system, which contains two branches, each comprising different cell populations and neurotransmitters (Moruzzi and Magoun, 1949; Saper et al., 2001). The first branch projects to the thalamus and finds its origin in the cholinergic pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei (*Light blue in* Fig. 1A). The projections are most active during rapid eye movement (REM) sleep and wakefulness, and least active during non-REM (NREM) sleep (Saper et al., 2005). The second branch originates from a heterogeneous group of monoaminergic cell populations, of which the noradrenergic locus coeruleus (LC), the serotonergic raphe nuclei and the histaminergic tuberomammillary nucleus (TMN) are most important. They project to the lateral hypothalamus, the basal forebrain and the cerebral cortex (*Dark blue in* Fig. 1A). Activity patterns of this branch are slightly different from those of the first branch: in contrast to the pedunculopontine and laterodorsal tegmental branch, this second branch of the arousal system displays little activity during REM sleep (Aston-Jones and Bloom, 1981). The different neurotransmitters involved in sleep-wake regulation have been extensively reviewed elsewhere (Baghdoyan and Lydic, 2012; Siegel, 2004; Watson et al., 2010), but are briefly summarized below (and also in Table 1).

2.1.1. Acetylcholine

Acetylcholine is majorly involved in cortical activation. Therefore, cholinergic activity is highest during REM sleep and wakefulness. Two neuronal clusters are responsible for the arousal-promoting effects. Firstly, PPT/LDT neurons inhibit EEG spindles and slow waves via thalamic projections and maintain REM by activation of the reticular formation. The second cluster is comprised of basal forebrain neurons, which project to the neocortex and hippocampus and contribute to EEG activation, as well as to behavioral arousal, selective attention, and learning and memory (Steriade and McCarley, 2005; Baghdoyan and Lydic, 2012).

2.1.2. Noradrenaline

Similar to ACh, noradrenaline (NA) is one of the main neurotransmitters involved in arousal. The LC is the main production site of NA in the brain, and its release exerts wakefulness by activation of α and β receptors in the medial septal area or medial preoptic area (Mitchell and Weinshenker, 2010). LC neurons are highly active during wake, fire slowly during non-REM sleep, and are almost completely quiescent during REM sleep. However, to initiate REM, the presence of NA is required, as demonstrated by dramatic REM reductions in β-hydroxylase knockout mice (Ouyang et al., 2004). Probably, activation of α_2 adrenergic receptors inhibits LC neurons, and this autoinhibitory mechanism that turns off LC neurons, permits the onset of REM sleep (Baghdoyan and Lydic, 2012).

2.1.3. Serotonin

Serotonergic nuclei, of which the raphe nuclei are most extensively studied, lie along the midline of the brainstem. Early studies by Jouvet suggested that serotonin has a sleep promoting function (Jouvet, 1969), while later studies have demonstrated a 'Wake-On/REM-Off' discharge pattern in dorsal raphe nuclei. Extracellular serotonin levels in cortex, hippocampus and brainstem are greatest during wakefulness, intermediate during NREM and lowest during REM, and thus might confirm this discharge pattern (Brevig and Baghdoyan, 2010).

2.1.4. Histamine

Histaminergic neurons are located in the TMN of the posterior hypothalamus. Decreasing histamine levels in the rat and cat brain significantly decreased wakefulness and increased NREM (Lin et al., 1988; Monti, 2011b). Additionally, histamine release is greater during wakefulness than during sleep in the prefrontal cortex and anterior hypothalamus (Brevig and Baghdoyan, 2010).

2.2. Neurotransmitters involved in sleep

The sleep state is initiated by activation of the ventrolateral preoptic nucleus (VLPO) in the preoptic area. The neurons of this nucleus form a dense cluster and innervate the monoaminergic systems in the brainstem and hypothalamus that play a role in the modulation of cortical arousal (Fig. 1A). Via its gamma-aminobutyric acidergic (GABA) and galaninergic projections, the nucleus is able to silence the ascending monoaminergic arousal system. In turn, VLPO neurons are also inhibited by the afferents of the LC and raphe nuclei (Gallopin et al., 2000), thereby proving again the existence of a flip-flop switch (Fig. 1B).

2.2.1. GABA

Gamma-aminobutyric acid is the major inhibitory neurotransmitter of the brain and, similar to glutamate, its effects on sleep vary strongly between brain regions. The GABAergic neurons most important for sleep are located in the basal forebrain and the anterior hypothalamus. These neurons are more active during NREM sleep than during waking and REM sleep and even increase their discharge rates with sleep onset, thereby releasing high GABA levels while sleep continues. Arousal promoting neurons, such as cholinergic neurons of the basal forebrain, are directly inhibited by GABAergic sleep-active neurons (Siegel, 2004). Similarly, some galaninergic terminals of the VPLO inhibit wake-promoting regions, resulting in NREM sleep (Kroeger et al., 2018).

2.2.2. Other sleep-promoting substances

A whole array of neurotransmitters are involved in driving

Table 1
Neurotransmitters of sleep-wake regulation with their corresponding mode of action and timing of release.

Neurotransmitter	Site of cell bodies	Action	Activity levels during		
			Wake	NREM	REM
Noradrenaline	Locus coeruleus (pons)	Arousal (muscle tone, motor activity)	High	Low	Very low
Serotonin	Raphe nuclei (pons)	Arousal (muscle tone, motor activity)	High	Low	Very low
Acetylcholine	LDT, PPT (pons), basal forebrain	Arousal (wakefulness, REM sleep)	High	Low	High
Dopamine	VTA, substantia nigra pars compacta	Arousal	High	Low	High
Histamine	TMN (post. hypothalamus)	Arousal (forebrain)	High	Low	Very low
Hypocretin/orexin	Dorsolateral hypothalamus	Arousal (motor activity)	High	Very low	Low
Glutamate	Omnipresent	Arousal (wakefulness, REM sleep)	High	Low	High
GABA	Omnipresent	Inhibition, deactivation (Sleep)	Low	High	Very low

This table provides an overview of the different neurotransmitters that are involved in sleep-wake regulation. For every neurotransmitter, the major sites of where the cell bodies reside are provided. In addition, their main actions are listed as well as their activity levels during wake, rapid eye movement (REM) sleep and non-REM (NREM) sleep. LDT, laterodorsal tegmental nucleus; PPT, pedunculopontine nucleus; VTA, ventral tegmental area; TMN, tuberomammillary nucleus. Based on findings in literature (Baghdoyan and Lydic, 2012; Mileykovskiy et al., 2005; Miller et al., 1983; Mitchell and Weinshenker, 2010; Siegel, 2004; Watson et al., 2010).

wakefulness and sleep, of which the most important ones have been briefly mentioned above. An overview of the involved neurotransmitter systems is provided in Table 1. None of these neurotransmitters is absolutely necessary, but all rather contribute in some way, each forming a separate part of a greater system. Aside from these 'classic' pathways, other sleep-promoting substances have been suggested. Sleep deprivation experiments in which CSF of sleep-deprived animals is infused in naïve recipients (Nagasaki et al., 1974; Pappenheimer et al., 1967), and thalamic electric stimulation experiments (Monnier and Hoesli, 1964; Schoenenberger et al., 1977) have discovered different endogenous sleep-promoting substances, such as Factor S (Pappenheimer et al., 1967), Sleep-Promoting Substance (Nagasaki et al., 1974) and Delta-sleep-inducing peptide (Schoenenberger et al., 1977). However, the somnogenic effects of such substances could not be confirmed in all studies, rendering their actions quite ambiguous. Since all these neuromodulators and neurotransmitters are involved in other functional systems, sleep promotion may represent only a secondary effect (Borbely and Tobler, 1989).

