Chapter 15

The reciprocal interaction between sleep and Alzheimer's Disease

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Abstract

It is becoming increasingly recognized that patients with a variety of neurodegenerative diseases exhibit disordered sleep/wake patterns. While sleep impairments have typically been thought of as sequelae of underlying neurodegenerative processes in sleep-wake cycle regulating brain regions, including the brainstem, hypothalamus and basal forebrain, emerging evidence now indicates that sleep deficits may also act as pathophysiological drivers of brain-wide disease progression. Specifically, recent work has indicated that impaired sleep can impact on neuronal activity, brain clearance mechanisms, pathological build-up of proteins, and inflammation. Altered sleep patterns may therefore be novel (potentially reversible) dynamic functional markers of proteinopathies, and modifiable targets for early therapeutic intervention using non-invasive stimulation and behavioral techniques. Here we highlight research describing a potentially reciprocal interaction between impaired sleep and circadian patterns and the accumulation of pathological signs and features in Alzheimer's Disease, the most prevalent neurodegenerative disease in the elderly.

Keywords

Sleep impairment, sleep-wake cycle, slow oscillations, learning and memory, Alzheimer's Disease, amyloid-beta, tau, clinical, translational

1. Background

Sleep is a highly complex and regulated brain state which, although incompletely understood, has been implicated in cellular and network restitution, learning and synaptic plasticity, removal of neurotoxic waste products, and modulation of endocrine and immune functions, among other functions (Diekelmann and Born 2010; Klinzing et al. 2019; Tononi and Cirelli 2014; Zada et al. 2019; Xie et al. 2013; Besedovsky et al. 2019). Sleep deprivation, and even sleep fragmentation, can lead to the emergence of poor memory, impaired cognition and epileptic seizures, and even frank psychosis with disorganized thinking and a loss of ability to perceive reality (Krause et al. 2017; Joiner 2019). Sleep is therefore not a passive and quiescent, steady state, but rather is associated with specific and alternating neuronal rhythms that may be broadly classified as rapid-eye movement (REM) or non-REM phases. REM sleep is associated with oscillations in the theta and gamma frequency bands, whereas cortical slow-wave oscillations (< 1Hz), delta waves (1-4.5Hz), thalamocortical spindles and hippocampal sharp-wave ripples occur during non-REM (NREM) sleep. The different sleep stages and oscillations are believed to be related to aspects of sleep physiology and linked to a variety of physiological parameters such as changes in hormone release, cardiovascular control, regulation of breathing, convulsive thresholds, and gastrointestinal physiology (Taheri et al. 2002). In this regard, it is important to note that our knowledge of the function and role of REM sleep, beyond its inferred contribution to implicit procedural and emotional memory consolidation (Diekelmann and Born 2010; Tononi and Cirelli 2014; Klinzing et al. 2019) and forgetting (Izawa et al. 2019), significantly lags behind our emerging understanding of NREM sleep, and that of its deepest phase, slow wave sleep (SWS), which is the primary focus of the current chapter.

Memory consolidation is thought to occur during SWS and requires effective hippocampal-cortical communication involving the fine-scale temporal coupling between hippocampal ripples, neocortical slow wave oscillations and thalamocortical spindles (Diekelmann and Born 2010; Sirota et al. 2003; Latchoumane et al. 2017; Maingret et al. 2016; Helfrich et al. 2019). Distinct patterns of firing activity in specific hippocampal neuronal ensembles during awake behavior are reactivated during subsequent SWS and manifest as hippocampal sharp wave ripples (Wilson and McNaughton 1994; Rasch et al. 2007). Hippocampal memories are then posited to be transferred to neocortical regions for long-term storage, facilitated by a priming effect of thalamocortical spindles, and gated by the induction of up and down states (membrane depolarization and hyperpolarization, respectively) by neocortical slow oscillations (Huber et al. 2004; Sirota and Buzsáki 2005; Sirota et al. 2003; Klinzing et al. 2019; but see Yonelinas et al. 2019). Interestingly, whereas slow wave activity has been associated with memory consolidation, delta

waves, on the other hand, have recently been implicated in forgetting, and related to the differences in temporal coupling of spindles to both forms of activity (Kim et al. 2019). In turn, the synaptic homeostasis hypothesis theorizes that slow wave activity during sleep enables the brain to renormalize synaptic strength, that is potentiated during wakefulness, through relational synaptic downscaling that enables neural circuits to operate energy- and space-efficiently, and promotes learning and memory (Tononi and Cirelli 2014; Tononi and Cirelli 2006). It is important to note that the memory consolidation and homeostatic functions of NREM sleep, often tacitly perceived as independent, may not in fact be mutually exclusive, and may act differentially on neuronal populations according to their intrinsic firing rate properties (Levenstein et al. 2017).

Sleep is also associated with a dramatic increase in interstitial space due to shrinkage of glial cells, which allows for influx of cerebrospinal fluid (CSF) into the brain parenchyma along paravascular spaces surrounding penetrating vasculature, driven by slow-wave and, subsequently, hemodynamic oscillations, and enabling convective exchange between CSF and interstitial fluid (ISF) leading to 'glymphatic' clearance of waste and metabolites (Xie et al. 2013; Iliff et al. 2013; Fultz et al. 2019; Kiviniemi et al. 2016). Finally, it has also been suggested that sleep and immunity are bi-directionally related, with SWS associated with the promotion of inflammatory homeostasis and cytokine production, and sleep loss leading to low-grade systemic inflammation and immunodeficiency (Besedovsky et al. 2012; Besedovsky et al. 2019), as well as higher expression of genes characteristic of aged-microglia and microglial activation (Kaneshwaran et al. 2019).

