J Neurophysiol 122: 1–4, 2019.
First published March 13, 2019; doi:10.1152/jn.00118.2019.

NEURO FORUM | *Nervous System Pathophysiology*

Beyond the sleep-amyloid interactions in Alzheimer's disease pathogenesis

Shen Ning[1,2]* and Mehdi Jorfi[1,3]*

[1]*Genetics and Aging Research Unit, MassGeneral Institute for Neurodegenerative Disease, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts;* [2]*Graduate Program for Neuroscience, Boston University School of Medicine, Boston, Massachusetts; and* [3]*Center for Engineering in Medicine, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts*

Submitted 19 February 2019; accepted in final form 6 March 2019

Ning S, Jorfi M. Beyond the sleep-amyloid interactions in Alzheimer's disease pathogenesis. *J Neurophysiol* 122: 1–4, 2019. First published March 13, 2019; doi:10.1152/jn.00118.2019.—Cognitive impairment in older adults is associated with sleep and circadian rhythm disturbances. Numerous studies have linked disrupted sleep and circadian rhythms with amyloid-β (Aβ), a key pathological hallmark in Alzheimer's disease (AD). While previous evidence suggests that Aβ initiates AD pathogenesis, tau, another major hallmark of AD, seems to drive neurodegeneration. Recent studies imply that sleep-wake cycles affect brain tau more significantly than Aβ levels, leading to accelerated AD progression and cognitive decline. The study of sleep disturbances in AD is shedding light on our understanding of the mechanism underlying sleep disturbances in AD and dementia.

Alzheimer's disease; amyloid-β; sleep; tau

INTRODUCTION

Deciphering sleep mechanisms remains one of the most substantial challenges in neuroscience. Efficient and effective sleep is fundamental and crucial to memory consolidation and metabolic waste clearance (Xie et al. 2013). In humans, there are two major sleep phases: non-rapid eye movement sleep (NREM), characterized by high-voltage and slow-wave electrical activity (SWA), also referred as slow-wave sleep, and rapid eye movement sleep, which is defined by rapid eye movements, muscle paralysis, and lower-voltage electrical waves (Wang et al. 2011). Sleep disruption harms cognitive skills, inhibits learning, and is a prominent cause of seizures (Xie et al. 2013). Emerging evidence linking sleep disturbances with Alzheimer's disease (AD) has spurred an interest in examining the mechanism underlying sleep and the pathogenic hallmarks of this devastating neurodegenerative disease. AD is pathologically characterized by extracellular amyloid-β (Aβ) plaques and intracellular hyperphosphorylated tau accumulation in axons, dendrites, and cell bodies, resulting in progressive cognitive decline. Tau is a microtubule-associated protein that mediates normal neurotransmitter trafficking. Aβ, liberated from the intramembranous amyloid precursor protein via serial cleavage by β- and γ-secretases, has the propensity to oligomerize and trigger microgliosis and astrocytosis. Chronic exposure to these effects initiates oxidative stress and neuronal loss and alters ionic homeostasis and phosphatase and kinase activity that modifies soluble tau proteins into oligomers and insoluble paired helical filaments. This eventually leads to the formation of neurofibrillary tangles (Haass and Selkoe 2007). Sleep deprivation is a well-documented symptom in AD patients at the preclinical and later stages (Irwin and Vitiello 2019). Accumulating evidence links higher Aβ and tau burden with shorter sleep duration and poorer quality of sleep (Holth et al. 2019; Ju et al. 2013, 2014; Lucey et al. 2019). These new studies are shifting the paradigm in our current understanding of AD pathogenesis and the relationship between AD and sleep. This link serves as a new and potential therapeutic and diagnostic platform for not only AD, but also for other neurodegenerative and psychiatric diseases.

In this article, we describe the association between sleep disruption and brain Aβ and tau in AD. We focus on the pathogenetic mechanisms by which sleep disruption leads to the development of AD pathology and briefly note the implications of potential markers for diagnostic approaches. We also discuss the state-of-the-art model of the sleep-AD relationship and evaluate sleep disruption as either a risk factor or a consequence in AD. Finally, we discuss therapeutic approaches, future directions, remaining challenges, and current gaps in the field. This paper does not examine in detail the role and mechanisms of sleep disturbances on inflammation pathways, nor does it cover sleep disruption in brain plasticity, both of which have been extensively reviewed elsewhere (Irwin and Vitiello 2019; Wang et al. 2011).

