ROLES OF SLEEP DISRUPTION AND CIRCADIAN RHYTHM ALTERATIONS ON NEURODEGENERATION AND ALZHEIMER'S DISEASE

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ROLES OF SLEEP DISRUPTION AND CIRCADIAN RHYTHM ALTERATIONS ON NEURODEGENERATION AND ALZHEIMER'S DISEASE

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EDITORIAL
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Editorial: Roles of Sleep Disruption and Circadian Rhythm Alterations on Neurodegeneration and Alzheimer's Disease

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Editorial on the Research Topic

Roles of Sleep Disruption and Circadian Rhythm Alterations on Neurodegeneration and Alzheimer's Disease

Striking changes in circadian rhythms, including the sleep-wake rhythm, characterize many neurodegenerative processes, e.g., Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, and traumatic brain injury (TBI). Because disturbances in circadian rhythm and sleep can precede the overt cognitive impairment, they have been postulated as risk factors or predictors of these diseases (Musiek and Holtzman, 2016).

Circadian rhythms represent biological adaptations to dramatic and predictable daily changes in the physical environment experienced by virtually all organisms living on earth. By definition, circadian rhythms have an intrinsic period length of ∼24 h, are endogenously generated (i.e., persist under constant environmental conditions), are temperature compensated (i.e., the period is little affected by temperature) and can be entrained by temporal cues (zeitgebers). Although the light-dark cycle is the most robust zeitgeber, other factors including activity and timing of food can modify circadian phase. Circadian rhythms govern the rhythmic expression of a large portion of the genome (Zhang et al., 2014) and a wide range of cellular, physiological, and behavioral processes, including the daily sleep-wake rhythm.

Sleep is regulated not only by the circadian phase but also by the time elapsed since prior sleep (the homeostatic sleep drive), according to the two-process model of sleep regulation (Borbély, 1982). Although these processes were initially considered to be independent, they have since been shown to influence each other. Sleep deprivation can alter the phase of circadian rhythms (Antle and Mistlberger, 2000) and the expression of circadian clock genes (Franken et al., 2007). Destruction of the suprachiasmatic nucleus (SCN), the master mammalian circadian pacemaker, not only ablates the daily sleep-wake rhythm but also increases the total amount of sleep in squirrel monkeys (Edgar et al., 1993) and non-REM sleep in mice (Easton et al., 2004). Thus, loss of sleep affects the timing of circadian rhythms while circadian rhythm alterations impair sleep, underscoring a complex relationship between these processes (Mistlberger, 2005; Morin, 2013; Scammell et al., 2017).

Neural circuits regulating sleep and circadian rhythm output are vulnerable to brain damage and neurodegeneration (Coogan et al., 2013; Theofilas et al., 2017). For example, accumulation of amyloid-beta disrupts circadian rhythms and sleep (Tate et al., 1992; Roh et al., 2012). On

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the other hand, disruption of circadian rhythms or sleep deleteriously affects many physiological, behavioral, and neuronal functions (Musiek and Holtzman, 2016; Zhu et al., 2016). Current evidence suggests that the bi-directional interactions between neurodegeneration and disruption of circadian rhythms and sleep exacerbates neuropathology in AD and other neurological disorders (Wang and Holtzman, 2020). In this special issue, discrete circadian rhythm alterations in these disorders and their associations with specific neuropathological processes are described in articles by Fifel and Videnovic and Green et al.

Sleep disruptions appear prior to the prodromal stages of AD, and include fragmentation of the daily sleep-wake rhythm, reduced total sleep, and loss of deep sleep (i.e., slow wave sleep) (Tranah et al., 2011; Guarnieri et al., 2012; Lim et al., 2013; Guarnieri and Sorbi, 2015). Two articles in this issue focus on AD-related changes in discrete neuronal oscillations. As Mander describes, AD neuropathology is accompanied by deficits in three types of local sleep oscillations: (1) frequency-specific frontal slow-wave expression during non-REM sleep, (2) parietal sleep spindles expression, and (3) the quality of electroencephalographic desynchrony in REM sleep. The association of these specific sleep deficits with amyloid-beta and tau pathology and their potential roles in sleep-dependent memory processes and cognitive changes in AD are discussed. The mechanistic importance of AD-associated deficits in slow wave activity is emphasized in the article by Lee et al., which reviews studies showing that the frequency of slow waves affects memory consolidation, amyloid deposition, and neuronal calcium homeostasis. Slow wave sleep is proposed as a therapeutic target for AD.

Variations in neuronal oscillatory activity also occur in patients with moderate obstructive sleep apnea (OSA), a common breathing disorder associated with brain injury and memory impairment. As described by Zhou et al. in this issue, dynamic changes in EEG spectral power occur during respiratory events, including cortical hyperactivation during N2 sleep, suppression of β-band information transmission, abnormal interhemispheric effective connectivity, and intrahemispheric "rise-to-down" fluctuations in the γ band. This work provides insights into how OSA affects cognition and neuropsychiatric function.

To enable preclinical investigations of therapeutic strategies to ameliorate sleep and circadian dysfunction in AD, animal models that temporally replicate these disturbances and neurodegeneration are needed. While some AD mouse models exhibit changes in sleep and circadian rhythms resembling those seen in AD patients, these changes are not consistent across the models, as described by Sheehan and Musiek in this issue. This review provides a fine-grained analysis of the expression of circadian rhythms reported from various models and provides suggestions on how to standardize and optimize future studies of circadian rhythms in AD mouse models. Also in this issue, Lippi et al. describe daily activity rhythms and their responses to zinc in a novel mouse model that exhibits amyloid and tau pathology based on a cross between the J20 (hAPP) and P301L (Tau) lines. Sare et al. report on the TgF344-AD rat model of AD that expresses age-dependent tau and amyloid pathology. Age-related changes in rest-activity rhythms, cognitive performance, and hyposmia are exhibited by the TgF344-AD rats with interesting sex-dependent effects.

Several article in this issue described basic research focused on the underlying mechanisms linking sleep and circadian rhythm dysfunction to neurodegeneration. Sharma et al. review this topic with a special focus on the effect of aberrant circadian rhythmicity on E3 ligase and poly adenosine disphophate (ADP-ribose) polymerase 1 activity in Parkinson's disease. Cassar et al. developed a knock-in Drosophila model of tauopathy and reveal that mutant tau disrupts daily sleep rhythms independent of circadian rhythm changes by interfering with central pacemaker neuron output connectivity. Green et al. describe the role of sleep disruption-associated inflammation in mediating the increased risk of AD occurring with traumatic brain injury. Todd focuses on the potential neural pathways by which circadian rhythm disruption may cause the aggression and agitation that AD patients exhibit during "sundowning syndrome."

Together, the articles presented in this special issue highlight important questions to address regarding interactions between sleep, circadian rhythms, and neurodegeneration and describe newer models and approaches that may facilitate this work. Overall, the work substantiates the concept that study of neural consequences of circadian and sleep disturbances will provide insight into molecular bases of neurodegenerative processes, while study of sleep and circadian rhythms in animal models and humans with neurodegeneration will provide fundamental knowledge of sleep and circadian neurobiology. These efforts will meet with the greatest success when experts in all three fields collaborate.

AUTHOR CONTRIBUTIONS

MD wrote this editorial. SV and PZ provided revisions.

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BRIEF RESEARCH REPORT
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Disease-Associated Mutant Tau Prevents Circadian Changes in the Cytoskeleton of Central Pacemaker Neurons

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A hallmark feature of Alzheimer's disease (AD) and other Tauopathies, like Frontotemporal Dementia with Parkinsonism linked to chromosome 17 (FTDP-17), is the accumulation of neurofibrillary tangles composed of the microtubule-associated protein Tau. As in AD, symptoms of FTDP-17 include cognitive decline, neuronal degeneration, and disruptions of sleep patterns. However, mechanisms by which Tau may lead to these disturbances in sleep and activity patterns are unknown. To identify such mechanisms, we have generated novel *Drosophila* Tauopathy models by replacing endogenous fly dTau with normal human Tau (hTau) or the FTDP-17 causing hTau^{V337M} mutation. This mutation is localized in one of the microtubule-binding domains of hTau and has a dominant effect. Analyzing heterozygous flies, we found that aged hTau^{V337M} flies show neuronal degeneration and locomotion deficits when compared to wild type or hTau^{WT} flies. Furthermore, hTau^{V337M} flies are hyperactive and they show a fragmented sleep pattern. These changes in the sleep/activity pattern are accompanied by morphological changes in the projection pattern of the central pacemaker neurons. These neurons show daily fluctuations in their connectivity, whereby synapses are increased during the day and reduced during sleep. Synapse formation requires cytoskeletal changes that can be detected by the accumulation of the end-binding protein 1 (EB1) at the site of synapse formation. Whereas, hTau^{WT} flies show the normal day/night changes in EB1 accumulation, hTau^{V337M} flies do not show this fluctuation. This suggests that hTau^{V337M} disrupts sleep patterns by interfering with the cytoskeletal changes that are required for the synaptic homeostasis of central pacemaker neurons.

Keywords: FTDP-17, Tau^{V337M}, Tauopathy, sleep disruptions, synaptic homeostasis, PDF neurons, Alzheimer's disease

INTRODUCTION

The microtubule-associated protein Tau is a major component of the neurofibrillary tangles (Grundke-Iqbal et al., 1986) that are a hallmark of Alzheimer's disease (AD) and a number of other neurodegenerative diseases, together called Tauopathies (Lee et al., 2001; Lee and Leugers, 2012). The relevance of Tau in the pathogenesis of these diseases has been confirmed by the identification

of several mutations in Tau that cause Frontotemporal Dementia with Parkinsonism linked to chromosome 17 (FTDP-17). FTDP-17 Tauopathy is a dominant inherited disease and the most prominent symptoms are behavioral and personality changes, cognitive impairment, and motor symptoms (Wszolek et al., 2006). In addition, FTDP-17 patients and other Tauopathy patients show changes in their sleep patterns (McCarter et al., 2016; Holth et al., 2017; Liu et al., 2018). Disturbances in sleep-wake cycles and other circadian rhythms are also very common in Alzheimer patients (van Someren et al., 2007; Reddy and O'Neill, 2010; Kondratova and Kondratov, 2012; Hastings and Goedert, 2013; Musiek et al., 2018; Leng et al., 2019) and recent evidence in AD suggests that sleep abnormalities are not simply a consequence but an intimate and bi-directional component of the pathophysiology. Sleep disruptions impair long-term memory consolidation, thus probably actively contributing to the cognitive decline in AD (Kang et al., 2009; Lim et al., 2014; Roh et al., 2014). A more active role is further supported by findings that sleep disruptions can precede the development of other symptoms of AD, including cognitive decline (Guarnieri and Sorbi, 2015). However, while several studies have suggested a link between the accumulation of plaque-associated β-amyloid and sleep (Brown et al., 2016; Cedernaes et al., 2017; Macedo et al., 2017; Yulug et al., 2017), a role of neuropathic forms of Tau in disrupting sleep has only recently been addressed (Holth et al., 2017). Furthermore, in contrast to amyloid plaques which are characteristic for AD, Tau pathology is found in all Tauopathies and therefore effects of Tau on sleep could account for the sleep disruptions in many Tauopathies, including AD.

Circadian rhythms are controlled by the circadian clock system with the clock in the central pacemaker neurons controlling behavioral rhythms including sleep/wake cycles (Schibler et al., 2003). Daily rhythms are also observed in many other brain functions, such as neuronal plasticity, learning, and memory and generally these rhythms decay during aging (Hastings et al., 2007; Gerstner and Yin, 2010; Reddy and O'Neill, 2010; Smarr et al., 2014). This suggests a neuroprotective function of circadian clocks and, indeed mutations in clock proteins have been shown to cause or aggravate phenotypes in mouse or *Drosophila* models of neurodegenerative diseases (van Someren et al., 1996; Volicer et al., 2001; Harper et al., 2005; Krishnan et al., 2012; Musiek et al., 2013; Musiek, 2015). In contrast, promoting sleep has been shown to reverse the memory deficits observed when expressing the human Amyloid Precursor Protein in *Drosophila* (Dissel et al., 2017). While it has been shown in a variety of models that APP or Aβ expression disrupts sleep, it has only recently been described that a FTPD-17 mouse model shows changes in its sleep patterns. Knock-in mice expressing human Tau (hTau) with the disease-associated P301L or R406W mutation in the forebrain reveal decreased non-REM sleep and increased wakefulness (Koss et al., 2016; Holth et al., 2017). To study the emerging connection between mutant Tau and sleep, we used the *Drosophila* model to create knock-in flies that either express wild type human Tau ($hTau^{WT}$) or FTDP-17-causing mutant $hTau^{V337M}$ instead of *Drosophila* Tau (dTau). In addition to a disruption of their sleep pattern, $hTau^{V337M}$ flies showed changes in the axonal pattern of central pacemaker neurons and in their synaptic connection, suggesting that cytoskeletal alterations caused by this mutation prevent the synaptic homeostasis in sleep-regulating neurons.

MATERIALS AND METHODS

Drosophila Stocks

The knock-in lines were created by cloning a cDNA encoding the hTau 1N4R isoform (kindly provided by B. Kraemer, University of Washington) into the pHD-DsRed-attp vector together with 1.8 kb of the sequence upstream of the dTau coding region and 1.2 kb of the sequence downstream of dTau. hTau was inserted into the dTau coding region using the CRISPR/Cas9 genomic editing system (**Supplementary Figure S1A**) and guide RNAs (**Supplementary Figure S1B**) cloned into the pBTv-U6.2 vector using the BestGene injection service. UAS-GFP-tubulin was kindly provided by D. Applewhite (Reed College), UAS-EB1-GFP by M. Rolls (PennState University), and UAS-mCD4-GFP by M. Logan (OHSU). The *Pdf*-GAL4 lines are described in Renn et al. (1999). The dTau knock-out line was provided by the Bloomington Drosophila Stock Center. Flies were maintained on standard fly food under a 12:12h light:dark cycle at 26°C.

Fast Phototaxis

Fast phototaxis assays were conducted in the dark using the countercurrent apparatus described by Benzer (1967) and a single light source. A detailed description of the experimental conditions can be found in Strauss and Heisenberg (1993). Flies were collected every day and aged to the given age with fresh food vials provided every 4–5 days. Flies were then tested in groups of 10–15 flies. Five consecutive tests were performed in each experiment with a time allowance of 6 s to make a transition toward the light and into the next vial and a value determined for each fly based on which of the six vials it reached. Statistical analysis was done using GraphPad Prism and one-way ANOVA with Dunnett's post-tests.

Tissue Sections and Vacuole Measurements

Flies were obtained and aged as described for the phototaxis experiments. Paraffin sections for light microscopy were prepared and analyzed for vacuole formation as described in Botella et al. (2003) and Sunderhaus and Kretzschmar (2016). Briefly, whole flies were fixed in Carnoy's solution and dehydrated in an ethanol series followed by incubation in methyl benzoate before embedding in paraffin. Sections were cut at 7 μm and analyzed with a Zeiss Axioscope 2 microscope using the auto-fluorescence caused by the dispersed eye pigment. Semi-thin and ultrathin Epon plastic sections were prepared as described in Kretzschmar et al. (1997). Semi-thin sections were cut at 1 μm and stained with toluidine blue. Ultra-thin sections were cut at 50 nm and electron microscopic images taken with a FEI Tecnai G2 microscope. To quantify the vacuolization, we photographed the paraffin sections that contained the antennal lobes and the most prominent

vacuolization in each fly head without knowing the genotype. For a double-blind analysis, pictures were numbered and the number of vacuoles in the antennal lobes and AMMC counted before the genotype was revealed. Statistical analysis was done using GraphPad Prism and one-way ANOVA with Dunnett's post-tests to compare to CS and Student's *t*-test to compare the two knock-in lines.

Immunohistochemistry

For whole-mounts, brains were dissected in ice-cold PBS and transferred to 4% PFA in PBS. They were then fixed for 30 min to 1 h at room temperature (RT) and washed four times with PBS/0.5% Triton (PBS-T) for 10 min each before blocking with 5% normal goat serum in PBS overnight at 4^{o}C. To detect GFP, EB1-GFP, and GFP-tubulin, anti-GFP (Thermo Fisher Scientific A-11122) was used at 1:250 overnight at 4°C. Brains were then washed three times in PBS, 20 min each at RT and the secondary antibody applied (anti-rabbit-Cy2, Jackson ImmunoResearch) at 1:250 for 2 h at RT. Anti-Tau13 (Abcam ab19030) was used at 1:100 and detected with anti-mouse-Cy3 (VectorLabs) at 1:1000 or the anti-mouse Vecta Fluor Antibody kit (VectorLabs, DK-2488) following the instruction manual. Brains were washed three times for 20 min with PBS and mounted in Glycergel for confocal imaging using an Olympus FluoView 300 laser scanning confocal head mounted on an Olympus BX51 microscope.

Western Blots

To detect hTau, we modified a protocol from Feuillette et al. (2010). Thirty-five adult fly heads were dissected on an ice-cold plate, homogenized in 100 μl of RIPA lysis buffer [150 mM NaCl, 1% DOC, 1% SDS, 50 mM Tris, 5 mM EDTA, 5 mM EGTA, 1% triton X-100, and protease inhibitors (Cell Signaling Technology 5872S)], and immediately centrifuged at 10,000 × *g* for 10 min at 4°C. The supernatant was discarded and the pellet was homogenized in 100 μl of 70% formic acid and then incubated for 30 min at 37°C. Samples were centrifuged again at 10,000 × *g* for 10 min at 4°C. The supernatant was transferred to a fresh tube and the formic acid was evaporated by vacuum centrifugation. The resulting pellet was resuspended in 30 μl of 1.25 × LDS sample buffer (Thermo Fisher Scientific B0008), supplemented with 50 mM tris(2-carboxyethyl)phosphine (TCEP) as a reducing agent, and immediately denatured at 95°C for 5 min. Samples were stored at -20°C overnight, denatured again at 95°C for 5 min, and loaded onto 8% bis-tris gels (Thermo Fisher Scientific NW00082). After transfer, PVDF membranes (GE Healthcare 106000230) were blocked with 1× casein blocking buffer (Sigma C7594). Primary antisera/antibodies were used at the following dilution: mouse anti-tau 5 (1:200; Invitrogen MA5-12808) and mouse anti-GAPDH G-9 (1:1000; Santa Cruz sc-365062) incubated over night at 4°C. To detect hTau and GAPDH, we used a biotinylated secondary antibody (Vector Labs BA-2000) and Streptavidin-conjugated alkaline phosphatase (Vector Labs AK-6000) following the manufacturer protocol with the exception that all washing steps were carried out with 1× TBST. Enhanced chemiluminescent substrate (Vector Labs SK-6605) was used to visualize bands.

Locomotor Activity and Sleep Analysis

In two independent experiments, at least 22 adult males from each specified age and genotype were held individually in glass tubes containing diet in one end, and a piece of yarn plugging the other end. Tubes were placed in Drosophila Activity Monitors (DAM) models DAM2 or DAM5 (Trikinitecs, Waltham, MA, United States) to measure locomotor activity (the monitors are different sizes but hold the same tubes and take the same readings). Activity counts were taken once every minute for three days of light/dark (12h:12h LD), followed by at least seven days of constant darkness (DD). Activity experiments were performed at 25 ± 1°C and ∼1000–1200 l× during light phase. Analysis of activity counts, rhythmicity as measured by fast Fourier transform (FFT), and sleep was performed with ClockLab 6 (Actimetrics, Wilmette, IL, United States). Sleep bouts were defined as a 5-min interval in which no activity was detected. Graphs and statistical tests of data were done in GraphPad Prism 6 (San Diego, CA, United States). The indicated ages were their age at the beginning of the activity recording.

RESULTS AND DISCUSSION

hTau^{V337M} Knock-in Flies Show Degeneration and Locomotion Deficits

To investigate mechanisms by which mutations in Tau lead to pathology, we generated two knock-in lines in which dTau was replaced by the coding region of either normal hTau (hTau^{WT}) or FTDP-17-associated hTau^{V337M}. We confirmed the removal of dTau and correct insertion of the hTau sequence into the endogenous dTau gene in both knock-in lines by PCR (data not shown) and Western blots (**Supplementary Figure S2A**). We also confirmed that hTau is expressed in the CNS by immunohistochemistry (**Supplementary Figures S2B,C**). The hTau^{V337M} mutation was first identified in a Seattle family with an autosomal-dominant pattern of inheritance (Poorkaj et al., 1998) and as the name implies, FTDP-17 affects the frontal and temporal lobes, leading to neuronal loss and brain atrophy in the patients. We therefore tested whether we could detect degenerative phenotypes in aged heterozygous flies expressing hTau^{V337M}. Whereas we did not detect overt signs of degeneration in toluidine-stained tissue sections from heterozygous 30-day-old hTau^{V337M}/CS (Canton S wild type, **Figure 1A**) flies, by 60-day spongiform lesions had formed, primarily in the antennal lobes (al) and the antennal mechanosensory and motor center (AMMC) of hTau^{V337M}/CS flies (arrows, **Figure 1B**). Comparing the number of vacuoles in the antennal lobes and AMMC confirmed a significant increase in 60-day-old hTau^{V337M}/CS compared to age-matched CS and hTau^{WT}/CS (**Figure 1I**). We also analyzed 60-day-old hTau^{V337M}/hTau^{WT} flies and again found more and larger vacuoles in these areas but in addition some of these flies showed a spongiform appearance over a wide area in the AMMC (arrow, **Figure 1C**) which made it difficult to identify single vacuoles. Analyzing EM sections from these flies, we found small vacuoles and empty spaces between neuronal cell bodies

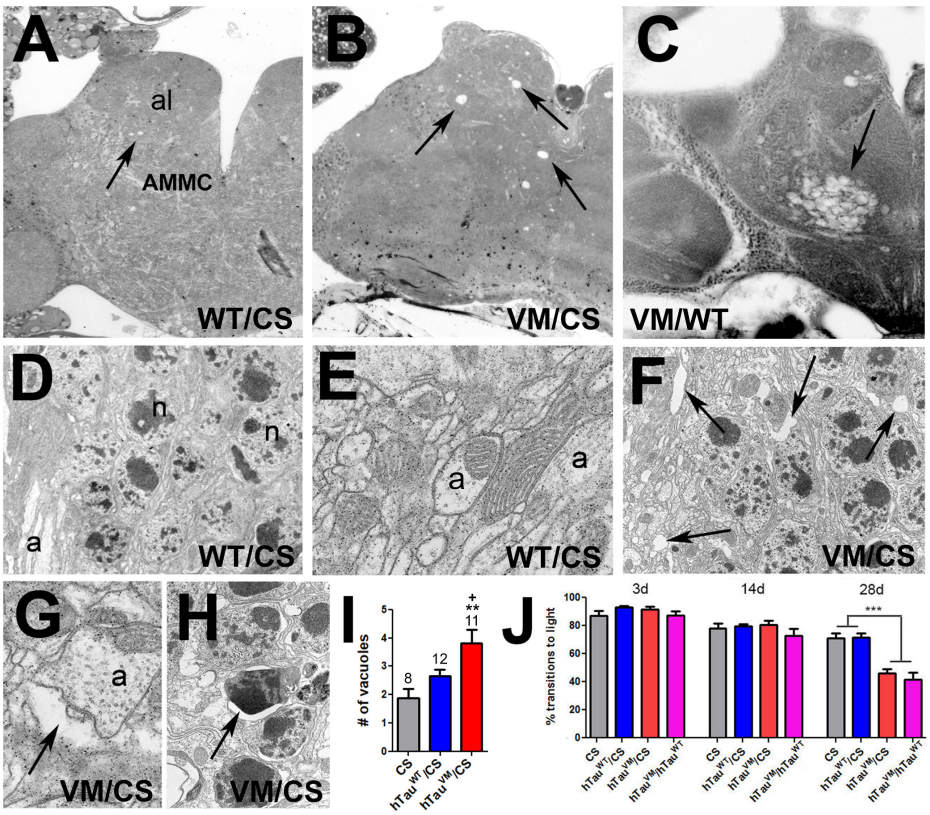

FIGURE 1 | (A) A 60-day-old hTau^{WT}/CS fly shows a few small vacuoles in the antennal lobes and AMMC (arrow). More and larger vacuoles are found in age-matched hTau^{V337M}/CS **(B)** and hTau^{V337M}/hTau^{WT} **(C)**. **(D,E)** EM images from hTau^{WT}/CS showing intact neuronal cell bodies (**D**, n = nucleus) and neurites (**E**, a = axon). **(F)** In hTau^{V337M}/CS, gaps appear between cell bodies (arrows) and around neurites (**G**, arrow). **(H)** Dark, shrunken nuclei, indicative of neuronal death, are also detectable in hTau^{V337M}/CS (arrow). **(I)** Number of vacuoles in the al and AMMC. Number of flies used indicated. **(J)** Heterozygous hTau^{V337M}/CS or hTau^{V337M}/hTau^{WT} flies show reduced locomotion when 28-day-old. At least 40 flies were tested for each genotype and age. Error bars indicate SEMs. One-way ANOVA with Dunnett's Post Test was used to compare to CS (*) and a Student's *t*-test to compare hTau^{V337M}/CS to hTau^{WT}/CS (+). $^{+}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

(arrows, **Figure 1F**) and neurites (arrow, **Figure 1G**) in 60-day-old Tau^{V337M}/CS in addition to shrinking and dying cells (arrow, **Figure 1H**). In contrast, age-matched hTau^{WT}/CS did not show these phenotypes (**Figures 1D,E**). Besides neuronal loss, prominent symptoms in FTDP-17 patients are behavioral and personality changes, as well as mobility impairments (Wszolek et al., 2006). To determine whether our model also reveals locomotion deficits, we performed fast phototaxis assays in which the flies are given 6 s to run toward a light source. Whereas no difference was detected in 3- and 14-day-old flies, hTau^{V337M}/CS performed significantly worse when aged to 4 weeks compared to hTau^{WT}/CS or CS (**Figure 1J**). A similar reduction in performance was also detected in 28-day-old heterozygous hTau^{V337M}/hTau^{WT} flies. This shows that hTau^{V337M} has dominant effects as in human patients and that it does induce locomotion deficits and degeneration in aged flies. The degeneration was most prominent in the antennal lobes and especially the AMMC, which has been show to play a role in a variety of behaviors, including social behaviors connected with courtship and locomotor responses triggered by air flow (Patella and Wilson, 2018). Whereas the behavioral deficits were already seen in mid-aged flies, the degeneration only became detectable in old flies, suggesting that changes in neuronal function may cause the locomotion deficits rather than neuronal degeneration.

hTau^{V337M} Disrupts Sleep/Activity Patterns but Not Rhythmicity

As mentioned above, increasing evidence link Tauopathies with sleep and other circadian disruptions (Musiek and Holtzman, 2016). We therefore analyzed activity and sleep patterns in the knock-in flies. Compared to CS, both 5-day-old hTau^{WT}/CS and hTau^{V337M}/CS flies kept in 12:12 light/dark (LD) cycles showed an increase in activity. However, hTau^{V337M}/CS was also significantly more active than hTau^{WT}/CS (**Figures 2A–C,F**), especially during the late night (arrow in **Figure 2C**). When 35-day-old, all the flies were less active but again both knock-in flies were hyperactive compared to CS. At this age hTau^{V337M}/CS was not significantly different from hTau^{WT}/CS (**Figures 2D,E,G**). As shown in **Figure 1J**, hTau^{V337M}/CS flies showed a significant decline in the fast phototaxis assays at this age and we therefore assume that the reduced locomotion at this age is preventing

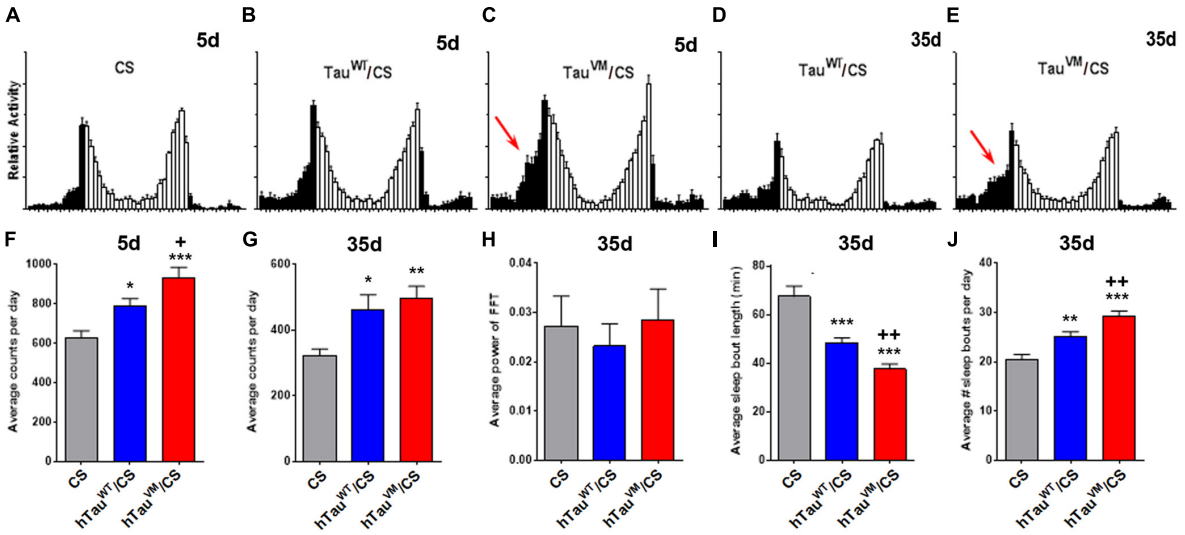

FIGURE 2 | (A–E) Activity patterns show increased activity toward the end of the night (black bars) in 5- and 35-day-old hTau^{V337M}/CS (arrows in **C,E**). **(F)** Counting the activity bouts per day shows an increase in 5-day-old hTau^{WT}/CS and hTau^{V337M}/CS compared to CS (asterisks) but hTau^{V337M}/CS is also significantly more active than hTau^{WT}/CS (plus sign). **(G)** At 35-day hTau^{WT}/CS and hTau^{V337M}/CS are more active than CS but no significant difference is found between hTau^{WT}/CS and hTau^{V337M}/CS. **(H)** Behavioral rhythmicity is not altered in hTau^{WT}/CS or hTau^{V337M}/CS. **(I,J)** Sleep is fragmented in 35-day-old hTau^{WT}/CS and hTau^{V337M}/CS compared to CS but hTau^{V337M}/CS also shows significantly shorter and more sleep bouts than hTau^{WT}/CS. * one-way ANOVA with Dunnett's Post Test comparing the hTau/CS lines to CS. $^{+}$Student's *t*-test comparing hTau^{WT}/CS and hTau^{V337M}/CS. $n > 22$. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{+}p < 0.05$, $^{++}p < 0.01$.

hyperactivity in 35-day-old hTau^{V337M}/CS. Maintaining the flies in constant darkness showed that hTau^{V337M} did not affect circadian behavioral rhythmicity when 5-day-old (data not shown) or 35-day-old (**Figure 2H**). The free-running period was 24.1 h for hTau^{V337M}/CS and 23.9 h for hTau^{WT}/CS. The % rhythmic was 84.4% for hTau^{V337M}/CS and 82.9% for hTau^{WT}/CS. Analyzing the sleep pattern of these flies by measuring sleep bout length and number of sleep bouts, we did not find any differences in 5-day-old flies (data not shown). However, 35-day-old knock-in flies showed a shorter sleep bout length with hTau^{V337M}/CS being significantly worse than hTau^{WT}/CS (**Figure 2I**). Counting the number of sleep bouts we found an increase in the average number per day and again hTau^{V337M}/CS was more affected than hTau^{WT}/CS (**Figure 2J**). Plotting the time of sleep over the day, 5-day-old flies did not show a change in daytime naps but sleep was reduced during the end of the night (more prominently in hTau^{V337M}/CS, **Supplementary Figure S3A**), consistent with the increased activity observed during that time. This was also detectable in 35-day-old hTau^{V337M}/CS flies which in addition showed a decrease in daytime naps in the morning while hTau^{WT}/CS flies did not (**Supplementary Figure S3B**). Together, these results show that both hTau expressing lines do affect the sleep pattern compared to CS. That hTau^{WT}/CS also showed changes in the sleep pattern may be due to it not being completely able to substitute for *Drosophila* dTau. This is supported by the recent finding that the loss of dTau reduces sleep and increases activity (Arnes et al., 2019). Furthermore, we found that also haploinsufficiency by using a dTau knock-out-line (Burnouf et al., 2016), impaired the sleep pattern (**Supplementary Figure S3C**) and induced hyperactivity when tested at 5-day (**Supplementary Figure S3D**). However, hTau^{V337M} was significantly worse than hTau^{WT}, showing that the mutation does impair the function of Tau in regulating sleep.

Axonal Terminals of Central Pacemaker Neurons Are Altered in Tau^{V337M}/CS Flies

As described above, hTau^{V337M}/CS flies show increased wakefulness during the late evening and in the morning. Morning activity is largely determined by the small ventrolateral neurons (sLNvs) that express the Pigment dispersing factor (PDF) (Tataroglu and Emery, 2014; Guo et al., 2018). The sLNvs form a small group of neurons, with four neurons in each hemisphere, that send their axons in a well described pattern to the dorsomedial protocerebrum (arrows, **Figure 3A**) (Helfrich-Forster et al., 2007; Tomioka and Matsumoto, 2009). We therefore tested whether the changes in the activity/rest pattern in hTau^{V337M}/CS could be due to effects on the PDF neurons. Expressing mCD4-GFP with *Pdf*-GAL4 revealed the normal arborization pattern in 30-day-old CS and in hTau^{WT}/CS (**Figures 3A–D**). However, 30-day-old hTau^{V337M}/CS flies showed an increase in branching in the termination field (**Figures 3E,F**, arrow) and some axons that extended beyond their normal target area (arrowhead). To determine whether this correlates with alteration in the cytoskeleton, we expressed GFP-tubulin via *Pdf*-GAL4. We also analyzed 5- and 30-day-old flies to address whether this phenotype is progressive. As expected, 5- and 30-day-old CS flies showed the normal projection pattern (**Figures 3G,H**) and so did 5-day-old hTau^{WT}/CS flies (**Figure 3I**). When 30-day-old, hTau^{WT}/CS occasionally showed elongated projections (arrowhead, **Figure 3J**). In contrast, in hTau^{V337M}/CS some axons extended beyond their target area

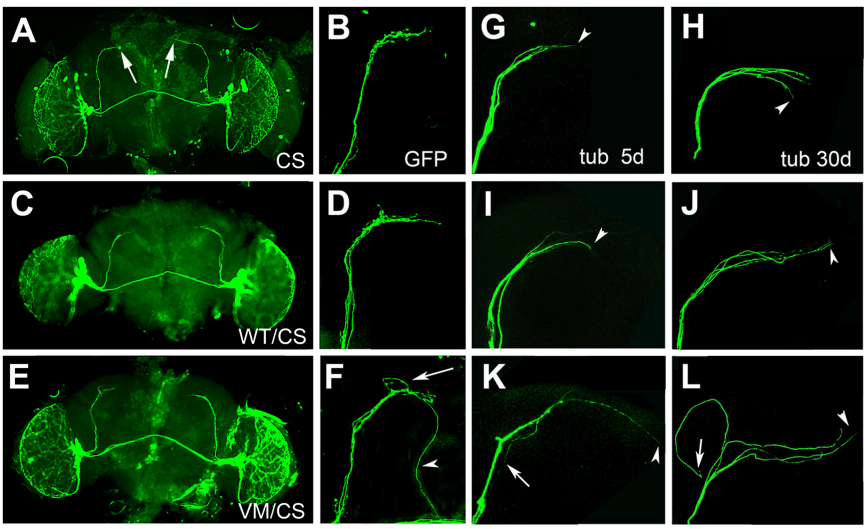

FIGURE 3 | (A–F) mCD4-GFP expressed via *Pdf*-GAL4 in 30-day-old flies. CS **(A,B)** and heterozygous hTau^{WT}/CS **(C,D)** show the normal axonal pattern. **(E,F)** In hTau^{V337M}/CS the branching in the target area appears more spread out (arrow in **F**) and some axons are elongated (arrowhead). **(G–L)** GFP-tubulin expression via *Pdf*-GAL4. Termination area of PDF neurons in 5-day **(G)** and 30-day-old CS **(H)**. hTau^{WT}/CS also show the regular pattern when 5-day-old **(I)** but occasionally extended axons are detected when 30-day-old (**J**, arrowhead). **(K)** hTau^{V337M}/CS show elongated (**K**, arrowhead) and misrouted (arrow) axons already when 5-day-old. **(L)** In a 30-day-old hTau^{V337M}/CS fly, three of the axons extend beyond the target area (arrowhead), while another one turned into the opposite direction (arrow).

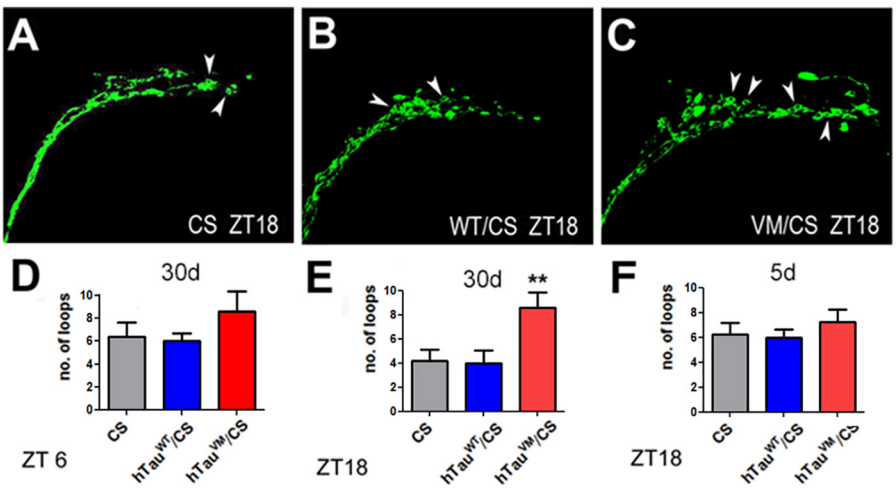

FIGURE 4 | EB1-GFP loops (arrowheads) in the axonal terminals of PDF neurons of 30-day-old CS **(A)**, hTau^{WT}/CS **(B)**, and hTau^{V337M}/CS **(C)**. Preparations were obtained at ZT 18. Counting the number of loops in 30-day-old flies showed no difference at ZT6 **(D)** but at ZT18 the number of loops was increased in hTau^{V337M}/CS compared to controls **(E)**. When 5-day-old, hTau^{V337M}/CS did not show an increase in EB1-positive loops at ZT18 **(F)**. 10 flies were analyzed for each bar. One-way ANOVA with a Dunnett's Multiple Comparison's test used. *$p < 0.05$, **$p < 0.01$.

already when 5-day-old (arrowhead, **Figure 3K**) while others turned back toward the cell bodies (arrow, **Figure 3K**). This phenotype became more prominent at 30-day, with most axons extending beyond their termination field (arrowhead, **Figure 3L**) or turning into different directions (arrow). The phenotype appeared stronger when expressing GFP-tubulin compared to mCD4-GFP, suggesting that the expression of additional tubulin promotes this phenotype. To quantify these changes, we grouped the terminals into three categories; normal, increased branching, and elongated and found that about 90% of the terminals in 30-day-old hTau^{V337M}/CS fell into the latter two groups (**Supplementary Figure S4**). Because *in vitro studies* showed that the V337M mutation impaired its function in stabilizing microtubules (Hasegawa et al., 1998; Hong et al., 1998), we analyzed microtubules size in EM sections. While we did find an increase in the mean cross-sectional area of microtubules in 60-day-old hTau^{V337M}/hTau^{V337M} flies compared to CS or hTau^{WT}/hTau^{WT}, this was only the case when homozygous

(**Supplementary Figure S5A**) but not when heterozygous (**Supplementary Figure S5B**). Although this confirms an effect of the mutation on the microtubules-stabilizing function *in vivo*, this does not seem to play a role in heterozygotes and therefore the changes in the axonal morphology of PDF neurons in hTau^{V337M}/CS are not caused by effects on microtubule formation or stability.

Tau^{V337M} Interferes With Circadian Changes in the Morphology of PDF Neurons

The PDF neurons regulate sleep as part of a network (Guo et al., 2018) and the changes in the termination pattern of the PDF neurons could therefore interfere with their connectivity with other neurons. PDF neurons show daily fluctuations in their connectivity, whereby synapses are potentiated during the day and altered or downscaled during sleep, a process generally referred to as "synaptic homeostasis" (Tononi and Cirelli, 2003, 2014). Remodeling of synapses requires cytoskeletal changes and it has been shown that the end-binding protein 1 (EB1), needed for microtubules to grow at their plus ends (Akhmanova and Steinmetz, 2010), accumulates in loops around forming synapses (Wang et al., 2007; Stone et al., 2008; Conde and Caceres, 2009). To determine whether hTau^{V337M} interferes with the cytoskeletal changes required for synaptic homeostasis of the PDF neurons, we expressed EB1-GFP via *Pdf*-GAL4 in PDF neurons and counted the number of loops in the terminals of the sLNvs (arrowheads, **Figures 4A–C**). Counting loops during the day (ZT5-6) in 30-day-old flies did not reveal a significant difference, although the number was slightly higher in hTau^{V337M}/CS (**Figure 4D**). However, counting during the night (ZT17-18) when the PDF neurons normally show less complexity and a reduced number of synapses (Fernández et al., 2008; Gorostiza et al., 2014), a significant increase in loops was detected in hTau^{V337M}/CS compared to controls (**Figure 4E**). As expected, the number of loops was decreased in the controls; from 6.4 to 4.2 in CS and from 6.0 to 4.0 in hTau^{WT}/CS however, in hTau^{V337M}/CS the mean number of loops was the same during the night as during the day (8.6). Lastly, to determine whether this phenotype is affected by age, we counted loops in 5-day-old flies at ZT17-18. Because we did not detect a significant difference in hTau^{V337M}/CS flies compared to the controls (**Figure 4F**), the effect on synaptic homeostasis appears to increase with age, correlating with the progressively worsening sleep fragmentation.

Together, our findings suggest that the disease-associated hTau^{V337M} has a reduced ability to support the cytoskeletal changes that are required for the day/night synaptic adaptations of PDF neurons. Over time, this results in a failure to downscale synapses during the night, thereby affecting the connectivity within the sleep circuit. This failure of synaptic homeostasis and appropriate changes in connectivity would then cause the sleep disruptions and hyperactivity. In addition to the sleep disruptions, we also detected locomotion deficits. While we do not think that this phenotype is due to the changes in PDF neurons it may also be caused by altered synaptic contacts of neurons that regulate locomotion. Similarly it remains to be determined whether cytoskeletal changes eventually lead to the degeneration.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

MC generated the knock-in lines and performed the fast phototaxis and immunohistochemical experiments as well as Western blots. AL also performed Western blots, fast phototaxis experiments, and tissue sections. EC performed the activity and sleep experiments. MC, JG, and DK designed and analyzed the experiments. DK wrote the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2020.00232/full#supplementary-material

FIGURE S1 | (A) Schematic of the knock-in approach. **(B)** Sequence of the used guide RNAs (highlighted in yellow). The 5' guide is localized in exon 1 and the 3' guide in exon 5 relating to isoform H (which contains the first and last exon in the dTau coding region).

FIGURE S2 | (A) Whereas no dTau (upper panel) is detectable in the homozygous knock-in lines, they do express hTau (lower panel). α-GAPDH was used as loading control. Immunohistochemistry showing hTau in the CNS of hTau^{WT} flies **(C)** but not in wild type CS **(B)**. Flies were 1–3-day-old.

FIGURE S3 | (A) Nighttime sleep is shortened in 5-day-old hTau^{V337M}/CS compared to hTau^{WT}/CS and CS (arrow). **(B)** 35-day-old hTau^{V337M}/CS also show shortened nighttime sleep (arrow) and less rest periods at the beginning of the day (arrowhead). **(C)** Like hTau^{WT}/CS and hTau^{V337M}/CS, 35-day-old dTau^{KO}/CS show less naps during the end of the day (arrowhead). **(D)** 5-day-old dTau^{KO}/CS flies are more active than CS. At least 30 flies analyzed. Mean and SEM indicated. Statistics done with Student's *t*-test. $^{**}p<0.01$.

FIGURE S4 | Average percentage of GFP-tubulin labeled PDF terminals with normal (lower part), more spread out (middle) or elongated axons (upper) in CS, hTau^{WT}/CS, and hTau^{V337M}/CS. Ten 30-day-old flies analyzed for each genotype.

FIGURE S5 | (A) Microtubule size, measured as cross sectional area, is increased in 60-day-old homozygous $hTau^{V337M}$ compared to $hTau^{WT}$ and CS. **(B)** Microtubules size is not different from controls in heterozygous $hTau^{V337M}$/CS. Between 52 and 123 microtubules were analyzed from at least 50 neurites from 3 flies for each genotype. Horizontal lines are medians; boxes are 25 and 75% quartiles; whiskers are 10 and 90% quantiles. Statistics done with one-way ANOVA and a Dunnett's Multiple Comparison's to compare means. $*p<0.05$.

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Sleep Electroencephalographic Response to Respiratory Events in Patients With Moderate Sleep Apnea–Hypopnea Syndrome

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Sleep apnea–hypopnea syndrome is a common breathing disorder that can lead to organic brain injury, prevent memory consolidation, and cause other adverse mental-related complications. Brain activity while sleeping during respiratory events is related to these dysfunctions. In this study, we analyzed variations in electroencephalography (EEG) signals before, during, and after such events. Absolute and relative powers, as well as symbolic transfer entropy (STE) of scalp EEG signals, were calculated to unveil the activity of brain regions and information interactions between them, respectively. During the respiratory events, only low-frequency power increased during rapid eye movement (REM) stage (δ-band absolute and relative power) and N1 (δ- and θ-band absolute power, δ-band relative power) sleep. But absolute power increased in low- and medium-frequency bands (δ, θ, α, and σ bands), and relative power increased mainly in the medium-frequency band (α and σ bands) during stage N2 sleep. After the respiratory events, absolute power increased in all frequency bands and sleep stages, but relative power increased in medium and high frequencies. Regarding information interactions, the β-band STE decreased during and after events. In the γ band, the intrahemispheric STE increased during events and decreased afterward. Moreover, the interhemisphere STE increased after events during REM and stage N1 sleep. The EEG changes throughout respiratory events are supporting evidence for previous EEG knowledge of the impact of sleep apnea on the brain. These findings may provide insights into the influence of the sleep apnea–hypopnea syndrome on cognitive function and neuropsychiatric defects.

Keywords: sleep apnea–hypopnea syndrome, respiratory events, electroencephalography, symbolic transfer entropy, effective connectivity

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INTRODUCTION

Sleep apnea–hypopnea syndrome (SAHS) is a breathing disorder characterized by partial or complete closure of the upper airways during sleep (Torabi-Nami et al., 2015; Liu et al., 2018). In addition to suffering from fatigue, fragmented sleep, and cardiovascular diseases, extensive evidence shows that major brain changes occur in SAHS patients. For instance, a magnetic resonance

imaging study revealed that the gray matter volume of patients with obstructive sleep apnea (OSA) increased in the insula, primary motor cortices, brainstem, left premotor cortex, cerebellum, and left hippocampus, whereas it decreased in the prefrontal cortex, right posterior cingulate cortex, occipital lobe, amygdala, and left cerebellar cortex (Fatouleh et al., 2014). Furthermore, OSA can impair the white matter integrity, which is related to disease severity (Chen et al., 2015). Some similar changes can be found in patients with depression (Grieve et al., 2013), for which SAHS may be a risk factor (Kerner and Roose, 2016). In addition, clear differences in various sleep-related electroencephalography (EEG) patterns have been found in SAHS patients (Carvalho et al., 2014; Sun et al., 2018). Sleep fragmentation, recurrent hypoxia, and cortical arousal induced by apnea events have been associated with these EEG variations (Carvalho et al., 2014; Fatouleh et al., 2014; Chen et al., 2015; Sun et al., 2018) and may interrupt the removal of metabolic waste products from the brain by cerebrospinal fluid, which affects cognitive function (Fultz et al., 2019). Therefore, the study of brain activity during apnea can provide insights on brain dysfunction due to SAHS and related complications.