2. Sleep Disruption in Alzheimer's Disease

Ageing alters sleep architecture, most evidently as a reduction of non-REM-associated SWS (Ohayon et al. 2004), but also in a variety of other manners, including an advance in circadian phase and reduced circadian amplitude, decreased REM sleep, reduced sleep efficiency, increased arousals, enhanced sleep fragmentation, and sleep-disordered breathing (e.g. obstructive sleep apnea, OSA). Sleep disturbances are exacerbated in AD relative to normal ageing (Prinz et al. 1982; Bombois et al. 2010), and become more severe with disease progression and are associated with increased cerebrospinal fluid (CSF) levels of orexin (also known as hypocretin), a hypothalamic neuropeptide that regulates sleep and arousal states but also appetite, with increased levels being linked to wakefulness, and predicted by CSF levels of Aβ and tau, the two hallmark proteins in AD (Liguori et al. 2014; Gabelle et al. 2017). Clinical sleep phenotypes in AD dementia include insomnia, nighttime wakefulness and wandering, excessive daytime

sleepiness and sundowning (a tendency to become confused and agitated towards the evening) (Cipriani et al., 2015), and have been associated with differential Aβ deposition patterns, e.g. Aβ deposition in brainstem and precuneus was reportedly linked to daytime sleepiness and nocturnal wakefulness, respectively (You et al. 2019). Sleep phenotypes may in turn be exacerbated by cognitive and behavioural symptoms and other factors such as medication, lack of exercise and nighttime lighting. Sleep appears to be both a global phenomenon, involving neuronal networks in brain stem, hypothalamus and basal forebrain, and pathological sleep phenotypes may thus arise due to disruption or degeneration of specific sleep-related circuits, for example those involving wake-promoting neurons in locus coeruleus, orexin-producing neurons in the lateral hypothalamic area (LHA), and histaminergic neurons in the tuberomammillary nucleus (TMN) (Oh et al. 2019b; Swaab et al. 1985; Clark and Warren 2013; Oh et al. 2019a), although local processes within specific brain areas, particularly the cortex, may also play a critical, albeit overlooked, role in sleep modulation (Krueger et al. 2019).

Sleep disturbances are thus prevalent in AD and have, historically, been considered an epiphenomenon of the associated neurodegenerative process in the disorder. However, it is now being increasingly realized that sleep perturbations are also manifest in early AD prior to the emergence of widespread neurodegeneration and cognitive symptoms (Musiek et al. 2015; Sprecher et al. 2017) and even in those at risk of developing the disorder (e.g. the presence of the apolipoprotein E epsilon4 (ApoE4) genotype, a risk factor for AD, is also associated with increased risk of sleep-disordered breathing, Kadotani et al. 2001). In addition, recent data indicates that sleep impairments, via direct or indirect processes, are, in of themselves, able to instigate the abnormal release and build-up of the pathogenic proteins characteristic of AD, Aβ and tau, thus intensifying the risk of developing the disorder and accelerating disease progression. This reciprocal interaction between sleep and AD is exemplified by the observation that sleep disturbances increase the risk of AD, whereas enhanced sleep hygiene has the antagonistic effect (Osorio et al. 2011; Yaffe et al. 2011; Lim et al. 2013a; Lim et al. 2013b). In the following sections, we highlight the groundswell of research which supports the mediating and reciprocal role of sleep and circadian dysregulation in the development of Aβ and tau pathology.

3. Sleep impairment promotes the emergence of AD-related pathological features

2.1.1 Clinical Evidence

Cerebrospinal fluid (CSF) Aβ and tau levels in healthy humans display inherent diurnal variations (decreases during sleep and increases during wakefulness) (Kang et al. 2009; Holth et al. 2019). Interestingly, similar oscillatory behavior in CSF Aβ levels was also observed in human subjects harboring a PS1 mutation (a major cause of familial AD) , but which was lost in subjects also exhibiting Aβ deposition by positron emission tomography (PET) imaging (Roh et al. 2012), and supported by a previous report of diurnal CSF Aβ oscillations that becomes attenuated with Aβ deposition (Huang et al. 2012). These reports indicate that CSF Aβ and tau levels exhibit a sleep-wake cycle which likely reflect associated broad state changes in neuronal activity (note that while overall firing rates and metabolism are decreased during sleep, sleep sub-states differentially affect neurons according to their firing properties with markedly heterogenous effects, see Watson et al. (2016)) and activity-dependent variations in production and/or extracellular release of Aβ and tau (Cirrito et al. 2005; Yamada et al. 2014; Pooler et al. 2013) as well as fluctuations in their clearance into the CSF, for example via the glymphatic/paravascular system (Xie et al. 2013) (**Figure 1**). As described below, impaired sleep and prolonged wakefulness in cognitively normal individuals markedly disrupt these behaviors and may initiate a deleterious cascade leading to AD-like pathophysiology and cognitive deficits.

Self-report measures of excessive daytime sleepiness, which may arise due to sleep-disordered breathing (e.g. OSA) or fragmented/insufficient sleep, but also the loss of wake promoting neurons (Oh et al. 2019a), in cognitively normal adults (>60yrs), was associated with greater than double the odds of PET Aβ deposition at follow-up ~15 years later (Spira et al. 2018), with increased sleep latency and sleep fragmentation also linked to cortical PET Aβ load in cognitively normal individuals (Ettore et al. 2019). One-night of total sleep deprivation (SD), monitored using polysomnography, in healthy middle-aged men, was associated with an increase in Aβ42 cerebrospinal fluid (CSF) levels (Ooms et al. 2014) and, similarly, overnight levels of Aβ38, Aβ40, and Aβ42 in CSF markedly increased (~30%) in sleep-deprived cognitively normal adults (30-60yrs) relative to controls (Lucey et al. 2018). Natural overnight decreases in Aβ42 plasma levels were also attenuated by sleep fragmentation in psychiatrists following 90 days of being on-call (Grimmer et al. 2020). Short-term (24hrs) SD in healthy adults (mean 27.3yrs) was also associated with significantly increased morning plasma Aβ40 and serum malondialdehyde levels (a marker for oxidative stress), significantly decreased Aβ42/Aβ40 ratio, and serum superoxide dismutase levels (a marker of antioxidant activity), and significantly decreased plasma lipoprotein receptor-related protein 1 (LRP-1 and receptor of advanced glycation end products (RAGE) concentrations that were correlated to Aβ42 and Aβ40 levels, suggesting increased oxidative stress and impaired peripheral clearance of Aβ (Wei et al. 2017). Self-reported diminished sleep quality in cognitively normal adults was also found to be

associated with increased PET Aβ load (Choe et al. 2019), with the number of nocturnal awakenings in healthy older adults also inversely correlated to insular grey matter volume, a region notably activated during sleep spindles (Branger et al. 2016). PET Aβ burden in healthy controls following one night of SD increased in the right hippocampus and thalamus with baseline burden in subcortical areas and precuneus negatively correlated to reported sleep time during rested sleep, but was not related to genetic risk for AD (APOE genotype) (Shokri-Kojori et al. 2018). Genetic variations in the water-channel protein aquaporin-4 (AQP4), expressed in astrocytic end-feet, in cognitively normal older adults, however, were associated with disrupted self-reported sleep quality (Pittsburgh Sleep Quality Index, PSQI) and found to moderate the coupling between sleep latency/duration and PET Aβ burden (Rainey-Smith et al. 2018; Brown et al. 2016). Given the implication of AQP4 in glymphatic transport (Mestre et al. 2018), as well as the modulatory effect of AQP4-haplotype on NREM slow wave energy (Larsen et al. 2019), these results support the notion of paravascular clearance of Aβ and suggest that genetic variations in AQP4 modulate the efficacy of this process.