2.3. The two-process model of sleep regulation

The regulation of sleep and wakefulness is suggested to be controlled according to a two-process model (Fig. 1*B*) (Borbely, 1982). Process S is defined as the homeostatic drive for sleep. With extended wakefulness, this process is responsible for eliciting the need for sleep. The underlying physiology remains unclear, although a role for adenosine has been suggested (Benington et al., 1995). Microdialysis and electrophysiological recordings have demonstrated that upon depletion of glycogen stores during periods of wakefulness, adenosine accumulates in the extracellular space of the basal forebrain, where it inhibits the basal forebrain arousal system and triggers the VLPO, thereby promoting sleep (Kong et al., 2002; Morairty et al., 2004; Porkka-Heiskanen et al., 2000; Scammell et al., 2000). Adenosine is a by-product of the breakdown of ATP and cAMP and originates from both neurons and astrocytes (Bjorness and Greene, 2009). Astrocyte-derived adenosine specifically affects slow-wave activity and recovery sleep, but not baseline sleep (Halassa et al., 2009). Since astrocytic ATP release is also caused by a rise in intracellular calcium due to AMPA and NMDA receptor activation (like neuronal ATP release), adenosine accumulation is tightly coupled to synaptic activity (Petit and Magistretti, 2016). The second process implicated in the sleep-wake regulation involves the circadian biological clock and is called Process C, as described by Borbely and colleagues (Borbely, 1982). The suprachiasmatic nucleus (SCN) is considered to be the main circadian pacemaker in mammals. The SCN exhibits a 24 -h firing pattern, which is entrained to the natural light-dark cycle. The nucleus exerts its effect on the sleep-wake regulatory system via projections towards the subparaventricular zone (SPZ) and dorsomedial nucleus of the hypothalamus (DMH). The SPZ receives by far the densest input and is presumed to integrate circadian input from the SCN and retina with behavioral inputs (e.g., from the ventromedial hypothalamus) (Lu et al., 2001). SCN and SPZ efferents then project further to the DMH, which is the key output nucleus with widespread downstream targets, including the sleep-promoting VLPO and the excitatory lateral hypothalamic area (Chou et al., 2003). This multistage circadian outflow system, together with Process S, regulates the sleep-wake behavior of most mammals. An elaborate summary of the regulation of the sleep-wake cycle falls beyond the scope of this review. For a more detailed overview of the basic physiology of the sleep-wake cycle, the flip-flop switch and the two-process model, we would kindly refer to several interesting reviews by experts in the field (Borbely, 1982; Borbely et al., 2016; Fuller et al., 2006; Saper et al., 2010; Schwartz and Roth, 2008).

3. Senescence-related effects on sleep

During the normal aging process, typical alterations in sleep architecture arise. Healthy aging individuals often present with a reduced total sleep time (TST), increased sleep latency and a fragmented sleep pattern, resulting in more frequent nighttime and morning awakenings (Miles and Dement, 1980; Weitzman et al., 1982). Consequently, they often wake unrested, resulting in excessive daytime sleepiness. This compels them to take diurnal naps, which probably again compromises their nighttime sleep. The deepest stages of NREM sleep, also referred to as slow wave sleep (SWS), are frequently reduced, while REM sleep reductions only start to appear at a later age (Van Cauter et al., 2000; Weitzman et al., 1982). Such deprivations of sleep exert effects on multiple levels. Epidemiological studies have demonstrated a relationship between sleep deprivation and hypertension (Gangwisch et al., 2006), coronary heart disease (Ayas et al., 2003; Liu and Tanaka, 2002), diabetes mellitus (Gottlieb et al., 2005; Yaggi et al., 2006) and immune deficiency (Cohen et al., 2009; Everson, 1993; Spiegel et al., 2002). A lack of sleep may also have detrimental implications for the brain itself. Poor sleep quality in non-demented elderly has been associated with cognitive decline (Nebes et al., 2009). Although the true function of sleep remains largely unknown, evidence suggests that sleep periods are favorable for brain plasticity and for learning and memory. Conventionally, sleep processes are presumed to participate in memory consolidation, an active process that relies on reactivation and reorganization of newly encoded representations (Born et al., 2006). Both REM and SWS are involved in memory consolidation. Although they are both essential in the formation of memories, their contribution to memory trace processing is fundamentally different. REM favors implicit memory tracing or procedural memory, while SWS is involved in explicit memory traces or declarative memory (Born et al., 2006; Maquet, 2001). According to the synaptic homeostasis hypothesis, proposed by Tononi and Cirelli, SWS not only serves to consolidate memory traces, but also prevents saturation and reduces place and energy demands, thereby preparing the network for the encoding of new information during succeeding wakefulness (Tononi and Cirelli, 2003). Slow oscillations (< 1 Hz) are assumed to proportionally downscale the potentiated synapses by a long-term depression-like mechanism, as neuronal firing at frequencies < 1 Hz is known to preferentially induce long-term depression (Kemp and Bashir, 2001). If memory consolidation (or possibly synaptic downscaling) during sleep is affected in aging, this might – at least partially – explain the cognitive decline often observed. Both the cognitive decline and the disturbances in the sleep-wake cycle that occur in senescence are even more pronounced in AD (Bliwise et al., 1995; Witting et al., 1990). Since sleep disruptions parallel the severity of the disease, a causal relationship underlying these phenomena has been suggested (Moe et al., 1995).

4. Sleep-wake alterations in AD

Clinically, 25 to 60% of all AD patients are diagnosed with sleep disorders and sleep abnormalities (Beaulieu-Bonneau and Hudon, 2009; Moran et al., 2005). These abnormalities often arise prior to the appearance of cognitive decline, and are among the first noticeable symptoms (Hatfield et al., 2004). The sleep architecture of AD patients is significantly different from healthy age-matched individuals, which manifests itself in a quantitative reduction of SWS and REM sleep and in alterations in spindles and K complexes, two NREM EEG characteristics that indicate suppression of arousal in response to external stimuli (Prinz et al., 1982). Furthermore, their sleep-wake cycle is often more fragmented and the overall daytime alertness is decreased compared to elderly of the same age (Bliwise et al., 1995; Huang et al., 2002; Witting et al., 1990), resulting in longer and more nocturnal awakenings and daytime naps (McCurry et al., 1999; Prinz et al., 1990).

As senescence-related reductions in TST can already cause deteriorations in cognitive function, extensively reduced amounts of sleep will even more so aggravate cognitive decline in AD.

4.1. Amyloid imbalance

In healthy human subjects, the concentration of Aβ in cerebrospinal fluid (CSF) shows diurnal oscillations, with higher Aβ levels during the day and reduced levels at night (Kang et al., 2009). One-day sleep deprivation also significantly increased amyloid brain burden in healthy controls as measured by florbetaben positron emission tomography (Shokri-Kojori et al., 2018). A recent study demonstrated that aged nondemented people with poor sleep quality and reduced sleep quantity, have a higher cerebral amyloid burden (Spira et al., 2013). Moreover, APOE ε4 carriers who showed restful sleep on actigraphic measurements were half less likely to develop AD, as those who slept more poorly (Lim et al., 2013). In addition, slow wave activity disruptions have been associated with increased CSF Aβ (Ju et al., 2017). These studies indicate that sleep disturbances are not merely a consequence of amyloid pathology, but may also affect one of these hallmarks of AD. Only recently, Holth et al. have shown in their pivotal paper that interstitial fluid (ISF) tau is regulated by the sleep-wake cycle and that both ISF tau in mice and CSF tau in humans are strongly increased by sleep deprivation. Increased wakefulness can result in rapid rises in extracellular monomeric tau, tau spreading and aggregation, thereby implicating the sleep-wake cycle in the regulation of tau pathology (Holth et al., 2019). If forthcoming studies should unambiguously identify poor sleep as a risk factor for AD, future generations should perhaps reconsider our modern, demanding lifestyle that brings along an increasing sleep pressure. The exact mechanisms underlying this relationship still remain to be elucidated. Since the circadian system co-forms the foundation of the sleep-wake cycle and given the fact that also other circadian rhythms, including motor activity, body temperature and several hormone secretions are affected, sleep disturbances probably arise from alterations in the circadian rhythm (Harper et al., 2008; Skene and Swaab, 2003; Van Erum et al., 2018; Witting et al., 1990). Although relatively few studies have been conducted to substantiate this hypothesis (Stopa et al., 1999; Swaab et al., 1985; Tranah et al., 2011), evidence is compelling, and underlying mechanisms should be further explored in the near future.