Polysomnography is considered as the gold standard for SAHS diagnosis, and the related EEG signals are essential for studying the dynamic changes of cortical activity. Four main frequency bands have been defined in EEG, namely, delta δ, theta θ, alpha α, and beta β (Schumacher et al., 2015; Wang et al., 2016), whereas sigma σ waves, which are relevant to study sleep spindles, have been related to memory consolidation and sensory processing (Holz et al., 2012; Barakat et al., 2013). In addition, gamma γ waves are related to cognitive functions, such as attention (Tombor et al., 2018), object recognition (Basar et al., 2000), semantic processes (He et al., 2018), and memory match and utilization (Herrmann et al., 2004). Sleep stages are related to respiratory events reaction, as they affect respiratory and muscle control (McSharry et al., 2013; Carberry et al., 2016). In previous studies, we found that the EEG spectral power during apnea–hypopnea is related to secondary respiratory events (Huang et al., 2018) and end-apneic cortical arousal (Yan et al., 2016), and thus sleep stages also influence cortical responses. Although spectral power variations during respiratory events have been studied (Dingli et al., 2002; Xavier et al., 2007; Yang et al., 2012), a thorough analysis during sleep stages and including high-frequency components is still required to resolve conflicting findings.

In many cases, brain activity originates from interactions that are regionally separate but functionally integrated. Two types of measures can be applied to evaluate interactions among regions. Functional connectivity is the temporal correlation among brain regions, while effective connectivity describes the dynamic causal influence of one neural system on another (Greenblatt et al., 2012). A previous study revealed that effective connectivity reflects the functional interactions of neurons in different areas (Brovelli et al., 2004). Symbolic transfer entropy (STE), a concept from information theory, is a common measure of effective connectivity given its robustness and fast computation (Staniek and Lehnertz, 2008). STE has been widely applied in EEG studies, including the effects of anesthesia on information processing in the brain (Jordan et al., 2013), interhemispheric information flow in sleep after stroke (Zubler et al., 2018), and analysis of epileptic networks (Lehnertz and Dickten, 2015). However, neither STE nor other effective connectivities have been thoroughly evaluated during respiratory events.

In this study, we investigated the impacts of apnea–hypopnea on the EEG power spectrum and STE at various frequency bands across sleep stages. We expect to provide insights and establish EEG biomarkers for brain dysfunction in patients with SAHS.

METHODS

Participants

Only patients with moderate SAHS were included in this study, because patients with mild SAHS did not provide enough event samples for statistical analysis, and the short interval between events in severe SAHS patients hindered the evaluation of independent events. Fifty-seven patients diagnosed with moderate SAHS (apnea–hypopnea index between 15 and 30) and without neurological or psychological complications were enrolled in this study. The patients' clinical characteristics are listed in **Table 1**. All the participants visited the recording room and laboratory surroundings and provided written informed consent 2 h before formal overnight polysomnography recordings at the Sleep-Disordered Breathing Center from the Sixth Affiliated Hospital of Sun Yat-sen University. No participant was taking medication that would interfere with respiratory control or psychophysiological conditions. This study was approved by the Ethics Committee of the Sixth Affiliated Hospital.

Selection of Respiratory Events

Scalp EEG signals (F3, F4, C3, C4, O1, and O2) following the 10–20 system and sampled at 500 Hz were acquired from overnight polysomnography. Reference electrodes were placed on contralateral auricle, and a ground electrode was on Fpz according to the recommendation of the American Academy of

TABLE 1 | Patients' demographics and general health indices.

Characteristic	Mean ± SD
Age (years)	49.53 ± 12.38
Gender (male/female)	46/11
BMI (kg/m^2)	26.52 ± 3.71
AHI (events/h)	21.46 ± 4.57
ESS	7.86 ± 4.80
TST (min)	378.10 ± 83.60
N1 sleep (% NREM)	32.24 ± 16.79
N2 sleep (% NREM)	55.08 ± 15.50
N3 sleep (% NREM)	12.68 ± 8.68
REM sleep (% TST)	15.66 ± 7.21
ODI (times/h)	23.87 ± 7.22

SD, standard deviation; BMI, body mass index; AHI, apnea–hypopnea index; ESS, Epworth Sleepiness Scale; TST, total sleep time; ODI, oxygen desaturation index ≥ 3%.

Sleep Medicine Scoring Manual (AASM). Electrode impedances were kept below 5 kΩ, and a 50-Hz notch filter was applied. Sleep stages and respiratory events were strictly verified by an experienced sleep physiologist, who was not aware of the study goal, following the AASM (Berry et al., 2017).

As sleep stages are relevant in this study, we only included respiratory events occurring within a single stage. In addition, events that did not have sufficient time intervals (<20 s) were excluded to consider the clear influence of independent events. Events included central sleep apnea (CSA), hypopnea, and OSA. Wakefulness and N3 sleep were not investigated in this study because their individual sample sizes were insufficient to conduct statistical analyses. Furthermore, EEG segments contaminated by electrode artifacts or limb movements were excluded. Overall, a total of 2804 respiratory events (2676 hypopnea/OSA and 128 CSA events) were obtained from all the participants. The distribution of sleep stages and durations are listed in **Table 2**.

TABLE 2 | Duration of apnea–hypopnea events.

Sleep stage	Number of apnea events	Duration (s) median (5%–95%)
N1	968	19 (11.5–36.5)
N2	1080	19.5 (12–35.5)
REM	756	22 (12–48)

Six EEG time segments of 5 s were investigated per event. A sample segment is shown in **Figure 1**. B1 and B2 (before event) indicate segments before apnea–hypopnea onset in chronological order (1 precedes 2). D1 and D2 (during event) indicate segments in the middle of the apnea–hypopnea, and A1 and A2 (after event) indicate segments immediately after apnea–hypopnea termination.

EEG Preprocessing and Spectral Power Estimation

Recursive least squares (RLS) was applied to remove electrocardiograph artifacts and wavelet threshold denoising was subsequently conducted. The power spectral density of each segment was determined by Burg autoregressive estimation with 1-s Hamming windows, where the order of the autoregressive model was obtained using the Akaike information criterion (Liu et al., 2016). Then, the relative power of each sub-band was calculated by normalization to the whole frequency band (0.5–50 Hz). Six sub-bands were analyzed: δ (0.5–4 Hz), θ (4–8 Hz), α (8–12 Hz), σ (12–15 Hz), β (15–30 Hz), and γ (30–50 Hz). In addition, an infinite impulse response bandpass filter was used to estimate the STE in different frequency bands. The calculations were implemented in MATLAB R2018b (MathWorks, Natick, MA, United States). A flow diagram of the signal processing and analysis is depicted in **Figure 2**.

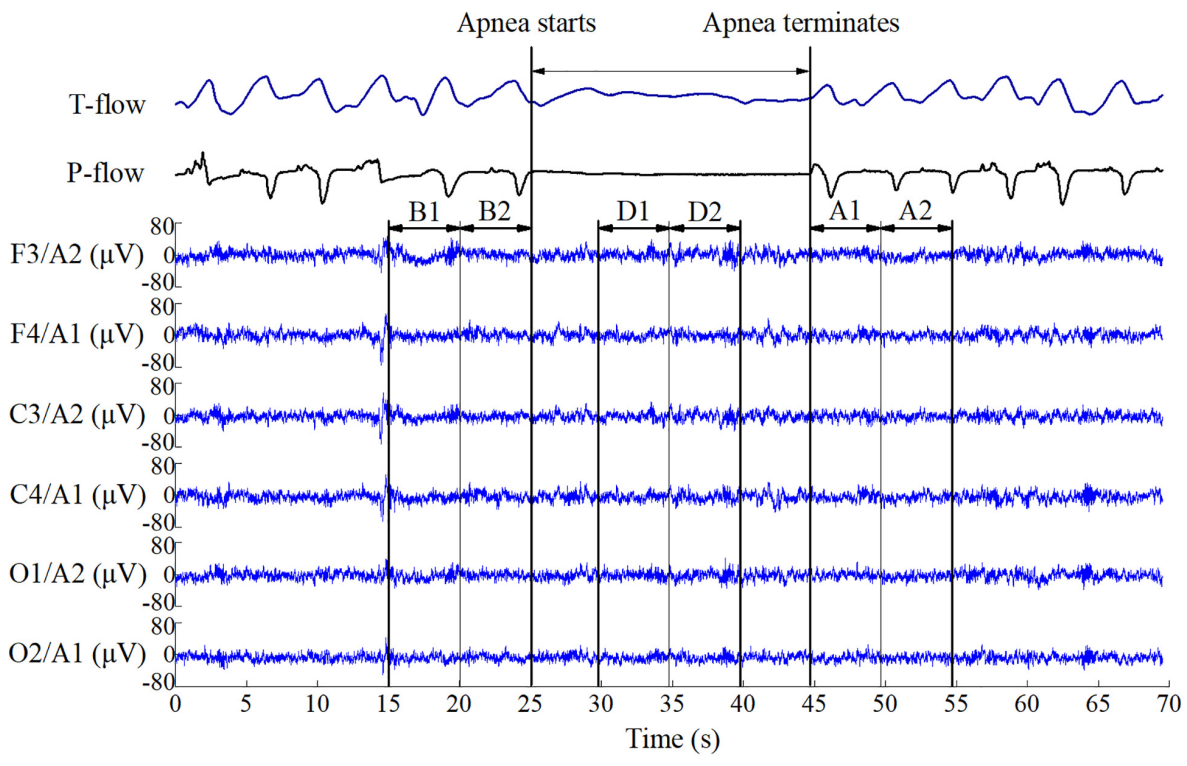

FIGURE 1 | Electroencephalography data segments used for event analysis. B1 and B2 indicate segments before respiratory apnea–hypopnea events; D1 and D2 indicate segments during apnea–hypopnea events; A1 and A2 indicate segments immediately after apnea–hypopnea termination. The duration of each segment is 5 s.

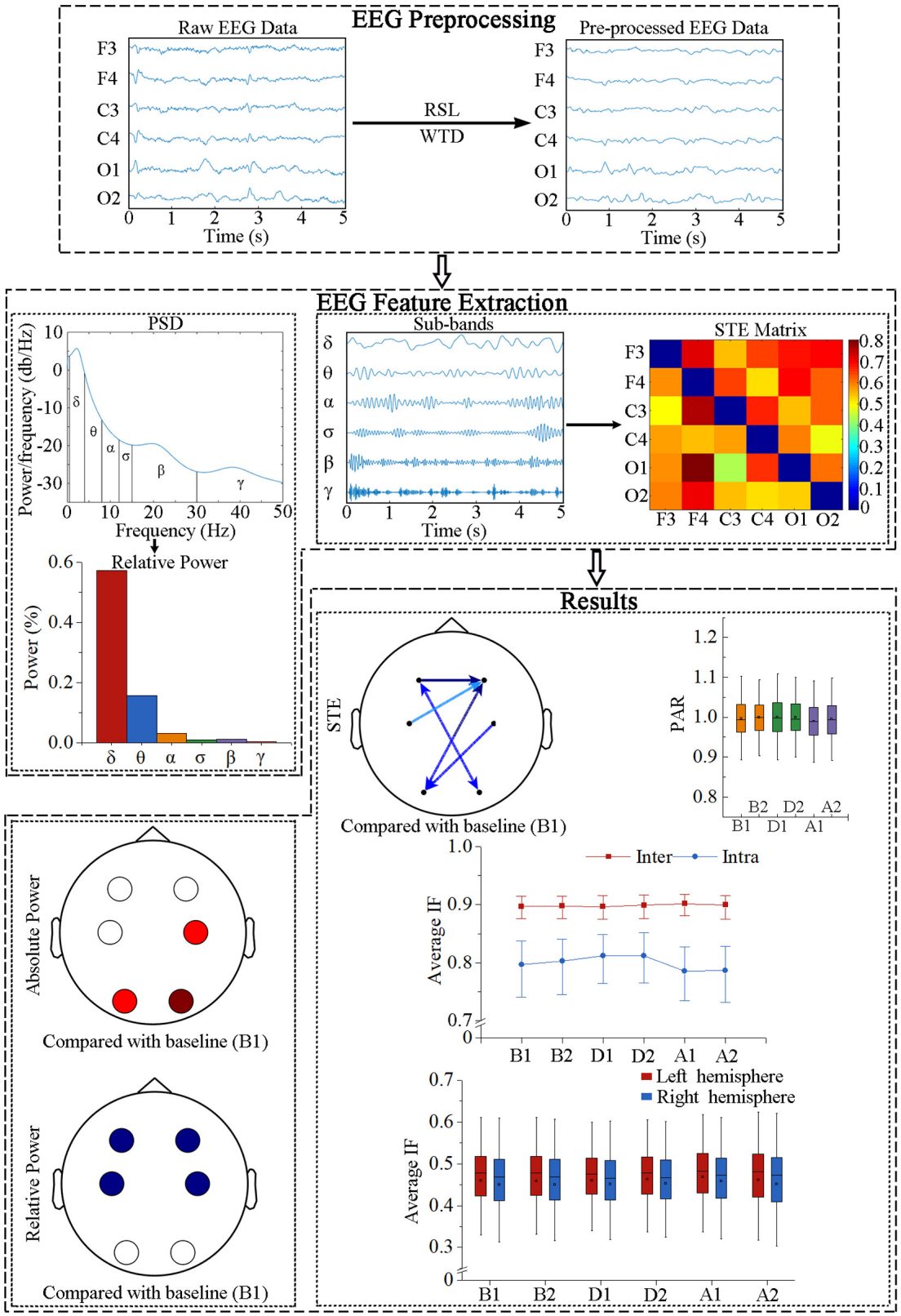

FIGURE 2 | Flow diagram of EEG data processing. RLS, recursive least squares; WTD, wavelet threshold denoising; PSD, power spectral density; STE, symbolic transfer entropy; PAR, posterior-to-anterior ratio; IF, information flow.

STE Estimation

To determine the directed information flow between EEG regions, STE was estimated based on the transfer and permutation entropies (Staniek and Lehnertz, 2008). Transfer entropy measures causal influence between two signals. Assuming a causal relation between source signal Y and target signal X, signal prediction would be improved by adding both its own past information and that of the target signal (Numan et al., 2017):

$$TE_{YX} = \sum p\left(X_t,\ X_{t-\delta},\ Y_{t-\delta}\right) \log\left(\frac{p\left(X_t|X_{t-\delta},\ Y_{t-\delta}\right)}{p\left(X_t|X_{t-\delta}\right)}\right)$$

Permutation entropy adopts the symbolization introduced by Bandt and Pompe (2002). For a random one-dimensional time series $x(t)$, $t = 1, 2, \ldots, T$, an m-dimensional vector $X_t = \left[x\left(t\right),\ x\left(t+l\right),\ \ldots,\ x\left(t+(m-1)\,l\right)\right]$ is obtained by taking m consecutive points spaced by l. The amplitude values are arranged in ascending order $[x(t+(j_1-1)l) \leq x(t+(j_2-1)l) \leq \ldots \leq x(t(j_m-1)l)]$, and the symbol is defined as $\hat{x}_t = \left[j_1,\ j_2,\ \ldots, j_m\right]$. Each X_t is uniquely mapped onto one of the $m!$ possible permutations. The STE is thus expressed as (Lehnertz and Dickten, 2015)

$$STE_{yx} = \sum p\left(\hat{x}_t,\ \hat{x}_{t-\delta}, \hat{y}_{t-\delta}\right) \log\left(\frac{p\left(\hat{x}_t|\hat{x}_{t-\delta}, \hat{y}_{t-\delta}\right)}{p\left(\hat{x}_t|\hat{x}_{t-\delta}\right)}\right)$$

Let embedding dimension $m = 5$ and time delay $l = 62, 31, 18, 16, 8, 4$, corresponding to bands δ, θ, α, σ, β, and γ, respectively (Li et al., 2017). Time lag δ = 20 reflects corticocortical information flow in EEG signals (Untergehrer et al., 2014). Additionally, the posterior-to-anterior ratio (PAR) was introduced to evaluate the continuity of direction of information flow (Numan et al., 2017):

$$dSTE_{xy} = \frac{STE_{xy}}{STE_{xy} + STE_{yx}},$$

$$\mathrm{PAR} = \frac{\left\{\overline{\mathrm{dSTE}}_{xy}\right\}_{\mathrm{posterior}}}{\left\{\overline{\mathrm{dSTE}}_{xy}\right\}_{\mathrm{anterior}}}.$$

When the information flow direction is posterior-to-anterior, PAR > 1, whereas the opposite direction retrieves 0 < PAR < 1, and a balanced direction retrieves PAR = 1.

Statistical Analysis

The absolute power and STE were normalized from 0 to 1 by min–max normalization for six frequency bands and three sleep stages per participant. Both measures and relative power were tested for normality using the Shapiro–Wilk test and for variance homogeneity using Levene test. The samples did not satisfy any test. Therefore, data were presented as interquartile range (first quartile, median, and third quartile) and compared by the Friedman test with Bonferroni correction for *post hoc* analysis. In every segment, 30 directional transmissions were computed by STE, and absolute power and relative power were calculated in six regions per sub-band. The six sets of characteristic changes between segments B1, B2, D1, D2, A1, and A2 were analyzed during different sleep stages and frequency bands: (1) absolute power across regions, (2) relative power across regions, (3) 30 STEs, (4) mean intrahemispheric information flow, (5) mean interhemispheric information flow, and (6) PAR changes. For these sets, the significance level was adjusted as $p < 0.05/C_6^2$. The mean left- and right-hemispheric information flows were also compared in every respiratory event. In this case, the significance level was $p < 0.05/C_{12}^2$. These analyses were performed on the IBM SPSS statistics software version 22.0 (New York, NY, United States).

RESULTS

Spectral Power

Absolute power (AP) and relative power (RP) of EEG frequency components were used in power spectrum analysis. The variations of spectral power during respiratory events are shown in **Figure 3**, in which the values before events (B1) were used as the baseline.

Figure 3A shows that during the events (D1 and D2) AP in rapid eye movement (REM) to stage N1 and to stage N2 sleep increased gradually in relatively high-frequency bands compared to B1. In REM sleep, the significantly increasing band was δ, and which were δ and θ in N1 stage. And in N2 stage, the increasing bands contained δ, θ, α, and σ. Correspondingly, the decreasing bands were α, σ, β, and γ in REM stage, which were β and γ in N1 stage, whereas only the γ-band power significantly decreased in N2 stage. **Figure 3B** shows that the variations in RP during the events were similar in REM and N1 stage, increasing in the δ band and decreasing in α, σ, β, and γ bands. In stage N2 sleep, the increased band moved to α and σ, and the RP decreased in the β and γ bands.

The AP after the events (A1 and A2) was significantly higher than that during B1 at all the researched frequencies and sleep stages, except in stage N2 sleep during segment A2, the AP increase in the δ and θ bands nearly recovered. Regarding RP, the differences in power distribution over frequency bands and sleep stages were more obvious. First, compared to the power distribution in B1, the difference was less significant during REM sleep, followed by N1 sleep, and N2 sleep showed the most significant difference. Common changes in researched sleep stages: the RP decreased in the θ band and increased in the α band during A2 (but not all regions showed significant differences during stage N1 and REM sleep). While no other significant differences were obtained during REM sleep after events. In stage N1 and N2 sleep, segments A1 and A2 exhibited different results in the δ, β, and γ bands. Furthermore, in these frequency bands, the period of A1 seems to be a transition between D2 and A2.

The changes of AP and RP in different regions are basically the same, and differences across the frontal (F3, F4), central (C3, C4), and occipital (O1, O2) lobes occurred in some situations.

STE Changes

Information transmission between different brain regions was determined using the STE, and various response characteristics were obtained in different frequency bands (**Figure 4**). But the

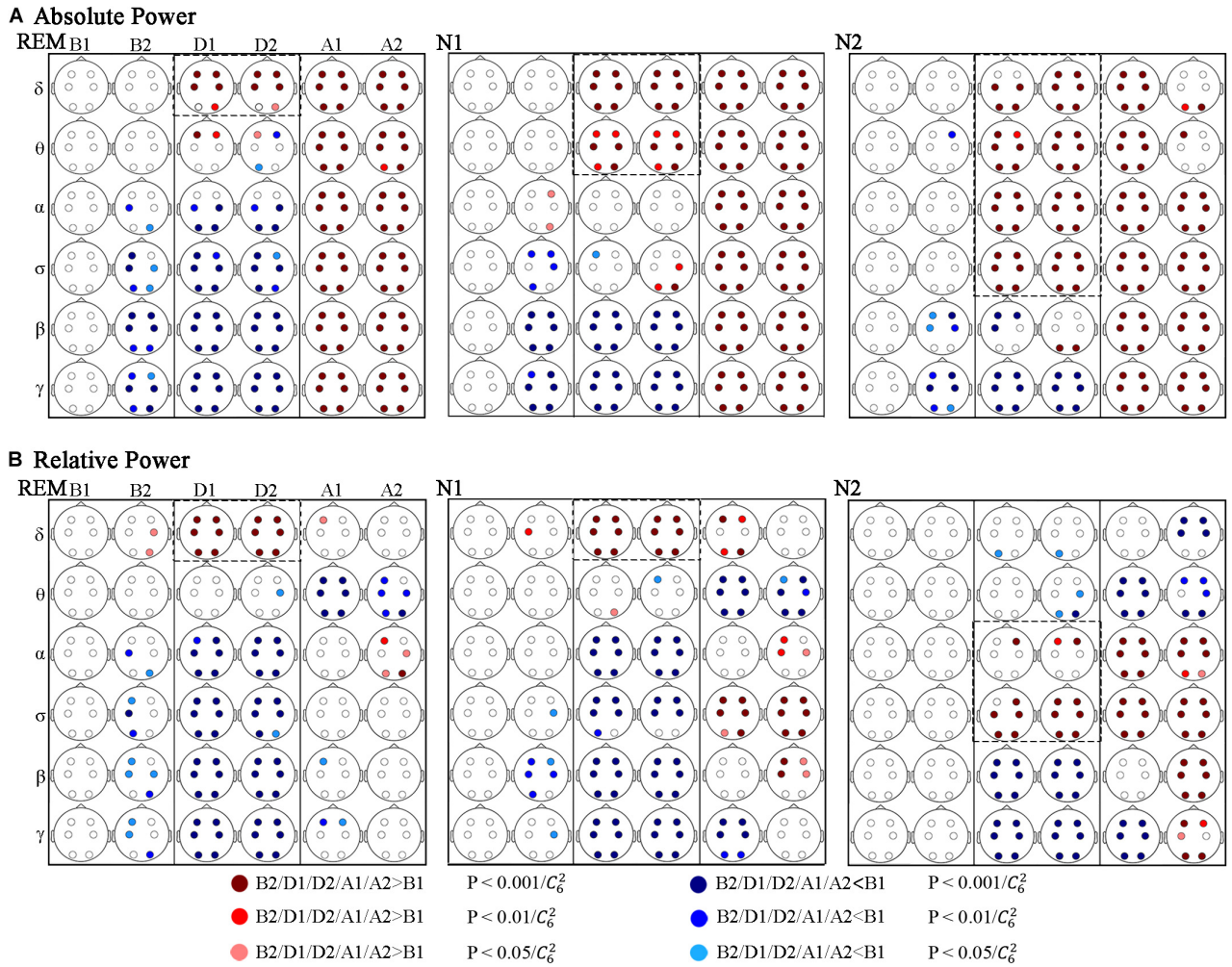

FIGURE 3 | Significant changes in spectral power across respiratory events. **(A)** Absolute and **(B)** relative power. Red and blue dots indicate a significant increase and decrease compared to B1, respectively.

responses in the θ, β, and γ bands show some similarities during the events across sleep stages.

In the θ band, the STE decreased during the events (D1 and D2), being more notable during stage N1, followed by REM sleep, and almost no significant change occurred during stage N2 sleep. The STE increased after the events (A1 and A2), and this increase continued to A2 during N2 and REM sleep. The STE from C4 to F4 increased in D2 during all three sleep stages, while most other STEs decreased during this period.

In the β band, the STE decreased from D1 to A2 in the three sleep stages. During the D1, D2, and A1 segments, the decrease was more significant during non-REM sleep (stages N1 and N2) than during REM sleep.

The intrahemispheric and interhemispheric patterns of cerebral information transmission were different in the γ band. To better describe this phenomenon, the intrahemispheric and interhemispheric information transmissions in the γ band were summarized, as shown in **Figure 5**.The intrahemispheric information flow during events (D1 and D2) was larger than that before events (B1), whereas it decreased to an even lower level after events (A1 and A2). The interhemispheric STE had an increase during the event process in the three sleep stages, but there was no significant difference between segments B1 and A2 except during the REM stage. The rise time of REM and N1 sleep occurred during A1, while that advanced to D2 during stage N2 sleep. In addition, the interhemispheric information flow across frontal (F3 and F4) and central (C3 and C4) regions increased in the A2 segment during REM sleep.

In the δ, α, and σ bands, responses after the events (A1 and A2) were mostly consistent across sleep stages: the δ-band STE decreased, which was obvious during REM sleep, followed by N2 sleep, and the least significant during stage N1 sleep. The STE changes in α and σ bands were not obvious after the events.

While in α and σ bands each stage showed its own characteristics during the events (D1 and D2), in the α band, increased STE was only observed in N1 stage. And the σ-band STE decreased during stage N1 and N2 sleep, being more notable during stage N2 sleep.

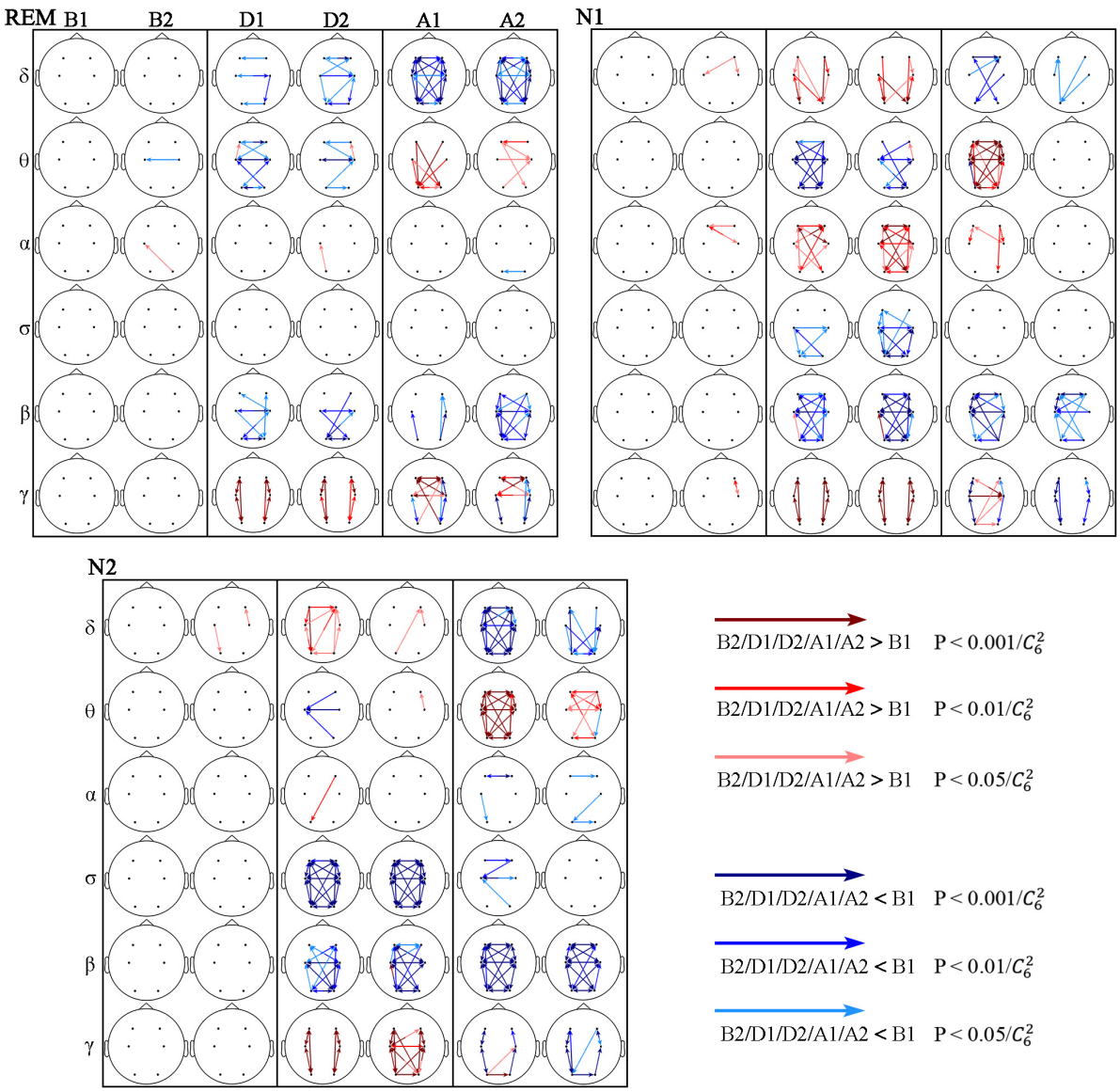

FIGURE 4 | Significant changes in STE across respiratory events. The red and blue arrows indicate STE significantly higher and lower than that during B1, respectively.

Information Flow Direction and Strength Across Respiratory Events

The anterior–posterior and left–right information flow was also estimated. Significant fluctuations in posterior–anterior information flow were found only in the θ and σ bands across events, with the θ-band PAR being smaller in A1 than that before the events during stage N2 and REM sleep (**Figure 6**). The σ-band PAR increased during the events in N2 sleep. No significant difference was obtained between segments B1 and A2, which meant these fluctuations recovered in A2.

Except for the δ and σ bands in the three sleep stages and the γ band in REM sleep, the information flow in the left hemisphere was higher than that in the right hemisphere (**Table 3** and **Supplementary Table S1**).

DISCUSSION

In this study, we investigated the short-term changes in cerebral cortex activity during respiratory events in patients with SAHS. Power spectral analysis was used to estimate activation in brain regions, and the STE was used for determining effective connectivity, revealing dynamic information interaction between brain areas. The STE is a non-linear measure that is robust, fast to compute, and noise mitigating, thus being suitable for EEG signal analysis (Thul et al., 2016; Zubler et al., 2018). Moreover, unlike previous studies, events during different sleep stages were studied independently. The results showed that the sleep stage affects the intensity and patterns of cortical responses. Even during light sleep, corresponding to stage N1 and N2 sleep, the

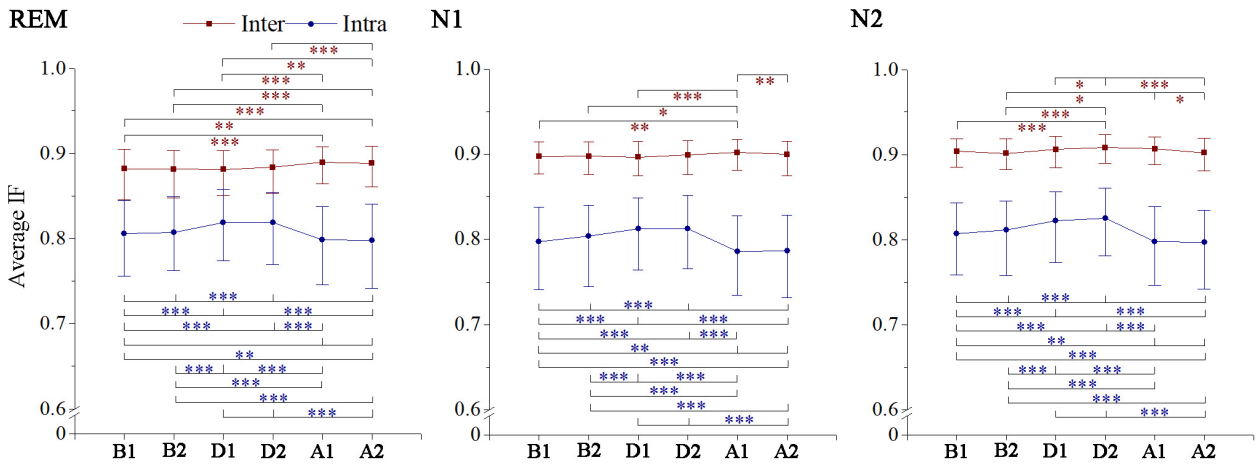

FIGURE 5 | Changes in interhemisphere and intrahemisphere average information flow in gamma band across respiratory events. IF, information flow. $^{*}p < 0.05/C_6^2$, $^{**}p < 0.01/C_6^2$, $^{***}p < 0.001/C_6^2$, Friedman test with Bonferroni correction.

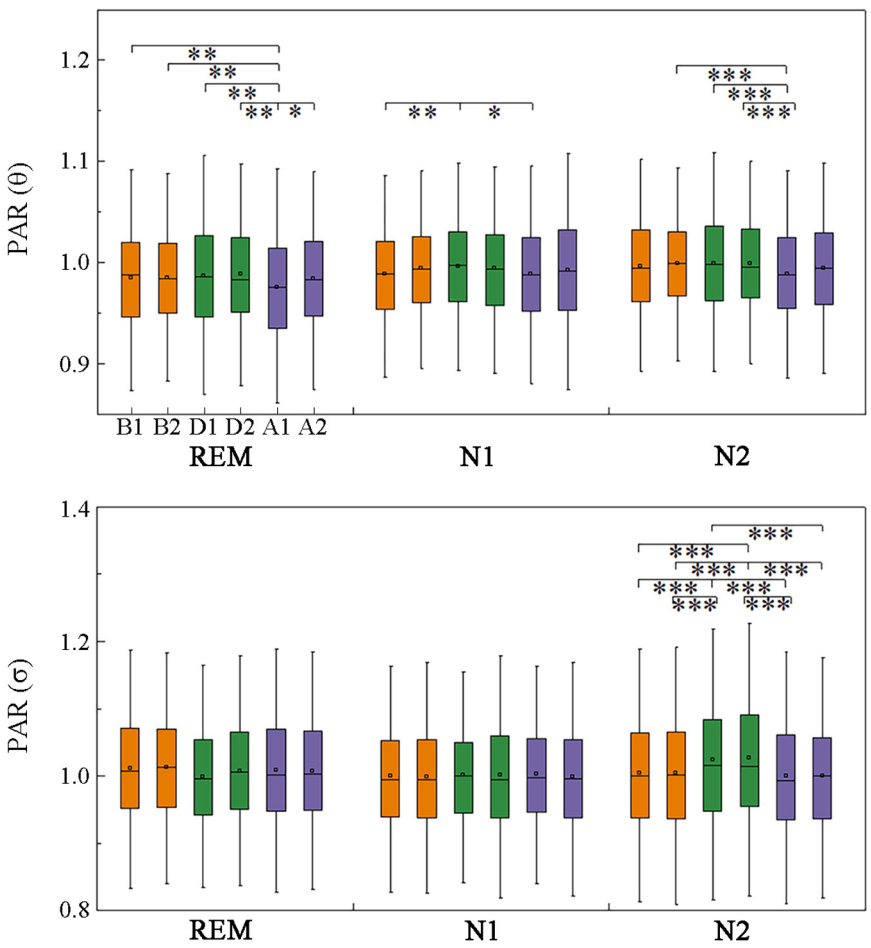

FIGURE 6 | Changes in posterior-to-anterior information flow across respiratory events. $^{*}p < 0.05/C_6^2$, $^{**}p < 0.01/C_6^2$, $^{***}p < 0.001/C_6^2$, Friedman test with Bonferroni correction.

TABLE 3 | Statistical analysis of STE between left and right hemisphere in different bands and sleep stages.

	θ Band			α Band			β Band			γ Band		
	N1	**N2**	**REM**	**N1**	**N2**	**REM**	**N1**	**N2**	**REM**	**N1**	**N2**	**REM**
B1	0.008	<0.001	0.006	0.003	<0.001	0.165	<0.001	<0.001	1	<0.001	0.005	1
B2	0.019	<0.001	0.121	0.003	<0.001	1	0.066	<0.001	1	<0.001	<0.001	1
D1	<0.001	0.003	<0.001	0.001	<0.001	1	<0.001	<0.001	0.002	<0.001	0.006	0.15
D2	0.005	<0.001	0.002	0.006	<0.001	0.005	<0.001	<0.001	<0.001	<0.001	<0.001	1
A1	0.037	<0.001	<0.001	0.829	<0.001	<0.001	1	<0.001	0.279	<0.001	0.017	0.107
A2	0.013	<0.001	0.001	0.053	<0.001	0.109	0.107	<0.001	1	<0.001	1	0.845

For demonstration, the p values are multiplied by C_{12}^2 (i.e., the significance level was already corrected by Bonferroni correction). Hence, statistical significance occurs for $p < 0.05$, which indicates that the information flow in the left hemisphere was higher than that in the right hemisphere.

performance varied. In addition, previous research conclusions about cognitive function were presented in this investigation, which may be related to some results of this study. However, the direct relationship between cognition and SAHS has not been assessed here; these results cannot be used to support these cognition conclusions, and further researches are needed.

Although the impact of respiratory events on the EEG power spectral density in patients with OSA has been reported (Dingli et al., 2002; Yang et al., 2012), the results are inconsistent, possibly due to the sample sizes, varying sample characteristics, and analysis methods. In this study, we found that the δ-band power increased during respiratory events, which is consistent with previous studies (Xavier et al., 2007). This may be related to the increased breathing effort, and higher slow-wave power has been observed before and during upper airway resistance regardless of the existence of cortical arousal (Black et al., 2000). The δ- and θ-band power increased by slight airflow restrictions during N2 sleep (Nguyen et al., 2016). Furthermore, sleep (D'Rozario et al., 2017; Appleton et al., 2019) and vigilance (Xiromeritis et al., 2011) EEG signal slowing was also discovered in patients with OSA. A reasonable speculation would be that the above EEG variations may be results of repetitive similar changes during apnea–hypopnea.

It is worth noting that during stage N2 sleep the power increased during the events not only at the δ band but also in the θ band and medium frequencies (α and σ bands). Additionally, after the events, the high-frequency relative power increased considerably. These results may be due to the frequency distribution differences in the normal EEG activity of each sleep stage. On the other hand, these may suggest that the body tends to be alert to protect itself under apnea–hypopnea during N2 sleep. In another study, the stage N2 sleep depth changed dramatically in the same individual under different conditions, which affected the overall sleep depth (Qanash et al., 2017). A more fragmented stage N2 sleep corresponds to weaker sleep-dependent learning ability in older adults (Pace-Schott and Spencer, 2015). Therefore, airway obstruction during this stage may play an important role in cognitive impairment in SAHS patients. The β band is important for human cognitive processes including attention (Gao et al., 2017), audiovisual integration (Wang et al., 2017), and working memory (Calmels et al., 2011). The suppression of this oscillation observed between different regions (decreased STE) may indicate disruption of memory consolidation, which may provide clues to the substantially slower working memory in patients with OSA (Thomas et al., 2005). In contrast, low-frequency information interactions resemble stress responses. The decreased δ-band STEs after the events may suggest that the signal to meet basic oxygen demand was received by the brain, and then the reward system was activated (Knyazev, 2007).

We found some special phenomena regulated by respiratory events related to the γ band. They were mainly reflected by stronger intrahemispheric processing in both hemispheres without an interhemispheric processing increase when patients were exposed to hypoxic stress. When the airways reopened, especially during REM sleep, greater interhemispheric interactions appeared with significant intrahemispheric processing decrease, indicating a specific activation pattern of brain networks, which were similar to those during execution of complex tasks (Jiang et al., 2008). Interhemispheric asynchrony measured by the spectral correlation coefficient has been linked to nocturnal EEG arousal (Swarnkar et al., 2006, 2007). Although such arousal does not generally cause awakening, it greatly contributes to sleep fragmentation (Swarnkar et al., 2006); this is consistent with our findings. Moreover, this desynchrony has been found in patients with depression (Guo et al., 2013; Wang et al., 2013) and OSA (Abeyratne et al., 2010), with the respiratory disturbance index of the latter being associated with the asynchrony degree (Abeyratne et al., 2010). The persistence of apnea–hypopnea with long-time activation and the pathological severity may explain the interhemispheric functional connectivity abnormity in neuropsychiatric disorders (e.g., depression and emotional instability) related to SAHS.

The δ-band STEs during D1 and D2 in stage REM showed significant different trends from stage N1 and N2, which may be affected by electro-oculogram. Although some respiratory events with artifacts were removed by visual inspection, its impacts may still exist.

This study has some limitations. Patients in a narrow range of the apnea–hypopnea index were selected. To unify the definition of events and the statistical methods, only moderate SAHS patients were enrolled in this study to ensure that the event separation is at least 20 s. Moreover, stage N3 sleep was not considered given the difficulty to obtain enough event samples per subject. In addition, many CSA events were not enrolled in this study, because the intervals between events were less than

20 s. According to the event definition, only in stage N1 sleep, the sample size of CSA (80 CSA events in N1) met the requirement of statistical sample size. Therefore, the variations of EEG activity during events in severe SAHS patients and the CSA events should be studied separately using a different definition of event process. Furthermore, the EEG changes during events may be related to arousals; our pre-experiment showed that the spectral powers indicated a more drastic variation in the events terminated with cortical arousal than which without it. But the effects of end-apneic cortical arousal on STE were not clear. Events with and without arousal were not investigated separately in this study, but this may be an interesting topic to explore.

Overall, the EEG spectral power and STE during sleep are different analyses to unveil variation patterns during respiratory events. Our results mainly include cortical hyperactivation during stage N2 sleep, the suppression of β-band information transmission, abnormal interhemispheric effective connectivity, and the intrahemispheric "rise-to-down" fluctuations in the γ band. It was known that SAHS patients suffered cognitive disorders and mental-related complications. Our findings provide new clues on the influence of SAHS on cognitive function and neuropsychiatric defects.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Sixth Affiliated Hospital of Sun Yat-sen University. All subjects provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL and GZ contributed to design of the study. GZ, YP, JY, and XZ collected the data. YP and JY performed the statistical analysis. GZ wrote the first draft of the manuscript. YL and XG interpreted the results. All authors provided comments, contributed to manuscript revision, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2020.00310/full#supplementary-material

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Behavioral Phenotype in the TgF344-AD Rat Model of Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disease resulting in cognitive decline. A unique rat model, TgF344-AD, recapitulates pathological hallmarks of AD. We used a longitudinal design to address the timing of expression of behavioral phenotypes in male and female TgF344-AD rats. In both sexes, we confirmed an age-dependent buildup of amyloid-β. In the open field, female, but not male, TgF344-AD rats were hypoactive at 6 and 12 months of age but at 18 months the two genotypes were similar in levels of activity response. Both male and female TgF344-AD rats had a deficit in performance on a learning and memory task. Male TgF344-AD, but not female, rats had evidence of hyposmia regardless of age. Rest-activity rhythms followed the typical active/inactive phase in all rats regardless of genotype or age. In males, home cage activity was similar across age and genotype; in females, regardless of genotype animals were less active as they aged. These changes highlight some behavioral markers of disease in the rat model. Early markers of disease may be important in early diagnosis and assessment of efficacy when treatment becomes available.

Keywords: Alzheimer's disease, amyloid-β, actigraphy, hyposmia, learning

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder of aging characterized by progressive cognitive decline and, ultimately, dementia. This disorder affects millions of people and is more prevalent in females than in males (Vina and Lloret, 2010). AD has distinctive pathological characteristics including neurofibrillary tangles (composed of hyperphosphorylated tau) and the accumulation of amyloid-β plaques. Whereas neurofibrillary tangles and amyloid-β plaques have been studied as potential targets for AD therapeutics, no effective treatment target has been established (Kumar et al., 2015).

It is generally accepted that AD pathology begins decades before symptoms of cognitive decline are apparent (Sperling et al., 2014). For a potential treatment to be effective, it is essential that the disease is diagnosed early in this "preclinical" window. In our study we characterized an animal model of AD over the course of the aging process from maturity to senescence to uncover additional behavioral phenotypes that might be markers of the appearance of this degenerative disorder. We used the TgF344-AD rat model developed in 2013 on a Fisher344 background (Cohen et al., 2013). This transgenic model contains two mutations implicated in AD: overexpressing human amyloid precursor protein (APPsw) and presenilin 1 (PSE1E9). This model recapitulates the pathological changes in AD including neurofibrillary tangles, amyloid-β plaques, neuronal loss, and gliosis. Moreover, the TgF344-AD rat has demonstrable age-dependent indications of declining memory function (Cohen et al., 2013; Do Carmo and Cuello, 2013) and cognitive impairments (Berkowitz et al., 2018; Munoz-Moreno et al., 2018).

Our findings confirm an age-dependent accumulation of amyloid-β accompanied by a deficit in learning and memory. In addition, we found several behavioral changes that may precede cognitive decline. Female TgF344-AD rats were hypoactive in the open field at 6 months of age. Male TgF344-AD rats exhibited evidence of hyposmia at 6 months of age. These data suggest novel phenotypes that may be used in conjunction with other diagnostic markers to aid in early disease identification.

MATERIALS AND METHODS

Animals

All procedures were approved by the National Institute of Mental Health Animal Care and Use Committee and followed the National Institutes of Health Guidelines on the Care and Use of Animals. Tg344-AD$^{+/-}$ breeder pairs (wild type females and heterozygous males) were obtained from Emory University (Atlanta, GA, United States) and mated to provide heterozygous and control male and female offspring. Rats were group housed with food and water *ad libitum* and maintained in a centralized facility with a normal 12-h light dark cycle. Behavior testing was performed in the light phase between 9:00 AM and 5:00 PM. Tail snips were taken at weaning from each animal for genotyping as previously described (Cohen et al., 2013).

Behavior analyses (open field, buried food task, and reward alternating T-maze) were performed in a longitudinal study. Home cage activity assessment was analyzed in a cross-sectional study. This change in design was necessitated by limitations in equipment availability for home cage activity assessment. For analysis of home cage activity, each animal was assigned to one age category in an unbiased manner.

Behavior Testing

Prior to behavior testing, animals were habituated to handling for 14 days. Seven days prior to testing, animals were habituated to the reward (Froot Loops^{TM}) in their home cages. Prior to all behavior testing, animals were habituated to the test room for

TABLE 1 | Repeated measures ANOVA results behavior testing in males.