Sleep deprivation was also observed to increase CSF tau by over half in a human cohort (Holth et al. 2019) with changes in phosphorylation being highly site-specific (Barthelemy et al. 2020). Acute sleep loss was similarly associated with increases in blood total tau in healthy young men (Benedict et al. 2020), and self-reports of poor sleep and daytime sleepiness in cognitively normal subjects (mean 63yrs) was associated with lower CSF Aβ42/Aβ40 and higher total-tau/Aβ42 (a ratio highly concordant with Aβ PET measures and predictive of cognitive decline, Hansson et al. 2018; Fagan et al. 2007), and ratio of chitinase-3-like protein 1 (YKL-40, a glial marker of neuroinflammation) to Aβ42 (Sprecher et al. 2017). Abnormal night-time behavior, as assessed by the Neuropsychiatric Inventory Sleep (NPI-sleep) inventory, was associated with increased PET measured accumulation of Aβ in precuneus, posterior cingulate and medial orbitofrontal, and tau in entorhinal cortex, in clinically normal elderly subjects (Shokouhi 2019).

OSA, in which the airway becomes transiently blocked, is associated with recurrent arousals from sleep and hypoxemia, and increases the risk of developing dementia and is associated with a hastened age of cognitive decline (Osorio et al., 2015), increased neuronal activity, as well as reduced slow wave activity and sleep spindle density (Ju et al. 2016; Ondze et al. 2003). OSA treatment, using positive airway pressure (PAP), may delay progression of cognitive decline (Osorio et al., 2015), and was notably linked to an enhancement in slow wave activity that was correlated to reduced post-treatment CSF Aβ levels (Ju et al., 2019). Sleep disordered breathing in cognitively normal older adults was associated with increased Aβ PET load and neuronal activity (as measured by functional magnetic resonance imaging, fMRI) most notably in the posterior cingulate cortex and precuneus (André et al. 2020), whereas witnessed apneas in

healthy elderly individuals were also linked to elevated tau-PET signals in entorhinal cortex and inferior temporal lobe (Carvalho et al. 2020). Patients with subjective cognitive impairment (SCI) and OSA exhibited lower CSF Aβ42 levels, higher lactate and total-tau/Aβ42 levels, and reduced sleep quality, in comparison to SCI controls and those with OSA and concurrent CPAP treatment (Liguori et al. 2017). Reduced CSF Aβ levels in OSA patients have been ascribed to the breathing disorder inducing internal high-pressure fluctuations disrupting paravascular/glymphatic flow during sleep between the interstitial fluid (ISF) and CSF (Xie et al. 2013; Iliff et al. 2013; Kiviniemi et al. 2016), and leading to increased ISF and reduced CSF Aβ levels, respectively (Ju et al. 2016). In addition, disrupted NREM sleep and impaired slow wave oscillations would be expected to compromise CSF influx and efflux within the brain (Fultz et al. 2019) leading to interstitial Aβ accumulation that could be further enhanced by increased neuronal activity during OSA-related arousals. Interestingly, diminished reductions in circadian blood pressure during sleep were also associated with disrupted cerebral blood flow (CBF) regulation and increased PET Aβ load in posterior cingulate of patients with amnestic mild cognitive impairment (Tarumi et al. 2015). The observed impairment of CBF dynamics could suggest a mechanism by which clearance of Aβ by glymphatic/paravascular or other processes (Iliff et al. 2013; Xie et al. 2013; Kiviniemi et al. 2016) is disrupted by disordered sleep, particularly in light of the recent observation of a link between slow activity, hemodynamic oscillations, and flow of CSF within the brain (Fultz et al. 2019). Nevertheless, it is difficult to exclude the possibility that sleep disturbances, such as breathing disorders, which impair such clearance (Xie et al. 2013), and have been associated with the absence of nocturnal BP reductions (Wolf et al. 2010), underpin these results.

One night of total sleep SD in healthy young men also resulted in a significant increase in morning serum levels of neuron-specific enolase (NSE) and S100 calcium binding protein B (S-100B) (Benedict et al. 2014). Since these factors are typically localized to neuronal and glial cytoplasm, these findings could reflect neuronal damage and/or disruption to the blood brain barrier (BBB) during sleep loss (He et al. 2014). Partial SD (maximum of 4hr sleep) in healthy adults (20-40yrs), with preserved slow-wave sleep (monitored using polysomnography and actigraphy), was also associated with increased CSF orexin-A (an isoform of orexin) concentrations (Olsson et al. 2018). Furthermore, CSF orexin-A was found to be upregulated in cognitively normal elder individuals and correlated to CSF Aβ42, phosphorylated-tau, and total-tau levels (Osorio et al. 2016).