AD pathology is able to cause sleep-wake disturbances and a lack of sleep is able to increase Aβ burden. Lim et al. proposed five possible mechanisms that could underlie this reciprocal relationship (Lim et al., 2014), three of which directly involve Aβ metabolism. Extracellular Aβ levels are tightly correlated with wakefulness and neuronal activity (Bero et al., 2011; Cirrito et al., 2005). Slow wave activity during NREM sleep is associated with reduced neuronal activity and thus should be protective against Aβ deposition. A reduction of SWS and concomitant increased neuronal activity, has, therefore, been proposed as a first possible mechanism. A second hypothesis, which is still under extensive investigation, is that synaptic neurotransmission facilitates the seeding of local Aβ aggregates and the spread of AD pathology (Harris et al., 2010). Recently, Aβ has been found in association with exosomes, which are small membranous vesicles secreted by various cell types including neurons. These exosomes could provide an explanation for the transport of Aβ in the brain (Rajendran et al., 2006).

The glymphatic system, a recently discovered other pathway for the clearance of toxic proteins, has been proposed as a possible third mechanism. In vivo two-photon imaging in mice has demonstrated that during sleep, the glymphatic system is upregulated, and thus more toxic proteins are cleared from the extracellular space. Reduced sleep, therefore, leads to a reduced clearance of toxic soluble Aβ (Xie et al., 2013).

4.2. Glutamate imbalance

AD pathology might be exacerbated by poor sleep as a result of a dysfunction of astrocyte-ApoE Aβ clearance regulated by lactate metabolism (Gerstner et al., 2012). Loss of diurnal Aβ oscillations upon aggregation leads to a favored localized astroglial response that prevents neurometabolic support of astrocytes, which results in excessive glutamate in the synaptic cleft and thus more wakefulness (Cramer et al., 2012). Since glutamate is fundamentally important for the synaptic mechanism of learning and memory through induction of long-term potentiation, and chronic N-methyl-D-aspartate (NMDA) receptor activation triggers pathological Ca^{2+} influx resulting in synaptotoxicity and neuronal death in AD, this hypothesis seems worth investigating in future research (Francis, 2003; Wenk et al., 2006).

4.3. Noradrenaline imbalance

Another possible mechanism, which has not received a lot of attention until now, is the involvement of the immune system. Poor sleep quality could alter immune function and affect AD pathogenesis, since certain immune modulators can affect sleep (Imeri and Opp, 2009) and microglial dysfunction has been described in AD (Mosher and Wyss-Coray, 2014). Remarkably, noradrenaline (NA), which also has a prominent role in the arousal system, has been postulated as a possible immunomodulator. Since NA is an anti-inflammatory molecule (which suppresses inflammatory gene expression) (Heneka et al., 2002), that can promote microglia-mediated degradation and phagocytosis of Aβ (Kong et al., 2010), loss of NA induces a proinflammatory state, suppresses anti-inflammatory responses and impairs Aβ degradation and clearance. Degeneration of the locus coeruleus, the major subcortical site for the synthesis of noradrenaline, is very common in AD and among the first identifiable pathological alterations, just around the timepoint when the first sleep problems arise (German et al. 1992). Therefore, locus coeruleus degeneration could form a (missing) link between the origin of sleep abnormalities and the simultaneous accumulation of senile plaques (Chalermpalanupap et al., 2013).

4.4. Serotonin imbalance

Serotonin, another monoamine that is involved in the regulation of the sleep-wake cycle, has been implicated in the regulation of Aβ metabolism. Activation of serotonergic receptors appears to increase α-secretase cleavage and reduce γ-secretase cleavage of amyloid precursor protein (APP) through activation of the ERK pathway, resulting in a reduced Aβ load (Cirrito et al., 2011). Concurrently, serotonin is implicated in the regulation of sleep and wakefulness, even though the exact where and how of this story is still under debate. The fact that it is unclear whether serotonin is a 'sleep' or 'wake' molecule is probably because serotonin exerts its effects via a multisynaptic pathway and because sleep is a process controlled by multiple neurotransmitter systems (Portas et al., 2000) (see paragraph 1, organization of sleep-wake behavior). Recent evidence points out that adult brain serotonin deficiency results in a hyperactivity phenotype and disturbed circadian and sleep-wake homeostasis in mice (Whitney et al., 2016). Yet, other studies that attempted to characterize the role of serotonin receptors in sleep by administration of (ant)agonists and generation of knock-out mouse models, remain ambiguous (as reviewed by Monti in 2011) (Monti, 2011a). Little information is available on the relation between serotonin depletion and the sleep-wake cycle in patients. Nevertheless, we can assume that serotonin imbalance might assist in the development of sleep disturbances. In AD, the serotonergic raphe nuclei show evidence of degeneration, causing a decreased serotonin content of the neocortex and the CSF (Engelborghs and De Deyn, 1997). Importantly, the impact of the microbiome on the serotonergic system in the brain may not be underestimated (reviewed by O'Mahony et al. in 2015 (O'Mahony et al., 2015)), since, in AD patients, the microbiome has been proven to significantly differ from age- and sex-matched controls (Vogt et al., 2017). Tryptophan, a serotonin precursor, which is ingested as part of the diet and whose availability depends on the metabolization by certain bacteria, can be transported across the blood-brain barrier and can affect the rate of brain serotonin synthesis (or the production of other neuroactive metabolites of the kynurenine

pathway) (O'Mahony et al., 2015). Hence, a shift in the composition of gut microbiota, as demonstrated in both AD patients and mouse models, might have profound effects on sleep health.

4.5. Acetylcholine imbalance

Not only the amount of sleep, but also the efficacy of the sleep cycle seems to play a role. Buzsaki hypothesized that during SWS 'quanta' of information are relayed back from the hippocampus, where memory traces are temporarily stored during wakefulness, to the neocortex, thereby aiding in the consolidation of memory traces into neocortical networks.

Gais and Born demonstrated that the loss of cholinergic tone is crucial for this process. Acetylcholine (ACh) levels are low during SWS, and the elevation of the central cholinergic tone with physostigmine resulted in a decrease of declarative memory performance (but not procedural memory performance) (Gais and Born, 2004). In contrast, ACh levels are high during REM sleep. Up until now, the contribution of REM to memory consolidation is not completely understood. REM episodes possibly provide periods of high plasticity to save SWS modifications of neocortical memory traces (Power, 2004). In AD, this cholinergic tone is severely affected. Basal forebrain cholinergic nuclei selectively degenerate (Bartus et al., 1982) and are, along with a reduction in choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) activity (Ikonomovic et al., 2005), the major culprit of cholinergic dysregulation in AD. It is possible that the loss of cholinergic tone is responsible for both cognitive and arousal dysfunction. AChE-inhibitors (AChEIs), which are the current mainstays of symptomatic treatment for AD patients and which increase the cholinergic tone, showed positive effects on cognitive functions (Hornung et al., 2007; Schredl et al., 2001) and sleep architecture (Cooke et al., 2006; Moraes Wdos et al., 2006). However, these therapeutic strategies typically only have a positive effect during diurnal hours. Donepezil for example, generally induces a stable increase of ACh for more than 24 h, and therefore interferes with the physiological dip in ACh during SWS. By consequence, donepezil can exacerbate sleep disorders and create adverse sleep-related events (Burns et al., 1999). Although the effects on REM and SWS seem to attenuate with continued administration of low doses and although aforementioned symptoms are also less common for galantamine and rivastigmine (Davis and Sadik, 2006; Grossberg et al., 2010; Nieoullon et al., 2008), AChEIs as a therapy in AD should be approached with caution. Pharmacokinetics of the drug often depend on its formulations. Galantamine administered once daily as a prolonged release capsule for instance, allows AChEI treatment to be synchronized to physiological cholinergic rhythms, while immediate release tablets b.i.d. appear to disturb the cholinergic dip at night. Hence, the type of drug, the formulation and the timing of administration are of crucial importance in the optimization of cholinergic treatment in AD patients. These flaws also call for other treatment strategies that can improve sleep abnormalities and concomitantly counteract cognitive deterioration.

5. Animal model-based evidence on the relation between sleep and AD

5.1. Amyloid pathology affects sleep physiology

To evaluate the effects of AD pathology on sleep, laboratory animal models, especially mice, have been proven very useful (Colby-Milley et al., 2015; Jyoti et al., 2010; Wisor et al., 2005). Although this rodent species is nocturnal (and therefore mostly sleeps during the day) and displays a polyphasic sleep pattern, the neurochemical mechanisms underlying sleep regulation are highly conserved (Allada and Siegel, 2008). In addition, mice can be uniformly bred and can easily be genetically modified, making them ideally suited to investigate sleep in different disease processes. Transgenic amyloidosis mouse models, which overexpress the human APP, are developed to partially mimic the AD pathophysiology and are often used in Alzheimer research (De Deyn and Van Dam, 2011).