Behavior	Interaction	Main effect	$F_{(df,error)}$ value	*P*-value	Cohen's f^2
T-maze					
Fraction correct	Genotype × age		$F_{(2,22)} = 1.124$	0.343	0.103
		Genotype	$F_{(1,11)} = 8.276$	0.015*	0.751
		Age	$F_{(2,22)} = 5.235$	0.014*	0.475
Buried food					
Latency	Genotype × age		$F_{(1.8,20)} = 1.012$	0.375	0.092
		Genotype	$F_{(1,11)} = 4.992$	0.047*	0.453
		Age	$F_{(1.8,20)} = 1.659$	0.216	0.151
Open field					
Total distance moved	Genotype × age × epoch		$F_{(6.6,73)} = 0.947$	0.443	0.086
	Age × epoch		$F_{6.6,73)} = 1.520$	0.177	0.138
	Genotype × epoch		$F_{(4.9,54)} = 1.837$	0.122	0.167
	Genotype × age		$F_{(2,22)} = 1.271$	0.300	0.116
		Genotype	$F_{(1,11)} = 0.348$	0.567	0.032
		Age	$F_{(2,22)} = 2.805$	0.082†	0.255
		Epoch	$F_{(4.9,54)} = 23.495$	0.001*	2.135
Home cage activity					
	Genotype × age × epoch		$F_{(31.4,424)} = 1.142$	0.277	0.071
	Age × epoch		$F_{(31.4,424)} = 1.004$	0.463	0.066
	Genotype × epoch		$F_{(15.7,424)} = 0.923$	0.542	0.031
	Genotype × age		$F_{(2,27)} = 1.589$	0.223	0.140
		Genotype	$F_{(1,27)} = 0.001$	0.979	0.029
		Age	$F_{(2,27)} = 0.638$	0.536	0.055
		Epoch	$F_{(15.7,424)} = 21.287$	<0.001*	0.524

30 min in their home cages. Animals were separated into two cohorts for testing. Both cohorts underwent behavioral testing as follows: open field testing, buried food task, then reward alternating T-maze. The first cohort had 26 animals and an average of 8 days between open field testing and the buried food task and an average of 26 days between buried food task and reward alternating T-maze testing. The second cohort had 10 animals and waited an average of 23 days between open field testing and buried food task and 4 days between buried food task and reward alternating T-maze testing.

Open Field Test

We assessed activity by means of a standard open field apparatus consisting of a clear Plexiglass chamber measuring 40.6 × 40.6 × 38 cm (Coulbourn Instruments, Whitehall, PA, United States). The test animal was placed in the center of the apparatus and allowed to explore for a 60 min period. Infrared beams were used to detect the animal's movements. We determined total horizontal distance moved for each animal in 10 min epochs.

Buried Food Task

We used an adapted version of the buried food task to measure olfaction (Yang and Crawley, 2009). Prior to testing, the animal was food-deprived 18–24 h and habituated to the testing cage (a standard cage with 3 cm of bedding) for 5 min. Following habituation, the animal was transferred to a temporary holding cage while the reward was buried in a randomly selected location 1 cm below the surface of the bedding in the testing cage. The animal was then returned to the opposite side of the test cage from the buried reward and the latency to find the reward was determined (15 min maximum). Of the 34 animals tested, 16 reached the time out criterion: eight at 6 months, three at 12 months and 11 at 18 months of age. These animals were assigned the maximum time (900 s).

Reward Alternating T-Maze

We used reward alternation in the T-maze as a measure of working memory (Deacon and Rawlins, 2006). Rats were habituated to the maze with a reward placed at both ends daily for 7 days with 10 min of free exploration. Animals were food-restricted 18–24 h before and during the 3-day testing phase. Testing consisted of two trials per day (with an inter-trial interval of 1 h). A reward was placed at both ends of the T-maze, but one arm (randomly chosen) was blocked. This was defined as the choice arm. The unblocked arm was defined as the sample arm. The animal was placed at the start of the maze and allowed to explore until it found and consumed the reward in the sample arm (maximum of 10 min allowed). The animal was then returned to the start of the maze and the barrier was removed from the choice arm. The number of times the animal correctly chose the choice arm was recorded as a percent correct over total choices. If the correct arm was selected, the animal could consume the reward before being returned to the home cage.

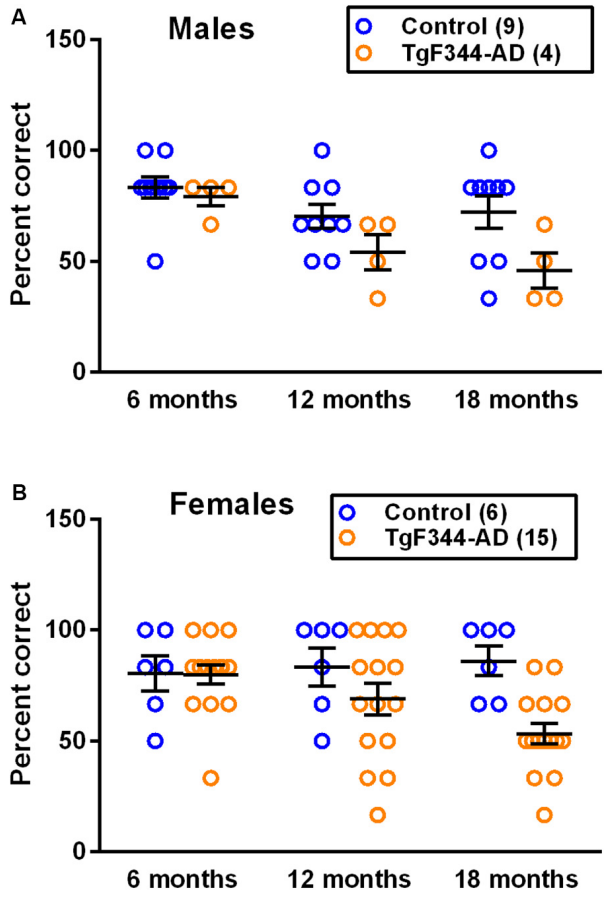

FIGURE 1 | Performance on the reward-alternation T-maze in **(A)** male and **(B)** female control and TgF344-AD rats. Each point is the percent correct alternations, and the lines represent the mean ± SEM for the number of male and female control and AD rats indicated in parentheses. The main effect of genotype was statistically significant in both males ($p = 0.015$) and females ($p = 0.024$). The main effect of age was statistically significant in males ($p = 0.014$) but not in females. Results indicate a decreased performance in AD rats in both sexes. In males, performance of both genotypes declines with age.

Home Cage Activity

We used the Comprehensive Laboratory Animal Monitoring System and Oxymax software (Columbus Instruments, Columbus, OH, United States) to monitor activity in the home cage over a 24-h period. The home cage containing the test animal was placed in the recording apparatus in which photobeams were used to detect movement in the *y* axis. Movement was recorded every 10 s and binned in 1-h epochs. Animals were allowed 2 days of habituation to the recording environment. Activity was recorded in the inactive (light) and active (dark) phases across a 24-h period.

Immunohistochemistry

In a separate group of 14 TgF344-AD animals, we stained for amyloid-β with immunohistochemistry. We analyzed (one male and three females at 4–6 months, one female at 12 months,

TABLE 2 | Repeated measures ANOVA results behavior testing in females.

Behavior	Interaction	Main effect	$F_{(df,error)}$ value	*P*-value	Cohen's f^2
T-maze					
Fraction Correct	Genotype × age		$F_{(1.66,31)} = 3.005$	0.073†	0.159
		Genotype	$F_{(1,19)} = 5.989$	0.024*	0.316
		Age	$F_{(1.66,31)} = 1.301$	0.280	0.068
Buried food					
Latency	Genotype × age		$F_{(2,38)} = 2.464$	0.099†	0.130
		Genotype	$F_{(1,19)} = 2.287$	0.147	0.120
		Age	$F_{(2,38)} = 2.450$	0.100†	0.129
Open field					
Total distance moved	Genotype × age × epoch		$F_{(9,174)} = 0.893$	0.534	0.047
	Age × epoch		$F_{(9,174)} = 3.614$	<0.001*	0.190
	Genotype × epoch		$F_{(4.3,81.7)} = 1.020$	0.405	0.054
	Genotype × age		$F_{(2,37.7)} = 4.886$	0.013*	0.258
		Genotype	$F_{(1,19)} = 8.535$	0.009*	0.449
		Age	$F_{(2,37.7)} = 23.081$	<0.001*	1.212
		Epoch	$F_{(4.3,81.7)} = 78.147$	<0.001*	4.102
Home cage activity					
	Genotype × age × epoch		$F_{(21,327)} = 1.399$	0.115	0.096
	Age × epoch		$F_{(21,327)} = 1.861$	0.013*	0.121
	Genotype × epoch		$F_{(10.6,327)} = 1.297$	0.227	0.056
	Genotype × age		$F_{(2,31)} = 1.131$	0.336	0.073
		Genotype	$F_{(1,31)} = 1.090$	0.305	0.035
		Age	$F_{(2,31)} = 8.733$	0.001*	0.563
		Epoch	$F_{(10.6,327)} = 29.077$	<0.001*	1.475

and four males and five females at 24–25 months). Given the low number of males at 6 and 12 months of age, we combined sexes for analysis of age-effects of amyloid plaque buildup. Brain tissue was embedded in paraffin and sections 5 μm in thickness were prepared. Sections were taken at the level of hippocampus, cortex, and cerebellum. The antigen was retrieved with citrate buffer, pH 6.0 for 20 min at 95°C in a pressure cooker and allowed to cool to room temperature. The slides were rinsed in TBST followed by distilled water, treated with SNIPER (Biocare, Pacheco, CA, United States) for 10 min, and blocked with serum free protein block from DAKO (Cat No X0909) for 5 min. Slides were incubated with amyloid-β antibody (Clone DE2) (1:100, Millipore, Temecula, CA) for 45 min. The slides were rinsed two times with TBST, incubated with DAKO Envision mouse peroxidase (DAKO, Carpentaria, CA, United States) for 30 min followed by 3,3′-diaminobenzidine (DAB+; DAKO) for 7 min, and counterstained with hematoxylin. For a negative control, the primary antibody was replaced with mouse IgG at the same concentration. Amyloid-β plaques appeared as brown stellate structures 5–80 μm in diameter. We measured amyloid-β positive plaque area in four brain regions defined by reference to an atlas of the rat brain (Paxinos and Watson, 1986). We expressed results as % of total regional area in the field of view.

Statistical Analyses

Data are expressed as means ± standard errors of the mean (SEM). Results of behavior testing were analyzed by means of repeated measures ANOVA (RMANOVA) with SPSS version 21 (IBM, Armonk, NY, United States) with genotype as the between subjects variable and age as a within subjects variable. Males and females were analyzed separately. Open field testing was analyzed with epoch as an additional within subjects variable. Since home cage activity was studied in a cross-sectional design, both genotype and age were between subjects variables and epoch was a within subjects variable. *P*-values < 0.05 were considered statistically significant and are marked with a "*," and *p*-values $0.10 \geq p > 0.05$ are indicated with a "†."

RESULTS

Survival

Rats were bred in-house, such that control and TgF344-AD rats were littermates. For these behavioral studies, we began with 20 control (14 male and 6 female) and 22 TgF344-AD (6 male and 16 female) rats, and we include data from animals [15 controls (nine male, six female) and 19 TgF344-AD (15 female, 4 male)] that were tested at all three ages, 6, 12, and 18 months. Of the original cohorts, five control (all male) and three TgF344-AD (two male and one female) rats died before all the tests at 18 months. The cause of death for the TgF344-AD rats was pituitary hemorrhage in one male rat and testicular cancer in another. The cause of death for the female TgF344-AD rat was not determined. The cause of death for three of the control males was as follows: one died during surgical removal of an islet tumor, one was euthanized because of a large subcutaneous tumor on a forelimb,

and one from testicular cancer. The cause of death in the other two animals could not be determined. Of our original cohort, survival at 6 and 12 months of age was 100% for both groups. At 18 months of age survival was 75 and 91% for control and TgF344-AD rats, respectively. For control males and females at 18 months of age, survival was 64 and 100%, respectively. For TgF344-AD rats, survival at 18 months of age was 67 and 94% in males and females, respectively.

T-Maze

We used the alternating T-maze task to examine learning and memory. We found statistically significant main effects of genotype in both male (**Table 1** and **Figure 1A**) and female rats (**Table 2** and **Figure 1B**) on the reward-alternation T-maze task indicating that, regardless of age, performance was worse in the TgF344-AD rats compared to controls. In males, but not females, the effect of age was also statistically significant indicating that regardless of genotype performance declined as males aged (**Figure 1A**).

Buried Food Task

Hyposmia is common in patients with AD and worsens with progression of the disease, but the timing of the initial presentation of this symptom is not known (Serby et al., 1991). To study hyposmia and the development of this phenotype, we performed the buried food task in a longitudinal study. We found a statistically significant main effect of genotype (p = 0.047) in males (**Table 1** and **Figure 2A**), but not in females (**Table 2** and **Figure 2B**). These results indicate that in males, regardless of age, the latency to locate the buried food is longer in TgF344-AD rats compared to controls.

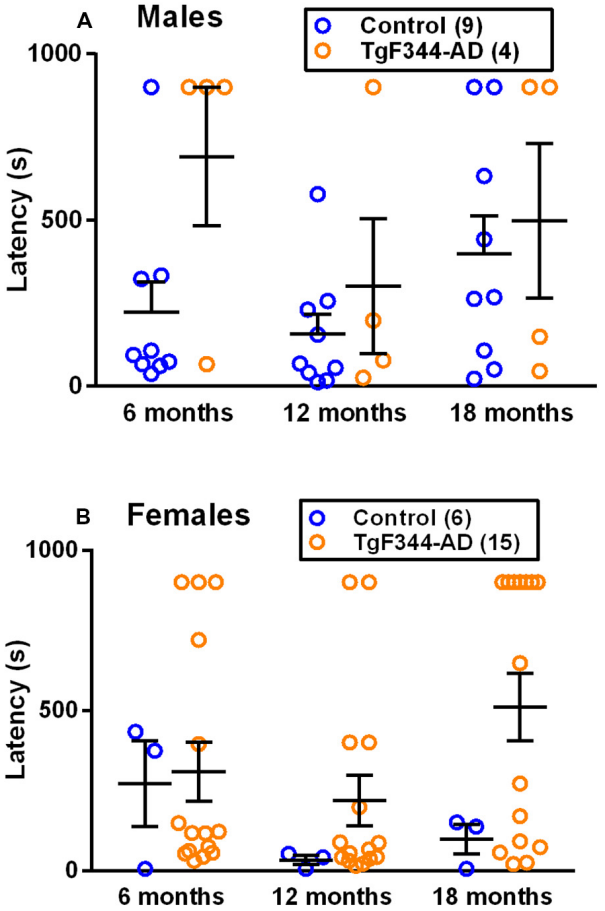

FIGURE 2 | Performance on the buried food task in **(A)** male and **(B)** female TgF344-AD and control rats. Each point is the latency to find the buried food, and the lines represent the mean ± SEM for the number of male and female control and AD rats indicated in parentheses. The main effect of genotype was statistically significant (p = 0.047) in males but not in females. Latency to find the buried food was longer in male AD rats compared to controls.

Activity in the Open Field

To determine activity levels in response to a novel environment, we performed open field testing for 1 h. In males, only the main effect of epoch was statistically significant indicating that animals, regardless of age or genotype, showed habituation to the arena (**Table 1** and **Figures 3A–C**). In females, the age × epoch interaction was statistically significant (**Table 2** and **Figures 3D–F**). In the first three epochs, animals at 6 months of age moved more in response to the novel environment compared with older rats suggesting that the younger animals were more reactive than older animals (**Supplementary Figure S1**). This effect was not different in the two genotypes. In addition, in female rats, the age × genotype interaction was statistically significant (**Table 2**) indicating that hypoactivity in the TgF344-AD rats was evident at 6 and 12 months of age, but at 18 months of age the activity curves were coincident for the two genotypes (**Figures 3D–F** and **Supplementary Figure S1**).

Home Cage Activity

We used a home-cage monitoring system to assess home cage activity in a cross-sectional analysis. In males, we found no statistically significant interactions or main effects of genotype or age. Only the main effect of epoch was statistically significant reflecting a normal circadian rhythm of activity (**Table 1** and **Figures 4A,C,E**). In females, only the age × epoch interaction was statistically significant indicating that regardless of genotype, activity was higher in the younger animals compared with either the 12- and 18-months old groups at epochs 8, 11, 12, and 20. Activity was higher in the younger animals compared with only the 18-month old group at epoch 18 (**Table 2** and **Figures 4B,D,F**). These epochs are in both the active and inactive phases.

Immunohistochemistry

The presence of amyloid-β in brain was analyzed in a separate series of rats by means of immunohistochemistry (**Figure 5**). Fourteen TgF344-AD animals were analyzed. We counted amyloid-β deposits (plaques) and measured the area occupied by plaques in four 4–6 months old (three females, one male), one 12 months old (one female, zero males), and nine 24–25 months old (five females, four males) TgF344-AD rats (**Figure 6**). We expressed results as plaque area as a percent of region area

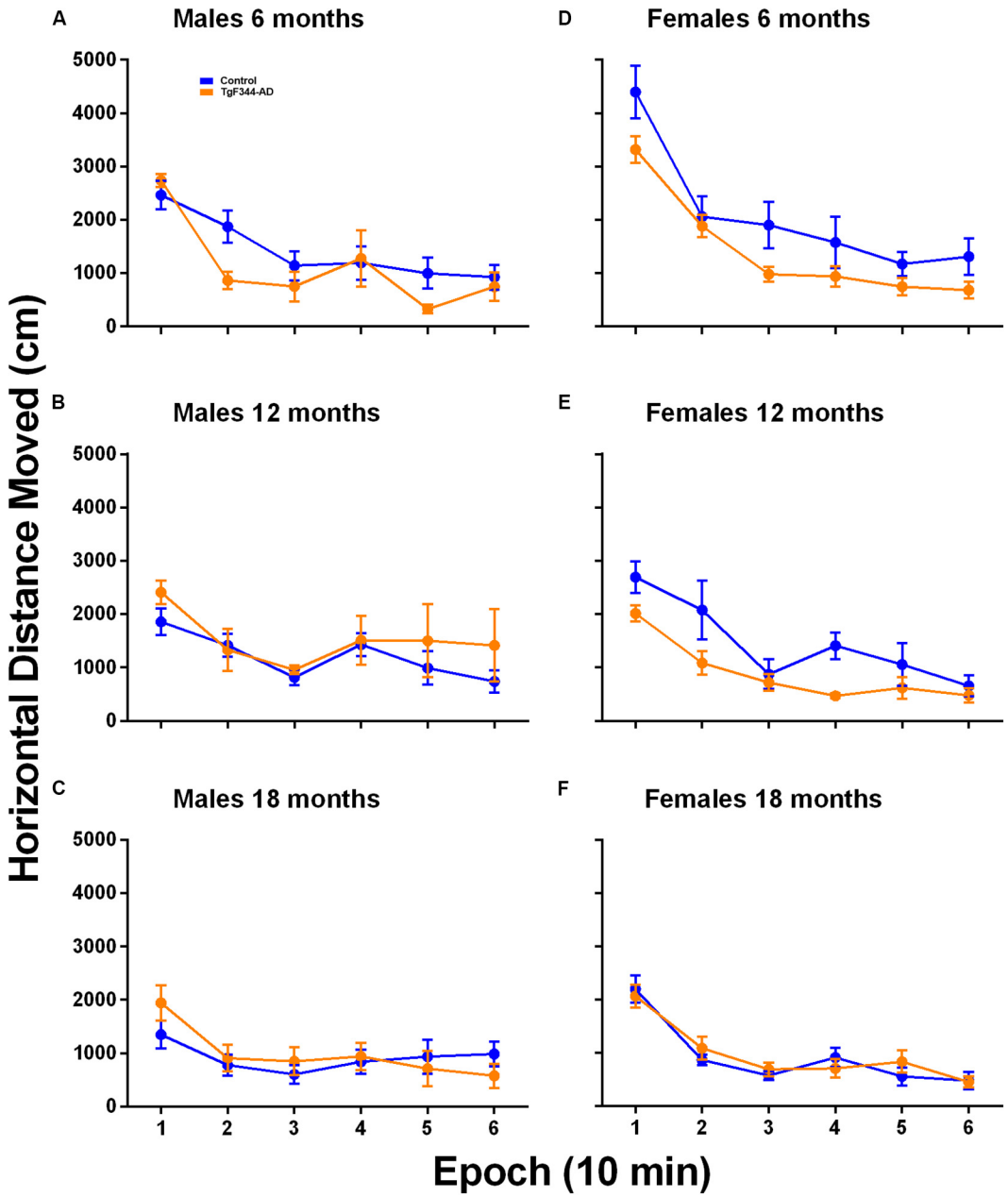

FIGURE 3 | Open field activity in **(A–C)** male and **(D–F)** female TgF344-AD and control rats at **(A,D)** 6 months, **(B,E)** 12 months, and **(C,F)** 18 months of age. Each point is the mean ± SEM in nine male controls, five male TgF344-AD, six female control and 15 female TgF344-AD rats. For males, only the main effect of epoch was statistically significant ($p < 0.001$) indicating habituation over the 60 min testing period regardless of either age or genotype. For females, the age × epoch ($p < 0.001$) interaction was statistically significant indicating that regardless of genotype habituation decreased with increasing age likely due to decreased responsivity to the environment in the 12- and 18-month old animals. Moreover, in females, the genotype × age ($p = 0.013$) interaction was statistically significant, indicating that in the 6 and 12 month old groups, AD rats were hypoactive compared with controls; activity levels were similar in the two genotypes at 18 months of age.

in the section. We analyzed piriform cortex, perirhinal cortex, hippocampus, and cerebellum. Plaque area was very low at 4–6 months of age and increased significantly in hippocampus (82 fold), perirhinal cortex (63 fold), and piriform cortex (73 fold) at 24–25 months of age. In a single female TgF344AD rat at 12 months of age values were intermediate between the young and aged groups. We compared male (4) and female (5) values at 24–25 months of age by means of unpaired *t*-tests, and we found no significant sex differences in any region (cerebellum, $p = 0.373$; hippocampus, $p = 0.730$; perirhinal cortex, $p = 0.674$; piriform cortex, $p = 0.477$), therefore, sexes were combined for the analysis of age.

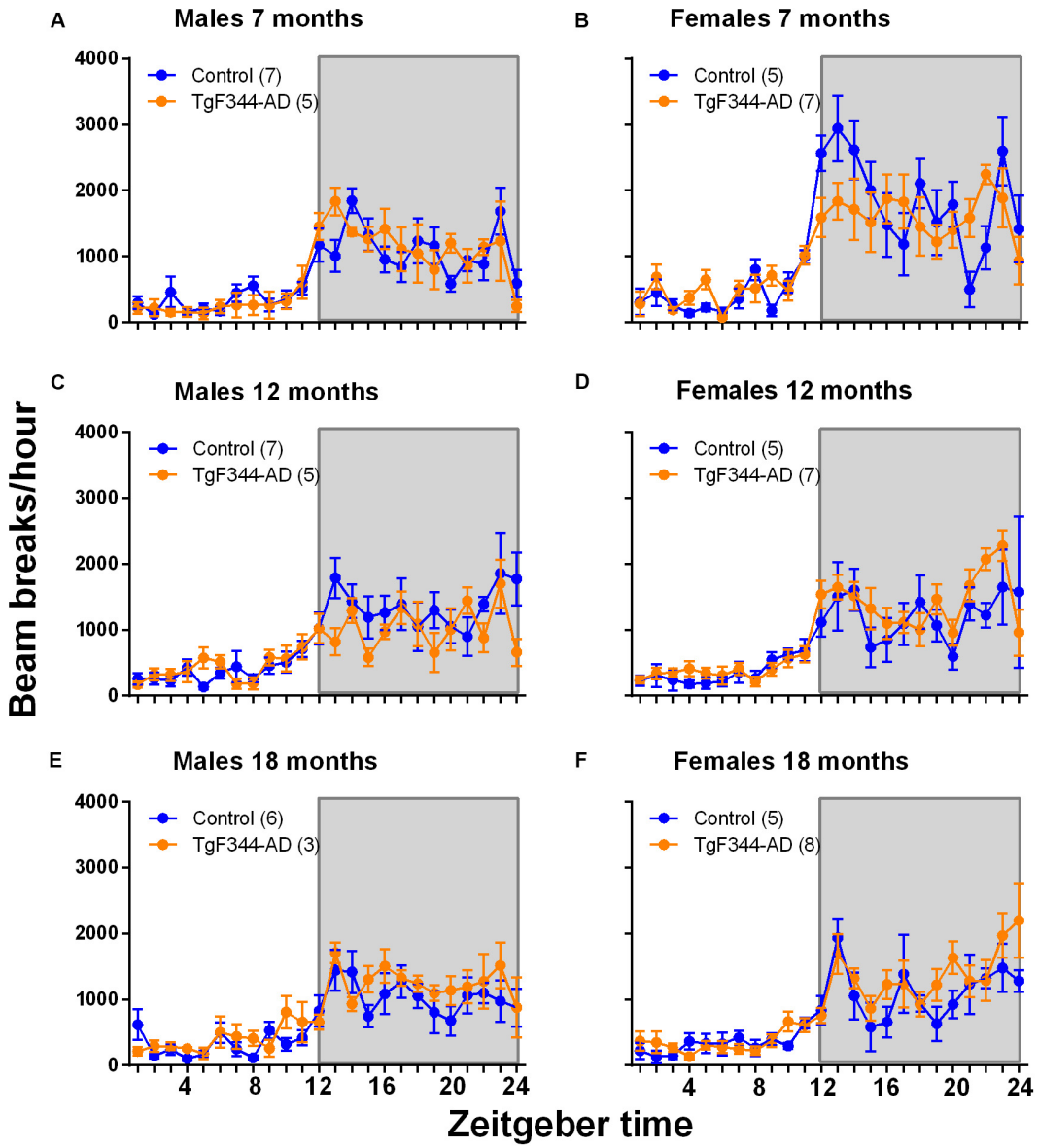

FIGURE 4 | Home cage activity in a cross-sectional study in control and TgF344-AD male **(A,C,E)** and female **(B,D,F)** rats at 7 **(A,B)**, 12 **(C,D)**, and 18 **(E,F)** months of age. Each point represents the mean ± SEM for the number of rats indicated in parentheses. The abscissa represents 1-h epochs across time with epoch 1 representing 6 am–7 am; lights were on at 6 am and lights were off at 6 pm, as indicated by the shaded area. In males, only the main effect of epoch was statistically significant, indicating regardless of age or genotype, activity varies with epoch. In females, the age × epoch interaction was statistically significant indicating that regardless of genotype, younger rats were more active compared with the 12- and 18-month old animals; effects were statistically significant at 8th, 11th, 12th, and 20th epochs. Younger rats were more active than 18-month old rats at the 18th epoch.

DISCUSSION

Results of our present study of the TgF344-AD transgenic rat confirm an age-dependent and region-dependent accumulation of amyloid-β plaques and a deficit in performance on a test of learning and memory. Female TgF344-AD rats at 6 and 12 months of age were hypoactive in the open field compared to controls. Our data also show evidence of hyposmia in maleTgF344-AD rats regardless of age and normal rest-activity rhythms at all three ages for both genotypes. These changes further elaborate the behavioral phenotype of this rodent model of AD.

At the outset we designed our study of the TgF344-AD rat model to include both male and female rats and to analyze the data from both sexes together. This was based on the initial report of this model in which no sex differences were found (Cohen et al., 2013). Our study addressed different phenotypes from the original study, however, and with respect to some of these phenotypes, we see sex differences. Male and female TgF344-AD animals appear to differ with respect to the buried

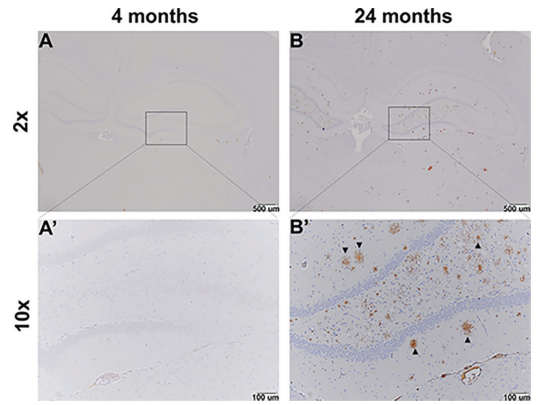

FIGURE 5 | Representative immunohistochemistry images of amyloid-β in the hippocampus of TgF344-AD animals. Amyloid-β positive plaques are not evident in images from a 4-month-old rat **(A,A')**. Whereas amyloid-β positive plaques are visible (arrows) in images from a 24-month-old rat **(B,B')**.

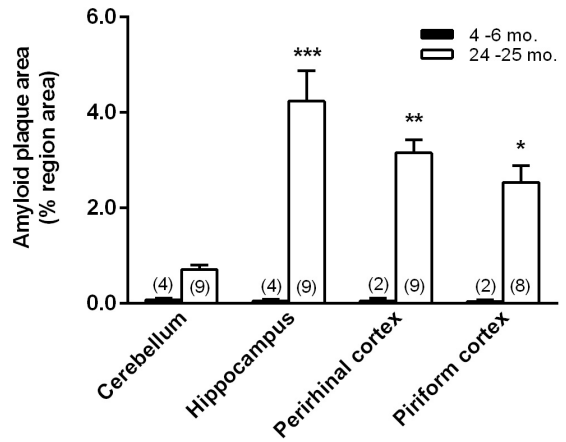

FIGURE 6 | Amyloid-β positive plaque areas as a percent of region area in the field of view in 4–6 and 24–25 months old TgF344-AD rats in cerebellum, hippocampus, perirhinal cortex, and piriform cortex. We had good sections from only one TgF344-AD rat at 12 months of age, so these data are not shown. The rat analyzed at 12 months of age was female and values for cerebellum, hippocampus, and perirhinal cortex were 0.33, 1.76, and 2.53%, respectively. These values were intermediate between the values in the 4–6 and the 24–25 month rats. Bars represent means ± SEM for the number of animals indicated in parentheses. We compared male (4) and female (5) values at 24–25 months of age by means of unpaired *t*-tests, and we found no significant sex differences in any region (cerebellum, $p = 0.373$; hippocampus, $p = 0.730$; perirhinal cortex, $p = 0.674$; piriform cortex, $p = 0.477$). As a consequence, further analyses were performed with males and females at each age combined. Data were analyzed by means of ANOVA with age and region as between subject variables. Main effects of both age ($F_{1,39} = 51.25$, $p < 0.0001$) and region ($F_{3,39} = 5.459$; $p = 0.0031$) were statistically significant. The age × region interaction was also statistically significant ($F_{3,39} = 5.557$; $p = 0.003$) so we compared the two ages in each region by means of Sidak's corrected *t*-tests. Levels of statistical significance are denoted as follows: *, $0.01 \leq p \leq 0.05$; **, $0.001 \leq p \leq 0.01$; ***, $p \leq 0.0001$.

food task. These results will be discussed below. Analysis of these data for each sex separately may leave our study somewhat underpowered, but analysis of the data from both males and females grouped together may lack validity given the presence of sex differences. Despite these limitations, our results demonstrate behavioral phenotypes in TgF344-AD rats. Subsequent studies investigating AD models should consider the likelihood of sex-differences at the outset.

Our study confirms and expands on the results reported previously on amyloid-β deposition in brain in the TgF344-AD model (Cohen et al., 2013). In the previous study amyloid-β deposition was observed in rats at 16 months of age in cingulate cortex and hippocampus and increased in density in 26 months old rats. Our results reveal some regional selectivity in brain regions affected. Three brain regions were particularly affected: hippocampus, piriform cortex, and perirhinal cortex. In these regions, plaque counts were very high in rats at 24–25 months of age. In view of the fact that deficiencies in spatial cognition are a primary symptom of AD, it is interesting that regions of the brain in which plaque counts are particularly affected in this rat model include regions of the navigation network (hippocampus and perirhinal cortex) (Pengas et al., 2012; Miller et al., 2014; Mitchell et al., 2018). The effects seen in piriform cortex are of interest in light of the involvement of piriform cortex in identification of odors and the deficiencies in olfaction in the rat model and in human subjects.

The learning and memory impairment confirms previous results in which the Barnes maze and novel object recognition task were used for assessment (Cohen et al., 2013). They also align with data from these rats using a Morris Water Maze (Berkowitz et al., 2018). Taken together, results indicate that these behavioral impairments are correlated with the histological abnormalities and neurodegeneration originally reported (Cohen et al., 2013).

We did not see hyperactivity in the open field in either 12- or 18-month old TgF344-AD rats as reported previously (Cohen et al., 2013). Higher activity in the first few epochs of the open-field as seen in the younger rats of both genotypes is indicative of an increased responsiveness to the novel environment. One possibility is that responsiveness to the open field declined with age because the rats remembered the open field arena from the prior test at 6 months. Our data indicate that 6- and 12-month old femaleTgF344-AD rats were hypoactive in the open field compared with controls. Hypoactivity in the younger TgF344-AD rats may also be apparent in the home cage activity record. Whereas rest-activity rhythms follow the typical active/inactive cycle in both genotypes, in females activity levels are higher in the younger rats. It is important to note that we did not control for the estrous cycle in the females and do not know what phase of the cycle the animals were in during the course of the experiment. It has been shown that the estrous cycle can affect activity levels of female rats (Finger, 1969).

One of the questions we set out to address with the buried food task was the development of a potential hyposmia phenotype. Our data are suggestive of an early appearing hyposmia phenotype in males, supporting the notion that hyposmia may be an early phenotype in AD and a possible clinical predictor (Fioretti et al., 2011). In females, hyposmia is not apparent until 18 months of age after we began noting differences in learning and memory and after amyloid-β plaques were apparent. Our data from the female rats are more consistent with the

hypothesis that differences in odor detection (different from olfactory identification) are not present until later stages of the disorder (Serby et al., 1991; Xu et al., 2014). High levels of variability and limited numbers of rats per group prevent firm conclusions from these studies.

CONCLUSION

The results of this study highlight the timing of changes in important behaviors in the TgF344-AD transgenic rat and suggest that some of these may be sex-dependent. Our results suggest a correlation between cognitive impairment and amyloid-β plaque formation. Hyposmia characterized TgF344-AD animals in general, and this phenotype appeared to be stronger in young adult males, whereas hypoactivity was evident in young TgF344-AD females. Some of these behaviors may represent early markers of AD progression and should be considered in future studies for early diagnosis of AD. We recommend that subsequent studies of AD in both animal models and in human subjects should further investigate sex-differences in AD progression and pathology.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The animal study was reviewed and approved by the NIMH Animal Care and Use Committee.

AUTHOR CONTRIBUTIONS

RS helped design the study, carried out the home cage activity studies and the analysis of the IHC results, analyzed the data, interpreted results, and wrote the manuscript. SC made pictures for the IHC studies, analyzed the data, and helped to writing the manuscript. LK designed the study and carried out the behavioral experiments. PZ carried out the IHC studies. RC interpreted results and edited the manuscript. CS designed the study, analyzed the data, interpreted results, and wrote the manuscript.

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REVIEW
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Slow Wave Sleep Is a Promising Intervention Target for Alzheimer's Disease

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Alzheimer's disease (AD) is the major cause of dementia, characterized by the presence of amyloid-beta plaques and neurofibrillary tau tangles. Plaques and tangles are associated with sleep-wake cycle disruptions, including the disruptions in non-rapid eye movement (NREM) slow wave sleep (SWS). Alzheimer's patients spend less time in NREM sleep and exhibit decreased slow wave activity (SWA). Consistent with the critical role of SWS in memory consolidation, reduced SWA is associated with impaired memory consolidation in AD patients. The aberrant SWA can be modeled in transgenic mouse models of amyloidosis and tauopathy. Animal models exhibited slow wave impairments early in the disease progression, prior to the deposition of amyloid-beta plaques, however, in the presence of abundant oligomeric amyloid-beta. Optogenetic rescue of SWA successfully halted the amyloid accumulation and restored intraneuronal calcium levels in mice. On the other hand, optogenetic acceleration of slow wave frequency exacerbated amyloid deposition and disrupted neuronal calcium homeostasis. In this review, we summarize the evidence and the mechanisms underlying the existence of a positive feedback loop between amyloid/tau pathology and SWA disruptions that lead to further accumulations of amyloid and tau in AD. Moreover, since SWA disruptions occur prior to the plaque deposition, SWA disruptions may provide an early biomarker for AD. Finally, we propose that therapeutic targeting of SWA in AD might lead to an effective treatment for Alzheimer's patients.

Keywords: Alzheimer's disease, sleep, NREM sleep, slow wave activity, slow oscillations

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia in the elderly (Alzheimer's Association, 2016). The pathological hallmarks of AD are the presence of extracellular plaques composed of amyloid-beta (Aβ) and intracellular neurofibrillary tangles composed of the microtubule binding protein tau in the brain (Bloom, 2014; Calderon-Garcidueñas and Duyckaerts, 2017). According to the amyloid cascade hypothesis, Aβ accumulation leads to tau deposition, triggers neuronal dysfunction and results in neuronal

death (Hardy and Higgins, 1992; Selkoe and Hardy, 2016). Although, amyloid cascade hypothesis is widely debated, soluble Aβ and tau protein aggregations have been shown to lead to synaptic dysfunction and loss of synaptic density (Spires-Jones and Hyman, 2014), resulting in memory and cognitive deficits in AD patients (DeKosky and Scheff, 1990). The clinical features of AD include progressive memory loss, impaired judgment and decision-making (Förstl and Kurz, 1999). Current therapeutics are limited to alleviation of symptoms, not reversing or slowing the disease progression (Yiannopoulou and Papageorgiou, 2013; Cummings et al., 2019). Therefore, there is an urgent need to identify effective treatment strategies for alleviating the disease burden.

In addition to memory and cognitive impairments, Alzheimer's patients experience sleep disruptions (Bliwise et al., 1995; McCurry et al., 1999; Moran et al., 2005), leading to reductions of non-rapid eye movement (NREM) sleep and slow wave activity (SWA), a brain rhythm prevalent during NREM sleep (Prinz et al., 1982). These disruptions include increased amounts and frequencies of nighttime wakefulness as well as daytime napping (Vitiello and Prinz, 1989; McCurry et al., 1999). Sleep disturbances manifest early since individuals with mild cognitive impairment (MCI), a pre-clinical stage of AD, suffer from sleep disruptions (Vitiello and Prinz, 1989; Westerberg et al., 2012). Similarly, individuals with detectable amyloid beta, but cognitively healthy also suffer from sleep disturbances, defined as lower sleep quality and increased number of day-time naps (Ju et al., 2013). Thus, sleep and memory disruptions manifest early in the disease progression, prior to symptom onset.

Sleep mediates several forms of memory consolidation (Diekelmann and Born, 2010; Born and Wilhelm, 2012; Rasch and Born, 2013). Sleep disturbances are correlated with deteriorated memory function and cognitive decline in AD and MCI patients (Moe et al., 1995; Brzecka et al., 2018). Increased night-time wakefulness and decreased slow wave sleep (SWS), which is dominated by SWA, was associated with impaired memory and cognitive functions (Moe et al., 1995). NREM, in particular SWS, plays an important role in declarative memory consolidation (Walker, 2009; Lu and Göder, 2012). This review will provide an overview of the SWA disruptions in AD. It will also summarize the evidence for the causal relationship between AD pathology, Aβ/tau, and sleep-dependent memory consolidation deficits that are driven by the SWA disturbances in AD patients and animal models of AD. Furthermore, we will propose possible mechanisms underlying the SWA disruptions. Finally, we will discuss therapeutic strategies for targeting SWS in AD aimed at slowing the disease progression and restoring the sleep-dependent memory consolidation. This review is focused on the SWA, the most prominent neocortical activity with the increased power density in 0.5–4.0 Hz frequency range occurring during NREM sleep. It will not cover other NREM sleep-associated rhythms, such as thalamo-cortical sleep spindles, or hippocampal ripples, nor will it discuss REM sleep disruptions in AD, that have been reviewed or described elsewhere (Christos, 1993; Rauchs et al., 2008; Pase et al., 2017).

SWA AND SLEEP-DEPENDENT MEMORY CONSOLIDATION

Sleep consists of rapid eye movement (REM) and NREM sleep. REM sleep is characterized by desynchronized EEG activity with faster oscillations and lower voltage waveforms (Carskadon and Dement, 2011). Human NREM sleep is subdivided into stages N1–N3 (previously stages 1–4) and is defined by the electroencephalogram (EEG) activity as synchronous waveforms, including sleep spindles (12–14 Hz), K-complexes in stage 2 as well as slow (<1 Hz) and delta (1–4 Hz) activity in stage 3 (Iber et al., 2007). Slow and delta oscillations or isolated slow waves are commonly called SWA (Timofeev et al., 2020). Stage N3, also referred to as Delta Sleep or SWS, is characterized by the high amounts of SWA (Carskadon and Dement, 2011).

Slow oscillation is a major rhythm of deep sleep. During slow oscillations, excitatory and inhibitory neocortical neurons from all layers (unknown for layer 1) in anesthetized (Steriade et al., 1993a,b,c) and sleeping animals (Timofeev et al., 2000b, 2001; Steriade et al., 2001; Chauvette et al., 2010) oscillate between depolarized (active or UP) and hyperpolarized (silent or DOWN) states. Despite involvement of the entire thalamocortical system (Steriade et al., 1993a; Contreras and Steriade, 1995; Sheroziya and Timofeev, 2014), the slow oscillations originate in neocortex as can be recorded in neocortical slices (Sanchez-Vives and McCormick, 2000; Sanchez-Vives et al., 2010), cortical cell cultures (Sun et al., 2010; Hinard et al., 2012) and isolated cortical slabs maintained *in vivo* (Timofeev et al., 2000a; Lemieux et al., 2014). Slow oscillation is absent from the thalamus of decorticated animals (Timofeev and Steriade, 1996). The silent (hyperpolarized or DOWN) states of slow oscillations are periods of disfacilitation, i.e., absence of synaptic activity. Leak currents primary mediate silent states (Timofeev et al., 1996, 2001). The active (depolarized or up) states are mediated by barrages of excitatory and inhibitory synaptic activities at the level of soma (Steriade et al., 2001; Timofeev et al., 2001; Rudolph et al., 2007) and major Ca^{2+} activities in dendrites (Milojkovic et al., 2007; Seibt et al., 2017). Neocortex generates slow oscillations while thalamus contributes to their maintenance as thalamic inactivation temporally modifies cortical SWA (David et al., 2013; Lemieux et al., 2014).

To control the slow oscillations, it is important to understand the major cellular events taking place during SWA. The neuronal firing and thus synaptic activity in local cortical networks, is essentially absent in the silent state. Two major mechanisms for the active state onset are proposed. (i) The silent state is partially mediated by Ca^{2+}- and Na^{+}-dependent K^{+} currents. A reduction in these currents leads to the onset of a new active state (Sanchez-Vives and McCormick, 2000). (ii) Silent states are characterized by the absence of synaptic activity, but spike-independent neurotransmitter release (miniature postsynaptic potentials, minis) are still present. Co-occurrence of minis in large neurons that possess a high number of postsynaptic sites

can lead to significant depolarizations and initiations of spikes, that would drive the whole network into an active state (Timofeev et al., 2000a; Bazhenov et al., 2002; Chauvette et al., 2010). Since this is a stochastic process, it can start in any cell, but more often, it starts in larger neurons, typically layer 5 large cortical pyramidal cells in experimental animals (Chauvette et al., 2010; Fiáth et al., 2016). In human, however, slow wave active states more often start in layer 3 (Cash et al., 2009; Csercsa et al., 2010). There might be two reasons for this difference: (a) human pyramidal cells from layer 3 are very large (Mohan et al., 2015), and therefore, they are well situated to summate minis and to trigger active states; and (b) enhanced electrical compartmentalization in layer 5 pyramidal neurons in humans does not allow dendritic depolarizing events to reach soma, even in the presence of dendritic spikes (Beaulieu-Laroche et al., 2018), therefore reducing overall implication of layer 5 cells in network operation. Local origin of active states and dense synaptic interactions in the cortex trigger propagation of slow waves across cortical mantle (Massimini et al., 2004; Volgushev et al., 2006; Sheroziya and Timofeev, 2014). Active states are mediated by interactions of excitatory and inhibitory conductances (Haider et al., 2006; Haider and McCormick, 2009; Chen et al., 2012) with overall stronger inhibition at the level of soma (Rudolph et al., 2007; Haider et al., 2013). A termination of active states and transition to silent states occurs due to several factors: (i) activation of Na^+- and Ca^{2+}-dependent potassium currents (Sanchez-Vives and McCormick, 2000), (ii) synaptic depression (Timofeev et al., 2000b), and (iii) synchronous active inhibitory drive (Steriade et al., 1993b; Lemieux et al., 2015). Because active states terminate nearly simultaneously across large cortical territories (Volgushev et al., 2006; Sheroziya and Timofeev, 2014), intrinsic current activation or synaptic depression likely do not play a leading role, because they are cell specific. Thus, we suggest that active inhibitory mechanisms terminate active states and provide network-wide synchronous onset of silent states. First, somatostatin-positive GABAergic interneurons increase activity prior to the onset of silent states (Funk et al., 2017; Niethard et al., 2018). Most of these interneurons have short axons, therefore an external trigger, possibly from thalamus, synchronizes them. Indeed, thalamic inactivation abolishes synchronous onset of silent states (Lemieux et al., 2015). Furthermore, some thalamocortical neurons fire during silent states driving parvalbumin-positive interneurons (Zucca et al., 2019). Another potential source is claustrum, the structure that has widespread cortical projections and, if activated optogenetically, induces cortical down states (Narikiyo et al., 2018). It appears that claustrum is well situated to drive simultaneously cortical interneurons across different areas just prior to the onset of silent states.

Sleep slow oscillations play an important role in cortical plasticity. However, the direction of these plastic changes is still under discussion. A subset of studies, based mainly on indirect measurements, propose that cortical synaptic connections are strengthened during wakefulness and are weakened during sleep (Tononi and Cirelli, 2003, 2014). Other studies demonstrate that slow oscillations and overall sleep strengthens efficacy of cortical synapses (Aton et al., 2009; Chauvette et al., 2012; Seibt et al., 2012; Yang et al., 2014; Jasinska et al., 2015; Timofeev and Chauvette, 2017). Finally, there is an attempt to reach agreement in this debate which proposes that some synapses are upregulated and others are downregulated by sleep (Seibt and Frank, 2019).

Irrespective of the synaptic mechanisms, slow oscillations play an important role in sleep-dependent declarative memory consolidation (Steriade and Timofeev, 2003; Marshall et al., 2006; Walker, 2009; Lu and Göder, 2012). Born and colleagues proposed a model of declarative, hippocampus-related memory consolidation during SWS. Cortical slow oscillations drive the reactivation of short-term hippocampal memories by synchronizing hippocampal sharp wave ripples with spindle activity in the thalamus during slow oscillation UP states. This mechanism thereby contributes to the long-term synaptic plasticity changes in neocortical networks and supports the consolidation of long-term memory in neocortex (Diekelmann and Born, 2010; Rasch and Born, 2013). SWS declines with increasing age especially after the age of 30 (Van Cauter et al., 2000). Age-related reduction in SWS was correlated with impaired sleep-associated memory consolidation (Backhaus et al., 2007). Furthermore, insomnia patients with less SWS showed declines in overnight declarative memory consolidation compared to age-matched controls (Backhaus et al., 2006). Boosting SWA facilitated sleep-dependent memory consolidation (Marshall et al., 2006). Thus, SWA, slow oscillations in particular, is necessary and sufficient for memory consolidation during sleep, and we propose that SWA disruptions might contribute to memory impairments in AD.

SWA DISRUPTIONS IN AD PATIENTS

Toxic Aβ is thought to initiate pathological events and drive the formation of pathological tau aggregates that ultimately lead to synaptic loss and cell death (Hardy and Higgins, 1992; Selkoe and Hardy, 2016; Henstridge et al., 2019), which in turn compromises neuronal circuitry. Aβ levels correlate with sleep alterations in cognitively normal individuals with preclinical AD (Ju et al., 2013; Spira et al., 2013). Neuronal activity disturbances including slow oscillation disruptions were reported in older adults (Mander et al., 2013, 2015; Lucey et al., 2019). Aβ and tau deposits were associated with decreased NREM SWA in cognitively normal older adults and in early stages of AD (Mander et al., 2015; Lucey et al., 2019). Decreased NREM slow oscillations (0.6–1 Hz) were associated with increased Aβ accumulation in the medial prefrontal cortex (Mander et al., 2015). Also, higher tau deposition was correlated with decreased delta power (1–4 Hz) (Lucey et al., 2019). This evidence provides strong support for a relationship between SWA disruptions and AD pathology (**Figure 1**). In addition to SWA disruptions in asymptomatic cognitively normal adults, SWA was reduced in MCI individuals (Westerberg et al., 2012). Sleep disturbances in cognitively normal older adults could predict the Aβ burden and tau accumulation later in life (Winer et al., 2019). Taking into account all of the above, we propose that, sleep-wake cycle disturbances, especially decreases in NREM SWA, may serve as a potential early biomarker for AD.