SLEEP DISRUPTION AND AMYLOID-β PROTEIN

The pathology of AD emerges more than a decade before the first onset of cognitive symptoms. At earlier stages, Aβ plaques form through the aggregation of insoluble Aβ (Holth et al. 2019; Ju et al. 2014; Lucey et al. 2019). Previous research has found a link between sleep deprivation and increased Aβ in the cerebral spinal fluid (CSF) in healthy middle-aged and older adults. Shokri-Kojori et al. (2018) showed significant increases in Aβ burden in the hippocampus and thalamus just after one night of sleep deprivation in cognitively healthy adults. Likewise, animal studies showed that sleep disturbances after 24 h drastically increased proinflammatory cytokines, such as IL-6, and C-reactive protein selectively in the hippocampus (Zhu et al. 2012). The

* S. Ning and M. Jorfi contributed equally to this work.
Address for reprint requests and other correspondence: M. Jorfi, Massachusetts General Hospital, 114 16th St., Charlestown, MA 02129 (e-mail: mjorfi@mgh.harvard.edu).

0022-3077/19 Copyright © 2019 the American Physiological Society

Downloaded from journals.physiology.org/journal/jn (065.021.193.086) on February 24, 2022.

association between inflammatory markers in the hippocampus and impaired hippocampus-dependent learning and memory revealed another pathway bridging sleep disruption and neuroinflammatory cascades, which plays a prominent role in the pathogenesis and progression of cognitive decline in AD.

Aβ protein levels are the highest in the CSF before sleep and lowest after wakening, suggesting that Aβ clearance might be modulated by sleep, though the specific mechanism remains elusive (Xie et al. 2013). Some headway has been made in recent years in animal and human studies. For instance, Kang et al. (2009) found that orexin and the sleep-wake cycles can modulate interstitial fluid (ISF) Aβ levels in mice. Other investigators attempted to understand the mechanism underlying the sleep-wake cycles on Aβ and found a link between glymphatic clearance of Aβ and the circadian rhythm. Remarkably, Xie et al. (2013) observed that anesthesia modulates Aβ influx, implicating that glymphatic clearance of Aβ is independent of the circadian rhythm and driven directly by the sleep-wake cycle. This was a crucial distinction for the field in understanding which aspect of sleep contributes to Aβ modulation. In human studies, Ju et al. (2017) further examined the stage of sleep responsible for Aβ clearance. The researchers found that disruption specifically in SWA increases CSF Aβ levels by 10–30%. This connection between SWA and Aβ clearance revealed the potential of modulating the duration of SWA to enhance Aβ clearance as a possible AD treatment. However, the timeline of sleep disruption in AD is still unclear, which limits the ability of sleep research to adequately design clinical trials and treatments. Taken together, this evidence demonstrates the significance of sleep in clearing metabolic waste and sleep disruption as a significant mediator in the development of AD.