In some of these transgenic models, sleep architecture was thoroughly investigated using polysomnographic and cage activity measurements. TgCRND8 mice, which encode a double mutant form of APP (KM670/671 N L + V717 F) under the control of the hamster prion (PrP) gene promoter, were found to display an increased wakefulness and reduced NREM sleep during the resting as well as the active phase, although these changes in sleep architecture were more pronounced during the active phase. Additionally, during waking, EEG power is shifted towards higher frequencies, suggesting a state of hyperarousal in these mice (Colby-Milley et al., 2015). Similarly, the APPswe/PSEN1A246E mouse model, that expresses mutant APP and presenilin 1 (PSEN1) genes, displays increased wakefulness and reduced NREM in the dark and light phase (Jyoti et al., 2010). By contrast, Roh et al. demonstrated that in the APPswe/PS1δE9, which expresses a different mutated form of PSEN1, the differences in sleep architecture are more pronounced during the light phase, instead of the dark phase (Roh et al., 2012). However, it should be noted that only a 9-month-old control group was used for the comparison of genotype-related effects. With the inclusion of more control groups at other stages of the pathology (3 months and 6 months), a different pattern might become apparent. Remarkably, NREM and REM sleep was conserved throughout the light-dark cycle in the Tg2576 model, which overexpresses mutated (KM670/671 N L) human APP, within the age range of 8 to 17 months (Wisor et al., 2005). Hence, no unambiguous conclusion can be drawn concerning the development of sleep disturbances in amyloidosis mouse models. More importantly however, none of the previously discussed mouse models is able to fully mimic the sleep disturbances in clinical AD. AD patients present with insomnia and a fragmented sleep pattern during the resting phase with a concomitant excessive daytime sleepiness during the active phase. So far, only the 3xTg mouse model, often considered the current golden standard in rodent AD research, is able to mimic this specific pattern. Yet, only circadian locomotor rhythmicity was characterized and no specific EEG study was performed. Possibly, the neuropathological lesions in sleep centers in these mice, arising from the triple mutation in APP, microtubule-associated protein tau (MAPT) and PSEN1 gene, give rise to a specific effect that is not reached in other models. However, such multi-transgenic models are less relevant for the clinical situation, and the multiple inflicted mutations could just have an exaggerated effect. Moreover, mice are indeed nocturnal animals and exhibit a polyphasic sleep pattern. Although the major underlying sleep mechanisms are relatively well preserved, certain downstream effects might have evolved differently, rendering preclinical results difficult to interpret. The firing pattern of the SCN for example, is similar in diurnal versus nocturnal rodents, while the downstream effects must be different to result in a reversed day/night rhythm (Inouye and Kawamura, 1979; Sato and Kawamura, 1984).

During wakefulness, quantitative EEG measurements have revealed increased delta and theta power along with a decrease in alpha and beta power in AD patients (Jeong, 2004). Up until now, the triple mutant knock-in model PLB1, generated by targeted knock-in of a human APP-Tau cDNA construct under the control of the endogenous mouse CaMKIIα promoter and crossed with PS1 mice, is the only model recapitulating this phenotype (Platt et al., 2011). All other (transgenic) models, such as the Tg2576 and TgCRND8 that were previously described, show a shift towards fast-frequency oscillations (Colby-Milley et al., 2015; Jyoti et al., 2010; Wisor et al., 2005). Therefore, we could question if the increase in delta power observed in AD is even associated with amyloid pathology. In the PS19 mouse model, which expresses a P301S mutation of the MAPT gene, a similar reduction of delta power has been observed from the age of 11 months as well (Holth et al., 2017b). Thus, the slowing of EEG rhythms is probably not a result of tauopathy, neither of amyloidosis. It is hypothesized that, at least in

patients, the EEG slowing is due to cholinergic deafferentation. Several studies demonstrated that the cholinergic system maintains desynchronized EEG activity (Metherate et al., 1992; Spehlmann and Norcross, 1982), and that a loss of proper cholinergic neocortical and thalamic innervation from the nucleus basalis (NB) might play a critical role (Riekkinen et al., 1991). In transgenic mice however, the NB is relatively well preserved, although other cholinergic alterations have been observed (Boncristiano et al., 2002), and could potentially account for the absence of EEG slowing in these AD models. By contrast, the PLB1 triple knock-in model does exhibit the EEG slowing phenotype. This model makes use of an endogenous promoter for the expression of exogenously mutated genes, which results in more 'physiological' expression levels than in traditional transgenic overexpression models. Might it be possible that the cholinergic system (more specifically the NB) is differentially affected in this model, and thereby induces increased slow wave activity? Or could it be that the overexpression of transgenes plays an unsuspected role herein? Question remains then what underlies the tendency towards fast-frequency oscillations in the amyloidosis mouse models.

5.2. Sleep physiology affects amyloid pathology

Recent preclinical evidence in an amyloidosis model has indicated that the sleep-wake cycle is implicated in the pathogenesis of AD itself, although sleep abnormalities were initially thought to merely reflect the effect of AD pathology on the brain. In the Tg2576 model, the sleep-wake cycle significantly affected the ISF Aβ dynamics (Kang et al., 2009). ISF Aβ levels were reduced during sleep and increased during wakefulness. In addition, both sleep deprivation, as well as administration of the wake-promoting orexin increased ISF Aβ and, consequently, plaque burden. As previously discussed, sleep is probably important to remove toxic proteins and peptides from our brain. Also, these results suggest the possibility that poor sleep might be a risk factor for the development of AD. In the APPswe/PS1δE9 mouse model for AD, the disruption of the sleep-wake cycle and the loss of diurnal fluctuations of ISF Aβ are thought to be Aβ accumulation-associated and, therefore, deteriorate further with increasing pathology. Active immunization of 9-month-old APPswe/PS1δE9 mice with Aβ42 prevented sleep disruption and changes in diurnal Aβ fluctuations, thereby suggesting that Aβ accumulation, rather than overexpression of the transgene, is responsible for these changes. Moreover, changes in Aβ dynamics occurred prior to the changes in sleep quality, and thus suggest that the loss of Aβ fluctuations are probably caused by changes in Aβ metabolism induced by plaque formation and not by disruption of the sleep-wake cycle itself (Roh et al., 2012). However, it should be noted once more that not enough control groups were included to draw unambiguous conclusions. Also, in another study, primary insomnia appeared to be a predisposing factor for the development of dementia, thereby nuancing their hypothesis (Hung et al., 2018). It is likely though, that amyloid pathology probably alters Aβ dynamics, resulting in a disturbed sleep-wake cycle, thereby exacerbating the accumulation of toxic proteins and the progression of the pathology. Consequently, sleep abnormalities, in the presence of a disrupted Aβ metabolism, are probably not the initial causal factor of AD. However, poor sleep might still be considered a risk factor for the further progression of AD, once the first soluble neurotoxic Aβ oligomers have appeared. At this point, it is presumed that sleep disruption probably functions as a positive feedback loop in which deposition of Aβ disrupts sleep centers in the brainstem and hypothalamus, which leads to an increased Aβ load that again negatively affects sleep.

6. Conclusion

Physiologically, our sleep-wake cycle is ingeniously regulated. The multiple neurotransmitter systems and multi-synaptic pathways involved, not only hinder researchers to fully unravel the sleep process, but also render the system very robust. A small failure in a one pathway does not necessarily result in a catastrophic loss of sleep. From an evolutionary point of view, such a keen organization of sleep probably emphasizes its importance. However, when multiple neurotransmitter systems start to fail, as in neurodegenerative diseases like AD, the sleep process does not stay unaffected. By consequence, AD patients often present with severe sleep and circadian disturbances. Furthermore, transgenic animal models in which AD pathology is partly mimicked, also display disturbances in sleep architecture, strongly suggesting the presence of an underlying relationship.