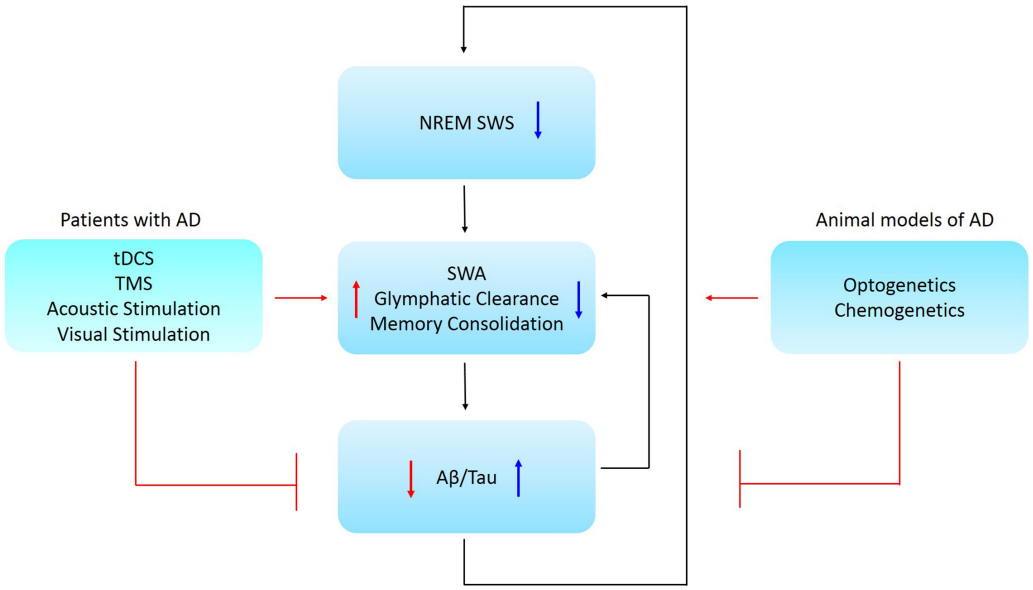

FIGURE 1 | Schematic representation of the causal relationship between NREM SWS, memory consolidation, and AD pathology. Low NREM SWS leads to reduced SWA and perivascular clearance of soluble Aβ and is associated with impaired memory consolidation. Further, low SWA is associated with increased Aβ/tau aggregation in AD patients. Ways to restore NREM SWA are proposed for animal models and Alzheimer's patients, where these might lead to a promising therapeutic strategy for AD. Abbreviations: NREM SWS, non-rapid eye movement slow wave sleep; SWA, slow wave activity; Aβ, amyloid-beta; AD, Alzheimer's disease; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

Aberrations in SWA correlated with disrupted memory consolidation in MCI patients (Westerberg et al., 2012) and older adults (Mander et al., 2015). Therefore, it stands to reason that slow oscillation disruptions in individuals with early AD might contribute to and accelerate the progressive memory and cognitive decline. In turn, AD pathology might further disrupt sleep-dependent brain rhythm activity that further exacerbates AD (**Figure 1**).

Glymphatic system hypothesis, although still debated (Abbott et al., 2018), states that soluble Aβ is cleared along perivascular pathways, including through the glymphatic system (Iliff et al., 2012). SWS enhanced the clearance of Aβ when compared to the waking state (Xie et al., 2013). Interestingly, soluble Aβ levels fluctuated with the sleep-wake cycle in humans. Aβ levels were elevated during waking and declined during sleep (Kang et al., 2009; Lucey et al., 2017), suggesting that sleep facilitates Aβ clearance. Thus, there is accumulating evidence for a relationship between Aβ, sleep and neuronal activity disruptions (**Figure 1**).

SWA DISRUPTIONS IN MOUSE MODELS OF AD

Mouse models of AD provide a powerful means to study SWA disruptions. Amyloidosis models recapitulate Aβ production, amyloid plaque deposition and associated neuropathology exhibited by Alzheimer's patients. Tauopathy models mimic tau production, intracellular tau tangles and associated neuropathology. Furthermore, slow oscillation disruptions were recapitulated in mouse models of amyloidosis and tauopathy (Holth et al., 2017; Kastanenka et al., 2017; Castano-Prat et al., 2019). Wide field imaging using voltage sensitive dyes (VSD) and genetically encoded reporters, in addition to traditional methods, such as electrophysiology, allowed monitoring SWA in mice. Similar to those in humans (Massimini et al., 2004), slow oscillations propagate across cortex in mice as traveling waves between two hemispheres (Mohajerani et al., 2010). We used a transgenic mouse model of amyloidosis (APPswe/PS1dE9 mice; APP mice) to show that the cortical slow wave power but not the frequency was decreased in young (Kastanenka et al., 2017) and older mice (Kastanenka et al., 2019). APP mice spent less time in NREM sleep (Roh et al., 2012). Tg2576 mice exhibited decreases in SWA; and their power spectral density was shifted to higher frequencies (Kent et al., 2018). As for tauopathy models, P301S human tau transgenic mice exhibited sleep-wake cycle disruptions, reductions in NREM sleep and increased wakefulness. Moreover, their SWA was significantly decreased during NREM sleep (Holth et al., 2017). Furthermore, the transgenic mouse model 3xTg-AD, which develops plaque and tangle pathology, exhibited slow waves at lower frequency and reduced firing rate (Castano-Prat et al., 2019). Thus, these animal models recapitulated SWA disruptions exhibited by Alzheimer's patients (Lucey et al., 2019). It should be noted that animal models do not recapitulate all aspects of human condition. Mice have more primitive cortex and hence slow oscillations present in mice are not as complex as those recorded in humans. During aging, sleep in mice undergoes changes, sometimes dissimilar to those in humans. For example, aged mice exhibit less SWS compared to young mice. The power of slow-wave activity in aging mice is increased when measured in frontal cortex, while

slow wave power in aging human adults is decreased. On the other hand, aging mice also exhibit similarities to aging humans. For example, aged mice exhibit increases in sleep fragmentation, increases in sleep duration during active phase of sleep-wake cycle (light for humans, dark for mice), and decreased REM sleep at the end of quiet phase of sleep-wake cycle (Soltani et al., 2019). Thus use of mouse models should be considered with caution when modeling human condition. Despite these limitations, the mouse models were successfully used to monitor and modulate activity of specific neuronal and non-neuronal populations that contribute to the disruptions of slow waves (see below). Uncovering the neural circuit mechanisms that underlie the SWA disruptions could lead to the discovery of novel therapeutic strategies.

MECHANISMS UNDERLYING SWA DISRUPTIONS IN AD

Observations from human studies demonstrated that disrupted SWA contributed to the impairments of memory consolidation in AD patients. However, the mechanisms that underlie SWA disruptions remain largely unknown. Aβ peptides target synapses and disrupt excitatory and inhibitory neurotransmission leading to neural network dysfunction (Selkoe, 2019). This indicates that, SWA anomalies in aMCI and AD patients might be due to the neuronal network dysfunction resulting from neuronal hyper- and hypoactivity. Animal studies using multiphoton microscopy elucidated deficits in inhibitory tone as one possible mechanism for disrupted SWA (Busche et al., 2008; Kastanenka et al., 2017). Deficits in synaptic inhibition led to neuronal hyperactivity (Busche et al., 2008) and caused desynchronized circuit activity within cortical excitatory neurons (Kastanenka et al., 2017). More than 20% of the layer 2/3 cortical neurons exhibited hyperactivity surrounding Aβ plaques. This hyperactivity was reduced when hyperactive neurons were treated with the gamma-aminobutyric acid A ($GABA_A$) agonist diazepam (Busche et al., 2008), while slow oscillations were rescued by topical application of GABA directly onto the somatosensory cortex (Kastanenka et al., 2017). In addition to low GABA levels, the expression of $GABA_A$ and $GABA_B$ receptors was downregulated in APP mice (Kastanenka et al., 2017). Interestingly, application of either $GABA_A$ or $GABA_B$ inhibitors disrupted slow oscillations in healthy wild-type animals, mimicking slow wave disruptions in APP mice (Kastanenka et al., 2017). As we indicated earlier, GABAergic neurons play a critical role in the onset of cortical silent states, the major element of SWA. Topical applications of a $GABA_A$ receptor agonist rescued slow waves and sleep-dependent memory consolidation in transgenic mice (Busche et al., 2015). Thus, APP mice exhibit cortical hyper- and hypoactivity due to deficits in inhibitory elements of the circuit, specifically GABA, $GABA_A$, and $GABA_B$ receptors, the activity of which is necessary and sufficient for normal SWA.

Alzheimer's disease is a truly progressive disorder. Deficits in inhibitory elements of the circuit were followed by deficits in excitatory elements (Kastanenka et al., 2019). The protein levels of the cortical excitatory neurotransmitter glutamate were examined in APP mice. Glutamate levels were comparable in APP and wild-type littermates at 7 months of age (Kastanenka et al., 2017). However, by 9 months of age, APP mice started showing deficits in glutamate levels (Kastanenka et al., 2019). These findings indicate that the disturbances of synaptic inhibition followed by a deficiency in synaptic excitation within the neuronal circuits may be related to the disruptions of slow oscillations in AD. Furthermore, administration of the glutamate receptor antagonists alleviated hyperactivity in APP mice (Busche et al., 2008). Taken together, inhibition deficits followed by excitation deficits within the slow wave circuits most likely contributed to the disruption of slow oscillations early in the disease progression and impaired sleep-dependent memory formation.

In addition to inhibitory and excitatory neurons, cortico-thalamic circuits rely on astrocytes to maintain their normal function (Araque et al., 1999; Poskanzer and Yuste, 2011, 2016). Astrocytes are the glial cells that maintain glutamate and GABA recycling via glutamate/GABA-glutamine cycles. Astrocytes form the tripartite synapses with pre- and post-synaptic neuronal compartments to regulate synaptic transmission via astrocytic calcium signaling (Araque et al., 1999; Newman, 2003). Astrocytic contributions to normal circuit function has been underappreciated until recently (Clarke and Barres, 2013; Kastanenka et al., 2020). Amyloid deposits disrupted astrocytic topology (Galea et al., 2015), and astrocytic calcium dynamics were altered in APP mice (Kuchibhotla et al., 2009). Furthermore, elevations in resting calcium concentrations were reported in astrocytes in APP mice (Kuchibhotla et al., 2009). Thus, aberrant astrocytic activity might contribute to the SWA disruptions in AD. Furthermore, the protein expression levels of glutamate transporters GLAST and GLT-1, which localize specifically to astrocytic plasma membrane, were decreased in the cortex and hippocampus in a mouse model of AD (Schallier et al., 2011). Alterations in astrocytic elements of the circuit were also reported in brain tissue from AD patients. The expression of astrocytic glutamine synthetase was decreased in close proximity to Aβ plaques in AD brains (Robinson, 2000). Interestingly, aberrant expression of glutamine synthetase was detected in a subpopulation of pyramidal neurons in AD individuals (Robinson, 2000), suggesting that the glutamate-glutamine cycle was disrupted. The abnormalities in astrocytic activity may contribute to aberrant neuronal firing and lead to the disruption of neuronal networks, thus perturbing SWA. Indeed, astrocytes participated in triggering slow oscillation UP states *in vitro* (Poskanzer and Yuste, 2011) and *in vivo* (Poskanzer and Yuste, 2016; Szabó et al., 2017). Poskanzer and Yuste (2016) visualized intracellular calcium transients and demonstrated that astrocytes had modulated extracellular glutamate, thus triggering the SWA in mouse brains. Furthermore, Szabó et al. (2017) showed that blocking astrocytic calcium transients resulted in reduced numbers of astrocytes and neurons participating in the SWA. This series of studies supports the idea that astrocytes are necessary and play a critical role in induction of slow oscillation UP states in the cortical circuits. Therefore, astrocytic network studies using animal models are important to understand the role of astrocytes in slow wave dysfunction in AD. Finally,

understanding the role of astrocytes in SWA disruptions might point to a novel therapeutic strategy for Alzheimer's patients.

OPTOGENETIC CONTROL OF SLOW OSCILLATIONS IN MOUSE MODELS OF AD

Optogenetics is a leading-edge research tool that can be used to gain valuable insight into the causal relationship between circuit dynamics and Alzheimer's progression using animal models (Boyden et al., 2005; Li et al., 2005). This methodology provides high spatiotemporal precision with cell-type specificity. Distinct cell types can be targeted *in vivo* using cell-type specific promoters with light-activatable channels or proton pumps (Fenno et al., 2011). Light activation of cells expressing the channels or pumps can be used to manipulate the activity within neural circuits of interest. Optogenetics has been successfully adopted to studies of AD using mouse models.

Optogenetics was used to increase neuronal activity chronically in hippocampal perforant pathway in AD mice. This exacerbated hyperactivity in the circuit and increased interstitial fluid Aβ42 levels as well as Aβ deposition in the projection areas (Yamamoto et al., 2015). Optogenetic-mediated increases in neuronal activity also elevated release and propagation of tau in htau mice (Wu et al., 2016). This evidence further solidified the fact that aberrant synaptic activity facilitated AD progression (Cirrito et al., 2005, 2008). Optogenetics was also used to shed light onto the state of brain rhythms in AD. Optogenetic entrainment of interneurons in the gamma frequency range restored gamma oscillations and reduced Aβ deposition in a mouse model of AD (Iaccarino et al., 2016). Our laboratory reported that light-activation of channelrhodopsin-2 (ChR2)-expressing excitatory neurons at the endogenous frequency of slow waves in APP mice for 4 weeks rescued aberrant slow oscillations by restoring slow wave power. It also restored GABA as well as $GABA_A$ and $GABA_B$ receptor levels (Kastanenka et al., 2017). In addition, chronic restoration of SWA halted Aβ plaque deposition and prevented intraneuronal calcium elevations (defined as calcium overload) (Kastanenka et al., 2017). Alternatively, driving slow waves at twice the endogenous frequency using optogenetics augmented Aβ production, increased neuronal calcium overload and decreased the synaptic spine density (Kastanenka et al., 2019). Optogenetic restoration of circuit activity slowed pathology progression in mouse models of AD, while optogenetic increases in the frequency of slow waves accelerated the progressive pathophysiology and resulted in neuronal network failure.

Similarly, modulations of brain wave activity restored memory deficits in experimental models using optogenetics. Synchronization of SWA in somatosensory and motor cortices using optogenetics was able to restore perceptual memory impairment and prolong memory retention in sleep-deprived mice (Miyamoto et al., 2016). In addition, restoration of hippocampal oscillations with optogenetics resulted in an improvement of recognition memory in APP mice (Giovannetti et al., 2018). Also, optogenetic activation of memory engram cells in hippocampus increased spine density in engram cells and restored long-term memory (Roy et al., 2016). Furthermore, gamma oscillation rescue using optogenetics improved spatial memory in an AD mouse model (Etter et al., 2019). Restoring brain oscillations by optogenetic approaches in mouse models provides insight into novel therapeutic approaches to treat and/or prevent AD altogether. Animal studies suggest that restoring brain oscillation activity, including SWA, may be an effective therapeutic strategy for reducing memory deficits in AD patients.

RESTORING SLOW WAVE SLEEP IS A PROMISING THERAPY FOR AD

Currently, there are no effective treatments able to slow AD progression and alleviate cognitive and memory impairments in patients. The majority of clinical therapeutic approaches focus on clearing Aβ and tau with monoclonal antibodies using passive immunotherapies (van Dyck, 2018). Light therapy had mixed results in the clinic (Dowling et al., 2005, 2008; Riemersma-van der Lek et al., 2008). However, a large number of clinical trial failures underscores the need to identify novel therapeutic strategies for treating AD.

Restoration of SWA during NREM sleep in Alzheimer's patients might slow the disease progression and rescue sleep-dependent memory consolidation. Transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are two noninvasive brain stimulation methodologies that could potentially be used to do so. Recently, tDCS was applied to human MCI subjects during daytime nap to investigate the patterns of SWA and sleep-dependent memory consolidation. Both the slow oscillation power and memory performance were improved after stimulating the brain at the slow oscillation frequency with tDCS (Ladenbauer et al., 2017). Furthermore, repeated applications of tDCS induced slow oscillations during SWS and led to enhanced declarative memory retention the next day in older (Westerberg et al., 2015) and in young healthy adults (Marshall et al., 2004, 2006). In a similar study, TMS was used to evoke slow waves during NREM sleep. TMS increased SWA power in healthy young subjects (Massimini et al., 2007). In addition to tDCS and TMS methodologies, slow oscillations can be enhanced with auditory stimulation (Ngo et al., 2013; Leminen et al., 2017; Papalambros et al., 2017; Ong et al., 2018). Applied auditory tones that were phase-locked to the up states of slow oscillations during sleep benefited declarative memory consolidation in healthy young adults (Ngo et al., 2013; Leminen et al., 2017) and in older subjects (Papalambros et al., 2017). Furthermore, phase-locked acoustic stimulation also enhanced memory encoding during nap in healthy young subjects (Ong et al., 2018). Another sensory stimulation strategy visual stimulation, can be used to induce SWA (Riedner et al., 2011). Using high-density EEG recordings in healthy young subjects during NREM sleep, SWA was successfully evoked by visual stimuli (Riedner et al., 2011). Thus, tDCS, TMS, acoustic, and visual stimulations could potentially be used to enhance sleep-dependent memory consolidation in healthy subjects and AD patients in early stages of the disease.

Targeting specific GABAergic neuronal circuit elements may be particularly attractive in designing new AD therapies. Whereas restoration of parvalbumin interneuron activity acutely restored gamma oscillations (Iaccarino et al., 2016) and prevented memory loss as well as network hyperexcitability (Hijazi et al., 2019), activation of either neuronal nitric oxide synthase (nNOS) or somatostatin neurons may be useful for restoring SWA. A recent study involving the chemogenetic activation of SST-positive cells in the cerebral cortex showed increased SWA, elevated slope of individual slow waves, and prolonged NREM sleep duration compared to control conditions. Alternatively, chemogenetic inhibition of these cells reduced SWA and slow-wave incidence without changing time spent in NREM sleep (Funk et al., 2017). We previously demonstrated that nNOS neurons are activated during episodes of NREM sleep associated with increased SWA (Gerashchenko et al., 2008). We also showed that optogenetically evoked responses in nNOS-positive cells of the cerebral cortex are consistent with their role in slow-wave sleep physiology (Gerashchenko et al., 2018). Furthermore, mice lacking nNOS expression in SST positive neurons exhibited significant impairments in both homeostatic low delta frequency range SWA production and a recognition memory task that relies on cortical input (Zielinski et al., 2019). Further studies will determine whether activation of nNOS/somatostatin neurons in the cerebral cortex is efficient in reducing AD pathology, and whether this effect is mediated by SWA enhancement. Finally, instead of activating endogenous interneurons, it would be promising to explore cell-based therapeutic strategies, such as transplantation of human stem cell-derived interneurons to increase inhibitory tone and restore SWA.

DISCUSSION

In addition to memory disruptions, Alzheimer's patients experience disturbances in their sleep-wake cycles, due to increased nighttime wakefulness and decreased NREM SWS. AD pathology is correlated with SWA disruptions at the early stages of AD. Decreased SWA was found in asymptomatic cognitively normal adults and aMCI patients. Since slow oscillation disruption is an early event, it has the potential to be used as an early biomarker for AD. It should be noted that a lot of human studies discussed here were based on a low sample size at higher risk for false positives due to random variations in a small number of data points. Thus replications are needed to validate the findings. Nevertheless, disruptions in slow oscillations might underlie the memory impairments as part of AD progression, since SWA plays a key role in declarative memory consolidation during sleep. Moreover, animal models of AD recapitulate the slow wave disruptions and can be used for mechanistic studies. Use of leading-edge technologies, including optogenetics, wide-field imaging and multiphoton microscopy, in addition to traditional technologies, including electrophysiology, provided insight into the mechanisms of slow wave disruptions in AD. A better understanding of the relationship between SWA disruptions and memory decline may shed light on the mechanistic pathways underlying AD-associated memory impairment. SWA restoration provides a promising novel therapeutic target for AD. Utilizing noninvasive brain stimulation technologies and medications that upregulate inhibitory elements of cortico-thalamic circuits may prove to become efficient therapeutic strategies. Development of novel therapeutic interventions targeting SWA during NREM sleep early in the disease progression might slow memory decline in the elderly and delay AD onset in MCI or healthy individuals at risk for developing AD.

AUTHOR CONTRIBUTIONS

YL and KK wrote the original draft of the manuscript. YL and KK prepared the figure. YL, DG, IT, BB, and KK reviewed and edited the final manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Neuroscience

MINI REVIEW
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Evaluating Circadian Dysfunction in Mouse Models of Alzheimer's Disease: Where Do We Stand?

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Circadian dysfunction has been described in patients with symptomatic Alzheimer's disease (AD), as well as in presymptomatic phases of the disease. Modeling this circadian dysfunction in mouse models would provide an optimal platform for understanding mechanisms and developing therapies. While numerous studies have examined behavioral circadian function, and in some cases clock gene oscillation, in mouse models of AD, the results are variable and inconsistent across models, ages, and conditions. Ultimately, circadian changes observed in APP/PS1 models are inconsistent across studies and do not always replicate circadian phenotypes observed in human AD. Other models, including the 3xTG mouse, tau transgenic lines, and the accelerated aging SAMP8 line, show circadian phenotypes more consistent with human AD, although the literature is either inconsistent or minimal. We summarize these data and provide some recommendations to improve and standardize future studies of circadian function in AD mouse models.

Keywords: circadian, Alzheimer's disease, clock, tau, amyloid

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INTRODUCTION

Numerous human studies have demonstrated that changes in circadian function are common in Alzheimer's disease (AD) patients and contribute to disease morbidity. Circadian changes observed in AD patients include circadian fragmentation and decreased amplitude of circadian rhythms, which generally manifest as increased wakefulness at night and increased napping during the day (Satlin et al., 1995; Ancoli-Israel et al., 1997). These changes are observed in patients with preclinical AD pathology, meaning that they harbor amyloid plaque and/or tau pathology but do not yet have cognitive symptoms (Musiek et al., 2018). They are also evident in the mild cognitive impairment stage and worsen with disease severity. In symptomatic AD patients, a phase delay has been described, which means that the peak of activity occurs later in the day (Satlin et al., 1995; Ancoli-Israel et al., 1997). This phase delay has been hypothesized as a possible cause of "sundowning" in AD, or increased confusion and agitation in the afternoon and evening (Volicer et al., 2001). As the disease progresses, some patients develop severe fragmentation of circadian rhythms, leading to poor behavioral differentiation between day and night (Ancoli-Israel et al., 1997; Hatfield et al., 2004). The underlying mechanisms governing this circadian dysfunction

Abbreviations: Aβ, amyloid-beta peptide; AD, Alzheimer's disease; ApoE, apolipoprotein E; APP, amyloid precursor protein; DD, constant darkness; LD; 12 h light:dark cycle; IV, intradaily variability; PS1, presenilin 1; SAMP8, senescence accelerated mouse P8; SCN, suprachiasmatic nucleus; 3xTG, APP/PS1/tau triple transgenic mouse.

are not well understood, creating a need for accurate mouse models which replicate some of these phenotypes.

Circadian biology can be a daunting field for AD researchers. Thus, a brief introduction to common circadian parameters may be helpful (Banks and Nolan, 2011). Circadian period is the length of time of a full circadian cycle. This can only be measured under "constant conditions" (usually meaning constant darkness for mice, indicated as "DD"). Most mice have a period just under 24 h in constant darkness; shortening or lengthening of period can be indicative of changes in the circadian clock itself. Amplitude indicates the difference between the peak and nadir of activity, averaged over several days. In general, mice should have minimal activity during the light phase (as they are nocturnal and sleeping), but are very active during the dark phase. Increased activity during the light phase and decreased activity in the dark would indicate blunted circadian amplitude, as is seen in AD patients. However, generally hyperactive animals can be overactive during the dark phase and have a high amplitude, while hypoactive animals may be inactive during both phases and show artificially blunted amplitude. If these differences in baseline activity levels are altered in transgenic mouse models, it may lead to difficulty interpreting circadian behavioral analyses. Phase indicates the time of day of peak activity, averaged over several days. A later peak (phase delay) is seen in AD patients. Fragmentation indicates a breakdown of circadian timing to drive consolidated periods of rest and activity. Fragmentation usually leads to a blunted amplitude, or can be measured by a non-parametric test called intradaily variability (IV) (Huang et al., 2002). Of note, circadian rhythms in behavior are largely driven by the activity of the suprachiasmatic nucleus (SCN) of the hypothalamus, the "master clock" of the body. Degeneration or dysfunction of the SCN, as has been described in human AD (Swaab et al., 1985), can lead to weaker circadian synchronization, increased fragmentation, and decreased amplitude (Nakamura et al., 2011). At a molecular level, circadian rhythms are driven by oscillations of circadian clock genes in the SCN and other tissues. These circadian clock genes include *Bmal1* and *Clock*, which function as transcription factors to drive transcription of their own repressors: *Per1, Per2, Per3, Cry1, Cry2*, and Rev-erbα and β. Levels of these clock gene transcripts oscillate with a 24-h period in most tissue and are entrained to daily light cycles (Buhr and Takahashi, 2013). Thus, measurement of clock gene oscillations in SCN and other tissues can be a molecular marker of clock function.

Over the past 20 years, a considerable literature has arisen in which circadian parameters have been examined in various AD models. Many of these studies have described modest changes in AD model mice, though these changes vary considerably between studies. The sheer number of distinct AD mouse models, as well as the age- and sex-dependency of pathology in these models, has complicated things further. Thus, it remains difficult to identify AD models which consistently and faithfully recapitulate the findings observed in human AD. Below, we have attempted to divide AD mouse models into their most common categories, and to review the existing literature on circadian rhythms in these models. These data are compiled in **Table 1**. While not an exhaustive or systematic review, the included studies represent many of the vast majority of published studies, as well as the most commonly cited and most thorough studies of circadian function in AD mouse models (other species were excluded), and thus provide what we believe is a representative sample of the literature.

APP and APP/PS1 Mice

There are a multitude of different transgenic mouse lines which express human amyloid precursor protein (APP) and in some cases human presenilin 1 (PS1), both harboring a variety of AD-associated mutations which promote amyloid-beta (Aβ) generation and aggregation. These mice accumulate amyloid plaque pathology at variable ages and in varying brain regions depending on the specific transgene and sex of the animal. APP/PS1 mice also vary in the biochemical character of the plaques that are formed, as well as the presence or absence of intracellular amyloid. Presumably, APP and APP/PS1 mice model the earliest stage of AD, that being amyloid plaque deposition, as most of these models develop minimal tau pathology or overt neurodegeneration. Humans with preclinical AD or MCI have been shown to have decreased circadian amplitude, increased fragmentation, and, in MCI, a phase delay (Naismith et al., 2014; Ortiz-Tudela et al., 2014). However, results of circadian studies in APP and APP/PS1 mice do not clearly demonstrate consistent AD-like phenotypes. Several studies have shown increased activity in these mouse lines during the dark phase (the active phase of mice), as well as increases in circadian amplitude (Ambrée et al., 2006; Bedrosian et al., 2011; Baño Otalora et al., 2012; Oyegbami et al., 2017). Aside from this, the wide variety of subtle and oft-conflicting circadian phenotypes in APP and APP/PS1 mouse studies can be appreciated in **Table 1**. Thus, a clear circadian phenotype which models early human AD has not emerged from the literature. Recently, Kent et al. conducted a very thorough study of APPswe/PS1dE9 mice, a commonly used APP/PS1 model which developed plaques around 6 months old (mo). This study, which examined mice at multiple ages and included a variety of light manipulations and *Per2*-luciferase rhythm recordings in SCN and various peripheral tissues (such as liver, lung, and spleen), revealed only a minimal delay in activity onset after lights-off in transgenic mice (Kent et al., 2019). Moreover, several studies demonstrate circadian changes which precede amyloid plaque pathology, suggesting possible strain or transgene effects, though an effect of soluble Aβ cannot be excluded (Bedrosian et al., 2011; Ortiz-Tudela et al., 2014; Oyegbami et al., 2017; Ni et al., 2019). While not a true circadian study, Roh et al. (2012) demonstrated blunting of amplitude in diurnal rhythms in sleep and brain lactate levels in APPswe/PS1dE9 mice, which was reversible with immunization of an anti-Aβ antibody, suggesting that amyloid pathology may indeed contribute to some aspects of rhythm dysfunction. Paul et al. (2018) examined the TgSwDI APP mutant mouse and observed shortened period and increased variability in activity onset/offset that were associated with blunted amplitude of neuronal firing in the SCN, providing an electrophysiological basis for rhythm disturbance. A human BACE1 knockin mouse, which drives intracellular amyloid accumulation without APP overexpression, showed decreased dark-phase activity but no

TABLE 1 | Summary of studies of circadian function in mouse models of AD.

Citation/PMID	Mouse model	Age	Conclusions/effects observed	DD	Comments
Oyegbami et al., 2017 28317486	APPswe/PS1dE9	2 months	Transgenic (Tg) mice have increased daily activity and increased activity amplitude with a slightly shorter period. *Cry1* and *Cry2* expression seems blunted in the medulla pons at ZT2 and ZT14	Yes	No pathology shown. Measurements are taken before pathology should be present. Difficult to tell whether oscillations in clock genes are blunted with only two time points
Baño Otalora et al., 2012 22823866	APPswe/PS1dE9	3.5–5.5 months	Response to phase shifting paradigms was not altered in Tg mice. Body temperature increased in the light phase in Tg mice and intradaily variability of body temperature was not affected. Tg mice showed no difference in period or locomotor activity	Yes	No pathology shown. Measurements are taken before pathology should be present
Kent et al., 2019 30884411	APPswe/PS1dE9	6, 9, 12, and 19 months	No difference in period, response to phase shifting, total daily activity, melanopsin expression, ultradian rhythms, intradaily variability, number or duration of activity bouts, food anticipatory behavior, synchrony in peripheral oscillators or total time spent asleep. Tg mice have slightly delayed activity onset and exhibit increased activity in the second half of the night	Yes	Pathology was only shown at 7 and 10 months of age and was not correlated to circadian parameters assessed
Ma et al., 2016 27796320	APPswe/PS1dE9	12–15 months	*Per2* and *Cry1* mRNA amplitudes decreased in hippocampus in Tg mice sampled at 6-h time intervals	No	mRNA rhythms were not quantified. Age is appropriate to have plaque pathology
Paul et al., 2018 29540298	tg-SwDI (APP mutant)	3, 6, 10 months	Tg mice with shortened period in DD, more variable activity onset/offset. SCN neuronal firing amplitude decreased (less during day, more during night)	Yes	SCN electrical records are unique. No pathology shown
Ni et al., 2019 31470863	APP-KI	2 months	Isolated cortical microglia from 2-month-old Tg mice at 4-h time intervals have less *Bmal1*, *Per2,* and *Rev-erbα* on average. Amplitude of most clock genes were decreased in these microglia	No	Did not show pathology. Mice this young should not have disease pathology
Bedrosian et al., 2011 21709248	Tg2576 (APPswe)	5 and 9 months	Increased daily activity in the dark phase in Tg mice	No	No constant conditions or pathology shown
Wisor et al., 2005 15708480	tg2576 (APPswe)	5–17 months	Age-dependent increase in period in DD. No other circadian analyses	Yes	No pathology shown
Sundaram et al., 2019 31551449	APPSwe crossed with PS1 line 5.1	9–10 months	Tg mice have a slightly shorter period in DD and increased intradaily variability. No difference in overall activity observed but Tg mice had an increased activity amplitude at the peak of the active cycle which did not persist in DD	Yes	
Duncan et al., 2012 22634208	APP^{NLH}/PS-1^{P264L}	4, 11, and 15 months	Tg mice show no difference in activity rhythms. VIP and vasopressin were not altered in the SCN. No change in AM/PM *Per2* expression in the hippocampus, cingulate or motor cortex, but blunted PM *Per2* expression in SCN of Tg mice. Amount of wheel running activity in the light phase was significantly decreased in Tg mice	No	Showed pathology at all time points using an Aβ ELISA. No constant conditions
Lee et al., 2020 31800167	5x FAD (APP/PS1)	6.5 months	BMAL1 protein is decreased in the cortex of Tg mice. *Per2* mRNA is decreased in the hippocampus and cortex of Tg mice while *Per1* is only shown to decrease in the hippocampus	No	Only checked expression level at a single time point throughout the day

(Continued)

TABLE 1 | Continued

Citation/PMID	Mouse model	Age	Conclusions/effects observed	DD	Comments
Song et al., 2015 25888034	5x FAD (APP/PS1)	2 and 8 months	Tg mice have decreased activity at 8 months of age and decreased body temperature amplitude that persists in DD. Protein levels and mRNA expression of *Bmal1* and *Rev-erbα* are altered in the SCN of 2-month-old Tg mice measured at 4-h intervals. BMAL1 protein rhythms are blunted	Yes	No rhythmic analysis on mRNA or protein measurements. No pathology shown. mRNA analysis was done before pathology should be present
Boggs et al., 2017 28958954	J20 APP/Apoe4	6 and 12 months	Activity onset was delayed in Tg mice at 6 and 12 months of age. Tg mice show decreased activity in the light phase at 12 months of age and no difference in activity in the dark phase	No	No pathology shown
Ambrée et al., 2006 15993515	TgCRND8	30, 60, 90, 120 days	Increased daily activity in Tg mice at all ages	No	No constant conditions and no pathology shown. Circadian changes occur before pathology is likely present
Adler et al., 2019 31334659	3xTG-AD	10–11 months	Tg mice have a slightly shorter period in DD and displayed irregular activity onsets	Yes	No pathology shown
Knight et al., 2013 22864021	3xTG-AD	4, 6, 8, 9, 10 months	Tg mice have a higher body temperature amplitude as they age. Increase in activity amplitude not seen until mice are 10 months of age. No pathology seen in the hypothalamus of 12-month-old Tg mice	No	No constant conditions and pathology is only shown at one time point (12 months old)
Wu et al., 2018 29626648	3xTG-AD	6 months	Tg mice have a slightly shorter period with a lower daily activity and a smaller activity amplitude. Tg mice also have an increase in intradaily variability. *Per1* and P*er2* mRNA in the SCN seem to have a phase delay of 4 h in Tg mice	Yes	Never show differences in pathology, no statistical analysis of rhythms or phase. mRNA not harvested under DD
Bellanti et al., 2017 28671110	3xTG-AD	6 and 18 month old	Examine mRNA of several clock genes in SCN, hippocampus, and frontal cortex of 3xTG mice, at lights on (ZT0, 7 am) or lights off (ZT12, 7 pm). Two ages assessed. Blunting of Bmal1 expression in the SCN, along with some other changes in clock gene expression in older mice	No	No constant conditions, cannot differentiate effects of light exposure from those of circadian time. Multiple brain regions and ages is a strength
Sterniczuk et al., 2010 20471965	3xTG-AD	Various	Tg male mice have elevated light and dark phase activity, not age-dependent. Female Tg mice post-plaque pathology show decreased activity during dark. Shorter period in males only in DD. Male Tg mice have fewer AVP and VIP cells in the SCN (females not assessed). No difference observed in response to phase shifting	Yes	Only period is assessed in DD. No pathology shown outside of SCN, although SCN pathology and sex discrimination is a strength
Stevanovic et al., 2017 28461004	Tg4510 Tau	8 months	Tg mice have a longer free running period and are more active in the light phase, which does not persist in constant conditions. PER2 protein is decreased in the hypothalamus and hippocampus of Tg mice at two time points, with no difference in BMAL1 expression. Phosphorylated tau is present in the SCN at 8 months of age	Yes	Only checked at one age-unclear if these effects are due to the progression of pathology. Harvest of tissue in DD is a strength. Difficult to make conclusions of Bmal1 and Per2 oscillations with only two time points
Miyamoto et al., 1986 3786521	SAMP8	2,6,8,12 months	Tg mice have increased activity in the light phase and decreased in dark phase, decreased amplitude	No	No constant conditions

(Continued)

TABLE 1 | Continued

Citation/PMID	Mouse model	Age	Conclusions/effects observed	DD	Comments
Pang et al., 2004 14675737	SAMP8	2, 7, 12 months	Period of SAMP8 mice does not change with age, although overall activity declines	Yes	Compared Tg mice to themselves at various ages, not to WT mice
McAuley et al., 2002 12009511	SAMP8	2, 7, 12 months	SAMP8 mice show decreased amplitude, increases activity during light phase, and rhythm "splitting" with additional peak of activity	Yes	Compared Tg mice to themselves at various ages, not to WT mice
Sánchez-Barceló et al., 1997 9383106	SAMP8	4-5 months	SAMP8 mice show no difference in vasopressin staining in the SCN at ~5 months of age. They also entrain faster to a 6-h phase shift	N/A	
Zhou et al., 2016 7824104	Apoe$^{-/-}$	6 weeks	KO mice show increased onset variability, decreased activity amplitude in DD, slower entrainment to light shift. Increased clock gene expression variability in SCN, increased tau aggregation and synaptic degeneration in SCN, and decreased melanopsin in retina	Yes	Not a true AD model, relevance of ApoE KO to AD is unclear
Wang et al., 2016 27021954	$A\beta_{31-35}$ injection into hippocampus of WT mice	6–8 weeks	Injected mice had lengthened period in DD, blunted clock gene expression in SCN and heart	Yes	Unusual AD model, relevance to AD pathogenesis is unclear
Plucinska et al., 2014 25100603	PLB4 mice (hBACE1 knockin)	3, 6, 12 months	No differences noted in circadian rhythms, except for a significant decrease in activity in both the light and dark phase in Tg mice at 6 months of age. This measurement was trending but not significant at 12 months	No	Model avoids APP overexpression. Pathology is shown. Mouse develops intracellular amyloid rather than plaques, relevance is unclear

other major circadian alterations, though assessment was limited (Plucinska et al., 2014). An issue with the wide array of APP and APP/PS1 is that these transgenes are driven by specific promoters (including the Thy1 and prion protein promoters) which may not express in all relevant cell types and regions (such as the SCN and circadian output pathways). This variability of transgene expression may account for some of the inconsistency in circadian phenotypes across APP/PS1 models. While APP and APP/PS1 models have been the most studied in terms of circadian function, the wide array of unique APP and APP/PS1 lines, as well as the possible amyloid-independent effects of these transgenes on activity level, has led to a murky literature which undermines the utility of these models for examining circadian changes.

Tauopathy Models

Tau transgenic mice overexpress the human MAPT gene with disease-causing mutations (often P301S or P301L) and are often used to model tauopathy associated with AD. Unlike APP mice, tau transgenics generally develop striking neurodegeneration and premature death. The Tg4510 mouse, an aggressive model of tauopathy which expresses $MAPT^{P301L}$ (Ramsden et al., 2005), develops a lengthened circadian period and decreased circadian amplitude, as well as seemingly blunted circadian clock gene expression in the hypothalamus and hippocampus when measured at two times of day (Stevanovic et al., 2017). These changes were observed at 8 mo, when severe tau pathology is present. SCN tau pathology was also noted in this study. A study of $MAPT^{P301S}$ PS19 mice, which focused exclusively on sleep, showed a decrease in sleep and an increase in wakefulness, suggesting a possible underlying circadian deficit, very late in the disease progression (Holth et al., 2017). While promising, further studies of circadian function in tauopathy models are needed to determine how robust and consistent these changes are across tau models and studies.

3xTG Mice

The 3xTG mouse was introduced in 2003 as a murine model of both of the hallmark neuropathologies of human AD: amyloid plaques and tau tangles. 3xTG mice express three transgenes (APP Swedish, MAPT P301L, and PS1 M146V) and develop amyloid plaque pathology starting around 4 months, with aggregated tau pathology beginning around 12 months (Oddo et al., 2003). Several studies have examined circadian function in 3xTG mice, some of which describe phenotypes which more closely resemble human AD. However, results are fraught with inconsistency across different studies. Wu et al. (2018) show a striking decrease in amplitude, less daily activity, and fragmentation (increased IV) in 6 mo 3xTG mice, reminiscent of human AD circadian dysfunction. Knight et al. (2013) report no changes in activity profile in 6 mo 3xTG mice and go on to show an increased amplitude in daily activity and temperature rhythm by 10 months. Moreover, Sterniczuk et al. (2010) show increased amplitude and daytime activity in four month old male mice while female mice show a decreased amplitude by 11 months. Finally, Adler et al. (2019) showed a shortened period and decreased amplitude in 3xTG mice which was ameliorated by inhibiting casein kinase 1δ and 1ε, enzymes that are important

for the degradation of PER proteins and maintenance of core clock function. Thus, while the 3xTG mouse shows some promise as a more accurate model of AD-like circadian changes, the inconsistency across studies makes interpretation difficult. It is also notable that these circadian changes were all observed at ages prior to the accumulation of considerable tau pathology. Of note, a different triple-transgenic mouse expressing APP, hTau, and PS1, specifically in the forebrain (PLB1 mice), did not show obvious circadian deficits, suggesting that SCN-dependent expression of pathology may be important (Platt et al., 2011).

Other AD Models

The Senescence Accelerated Mouse, line P8 (SAMP8 mouse) is a unique, non-transgenic mouse line that has been selectively bred to promote accelerated aging (Butterfield and Poon, 2005; Ramsden et al., 2005; Holth et al., 2017; Stevanovic et al., 2017). SAMP8 mice are usually compared to another SAM mouse line which is aging-resistant (SAMR1) as a control. SAMP8 mice spontaneously develop mild amyloid-beta accumulation, mild tauopathy, synapse loss, and cognitive impairment early in life, and have been used as a model of AD (Morley et al., 2012). SAMP8 mice show striking circadian changes, including increased activity during light phase, decreased circadian amplitude, and fragmentation (Miyamoto et al., 1986; McAuley et al., 2002; Pang et al., 2004), although this has not always been reported (Sánchez-Barceló et al., 1997). Like APP mice, they show a general hyperactivity phenotype, which complicates interpretation. However, the striking circadian changes observed in several studies suggest that SAMP8 mice have potential as a model of age and AD related circadian dysfunction.

Apolipoprotein E (ApoE) genotype is the major genetic risk factor for sporadic AD, with the E4 allele imparting increased risk. Apoe−/− mice have been reported to have more variable activity rhythms in DD, impaired entrainment, and alterations of SCN clock gene expression rhythms (Zhou et al., 2016). However, APP mice expressing human ApoE4 do not have more severe circadian changes than APP with wild type mouse ApoE (Graybeal et al., 2015; Boggs et al., 2017). This is an unexpected finding, as ApoE4 increases amyloid pathology in mice (Castellano et al., 2011) and might be expected to exacerbate circadian dysfunction. More detailed studies which incorporate pathology assessments are needed. Injection of Aβ peptide into the brain of wild type mice has also been used to model AD, and has been reported to lengthen period and blunt clock gene rhythms in the SCN (Navigatore-Fonzo et al., 2017), and to alter expression patterns of *Apoe* and other mRNAs in the hippocampus (Wang et al., 2016), though this model is not widely used.

Impact of AD Pathology on Clock Gene Expression

Differences in circadian outputs at the level of sleep-wake cycles can generally be correlated to changes in the molecular clock. However, differences in clock gene expression in studies of AD models are generally difficult to interpret. For example, some studies have suggested decreased expression of clock genes in AD models before the onset of pathology. Oyegbami et al. (2017) show a decrease in *Cry1* and *Cry2* in the medulla pons of 2-month-old APPswe/PS1dE9 mice, while Ni et al. (2019) show a decrease in *Bmal1*, *Per2,* and *Rev-erbα* in isolated cortical microglia from 2-month-old APP-KI mice (both well before plaque deposition occurs). Song et al. (2015) showed blunting of rhythmic BMAL1 protein levels prior to disease pathology in the SCN of 2 mo 5xFAD mice (an APP/PS1 mutant model). These may indicate an effect of soluble Aβ, or effects of the transgene/mutation introduced, highlighting the importance of these assays at multiple ages over the course of disease pathology. Wu et al. (2018) showed a slight phase delay and decreased expression of *Per1/2* in the SCN of 3xTG mice, while Ma et al. (2016) showed altered rhythms in hippocampal *Bace2* and *Apoe* mRNA. Other studies in AD models have examined clock gene expression at one or two time points throughout the circadian cycle, usually early morning and early evening, in some case showing a loss of variation in AD mice (Duncan et al., 2012; Bellanti et al., 2017; Stevanovic et al., 2017; Lee et al., 2020). While these can be used to make general conclusions, it is difficult to interpret if clock genes are changing amplitude, or if there is just a difference in phase of expression of that particular gene. Detailed time courses of circadian gene expression in different brain regions of AD mouse models at pathology-bearing ages are needed to thoroughly address this issue.

Recommendations for Circadian Studies in AD Mouse Models

Considering the complexity of this literature, we offer here some recommendations for future studies of circadian rhythms in AD mouse models:

Constant conditions: Mouse activity must be recorded under constant conditions (usually constant darkness or dim light) in order to make firm conclusions about the circadian system. Many studies of behavioral rhythms in AD model mice are conducted in 12:12 h light:dark, which introduces factors related to light intensity, as well as the issue of "masking," or behavioral suppression by light which occurs independently of the circadian system. Furthermore, previous studies have shown some rhythm abnormalities in AD models in 12:12 h light:dark cycles that resolve in constant conditions (Stevanovic et al., 2017; Sundaram et al., 2019). Moreover, tissue harvests for clock gene expression studies should also be conducted in DD, as light can impact clock gene expression (Moriya et al., 2000).

Correlation with pathology: Many studies of circadian function in AD models do not describe or quantify the degree of pathology in their mice. It is important to demonstrate the degree of pathology (amyloid plaque burden, tau pathology, etc.) in the mice at the same age and in the same sex that are used for behavioral studies. While previous papers can be used as general guidelines, mice of a similar genotype can have very different pathology when raised in different colonies and facilities. Moreover, circadian deficits arising in AD mice well before pathology may suggest behavioral effects of transgene overexpression, rather than true pathology-driven changes. Indeed, behavioral changes in 3xTG can be dependent

on genetic background (Pardossi-Piquard et al., 2016). Finally, it is potentially important to assess the degree of pathology in the SCN in these mouse models, to see if there is a direct effect on the central pacemaker. SCN pathology has only been analyzed in a few models, as 3xTG mice do not have plaques or tangles at 12 months, while Tg4510 mice do have SCN tau pathology at 8 months (Knight et al., 2013; Stevanovic et al., 2017). Even in the absence of clear plaque pathology, it is possible that soluble Aβ species (such as oligomers) may impact SCN function, though levels and dynamics of soluble Aβ species in the SCN have not been examined. Finally, human post-mortem AD SCN generally shows neuronal loss and tau pathology, rather than plaques, which may not be recapitulated in amyloid-based models (Stopa et al., 1999).

Multiple endpoints: Most studies focus on rhythms in wheel running as the primary endpoint. While some have included temperature or some limited clock gene investigation, little is known about other circadian endpoints. Peripheral clocks, for instance, could be disrupted even in the face of normal-appearing wheel running behavior. Some studies do examine *Per2*-luciferase rhythms in SCN explants (Kent et al., 2019), clock gene expression in SCN (Song et al., 2015; Stevanovic et al., 2017), or SCN firing rate (Paul et al., 2018). Integration of multiple endpoints in future studies may reveal important phenotypes.