SLEEP DISRUPTION AND TAU PROTEIN

While previous studies have examined the relationship between sleep and Aβ, recent efforts have shifted to investigate the link between sleep and tau protein in the brain. CSF tau is a marker for neuronal injury and CSF p-tau is an indicative of neurofibrillary tangles, another hallmark of AD pathology. One of initial questions to be resolved is which stage of sleep contributes to the tau fluctuations: the sleep-wake cycle or the circadian rhythm? Holth et al. (2019) are the first to convincingly show that the sleep-wake cycle is a key regulator in tau seeding and spreading. The authors found that tau levels in the hippocampal ISF of wild-type mice increased by 90% during the dark cycle. They showed that acute sleep deprivation increased ISF tau by twofold and were able to pinpoint the direct modulation of ISF tau to the sleep-wake cycle. This suggests that a potential mechanism beyond ISF clearance modulates tau levels across sleep-wake cycles. The authors also found that, in humans, CSF tau increased by 50% after one night of sleep deprivation, outpacing the 30% increase in Aβ_{42}. This proposes that acute sleep disruptions can immediately impact CSF tau levels in the brain. To determine whether sleep deprivation can further promote tau spreading, they injected recombinant P301S human tau fibrils into the hippocampus of 8- to 9-wk-old P301S mice and found that sleep deprivation hastens tau spreading. Specifically, the results showed a 40% increase in ISF tau and a 90% increase in lactate in the clozapine-*N*-oxide-treated mice. The implications of tau seeding and spreading for AD progression seen in this study contributes to a new understanding of how sleep disturbances can potentiate AD tauopathy and synaptic death. It will be crucial for future studies to test the different effects of acute and chronic tau accumulation in the ISF and CSF. Another compelling point in this study is that tau levels showed expanded error bars between individuals after sleep deprivation compared with rested conditions, implying that some people are more susceptible to taupathy related to sleep loss than others. It would be worthwhile to evaluate whether this can predict an individual's susceptibility to developing AD and, in particular, a tau pathology.

In parallel with this study, Lucey et al. (2019) provided further evidence showing a bidirectional relationship between non-rapid eye movement (NREM) SWA deficits and neurofibrillary tangles in humans. Using Aβ and tau tracers, the authors found that individuals with higher tau tangles correlated with less NREM SWA sleep. Diminished NREM SWA also corresponds with an increase in Aβ deposition, CSF tau/Aβ_{42} and p-tau/Aβ_{42} ratios. The relationship between NREM SWA sleep deficit and AD proteins was stronger for tau than for Aβ. Interestingly, the absolute CSF Aβ_{42} levels are not associated with decreases in NREM SWA, suggesting that the tau/Aβ_{42} ratio could be a better diagnostic indicator for future clinical applications. NREM SWA could also be another robust and important diagnostic biomarker for neurofibrillary tangle development in AD patients. Further longitudinal studies in early or midlife patients may specify which comes first, taupathy or sleep disruption.

This new evidence linking tau and sleep deprivation is further supported by the anatomical location of tau accumulation. Previous studies have found that locus coeruleus, a key brain stem region for norepinephrine production, blood flow, and glial responses, is one of the first locations for hyperphosphorylated tau and tau spreading after sleep disruptions (Zhu et al. 2018). Accumulation of AD pathology is a crucial regulator for cerebral blood flow and clearance, due to the mounting evidence signifying the role of the neurovasculature and lymphatic systems in the progression of cognitive decline in AD (Louveau et al. 2018; Nation et al. 2019). This may reveal a key underlying mechanism for AD development. However, while the synergy of the neurovascular system, the lymphatic system, and sleep disturbances has been heavily implicated, scientists have yet to untangle these complex relationship between these contributors in AD pathology.

SLEEP DISRUPTION IN ALZHEIMER'S DISEASE: CONSEQUENCE OR RISK FACTOR?

The association between glymphatic efflux of metabolites and sleep has led to alternative theories about AD disease progression. For one, amyloid and p-tau accumulation seems to be a problem of excessive production and reduced clearance. Sleep appears to facilitate clearance via convective movement of the ISF through the glymphatic system. In our current understanding, proteins associated with neurodegenerative diseases are present in the peripheral tissues and lymph vessels and will return to the vascular circulatory system for degradation in the liver (Xie et al. 2013). However, the question remains whether sleep disruption aggravates AD symptoms and augments disease progression, or whether sleep disruption actually initiates the cascade of AD development. Thus far,

Downloaded from journals.physiology.org/journal/jn (065.021.193.086) on February 24, 2022.

studies have largely examined the first possibility with limited convincing evidence for the latter. One previous model links sleep disturbances with glymphatic clearance, increased tau, neuronal activity, and augmented Aβ accumulation before the onset of AD (Musiek et al. 2015). In aging, the convective clearance mechanisms through the glymphatic system are reduced. This reduction, in addition to genetic, environmental, and inflammatory factors, contributes to AD and primes the progression of neurodegeneration (Zhu et al. 2012). Sleep disruption will therefore further expedite the process to a clinically detectable stage. We propose that genetic and/or environmental influences predispose individuals to circadian rhythm malfunction, which then propagates the accumulation of AD pathology, including phosphorylated tau and Aβ in the central nervous system. Decades of accumulation of these aberrant proteins in the central nervous system, plus the vascular changes and glymphatic blockage seen in aging ultimately culminate into the later cognitive symptoms of AD (Fig. 1).