Up to now, these models remain very useful for current fundamental research and serve as a unique approach to investigate the relation between sleep function and a disease of interest. Sleep-wake alterations in these AD animal models have been numerously described, but little consensus has been reached about their underlying etiology, let alone the impact of EEG alterations on memory impairment. Of course, we cannot deny the differences between man and rodent, even though sleep-wake mechanisms are strongly preserved between different species. Possibly, that is also why results are not always equally translatable and sometimes difficult to interpret. Therefore, we are desperately in need of a multidisciplinary approach and the use of new EEG parameters that can bridge the gap between sleep and memory. With the rise of machine learning, we might be able to identify new EEG characteristics that represent the same physiological process in lab animals as in humans and hence, translate better to the human condition. In-depth electrophysiology of important sleep regulating centers in different AD animal models (including knock-in mice) will need to bring together electric engineers and molecular biologists. Moreover, to improve diagnosis in an ambulatory setting (e.g., temperature monitoring, piezoelectric systems), a greater interaction between the clinicians and preclinical researchers is advised. That might allow us to eventually discover the underlying etiologies of sleep disturbances and even better predict the effects of future medications.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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References

Allada, R., Siegel, J.M., 2008. Unearthing the phylogenetic roots of sleep. Curr. Biol. 18, R670–R679.
Aston-Jones, G., Bloom, F.E., 1981. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J. Neurosci. 1, 876–886.
Ayas, N.T., White, D.P., Manson, J.E., Stampfer, M.J., Speizer, F.E., Malhotra, A., Hu, F.B., 2003. A prospective study of sleep duration and coronary heart disease in women. Arch. Intern. Med. 163, 205–209.
Baghdoyan, H.A., Lydic, R., 2012. Chapter 57 - the neurochemistry of sleep and wakefulness A2 - Brady, Scott T. In: Siegel, G.J., Albers, R.W., Price, D.L. (Eds.), Basic Neurochemistry, eighth edition. Academic Press, New York, pp. 982–999.
Bartus, R.T., Dean 3rd, R.L., Beer, B., Lippa, A.S., 1982. The cholinergic hypothesis of geriatric memory dysfunction. Science 217, 408–414.
Beaulieu-Bonneau, S., Hudon, C., 2009. Sleep disturbances in older adults with mild cognitive impairment. Int. Psychogeriatrics/IPA 21, 654–666.
Benington, J.H., Kodali, S.K., Heller, H.C., 1995. Stimulation of A1 adenosine receptors mimics the electroencephalographic effects of sleep deprivation. Brain Res. 692, 79–85.
Bero, A.W., Yan, P., Roh, J.H., Cirrito, J.R., Stewart, F.R., Raichle, M.E., Lee, J.M., Holtzman, D.M., 2011. Neuronal activity regulates the regional vulnerability to amyloid-beta deposition. Nat. Neurosci. 14, 750–756.
Bjorness, T.E., Greene, R.W., 2009. Adenosine and sleep. Curr. Neuropharmacol. 7, 238–245.