Sex and age considerations: Sex has a strong effect on both circadian rhythms, as well as on pathology in AD models. In general, female APP and APP/PS1 mouse lines develop amyloid plaques faster than males, while this relationship is reversed for the accumulation of tau pathology in MAPT mice (Carroll et al., 2010; Sun et al., 2020). Furthermore, there is potentially conflicting effects of sex on circadian biology that could further complicate these studies (Bailey and Silver, 2014). Thus, sex must always be considered. Age also has strong effects on circadian function, but is less clearly tied to amyloid/tau pathology in mouse models, as specific transgene/mutations can drive pathology at vastly different ages. In some cases, mice develop plaques when they are still young, while in others age and amyloid pathology come together and may interact (Wisor et al., 2005). Thus, the effects of age itself, and the rate of pathology accumulation, must be considered.

CONCLUSION

In summary, while many AD mouse models exhibit alterations in circadian behavioral rhythms and/or gene expression, these changes are generally not consistent across studies or models, or have questionable relevance to human AD. As such, it is still unclear if specific protein pathologies (such as amyloid or tau aggregation) directly drive circadian changes, or if these observed changes are due to other factors (such as transgene overexpression, genetic background, sex, or age). As new AD models are developed, circadian studies must consider basic study design principles, degree of pathology, age, and sex, in order to provide interpretable and consistent results.

AUTHOR CONTRIBUTIONS

PS and EM assessed the literature and wrote the manuscript. PS created **Table 1**. PS and EM edited the manuscript. Both authors contributed to the article and approved the submitted version.

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REVIEW
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Molecular Crosstalk Between Circadian Rhythmicity and the Development of Neurodegenerative Disorders

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Neurodegenerative disorders have been shown to exhibit substantial interconnectedness with circadian rhythmicity. Alzheimer's patients exhibit high degradation of the suprachiasmatic nucleus (SCN), the central endogenous circadian timekeeper, and Parkinson's patients have highly disrupted peripheral clock gene expression. Disrupted sleep patterns are highly evident in patients with neurodegenerative diseases; fragmented sleep has been shown to affect tau-protein accumulation in Alzheimer's patients, and rapid eye movement (REM) behavioral disorder is observed in a significant amount of Parkinson's patients. Although numerous studies exist analyzing the mechanisms of neurodegeneration and circadian rhythm function independently, molecular mechanisms establishing specific links between the two must be explored further. Thus, in this review, we explore the possible intersecting molecular mechanisms between circadian rhythm and neurodegeneration, with a particular focus on Parkinson's disease. We provide evidence for potential influences of E3 ligase and poly adenosine diphosphate (ADP-ribose) polymerase 1 (PARP1) activity on neurodegenerative pathology. The cellular stress and subsequent DNA damage signaling imposed by hyperactivity of these multiple molecular systems in addition to aberrant circadian rhythmicity lead to extensive protein aggregation such as α-synuclein pre-formed fibrils (α-Syn PFFs), suggesting a specific molecular pathway linking circadian rhythmicity, PARP1/E3 ligase activity, and Parkinson's disease.

Keywords: circadian rhythm, DNA damage, PARP1, PAR-dependent E3 ligase, α-synuclein pre-formed fibrils, β-amyloid peptides, Parkinson's disease, Alzheimer's disease

MOLECULAR MACHINERY OF CIRCADIAN RHYTHMICITY

Living systems on earth are governed by many natural laws, but circadian rhythms play one of the most important roles in sustaining organisms, acting as the biological timekeepers that perpetuate life from mere seconds to the full Gregorian year. Mammalian circadian rhythms can be observed from the genetic level to the tissue level, and even to the macroscopic level, affecting

behavior, biochemical and physiological processes. Genetic and cellular clocks dictate *tau* (free running period of the organism ∼24 h) and are often entrained by photo-optic cues (Dunlap and Loros, 2017). Light, as the external stimulus, activates intrinsically photosensitive retinal ganglion cells (ipRGCs), which innervate the suprachiasmatic nucleus (SCN) in mammals, entraining the mammal to the 24-h day (Do and Yau, 2010). The SCN assumes the role as the central pacemaker, and through a series of genetic feedback loops and highly coordinated neuronal innervation, endogenous timekeeping activity arises, giving way to the production of circadian rhythm. To garner a more comprehensive understanding of the effects of circadian rhythms on health and neurodegeneration, the underlying fundamental molecular mechanisms and interrelated processes must be explored (Cox and Takahashi, 2019).

A set of core genes constitutes this transcriptional pathway that forms the identity of the endogenous circadian pacemaker. Two heterodimerization transcription factors, CLOCK and BMAL1, activate the production of the period (*Per*) and cryptochrome (*Cry*) genes (Yoo et al., 2005; **Figure 1**). The resulting PER and CRY proteins heterodimerize and are phosphorylated by casein kinase 1 (CK1), allowing for translocation into the nucleus, consequently inhibiting CLOCK and BMAL1 transcriptional activity, preventing the production of PER and CRY, forming the central negative feedback loop that gives rise to endogenous circadian rhythmicity at the most basic cellular level in mammals (Philpott et al., 2020). Mutations in these genes result in altered displays of circadian behavior in affected model organisms (Patke et al., 2020).

Irregularities in circadian rhythms have been shown to alter sleep–wake cycles, as well as alter metabolic processes that may result in the development of certain diseases or other health-related complications like diabetes, cardiovascular disease, cancer, and neurodegenerative disorders (Wilking et al., 2013; Qian and Scheer, 2016).

CIRCADIAN RHYTHMICITY IN THE CONTEXT OF NEURODEGENERATIVE PATHWAYS

More prevalent in old age, neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) are widely believed to be driven by protein deposition in the form of insoluble aggregates, resulting in loss of physiological functions and pathological dysregulation of neurons (Delenclos et al., 2019; Huseby et al., 2019; **Figure 2**). Severe degradation of the SCN, as well as negatively altered patterns of circadian expression are prevalent in AD patients, but in PD much more targeted degradation of dopaminergic (DA) striatal neurons occurs (Dauer and Przedborski, 2003). Lower levels of BMAL1 are directly proportional to the gravity of an individual's development of PD (Cai et al., 2010; Ding et al., 2011). Melatonin treatment was shown to prevent DA neuronal cell degradation, but the mechanism through which the protection of DA neurons occurs is unclear, whether it be oxidative or circadian (Radogna et al., 2010; Wilking et al., 2013).

Circadian irregularities can also be symptomatic and result in comorbidities, such as cases of individuals with rapid eye movement (REM) behavioral disorder that will ultimately develop PD (Breen et al., 2014). Sleep serves a critical role in the maintenance of circadian rhythms and can strongly affect the buildup of neuronal stress (Breen et al., 2014). In the case of AD, β-amyloid peptide (Aβ) plaques build up in neurons, causing severe systemic stress and eventually leading to the destruction of the cell (Kocahan and Dogan, 2017). Aβ accumulation occurs from natural activity of the cell, and fluctuates with circadian rhythmicity, with higher levels apparent during waking hours and drop-offs during periods of inactivity (Kang et al., 2009).

Alzheimer's disease models have exhibited disrupted patterns of glymphatic flow (GF) in rodents, and GF has also been shown to be regulated by sleep activity, where slow wave sleep in mice resulted in a 60% increase in interstitial brain fluid and increased GF. This phenomenon is crucial for the removal of excess molecular buildup, particularly Aβ, in the extracellular space of areas with high neuronal activity in the central nervous system (Rasmussen et al., 2018). A vital protein associated with Aβ plaque aggregation and tau protein pathology is Orexin, a compound involved in the sleep–wake pathway that promotes wakefulness. Through analyzing its activity, researchers found that cyclic levels of orexin during normal rhythmic activity were inversely proportional to tau protein aggregation; high Aβ plaque aggregation and tau protein pathology also result in disturbances in non-REM sleep activity, ascertaining the bidirectional influence of circadian rhythmicity and AD pathology (Kilduff et al., 2008; Kang et al., 2009; Liu et al., 2019). Multiple studies found that reduced wakefulness as a result of orexin inhibition reduced levels of Aβ buildup in cells (Davies et al., 2015; Liu et al., 2019). The SCN of affected AD patients was also found to have experienced severe degeneration, and clock gene expression in various regions of the brain was highly asynchronous.

Parkinson's disease patients exhibit asynchronous peripheral clock gene expression, therefore single nucleotide polymorphisms in various clock genes have been proposed to indicate the risk of PD development in affected individuals (Gu et al., 2015). Patients affected with PD exhibit much more flattened circadian diurnal curves as a result of increased activity during inactive hours and decreased activity during waking hours (Porter et al., 2008; Verbaan et al., 2008). The majority of PD patients suffer from sleep disturbance as one of the primary symptoms, most likely a result of severe degeneration of the raphe nucleus and locus coeruleus (Braak and Del Tredici, 2008). Circadian melatonin rhythmicity is also altered in PD patients, with the curve being flattened over the course of 24 h (Videnovic and Golombek, 2017).

Numerous articles of evidence discovered strongly accentuate the interconnected activity between circadian rhythms, metabolic and molecular pathways, aging, diseases, as well as neurodegenerative disorders. Aberrant normal pathological function in the form of neurodegenerative effects has been discussed, but proper ubiquitination of proteins offers stark neuroprotection against development of neurodegenerative disorders characteristic of protein

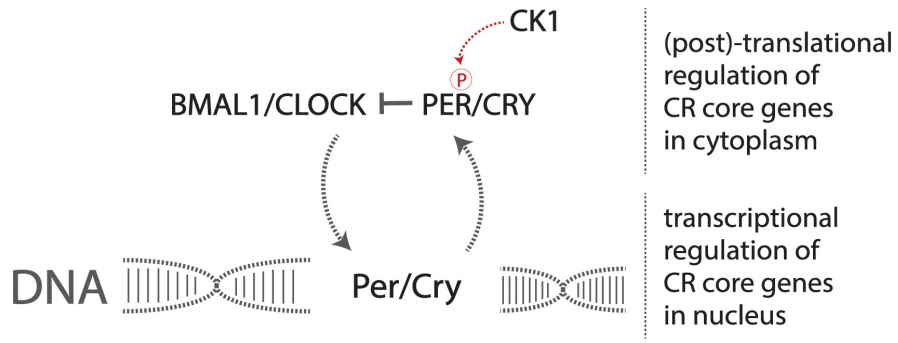

FIGURE 1 | The core circadian molecular machinery gives rise to endogenous timekeeping activity. The CLOCK/BMAL1 heterodimer activates the transcription of *Per/Cry* genes, and the production and resulting phosphorylation of PER/CRY inhibit the CLOCK/BMAL1 heterodimer, reducing the transcription of *Per/Cry* forming the negative feedback loop required to maintain circadian rhythmicity at a basic molecular level.

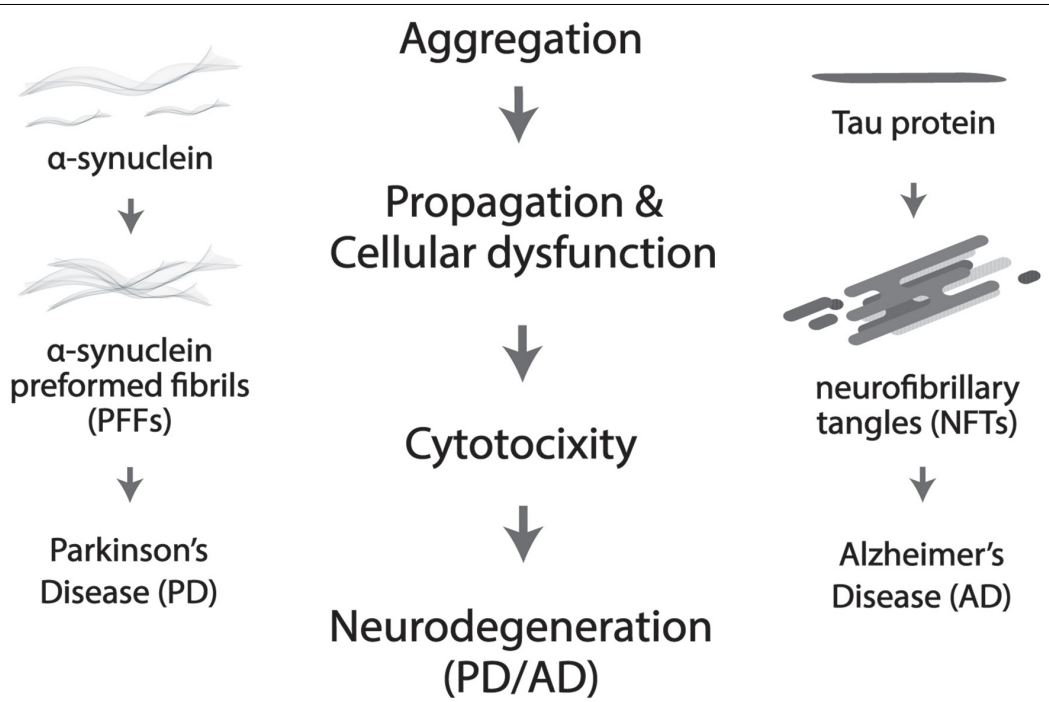

FIGURE 2 | Protein aggregation results in cellular dysfunction and cytotoxicity, which further leads to neurodegeneration. More specifically, neurofibrillary tangles (NTFs) caused by Tau aggregation is the culprit in Alzheimer's disease (AD) and α-synuclein pre-formed fibrils (α-Syn PFFs) by α-synuclein accumulation in Parkinson's disease (PD).

aggregation. Proteasomal activity has been shown to follow circadian rhythmicity, and distortions in this process may result in increased risks of developing neurodegenerative diseases (Musiek and Holtzman, 2016; **Figure 3**).

THE EFFECT OF ANTAGONISTIC E3 LIGASES ON CIRCADIAN PERIOD LENGTH

Functional protein families such as kinases, E3 ligases, (de)acetylases and poly adenosine diphosphate (ADP-ribose) polymerases can directly or indirectly affect patterns of circadian behaviors through post-translational modifications of core proteins. Ubiquitination of PER and CRY proteins is a vital step in maintaining the integrity of the cellular circadian clock. The 26S proteasome uses a series of enzymes such as E3 ligases like FBXL3 and FBXL21 to regulate the degradation of PER, CRY, and other proteins, resulting in disinhibition of CLOCK and BMAL1 transcriptional factors, allowing for the molecular circadian clock to reset and begin the negative feedback loop once again (Nandi et al., 2006). Moreover, there are numerous studies that highlight the relationship between other circadian rhythm proteins and E3 ligases (**Table 1**).

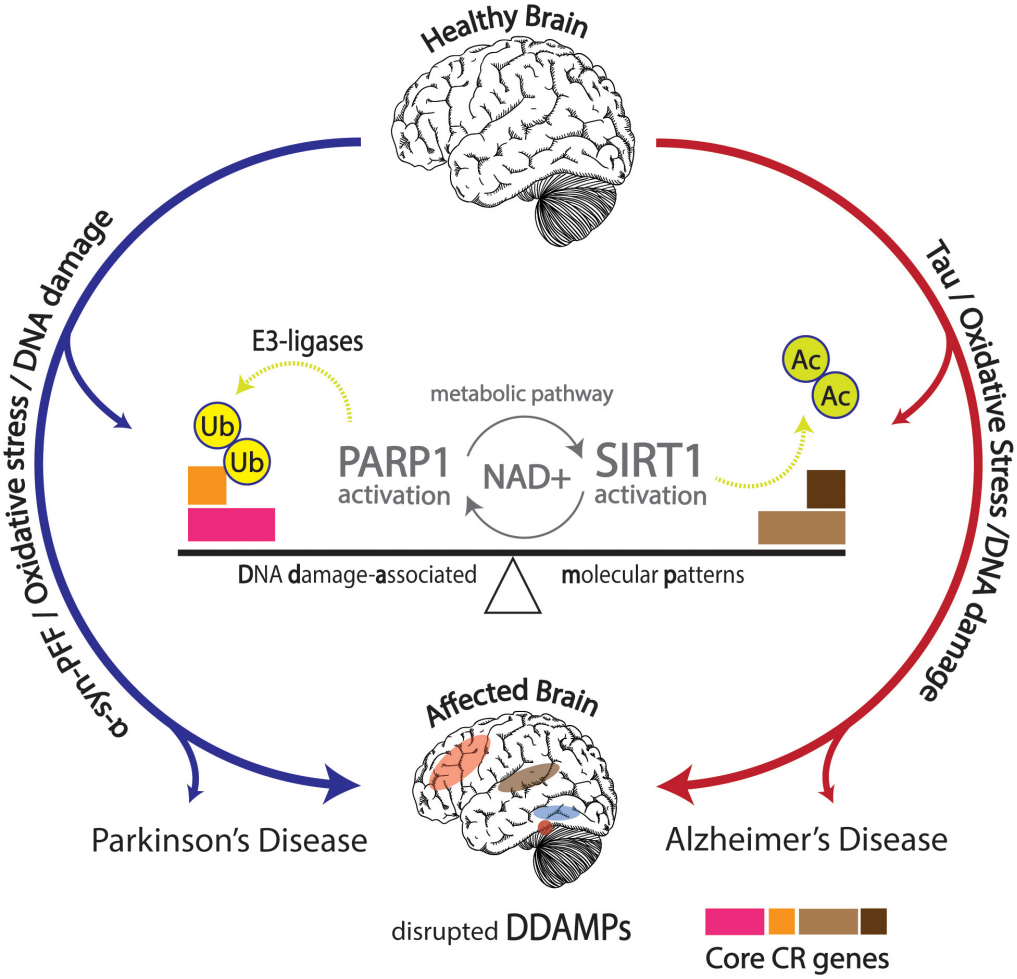

FIGURE 3 | Effects of DNA damage in conjunction with α-synuclein pre-formed fibrils (α-Syn PFFs) and tau pathology shown in the affected brain with disrupted DNA damage-associated molecular patterns (DDAMPs) in Parkinson's disease (PD) and Alzheimer's disease (AD), respectively. Disruptions in metabolic pathways lead to altered DNA repair mechanisms, and subsequent poly (ADP-ribose) polymerase 1 (PARP1) and E3 ligase activity, leading to the ubiquitination of core circadian genes in particular, further influencing the course of PD pathology in terms of α-Syn PFFs formation and propagation.

Furthermore, recent studies have provided strong evidence confirming the link between metabolic processes, neurodegenerative disorders, and circadian dysfunction, through a focus on the E3 ligase pathways, namely mitochondrial ubiquitin ligase 1 pathway (*Mul1*) and *Parkin* pathways. *Mul1* mutations have been shown to lead to PD symptoms in a similar fashion as *Parkin*/*Pink1* mutations, the usual culprits of the neurodegenerative disorder (Yun et al., 2014). *Mul1* and *Park1* mutations resulted in shorter lifespans and longer amounts of physical activity during a given 24-h period (Doktor et al., 2019). *Mul1* mutants showed a disrupted expression pattern of *Per, Tim,* and *Clock* mRNA compared to wild-type flies, and *Mul1* mutants exhibited a severe drop-off in ATG5 compared to *Park1* mutants and controls (Doktor et al., 2019). ATG5 and other related proteins are critical in autophagy; these proteins form complexes and drive clearance of protein aggregation universally characteristic of neurodegenerative disorders (Doktor et al., 2019).

Competing E3 ligase mechanisms involved with CRY ubiquitination have been shown to affect tau in mice. Missense mutations in the *Fbxl*21 gene, the gene expressing a protein which targets CRY for ubiquitination, results in shortened circadian periods due to an accelerated degradation of the CRY protein in the nucleus and the cytoplasm, whereas alterations in the competing ligase FBXL3 results in a longer circadian period (Busino et al., 2007; Godinho et al., 2007; Siepka et al., 2007; Yoo et al., 2013). The duality of these two E3 ligases works to preserve the balance of CRY degradation in the cytoplasm and the nucleus (Yoo et al., 2013). An SKP1-Cul1-F-box protein (SCF) E3 ligase complex is formed constituting FBXL3, targeting CRY proteins for proteasomal degradation; FBXL21 has been inferred to exist as a clock-controlled E3 ligase concerning ovine CRY1 degradation (Siepka et al., 2007; Dardente et al., 2008). The existing mutation Overtime (*Ovtm*) in the FBXL3 protein exists as the functionally antagonistic counterpart to the *Psttm* mutation in FBXL21 by lengthening the period rather than shortening (Siepka et al., 2007;

TABLE 1 | Circadian rhythm proteins shown to be associated or dependent on E3 ligase activity.

Circadian rhythm Gene	E3 Ligase	Source
CRY1/2	FBXL3	Busino et al. (2007); Godinho et al. (2007), Siepka et al. (2007); Yoo et al. (2013)
CRY1/2	FBXL21	Dardente et al. (2008); Hirano et al. (2013), Yoo et al. (2013)
PER1	β-TRCP1 (FBW1A), β-TRCP2 (FBW1B)	Shirogane et al. (2005)
PER2	β-TRCP1 (FBW1A), β-TRCP2 (FBW1B)	Eide et al. (2005); Reischl et al. (2007), Ohsaki et al. (2008)
REV-ERBα	HUWE1 (ARF-BP1), PAM (MYCBP2)	Yin et al. (2010)
BMAL1	UBE3A	Gossan et al. (2014)
TIM (*Drosophila*)	JETLAG	Naidoo et al. (1999); Koh et al. (2006)
CRY	CG17735, CG11321, and CG5604 (HECT or RING domain-containing E3 ligases), Bruce (E2–E3 ligase)	Sathyanarayanan et al. (2008)
CLOCK/PERIOD	CTRIP	Lamaze et al. (2011)
PER	SUPERNUMERARY LIMBS	Chiu et al. (2008)
PER2	MDM2	Liu et al. (2018)
CRY1	CUL4-DDB1-CDT2	Tong et al. (2015)
Unknown	UBR4 (ubiquitin protein ligase E3 component N-recognin 4) found as a time-of-day-dependent and light-inducible protein	Ling et al. (2014)

Yoo et al., 2013). Due to the diminished presence of CRY as a result of the *Psttm* mutation in the *Fbxl*21 gene, inhibition of the CLOCK:BMAL1 transcriptionally enhancing complex is further diminished, leading to an increase of RNA expression of target genes. The accelerated degradation of CRY1 is a result of the reduced levels of FBXL21 protein levels. CRY1 was shown to be polyubiquitinated in the presence of the SCFBXL3 complex, but the presence of SCFFBXL21 and SCFPSTTM significantly reduced the ubiquitination of CRY1 by SCFFBXL3, enhancing the antagonistic interactions between FBXL3 and FBXL21. FBXL21 and *Psttm* have been shown to prevent CRY1 degradation due to FBXL3 as well, further exemplifying the competing characteristics between the two E3 ligases. FBXL21's specificity for CRY1 degradation may hint to the reduced rate at which it ubiquitinates the CRY1 protein, contrasting from the rather liberal utilization of lysine residues by FBXL3 for CRY1 degradation. The fundamental importance of the family of CRY proteins in regulating circadian period length has been fully emphasized through the analysis of competing E3 ligases FBXL21 and FBXL3 mutations. The "paralogous" nature of FBXL21 and FBXL3 interestingly produced antagonizing behavior in the two E3 ligases, competing for the regulation of CRY1 degradation. The preferential interactions between FBXL21 and CRY may support the finding that FBXL21 is able to protect CRY degradation from SCFFBXL3 activity within the nucleus, accentuating the role of E3 ligases in regulating and dictating circadian period through complex molecular interactions within the nucleus (Yoo et al., 2013; **Figure 4**).

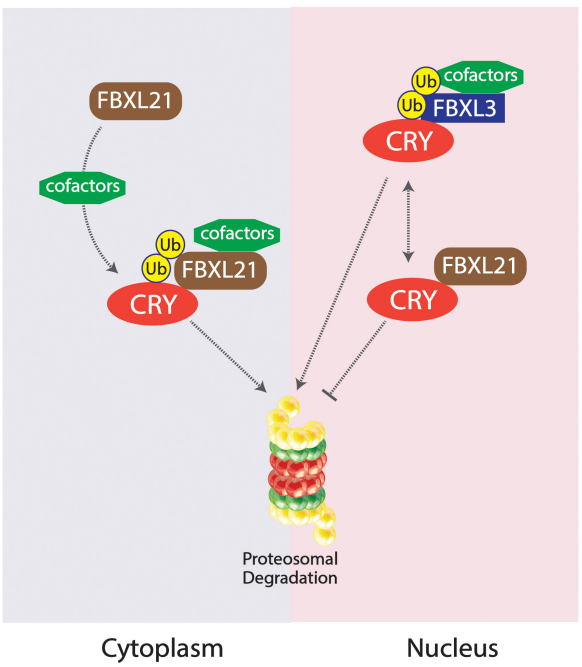

FIGURE 4 | Competing SKP1-Cul1-F-box protein (SCF) E3 ligase complexes SCFFBXL21 and SCFFBXL3 and their effects on CRY degradation in the cytoplasm vs. nucleus. SCFFBXL21 degrades CRY in the cytoplasm but exhibits protective abilities in the nucleus, contrary to the degradative properties of SCFFBXL3 on the CRY protein within the nucleus.

POLY [ADP-RIBOSE] POLYMERASE 1 ACTIVITY AND ITS INFLUENCE ON CIRCADIAN RHYTHMICITY

The cyclic influence of core circadian proteins on nicotinamide phosphoribosyltransferase/nicotinamide adenine dinucleotide (NAMPT/NAD) + activity ultimately relates to a vital protein: Poly (ADP-ribose) polymerase 1 (PARP1), a nuclear protein responsible for facilitation of DNA strand repair. It is activated in response to single-strand breaks within DNA, attaching a poly ADP-ribose (PAR) chain for subsequent repair by DNA ligases. After the process nears completion, poly ADP-ribose glycohydrolase (PARGs) degrade the remaining attached PAR

chain (Herceg and Wang, 2001). The interwoven nature of the mechanisms between PARP1 and NAD + activity possibly hint to the involvement in the development and course of neurodegenerative disorders (Martire et al., 2015). In addition to PARP1 being a critical component of the DNA repair mechanism, it is also a critical component of parthanatos, the cell death pathway involved in cellularly destructive diseases such as stroke and PD (David et al., 2009). The accumulation of PAR within the cell due to hyperactivity of PARP1 in response to DNA damage in conjunction with the translocation of mitochondrial-associated apoptosis-inducing factor (AIF) into the nucleus results in activation of the parthanatos pathway, leading to extensive DNA fragmentation and cell death (Wang et al., 2011). PARP1 activation occurs following any magnitude of DNA damage, with the amount of activation proportional to the severity of genetic stress. The activity of PARP1 results in the formation of PAR polymer chains which ultimately becomes highly toxic to the cell (Andrabi et al., 2006).

The high dependency of PARP1 on NAD + availability leads to the depletion of the NAD + surplus, leading to subsequent cellular stress. Administration of NAD + to energetically starved cells, or the reinstatement of glycolytic factors within the glycolysis cycle, have been shown to reverse the effects of NAD + depletion, offering neuroprotection and preventing the activation of the parthanatos pathway (Fatokun et al., 2014). Circadian expression patterns of NAMPT, the rate limiting enzyme of the NAD + salvage pathway, results in a circadian rhythm of NAD + abundance within the cell, giving rise to circadian activity of PARP1 (Nakahata et al., 2009; Ramsey et al., 2009). Opposing duality of PARG and PARP1 processes may contribute to rhythmicity, but studies have shown that rhythmicity of PARP1 auto-ADP-ribosylation is maintained in spite of manipulation of PARG activity (Davidovic et al., 2001). Studies have shown that circadian PARP1 activity is independent of central pacemakers and heavily regulated by feeding (Damiola et al., 2000; Stokkan et al., 2001). Moreover, abundance of NAD + has been shown to not sufficiently account for the circadian activity of auto-ADP-ribosylation of PARP1, at least *in vitro* (Asher et al., 2010). However, unlike PARP1's endogenous activity, NAD + activity has been shown to be under the influence of the central clock (Ramsey et al., 2009).

Poly (ADP-ribose) polymerase 1 has also been shown to co-immunoprecipitate with CLOCK and BMAL1. PARP1 has the ability to rhythmically affect CLOCK activity, and highly disrupted circadian and rhythmic activity of the CLOCK-BMAL1 dimer is attributed to inhibition of PARP1 activity (Asher et al., 2010). Wild type CLOCK and BMAL1 forms have exhibited circadian rhythmicity when binding to *Per2* promoters, whereas PARP1 knockout mice exhibited much higher levels of CLOCK and BMAL1 activity. PARP1 knockout and wild type animals exposed to arrhythmic feeding patterns did not exhibit altered differences in genetic expression, but PARP1 knockout mice exhibited a lower level of mRNA of target genes of CLOCK and BMAL1. Additionally, PARP1 knockout mice exhibited a lengthened Tau compared to wild-type mice, suggesting that direct consequences of PARP1 activity could possibly manifest in the SCN (Asher et al., 2010).

ALTERATION OF PAR-DEPENDENT E3 LIGASE ACTIVITY ON PARKINSON'S DISEASE IN RESPONSE TO DNA DAMAGE

Another highly apparent interaction between E3 ligases, DNA repair and PARP1 activity has been portrayed through the E3 ligase, Iduna. Iduna's really interesting new gene (RING) finger domain's zinc binding activity is responsible for its E3 ligase activity, and mutations in the H54A and C60A domains result in absence of ubiquitination activity. The Iduna YRAA mutant disrupts the PAR-binding abilities, and the autoubiquitination abilities of Iduna's E3 ligase activity have been shown to be directly dependent on PAR concentrations. Two of the primary targets of Iduna have been shown to be PARP1 and PARsylated PARP1. The presence of proteasomal inhibitors, such as MG132, has been shown to inhibit Iduna's ability to degrade PARP1 and PARsylated PAR, affirming the ubiquitinated PAR-dependent degradation of PARP1 by Iduna. Microirradiation induced DNA damage resulted in an eightfold increase in the amount of apurinic/apyrimidinic sites. The prevention of this increase is possible through overexpression of Iduna. However, Iduna YRAA mutants were unable to suppress the increase of apurinic/apyrimidinic sites due to the lack of PAR binding ability, showing that PAR-binding is crucial for suppression of genetic lesions. Iduna C60A mutants also failed to reduce the increase in DNA lesions, emphasizing that the E3 ligase activity of Iduna is also crucial for DNA maintenance and repair. These complex interactions between DNA damage, PAR-related activity, and E3 ligase activity begin to paint a picture of highly interrelated intricacy, affirming that Iduna acts as a PAR-dependent ubiquitin E3 ligase. Iduna has also been shown to protect the brain from stroke by disruption of the parthanatos mechanism (Kang et al., 2011).

The earlier explored interactions allow for the analysis of the effects of PARP1 activity and subsequent PAR accumulation on the development and course of PD. Accumulation of α-Syn PFFs has been shown to activate PARP1, leading to the generation of PAR aggregates, compounding into large combined aggregates that become toxic for given cells, eventually resulting in cell death via parthanatos (Kam et al., 2018). After administration of α-Syn PFFs in mice, higher PARP1 activity was observed for a period of 2 weeks, whereas administration of PAR inhibitors prevented α-syn PFFs induced cell death. Deletion of PARP1 through CRISPR similarly resulted in prevention of α-syn PFFs induced PARP1 activity, cell death, α-Syn aggregation, as well as cell-to-cell α-Syn PFFs transmission. Nitric oxide (NO) synthesis was also increased after α-syn PFFs administration, whereas NO inhibitors prevented this activation. After administration, increased PAR levels and PARP1 activity were observed, but PAR levels were not increased due to the absence of PARP1 in PARP1 knockout mice, and can be attributed to the fact that PAR aggregation is a result of PARP1 activity. Parthanatos in DA neurons was observed after administration in wild-type mice, but loss of DA neurons was not observed in

PARP1 knockout mice and in mice previously injected with ABT-888, a PARP1 inhibitor. PAR has been shown to directly increase the rate of aggregation of α-Syn PFFs in neuronal cells, and 20% of PAR binding to these fibrils was observed in the mouse brain. PAR has also been shown to produce a toxic strain of α-Syn PFFs in the form of more compact and misfolded aggregation. The highly accelerated initial degradation of DA neurons *in vivo* can be attributed to the presence of PAR α-Syn PFFs rather than the generic species of α-Syn PFFs. PD patients have also exhibited higher levels of PAR in their cerebrospinal fluid as well as in the substantia nigra (Kam et al., 2018). The link between PARP1 and E3 ligase activity, the affected pathology in PD, and underlying circadian processes all ultimately point to a highly interrelated mechanism, implying the possibilities of circadian treatment as a preventative and treatable measure for PD.

CONCLUSION

The complex web of molecular interactions points to the possibility of much more entangled pathological similarities between PD pathology, DNA damage and repair, and the endogenous regulation of core circadian genetic elements through E3 ligase and PARP1 activity. This specific targeting of PARP1 in respect to PD treatment exhibits mirrored similarity to the mechanism through which SIRT1 is targeted in AD treatment (Wong and Tang, 2016). The interconnectedness between circadian rhythmicity, protein aggregation, and metabolic activity is exemplified by PARP1, suggesting its role as a therapeutic target in treatment for aggressive progression of PD (**Figure 3**).

Circadian irregularities have been shown to have bi-directional physiological and metabolic implications on general health, as well as influence on and influence from neurodegenerative disorders. E3 ligase and PARP1 activity are essential in regulating both circadian rhythmicity and proper neuronal function. Thus, the dysregulation of these pathways have the capability of causing cellular stress and DNA damage that could further lead to neurodegenerative diseases like AD and PD. DNA damage response (DDR) has been shown to be reliant on the circadian properties of the cell through previously explored mechanisms of PARP1 and E3 ligases. Aberrant circadian qualities may disrupt the DDR or in turn be disrupted by hyperactivity of PARP1 and E3 ligases, ultimately leading to PAR induced accelerated accumulation of neurotoxic strains of α-Syn, further activating PARP1, contributing to the pathogenesis of PD. Regulating proper circadian function may be crucial for preventing the mechanistic onset of molecular complications heralding neurodegenerative distress.

AUTHOR CONTRIBUTIONS

AS, SL, and SK designed and planned this review manuscript. AS, SL, HY, and SK wrote the manuscript. AS, SL, HK, SH, and SK contributed to the literature search, collection, and summary. HY provided amendments to draft versions of the manuscript. All authors contributed to the article and approved the submitted version.

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Wheel-Running Behavior Is Negatively Impacted by Zinc Administration in a Novel Dual Transgenic Mouse Model of AD

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Alzheimer's disease (AD) is a neurocognitive disorder that impacts both the brain and behavior. Metal ions, including zinc (Zn), have been seen to play an important role in AD-related pathology. In this study, we show alterations in wheel-running behavior both early and late in disease progression in a novel dual Tg mouse model of AD. This mouse includes both amyloid and tau pathology through its cross with the J20 (hAPP) and P301L (Tau) parentage. Animals were given either lab water or water that had been supplemented with 10 ppm Zn. Wheel running was assessed through individually housing mice and measuring wheel-running activity in both the light and dark cycles. Dual Tg mice showed significantly less activity in the first part of the dark cycle than WT mice at both 3.5 and 7 months of age ($p < 0.05$). Dual Tg mice given Zn water showed less activity compared to dual Tg mice on lab water, tau mice on Zn water, or WT mice given either lab or Zn water ($p < 0.05$) at 7 months. Female mice in this study consistently showed higher activity compared to male mice in all groups whereas Zn led to reduced activity. Daily activity rhythm was altered in both the tau and dual Tg mice, and Zn impacted this alteration through effects on amyloid, tau, and through circadian pathways.

Keywords: zinc, circadian activity, Alzheimer's disease, mouse model, sex, age

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative condition that involves accumulations of harmful proteins, including amyloid plaques and tau tangles. The prevalence of AD is significant: approximately 5.8 million Americans are diagnosed today and, with populations living longer, these statistics are projected to increase substantially by the year 2025 (Alzheimer's Association, 2019). Apart from progressive neuronal pathology, AD leads to many behavioral problems, the most characteristic of which is loss of memory. Apart from substantial memory deficits, which worsen as the disease progresses, there are other behaviors that are impaired. One which causes significant problems for caregivers is a disturbance in the circadian rhythms (CR) of AD patients; this is one of the major reasons for institutionalization (Bianchetti et al., 1995; Coogan et al., 2013; Duncan and Zee, 2013; Holth et al., 2017).

Previous research and drug development has focused on amyloid (Cummings et al., 2018) but tau is becoming increasingly important to examine when studying AD. Tau pathology is considered to correlate better with cognitive diminishment than amyloid based on its distribution and progression across the brain (Braak and Braak, 1991) and no amyloid-targeting therapies in the drug-development pipeline have been successful to date (Kametani and Hasegawa, 2018).

Disturbances in the sleep-wake cycle are noted in AD patients (Musiek et al., 2015) and have been seen in numerous mouse models of AD. These disruptions have been seen in not only the 3xTgAD (Sterniczuk et al., 2010) and 5xFAD mouse models (Sethi et al., 2015) but also in solely amyloid (Wisor et al., 2005) and tau (Craven et al., 2018) mice. As a non-cognitive measure, disturbances in circadian activity can be an early indicator of and a precursor to upcoming dementia (Tranah et al., 2011; Leng et al., 2019).

One factor that may be mediating AD behavioral changes is the bio-metal, zinc (Zn). Zinc, Iron (Fe), and Copper (Cu) are all found in the plaques associated with AD (Lovell et al., 1998; Suh et al., 2000) and these metals can affect both behavior and the progression of the disease (Linkous et al., 2009; Railey et al., 2011; Bush, 2013; Adlard and Bush, 2018; Craven et al., 2018). In AD, the homeostasis of these crucial metals is disturbed and can cause exacerbations in neuronal pathology. Zinc's interaction with amyloid leads to decreased amounts of Zn availability; this can impact neuronal signaling as less Zn is available for co-release with glutamate in synaptic transmissions. Both amyloid (Aβ) and neurofibrillary tau interact with Zn (Mo et al., 2009; Barnham and Bush, 2014; Huang et al., 2014). Zinc can affect both kinase activity (Boom et al., 2009) and phosphatase activity (Xiong et al., 2013) which leads to alterations in tau's structure and its propensity to aggregate.

In vitro studies are valuable in assessing the impact of Zn on tau and Aβ, however, changes in the levels of one metal can affect the levels of others *in vivo* (Maret and Sandstead, 2006). The use of animal models for AD allows for more translational findings and the ability to see the impact that Zn has on behavior in conjunction with AD pathology. Excess zinc causes impairments in many behaviors, including CR, in mice modeling AD which contain either human amyloid or human tau (Graybeal et al., 2015; Boggs et al., 2017; Craven et al., 2018). We have now examined changes in daily activity rhythm in a mouse model of AD containing *both* human amyloid and human tau (Lippi et al., 2018) and examined the effect of zinc administration in these mice. Mice were examined at both 3.5 and 7 months; sex differences in activity were also examined. We report here the results of a study of daily activity rhythm in a mouse model of AD that contains both human amyloid and human tau. Genotype (Tg v. WT) had a significant effect; in addition, zinc administration, sex, and age all had effects on daily activity rhythm in the Tg mice, but not on the Wt mice, with zinc having the greatest effect on the dual Tg mice.

MATERIALS AND METHODS

Animals

Dual Tg mice (those mice arising from the cross between the J20 and rTg4510 mouse models, Jax) have been previously characterized by Lippi et al. (2018) and were used to assess wheel-running activity compared to those mice containing P301L tau under the tetracycline transactivator system, and mice containing no AD mutations (wildtype, WT). Male mice used in the breeding were those harboring the SWE and IND APP mutations (J20 – B6.Cg-Zbtb20$^{Tg(PDGFB-APPSwInd)20Lms}$/2Mmjax); these mice are on a B6 background and are hemizygous. Female mice used in the breeding were those with the P301L tau mutation under control of the tetracycline transactivator (rTg4510 – Tg(Camk2a-tTA)1Mmay *Fgf14*$^{Tg(tetO-MAPT*P301L)4510Kha}$/J); the female mice were on a mixed FVBxC57BL/6 background, as they are maintained on this background at the Jackson Lab. The rTg4510 mice used were hemizygous for Tg(Camk2a-tTA)1Mmay and hemizygous for Fgf14$^{Tg(tetO-MAPT*P301L)4510Kha}$. These breeding mice were paired and offspring were genotyped (Transnetyx, Inc.). Offspring used in this study were of the F1 generation. "Wildtype" mice used and discussed in this paper are those mice that were genotyped and had no presence of any of the used mutations. Mice were assessed at both 3.5 and 7 months, to assess early and later stage changes in pathology.

Mice were housed based on sex and genotype. Additionally, mice were housed with littermates. Each cage (Animal Care Systems) contained a running wheel and an igloo with food and water given *ad libitum*. Rat cages were used, as opposed to mouse cages, to allow enrichment devices to fit while having multiple mice in a cage. The light cycle was maintained on a 12-h light/12-h dark cycle consistent with animal colony housing.

All procedures done involving animals in this project were approved by the George Mason University IACUC.

Zinc Water

Mice were given either standard laboratory water or water with 10 ppm Zn added. Zinc water (ZnCO3) was prepared with a 10,000 ppm solution dissolved in 5% nitric acid and buffered with sodium carbonate to reach neutral pH (∼7). Samples were sent to the United States Geological Survey (USGS) (Reston, VA, United States) to ensure accurate Zn levels throughout the duration of the experiment. This formulation of 10 ppm Zn has been done in prior studies assessing Zn's impact on Tg mice from our lab (Linkous et al., 2009; Flinn et al., 2014; Craven et al., 2018). Mice in the Zn water condition began receiving Zn water at 8 weeks of age and continued throughout the length of the study. A breakdown of animals by sex, genotype, and water condition can be seen in **Table 1**. This table represents the group Ns at both time periods (the same mice that were assessed at 3.5 months are the same as those analyzed at 7 months).

Wheel Running (Daily Activity Rhythm Measurement)

Mice in the current experiment underwent a battery of behavioral tests, including those to measure learning and memory (Barnes

TABLE 1 | Study sample size.

	Dual Transgenic (*n* = 18)		Tau (*n* = 23)		Wildtype (*n* = 20)	
	Male	Female	Male	Female	Male	Female
Lab Water	4	4	4	7	5	5
Zinc Water	5	5	5	7	6	4

***N* = 61**

Maze), anxiety [open field test and elevated zero maze (EZM)], depression (forced swim test), and activities of daily living (burrowing and nesting) (Lippi et al., 2018). After burrowing and nesting behavior were assessed, and prior to forced swim activity data collection, mice were tested for daily wheel-running activity.

Each mouse was singly housed in a circadian rhythm (CR) running wheel cage (Coulbourne Instruments). Cages consisted of one voluntary running wheel, corncob bedding (to avoid entanglement with the wheel), and a hopper for food and water (whether lab or Zn-supplemented). Actiview Biological Rhythm Analysis software (Minimitter Co.) was used to record the number of wheel rotations for each minute.

Wheel-running activity for respective CR cages was recorded for a total of 9 days, with the first (cage set-up) and last (cage take-down) days excluded from analysis. Total wheel rotations were averaged across the median 7 days to generate a mean number of wheel rotations for each hour of the 24-h cycle.

Statistical Analysis

Wheel-running data from the CR cages were summed for each hour and then analyzed by days. The hourly data for each day were averaged to give an average for each hour. This data was then split into separate 12-h light (ZT0-12) and dark (ZT12-23) cycles for analysis. Light and dark cycle data were analyzed using a 3 × 12 repeated measures ANOVA with factors of genotype, water type, and sex by hour. Significant results were followed-up with an ANOVA to see at what times significant differences were present, using three or more consecutive significantly different time intervals as a post-hoc. All data were analyzed using $p < 0.05$ as the cutoff for significance, and $p < 0.10$ to indicate a trend.

RESULTS

Animals were tested twice, once at age 3.5 months and again at 7 months. We were interested in assessing pathology early and late in disease progression, so analyses for each testing session/age were performed separately. Mauchly's Test of Sphericity was significant for all analyses so a Greenhouse-Geisser correction was used. Analysis of light cycle data revealed a significant hour × genotype effect at 3.5 months ($p < 0.05$), however, post-hoc analysis was unable to reveal an individual effect or time range for significance, and no differences were observed at 7 months. Therefore, this analysis focuses solely on dark cycle data. Data were analyzed in the following order: effect of genotype, effect of water, and effect of sex. Finally, all data were considered together.

Effect of Genotype

This analysis collapsed animals across sex and water. No overall effect was seen for the 3.5 month mice; however, effects of hour × genotype were seen at both 3.5 months [$F(5.86,143.48) = 9.771$, $p < 0.001$, **Figure 1A**], and 7 months [$F(5.789,141.66) = 14.331$, $p < 0.001$, **Figure 1A**]. Follow-up analysis of the hour × genotype effect showed the dual transgenic animals were less active than the wild type animals at hours ZT12-17 at 3.5 months, (consecutive $p < 0.05$) and ZT 12-16 at 7 months (consecutive $p < 0.05$) (**Figure 1A**). Additionally, at 7 months tau animals were less active than wild type animals at hours ZT12-15 (consecutive $p < 0.05$), and more active at hours ZT21-23 (consecutive $p < 0.05$). An effect of genotype on total dark cycle activity was present at 7 months [$F(2,49) = 3.18$, $p = 0.05$, **Figure 1A**], Follow-up analysis of the effect of genotype on total dark cycle activity showed that dual transgenic animals were less active than wild type animals at 7 months ($p < 0.05$).

Effect of Drinking Water

The effect of adding zinc to the drinking water was then examined. This analysis collapsed animals across sex. An effect of hour × water was observed at 3.5 months [$F(2.93,143.48) = 4.29$, $p < 0.01$, **Figure 2A**], but not at 7 months. We observed a trend for an effect of hour × water × genotype at 3.5 months [$F(5.86,143.48) = 1.89$, $p < 0.1$, **Figure 2B**]. Follow-up analysis of the hour × water × genotype effect at 3.5 months showed that zinc increased activity only in the tau animals early in the dark cycle from hours ZT 13-15, (all consecutive $p < 0.05$). Although there was not an effect of adding Zn at 7 months, there was an interaction between water × genotype which affected total dark cycle activity at 7 months [$F(2,49) = 4.10$), $p < 0.05$, **Figure 2C**] (Follow-up analysis of the interaction at 7 months showed that the dual transgenic animals on zinc water were less active than dual transgenic lab, tau zinc, WT lab, and WT zinc animals), i.e., significantly less active than all other groups except for tau lab.

Effect of Sex

We then examined the effect of the sex of the mice. This analysis collapsed animals across water type. We observed an effect on total dark cycle activity at both 3.5 [$F(1,49) = 6.29$], $p < 0.05$ and 7 [$F(1,49) = 11.50$, $p < 0.001$, **Figure 3A**] months. Female animals were more active in the dark cycle than the males. A trend for an effect of hour × sex was present only at 7 months [$F(2.89,141.66) = 2.18$, $p < 0.1$, **Figure 3A**]. The hour × sex effect at 7 months showed female animals were more active from ZT 15-22, from the mid to late dark cycle (all consecutive $p < 0.05$). There was a significant effect of sex in wild type animals on total dark cycle activity levels at both 3.5 [$F(1, 18) = 7.15$, $p < 0.05$] and 7 [$F(1, 18) = 9.5$, $p < 0.05$] months.

Genotype, Water, and Sex Together

The effect of water type by sex on dark cycle activity was broken down by genotype and age (**Figure 4**). The data show that in general, females were more active than males and zinc reduced activity. This was most notable in the 7 month dual transgenic mice, where the lab females had significantly higher activity than either sex on zinc (both $p < 0.05$). but did not differ significantly from males on lab water.