Disruption of NREM slow wave activity (SWA) has been associated with age-related memory impairment (Mander et al. 2013) and even mild disruption and suppression of slow-wave activity can negatively impact memory performance in healthy individuals (Van Der Werf et al. 2009). In turn, reduced

and fragmented slow wave sleep, evinced by polysomnography, was shown to be associated with increases in CSF Aβ42 levels in cognitively normal elderly individuals at low risk of AD (Varga et al. 2016). Importantly, the degree of impairment of SWA correlates with PET Aβ burden in medial prefrontal cortex, and predicts overnight memory retention (Mander et al. 2015; and see Winer et al. 2019), suggesting that cortical Aβ pathology affects memory by disturbing hippocampal-cortical communication (as confirmed and extended in our translational work, described below). An inverse relationship between NREM SWA measured using single channel electroencephalography (EEG), and tau PET levels was also found in several brain areas of predominantly cognitively normal participants (>60yrs), including entorhinal, parahippocampal, orbital frontal, precuneus, inferior parietal and temporal regions, and also with CSF tau/Aβ42 levels (Lucey et al. 2019). The degree of impairment in slow oscillation-sleep spindle coupling also predicted tau burden in medial temporal lobe, but not cortical Aβ load, such that weaker coupling was associated with increased tau (Winer et al. 2019). Targeted suppression of slow-wave sleep in healthy older adults (35-65yrs, confirmed using polysomnography) increased CSF Aβ40, with worse home sleep quality (measured by actigraphy) also associated with increased CSF tau (Ju et al. 2017). Indeed, sleep spindle density during NREM sleep in clinically normal elderly subjects undergoing polysomnography was significantly and inversely correlated with CSF total tau levels and suggested to be a mechanism by which tau may disrupt memory consolidation (Kam et al. 2019a). Adults with amnestic mild cognitive impairment displayed a significant relationship between impaired SWS and increased Aβ42 plasma levels, whereas, interestingly, reduced REM sleep in the same population was correlated to thinning of the posterior cingulate and precuneus (Sanchez-Espinosa et al. 2014), the functional hubs of the default mode network (DMN). Since SWA is also associated with reduced activity of the DMN, a distributed brain network in which Aβ accumulation is initiated (Samann et al. 2011; Palmqvist et al. 2017), it is possible that a loss in slow wave activity leads to heightened activity of the DMN and subsequently more Aβ accumulation.

2.1.2 On the interaction between sleep, memory, and epilepsy in AD

Epileptiform activity is a prevalent phenomenon in AD patients, the incidence of which exceeds that observed in the general population, and is associated with an earlier onset of cognitive deficits, exacerbated neurodegeneration, and an enhanced risk of mortality (Forstl et al. 1992; Scarmeas et al. 2009; Vossel et al. 2013; Vossel et al. 2016). Notably, recent work has suggested that the prevalence of epileptiform activity in AD is likely underestimated, as many may be sub-clinical in nature, localized to deep brain regions undetectable to surface recordings, and to markedly preponderate during sleep (Lam

et al. 2017; Vossel et al. 2016). Sleep and epilepsy have long been associated as familiar bedfellows (Derry and Duncan 2013), with reports of increased epileptiform activity during sleep in focal epilepsy (Malow et al. 1998) and an association between nocturnal seizures, respiratory disorders (such as OSA) and sudden death in epilepsy (SUDEP) (Ryvlin et al. 2013; Lamberts et al. 2012). The presence of pathological epileptiform activity during sleep, a period critical for memory consolidation (Diekelmann and Born 2010), may therefore underpin the hastened cognitive decline seen in AD patients with epilepsy. Indeed, emerging research has now posited that physiological sleep circuits are "hijacked" by epileptic activity (Beenhakker and Huguenard 2009). More specifically, recent work has indicated that post-ictal sleep is associated with the reactivation of interictal discharges (IEDs) and seizure-related neuronal activity patterns, mimicking natural processes involved in memory consolidation during slow-wave sleep following a behavioural experience (Bower et al. 2017; Bower et al. 2015; Wilson and McNaughton 1994; Diekelmann and Born 2010; Klinzing et al. 2019). In this context, it is interesting to note that hippocampal IEDs in a rodent model of temporal lobe epilepsy have been shown to co-opt hippocampal-cortical communication during NREM sleep, essential for memory consolidation (Colgin 2011), by replacing hippocampal ripples and autonomously driving thalamocortical spindles in prefrontal cortex, the extent to which being correlated to memory impairment (Gelinas et al. 2016). Importantly, IEDs were also found to induce cortical spindles with high temporal reliability in humans with focal epilepsy, suggesting that the mechanisms subserving physiological sleep-related memory consolidation are usurped by epileptic processes and underscoring the potential of therapeutically targeting aberrant oscillatory network activity in AD (Gelinas et al. 2016).

2.1.3 Mechanistic lessons from translational models

Prior to Aβ aggregation into plaques, young APP/PS1 mice (a transgenic mouse model of AD which overproduces Aβ) display diurnal variations in hippocampal ISF Aβ levels (decreases during sleep and increases during wakefulness) that are correlated to ISF lactate levels, but which become markedly attenuated with the emergence of plaque pathology, but can be 'rescued' by Aβ immunization (Roh et al. 2012; Kang et al. 2009). Acute sleep deprivation and orexin infusion (to promote wakefulness) were found to enhance ISF Aβ levels in mice, while chronic (21 day) sleep restriction increased plaque deposition, and was counteracted by treatment with a dual orexin receptor antagonist (Kang et al. 2009). Accordingly, APP/PS1 mice harboring an orexin gene knockout exhibited reduced Aβ pathology and increased sleep time, which was reversed by SD and rescue of orexigenic neurons, although hippocampal overexpression

of orexin did not recapitulate these effects (Roh et al. 2014). As well as increased Aβ deposition being correlated to induced sleep fragmentation in APP/PS1 mice (Minakawa et al. 2017), chronic SD in wild-type rats and mice was associated with increased expression of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) (Chen et al. 2017; Zhao et al. 2017), but decreased levels of plasma Aβ levels and plasma soluble LRP-1 (Zhao et al. 2019). Notably, LRP-1 has been implicated in modulating amyloid precursor protein (APP) processing (Ulery et al. 2000), mediating Aβ transport across the blood brain barrier (Storck et al. 2016), and recently shown to regulate tau endocytosis of tau and subsequent inter-neuronal propagation (Rauch et al. 2020). Intracerebroventricular injection of Aβ oligomers into 8-10 week wild-type mice disrupted sleep patterns, and a one month chronic sleep restriction protocol was associated with significant reduction in synaptophysin and postsynaptic density protein 95 (PSD-95) (markers of pre and post synaptic integrity, respectively) in hippocampus, but not frontal cortex (Kincheski et al. 2017). Reduced and fragmented sleep was also observed in a *Drosophila* model of AD which overexpresses Aβ pan-neuronally, with SD enhancing intrinsic neuronal hyperexcitability and increasing Aβ burden, that was rescued through suppression of neuronal excitability (Tabuchi et al. 2015).