Bliwise, D.L., Hughes, M., McMahon, P.M., Kutner, N., 1995. Observed sleep/wakefulness and severity of dementia in an Alzheimer's disease special care unit. J. Gerontol. A Biol. Sci. Med. Sci. 50, M303–306.
Boivin, D.B., 2005. Disturbances of hormonal circadian rhythms in shift workers. In: Cardinali, D.P., Pandi-Perumal, S.R. (Eds.), Neuroendocrine Correlates of Sleep/Wakefulness. Springer, US, Boston, MA, pp. 325–353.
Boncristiano, S., Calhoun, M.E., Kelly, P.H., Pfeifer, M., Bondolfi, L., Stalder, M., Phinney, A.L., Abramowski, D., Sturchler-Pierrat, C., Enz, A., Sommer, B., Staufenbiel, M., Jucker, M., 2002. Cholinergic changes in the APP23 transgenic mouse model of cerebral amyloidosis. J. Neurosci. 22, 3234–3243.
Borbely, A.A., 1982. A two process model of sleep regulation. Hum. Neurobiol. 1, 195–204.
Borbely, A.A., Achermann, P., 1999. Sleep homeostasis and models of sleep regulation. J. Biol. Rhythms 14, 557–568.
Borbely, A.A., Daan, S., Wirz-Justice, A., Deboer, T., 2016. The two-process model of sleep regulation: a reappraisal. J. Sleep Res. 25, 131–143.
Borbely, A.A., Tobler, I., 1989. Endogenous sleep-promoting substances and sleep regulation. Physiol. Rev. 69, 605–670.
Born, J., Rasch, B., Gais, S., 2006. Sleep to remember. Neuroscientist 12, 410–424.
Brevig, H.N., Baghdoyan, H.A., 2010. Neurotransmitters and neuromodulators regulating sleep and wakefulness. In: Koob, G.F., Moal, M.L., Thompson, R.F. (Eds.), Encyclopedia of Behavioral Neuroscience. Academic Press, Oxford, pp. 456–463.
Brzecka, A., Leszek, J., Ashraf, G.M., Ejma, M., Ávila-Rodriguez, M.F., Yarla, N.S., Tarasov, V.V., Chubarev, V.N., Samsonova, A.N., Barreto, G.E., Aliev, G., 2018. Sleep disorders associated with Alzheimer's disease: a perspective. Front. Neurosci. 12 330-330.
Burns, A., Rossor, M., Hecker, J., Gauthier, S., Petit, H., Moller, H.J., Rogers, S.L., Friedhoff, L.T., 1999. The effects of donepezil in Alzheimer's disease - results from a multinational trial. Dement. Geriatr. Cogn. Disord. 10, 237–244.
Byars, K.C., Amin, R.S., 2008. Chapter 17 - fatigue and sleep disorders. In: Slap, G.B. (Ed.), Adolescent Medicine. Mosby, Philadelphia, pp. 110–116.
Cedernaes, J., Osorio, R.S., Varga, A.W., Kam, K., Schiöth, H.B., Benedict, C., 2017. Candidate mechanisms underlying the association between sleep-wake disruptions and Alzheimer's disease. Sleep Med. Rev. 31, 102–111.
Chalermpalanupap, T., Kinkead, B., Hu, W.T., Kummer, M.P., Hammerschmidt, T., Heneka, M.T., Weinshenker, D., Levey, A.I., 2013. Targeting norepinephrine in mild cognitive impairment and Alzheimer's disease. Alzheimers Res. Ther. 5, 21.
Chou, T.C., Scammell, T.E., Gooley, J.J., Gaus, S.E., Saper, C.B., Lu, J., 2003. Critical role of dorsomedial hypothalamic nucleus in a wide range of behavioral circadian rhythms. J. Neurosci. 23, 10691–10702.
Cirrito, J.R., Disabato, B.M., Restivo, J.L., Verges, D.K., Goebel, W.D., Sathyan, A., Hayreh, D., D'Angelo, G., Benzinger, T., Yoon, H., Kim, J., Morris, J.C., Mintun, M.A., Sheline, Y.I., 2011. Serotonin signaling is associated with lower amyloid-beta levels and plaques in transgenic mice and humans. Proc. Natl. Acad. Sci. U.S.A. 108, 14968–14973.
Cirrito, J.R., Yamada, K.A., Finn, M.B., Sloviter, R.S., Bales, K.R., May, P.C., Schoepp, D.D., Paul, S.M., Mennerick, S., Holtzman, D.M., 2005. Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. Neuron 48, 913–922.
Cohen, S., Doyle, W.J., Alper, C.M., Janicki-Deverts, D., Turner, R.B., 2009. Sleep habits and susceptibility to the common cold. Arch. Intern. Med. 169, 62–67.
Colby-Milley, J., Cavanagh, C., Jego, S., Breitner, J.C., Quirion, R., Adamantidis, A., 2015. Sleep-wake cycle dysfunction in the TgCRND8 mouse model of alzheimer's disease: from early to advanced pathological stages. PLoS One 10, e0130177.
Cooke, J.R., Loredo, J.S., Liu, L., Marler, M., Corey-Bloom, J., Fiorentino, L., Harrison, T., Ancoli-Israel, S., 2006. Acetylcholinesterase inhibitors and sleep architecture in patients with Alzheimer's disease. Drugs Aging 23, 503–511.
Cramer, P.E., Cirrito, J.R., Wesson, D.W., Lee, C.Y., Karlo, J.C., Zinn, A.E., Casali, B.T., Restivo, J.L., Goebel, W.D., James, M.J., Brunden, K.R., Wilson, D.A., Landreth, G.E., 2012. ApoE-directed therapeutics rapidly clear beta-amyloid and reverse deficits in AD mouse models. Science 335, 1503–1506.
Daan, S., Beersma, D.G., Borbely, A.A., 1984. Timing of human sleep: recovery process gated by a circadian pacemaker. Am. J. Physiol. 246, R161–183.
Davis, B., Sadik, K., 2006. Circadian cholinergic rhythms: implications for cholinesterase inhibitor therapy. Dement. Geriatr. Cogn. Disord. 21, 120–129.
De Deyn, P.P., Van Dam, D., 2011. Animal Models of Dementia. Humana Press.
Engelborghs, S., De Deyn, P.P., 1997. The neurochemistry of Alzheimer's disease. Acta Neurol. Belg. 97, 67–84.
Everson, C.A., 1993. Sustained sleep deprivation impairs host defense. Am. J. Physiol. 265, R1148–1154.
Ferreira-Vieira, T.H., Guimaraes, I.M., Silva, F.R., Ribeiro, F.M., 2016. Alzheimer's disease: targeting the cholinergic system. Curr. Neuropharmacol. 14, 101–115.
Francis, P.T., 2003. Glutamatergic systems in Alzheimer's disease. Int. J. Geriatr. Psychiatry 18, S15–21.
Francis, P.T., 2005. The interplay of neurotransmitters in Alzheimer's disease. CNS Spectr. 10, 6–9.
Fuller, P.M., Gooley, J.J., Saper, C.B., 2006. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. J. Biol. Rhythms 21, 482–493.
Gais, S., Born, J., 2004. Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. Proc. Natl. Acad. Sci. U.S.A. 101, 2140–2144.
Gallopin, T., Fort, P., Eggermann, E., Cauli, B., Luppi, P.H., Rossier, J., Audinat, E., Muhlethaler, M., Serafin, M., 2000. Identification of sleep-promoting neurons in vitro. Nature 404, 992–995.
Gangwisch, J.E., Heymsfield, S.B., Boden-Albala, B., Buijs, R.M., Kreier, F., Pickering, T.G., Rundle, A.G., Zammit, G.K., Malaspina, D., 2006. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. Hypertension 47, 833–839.
Gerstner, J.R., Perron, I.J., Pack, A.I., 2012. The nexus of Abeta, aging, and sleep. Sci. Transl. Med. 4, 150fs134.