It is likely that chronic sleep disruption is a catalyst to promote Aβ plaque accumulation in humans (Ju et al. 2017). Future studies should focus on unraveling the specific mechanisms linking chronic sleep disruptions and instigation of AD. It is critical to explore how various cell types in the brain respond to a transient surge in tau and Aβ levels and whether/how the human brain compensates for neuronal damages after sleep disruption. The different consequences of acute and chronic sleep disruption, both of which raise the Aβ and tau levels in the CSF, have yet to be examined. All in all, both very recent and prior studies on the effect of sleep-wake cycles in AD support two ideas. The first is that sleep disruption and deprivation are consequences of late-stage AD pathology. The second, as shown by two recent studies from the Holzman group (Holth et al. 2019; Lucey et al. 2019), suggests a bidirectional relationship between sleep disruption and pathology progression in AD patients, confirming that sleep disruption should be considered as a major contributing risk factor for early-stage AD and progression.

THERAPEUTIC APPROACHES AND FUTURE DIRECTIONS

Recent research directions investigating sleep-AD relationships hold immense diagnostic and therapeutic potential. There are several advantages in developing therapies targeted at sleep

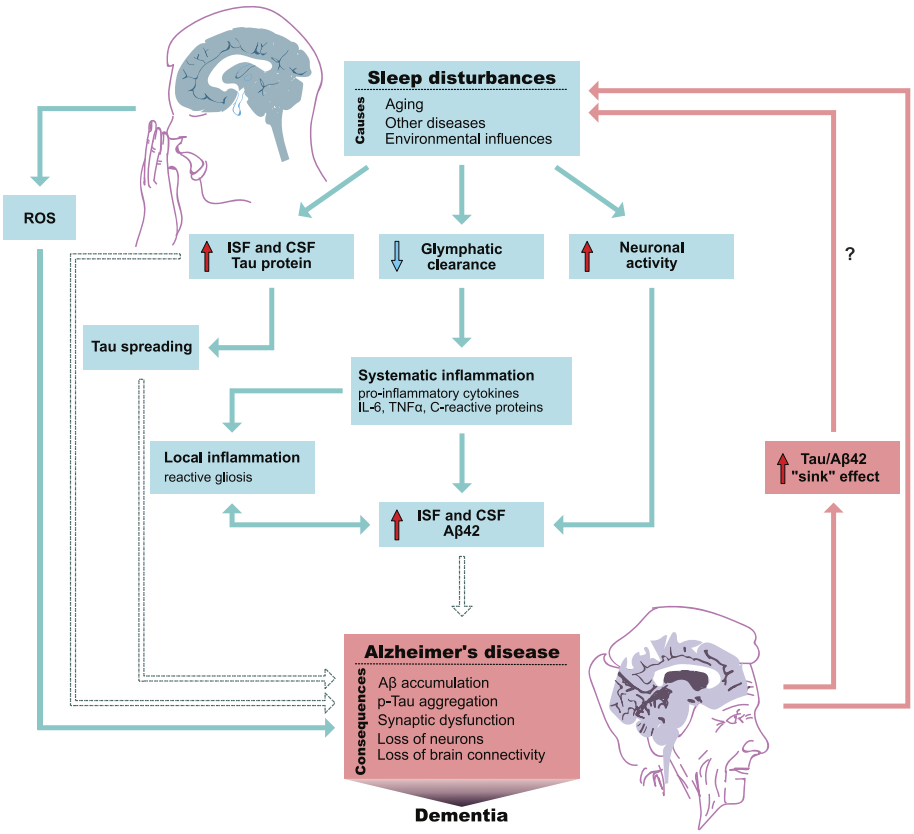

Fig. 1. Bidirectional relationships between sleep disruption and Alzheimer's disease (AD). Sleep disturbance as a factor of aging, environmental influences, and other psychiatric or neurological diseases leads to the development of AD. Sleep disturbances lead to an increase in interstitial fluid (ISF) and cerebrospinal fluid (CSF) tau, neuronal activity, reactive oxygen species (ROS) production, systematic inflammation, and decrease in glymphatic clearance of amyloid-β (Aβ) protein. Oxidative stress can initiate or augment the neuropathological hallmarks in AD. Accumulation of Aβ and tau proteins initiates inflammatory cascades, including the production of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα). In response to IL-6 production, C-reactive proteins will be secreted from the liver. High levels of C-reactive protein in the blood is linked with impaired cognitive and executive functions. The systematic inflammation cascades contribute to the transition of resident immune cells, i.e., microglia to the primed microglia, resulting in reduced clearance of Aβ and more buildup of AD pathology. In parallel, the increase in tau due to sleep disruption initiates tau seeding and spreading, directly contributing to synaptic dysfunctions and loss of brain connectivity. Chronic exposure to tau and its spreading results in accumulation of neurofibrillary tangles, the other key hallmark in AD progression and dementia. AD then reciprocally disturbs sleep patterns and exacerbate sleep symptoms, thereby restarting the cycle. Another interesting pathway is that Aβ plaques in AD patients act as a "sink" for toxic soluble Aβ_{42}, which manifests as a reduction of Aβ_{42} in the CSF. Solid arrows represent established acute processes, whereas dashed arrows signify chronic states. Question mark indicates hypothesized link between AD and sleep disruption.