Sleep deprivation exacerbates ISF tau sleep-wake cycle fluctuations, and chronic SD, interestingly, was found to promote the spread of tau pathology from hippocampus to locus coeruleus (LC) in a P301S mouse model of tauopathy (Holth et al. 2019). Notably, since tetrodotoxin (TTX) abolished the SD–induced elevation in ISF tau levels, and in light of other reports of enhanced tau propagation with increased neuronal activity (Wu et al. 2016) and activity dependent tau release (Pooler et al. 2013; Yamada et al. 2014), this suggests a putative process by which tau increases with wakefulness and sleep deprivation (Holth et al. 2019). SD in APP/PS1 mice was associated with phosphorylation of endogenous tau (alongside increased plaque deposition) and mitochondrial dysfunction (Qiu et al. 2016), the latter also observed in frontal cortex in WT mice subjected to sleep restriction (Zhao et al. 2016). SD in young 3xTg mice, a transgenic model of AD with both plaques and tangles, induced a decline in learning and memory alongside a significant increase in total insoluble tau and MC-1 immunoreactivity, indicating an effect on tau solubility and conformation, respectively (Di Meco et al. 2014). Interestingly, no effects on Aβ were found, although the authors did report a significant increase in glial fibrillary acidic protein (GFAP) expression, a marker for astrocytosis, as well as a significant reduction in PSD-95 in sleep deprived mice similarly to Kincheski et al. (2017) (Di Meco et al. 2014). Also, of note, chronic short sleep in P301S mice was also seen to prompt an early increase in AT8 and MC-1, indicative of increased tau phosphorylation and pathological conformational changes, in the brainstem locus coeruleus (a putative site for early tau pathology), as well increased microglial (Iba-1) and astrocytic activation (GFAP) in hippocampus (Zhu et

al. 2018). It is interesting to note that tau itself may play a role in the regulation of the sleep-wake cycle, with tau knockout mice exhibiting increased wakefulness and decreased NREM sleep time (Cantero et al. 2010). Moreover, tau deficient *Drosophila* exhibit dysregulation of circadian and sleep patterns alongside disruption of circadian pacemaker neurons (Arnes et al. 2019), and expression of the 0N4R isoform of tau in the Drosophila clock network was reported to result in elevated locomotor activity and loss of nighttime sleep, as well as increased diurnal and nocturnal spiking in large lateral ventral clock neurons (Buhl et al. 2019).

Our recent work has provided evidence of Aβ-dependent neuronal hyperactivity (Busche et al. 2012a; Busche et al. 2008) as well as impairment in slow-wave oscillations in APP mouse models of AD, which correlates with deficits in learning and memory and can be rescued by BACE inhibition (i.e. Aβ suppression) or enhancement of GABA$_A$ergic inhibition (Busche et al. 2015; Keskin et al. 2017) (**Figure 2**). In particular, these slow-wave oscillations, which manifest as propagating travelling waves similarly to that observed in humans (Massimini et al. 2004; Muller et al. 2018), were disrupted by both endogenous or exogenous Aβ, resulting in impaired long-range coherence of cortical slow wave activity, as well as large-scale functional decoupling of coherent activity between cortex and hippocampus, and cortex and thalamus (Busche et al. 2015; Keskin et al. 2017) (**Figure 2**). These findings are consistent with another report that optogenetic activation of parvalbumin-positive interneurons in sleep deprived mice rescued contextual fear memory consolidation (Ognjanovski et al. 2018). Our results are also in line with another report of disrupted slow-wave connectivity between hippocampal CA1 and medial frontal cortex during NREM sleep in APP/PS1 mice, and decreased coupling between cortical spindles and hippocampal ripples relative to WT animals (Zhurakovskaya et al. 2019). Impairment of slow wave oscillations, characterized by prolonged down states and reduced neuronal firing, has also been reported in the Tg4510 mouse model of tauopathy (Menkes-Caspi et al. 2015), and the coupling between sleep spindles and cortical slow oscillations was observed to be markedly reduced in the PS19 mouse model of tauopathy (Kam et al. 2019b). These experimental reports therefore support the notion that disrupted NREM slow wave activity is a feature of several AD mouse models and recapitulate clinical findings. While less is known on the relationship between AD pathologies and REM sleep in animal models, it is interesting to note that intra-hippocampal injection of Aβ was observed to induce a pronounced decrease in theta-band frequency power during REM sleep in rats (Maleysson et al. 2019). Optogenetic inhibition of hippocampal theta oscillations during REM sleep also impaired object recognition and contextual fear memory (Boyce et al. 2016).

4. A putative multi-level feedback model of pathophysiology

Taken together, the above clinical and translational literature indicates that sleep impairment, *per se*, is associated with aberrant production/release and, ultimately, deposition of Aβ and tau pathology. These effects have multiple probable etiologies, including an increase in neurometabolic rate due to disrupted sleep and increased wakefulness (Scalise et al. 2006; Buchsbaum et al. 1989), leading to enhanced activity-dependent release of Aβ and tau (Cirrito et al. 2005; Yamada et al. 2014; Pooler et al. 2013), as well as oxidative stress promoting further production of Aβ (Frederikse et al. 1996; Gabuzda et al. 1994) and tau phosphorylation (Melov et al. 2007). In turn, increased levels of Aβ in the brain induce neuronal hyperexcitability (Busche et al. 2012a; Busche et al. 2008) providing positive feedback to the aforementioned effects, and impairing slow-wave activity and long-range networks, thus affecting memory processing (Busche et al. 2015; Keskin et al. 2017), as well as glymphatic clearance mechanisms that rely on slow-wave oscillations to drive brain metabolites into the periphery (Fultz et al. 2019; Iliff et al. 2013; Kiviniemi et al. 2016; Xie et al. 2013; van Veluw et al. 2020). In a toxic *pas de deux*, disrupted sleep, in of itself, exacerbates deficits in clearance of pathogenic proteins by the glymphatic system and/or via the BBB (the permeability of which is vulnerable to inflammation, disordered sleep and subject to the sleep-wake cycle) (He et al. 2014; Cuddapah et al. 2019; Haruwaka et al. 2019), and thwarts restorative cellular processes, including nuclear maintenance, that might ameliorate the above pathological processes (Everson et al. 2014; Zada et al. 2019), and affects inflammatory homeostasis, further contributing to a vicious cycle leading to the accumulation of Aβ and tau pathology. Finally, several of these processes, including disordered sleep, impairment of slow wave activity, Aβ-dependent neuronal hyperactivity, perturbed DNA repair, and reduced BBB integrity, conspire to promote the emergence of epileptiform activity, that appropriates and recurrently amplifies these pathological mechanisms and sets in motion a feedback system leading to accelerated accumulation of AD-related peptides and, ultimately, neurodegeneration and dementia (**Figure 3**).