DISCUSSION

We have shown that a novel mouse model, previously shown to exhibit deficits in both cognitive (Barnes maze) and non-cognitive (burrowing and nesting) behaviors (Lippi et al., 2018), exhibited disturbances in wheel-running activity both early and

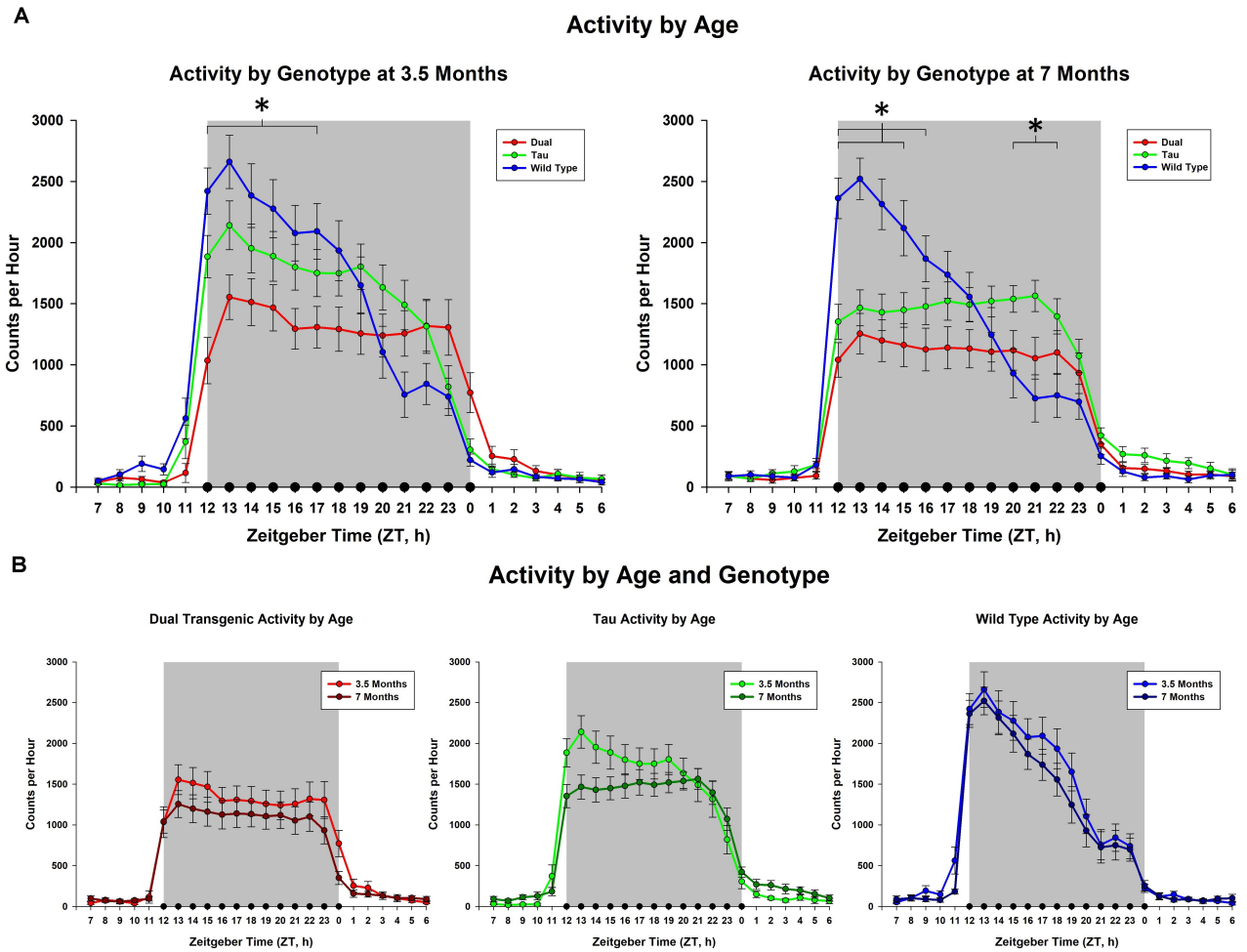

FIGURE 1 | Comparison of dark cycle activity by **(A)** Genotype by age and **(B)** age by genotype. Wildtype animals showed significantly higher total dark cycle activity than dual Tg animals at 7 months; hourly differences showed dual Tg animals were significantly less active than wildtypes early in the dark cycle, ZT12-17 at 3.5 months and ZT12-16 at 7 months. At 7 months tau animals were significantly less active than WT mice early in the dark cycle, ZT12-15, and significantly more active than WT mice later, ZT21-23 (*$p < 0.05$).

late in development of AD pathology. Analysis showed that the activity of the Wt mice did not vary with age, zinc administration, or sex; however, these variables did affect both the tau and dual Tg mice, with the dual Tg mice being the most affected, particularly with respect to zinc administration.

Activity during the dark cycle typically starts at a high rate and falls off as the night progresses in Wt mice (Boggs et al., 2017; Logan et al., 2018), and this pattern was seen here in the Wt mice at both 3.5 and 7 months. The pattern was similar in the tau mice at 3.5 months, but began to differ from the Wt mice at 7 months, where the level of activity in the tau mice showed less variation across the night, as shown in **Figure 1**. The dual Tg mice had an atypical pattern at both 3.5 and 7 months, with a consistent level of activity across the dark cycle at both ages. Activity in AD mice in our sample was lower than that of the WT mice in the early part of the night cycle at both 3.5 months and 7 months. This lowered activity in AD mice is in agreement with Wu et al. (2018) who used the 3xTg-AD mouse, containing mutations in amyloid, tau, and the PS1 gene, and found that AD mice had lower total daily activity in running compared to WT mice.

We noted significant differences in the *pattern* of activity across the night in the three groups at both 3.5 and 7 months (see **Figure 1**); the greatest difference was between the WT and dual Tg animals. Compared to WT mice, who at both testing ages showed similar characteristic patterns of falling activity across the dark cycle, dual Tg mice had relatively constant activity at both ages.

This mouse model may be suitable for future daily activity rhythm analysis since wheel-running activity was disrupted early on; others have assessed wheel running in AD mice at later ages (Duncan et al., 2012; Boggs et al., 2017; Craven et al., 2018; Wu et al., 2018). Further analysis showed that the activity of the Wt mice did not vary significantly with age, zinc administration, or sex; however, these variables did affect both the tau and dual Tg mice, with the dual Tg mice being the most affected, particularly with respect to zinc administration. There was an overall effect

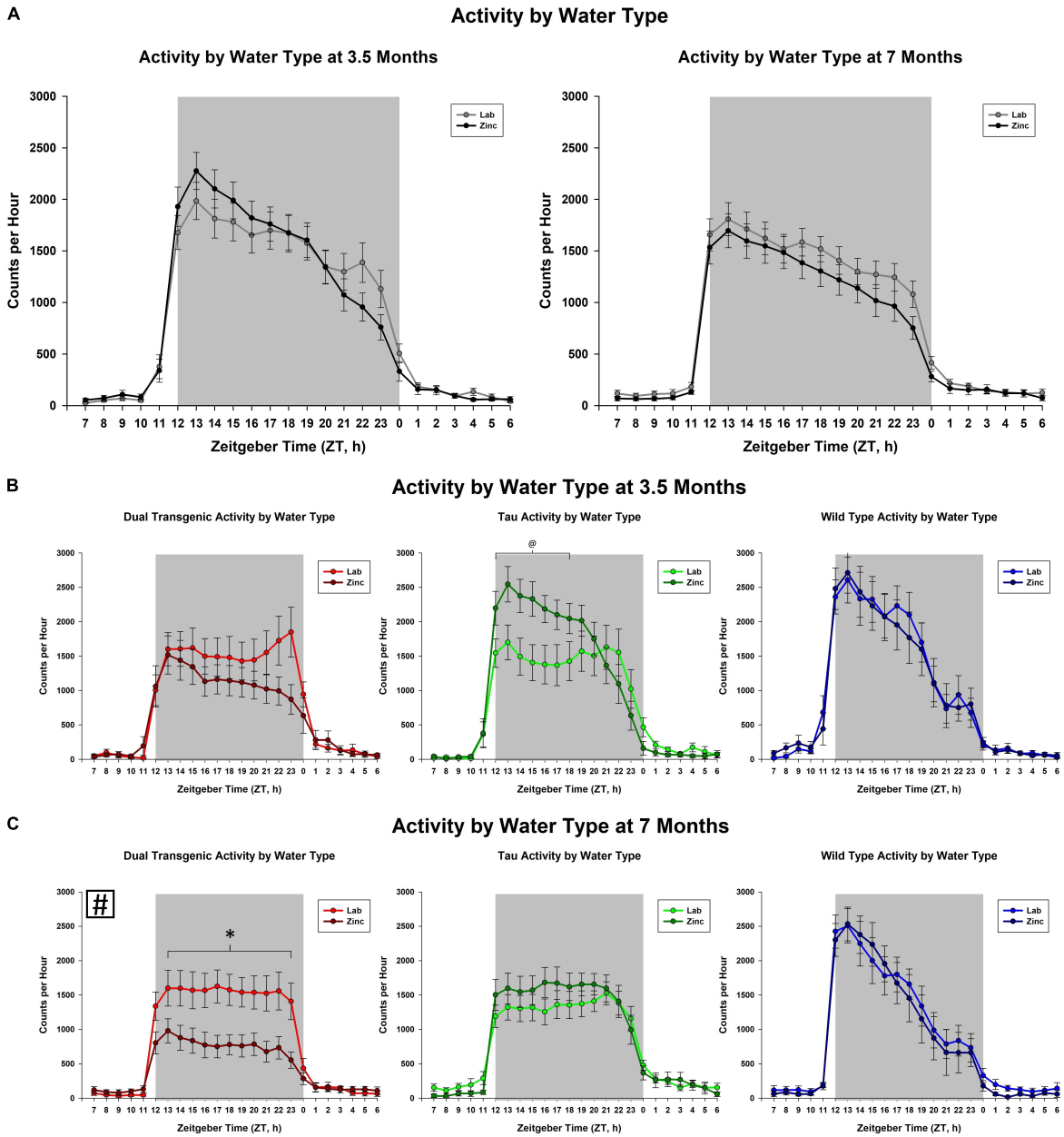

FIGURE 2 | Comparison of dark cycle activity by **(A)** water type by age, **(B)** water type by genotype at 3.5 months, and **(C)** water type by genotype at 7 months. Tau animals exclusively showed a trend for increased activity from ZT 13-15 ($^{\#}$) when administered Zn at 3.5 months. Dual Tg animals on Zn were significantly less active than all other groups except tau lab at 7 months ($^{*}p < 0.05$, $^{@}p < 0.10$, boxed $^{\#}$ indicates a change summed across dark cycle hours).

of sex, with females showing greater activity than the males. The greatest differences in activity due to Zn administration were seen in the dual Tg mice at 7 months. These results are discussed in more detail below.

Alzheimer's Disease Pathology and Circadian Activity in Mice

Previous studies have shown that progression of amyloid and tau pathology can lead to disruptions in circadian rhythm activity in mice. In C57BL/6J mice with no AD mutations, administration of the Aβ31-35 fragment into the hippocampus led to an increase in free-running period and changes in Per1 and 2 in both the suprachiasmatic nucleus (SCN) and hippocampus in constant darkness (Wang et al., 2016). Per1 and Per 2 were shown to be lower in mice receiving the fragment in both the SCN and the hippocampus.

Transgenic mice harboring mutations in AD genes have also shown disruptions in wheel-running activity. Sterniczuk et al. (2010) assessed circadian wheel-running activity in the 3xTgAD

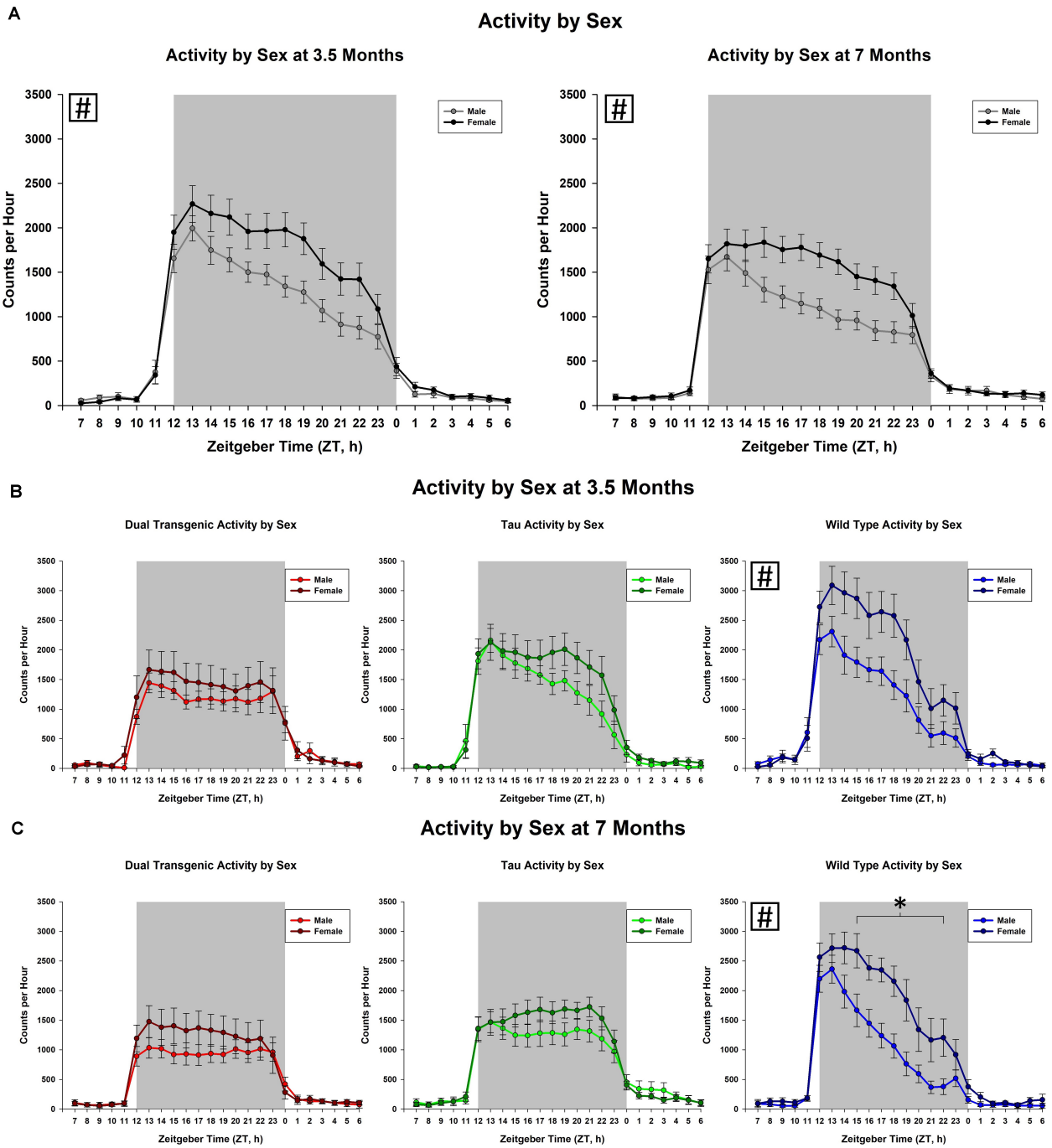

FIGURE 3 | Comparison of dark cycle activity by **(A)** sex by age, **(B)** sex by genotype at 3.5 months, and **(C)** sex by genotype at 7 months. Female animals showed significantly higher dark cycle activity compared to males at both 3.5 and 7 months **(A)**. At 7 months, this increase was present in hours ZT 15-22 (all time intervals, $p < 0.05$). Female wild type animals were significantly more active than wild type males at both 3.5 and 7 months (*$p < 0.05$, boxed # indicates a significant effect summed across dark cycle hours).

mouse model. Their results corroborate the findings in the present study: both young and old 3xTgAD mice exhibited less nighttime activity compared to WT/control mice. Tau mice harboring the P301L mutation had delayed activity onset compared to WT mice (Craven et al., 2018) and this delay was exacerbated by Zn administration. P301L tau mice, that have tau expression regulated through CaMKIIa promotion, had delayed activity onset during the evening, with P301L tau mice receiving Zn water showing a further delay in activity onset compared to those receiving lab water (Craven et al., 2018). The present

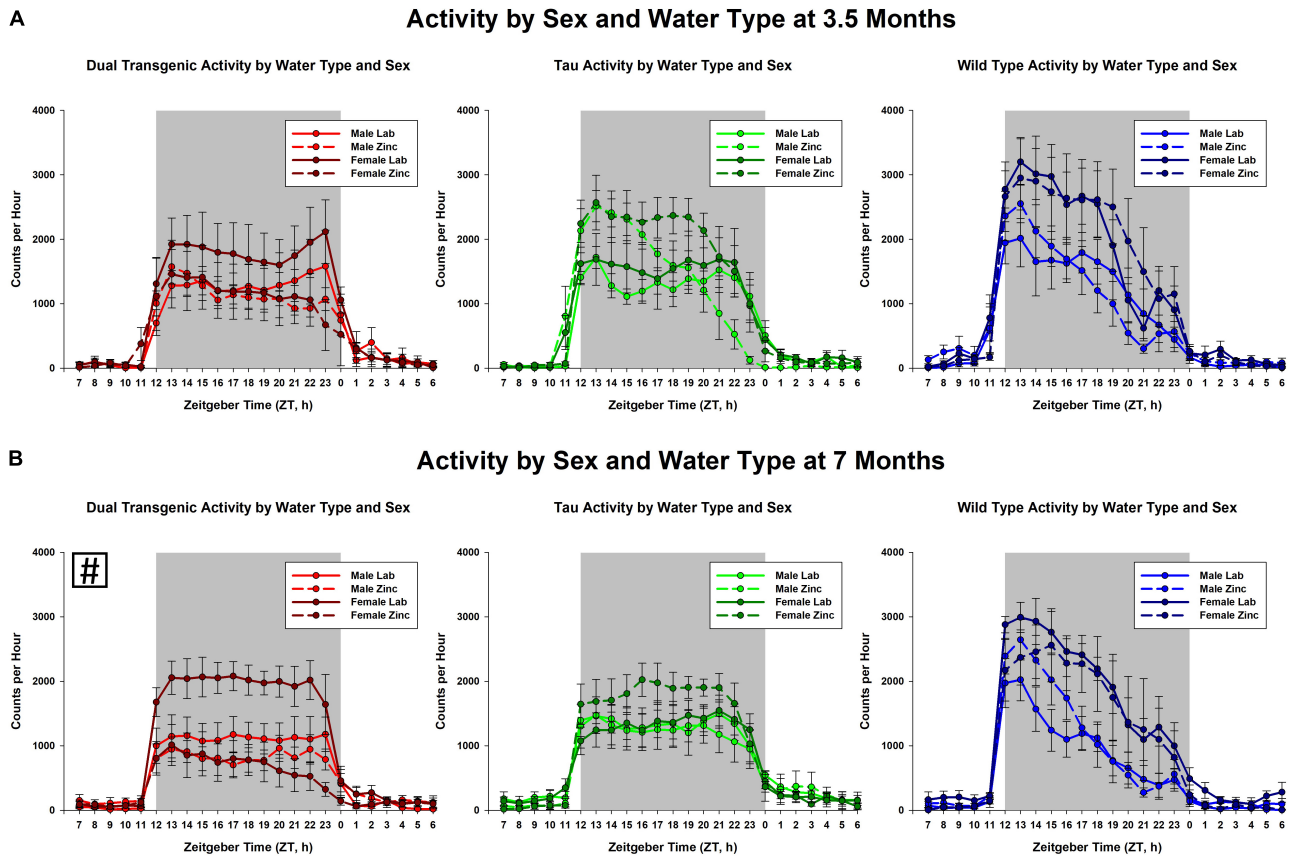

FIGURE 4 | Comparison dark cycle activity by **(A)** sex by water type by genotype at 3.5 months, and **(B)** sex by water type by genotype at 7 months. At 7 months, dual Tg females on lab water were significantly more active than either sex on Zn water, $p < 0.05$ (boxed # indicates a significant effect summed across dark cycle hours).

study showed that Zn led to alterations early on in the P301L tau animals, with Zn unexpectedly increasing the activity early in the dark cycle (**Figure 2B**).

A late-onset model of AD explored by Boggs et al. (2017) showed that, compared to C57 controls, APP/E4 (transgenic) mice did not exhibit a typical decline in activity throughout the night. Instead, similar to the dual Tg mice here, there was only a slight decrease, with lower activity compared to control mice during the beginning of the dark cycle and higher levels at the end of the dark cycle at both young (pre-plaque) and old (post-plaque) ages.

The Role of Zinc in Daily Rhythm Activity

Increasing zinc through the drinking water had no effect on the daily rhythm activity in Wt mice in this study, which is consistent with results from other studies (Craven et al., 2018; Moshirpour et al., 2020). However, there was a significant effect for the dual Tg mice, where activity decreased, and a smaller effect for the tau mice, where activity increased.

As shown in **Figure 2C**, the dual Tg mice given Zn water had lower activity than all groups except tau lab mice at 7 months, but this was not seen at 3.5 months. They also had the lowest activity of all groups studied.

Zinc is found in a number of regions in the circadian rhythm circuit (Moshirpour et al., 2020) including the intergeniculate leaflet (IGL) of the thalamus and the melanopsin-containing retinal ganglion cells which feed into the suprachiasmatic nucleus and the IGL. The data indicate that Zn interacts with amyloid and or tau in some region of the circuit, as yet unknown. Overall, what we present here is that there was a much stronger effect at 7 months; this may be due to the effect of increased levels of tau and/or amyloid interacting with Zn ions.

Zinc does not affect daily activity rhythms in wildtype mice at 7 months, thus indicating that the reduced activity seen in the dual Tg mice is due to an interaction with Zn and amyloid or tau. The changes are not due to a loss of activity in general in the 7 month dual Tg mice since there were no significant differences in distance traveled in the open field test between dual and tau mice at this age (Lippi et al., 2018).

The Role of Zinc in Sleep

Zinc's impact on sleep has been investigated in both humans and animals. Cherasse et al. (2015) showed that Zn, in the form of a Zn-containing yeast extract, led to decreases in locomotor activity in a dose-dependent manner, but only when given at the beginning of the dark cycle. This decrease in activity was

accompanied by an increase in NREM sleep. Zinc concentrations in this range 1–160 mg/kg were administered; there was a dose-dependent effect. The 40 mg led to a drop of ∼16% but the maximum effect was seen at 80 mg/kg where the reduction was over 50% and similar to that at 160 mg. Additionally, yeast extract led to an increase in NREM sleep in mice given either 40 mg/kg or 80 mg/kg Zn compared to vehicle; in both cases, the NREM sleep increased in the first hour. This dose is higher than what was used in the current study; the lower concentrations of Zn-enriched yeast are more similar to the present study's make up of Zn administration. These lower doses were not significantly different from vehicle administration given by Cherasse et al. (2015). Therefore, the lower activity seen in the dual Tg mice given Zn could be a product of Zn administration and interaction with AD pathology, rather than the Zn itself.

In a review on the way that dietary Zn can impact sleep, Cherasse and Urade (2017) discussed how Zn administration can impact sleep quality and amount in mice and humans. As evidence for the effects of Zn supplementation in humans, latency for sleep-onset and sleep efficiency were measured after being given either oysters, a food rich in Zn, or supplements aimed to impact Zn absorption. Specifically, the group eating oysters were shown to have significantly improved sleep efficiency and lower sleep-onset latency compared to the placebo group (Saito et al., 2016). This study showed that Zn has the ability to improve sleep after being ingested for several months. Baradari et al. (2018) also found that zinc improved sleep quality and sleep latency in nurses; the dose used was 220 mg. However, ingestion of too much Zn may be problematic in AD patients since administration of Zn could possibly lead to enhanced AD pathology as discussed below.

The Effect of Zinc on Alzheimer's Disease as a Function of Age

The impairments in daily activity rhythms were seen at 3.5 months in both mice raised on lab water and Zn enhanced water, with the Zn effects increasing significantly at 7 months in the dual Tg mice. This is a different pattern than that seen with other measures in these mice, such as the Barnes maze, nesting, or burrowing (Lippi et al., 2018). In these cases, the impairment of mice on lab water was already severe at 3.5 months and Zn had no further effect. The fact that Zn produced a stronger effect on daily activity rhythms at 7 months, with the dual Tg mice showing such low levels of activity in both male and female mice, suggests that there may be a different mechanism at work, potentially involving the eye.

The relationship between Zn and AD is complex. Zinc can interact with both amyloid and tau as these species tightly bind the metal, leading to higher propensities of Aβ aggregation and tau fibrillization (Mo et al., 2009; Miller et al., 2010). One theory of AD (Bush, 2008) suggests that Zn and Cu both bind with amyloid in the synaptic cleft; thus, the levels of both could be reduced. Lippi et al. (2018) confirmed this reduction in Zn through use of Zinpyr-1 fluorescence in the hippocampus, demonstrating that dual Tg mice had less free Zn than wildtype mice. Since Zn competes with Cu for entry into the body, increased Zn in the drinking water could enhance the Cu deficiency, and one study shows that a Zn-related spatial memory deficit in mice with APP is remediated by adding Cu (Railey et al., 2011). However, Zn also interacts with tau, and Craven et al. (2018) and Lippi et al. (2018) both show that Zn can increase hyperphosphorylation in tau mice. Additionally, Lippi et al. (2018) showed that the dual Tg mice had less free Zn in the hippocampus compared to wildtype mice; this is hypothesized to be due to increased binding with amyloid and tau pathology present within the hippocampus of these mice. Thus, Zn can have a negative effect in AD due to its interaction with both tau and APP.

Measuring Zinc in the Brain

As indicated above, we did find reduced free Zn in the hippocampus of the dual Tg mice (Lippi et al., 2018). Although Zn measurements are not presented in this paper, in other research, our method of Zn administration (10 ppm ZnCO3) was shown to increase free Zn fluorescence in the hippocampus of wildtype mice (Lippi et al., 2019).

In order to measure total Zn, both bound and free, researchers can use a number of methods such as ICPMS and X-ray synchrotron fluorescence (Flinn et al., 2005; Neely et al., 2019). However, levels of free Zn are notoriously hard to measure. Lippi et al. (2018) showed that dual Tg mice had significantly less free Zn in the hippocampus compared to wildtype mice, using Zinpyr-1 (a probe measuring free Zn fluorescence). This reduction in free Zn is hypothesized to be due to interactions with AD proteins that can bind Zn ions directly. Zinpyr-1 has also been used by Lippi et al. (2019) to show that the dose of Zn water given to these animals (10 ppm ZnCO3) leads to greater amounts of free Zn fluorescence (an indicator of more free Zn) in the hippocampus of wildtype mice. Despite use of these Zinpyr probes or X-ray synchrotron fluorescence, levels of free Zn are notoriously hard to measure. Maret (2015) states that although probes and sensors can provide qualitative differences in free Zn ion concentrations, when researchers seek to establish quantitative differences, there needs to be consideration for the assumptions underlying the use of probes and sensors. Additionally, changes in free Zn ions tend to be compared using ratios.

Sex Differences

An important factor to consider when measuring behavioral changes in mouse models of AD is biological sex of the animal subjects. Sex differences were noted at both testing ages. At 3.5 months, overall, female animals showed significantly more dark cycle activity than males and at 7 months they were significantly more active than males from the mid to late dark cycle (**Figure 3A**). These differences were significant in the Wt mice and similar patterns of activity were seen amongst the other conditions (dual Tg and tau), although not statistically significant (**Figures 3B,C**). Wu et al. (2018) showed similar results, in that the total daily activity in female mice was greater than that of male mice, regardless of genotype (WT v. 3xTg-AD). While Wu et al. (2018) tested at 6 months of age, we saw these differences at an

early testing age; at 3.5 months; however, the differences were less in the transgenic mice than in the Wt mice.

While research shows that women experience AD more than men (Viña and Lloret, 2010; Li and Singh, 2014), as compared to mild cognitive impairment (MCI) (Mielke et al., 2014), studies conducted in non-human models still often only use male mice. However, a number of studies included both sexes and showed different circadian rhythms in the sexes. Mouse models assessing circadian rhythms and sleep solely in male mice, have shown that age can impact sleep and wheel running activity in non-Tg inbred mouse strains (Valentinuzzi et al., 1997; Hasan et al., 2012). The 3xTg-AD mouse model showed altered circadian locomotor rhythms (Wu et al., 2018) with female mice showing less disruptions compared to males. Female 3xTgAD mice have also been found to be less active than non-Tg mice during the evening (lights-off) period (Sterniczuk et al., 2010). By including sex as a factor, research with AD mouse models can be more inclusive of the actual population as well as highlight differences between males and females which may lead to a better understanding of why females are different than males with regards to AD.

Interaction Between Sex, Zinc, and Genotype

The dependence of activity on sex, water type, and genotype is shown for 3.5 and 7 months in **Figure 4**. The greatest effect was seen for the dual Tg mice at 7 months, where both the male and female mice on Zn had significantly lower activity than the females on lab water.

Background Strains and Their Impacts on Circadian Activity

Daily activity rhythms, as well as open field activity and body temperature have been shown to be impacted by background strains of mice (Connolly and Lynch, 1981). Circadian disruption (leaving the lights on constantly) has been shown to lead to behavioral differences in male C57BL6/N and C57BL6/J mice (Capri et al., 2019). Earlier research has also shown that control strains of mice also differ in stability of circadian rhythms when exposed to constant darkness (Ebihara et al., 1978). These differences in activity, temperature, and circadian rhythms could impact research involving groups of mice not all bred from the same set of breeder parents or in projects involving ordering different control animals than a mixed background breeding scheme allows.

The mixed strain characteristic of the F1 mice used in this study is a component to address. The FVB/N and C57BL6/J strains have been compared in the literature as it relates to circadian wheel activity (Pugh et al., 2004). They found that, compared to C57BL6/J mice, FVB/N mice had greater activity in the light phase and never reached the same level of activity during the dark period. C57BL6J mice were also shown to entrain well to a 12:12 light/dark cycle compared to the FVB/N mice. It is important to note, however, that only male mice were used in the circadian wheel activity analysis and that in the current project, the F1 generation was of a mixed background. Wildtype mice (those genotyped as having no mutations in hAPP or tau, and those not including the promoter to express tau) were littermates and produced through the breeding process, helping to control for any additional background differences that may have impacted behavioral differences.

One possible confound is that the genetic makeup of the rTg4510 mouse contains a deletion involving a portion of Vipr2, a gene that plays a role in circadian activity and is found in the suprachiasmatic nucleus (Harmar et al., 2002). Harmar et al. (2002) have shown that the overall activity of Vipr2-/- mice is significantly less than that of Wt animals; thus affecting Vipr2 could have caused a loss in activity in the tau mice. Vipr2+/- mice have a reduced ability to bind their selective ligands, which indicates a gene-dose effect (Harmar et al., 2002); these mice would be similar to those mice used in the current study containing the CaMKIIa-tTA transgene. The tau mice did show a lower rate of activity overall than the WT mice at 3.5 months (**Figure 1A**), although this difference was not significant. However, at 7 months tau animals had a different overall pattern of activity, being significantly less active than WT animals at ZT 12-15 and more active than WT mice at ZT 21-23 (**Figure 1B**). In contrast, at 3.5 months, the dual Tg mice were significantly less active than the WT mice in ZT 12-17, and at 7 months they were less active than the WT mice at ZT 12-16. As AD pathology worsened, their activity decreased; this behavior in the dual Tg mice indicates an effect above and beyond that of the tau transgene and its effect on the Vipr2 gene. Additionally, Boggs et al. (2017) found that mice with both APP and E4 had a reduced level of activity, again showing an impairment due to AD pathology. Future studies assessing daily rhythm activity in the rTg4510 mouse or any offspring of crosses with this strain should be mindful of the genetic impact that may be playing a role.

IMPLICATIONS

In addition, research should explore whether mice with solely amyloid mutations exhibit similar disruptions in wheel-running as the dual Tgs examined here. This should be examined as a function of age and zinc administration. Zinc intake can also disturb the balance of other biometals, including copper. Excess Zn can lead to deficiencies in Cu (Maret and Sandstead, 2006). Rats given 10 ppm Zn had spatial memory deficits; however, when also given 0.025 ppm Cu, these spatial memory deficits were remediated (Chrosniak et al., 2006; Railey et al., 2010, 2011). Thus the effect of Zn plus Cu on circadian activity should also be examined.

CONCLUSION

In summary, we have shown that the dual Tg mouse model of AD has alterations in wheel-running behavior that is impacted by Zn administration. Dual Tg mice showed lower activity compared to

other genotype groups, particularly as a function of age, and Zn led to a significant reduction in their wheel-running activity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by the George Mason University IACUC.

AUTHOR CONTRIBUTIONS

SL and JF wrote and revised the manuscript. PK conducted the statistical analyses and provided plots and captions of the all data. MS conducted the wheel-running experiments and gathered all data used in this manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Neuroscience

REVIEW
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The Bidirectional Relationship Between Sleep and Inflammation Links Traumatic Brain Injury and Alzheimer's Disease

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Traumatic brain injury (TBI) and Alzheimer's disease (AD) are diseases during which the fine-tuned autoregulation of the brain is lost. Despite the stark contrast in their causal mechanisms, both TBI and AD are conditions which elicit a neuroinflammatory response that is coupled with physical, cognitive, and affective symptoms. One commonly reported symptom in both TBI and AD patients is disturbed sleep. Sleep is regulated by circadian and homeostatic processes such that pathological inflammation may disrupt the chemical signaling required to maintain a healthy sleep profile. In this way, immune system activation can influence sleep physiology. Conversely, sleep disturbances can exacerbate symptoms or increase the risk of inflammatory/neurodegenerative diseases. Both TBI and AD are worsened by a chronic pro-inflammatory microenvironment which exacerbates symptoms and worsens clinical outcome. Herein, a positive feedback loop of chronic inflammation and sleep disturbances is initiated. In this review, the bidirectional relationship between sleep disturbances and inflammation is discussed, where chronic inflammation associated with TBI and AD can lead to sleep disturbances and exacerbated neuropathology. The role of microglia and cytokines in sleep disturbances associated with these diseases is highlighted. The proposed sleep and inflammation-mediated link between TBI and AD presents an opportunity for a multifaceted approach to clinical intervention.

Keywords: sleep, inflammation, traumatic brain injury, concussion, Alzheimer's disease, cytokines, microglia, neurodegeneration

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INTRODUCTION

In diseased states affecting the central nervous system (CNS), the fine-tuned autoregulation of the brain is lost, which contributes to the affective and cognitive symptoms seen in psychiatric, neurological, and mental health disorders (Charrier et al., 2017). Alzheimer's disease (AD) is a neurodegenerative disorder that impacts approximately 1 in 10 people over the age of 65 and 1 in 3 people over the age of 85 (Newcombe et al., 2018). AD has a long prodromal phase and progresses slowly, across a span of typically around 10 years. In contrast, traumatic brain injury (TBI) is a rapid

onset condition which can occur at any age due to impact to the head. It has been suggested that TBI heightens the risk of subsequent development of AD (Mendez, 2017). Despite the stark contrast in their causal mechanisms, both AD and TBI are conditions which elicit a neuroinflammatory response that is coupled with physical, cognitive, and affective symptoms. A commonly reported symptom in both AD and TBI is sleep disturbance (Vitiello and Borson, 2001; Castriotta et al., 2007; Viola-Saltzman and Watson, 2012; Sandsmark et al., 2017). Sleep is regulated by circadian and homeostatic processes, such that pathological inflammation may disrupt the chemical signaling required to maintain a healthy sleep profile. In this way, immune system activation can influence sleep physiology. Conversely, sleep disturbances can exacerbate symptoms or increase the risk of inflammatory/neurodegenerative diseases. The coupling between sleep and inflammation may indicate clinical disease status or outcome of disease processes (Wiseman-Hakes et al., 2013; Rao et al., 2014). The self-perpetuating cycle of sleep disturbance and neuroinflammation seen in TBI and AD encourage a comparison of these seemingly disparate conditions to gain greater insight into the shared mechanisms of progressive symptomology. This review will discuss the possibility of a sleep- and inflammation-fueled progression from TBI to AD.

TBI is characterized by a primary insult, initiated by mechanical forces applied to the head or brain. Immediately, sequential pathophysiological processes are initiated, which often result in a chronic inflammatory microenvironment. Microglia and resident mononuclear phagocytes throughout the CNS are activated as part of this secondary injury process in an attempt to preserve homeostasis and repair injured tissue. TBI-induced inflammation is communicated by pro- and anti-inflammatory cytokines, which are below detectable levels in healthy tissue but rapidly increase upon impact (Wang and Shuaib, 2002; Lucas et al., 2006). Cytokines are powerful chemical communicators, essential for maintaining homeostasis throughout the body. However, unregulated release of pro-inflammatory cytokines following an injury can cause pathological functions that lead to detrimental inflammation and progressive tissue damage (Kumar and Loane, 2012; Morganti-Kossmann et al., 2018). Cytokines released by microglia act as sleep regulatory substances (SRSs) and help to maintain healthy sleep (Krueger and Majde, 1995). Therefore, TBI-induced elevation of cytokines can lead to sleep disturbances. Hereon, cytokine-mediated inflammatory cascades and sleep enter a self-perpetuating positive-feedback loop, containing many of the components seen in the molecular circuitry of sleep disturbances in AD (as shown in **Figure 1**).

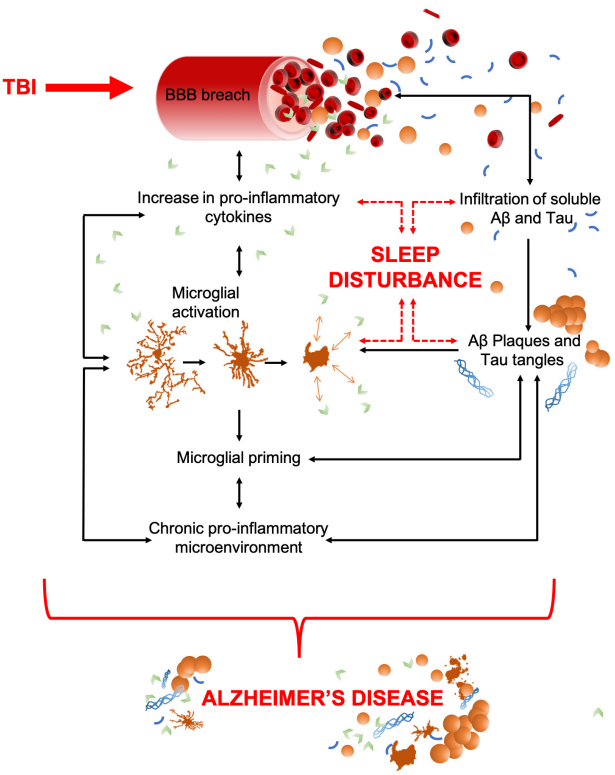

FIGURE 1 | TBI to AD, an inter-disease trajectory. TBI disrupts the blood brain barrier (BBB) upon insult which results in an infiltration of peripheral pro-inflammatory cytokines and any soluble pools of amyloid-β (Aβ) and Tau. Together, these can precipitate AD. As some pro-inflammatory cytokines have dual (opposing) roles as sleep regulatory substances, their increase can also lead to sleep disturbances, a characteristic that commonly precedes the cognitive decline in AD. Pro-inflammatory cytokines upregulate the activation of microglia, which act as a positive feedback mechanism, resulting in increased pro-inflammatory cytokine production and an increased breach of the BBB. Unregulated cytokine release also sustains microglial activation and priming which results in a chronic pro-inflammatory microenvironment. This includes astrocytosis, hypoxia, reactive oxygen species (ROS), elevated cytokine levels, and microglial activation. The movement of amyloid-β (Aβ) and Tau through the breach in the BBB could potentially seed protein oligomerization and aggregation, thereby acting as possible drivers of central plaque and tangle pathology. Such aggregates in the brain further contribute to microglial activation, the pro-inflammatory microenvironment, and neuronal apoptosis. Together, these contribute to cognitive dysfunction and brain atrophy, the key pathological features of AD. Both brain atrophy and neuronal death help to sustain the pro-inflammatory microenvironment creating a self-perpetuating feedback loop.

AD, much like TBI, is associated with a range of cognitive and non-cognitive symptoms that include memory loss, disturbed sleep, speech difficulties, depression, and loss of executive function (Burns and Iliffe, 2009). Preceding cognitive decline, the aggregation of amyloid-β plaques and tau neurofibrillary tangles occurs in the brain, both of which are required for a retrospective AD diagnosis after death (Murphy and LeVine, 2010). While a minority of cases are genetically linked, most do not have an identified cause which makes AD hard to predict, characterize, diagnose, and treat (Newcombe et al., 2018). Preexisting diseases and lifestyle factors can also contribute to an increased risk of AD (Faden and Loane, 2015). These include TBI, a common injury which increases the frequency and onset of AD and other related dementias (McKee et al., 2009; Gavett et al., 2010; Gavett et al., 2011; Baugh et al., 2012). Similar to TBI, AD has a neuroinflammatory component that is orchestrated by pro-inflammatory cytokines and activated microglia. Although inflammation has a beneficial role in clearing cellular debris and apoptotic cells associated with AD, chronic inflammation can be damaging due to pro-inflammatory intermediates that compromise future clearance mechanisms, synaptic pruning,

and neuronal survival (Solito and Sastre, 2012; Sarlus and Heneka, 2017). Moreover, the cytokine storm associated with chronic inflammation can disrupt sleep-wake cycles, a symptom frequently observed in AD patients. Sleep disturbances cause further cytokine release and microglial activation, hence a positive feedback loop of chronic inflammation and sleep disturbance is initiated (as shown in **Figure 1**).

In this review, we discuss the bidirectional relationship between sleep disturbance and inflammation, such that chronic inflammation associated with TBI and AD can lead to sleep disturbances that exacerbate neuropathology. We also highlight the role of microglia and cytokines in sleep disturbances associated with these diseases.

THE ROLE OF SLEEP ON HOMEOSTASIS

While sleep is an evolutionarily conserved phenomenon that is essential for survival (Banks and Dinges, 2007), its function is not fully understood. The roles of sleep in the elimination of waste, restoration of depleted energy sources (Oswald, 1980; Dworak et al., 2010), and energy conservation (Walker and Berger, 1980; Xie et al., 2013) have long been characterized. Sleep plays a physiological role in the cardiovascular, metabolic, thermoregulatory, respiratory, and sexual systems, as well as having a major role in regulating brain health and function. More recent hypotheses suggest a cellular need for sleep in regulating brain plasticity (Puentes-Mestril and Aton, 2017), learning, and memory (Tononi and Cirelli, 2003; Huber et al., 2004; Tononi and Cirelli, 2014; Miyamoto et al., 2017; Raven et al., 2018). Indeed, in the absence of sleep, there is significant detriment to cognitive function (Krueger et al., 1999).

The sleep-wake cycle is essential in regulating many of the body's fine-tuned homeostatic processes, even on a molecular level (Cirelli and Tononi, 2008). A study, using two-photon imaging of live mice after infusion of fluorescent tracers, showed that during sleep there was a 60% increase in the interstitial space, allowing an increase in exchange between cerebrospinal fluid (CSF) and interstitial fluid. This has important implications for the clearance of interstitial disease-associated proteins (Xie et al., 2013) and highlights a role for sleep in maintaining brain homeostasis.

TBI – INFLAMMATION AND SLEEP PATHOLOGY

Mechanical forces applied to the head or brain initiate TBI, wherein sequential pathophysiological processes permanently change neurological function (Masel and DeWitt, 2010; Corrigan and Hammond, 2013). TBI survivors suffer irreversible cognitive, sensory, sleep, mental health, and emotional morbidities as a consequence of injury-induced pathological processes (McAllister, 1992; Kempf et al., 2010). TBI can cause neuronal cell death, ischemia, hemorrhage, and the disruption of the blood-brain barrier (BBB) which elicit neuroinflammatory cascades (Pleines et al., 2001). Such secondary injury can exacerbate the damage caused by the initial impact if left unresolved. Although the primary brain injury from TBI is irreversible, the subsequent injury processes occur in a delayed fashion and may be responsive to treatment.

Ongoing cellular events post-TBI often cause further damage and lead to physiological consequences (Werner and Engelhard, 2007; Prins et al., 2013). Among these, sleep disturbances after TBI are commonly reported in the acute timeframe post-injury by up to 70% of TBI survivors (Cohen et al., 1992; Orff et al., 2009). Sleep disturbances may persist chronically (Castriotta et al., 2007; Verma et al., 2007; Kempf et al., 2010), and are experienced across the spectrum of TBI patients, including children and adolescents (Tham et al., 2012). These sleep disturbances in TBI survivors ultimately impact their quality of life. Identification and treatment of sleep-wake disturbances following TBI can improve outcomes in vigilance, working memory, and capacity of language processing (Wiseman-Hakes et al., 2013). Excessive daytime sleepiness is the most common sleep-wake disturbance reported among TBI patients (Castriotta et al., 2007; Kempf et al., 2010; Baumann, 2012) and is characterized primarily by an increase in sleep propensity. Other commonly reported disorders include post-traumatic hypersomnia, narcolepsy, delayed sleep phase, insomnia, and fatigue (Ouellet and Morin, 2006; Verma et al., 2007; Kempf et al., 2010; Baumann, 2012; Billiard and Podesta, 2013). These sleep disturbances negatively impact rehabilitation of TBI patients and can exacerbate symptoms such as pain and cognitive deficits (Mathias and Alvaro, 2012; Bhalerao et al., 2013).

Extensive pre-clinical research has focused on the detrimental effects of inflammation on the injured brain. In rodent models of TBI, microglia respond immediately to brain injury-induced tissue damage and release inflammatory mediators such as inflammatory cytokines and chemokines that have been shown to alter sleep (Morganti-Kossmann et al., 2001; Davalos et al., 2005; Nimmerjahn et al., 2005; Frugier et al., 2010; Semple et al., 2010; Ziebell and Morganti-Kossmann, 2010; Bachstetter et al., 2013). Two-photon microscopy images of fluorescently labeled microglia following a laser-induced injury demonstrated rapid proliferation and migration of microglia to the site of injury, where their processes fused (Davalos et al., 2005). It was hypothesized that this fusion event was to create a barrier between healthy and injured tissue (Davalos et al., 2005). These findings suggest that microglia may be the first line of defense following TBI (Kumar and Loane, 2012). However, microglia can become over-activated and induce detrimental neurotoxic effects through the overproduction of cytotoxins, including cytokines (Block and Hong, 2005). Uncontrolled cytokine production by activated microglia can significantly influence activation of astrocytes, which can increase neuronal cell death and worsen outcomes after TBI (Myer et al., 2006). Together, these results support the view that the inflammatory response to TBI possesses both beneficial and detrimental effects that likely differ in the acute and delayed phase after injury.