Downloaded from journals.physiology.org/journal/jn (065.021.193.086) on February 24, 2022.

and circadian modification: *1*) sleep modification is inexpensive and noninvasive, *2*) it can target AD at earlier stages to prevent cognitive decline and dementia, and *3*) as sleep disruption is implicated in a variety of diseases, the same approach may be adopted for the prevention of other neurodegenerative diseases. Studies are already underway for applying our understanding of AD and sleep to develop therapies for preclinical AD (Musiek et al. 2015). However, there are still many challenges that must be addressed before adoption. First, would increasing the duration of SWA sleep be effective to ameliorate symptoms and prevent AD? Second, at which stage of the disease, if any, would sleep alterations be inadequate as a disease-modifying therapy? Third, how can one best combine our understanding of sleep rhythm patterns with other diagnostic markers to accurately diagnose, predict, and track disease progression such that AD becomes a chronically managed disease similar to diabetes or hypertension? To summarize, although integration of sleep and neurodegeneration is still in its infancy, sleep and AD research is a convergence point for basic and translational biological sciences. Recent ongoing work in this area is certainly exciting and holds great promise in bridging the molecular and cellular biology of sleep with the development of AD. It may even provide helpful therapeutic benefits not only in preventing AD, but also in improving diagnosis and treatments for psychiatric and metabolic diseases.

ACKNOWLEDGMENTS

We thank Emma Brand at Massachusetts General Hospital for designs in Fig. 1, and Drs. Doo Y. Kim and Rudolph E. Tanzi for constructive discussions. We also acknowledge Drs. Alexander J. Creely and Alex Hopke for comments.

GRANTS

S. Ning is supported by Boston University School of Medicine MD/PhD Dean's Scholarship, and M. Jorfi is supported by Cure Alzheimer's Fund.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.N. and M.J. conceived and designed research; S.N. and M.J. prepared figures; S.N. and M.J. drafted manuscript; S.N. and M.J. edited and revised manuscript; S.N. and M.J. approved final version of manuscript.

REFERENCES

Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide. *Nat Rev Mol Cell Biol* 8: 101–112, 2007. doi:10.1038/nrm2101.

Holth JK, Fritschi SK, Wang C, Pedersen NP, Cirrito JR, Mahan TE, Finn MB, Manis M, Geerling JC, Fuller PM, Lucey BP, Holtzman DM. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science* 363: 880–884, 2019. doi:10.1126/science.aav2546.