Gottlieb, D.J., Punjabi, N.M., Newman, A.B., Resnick, H.E., Redline, S., Baldwin, C.M., Nieto, F.J., 2005. Association of sleep time with diabetes mellitus and impaired glucose tolerance. Arch. Intern. Med. 165, 863–867.
Grossberg, G.T., Sadowsky, C., Olin, J.T., 2010. Rivastigmine transdermal system for the treatment of mild to moderate Alzheimer's disease. Int. J. Clin. Pract. 64, 651–660.
Halassa, M.M., Florian, C., Fellin, T., Munoz, J.R., Lee, S.Y., Abel, T., Haydon, P.G., Frank, M.G., 2009. Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron 61, 213–219.
Harper, D.G., Stopa, E.G., Kuo-Leblanc, V., McKee, A.C., Asayama, K., Volicer, L., Kowall, N., Satlin, A., 2008. Dorsomedial SCN neuronal subpopulations subserve different functions in human dementia. Brain 131, 1609–1617.
Harris, J.A., Devidze, N., Verret, L., Ho, K., Halabisky, B., Thwin, M.T., Kim, D., Hamto, P., Lo, I., Yu, G.Q., Palop, J.J., Masliah, E., Mucke, L., 2010. Transsynaptic progression of amyloid-beta-induced neuronal dysfunction within the entorhinal-hippocampal network. Neuron 68, 428–441.
Hatfield, C.F., Herbert, J., van Someren, E.J., Hodges, J.R., Hastings, M.H., 2004. Disrupted daily activity/rest cycles in relation to daily cortisol rhythms of home-dwelling patients with early Alzheimer's dementia. Brain 127, 1061–1074.
Heneka, M.T., Galea, E., Gavriluyk, V., Dumitrescu-Ozimek, L., Daeschner, J., O'Banion, M.K., Weinberg, G., Klockgether, T., Feinstein, D.L., 2002. Noradrenergic depletion potentiates beta -amyloid-induced cortical inflammation: implications for Alzheimer's disease. J. Neurosci. 22, 2434–2442.
Holth, J., Patel, T., Holtzman, D.M., 2017a. Sleep in alzheimer's disease - beyond amyloid. Neurobiol. Sleep Circadian Rhythms 2, 4–14.
Holth, J.K., Fritschi, S.K., Wang, C., Pedersen, N.P., Cirrito, J.R., Mahan, T.E., Finn, M.B., Manis, M., Geerling, J.C., Fuller, P.M., Lucey, B.P., Holtzman, D.M., 2019. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. Science 363, 880.
Holth, J.K., Mahan, T.E., Robinson, G.O., Rocha, A., Holtzman, D.M., 2017b. Altered sleep and EEG power in the P301S Tau transgenic mouse model. Ann. Clin. Transl. Neurol. 4, 180–190.
Hornung, O.P., Regen, F., Danker-Hopfe, H., Schredl, M., Heuser, I., 2007. The relationship between REM sleep and memory consolidation in old age and effects of cholinergic medication. Biol. Psychiatry 61, 750–757.
Huang, Y.L., Liu, R.Y., Wang, Q.S., Van Someren, E.J., Xu, H., Zhou, J.N., 2002. Age-associated difference in circadian sleep-wake and rest-activity rhythms. Physiol. Behav. 76, 597–603.
Hung, C.-M., Li, Y.-C., Chen, H.-J., Lu, K., Liang, C.-L., Liliang, P.-C., Tsai, Y.-D., Wang, K.-W., 2018. Risk of dementia in patients with primary insomnia: a nationwide population-based case-control study. BMC Psychiatry 18 38-38.
Ikonomovic, M.D., Mufson, E.J., Wuu, J., Bennett, D.A., DeKosky, S.T., 2005. Reduction of choline acetyltransferase activity in primary visual cortex in mild to moderate Alzheimer's disease. Arch. Neurol. 62, 425–430.
Imeri, L., Opp, M.R., 2009. How (and why) the immune system makes us sleep. Nat. Rev. Neurosci. 10, 199–210.
Inouye, S.T., Kawamura, H., 1979. Persistence of circadian rhythmicity in a mammalian hypothalamic "island" containing the suprachiasmatic nucleus. Proc. Natl. Acad. Sci. U.S.A. 76, 5962–5966.
Jeong, J., 2004. EEG dynamics in patients with Alzheimer's disease. Clin. Neurophysiol. 115, 1490–1505.
Jouvet, M., 1969. Biogenic amines and the states of sleep. Science 163, 32–41.
Ju, Y.-E.S., Ooms, S.J., Sutphen, C., Macauley, S.L., Zangrilli, M.A., Jerome, G., Fagan, A.M., Mignot, E., Zempel, J.M., Claassen, J.A.H.R., Holtzman, D.M., 2017. Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. Brain 140, 2104–2111.
Jyoti, A., Plano, A., Riedel, G., Platt, B., 2010. EEG, activity, and sleep architecture in a transgenic AbetaPPswe/PSEN1A246E Alzheimer's disease mouse. J. Alzheimers Dis. 22, 873–887.
Kang, J.E., Lim, M.M., Bateman, R.J., Lee, J.J., Smyth, L.P., Cirrito, J.R., Fujiki, N., Nishino, S., Holtzman, D.M., 2009. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 326, 1005–1007.
Kemp, N., Bashir, Z.I., 2001. Long-term depression: a cascade of induction and expression mechanisms. Prog. Neurobiol. 65, 339–365.
Kong, J., Shepel, P.N., Holden, C.P., Mackiewicz, M., Pack, A.I., Geiger, J.D., 2002. Brain glycogen decreases with increased periods of wakefulness: implications for homeostatic drive to sleep. J. Neurosci. 22, 5581–5587.
Kong, Y., Ruan, L., Qian, L., Liu, X., Le, Y., 2010. Norepinephrine promotes microglia to uptake and degrade amyloid beta peptide through upregulation of mouse formyl peptide receptor 2 and induction of insulin-degrading enzyme. J. Neurosci. 30, 11848–11857.
Kroeger, D., Absi, G., Gagliardi, C., Bandaru, S.S., Madara, J.C., Ferrari, L.L., Arrigoni, E., Münzberg, H., Scammell, T.E., Saper, C.B., Vetrivelan, R., 2018. Galanin neurons in the ventrolateral preoptic area promote sleep and heat loss in mice. Nat. Commun. 9, 4129.
Lanari, A., Amenta, F., Silvestrelli, G., Tomassoni, D., Parnetti, L., 2006. Neurotransmitter deficits in behavioural and psychological symptoms of Alzheimer's disease. Mech. Ageing Dev. 127, 158–165.
Lim, A.S., Yu, L., Kowgier, M., Schneider, J.A., Buchman, A.S., Bennett, D.A., 2013. Modification of the relationship of the apolipoprotein E epsilon4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. JAMA Neurol. 70, 1544–1551.
Lim, M.M., Gerstner, J.R., Holtzman, D.M., 2014. The sleep-wake cycle and Alzheimer's disease: what do we know? Neurodegener. Dis. Manag. 4, 351–362.
Lin, J.S., Sakai, K., Jouvet, M., 1988. Evidence for histaminergic arousal mechanisms in the hypothalamus of cat. Neuropharmacology 27, 111–122.
Liu, Y., Tanaka, H., 2002. Overtime work, insufficient sleep, and risk of non-fatal acute myocardial infarction in Japanese men. Occup. Environ. Med. 59, 447–451.
Lu, J., Zhang, Y.H., Chou, T.C., Gaus, S.E., Elmquist, J.K., Shiromani, P., Saper, C.B., 2001. Contrasting effects of ibotenate lesions of the paraventricular nucleus and subparaventricular zone on sleep-wake cycle and temperature regulation. J. Neurosci. 21, 4864–4874.