In the mouse, diffuse brain injury has been shown to increase the parameters of sleep for 6 h post-injury, regardless of sex, injury severity, or time of day the injury occurs (Rowe et al., 2014b; Saber et al., 2019). This period of post-traumatic

sleep correlates with elevated central and peripheral cytokine levels, particularly SRSs. Subsequent studies have shown sleep impairment at light-dark transitions, suggesting possible TBI-induced disruption of circadian rhythms (Lim et al., 2013; Rowe et al., 2014a). Whether post-traumatic sleep is beneficial or detrimental to neurological outcome from TBI remains unresolved. To advance the understanding of post-traumatic sleep, a gentle handling approach was used to keep both uninjured and brain-injured mice awake over the 6 h of post-traumatic sleep. In this study, a single period of sleep deprivation demonstrated no adverse, long-standing neurological effects (Rowe et al., 2014a), although, the course of recovery from injury may have been altered. Three days of transient sleep disruption following experimental TBI in the mouse worsened inflammation and altered stress-immune pathways (Tapp et al., 2020). Total sleep deprivation for 24 h following diffuse TBI in rats reduced morphological damage and improved functional outcome in the acute recovery period (Martinez-Vargas et al., 2012). The effect of sleep deprivation prior to TBI has also been investigated and 48 h of sleep deprivation or chronic sleep restriction (10 days, 6-h sleep/day) prior to mild or moderate TBI in rats did not exacerbate brain injury-induced neuronal damage (Caron and Stephenson, 2015). Sleep after TBI has also been inhibited pharmacologically. The therapeutic treatment of mice with an anti-inflammatory lipid mediator, and treatment with a novel TNF-α inhibitor, attenuated TBI-induced sleep and subsequently improved functional outcome (Harrison et al., 2015; Rowe et al., 2018b). When a second TBI was introduced during post-traumatic sleep (3 h apart), more severe functional and histopathological outcomes were observed, when compared with mice that received a second TBI after sleep from the initial impact subsided (Rowe et al., 2018a). Taken together, these studies suggest that more evidence is needed to determine if acute sleep after TBI is beneficial or detrimental, however, the underlying pathological response to brain injury that results in increased sleep may be amenable to therapies. Furthermore, post-traumatic sleep may be a physiological response to brain injury that could serve as a personalized biomarker to pathological conditions. In moderate to severe clinical cases of TBI, sleep-wake cycles can be altered due to a loss of consciousness. Clinical data indicate when the brain has not recovered consciousness from a moderate to severe TBI, it is not able to consolidate sleep or generate a 24-h sleep-wake cycle (Duclos et al., 2017). These clinical data parallel experimental data and suggest in the acute phase of TBI, injury-induced pathophysiology contributes to sleep disturbances.

Although inflammation has emerged as a major player in sleep disturbances post-TBI, there are other influences that should be considered. TBI can cause widespread mechanical damage to regions of the brain, many of which exert a role in sleep and inflammation. One region of particular interest to understanding sleep disturbances post-TBI is the hypothalamus (Sundaram et al., 2013). Damage or loss of hypothalamic neurons can disrupt orexin (a.k.a. hypocretin) secretion which has a well-established role in arousal and wakefulness. Extensive loss of orexin neurons and consequent excessive daytime sleepiness have been observed both pre-clinically and clinically after TBI (Baumann et al., 2009; Thomasy et al., 2017; Thomasy and Opp, 2019). Experimental TBI in the mouse decreased wake and increased non-rapid eye movement (NREM) sleep during the dark period and reduced orexin cells as a function of injury severity up to 2 weeks post-injury (Thomasy et al., 2017). Orexin (hypocretin) knockout mice subjected to TBI did not exhibit altered sleep, whereas control wild type mice had increased NREM sleep and decreased wake up to 1 month post-TBI (Thomasy and Opp, 2019). A prospective clinical study found that TBI survivors who reported excessive daytime sleepiness had reduced CSF orexin levels up to 6 months post-injury (Baumann et al., 2007). Together, these data support that the orexinergic system may be involved in long-term sleep-wake alterations that persist after the acute inflammatory response to TBI has subsided. Therefore, orexins should be considered when discussing the sleep-mediated links between TBI and AD (Liguori, 2017). However, the complexity of this relationship must be noted as not only has increased orexinergic signaling been associated with the progression of AD, orexins have been shown to increase amyloid-β in the interstitial fluid (Kang et al., 2009) and there is a documented correlation between tau proteins and orexin CSF levels and sleep-wake dysregulation in AD patients (Liguori et al., 2020b). Furthermore, damage to the hypothalamus and pituitary can affect the endocrine system in general (Sundaram et al., 2013), with potential for further impact on sleep architecture that is currently poorly understood.

DYSREGULATED IMMUNE FUNCTION AND SLEEP

The immune system is the body's defense system which monitors, detects, and attempts to eliminate threats to health and homeostasis. Immune cells communicate via chemical mediators such as cytokines and chemokines allowing them to respond to pathological changes within tissues with a high degree of specificity. While the peripheral immune system plays a role in the disease progression of TBI and AD, the inflammatory reactions observed in these conditions are largely driven by microglia, the immune cells exclusive to the CNS. There are bidirectional links between sleep and the immune system, such that sleep loss impairs immune function and physiological sleep is modified in response to an immune challenge (Ingiosi and Opp, 2016). Sleep/circadian disturbances, particularly states of sleep disruption and deprivation, can lead to serious consequences; for example, dysregulation of the inflammatory response (Castanon-Cervantes et al., 2010; Besedovsky et al., 2019), leading to a state of systemic inflammation with increased pro-inflammatory cytokines in the brain (Marshall and Born, 2002; Opp and Toth, 2003; Maurovich-Horvat et al., 2008; Aldabal and Bahammam, 2011).

Cytokines and Sleep

Cytokines have an essential role in regulating the immune system at multiple stages throughout the body and have long been characterized as a contributing factor to sleep and sleep disturbances. Under normal conditions, cytokines have been shown to play a role in NREM sleep (Shoham et al., 1987; Morrow and Opp, 2005; Krueger, 2008), as well as

altering neuronal firing patterns in both the hypothalamus and brainstem, with consequent effects on sleep regulation (Opp, 2005). Interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β, are well characterized for their essential role in both sleep and inflammation and mediate the crosstalk between the peripheral immune system and the brain (Krueger and Majde, 1995; Krueger, 2008; Besedovsky et al., 2019). Mechanistically, this property of IL-6, TNF-α, and IL-1β, could be linked to their neuromodulatory effect in contributing to the fine-tuned control of synaptic transmission and plasticity (Jewett and Krueger, 2012; Vezzani and Viviani, 2015), which contributes to the function of memory formation during intermittent rapid eye movement (REM) sleep and NREM sleep (Walker, 2017). As such, increased production of these pro-inflammatory cytokines mediates increases in sleep under inflammatory conditions such as TBI or AD.

There is also a relationship between sleep disturbances and cytokine production [Please see (Irwin, 2019) for an excellent review on sleep and cytokines]. The sleep disturbances that occur in neurological disease and injury (Musiek and Holtzman, 2016; Leng et al., 2019; Logan and McClung, 2019) are likely due to common pathological pathways that activate the immune response; specifically, inflammation and cytokine production. Prolonged wakefulness increased cytokines in the CSF (Borbely and Tobler, 1989; Krueger et al., 2001), which can lead to subsequent sleep disturbances. In one study, REM sleep deprivation for 72 h in rats led to significant increases in plasma IL-6, IL-1β, and TNF-α expression, but the expression of IL-6 and IL-1β returned to levels of controls 1-week after the period of sleep deprivation ended, while TNF-α remained elevated (Yehuda et al., 2009). Moreover, sleep deprivation increased IL-1β and TNF-α mRNA expression in cortical and subcortical brain regions in rats (Zielinski et al., 2014). Similarly, in humans with experimental chronic circadian sleep disruption, there was a significant increase in plasma TNF-α expression (Wright et al., 2015). A meta-analysis also showed that in humans, sleep disturbances increased plasma IL-6, although no significant changes were found in TNF-α expression, likely owing to the low statistical power in the analysis (Irwin et al., 2016). These studies support a bidirectional relationship between these pro-inflammatory cytokines and sleep. Increases in these cytokines lead to increased sleep, and conversely, sleep deprivation and disruption can increase these cytokines. However, a recent study showed that TNF-α knockout mice display similar patterns of sleep and no deficiency in sleep regulation compared with wild type mice (Szentirmai and Kapás, 2019). In fruit flies, knockdown of the TNF-α homologue in astrocytes, but not neurons, reduced sleep duration and disrupted sleep-rebound following sleep deprivation (Vanderheyden et al., 2018). As such, although IL-6, IL-1β, and TNF-α promote sleep, these cytokines may have a larger role in regulating sleep following inflammatory insults such as after TBI or during the chronic inflammatory events of AD.

Moreover, cytokines have functional implications in both TBI and AD. Following a TBI, there is a profound increase in the production and release of cytokines (**Figure 1**). Acutely, the increased release of cytokines is believed to have therapeutic implications that can help improve primary and secondary injury (Gyoneva and Ransohoff, 2015; Plesnila, 2016). However, chronically elevated cytokine levels can further perpetuate the initial damage and lead to robust secondary damage (Morganti-Kossman et al., 1997; Zeiler et al., 2017). Similarly, in AD, a dysregulation of cytokines may potentiate the pathogenesis of the disease leading to irreversible damage (Su et al., 2016; **Figure 1**). Indeed, plasma cytokines are higher in the AD population when compared with healthy controls (Swardfager et al., 2010). In the context of this review, we assert that sleep disturbances, brought about by either TBI or AD, lead to changes in cytokine production and may further exacerbate disease-related damage to the brain.

ALZHEIMER'S DISEASE – INFLAMMATION AND SLEEP PATHOLOGY

Sleep disturbances have long been a symptom associated with AD but more recently have been recognized as an early feature of the disease, thought to precede cognitive decline and contribute to disease progression (Musiek et al., 2015; Musiek and Holtzman, 2016). Literature reports that 25–70% of all suspected AD patients report disturbances in sleep which are linked to poorer disease prognosis (Moran et al., 2005; Craig et al., 2006; Beaulieu-Bonneau and Hudon, 2009; Lim et al., 2014; Wennberg et al., 2017). A recent study found that 20% of people between 25 and 45 were sleeping 90 min less than the recommended amount for their age group (Léger et al., 2011). This raises the question as to whether irregular sleep in early life contributes to developing AD later in life.

Sleep is important for clearing pathological and inflammatory-associated proteins from the brain. The recently discovered glymphatic system clears unwanted or pathological proteins from the interstitial space in the brain by exchange between the CSF the interstitial fluid (ISF) (Xie et al., 2013). Aquaporin-4 water channels, located on the end feet on astrocytes, mediate the process by allowing ISF flow from the interstitial space into the paravenous region, which in turn drains through the lymphatic system (Verheggen et al., 2018). This is the process by which solutes are removed from the brain. Further, it has been shown that the level of amyloid-β in the brain fluctuates rapidly with the daily sleep-wake cycle. During sleep, there is a 60% increase in the flow of ISF to CSF. Therefore, it is postulated that the disturbed sleep of AD patients decreases the exchange of ISF and CSF which may lead to reduced clearance of soluble amyloid-β, contributing to the formation of plaques (Xie et al., 2013; Rasmussen et al., 2018). In turn, increased amyloid burden can lead to an upregulated level of inflammation, perpetuating the cycle. Clinically, this effect has been observed using accelerated neuroimaging; blood oxygen level, functional magnetic resonance imaging, electroencephalogram, and CSF flow. Using these techniques, waves of CSF flow were observed during slow wave sleep, which appeared to be coupled with the hemodynamic rhythm during sleep (Fultz et al., 2019). Further, a recent clinical study that examined the sleep architecture and CSF biomarkers (tau and amyloid-β_{42}) in patients with AD (which progressed

from having subjective cognitive impairment to mild cognitive impairment to AD), found that both REM and NREM sleep were disturbed. They also found that AD patients displayed a decrease of CSF amyloid-β_{42} (Liguori et al., 2020a). In the clinic, amyloid-β deposition has been shown to accumulate prior to cognitive and memory decline (Liguori et al., 2020a) and this effect was significantly higher in those who also had poor sleep efficiency (Molano et al., 2017). Other experimental studies on human volunteers have also suggested that dysregulated sleep patterns increase amyloid-β deposition in the human brain (Shokri-Kojori et al., 2018). Together, these data demonstrate how the self-perpetuating cycle of sleep disturbance and inflammation are associated with a decline in cognitive function.

Pre-clinically, transgenic mice overexpressing disease-associated APPswe/PS1δE9 mutations which drive amyloid-β pathology, exhibit disturbed sleep patterns prior to developing amyloid-β plaques (Roh et al., 2012). This disturbance further emphasizes the potential bidirectional relationship between amyloid-β deposition and sleep regulation. However, whether the detrimental cycle is between sleep and amyloid-β directly, or rather associated inflammatory factors (or a combination of both) is unknown. The extent to which amyloid-β acts as a driver of AD progression remains controversial, but it does appear very likely that inflammation increases amyloid-β deposition (Irwin and Vitiello, 2019). Clinically, the AD brain presents with activated microglial phenotypes, most notably aggregated in the penumbra of amyloid-β plaques (Navarro et al., 2018) (see **Figure 2**; further discussed in section "TBI as a Contributor to AD"), where their likely/presumed function is to reduce neuronal exposure to soluble amyloid β-mediated toxicity (Wang et al., 2016). In the post-mortem AD brain, other morphological changes in microglia are seen, such as rod and dystrophic phenotypes, as well as an overall increase in microglial density (**Figure 2**; Bachstetter et al., 2015). This suggests that the role of microglia in AD is probably more complex than simply clearing amyloid-β and associated proteins (as represented in **Figure 2**). Despite the elusiveness of their function, these altered microglial phenotypes are associated with an increased release of pro-inflammatory cytokines known to cause sleep disturbances and neuronal toxicity (Lull and Block, 2010), thus, through this mechanism microglia can contribute to the progression of AD. In summary, both pre-clinical and clinical research suggests a complex interaction between sleep and the microglia-mediated inflammatory response in the AD brain.

Both sleep and inflammation are tightly coupled to the cholinergic system, which promotes wakefulness and REM sleep (Platt and Riedel, 2011). Irreversible damage to the basal forebrain cholinergic system correlates with the memory and cognitive symptoms seen in AD (Ferreira-Vieira et al., 2016). Moreover, the immune response is in part regulated by the cholinergic anti-inflammatory pathway by control of macrophages and microglia through α7 nicotinic receptors. Such modulation attenuates the release of pro-inflammatory cytokines, namely TNF-α, as shown *in vitro* and *in vivo* (Shytle et al., 2004; Lehner et al., 2019) and might be compromised by the loss

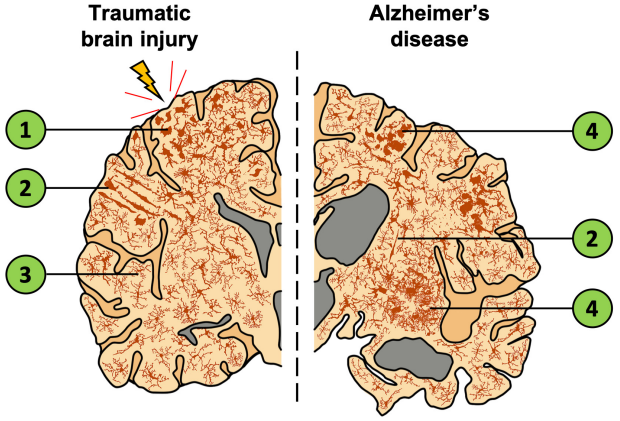

FIGURE 2 | Depiction of a coronal brain slice showing the global expanse of microglial phenotypes in TBI and AD. The left illustrates localized effects of TBI which include increased microglial activation near the injury site and decreased activation in distal regions. In comparison, the right represents the AD brain with widespread changes in microglia morphology, gross structural changes to the cortex, and an enlargement of ventricles (gray). Both TBI and AD lead to increased inflammation and activated microglia. Despite this similarity, distinct microglial morphologies are observed in these conditions. (1) Microglia are activated, migrate to the injury site, and display an amoeboid or phagocytic morphology. (2) Rod-cell morphology is often observed in the cortex after TBI and have also been documented in AD tissue. However, the function of this cell phenotype is currently unknown, and the morphology is not restricted to TBI/AD or the region in which they are shown. (3) Distal to the injury site, microglia are ramified and occur at a lower density. (4) Microglia that surround amyloid-β plaques show activated, amoeboid, and dystrophic morphologies. Cells of each phenotype pictured are not restricted to the brain regions shown.

of acetylcholine from basal forebrain neurons in AD. Although the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine (drugs currently licensed to treat the symptoms of AD) would be anticipated to boost acetylcholine levels, they have a poorly defined effect on sleep architecture (Cooke et al., 2006). One study found an 81.8% improvement in sleep quality with galantamine treatment, 75% with rivastigmine, and 50% from donepezil (Naharci et al., 2015). Despite these reported improvements, the treatment of sleep disturbances in AD patients remains a clinical challenge. Glutamatergic signaling, which plays an integrated role in the regulation of sleep stages and arousal (Shi and Yu, 2013), also deteriorates in AD patients. Memantine, a moderate affinity N-methyl-D-aspartate receptor antagonist, has been shown to increase total time spent sleeping in AD patients treated with 20 mg/day for 4 weeks (Ishikawa et al., 2016). However, due to the nature of receptor desensitization and transient efficacy of this drug, it is not a good long-term pharmacological candidate to break the altered sleep architecture and inflammation cycle discussed here. In the search for a more effective intervention, multiple neuroinflammatory molecules have been targeted as potential treatments for AD but have had limited success in measurable outcomes. Currently, there is renewed interest in microglia as a therapeutic target to stop the pathological inflammatory cascades seen in AD which could then potentially treat sleep

disturbances, as discussed in section "TBI to AD – A Microglial Mediated Progression?".

TBI as a Contributor to AD

Meta-analyses have found that a history of TBI is associated with development of AD (Mortimer et al., 1991; Fleminger et al., 2003). Despite different mechanisms of onset, these conditions are mechanistically interlinked by a complex web of pathologies, as demonstrated by **Figure 1**. Furthermore, increased amyloid-β levels are seen after TBI (Sivanandam and Thakur, 1995; Rasmusson et al., 1995; Nemetz et al., 1999; Jellinger et al., 2001) and post-mortem examination of TBI brains found that amyloid-β plaques, a hallmark of AD, had developed acutely in 30% of TBI brains (Roberts et al., 1991; Roberts et al., 1994; Johnson et al., 2010). However, as amyloid-β plaques are also seen in the healthy brain (Rodrigue et al., 2009), the meaning of these findings are unclear. While there is an increased risk of AD after TBI, most individuals with AD do not have a history with TBI, thus, other factors may interact with TBI-induced damage and lead to exacerbated cognitive decline and dementia (Plassman and Grafman, 2015). As discussed above, sleep disturbances post-TBI correlate with microglial activation and a concomitant rise in pro-inflammatory cytokine levels (Rowe et al., 2014b). As sleep disturbances have been identified as an early symptom of AD, it is plausible that TBI-induced sleep disturbances are a risk factor for AD. Until this is understood, the opportunity for therapeutic intervention in this inter-disease period is stunted.

Breach of the Blood Brain Barrier – Unregulated Infiltration of Plasma Proteins

TBI, despite the varying causal mechanisms, initiates breach of the BBB. Whether it be a transient opening due to the shearing of blood vessels, or a chronic inflammation-mediated opening, cross-talk between the CNS and the blood can occur. This is due to disruption of the tight junctions that prevent uncontrolled infiltration of substances from the blood, as summarized by **Figure 1**. A scanning electron microscopy (SEM) study of the human brain after death from TBI showed altered vascular features (Rodríguez-Baeza et al., 2003). Microvascular casts examined by SEM showed a sunken vascular surface, longitudinal creases, and flattened luminal morphology (Rodríguez-Baeza et al., 2003). A similar breach in neurovascular membranes has been observed in many pre-clinical studies (Tanno et al., 1992; Baldwin et al., 1996; Sangiorgi et al., 2013). Not only does the initial brain injury cause BBB breach from the sheering caused by the mechanical force exerted on the brain, but secondary processes such as inflammation and hypoxia contribute to prolonged breach of the BBB creating a self-perpetuating, unregulated cycle of cross-talk between the CNS and the blood. Alongside TBI, BBB breach is a well-known consequence of many other inflammation-inducing conditions such as viral or bacterial infection. Amyloid-β has also been shown to cause cerebral-amyloid angiopathy (the presence of amyloid-β aggregates in the vasculature of the brain) which adds to the perpetual, unregulated infiltration of blood components into the brain as this also causes further loss of blood vessel integrity leading to brain hemorrhage (Smith and Greenberg, 2009). As both mechanical damage and infiltration of pro-inflammatory molecules that travel in the blood increase the inflammatory microenvironment after TBI, this may increase the likelihood of developing AD, and its consequent sleep disturbances, that are known to be tightly associated with inflammation.

Matrix metalloproteases (MMPs) are key enzymes that cause breakdown of BBB integrity, and therefore the infiltration of products into the brain (Nissinen and Kähäri, 2014). MMP9 knockout mice have shown the deleterious role of MMPs in maintaining a chronic ischemic environment after a transient, focal ischemic injury (Asahi et al., 2001), as the absence of MMP9 reduced proteolytic breakdown of the BBB. Further, MMPs increase the bioavailability of both TNF-α (Haro et al., 2000; Vandenbroucke et al., 2013) and IL-1β (Schönbeck et al., 1998; Nissinen and Kähäri, 2014), two major inflammatory cytokines that can cause breach of the BBB independent of injury (Siegel et al., 2009). Not only does this lead to a chronic pro-inflammatory environment of the brain, but TNF-α and IL-1β act as SRSs, the increase of which can cause sleep disturbances. The disruption of sleep patterns feeds into the upregulation of inflammation and is a key feature of AD which can precede cognitive decline. When considered together, this body of literature suggests that MMPs are mediators of the perpetual pathological feedback loop initiated by TBI and postulated to increase the risk of developing AD.

Amyloid-β and Tau as Mediators of Inflammation and Sleep Disturbance

It is well established that TBI can cause disruption to the BBB, henceforth, crosstalk between the CNS and peripheral organ systems is initiated. Not only can this allow infiltration of peripheral cytokines (which further exacerbate neuroinflammation), but soluble forms of amyloid-β and tau can move across the BBB. The following section will discuss the role of these proteins in the inflammatory mediated sleep disturbances seen during the progression of both TBI and AD.

There is little known about the brain-wide concentration of oligomeric and unaggregated forms of amyloid-β, a protein that is found in high abundance peripherally with respect to the brain. As TBI creates an opportunity for amyloid-β proteins to cross the BBB, the clinical and biochemical impact of this is under much dispute. One study examined patients with a severe TBI and found that amyloid-β peptides (amyloid-β 1–42 and 1–40) were increased in the CSF, peaking 1 week post-injury (Raby et al., 1998). Increased levels of tau and amyloid-β were also observed in blood exosomes (Gill et al., 2018). Such increases in these proteins may be reflected in increased levels in CSF, however, evidence has proven inconsistent. For example, two studies reported that amyloid-β in the CSF was significantly lower than in controls during the week following TBI (Franz et al., 2003; Kay et al., 2003). Despite the disparity of these findings, it could be interpreted that CSF amyloid-β decreased post-injury due to possible deposition in the brain. However, as sleep disturbance post-TBI peaks in the acute

time phase, and sleep disturbance increases soluble amyloid-β in the CSF (Lucey et al., 2018), the findings of these studies are conflicting. Moreover, researchers have shown that the anti-inflammatory antibiotic doxycycline can attenuate the acute behavioral deficits associated with intracerebral delivery of oligomeric amyloid-β (Forloni and Balducci, 2018), which acts as proof of principle; unaggregated forms of amyloid-β and inflammation are tightly coupled.

Not only does infiltration of amyloid-β and tau directly affect the formation of plaques and tangles and increase oligomeric toxic species, but infiltration of associated proteins can also have an effect. For example, S100A9 (a pro-inflammatory protein) has been shown to contribute to amyloid plaques that accumulate rapidly after TBI. These plaques were found to be positive for oligomeric forms of amyloid-β and not fibrillar forms, suggesting that these could be a precursor to the plaques seen in later stage AD (Wang et al., 2014). Further, it has been well accepted that the levels of iron, copper and zinc are altered in the brain of AD patients and that amyloid-β plaques are sites of metal aggregation. Experimental models of TBI have also shown that there is increased infiltration of metal ions (iron, copper and zinc) post-TBI. Under normal physiological conditions, such ions are found in the blood and are prevented from freely moving across the BBB. Amyloid-β has been shown to associate with zinc, copper and iron ions (Lovell et al., 1998), which are all present in the blood, therefore, the increased level of blood in the brain after TBI is likely to exacerbate this association. This increase in ion concentration is therefore likely to augment plaque formation, increasing plaque-associated inflammation. Another well characterized contributor to AD is oxidative stress caused by the rapid production of free radicals. As sleep fosters antioxidant activity, sleep disruption may exacerbate ROS activity and associated inflammation post-TBI, which can lead to neuronal cell death and further aggregation of amyloid-β (Molina-Holgado et al., 2007).

TBI can also augment the formation of amyloid-β plaques and tau neurofibrillary tangles (NFTs) through inflammation-dependent gene expression and transcription factor activation. Experimental TBI in the 3xTg mouse model of AD, showed that TBI activated transcription factors (CCAAT/Enhancer Binding Protein Beta), and increased the expression of delta-secretase (Wu et al., 2019). Delta-secretase is an enzyme that mediates pathology by cleaving amyloid-β and tau which allows the formation of amyloid-β plaques and hyperphosphorylated tau, and consequently induces the neuroinflammatory cascade (Zhang et al., 2020). Support for the hypothesis that TBI augments the formation of amyloid-β plaques and NFTs was strengthened by the fact that the authors reversed the effect using viral expression of tau in 3xTg mice, that was resistant to cleavage by delta secretase (Wu et al., 2019). These data demonstrate how amyloid- β and tau contribute to the inflammatory microenvironment (and consequent sleep disturbances) associated with both TBI and AD.

NFTs are another hallmark of AD. In both mice and humans, NFTs have been found post-TBI (Kondo et al., 2015) and play a critical role in post-injury neuronal damage (Smith et al., 1999; Duda et al., 2000; Uryu et al., 2007; Yao et al., 2008; Johnson et al., 2012). NFTs impair axonal transport, notably of mitochondria (which are necessary for supporting nerve terminal function), contributing to the neuronal death associated with TBI (Kondo et al., 2015). Tau acts intracellularly as a microtubule stabilizer; however, its accumulation can occur both intracellularly and extracellularly (Swanson et al., 2017). Intracellularly tau abnormalities may cause neuronal death through disruption of intracellular cargo transport, whereas extracellular oligomers of tau are released from degenerating neurons. This was shown by in-vitro studies, revealing addition of un-aggregated tau protein increased the amount of cell death in tau-treated cells compared to controls (Gómez-Ramos et al., 2006). This suggests that extracellular tau is able to transmit the pathology to neighboring neurons, which causes spread of neuronal death from tauopathy (Swanson et al., 2017). Further, tau induces synaptic loss through microglial phagocytosis of synaptic compartments containing tau, leading to synaptic loss and cognitive decline (Jadhav et al., 2015). Alongside mediating the spatiotemporal spread of pathology, tau can prolong microglial activation, exacerbating a chronic pro-inflammatory environment in the brain, as shown in **Figure 2**.

A recent study using positron emission tomography has identified an increased level of tau deposition in patients that had suffered a single, moderate-severe TBI compared to controls (Gorgoraptis et al., 2019). Pre-clinical rodent models have also found an increase in oligomeric tau in the brain acutely (4 h) after parasagittal fluid percussion injury, which remained elevated for 2 weeks post-injury compared to uninjured shams (Hawkins et al., 2013). These studies support an increase in tau protein in the brain after TBI and provides another link for an inter-disease progression to AD triggered by TBI-induced BBB disruption.

Not only has tau been shown to have inflammatory consequences, but a recent human study, using regression analysis on positron emission tomography measures of amyloid-β and tau, and EEG sleep recording, showed that the extent of slow wave sleep disturbance predicted a greater presence of tau in the medial temporal lobe (Winer et al., 2019). Numerous studies using animal models also associate aggregates of tau with disturbance to sleep or circadian regulation (Musalek et al., 1989; Witton et al., 2016; Holth et al., 2017; Arnes et al., 2019). Taken together the data presented in this section suggest a plausible inter-condition link between TBI, AD through the inflammatory and sleep mediated pathological cycle.

TBI TO AD – A MICROGLIAL MEDIATED PROGRESSION?

Microglia, the immune cells exclusive to the CNS (Loane and Byrnes, 2010), play a role in perpetuating homeostasis in the CNS (Inoue, 2002), where they act as a biological surveillance system continuously monitoring the microenvironment. This allows them to be the first responders upon detection of pathological stimuli (Glenn et al., 1992). Microglial activation displays a morphological (and genetic) continuum, with changes in characteristics enabling the cells to rapidly respond to stimuli. Under normal conditions, microglia have a small cell soma

and highly branched processes. After detection of pathological stimuli, or sleep disturbance, the cell soma enlarges, and the processes retract. This activated phenotype permits phagocytic activity (Liu and Quan, 2018). Upon activation, microglia release cytokines to trigger pro-inflammatory pathways. Despite some immediate benefit seen from microglial activation, such as clearing of cellular debris, their reactivity has been associated with potentially damaging intermediates. These include reactive oxygen species and pro-inflammatory cytokines (Norden and Godbout, 2013; Iizumi et al., 2016), which can cause damage to nearby neurons, prolong the inflammatory response, hinder CNS repair, and exacerbate neurological symptoms, such as inflammation-induced sleep (Dheen et al., 2007; Ziebell and Morganti-Kossmann, 2010; Bilbo and Stevens, 2017). Further, chronic microglial activation increases astrocyte activation, which can worsen the outcome after an inflammatory challenge, increasing neuronal cell death (Myer et al., 2006).

In response to pathological stimuli, microglia upregulate their release of certain cytokines, including TNF-α, IL-1β, and IL-6 which act as SRSs (see section "Cytokines and Sleep"). A further consideration is that higher levels of microglial activation are observed during waking hours; microglia return to their non-activated status during sleep (Fonken et al., 2015). As microglia upregulate their release of IL-1β and TNF-α upon activation, it is likely that these cytokines fluctuate in response to endogenous circadian regulation, though this is beyond the scope of current experimental literature. If microglia return to non-activated states during sleep, one would predict sleep is neuroprotective following pathological stimuli, however, these data are inconclusive and require further research (see section "Alzheimer's Disease – Inflammation and Sleep Pathology").

The inflammatory cascade present in both AD and TBI presents as an attractive target for therapeutic intervention. Historically, cyclooxygenase, a key enzyme in prostaglandin production, was identified as a target for reducing the inflammatory response seen in AD, however, its inhibition with nonsteroidal anti-inflammatory drugs (Aisen, 2002) had limited efficacy in stalling the progression of AD. Due to observed clustering of microglia around amyloid-β plaques, microglia have emerged as a therapeutic target. Despite the growing volume of multidisciplinary research on the activation of microglia and pro-inflammatory cytokines as SRSs, the nuances of their involvement in sleep are not yet fully understood. As dysregulation of sleep has been associated with neurological deficits, a complex, multifaceted feedback loop is created. This poses a difficult target for therapeutic intervention, until the role of microglia in sleep is fully unveiled.

Multiple areas of neuroscientific research have presented cogent evidence suggesting that microglia can become "primed" and display an activated phenotype chronically (Fenn et al., 2014; Witcher et al., 2015; Hoeijmakers et al., 2016; Ziebell et al., 2017). Microglia in the aged brain express "primed" morphology, even under healthy conditions, a facet not observed in the younger adult brain (Norden and Godbout, 2013; Loane et al., 2014). Hypotheses suggest priming allows microglia to respond more rapidly to injury and infection, however, the link between chronic microglial priming and neurodegeneration is under-explored (Norden and Godbout, 2013). Furthermore, other cells of the glial network also show a more reactive phenotype in the aging brain. Activation of astrocytes, with their physical role in maintaining the integrity of the BBB, may allow greater influx of soluble β-amyloid proteins into the brain (see section "Amyloid-β and Tau as Mediators of Inflammation and Sleep Disturbance"), thus advancing the pathologies of the disease.

Much like in AD, a primed microglial phenotype has been observed after TBI. One study in rodents showed that after TBI, microglia remained sensitized and quickly became activated after a peripheral immune challenge provided by lipopolysaccharide (LPS). Mice that had received a TBI and LPS appeared to have a poorer cognitive outcome, suggesting that microglial priming worsens cognition (Muccigrosso et al., 2016). Another study found that microglia displayed a primed morphology up to a year after controlled cortical impact which appeared to augment pathologies such as lesion volume, degeneration of hippocampal neurons and myelin loss, which suggests microglial priming may be, at least in part, a contributor to neurodegeneration post-TBI (Loane et al., 2014). However, this relationship is hard to pinpoint as not only do microglia express a primed morphology with age and TBI, but also with other inflammatory-associated conditions such as HIV (Hains et al., 2010), stroke (Espinosa-Garcia et al., 2017), and even exposure to air pollution (Mumaw et al., 2016).

After TBI, activated microglia have an increase in the number of lysosomes (Tanaka et al., 2013). This has been suggested to provide a link to the development of amyloid-β plaques, because of the acidic lysosomal pH in comparison with the extracellular microenvironment (Spangenberg et al., 2019). This work was continued using histological staining in human tissue and found an association between microglia containing amyloid-β-aggregates which are hypothesized to lead to progressive amyloid-β pathology (Spangenberg et al., 2019). To further demonstrate the role of microglia in plaque formation, elimination of microglia in a transgenic mouse model of AD eliminated plaque formation, but plaques returned with the recovery of microglia, which supports them having a role in plaque formation.

Eliminating and repopulating microglia have shown therapeutic efficacy in both AD and TBI. Eliminating microglia using a bioavailable colony stimulating factor 1 receptor (CSF1R) inhibitor, a receptor necessary for microglia survival, in a 5xFAD mouse model of AD showed amyloid-β plaques failed to form in the absence of microglia but when the CSF1R inhibitor was withdrawn, microglia repopulated and amyloid-β plaques developed similar to those in controls (Spangenberg et al., 2019). Similarly, the elimination of microglia with a low dose of a bioavailable CSF1R inhibitor in 3xTg-AD mice prevented microglia association with plaques and improved cognitive function (Dagher et al., 2015). Another study showed chronic microglia elimination did not alter amyloid-β loads but prevented neuronal loss, rescued dendritic spine loss, and improved cognitive behavior (Spangenberg et al., 2016). Microglia elimination has been used in experimental TBI studies where microglia elimination with a CSF1R inhibitor prevented acute and chronic inflammatory responses in the mouse and attenuated astrogliosis (Witcher et al., 2018). As a

therapeutic intervention, chronically activated microglia were eliminated using a CSF1R inhibitor 1 month following a focal TBI, and the inhibitor was withdrawn 1 week later to allow microglia to repopulate. These studies indicated that removal of microglia after TBI reduced chronic neuroinflammation and associated neurodegeneration and mice had improved functional outcome (Henry et al., 2020). Taken together, these studies support that microglia play a role the chronic inflammatory response following TBI and contribute to AD pathology. If eliminating microglia changes sleep profiles in the context of TBI or AD has yet to be explored, however, these experiments may offer further therapeutic approaches to mitigate inflammation-mediated sleep disturbances.

CONCLUSION

This review documents the complexity of the multidirectional relationship between sleep, microglia, and inflammation in the clinical and pre-clinical contexts of TBI and AD. It is posited that the inflammatory cascades triggered by the disturbed sleep observed in TBI and AD creates the perfect storm, resulting in a highly dynamic inter-disease trajectory. To this end, the proposed sleep and inflammation-mediated link between TBI and AD presents an opportunity for a multifaceted approach to clinical intervention.

AUTHOR CONTRIBUTIONS

TG and RR are responsible for the conceptualization and organization of this review. TG wrote the first draft of the manuscript. JO, SW, RW, and RR contributed to content and edited the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Potential Pathways for Circadian Dysfunction and Sundowning-Related Behavioral Aggression in Alzheimer's Disease and Related Dementias

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Patients with Alzheimer's disease (AD) and related dementias are commonly reported to exhibit aggressive behavior and other emotional behavioral disturbances, which create a tremendous caretaker burden. There has been an abundance of work highlighting the importance of circadian function on mood and emotional behavioral regulation, and recent evidence demonstrates that a specific hypothalamic pathway links the circadian system to neurons that modulate aggressive behavior, regulating the propensity for aggression across the day. Such shared circuitry may have important ramifications for clarifying the complex interactions underlying "sundowning syndrome," a poorly understood (and even controversial) clinical phenomenon in AD and dementia patients that is characterized by agitation, aggression, and delirium during the late afternoon and early evening hours. The goal of this review is to highlight the potential output and input pathways of the circadian system that may underlie circadian dysfunction and behavioral aggression associated with sundowning syndrome, and to discuss possible ways these pathways might inform specific interventions for treatment. Moreover, the apparent bidirectional relationship between chronic disruptions of circadian and sleep-wake regulation and the pathology and symptoms of AD suggest that understanding the role of these circuits in such neurobehavioral pathologies could lead to better diagnostic or even preventive measures.

Keywords: circadian, aggression, sundowning, Alzheimer's disease, dementia, agitation

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INTRODUCTION

Behavioral aggression and circadian dysfunction are both prevalent in several neural disorders (Todd and Machado, 2019), including Alzheimer's disease (AD) and related dementias, and there has been an abundance of work over the last decade highlighting the general importance of circadian function on the regulation of mood and emotional behavior, including aggression (Bronsard and Bartolomei, 2013; Hood and Amir, 2018; Taylor and Hasler, 2018; Logan and McClung, 2019; Ketchesin et al., 2020). For example, circadian disruptions such as rotating shift work and jet lag due to transmeridian travel have been shown to precipitate or exacerbate mood symptoms (Asaoka et al., 2013; Kalmbach et al., 2015; Inder et al., 2016). More specifically,

social jet lag (defined as a discrepancy between the body's internal circadian clock and the actual sleep schedule) has been associated with increased physical and verbal aggression (Randler and Vollmer, 2013; Lin and Yi, 2015). Converging evidence also supports the notion that evening chronotypes exhibit a greater predisposition for behavioral aggression (Schlarb et al., 2014; Deibel et al., 2020). Recent work in transgenic mice also suggests that the master circadian pacemaker, located within the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, directly modulates a rhythm in the propensity for aggressive behavior via a polysynaptic pathway contained entirely in the hypothalamus (Todd et al., 2018). Todd et al. (2018) showed that a functionally connected circuit from the SCN, through the nearby subparaventricular zone (SPZ), gates the activity of neurons within the ventromedial hypothalamus (VMH) that drive aggressive behavior (the SCN → SPZ → VMH pathway, see **Figure 1**). This pathway may be a substrate through which circadian dysfunction can lead to increased aggression, both acutely and chronically in disorders that are characterized by circadian disruption and high levels of aggression and agitation.

Agitation and aggression, circadian dysfunction, and several other non-cognitive symptoms of AD and dementia seem to point to an underlying disruption in the hypothalamus (Ishii and Iadecola, 2015; Hiller and Ishii, 2018), even though brainstem and cortical structures are normally the foci of most neuropathological investigations concerning these disorders. While circadian disruption of sleep-wake and other rhythms is a typical component of normal healthy aging, such dysfunction is greatly exacerbated in neurodegenerative disorders such as AD and dementia. Indeed, a growing body of evidence suggests a bidirectional interaction between the circadian system, AD pathology, and the progression of the disease (Musiek, 2015; Videnovic and Zee, 2015; Musiek and Holtzman, 2016; Duncan, 2020). Since such neurodegenerative disorders clearly disrupt the circadian rhythmicity of sleep-wake, it is likely that they also disrupt the circadian regulation of emotional processing and aggression propensity as well. Indeed, the interaction between the circadian system and processes modulating aggression may be a key contributor to the clinical phenomenon known as "sundowning syndrome", which is commonly reported in AD and dementia patients. Sundowning is characterized by increased confusion and emotional behavioral disruptions, such as agitation and aggression, particularly during the late afternoon and early evening hours (Bachman and Rabins, 2006; Khachiyants et al., 2011; Bedrosian and Nelson, 2013; Canevelli et al., 2016). This syndrome can create a major burden on both patients and caretakers, with organizations such as the Alzheimer's Association and the National Institute on Aging providing online caretaker resources to help them better cope with sundowning symptoms (Aging, 2017; Association, 2020). Indeed, sundowning symptoms have been cited as among the most important factors leading to the decision to seek institutionalization (Pollak and Perlick, 1991; Hope et al., 1998).

Sundowning was first described in the medical literature over 80 years ago as "senile nocturnal delirium" (Cameron, 1941), when D. Ewen Cameron noted an exacerbation of delirium and agitation that occurred within an hour of placing dementia patients into a darkened room. The term "sundowning syndrome," due to the phenomenon's association with the onset of daily darkness, was first coined in the late 1980s by Lois K. Evans, who described it as a recurring condition among institutionalized older adults similar to delirium, but lasting much longer (Evans, 1987). However, since that time, the relevant literature on sundowning has been relatively scarce, and the underlying pathophysiology of the syndrome remains enigmatic. Perhaps one of the primary reasons sundowning remains poorly understood is that the symptoms and criteria used to define it have differed widely across groups (Bachman and Rabins, 2006; Canevelli et al., 2016). For instance, some groups have focused more on the emotional components of the syndrome, some more on the increased nocturnal locomotor activity such as wandering, whereas fewer have described sundowning as primarily a sleep-related disturbance (Boronat et al., 2019). It is also important to note that sundowning is not an official diagnosis (it does not appear in the DSM-5), but rather a loose grouping of symptoms. These challenges probably contribute to the wide range of prevalence reported for sundowning across studies, with some studies reporting as high as 60%, while others reporting as low as 2.5% for dementia patients depending on the setting (Khachiyants et al., 2011; Canevelli et al., 2016). However, more recent work suggests a more narrow prevalence between 20 and 27.8% (Angulo Sevilla et al., 2018; Pyun et al., 2019).

Research done during the 1990s and 2000s led some to question whether sundowning represents an actual time-dependent worsening of behavioral disturbances, or instead an increase in caretakers' perceptions of the stress caused by these disruptions at a particular time of day (Gallagher-Thompson et al., 1992; Bliwise et al., 1993; Cohen-Mansfield, 2007). Additionally, some studies did not find support for an exacerbation of behavioral symptoms occurring specifically around sunset (Bliwise et al., 1993; Friedman et al., 1997), with one suggesting that peak agitation actually occurs during the early afternoon (Martin et al., 2000). However, in a later discussion of diagnostic criteria for sleep disorders in AD (Yesavage et al., 2003), several of these same authors noted that "other research does support the notion that the nocturnal hours or the period of sunset (ranging from 4:00 to 8:00 PM depending on the study) are vulnerable to agitation," and that "(t)aken together, these results lend support to the existence of a circadian rhythm for agitated behaviors in many AD patients that peaks late in the day, although its precise delineation in real time and its association with sunset, sleep, and patient and/or disease characteristics remain unclear." Yesavage et al. (2003) further stressed the important point that "although there is mixed evidence for the existence of sundowning and it may be useful descriptively, the term, when used to define sleep disturbance, is too broad to be of practical diagnostic value." Altogether, this raises the possibility that the sundowning phenomenon reflects a time-dependent disturbance in emotional regulation rather than a direct sleep disturbance. And, its occurrence may be more generally tied to a 4-h window within the late afternoon and early evening instead of being directly tied to sunset.

Indeed, during this same time, numerous more groups reported disturbances in AD and dementia patients that

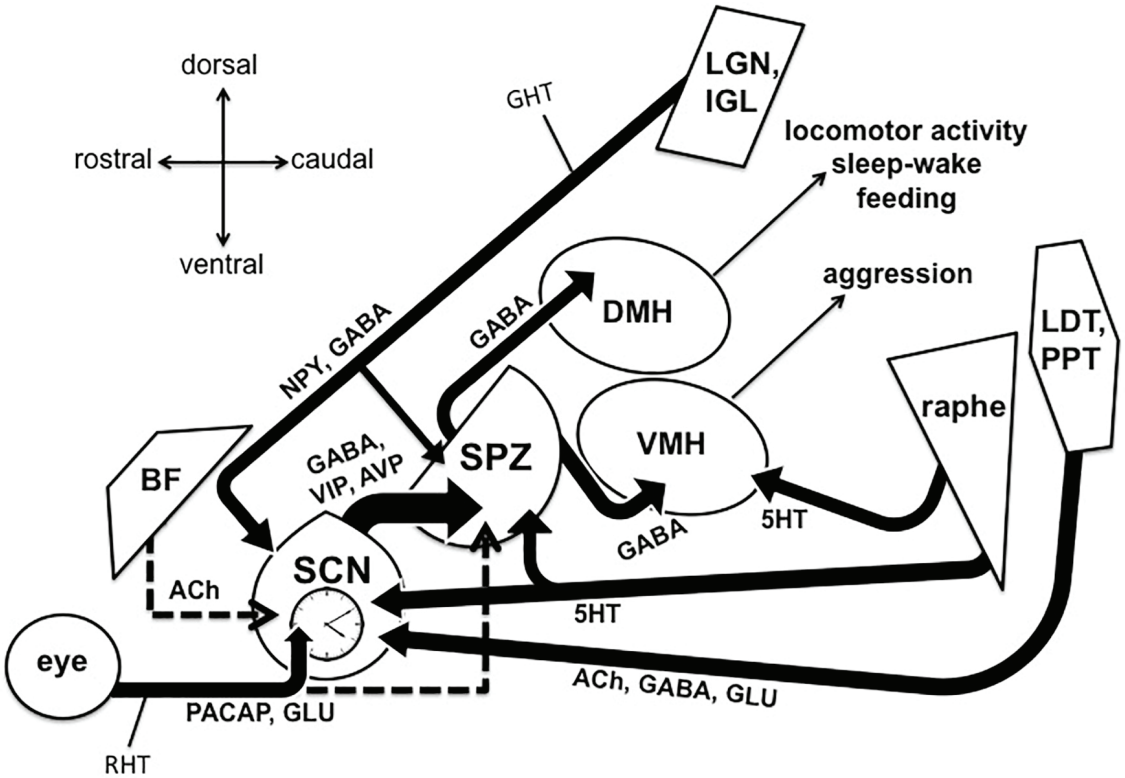

FIGURE 1 | Output and input pathways of the central circadian timing system in the mammalian brain that may be involved sundowning–related behavioral aggression and circadian dysfunction in Alzheimer's disease and related dementias. The master circadian pacemaker, is the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN releases the fast neurotransmitter GABA, as well as several peptides including vasoactive intestinal peptide (VIP) and argine vasopressin (AVP) from its major axonal output pathway to the nearby subparaventricular zone (SPZ). The GABAergic SPZ regulates rhythms of locomotor activity, sleep-wake, and feeding via pathway to the dorsomedial hypothalamus (DMH), and regulates rhythms of aggression propensity via a pathway to the ventromedial hypothalamus (VMH). The SCN is entrained to the daily light-dark cycle by input from intrinsically photosensitive retinal ganglion cells, which release pituitary adenylate cyclase activating polypeptide (PACAP) and glutamate (GLU) via the retinohypothalamic tract (RHT). The RHT also densely innervates the SPZ in most nocturnal mammals, but provides little or no innervation of the SPZ in many diurnal mammals, including humans (indicated by dashed line). A cholinergic (ACh) input to the SCN from the basal forebrain has been suggested in rats, but is absent in mice (indicated by dashed line). Cholinergic input to the SCN has also been reported from the laterodorsal tegmentum (LDT), pedunculopontine tegmentum (PPT) complex, which also releases GABA and GLU. Serotonergic (5HT) inputs to both the SCN and SPZ have been reported from the midbrain raphe complex. Finally, the geniculo-hypothalamic tract (GHT), originating from the retinoreceipient (not shown here) ventral lateral geniculate nucleus (LGN) and intergeniculate leaflet (IGL) of the thalamus, provides an input of GABA and neuropeptide Y (NPY) to both the SCN and SPZ. Structures are not drawn to scale.

temporally and qualitatively match the traditional description of sundowning-related agitation and aggression (Martino-Saltzman et al., 1991; Cohen-Mansfield et al., 1992; O'Leary et al., 1993; Burgio et al., 1994; Sloane et al., 1998). Even more recently, several observational studies defining sundowning as an increase in neuropsychiatric behaviors (including agitation and aggression) in the late afternoon and early evening have observed this phenomenon in AD patients in association with important circadian or AD-related factors (Silva et al., 2017; Angulo Sevilla et al., 2018; Menegardo et al., 2019; Pyun et al., 2019; Shih et al., 2019). For instance, Menegardo et al. (2019) associated the aggressiveness and irritability of sundowning with increased nocturnal behavior such as wandering. Silva et al. (2017) also associated sundowning with increased depressive and cognitive symptoms, suggesting that multiple emotional systems are disrupted in this syndrome and that these become even more compromised as AD progresses with more associated cognitive decline. Angulo Sevilla et al. (2018) also noted an association of such sundowning symptoms with an increased severity of dementia, but also in association with insomnia and hypersomnia. Interestingly, Pyun et al. (2019) found a strong association between these sundowning symptons and the presence of the apolipoprotein E (APOE) ε4 allele, an important genetic risk factor in the development of late-onset AD that promotes amyloid pathology (Corder et al., 1993).