5. Methodological Considerations

Polysomnography remains the gold standard for quantitative sleep assessment, but it is manually scored by sleep-specialists and based only on short intervals of data with only summary statistics provided. This results in large amounts of potentially informative data being discarded. New methods in

deep learning may help to access the full richness of the data in the future, but currently the technique cannot be performed in a home environment, and this limitation will introduce confounds and alterations in sleeping behaviors within the clinical setting. Actigraphy, in turn, currently only provides crude measures of rest and activity, and it is thus paramount that more advanced home monitoring systems are developed which allow continuous recording of sleep variables in the patient's natural environment. In addition, sleep assessments based on clinical history and patient self-report scales are inherently unreliable, perhaps more so in the elderly and in patients with neurodegenerative disorders, and there is a lack of standardized instruments that allow comprehensive screening for a spectrum of sleep problems in the context of dementia. Quantitative unbiased biomarkers, including those for sleep debt, hypoxia, and circadian phase, are therefore urgently needed. However, in this regard, methodological approaches remain imperfect, with the recent report of erroneous CSF AD biomarkers resulting from repeated lumbar punctures (Olsson et al. 2019), and the limitations of PET imaging approaches to quantify Aβ and tau deposition at the earliest stages, being two cases in point. In addition, further research is needed to clarify what forms of AD-related proteins are most critical to disease progression, with recent work by us indicating that soluble forms of Aβ and tau, as opposed to Aβ plaques and neurofibrillary tangles, are key drivers of neuronal dysfunction (Busche et al. 2012b; Busche et al. 2019; Keskin et al. 2017). Moreover, in the case of translational experiments, transparent efforts must be made to disambiguate the effects of induced sleep disruption from those arising epiphenomenologically as a result of other factors, such as stress (Kang et al. 2007).

6. Conclusions and future directions

It is evident that sleep and its physiological mechanisms are disrupted in AD, but it is becoming increasingly recognized that sleep impairment and its sequelae can manifest before widespread neurodegeneration and cognitive symptoms emerge. Growing evidence now suggests that sleep perturbations, either directly or indirectly, modulate the release and accumulation of pathogenic proteins in AD, through a myriad of recurrent processes, and thereby increase the risk of development of AD and accelerate disease progression. Importantly, these data, concerning the relationship between tau pathology and sleep disruption in particular, also highlight the value in examining the role of pathological sleep phenotypes in other tauopathies such as frontotemporal dementia, in which evidence of marked sleep impairment has recently emerged and become the focus of intense research (Warren and Clark 2017). Despite the complexity of the interaction between sleep and AD, and while it is currently not

possible to point to the initiating mechanism which drives this pathological coupling, sleep has emerged as a potentially modifiable target for early therapy in AD, for which no disease-modifying treatment has yet been found. For example, non-invasive circuit-based interventions that enhance slow wave sleep such as transcranial magnetic and direct current stimulation have been shown to improve memory and cognitive performance in AD patients and healthy older individuals (Marshall et al. 2006) (Nguyen et al. 2017; Westerberg et al. 2015; Ladenbauer et al. 2017; Diep et al. 2020). Other approaches to enhance cognition have included the use of pharmacological agents (e.g. GABA modulators or orexin receptor antagonists, see Herring et al. 2020) to increase sleep spindle density (Mednick et al. 2013) or the use of closed-loop auditory stimulation of slow wave activity and sleep spindles (Ngo et al. 2013), albeit there is some debate whether the latter technique is able to reliably improve memory performance (Henin et al. 2019). In addition, sleep impairment is also, importantly, amenable to cognitive behavioral therapies (Geiger-Brown et al. 2015; Morin and Benca 2012) as well as environmental adjustments and interventions (Herberger et al. 2019). In turn, a greater understanding of sleep in AD may render sleep readouts as valuable diagnostic tools to identify risk of developing the disease and/or disease stage, particularly when integrated with blood-based, CSF or neuroimaging biomarkers. It remains to be seen whether sleep disruption can explain, in part, the marked clinical heterogeneity in AD, such as age of disease onset and disease course, and whether it is truly causal for disease progression. For that level of understanding it will be necessary to better elucidate the mechanisms and functions of sleep, and the role of different sleep stages, about which we still know surprisingly little. This, unfortunately, parallels our lack of knowledge on how variant AD affects the awake brain and its physiology, and further technical advances will be essential to addressing these open questions in the future.

Acknowledgements

Figures Legends

Figure 1: Schematic of sleep-wake cycle fluctuations in interstitial and cerebrospinal fluid protein levels, neuronal activity and glymphatic clearance. A) Levels of Aβ and tau in interstitial and cerebrospinal fluid (ISF/CSF) undergo sleep-wake cycle variations under normal conditions (control, blue trace), with an increase during wakefulness and a decrease during sleep. Sleep deprivation (SD) exacerbates (red trace), while suppression of neuronal activity attenuates (green trace), increases in Aβ and tau ISF/CSF levels during wakefulness. B) Overall levels of neuronal activation are enhanced during wakefulness (right inset) but diminished during sleep (left inset), the latter period also associated with an increase in glymphatic clearance (blue trace).