M. Steriade, M., McCarley, R., 2005. Brain Stem Control of Wakefulness and Sleep.
Maquet, P., 2001. The role of sleep in learning and memory. Science 294, 1048–1052.
McCurry, S.M., Logsdon, R.G., Teri, L., Gibbons, L.E., Kukull, W.A., Bowen, J.D., McCormick, W.C., Larson, E.B., 1999. Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. J. Geriatr. Psychiatry Neurol. 12, 53–59.
Metherate, R., Cox, C.L., Ashe, J.H., 1992. Cellular bases of neocortical activation: modulation of neural oscillations by the nucleus basalis and endogenous acetylcholine. J. Neurosci. 12, 4701–4711.
Miles, L.E., Dement, W.C., 1980. Sleep and aging. Sleep 3, 1–220.
Mileykovskiy, B.Y., Kiyashchenko, L.I., Siegel, J.M., 2005. Behavioral correlates of activity in identified hypocretin/orexin neurons. Neuron 46, 787–798.
Miller, J.D., Farber, J., Gatz, P., Roffwarg, H., German, D.C., 1983. Activity of mesencephalic dopamine and non-dopamine neurons across stages of sleep and walking in the rat. Brain Res. 273, 133–141.
Mitchell, H.A., Weinshenker, D., 2010. Good night and good luck: norepinephrine in sleep pharmacology. Biochem. Pharmacol. 79, 801–809.
Moe, K.E., Vitiello, M.V., Larsen, L.H., Prinz, P.N., 1995. Symposium: cognitive processes and sleep disturbances: Sleep/wake patterns in Alzheimer's disease: relationships with cognition and function. J. Sleep Res. 4, 15–20.
Monnier, M., Hoesli, L., 1964. Dialysis of sleep and waking factors in blood of the rabbit. Science 146, 796–798.
Monti, J.M., 2011a. Serotonin control of sleep-wake behavior. Sleep Med. Rev. 15, 269–281.
Monti, J.M., 2011b. Serotonin control of sleep-wake behavior. Sleep Med. Rev. 15, 269–281.
Moraes Wdos, S., Poyares, D.R., Guilleminault, C., Ramos, L.R., Bertolucci, P.H., Tufik, S., 2006. The effect of donepezil on sleep and REM sleep EEG in patients with Alzheimer disease: a double-blind placebo-controlled study. Sleep 29, 199–205.
Morairty, S., Rainnie, D., McCarley, R., Greene, R., 2004. Disinhibition of ventrolateral preoptic area sleep-active neurons by adenosine: a new mechanism for sleep promotion. Neuroscience 123, 451–457.
Moran, M., Lynch, C.A., Walsh, C., Coen, R., Coakley, D., Lawlor, B.A., 2005. Sleep disturbance in mild to moderate Alzheimer's disease. Sleep Med. 6, 347–352.
Moruzzi, G., Magoun, H.W., 1949. Brain stem reticular formation and activation of the EEG. Electroencephalogr. Clin. Neurophysiol. 1, 455–473.
Mosher, K.I., Wyss-Coray, T., 2014. Microglial dysfunction in brain aging and Alzheimer's disease. Biochem. Pharmacol. 88, 594–604.
Nagasaki, H., Iriki, M., Inou, Eacute, Shojiro Uchizono, K., 1974. The presence of a sleep-promoting material in the brain of sleep-deprived rats. Proc. Jpn. Acad. 50, 241–246.
Nebes, R.D., Buysse, D.J., Halligan, E.M., Houck, P.R., Monk, T.H., 2009. Self-reported sleep quality predicts poor cognitive performance in healthy older adults. J. Gerontol. B Psychol. Sci. Soc. Sci. 64, 180–187.
Nieoullon, A., Bentue-Ferrer, D., Bordet, R., Tsolaki, M., Forstl, H., 2008. Importance of circadian rhythmicity in the cholinergic treatment of Alzheimer's disease: focus on galantamine*. Curr. Med. Res. Opin. 24, 3357–3367.
O'Mahony, S.M., Clarke, G., Borre, Y.E., Dinan, T.G., Cryan, J.F., 2015. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behav. Brain Res. 277, 32–48.
Ouyang, M., Hellman, K., Abel, T., Thomas, S.A., 2004. Adrenergic signaling plays a critical role in the maintenance of waking and in the regulation of REM sleep. J. Neurophysiol. 92, 2071–2082.
Pappenheimer, J.R., Miller, T.B., Goodrich, C.A., 1967. Sleep-promoting effects of cerebrospinal fluid from sleep-deprived goats. Proc. Natl. Acad. Sci. U.S.A. 58, 513–517.
Peter-Derex, L., Yammine, P., Bastuji, H., Croisile, B., 2015. Sleep and Alzheimer's disease. Sleep Med. Rev. 19, 29–38.
Petit, J.M., Magistretti, P.J., 2016. Regulation of neuron-astrocyte metabolic coupling across the sleep-wake cycle. Neuroscience 323, 135–156.
Platt, B., Drever, B., Koss, D., Stoppelkamp, S., Jyoti, A., Plano, A., Utan, A., Merrick, G., Ryan, D., Melis, V., Wan, H., Mingarelli, M., Porcu, E., Scrocchi, L., Welch, A., Riedel, G., 2011. Abnormal cognition, sleep, EEG and brain metabolism in a novel knock-in Alzheimer mouse, PLB1. PLoS One 6, e27068.
Porkka-Heiskanen, T., Strecker, R.E., McCarley, R.W., 2000. Brain site-specificity of extracellular adenosine concentration changes during sleep deprivation and spontaneous sleep: an in vivo microdialysis study. Neuroscience 99, 507–517.
Portas, C.M., Bjorvatn, B., Ursin, R., 2000. Serotonin and the sleep/wake cycle: special emphasis on microdialysis studies. Prog. Neurobiol. 60, 13–35.
Power, A.E., 2004. Slow-wave sleep, acetylcholine, and memory consolidation. Proc. Natl. Acad. Sci. U.S.A. 101, 1795–1796.
Prinz, P.N., Peskind, E.R., Vitaliano, P.P., Raskind, M.A., Eisdorfer, C., Zemcuznikov, N., Gerber, C.J., 1982. Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. J. Am. Geriatr. Soc. 30, 86–93.
Prinz, P.N., Vitiello, M.V., Raskind, M.A., Thorpy, M.J., 1990. Geriatrics: sleep disorders and aging. N. Engl. J. Med. 323, 520–526.
Rajendran, L., Honsho, M., Zahn, T.R., Keller, P., Geiger, K.D., Verkade, P., Simons, K., 2006. Alzheimer's disease beta-amyloid peptides are released in association with exosomes. Proc. Natl. Acad. Sci. U.S.A. 103, 11172–11177.
Riekkinen, P., Buzsaki, G., Riekkinen, P., Soininen, H., Partanen, J., 1991. The cholinergic system and EEG slow waves. Electroencephalogr. Clin. Neurophysiol. 78, 89–96.
Roh, J.H., Huang, Y., Bero, A.W., Kasten, T., Stewart, F.R., Bateman, R.J., Holtzman, D.M., 2012. Disruption of the sleep-wake cycle and diurnal fluctuation of beta-amyloid in mice with Alzheimer's disease pathology. Sci. Transl. Med. 4, 150ra122.
Saper, C.B., Chou, T.C., Scammell, T.E., 2001. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci. 24, 726–731.
Saper, C.B., Fuller, P.M., Pedersen, N.P., Lu, J., Scammell, T.E., 2010. Sleep state switching. Neuron 68, 1023–1042.
Saper, C.B., Scammell, T.E., Lu, J., 2005. Hypothalamic regulation of sleep and circadian rhythms. Nature 437, 1257–1263.
Sato, T., Kawamura, H., 1984. Circadian rhythms in multiple unit activity inside and outside the suprachiasmatic nucleus in the diurnal chipmunk (Eutamias sibiricus). Neurosci. Res. 1, 45–52.
Scammell, T.E., Estabrooke, I.V., McCarthy, M.T., Chemelli, R.M., Yanagisawa, M., Miller, M.S., Saper, C.B., 2000. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. J. Neurosci. 20, 8620–8628.
Schoenenberger, G.A., Maier, P.F., Tobler, J.H., Monnier, M., 1977. A naturally occurring delta-EEG enhancing nonapeptide in rabbits. X. Final isolation, characterization and activity test. Pflugers Arch. 369, 99–109.
Schredl, M., Weber, B., Leins, M.L., Heuser, I., 2001. Donepezil-induced REM sleep augmentation enhances memory performance in elderly, healthy persons. Exp. Gerontol. 36, 353–361.
Schwartz, J.R., Roth, T., 2008. Neurophysiology of sleep and wakefulness: basic science and clinical implications. Curr. Neuropharmacol. 6, 367–378.
Shokri-Kojori, E., Wang, G.-J., Wiers, C.E., Demiral, S.B., Guo, M., Kim, S.W., Lindgren, E., Ramirez, V., Zehra, A., Freeman, C., Miller, G., Manza, P., Srivastava, T., De Santi, S., Tomasi, D., Benveniste, H., Volkow, N.D., 2018. β-Amyloid accumulation in the human brain after one night of sleep deprivation. Proc. Natl. Acad. Sci. U.S.A. 115, 4483–4488.
Siegel, J.M., 2004. The neurotransmitters of sleep. J. Clin. Psychiatry 65 (Suppl 16), 4–7.
Simic, G., Babic Leko, M., Wray, S., Harrington, C.R., Delalle, I., Jovanov-Milosevic, N., Bazadona, D., Buee, L., de Silva, R., Di Giovanni, G., Wischik, C.M., Hof, P.R., 2017. Monoaminergic neuropathology in Alzheimer's disease. Prog. Neurobiol. 151, 101–138.
Skene, D.J., Swaab, D.F., 2003. Melatonin rhythmicity: effect of age and Alzheimer's disease. Exp. Gerontol. 38, 199–206.
Spehlmann, R., Norcross, K., 1982. Cholinergic mechanisms in the production of focal cortical slow waves. Experientia 38, 109–111.
Spiegel, K., Sheridan, J.F., Van Cauter, E., 2002. Effect of sleep deprivation on response to immunization. Jama 288, 1471–1472.
Spira, A.P., Gamaldo, A.A., An, Y., Wu, M.N., Simonsick, E.M., Bilgel, M., Zhou, Y., Wong, D.F., Ferrucci, L., Resnick, S.M., 2013. Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. JAMA Neurol. 70, 1537–1543.
Stopa, E.G., Volicer, L., Kuo-Leblanc, V., Harper, D., Lathi, D., Tate, B., Satlin, A., 1999. Pathologic evaluation of the human suprachiasmatic nucleus in severe dementia. J. Neuropathol. Exp. Neurol. 58, 29–39.
Swaab, D.F., Fliers, E., Partiman, T.S., 1985. The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. Brain Res. 342, 37–44.
Tononi, G., Cirelli, C., 2003. Sleep and synaptic homeostasis: a hypothesis. Brain Res. Bull. 62, 143–150.
Tranah, G.J., Blackwell, T., Stone, K.L., Ancoli-Israel, S., Paudel, M.L., Ensrud, K.E., Cauley, J.A., Redline, S., Hillier, T.A., Cummings, S.R., Yaffe, K., 2011. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Ann. Neurol. 70, 722–732.
Van Cauter, E., Leproult, R., Plat, L., 2000. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. Jama 284, 861–868.
Van Erum, J., Van Dam, D., De Deyn, P.P., 2018. Sleep and Alzheimer's disease: a pivotal role for the suprachiasmatic nucleus. Sleep Med. Rev. 40, 17–27.
Vermeiren, Y., Janssens, J., Aerts, T., Martin, J.J., Sieben, A., Van Dam, D., De Deyn, P.P., 2016. Brain serotonergic and noradrenergic deficiencies in behavioral variant frontotemporal dementia compared to early-onset alzheimer's disease. J. Alzheimers Dis. 53, 1079–1096.
Vogt, N.M., Kerby, R.L., Dill-McFarland, K.A., Harding, S.J., Merluzzi, A.P., Johnson, S.C., Carlsson, C.M., Asthana, S., Zetterberg, H., Blennow, K., Bendlin, B.B., Rey, F.E., 2017. Gut microbiome alterations in Alzheimer's disease. Sci. Rep. 7, 13537.
Watson, C.J., Baghdoyan, H.A., Lydic, R., 2010. Neuropharmacology of sleep and wakefulness. Sleep Med. Clin. 5, 513–528.
Weitzman, E.D., Moline, M.L., Czeisler, C.A., Zimmerman, J.C., 1982. Chronobiology of aging: temperature, sleep-wake rhythms and entrainment. Neurobiol. Aging 3, 299–309.
Wenk, G.L., Parsons, C.G., Danysz, W., 2006. Potential role of N-methyl-D-aspartate receptors as executors of neurodegeneration resulting from diverse insults: focus on memantine. Behav. Pharmacol. 17, 411–424.
Whitney, M.S., Shemery, A.M., Yaw, A.M., Donovan, L.J., Glass, J.D., Deneris, E.S., 2016. Adult brain serotonin deficiency causes hyperactivity, circadian disruption, and elimination of siestas. J. Neurosci. 36, 9828–9842.
Wisor, J.P., Edgar, D.M., Yesavage, J., Ryan, H.S., McCormick, C.M., Lapustea, N., Murphy Jr, G.M., 2005. Sleep and circadian abnormalities in a transgenic mouse model of Alzheimer's disease: a role for cholinergic transmission. Neuroscience 131, 375–385.
Witting, W., Kwa, I.H., Eikelenboom, P., Mirmiran, M., Swaab, D.F., 1990. Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. Biol. Psychiatry 27, 563–572.
Xie, L., Kang, H., Xu, Q., Chen, M.J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D.J., Nicholson, C., Iliff, J.J., Takano, T., Deane, R., Nedergaard, M., 2013. Sleep drives metabolite clearance from the adult brain. Science 342, 373–377.
Yaggi, H.K., Araujo, A.B., McKinlay, J.B., 2006. Sleep duration as a risk factor for the development of type 2 diabetes. Diabetes Care 29, 657–661.