Irwin MR, Vitiello MV. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. *Lancet Neurol* 18: 296–306, 2019. doi:10.1016/S1474-4422(18)30450-2.

Ju YE, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology—a bidirectional relationship. *Nat Rev Neurol* 10: 115–119, 2014. doi:10.1038/nrneurol.2013.269.

Ju YE, McLeland JS, Toedebusch CD, Xiong C, Fagan AM, Duntley SP, Morris JC, Holtzman DM. Sleep quality and preclinical Alzheimer disease. *JAMA Neurol* 70: 587–593, 2013. doi:10.1001/jamaneurol.2013.2334.

Ju YS, Ooms SJ, Sutphen C, Macauley SL, Zangrilli MA, Jerome G, Fagan AM, Mignot E, Zempel JM, Claassen JAHR, Holtzman DM. Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. *Brain* 140: 2104–2111, 2017. doi:10.1093/brain/awx148.

Kang J-E, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, Fujiki N, Nishino S, Holtzman DM. Amyloid-β dynamics are regulated by orexin and the sleep-wake cycle. *Science* 326: 1005–1007, 2009. doi:10.1126/science.1180962.

Louveau A, Herz J, Alme MN, Salvador AF, Dong MQ, Viar KE, Herod SG, Knopp J, Setliff JC, Lupi AL, Da Mesquita S, Frost EL, Gaultier A, Harris TH, Cao R, Hu S, Lukens JR, Smirnov I, Overall CC, Oliver G, Kipnis J. CNS lymphatic drainage and neuroinflammation are regulated by meningeal lymphatic vasculature. *Nat Neurosci* 21: 1380–1391, 2018. doi:10.1038/s41593-018-0227-9.

Lucey BP, McCullough A, Landsness EC, Toedebusch CD, McLeland JS, Zaza AM, Fagan AM, McCue L, Xiong C, Morris JC, Benzinger TL, Holtzman DM. Reduced non–rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Sci Transl Med* 11: eaau6550, 2019. doi:10.1126/scitranslmed.aau6550.

Musiek ES, Xiong DD, Holtzman DM. Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease. *Exp Mol Med* 47: e148, 2015. doi:10.1038/emm.2014.121.

Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, Sepehrband F, Nelson AR, Buennagel DP, Harrington MG, Benzinger TLS, Fagan AM, Ringman JM, Schneider LS, Morris JC, Chui HC, Law M, Toga AW, Zlokovic BV. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat Med* 25: 270–276, 2019. doi:10.1038/s41591-018-0297-y.

Shokri-Kojori E, Wang G-J, Wiers CE, Demiral SB, Guo M, Kim SW, Lindgren E, Ramirez V, Zehra A, Freeman C, Miller G, Manza P, Srivastava T, De Santi S, Tomasi D, Benveniste H, Volkow ND. β-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci USA* 115: 4483–4488, 2018. doi:10.1073/pnas.1721694115.

Wang G, Grone B, Colas D, Appelbaum L, Mourrain P. Synaptic plasticity in sleep: learning, homeostasis and disease. *Trends Neurosci* 34: 452–463, 2011. doi:10.1016/j.tins.2011.07.005.

Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M. Sleep drives metabolite clearance from the adult brain. *Science* 342: 373–377, 2013. doi:10.1126/science.1241224.

Zhu B, Dong Y, Xu Z, Gompf HS, Ward SA, Xue Z, Miao C, Zhang Y, Chamberlin NL, Xie Z. Sleep disturbance induces neuroinflammation and impairment of learning and memory. *Neurobiol Dis* 48: 348–355, 2012. doi:10.1016/j.nbd.2012.06.022.

Zhu Y, Zhan G, Fenik P, Brandes M, Bell P, Francois N, Shulman K, Veasey S. Chronic sleep disruption advances the temporal progression of tauopathy in P301S mutant mice. *J Neurosci* 38: 10255–10270, 2018. doi:10.1523/JNEUROSCI.0275-18.2018.

Downloaded from journals.physiology.org/journal/jn (065.021.193.086) on February 24, 2022.