Figure 2: The effects of Aβ on non-REM sleep slow wave activity, sleep-related neuronal networks, neuronal hyperexcitability and memory performance. Top panel) Slow wave oscillations, and their long range coherence, observed in wild-type (WT) mice (left), are impaired in mice which overexpress the amyloid precursor protein (APP) and overproduce Aβ (middle), but can be rescued by suppression of Aβ or enhancement of GABAergic inhibition in the same animals (right). Second panel from top) The impairment of slow waves results in a breakdown of long range coupling of activity between cortex, hippocampus and thalamus (denoted by cortical slow waves, hippocampal sharp wave ripples and thalamocortical spindles) in mice which overexpress APP/overproduce Aβ (middle) compared to WT animals (left), but can again be restored following suppression of Aβ or enhancement of GABAergic inhibition (right). Bottom panels) Neuronal hyperexcitability and impaired memory performance is also observed in APP/Aβ mice compared to controls and can be similarly rescued (labeling convention follows that in upper panels). The model is supported by mediation analysis (see supplementary figure S9 in Keskin et al. 2017).

Figure 3: A putative multi-level feedback model describing possible interactions between several pathological mechanisms that are self-amplifying and exacerbated by sleep impairments, leading to the development of AD features and accelerated AD progression.

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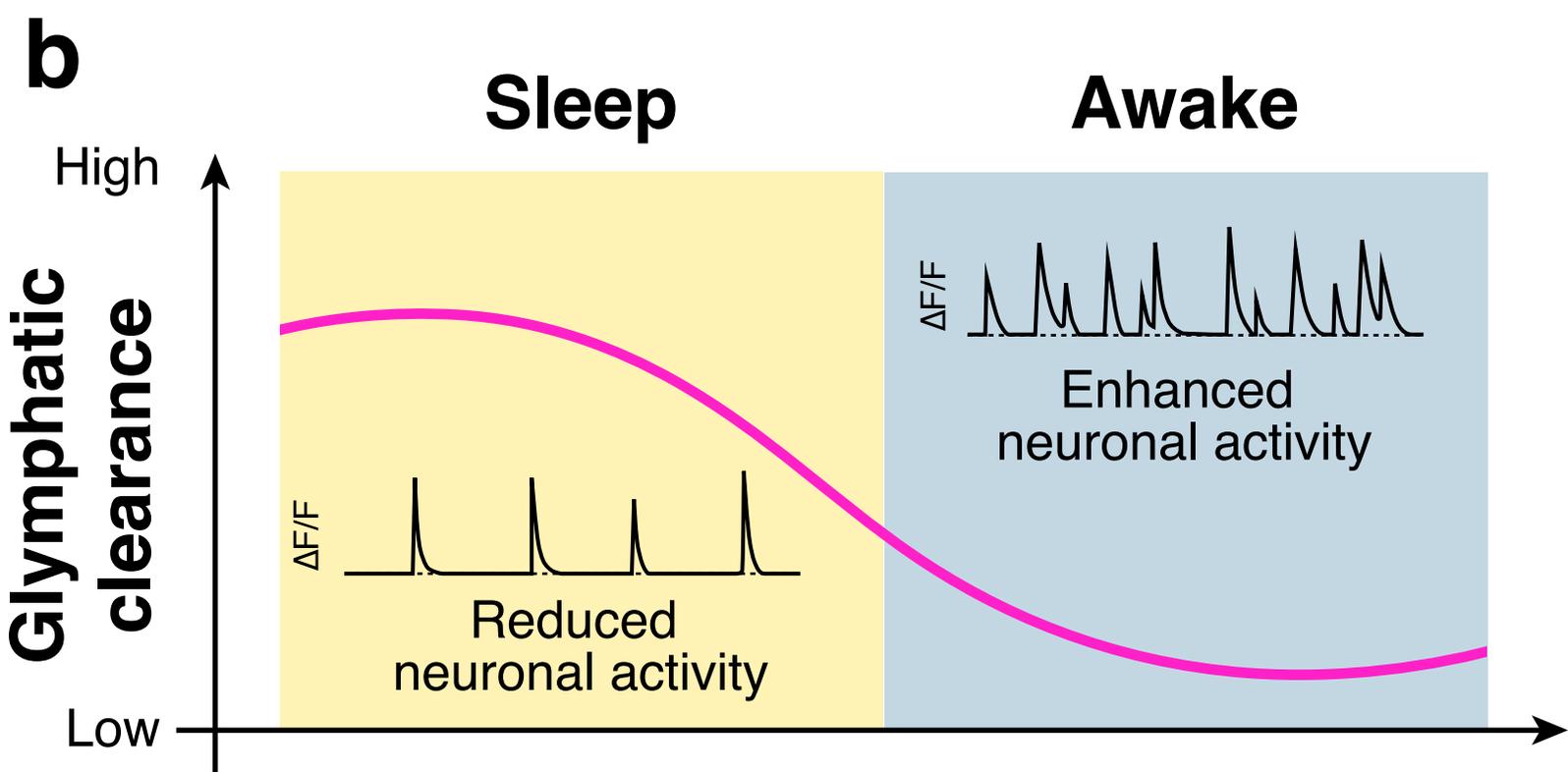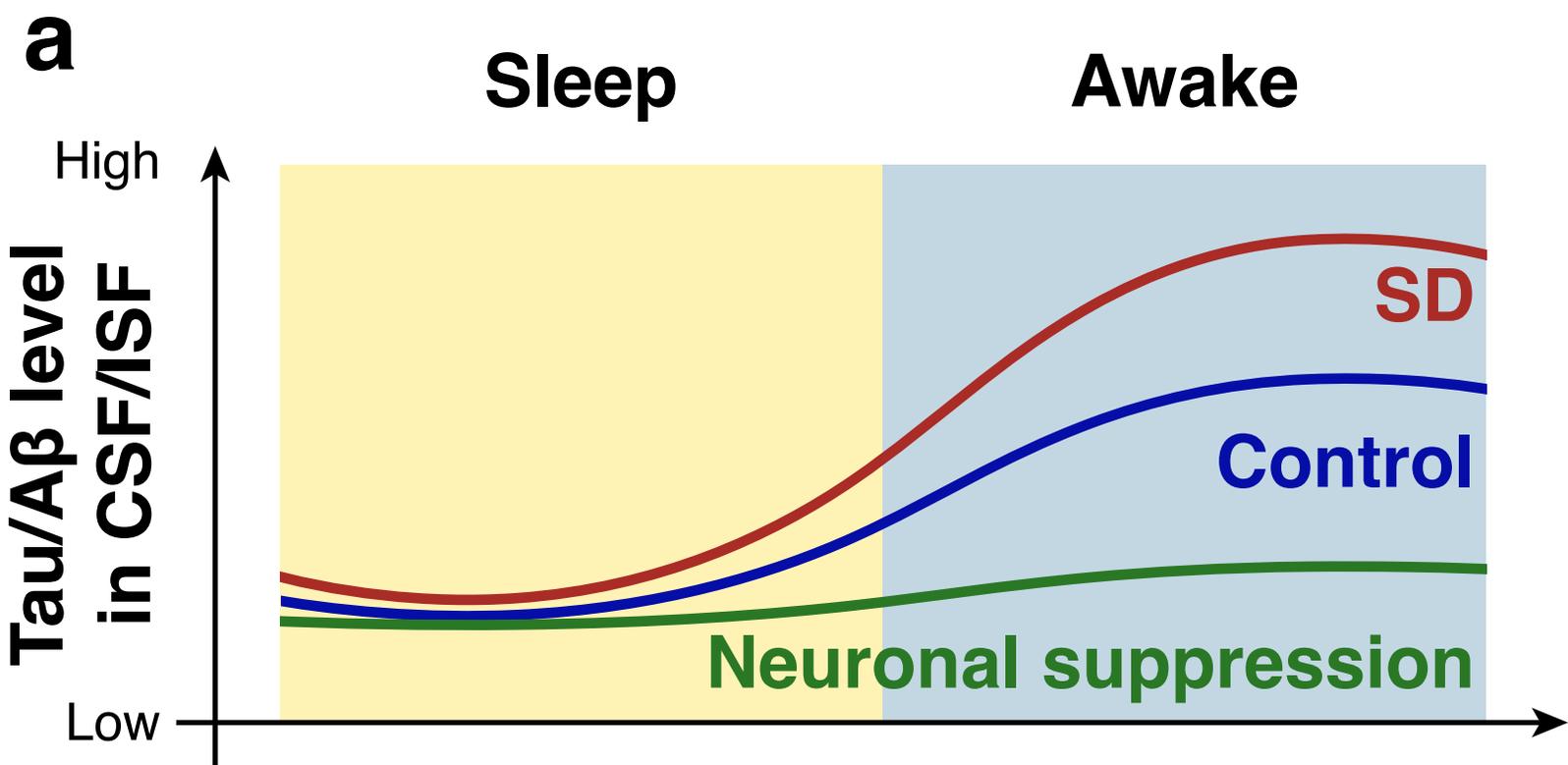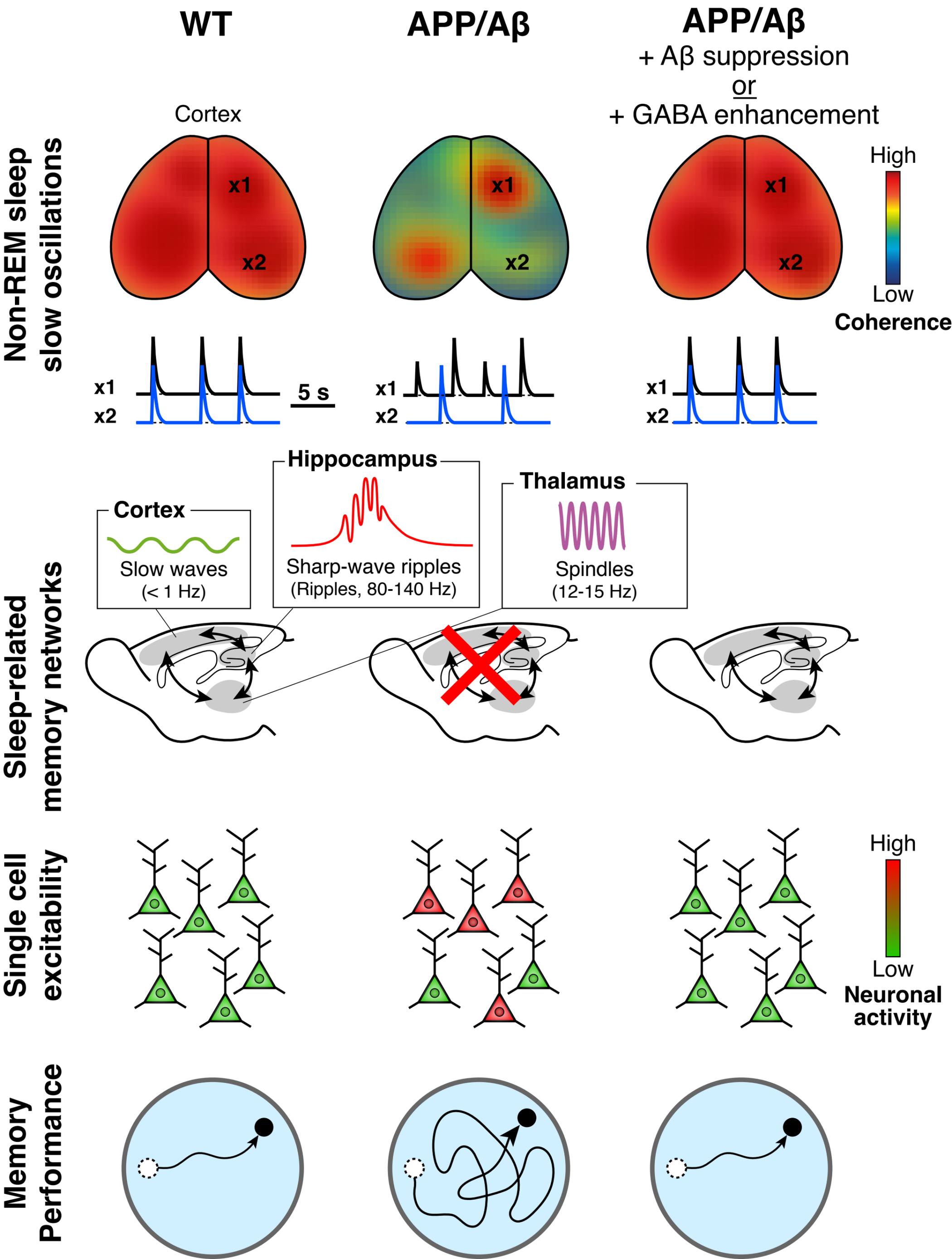
Figure 1

Figure 2

Figure 3