A recent scoping review across 23 studies focused on sundowning found that temporal periodicity was the most prevalent finding, with 90.0% of the studies that met their criteria for inclusion reporting an onset of behavioral disturbances occurring during the middle afternoon and early night (Boronat et al., 2019). The symptoms examined across these studies most commonly clustered into "psychomotor disturbances" at 83.3%, and included agitation, aggression, and restlessness, followed by

a cluster of symptoms categorized as "cognitive disturbances" at 66.7% including confusion, disorientation, and wandering. Importantly, these studies also largely support the notion that sundowning may reflect a time-dependent disturbance in emotional behaviors, rather than a sleep disturbance *per se*. Therefore, in order to better understand and treat sundowning symptoms, it is important to recognize the interacting neural components that modulate the production and daily timing of emotional behavioral states. Interestingly, Todd et al. (2018) found that disrupting the SCN → SPZ → VMH pathway led to increased behavioral aggression specifically during the early resting phase (the light phase for nocturnal mice), a time which appears to be temporally analogous to when AD and dementia patients have traditionally been reported to display sundowning symptoms (Todd et al., 2018). Such shared neural pathways may be promising targets for treatments that could greatly reduce sundowning and other symptoms associated with circadian dysfunction. This review examines the existing literature on specific pathways emanating from the circadian system and the behaviors they regulate, in addition to pathways that provide input to the circadian system and influence its function (**Figure 1**). It also focuses on the evidence concerning whether AD-related disruption of these circuits might underlie sundowning symptoms, as well as how these pathways might inform potential treatments options.

THE EXTENDED MAMMALIAN CIRCADIAN TIMING SYSTEM

The SCN (see **Figure 1**) is required for daily rhythms of physiology and behavior (Moore and Eichler, 1972; Stephan and Zucker, 1972), and SCN neurons function as individual oscillators with rhythms of electrical activity that have period lengths of about 24 h (Welsh et al., 1995). This electrical activity becomes highly coupled across SCN cells, resulting in an emergent ensemble circadian period (Herzog et al., 1998). The electrical activity rhythms within individual SCN neurons are under the control of canonical "clock genes," via a transcriptional-translational-post-translational negative feedback loop (Gekakis et al., 1998; Jin et al., 1999). This genetic machinery has been found to be present in cells throughout the brain and body, however, the integrity of the SCN is necessary to synchronize these peripheral oscillators and maintain rhythmic behavior (Mohawk et al., 2012). Specifically, SCN neuronal activity has been shown to be required for such circadian output, as the application of tetrodotoxin to the SCN *in vivo* reversibly disrupts circadian behavior, even while proper circadian timekeeping within the SCN remains intact (Schwartz et al., 1987).

Suprachiasmatic nucleus neurons are predominately GABAergic (Liu and Reppert, 2000), with subpopulations that differentially release several neuropeptides, including vasoactive intestinal peptide (VIP), arginine vasopressin (AVP), gastrin-releasing peptide (GRP), neuromedin S (NMS), and cholecystokinin (CCK). Some of these neuropeptides are arranged somatotopically, as the SCN is composed of "core" and "shell" subregions that express VIP and AVP, respectively (Abrahamson and Moore, 2001). The VIP neurons within the SCN core receive direct retinal input and are required for normal circadian rhythmicity (Harmar et al., 2002; Aton et al., 2005; Maywood et al., 2006). These VIP core neurons then appear to entrain the rhythmicity of AVP shell neurons and other SCN neuronal cell types in order to establish SCN-level synchrony (Aton et al., 2005; Maywood et al., 2006). The subpopulation of SCN neurons expressing NMS have also been implicated as playing a crucial role in circadian pacemaking (Lee et al., 2015), however, more recent work suggests that the critical neurons in this role belong to a molecularly distinct subpopulation that expresses *both* NMS and VIP together (Todd et al., 2020). Interestingly, Todd et al. (2020) found that SCN VIP neurons that also contain NMS are enriched with the transcript *Per2* associated with a core clock gene, whereas the non-NMS subpopulation of SCN VIP neurons that also contain GRP did not have such transcripts. Altogether, this suggests that SCN VIP neurons are composed of both pacemaker and non-pacemaker subpopulations, which is supported by previous work demonstrating that SCN VIP neurons can be divided into two groups based on the light-inducibility of clock genes, innervation of retinal afferents, day-night variability of VIP mRNA, and coexpression of GRP (Kawamoto et al., 2003).

Suprachiasmatic nucleus neurons have been suggested to synchronize downstream molecular clocks and coordinate circadian rhythms via the release of humoral factors, as encapsulated implants of fetal tissue (which prevent the establishment of new neural connections) into SCN-ablated animals have been shown to restore modest behavioral rhythms (Silver et al., 1996). Identified humoral factors that are released by the SCN and have been shown to modulate behavioral and physiological rhythms include transforming growth factor alpha and prokineticin 2 (Cheng et al., 2002; Li et al., 2006; Gilbert and Davis, 2009). However, developmental work suggests that the influence of SCN humoral factors may decrease during the early postnatal period as axonal connections develop between the circadian system and downstream areas regulating behavioral state (Gall et al., 2012; Blumberg et al., 2014). Overall, the SCN's major axonal output pathway through the SPZ (see below) appears to be the primary method for synchronizing downstream oscillators and maintaining circadian rhythms of behavior (Saper, 2013).

As also depicted in **Figure 1**, the majority of axons emanating from the SCN synapse onto neurons within the SPZ, an adjacent region of GABAergic cells located just dorsal to the SCN and ventral to the paraventricular hypothalamus (PV) (Watts and Swanson, 1987; Watts et al., 1987; Vujovic et al., 2015). Like the SCN, the SPZ displays circadian rhythms of multiunit activity *in vivo* (Nakamura et al., 2008), and this output pathway has been hypothesized to be the primary circuit by which the SCN synchronizes organismal-level circadian rhythmicity (Saper, 2013). Specifically, studies in rats have shown that circadian rhythms of sleep-wake, locomotor activity,

and feeding behavior are regulated by a pathway from the SCN, through the SPZ, to the dorsomedial nucleus of the hypothalamus (DMH) (Lu et al., 2001; Chou et al., 2003). As mentioned previously, it was recently demonstrated that rhythms of aggression propensity in male mice are regulated by SPZ neurons that project to VMH neurons known to promote attack behavior (Todd et al., 2018). These SPZ neurons were found to be active during the early light phase, the resting phase for nocturnal mice, and disrupting their GABAergic transmission resulted in a time-dependent increase in behavioral aggression. Importantly, this time point is temporally analogous to the early resting phase in humans, when sundowning symptoms are most commonly reported in AD patients (Boronat et al., 2019). In addition to aggression, neurons within the VMH have also been associated with the regulation of fear and anxiety (Silva et al., 2013; Kunwar et al., 2015), raising the interesting possibility that the SCN → SPZ → VMH pathway may also influence circadian aspects of these emotional processes in a circadian fashion (Bilu and Kronfeld-Schor, 2013; Albrecht and Stork, 2017). Given the wide range of rhythms that the SPZ appears to influence, this structure appears to be a likely candidate for which its dysfunction, or dysfunction of its inputs (from the SCN or elsewhere), could affect multiple aspects of circadian physiology and behavior that are seen in conditions such as sundowning syndrome.

DYSFUNCTION WITHIN MAJOR CIRCADIAN STRUCTURES ASSOCIATED WITH AGING AND AD PATHOLOGY

Interestingly, separate studies have reported conflicting results regarding the direct impact of AD pathology on SCN VIP and AVP neurons in humans. Such studies are often complicated by the fact that researchers often do not have access to both hypothalamic tissue and the profile of circadian behavior of the same patients. However, one study examined hypothalamic tissue containing the SCN in aged patients that had at least 1 week of actigraphy data within 18 months of their death, and found that an age-related decline in VIP, but not AVP, SCN neurons was associated with increased circadian dysfunction (Wang et al., 2015). A group of AD patients examined within this study, however, did not show a significantly greater loss of VIP SCN neurons compared to controls, even though they showed delayed acrophases of the locomotor activity rhythms. This led Wang et al. (2015) to suggest that structures that supply input to the SCN may instead be affected by AD pathology, therefore leading to a disruption of phase-setting and resulting in the delay found in their patients. Indeed, similar phase delays are a common report in AD and dementia patients from several other studies (Harper et al., 2005; Schlosser Covell et al., 2012; Manni et al., 2019). One other study using actigraphy reported that a loss in AVP neurons in the SCN in AD patients was associated with fragmented rhythmicity compared to healthy aged-matched controls (Harper et al., 2008), however, this group used a ratio of AVP neurons to glial cells in only a few selected fields of the SCN, whereas Wang et al. (2015) used a stereological rigorous method to quantify AVP and VIP throughout the entire nucleus. Finally, one other group reported reduced levels of AVP mRNA in the SCN but they did not count AVP mRNA-expressing neurons (Liu et al., 2000), and the same group had previously reported no change in AVP-expressing SCN neurons in elderly dementia patients compared to healthy age-matched controls (Swaab et al., 1985).

Evidence in healthy aging wild-type mice suggests an age-related decline in circadian output from the SCN to the SPZ (Nakamura et al., 2011). These researchers saw a reduction in the circadian amplitude of multi-unit activity rhythms (MUA) in the SCN with age, as well as a similar reduction in the amplitude of MUA rhythms within the SPZ. While the interpretation of these findings as a dysfunction in SCN output is sound, it is possible that these results might also reflect an age-related dysfunction in the SPZ neurons' ability to maintain rhythms as well (instead of *only* a decline in SCN output). Indeed, the SPZ has been largely overlooked as a possible locus for the circadian dysfunction that has been reported in neurobehavioral pathologies. However, since it regulates both sleep-wake and locomotor rhythms via its projections to the DMH, and also regulates the propensity for aggression via its projections to the VMH, the SPZ is in a logical position to underlie multiple symptoms associated with sundowning should its function become disrupted by AD pathology. It is interesting that, in both rats and mice, the SPZ has been shown to be composed of distinct subregions that differentially project to the DMH or VMH (Vujovic et al., 2015; Todd et al., 2018). Therefore, differences in the degree of dysfunction caused by AD pathology in different SPZ subregions might explain the reported differences in sundowning symptoms across patients, as some studies have reported sundowning to mainly be composed of mood related disturbances such as agitation and aggression, as compared to sleep disturbances, whereas other studies have reported both (Boronat et al., 2019).

CHOLINERGIC INPUTS TO THE CIRCADIAN SYSTEM

Multiple studies have shown a cholinergic innervation of the SCN (Ichikawa and Hirata, 1986; Kiss and Halasz, 1996; Castillo-Ruiz and Nunez, 2007), and that acetylcholine modulates the function of SCN neurons and circadian rhythmicity (Liu and Gillette, 1996; Liu et al., 1997; Hut and Van der Zee, 2011; Gritton et al., 2013). In the field of AD research, the so-called "cholinergic hypothesis" has long posited that neurodegeneration of neurons in the basal forebrain (BF) expressing acetylcholine, which extensively project to cortical areas, underlie much of the memory and cognitive decline seen during the progression of the disease (Contestabile, 2011; Craig et al., 2011; Pinto et al., 2011). Indeed, there is ample evidence in AD patients that the cholinergic neurons of sub-regions within the BF, such as the nucleus basalis of Meynert (NBM) (Cummings and Benson, 1987; Vogels et al., 1990; Mesulam, 2013; Liu et al., 2015), are a major site of neurodegeneration in AD. Several groups have proposed that a cholinergic BF input to the SCN may also be disrupted in

AD, leading to sundowning or other observed circadian deficits (Klaffke and Staedt, 2006; Hut and Van der Zee, 2011; Bedrosian and Nelson, 2013). Lending some support to this hypothesis, acetylcholinesterase inhibitors including donepezil, have been found to ameliorate neuropsychiatric symptoms such as agitation and aggression (Mega et al., 1999; Paleacu et al., 2002; Cummings et al., 2006; Carrasco et al., 2011). One case study also reported that donepezil reduced agitation and restlessness specifically in a sundowning dementia patient (Skjerve and Nygaard, 2000). Interestingly, donepezil has also been shown to enhance rapid eye movement (REM) sleep in AD patients (Moraes Wdos et al., 2006), but has also been associated with an increased prevalence of nightmares (Ridha et al., 2018).

However, the evidence for the existence of a cholinergic pathway from the BF to the SCN comes from only one study in rats using non-specific retrograde tracing from the SCN, and then co-labeling for the cholinergic transporter (CHAT) in BF neurons (Bina et al., 1993). Another study in rats suggested that chemical lesions of the NBM were associated with a reduction in VIP and AVP synthesis and expression in the SCN, however, anatomical tracing was not done in these experiments (Madeira et al., 2004). Importantly, recent work using more selective genetically targeted tracing from the BF in *CHAT-IRES-Cre* mice reported no evidence of such a cholinergic BF to SCN pathway (Agostinelli et al., 2019). While it is possible that this findings represent a species difference between mice and rats, the conservation of a BF to SCN pathway across mammalian species warrants further investigation (**Figure 1**). Yet, this does not discredit a cholinergic input to the SCN from other areas, such as the brainstem. Indeed, the same authors who reported the cholinergic BF to SCN in rats also reported retrogradedly labeled CHAT cells in the laterodorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT) complex of the brainstem (Bina et al., 1993). The LDT/PPT has been shown to display tau pathology in AD patients, but interestingly, not cholinergic cell loss (Mufson et al., 1988; Dugger et al., 2012; Kotagal et al., 2012). It may be possible that aging and tau pathology could disrupt the function of the LDT/PPT to SCN pathway, even without causing the loss of cholinergic cells, as synaptic changes associated with high levels of soluble of amyloid-β or tau have been reported to appear well before the insoluble plaques or tangles themselves (Scheff et al., 2006; D'Amelio et al., 2011).

In addition to cholinergic neurons, however, the LDT/PPT complex also contains GABAergic and glutamatergic neurons that are known to play different roles in sleep-wake regulation (Kroeger et al., 2017). It is unclear whether these cell populations also project to the SCN and influence circadian function or aggression; a cell type-specific approach to examine the presence of such pathways and their function would be greatly informative. And, although cholinergic cells appear to be spared in the LDT/PPT of AD patients, the presence of tau pathology in this region could instead lead to neurodegeneration of these GABAergic and glutamaterigic populations, which does not appear to have been previously examined. Interestingly, Bedrosian et al. (2011) showed reduced global c-Fos expression (a marker of neuronal activation) in PPT neurons in aged mice compared to healthy adult mice, which was also associated with temporal changes in anxiety behavior. These authors also found similar time-dependent changes in anxiety behavior in APP mice (which bear amyloid-β pathology), but at even earlier ages (however, it does not appear that c-Fos was examined in the PPT in these APP mice).

SEROTONERGIC INPUTS TO THE CIRCADIAN SYSTEM

There is also substantial evidence for a role in the disruption of serotonergic neurons in AD (Rodriguez et al., 2012; Vakalopoulos, 2017; Chakraborty et al., 2019), and serotonin is also known to play role in circadian regulation (Ciarleglio et al., 2011; Daut and Fonken, 2019). Several studies have suggested a dense serotonergic input from the midbrain raphe complex to the SCN and SPZ (see **Figure 1**). In hamsters, these serotonergic inputs appear to arise primarily from the median raphe nucleus (MRN) (Meyer-Bernstein and Morin, 1996; Leander et al., 1998; Yamakawa and Antle, 2010), while studies in rats have revealed serotonergic inputs from both the MRN and dorsal raphe nucleus (DRN) (Kawano et al., 1996; Moga and Moore, 1997). Such serotonergic inputs to the SCN appear to play a role in setting circadian phase, as administration of serotonin or serotonergic agonists into the SCN has been shown to produce phase shifts during certain parts of the light-dark cycle (Lovenberg et al., 1993; Ehlen et al., 2001; Sprouse et al., 2004). Additionally, developmental disruption of the serotonin transcription factor *Pet-1* disrupts locomotor activity rhythms and *in vitro* SCN activity (Ciarleglio et al., 2014). Serotonergic function is also highly implicated in the direct regulation of aggression (Nautiyal et al., 2015; Niederkofler et al., 2016), and serotonergic neurons have been shown to project from the raphe complex to the VMH (Kanno et al., 2008). So, its possible that AD-related disruptions in serotonergic signaling also underlie overall levels of aggression, as well as differences at certain times of the day. Indeed, several groups have reported serotonergic deficiencies in AD that were associated with either increased circadian dysfunction or behavioral aggression (Lai et al., 2003; Vermeiren et al., 2014; Chakraborty et al., 2019).

Serotonergic drugs have commonly been administered to AD patients in order to treat aggression, anxiety, and other emotional behavioral disturbances, as well as to treat sleep-wake and circadian disruption. Citalopram, a selective serotonin reuptake inhibitor (SSRI) widely used as an antidepressant, has been found to reduce irritability, anxiety, and aggression in moderately agitated AD patients (Leonpacher et al., 2016; Schneider et al., 2016), however, it was much less effective in the severely agitated patients. Interestingly, patients categorized as the most severely agitated actually showed an increase in nighttime behavioral or sleep disruptions when treated with citalopram (Leonpacher et al., 2016). An intriguing body of work also suggests that early administration of SSRIs may also slow the progression of mild cognitive impairment to AD, perhaps through a mechanism by which serotonin affects the amyloid-β precursor protein, thereby reducing the accumulation

of amyloid-β (Elsworthy and Aldred, 2019). It is also possible that serotonin's modulation of the circadian system could indirectly play a role in slowing or expediting this progression, as chronic circadian dysfunction exacerbates AD pathology (Musiek, 2015). Indeed, trazodone, a serotonin antagonist and reuptake inhibitor (SARI) that is also commonly used as an antidepressant, has been shown to improve circadian function and sleep-wake rhythms in AD patients (Camargos et al., 2014; Grippe et al., 2015). Risperidone and olanzapine, both atypical antipsychotics and antagonists for serotonin (as well as for dopamine), have been shown to have differential effects in AD patients. Risperidone, but not olanzapine, was found to reduce aggression and other neuropsychiatric symptoms in AD patients (Nagata et al., 2017), whereas a separate study in AD patients found olanzapine to reduce anxiety (Mintzer et al., 2001). While serotonin has historically been implicated in sleep-wake regulation, a recent study demonstrated that DRN serotonergic neurons actually promote sleep through anxiolysis, further highlighting the critical role of serotonin in mood and emotional regulation (Venner et al., 2020).

THE RETINOHYPOTHALAMIC TRACT

Perhaps the most extensively studied input to the SCN comes from a distinct set of retinal ganglion cells (RCGs) (see **Figure 1**), via the retinohypothalamic tract (RHT) (Moore et al., 1995). This pathway is required for circadian photoentrainment, as shown by enucleation studies where removing both eyes results in free-running rhythms under a light-dark cycle (Nelson and Zucker, 1981; Foster et al., 1991). A subset set of RGCs are intrinsically photosensitive and contain the photopigment melanopsin (Berson et al., 2002; Hattar et al., 2002; Sekaran et al., 2003). These melanopsin cells themselves comprise 5 different subtypes (M1–M5-type) (Ecker et al., 2010), and evidence suggests that a molecularly distinct subpopulation of M1-type RGCs, defined by their lack of expression of the transcription factor Brn3b and numbering around only 200 cells, are sufficient for driving entrainment of the SCN (Chen et al., 2011). To enable such photoentrainment, the RHT releases glutamate and pituitary adenylate cyclase activating polypeptide (PACAP) onto the SCN (Hannibal et al., 2000). While light during the day is required for proper circadian photoentrainment, light exposure at night has been shown to be deleterious to mood regulation and overall circadian function (Fonken and Nelson, 2014; Bedrosian and Nelson, 2017). Evidence in AD patients suggests altered function of melanopsin RGCs in preclinical AD (Oh et al., 2019), and post mortem studies suggest an AD-related loss of melanopsin RGCs (La Morgia et al., 2016). Bright light therapy has already been shown to improve circadian rhythmicity and mood in AD patients (Figueiro et al., 2014; Munch et al., 2017; Wahnschaffe et al., 2017). Additionally, one study reported that morning light exposure shifted the peak of agitated behavior in patients with severe AD (Ancoli-Israel et al., 2003).

Another interesting possibility for a future treatment of sundowning via this pathway could be using intravitrial injections of chemogenetic vectors into the eye and driving activity of RGCs via peripheral injection of the chemogenetic ligand. A similar strategy has been suggested to show promise as a potential therapy for other mood-related disorders (Bowrey et al., 2017; Venner et al., 2019). Interestingly, the RHT has been shown to densely project to the SPZ in some species, but not in others (**Figure 1**), and this pathway has been suggested to play a role in modifying nocturnal versus diurnal sleep-wake behavior in a species typical manner (Todd et al., 2012). Understanding how such species differences impact circadian function will be vital for teasing apart the underlying factors contributing to circadian phase preference (diurnality versus nocturnality), which will be critical for properly translating the findings of AD-related research in nocturnal rodents into potential treatment applications in diurnal AD patients.

THE GENICULOHYPOTHALAMIC TRACT

As also depicted in **Figure 1**, the SCN and SPZ are also known to receive input from photo receipient structures in the thalamus, the ventral lateral geniculate nucleus (LGN) and the adjacent intergeniculate leaflet (IGL), via the geniculohypothalamic tract (GHT) (Moore et al., 2000). Importantly, AD patients have been reported to show significant amyloid-β pathology in the LGN (Erskine et al., 2016). The GHT pathway releases GABA and neuropeptide Y (NPY), and this input has been shown to influence the response of SCN neurons to light, as well as to play a critical role in non-photic entrainment (Mrosovsky, 1996; Harrington, 1997). For instance, giving rodents time-dependent access to a novel running wheel leads to non-photic phase advances and ultimately entrainment of the circadian system (Reebs and Mrosovsky, 1989). NPY released from the IGL neurons that make up the GHT appears to underlie these non-photic effects on the SCN, as novelty-induced wheel running induces c-Fos expression in the IGL NPY neurons (Janik and Mrosovsky, 1992), and infusions of NPY directly into the SCN produce similar phase shifts (Albers and Ferris, 1984; Huhman and Albers, 1994). To further support this view, electrolytic lesions of the IGL (Janik and Mrosovsky, 1994), and SCN infusion of NPY antiserum (Biello et al., 1994), both block the phase-advancing effect produced by novelty-induce wheel running. Interestingly, these results may suggest a pathway by which daily exercise at a consistent time could improve circadian function and reduce possible sundowning symptoms in AD and dementia patients, which has previously been suggested as a strategy to counteract attenuation of circadian rhythms that come with normal aging and AD (Duncan, 2020). Lending support to this idea, timed access to a running wheel has already been shown to increase the robustness of circadian behavioral rhythms in mice lacking the VIP receptor, VPAC2 (Power et al., 2010). Additionally, two separate studies have indicated that daily exercise enhances circadian cortisol rhythms in patients with AD or mild cognitive impairment (Tortosa-Martinez et al., 2015; Venturelli et al., 2016). Moreover, one group found that routine walking at certain times of the day ameliorated sundowning symptoms in AD patients in two separate studies (Shih et al., 2017; Shih et al., 2019).

OTHER NEUROTRANSMITTER INPUTS TO THE SCN: DOPAMINE AND OREXIN

While less is known about their potential role in AD and related dementias, there is some evidence to suggest that dopaminergic and orexinergic inputs to the SCN may could also be comprised in these neurodegenerative diseases. For instance, recent work has implicated an important role for dopaminergic input to the SCN from the ventral tegmental area (VTA) (Grippo et al., 2017). Grippo et al. (2017) demonstrated that this dopaminergic input to the SCN is important for resynchronizing locomotor activity rhythms to shifts of the light-dark cycle, and that elevating levels of dopamine in the SCN actually accelerates photoentrainment. Interestingly, work in a transgenic mouse model of AD pathology revealed degeneration of VTA dopaminergic neurons (Nobili et al., 2017), and a imaging study in prodromal AD patients suggest a decrease in VTA volume (De Marco and Venneri, 2018).

Additionally, the neurotransmitter orexin, located in the lateral hypothalamus and perifornical region (de Lecea et al., 1998), is known for its role in maintaining consolidated wakefulness as the degeneration of orexinergic neurons results in the sleep disorder narcolepsy (Lin et al., 1999). Orexinergic fibers have also been shown to project to the SCN (Backberg et al., 2002), and have been shown to modulate SCN activity (Belle et al., 2014). Belle et al. (2014) found that orexin is upregulated at dusk in nocturnal mice, and suppresses the activity of SCN neurons that specifically express the clock gene *Per1*. These authors also demonstrated that orexin enhances the resetting ability of NPY in the SCN (that has been released from the IGL), highlighting how multiple input pathways may act together to modulate circadian rhythmicity. Interestingly, AD patients with high levels of neuropsychiatric symptoms, including agitation and aggression, have been found to have higher overall levels of orexinergic tone and fragmented sleep (Liguori et al., 2018). Indeed, other studies have found that similarly high cerebrospinal fluid (CSF) levels of orexin in AD patients are also associated with increased amyloid-β levels (Gabelle et al., 2017). While promising, more work is needed to better understand the role of orexinergic and dopaminergic influence on the circadian system in AD, in order to delineate their respective potential contributions to sundowning symptoms.

SUMMARY

Several characteristic non-cognitive symptoms of AD and related dementias involve behavioral and physiological processes known to be regulated by the hypothalamus (Ishii and Iadecola, 2015; Hiller and Ishii, 2018). These include, among others, circadian and sleep-wake dysfunction, and emotional behavioral disruptions such as agitation and aggression. These particular non-cognitive symptoms are comorbid in the clinical phenomenon known as sundowning syndrome. Whether this term is an appropriate descriptor is debatable, given that the direct linkage of this phenomenon to sunset is not always supported (Yesavage et al., 2003). However, the weight of the evidence does suggest that a time-dependent exacerbation of emotional behavioral disturbances, including agitation and aggression, is prevalent in AD and dementia patients during the late afternoon and early evening (Boronat et al., 2019). Interestingly, this phenomenon seems to be less connected to sleep disruption, *per se*, and more directly tied to disturbances in emotional state.

Although sundowning has been studied for several decades, its cause remains unclear. Evidence from basic research (Bedrosian and Nelson, 2013; Todd et al., 2018), along with pathological findings from AD patients (Wang et al., 2015; Erskine et al., 2016; Chakraborty et al., 2019), suggests several pathways that might be involved in the circadian dysfunction, and agitation and aggression, underlying sundowning. There is a strong association between circadian rhythms and emotional regulation (Hood and Amir, 2018; Ketchesin et al., 2020), and the shared circuitry between these two systems presents potential candidates for such pathology-related dysfunction. These include the major circadian structures themselves, the SCN, SPZ and its output pathways to the DMH and VMH (Venner et al., 2019), as well as several structures that project to circadian system.

Disrupting GABAergic transmission from SPZ cells that project to the VMH has been shown to cause increased behavioral aggression during the early resting phase, when these cells have been shown to be active in a time dependent manner (Todd et al., 2018). There is also some evidence for LDT/PPT dysfunction associated with a time-dependent change in anxiety in aged mice (Bedrosian et al., 2011) (but it is unclear whether the affected cells are cholinergic, glutamatergic, or GABAergic), and LDT/PPT neurons also to project to the SCN (Bina et al., 1993). Serotonergic function seems to be dysregulated in AD (Rodriguez et al., 2012; Vakalopoulos, 2017), and serotonergic neurons of the midbrain raphe complex project to and modulate the circadian system and are highly involved in mood regulation and aggression (Ciarleglio et al., 2011; Niederkofler et al., 2016; Daut and Fonken, 2019). Direct retinal input to the SCN, as well as the direct NPY input from the retinorecipient IGL, are also possible candidates as pathology and dysfunction have been reported in these structures in AD (Erskine et al., 2016; La Morgia et al., 2016), and properly timed light exposure improves circadian rhythms and mood whereas ill-timed light exposure has deleterious effects (Bedrosian and Nelson, 2017). Altogether, a better understanding of the role of these pathways in behavioral and emotional timing will be important for treating circadian dysfunction and sundowning-related symptoms in AD and dementia patients and may also lead to the identification of important early indicators of the progression of AD. For instance, agitation and aggression have been found to be important predictors of the progression from mild cognitive impairment to probable AD, suggesting such behavior could be an important early indicator that could inform treatment options

(Dietlin et al., 2019). Similarly, circadian dysfunction of locomotor activity has been shown to be present in preclinical AD patients, well before the cognitive and amnesiac symptoms appear (Musiek et al., 2018). Thus, such interventions hold the promise of improving quality of life for both patient and caregiver, and may even slow the progression of the disease.

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REVIEW
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Local Sleep and Alzheimer's Disease Pathophysiology

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Even prior to the onset of the prodromal stages of Alzheimer's disease (AD), a constellation of sleep disturbances are apparent. A series of epidemiological studies indicate that multiple forms of these sleep disturbances are associated with increased risk for developing mild cognitive impairment (MCI) and AD, even triggering disease onset at an earlier age. Through the combination of causal manipulation studies in humans and rodents, as well as targeted examination of sleep disturbance with respect to AD biomarkers, mechanisms linking sleep disturbance to AD are beginning to emerge. In this review, we explore recent evidence linking local deficits in brain oscillatory function during sleep with local AD pathological burden and circuit-level dysfunction and degeneration. In short, three deficits in the local expression of sleep oscillations have been identified in relation to AD pathophysiology: (1) frequency-specific frontal deficits in slow wave expression during non-rapid eye movement (NREM) sleep, (2) deficits in parietal sleep spindle expression, and (3) deficits in the quality of electroencephalographic (EEG) desynchrony characteristic of REM sleep. These deficits are noteworthy since they differ from that seen in normal aging, indicating the potential presence of an abnormal aging process. How each of these are associated with β-amyloid (Aβ) and tau pathology, as well as neurodegeneration of circuits sensitive to AD pathophysiology, are examined in the present review, with a focus on the role of dysfunction within fronto-hippocampal and subcortical sleep-wake circuits. It is hypothesized that each of these local sleep deficits arise from distinct network-specific dysfunctions driven by regionally-specific accumulation of AD pathologies, as well as their associated neurodegeneration. Overall, the evolution of these local sleep deficits offer unique windows into the circuit-specific progression of distinct AD pathophysiological processes prior to AD onset, as well as their impact on brain function. This includes the potential erosion of sleep-dependent memory mechanisms, which may contribute to memory decline in AD. This review closes with a discussion of the remaining critical knowledge gaps and implications of this work for future mechanistic studies and studies implementing sleep-based treatment interventions.

Keywords: Alzheimer's disease, sleep, slow waves, sleep spindle, REM sleep, beta-amyloid protein, tau and phospho-tau protein, neurodegeneration

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INTRODUCTION

Both macro and micro features of sleep architecture change across the adult lifespan, and the individual variability in the magnitude of change appears to be associated with the degree of cognitive decline and the severity of risk for dementias such as Alzheimer's disease (AD) (Ohayon et al., 2004; Redline et al., 2004; Yaffe et al., 2011; Lim et al., 2013a,b; Spira et al., 2013; Lo et al., 2014; Mander et al., 2015, 2016, 2017a; Osorio et al., 2015; Song et al., 2015; Sprecher et al., 2015, 2017; Chen et al., 2016; Bubu et al., 2017, 2019; Kabeshita et al., 2017; Pase et al., 2017; Shi et al., 2017; Tsapanou et al., 2017; Lutsey et al., 2018). While the mechanisms underlying these associations remain elusive, emerging evidence has elucidated bidirectional associations between biological mechanisms of aging and AD and the expression of sleep processes related to neuroplasticity (Ju et al., 2014; Mander et al., 2016). In particular, certain micro features of sleep are expressed locally within specific brain circuits supporting processes regulating systemic and synaptic neuroplasticity (McGaugh, 2000) in order to facilitate memory formation and consolidation (Buzsaki, 1998; Steriade, 2006; Walker, 2009; Diekelmann and Born, 2010; Wamsley and Stickgold, 2011; Watson and Buzsaki, 2015). New findings indicate that topographic and frequency-specific disruptions in the expression of these brain oscillations, including slow waves and sleep spindles during non-rapid eye movement (NREM) sleep and EEG desynchrony during REM sleep, occur in the context of AD pathophysiology—in some cases even prior to onset of mild cognitive impairment (MCI)—and these local sleep deficits differ from those observed in normal aging (Hassainia et al., 1997; Petit et al., 2004; Jyoti et al., 2015; Mander et al., 2015, 2016, 2017a; Brayet et al., 2016; Gorgoni et al., 2016; De Gennaro et al., 2017; Holth et al., 2017; Lucey et al., 2019). It is therefore possible that certain local sleep deficits may reflect an abnormal aging process in its initial stages, and that disruptions in sleep-dependent memory mechanisms may contribute to the biological and cognitive consequences of AD pathophysiology. In this review, we summarize the state of the science linking local sleep to core features of AD pathophysiology and AD-related hippocampus-dependent memory impairment.

LOCAL SLEEP

The brain expresses a complex and dynamic organization of oscillatory activities during sleep, cycling between NREM and REM sleep stages that each distinctly organize local brain activities across frequency, topography, and time (Landolt et al., 1996; Liscombe et al., 2002; Steriade, 2006; Diekelmann and Born, 2010; Staresina et al., 2015; Watson and Buzsaki, 2015; Sprecher et al., 2016; Helfrich et al., 2018; Scarpelli et al., 2019). The spatially circumscribed nature of the expression of these sleep-specific oscillatory activities and their frequency specificity highlight the local nature of some canonical sleep features. For example, most NREM slow wave and sleep spindle oscillations are expressed regionally and migrate across cortex in a predictable manner (Massimini et al., 2004; Nir et al., 2011; Muller et al., 2016). Further, in cases of excessive sleep pressure, isolated neuronal ensembles have even been shown to express these sleep-specific rhythms while the majority of cortex remains in a state of wakefulness (Van Dongen et al., 2011; Krueger et al., 2019). The fact that this occurs has led to the hypothesis that sleep is not entirely global, i.e., it does not always occur equally throughout the entire brain (Van Dongen et al., 2011; Krueger et al., 2019). Furthermore, even during sleep local expression of certain oscillatory activities, such as slow waves during NREM sleep, can be influenced by prior waking experiences in a topographically-specific manner. More specifically, neuronal ensembles more active during learning will exhibit greater local intensity of slow wave activity relative to surrounding cortex (Huber et al., 2004, 2006). These phenomena demonstrate that certain sleep features are local and not global.

Two specific NREM sleep oscillations of note that are organized in this fashion are slow waves and sleep spindles. Slow waves, defined as low frequency (0.5–4.5 Hz) and high amplitude (>75 μV) waveforms, are generated in cortex, predominantly within association cortices including medial prefrontal cortex, insular cortex, and the cingulate cortex (Steriade, 2006; Murphy et al., 2009). Their expression is dependent on the coordinated synchrony of hyperpolarized down states and depolarized up states of local neuronal ensembles (Steriade et al., 1993b; Steriade, 2006). The spectral power of slow waves, termed slow wave activity (SWA), peaks over frontal electroencephalography (EEG) derivations in the first quartile of the night, dissipating across the sleep period in a manner reflective of a homeostatic "Process S" (Borbely et al., 1981; Borbely, 1982; Landolt et al., 1996; Carrier et al., 2001; Mander, 2013; Mander et al., 2017a). Recent optogenetic findings support the existence of two kinds of slow waves: lower frequency slow oscillations (SO; <1 Hz) that support memory consolidation processes and faster delta waves (1–4.5 Hz) that facilitate forgetting (Steriade, 2006; Kim et al., 2019). Whether the temporal or topographical organization of these waveforms is distinct or is influenced by aging or AD differentially remains to be seen, and should be a focus of future studies.

A second characteristic sleep oscillation that is critically tied to neuroplasticity is the sleep spindle. Sleep spindles are transient (0.5–3 s) bursts of oscillatory activity in the sigma frequency range (11–16 Hz) with waxing and waning components. They are generated within the reticular nucleus of the thalamus and expressed through cortico-thalamic loops (De Gennaro and Ferrara, 2003; Steriade, 2006). Two kinds of sleep spindles have been described as well: fast (∼13–16 Hz) and slow (∼11–13 Hz) frequency sleep spindles (Jobert et al., 1992; De Gennaro and Ferrara, 2003). Though exact frequency definitions vary by study, the distinct topographic nature of their expression does not. Fast frequency sleep spindles tend to peak over midline central and parietal EEG derivations, while slow frequency sleep spindles tend to peak in expression over frontal EEG derivations (Jobert et al., 1992; De Gennaro and Ferrara, 2003). Moreover, while SWA may dissipate across the sleep period,

spindle activity tends to peak in the morning (Landolt et al., 1996). However, these NREM sleep oscillations are not expressed in isolation, tending to couple during the rising phase of the depolarizing slow wave up state (Steriade et al., 1993a; Steriade, 2006; Staresina et al., 2015). This phase-locking is specific to the SO and is also accompanied by phase locking of another oscillation, the hippocampus ripple, within the troughs of the sleep spindle oscillation (Staresina et al., 2015; Helfrich et al., 2018). Coordinated firing of neuronal ensembles during initial encoding has been observed to spontaneously reoccur during ripples (Wilson and McNaughton, 1994; Ji and Wilson, 2007; Davidson et al., 2009), with ripples instigating information transfer from the hippocampus to the cortex when phase locked to SOs and sleep spindles (Olcese et al., 2018; Helfrich et al., 2019). The coupling of these three cortical, thalamic, and hippocampal brain oscillations, and the "replay" associated with them, is thought to support the consolidation of memories acquired during prior wakefulness (Steriade, 2006; Diekelmann and Born, 2010; Watson and Buzsaki, 2015; Helfrich et al., 2018, 2019). Indeed, recent evidence demonstrates that stimulation and suppression of sleep spindles only impacts sleep-dependent memory consolidation if it occurs during the rising phase of the depolarizing up-state and in coordination with hippocampal ripples (Latchoumane et al., 2017).

The spectral content and topographic organization of REM sleep differs from that observed in NREM sleep. The apparent wake-like nature of EEG-measured neuronal activity during REM sleep is why it is also known as "paradoxical sleep" (Peever and Fuller, 2016), though there are important distinctions that are observed when using other neuroimaging modalities (Braun et al., 1997; Maquet, 2000) or analytic approaches (Lendner et al., 2020). Of particular note, while the low voltage mixed frequency content of the "desynchronized" EEG observed during wakefulness is supported by a series of brainstem, midbrain, and hypothalamic glutamatergic, monaminergic, and cholinergic inputs, cholinergic input plays a more dominant role in generating the desynchonized EEG in REM sleep than monaminergic inputs (Peever and Fuller, 2016; Scammell et al., 2017). Thus, while the EEG looks the same in wake and REM sleep, the neurobiological correlates are distinct.

In terms of spectral content, both alpha and theta power are particularly prominent in REM sleep (Landolt et al., 1996), with theta peaking over fronto-central derivations, and alpha peaking over occipito-parietal derivations (Scarpelli et al., 2019), Similar to theta activity, higher frequency content, including beta and gamma power, peak over fronto-central derivations, but while low frequency power, including delta and theta power decrease across successive REM sleep periods, high frequency content remains relatively stable (Liscombe et al., 2002). Little is known about the functional relevance of the organized expression of EEG activities during REM sleep, and this should be a topic of future study.

Substantial evidence indicates that both aging and AD influence local NREM and REM sleep expression in distinct ways, and these effects are reviewed below.

LOCAL SLEEP IN AGING AND ALZHEIMER'S DISEASE (AD)

Aging

Increasing age is associated with reductions in oscillatory activities across multiple frequency bands in non-rapid eye movement (NREM) sleep (Sprecher et al., 2016). The biggest reductions occur globally across the frequency bands of slow waves (0.5–4.5 Hz) and sleep spindles (12–16 Hz), with the largest reductions occurring over frontal EEG derivations, due to the reduced incidence and amplitude of slow wave and sleep spindle oscillations (Dijk et al., 1989; Landolt et al., 1996; Carrier et al., 2001; Mander, 2013; Martin et al., 2013; Mander et al., 2014, 2017a,b; Sprecher et al., 2016). Aging also disrupts the phase-locked synchrony between slow waves and sleep spindles, with slow wave-sleep spindle coupling being more variable and occurring at an earlier phase of the slow wave, closer to the hyperpolarized slow wave down state (Helfrich et al., 2018; Muehlroth et al., 2019). All these age effects on NREM sleep oscillation expression have been associated with age effects on frontal and hippocampal gray and white matter volume and integrity (see Mander et al., 2017a, for an in depth review). Central to this work is the consideration of whether these age-related changes contribute to cognitive decline in aging, and this will be reviewed in detail later in this review.

In addition to NREM sleep, a few studies have explored age effects on REM sleep architecture. These studies have shown that older adults experience a modest reduction in REM sleep duration (0.6% per decade) that emerges much later than age effects on NREM sleep (Ehlers and Kupfer, 1997; Van Cauter et al., 2000; Carrier et al., 2001; Gori et al., 2004; Ohayon et al., 2004; Redline et al., 2004; Floyd et al., 2007; Scarpelli et al., 2019). However, qualitative differences in REM sleep are also present in older adults even if REM duration reductions are minimal, including increased awakenings from REM sleep, decreased REM latency, decreased REM density, and shorter and more disorganized REM bursts, particularly in adults over 65 years (Gillin et al., 1981; Ehlers and Kupfer, 1989, 1997; Vegni et al., 2001; Darchia et al., 2003; Conte et al., 2014). In terms of REM sleep microarchitecture, a few reports have indicated spectral power is reduced across delta, theta, and alpha frequencies in older adults, particularly over central derivations (Landolt et al., 1996; Scarpelli et al., 2019). It remains unknown why REM sleep microarchitecture is reduced in aging, and whether these changes are functionally relevant or epiphenomenal.

Alzheimer's Disease

Local sleep deficits have been observed in the context of MCI, AD, and even in healthy older adults with AD pathology (**Figure 1**). These local sleep deficits diverge from those observed in the context of normal aging both in terms of topography and frequency (Petit et al., 2004; Mander et al., 2016, 2017a). Reports have shown that slow wave sleep (SWS) is reduced and more fragmented in MCI, AD, and in rodent models of AD (Prinz et al., 1982; Gagnon et al., 2008; Hita-Yanez et al., 2012, 2013; Roh et al., 2012; Westerberg et al., 2012; Mander, 2013; Jyoti et al., 2015;

Kam et al., 2016), SWA is lower over midline frontal, central, and parietal derivations in healthy older adults with AD pathology and patients with MCI (Westerberg et al., 2012; Mander et al., 2015; Varga et al., 2016b; Lucey et al., 2019), and there are fewer frontal K-complexes in AD (De Gennaro et al., 2017). However, this effect of AD pathology and diagnosis on slow wave expression appears to depend on slow wave frequency, particular AD pathology, and, potentially, disease stage (**Figure 1A**). More specifically, in healthy older adults with cortical Aβ pathology, SWA deficits appear to be specific to lower frequencies (i.e., in the SO frequency range; < 1 Hz), with increases in SWA observed in the delta frequency range (1–4 Hz) (Mander et al., 2015; Kastanenka et al., 2017, 2019). This effect may change to reflect a more global loss of SWA across frequencies once tau pathology reaches the cortex in the MCI stage (De Gennaro et al., 2017; Lucey et al., 2019). Similar findings were observed in transgenic mouse models of AD, though this depended on which model was examined. Decreases in fronto-parietal SWA and increases in higher frequency power were observed during NREM sleep in Tg2576 and APP/PS1 transgenic mouse models of AD, but not in 3xTgAD mice (Zhang et al., 2005; Kent et al., 2018). This is noteworthy given that Tg2576 and APP/PS1 transgenic AD mouse models both exhibit rapid increases in Aβ pathology in the absence of neurofibrillary tangles, while the 3xTgAD mice express a more mild level of both Aβ and tau pathology. Together, these findings indicate that the influence of AD pathophysiology on SWA may not be fixed, but instead may change depending on the location and degree of burden of distinct AD pathologies.

Reduction in sleep spindle expression has also been observed in the context of AD. There are fewer sleep spindles and lower spindle activity in patients with MCI and AD (Rauchs et al., 2008; Westerberg et al., 2012; Gorgoni et al., 2016). However, this effect appears to be specific to faster frequencies (13–16 Hz) over parietal derivations (**Figure 1B**), with no discernable effect on frontal sleep spindles in slower frequencies (11–13 Hz) (Westerberg et al., 2012; Gorgoni et al., 2016). This is in stark contrast to the effect of age, which selectively disrupts frontal sleep spindles regardless of frequency, leaving parietal fast frequency sleep spindles largely spared (Martin et al., 2013; Sprecher et al., 2016; Mander et al., 2017a). The reduction of sleep spindles, and in particular fast frequency sleep spindles, is also apparent in healthy older adults with tau pathology (Kam et al., 2019). The effect of AD pathologies and MCI and AD diagnosis on slow wave-sleep spindle coupling remain unclear, though a recent study showed that tau pathological burden in the medial temporal lobe was associated with reduced slow wave-sleep spindle coupling (Winer et al., 2019). Because these parietal fast frequency sleep spindle deficits associated with MCI and AD are so topographically distinct from age-related deficits in sleep spindles, it is possible that these deficits could represent an early physiological signal distinguishing between abnormal and normal aging processes.

A robust literature demonstrates that MCI and AD diagnosis is associated with characteristic changes in REM sleep microarchitecture in a topographically-specific manner (**Figure 1C**). Specifically, a loss of EEG desynchrony during REM sleep is observed as early as MCI (Brazete et al., 2013; Brayet et al., 2016), and can be used to differentiate individuals with and without AD with high diagnostic accuracy (Hassainia et al., 1997). This measure, quantified as the ratio of low frequency to high frequency power can even distinguish between individuals with amnestic versus non-amnestic MCI (Brayet et al., 2016), but can also predict non-AD dementia onset and cognitive decline in individuals with REM behavior disorder (Brazete et al., 2016). It is therefore possible that this signature may be more specific to dementia-related cognitive decline than AD, *per se*. The effect of MCI and AD diagnoses on EEG desynchrony is particularly prominent over central and posterior EEG derivations (Hassainia et al., 1997; Brazete et al., 2013, 2016; Brayet et al., 2016). Alongside these findings, others have found loss of central-parietal theta activity during REM sleep in patients with amnestic MCI (Westerberg et al., 2012), and both AD and tauopathy rodent models show reduced theta and alpha activity (Holth et al., 2017). Hence, the quantitative expression of REM sleep EEG is also impacted by MCI and AD, and these deficits may track cognitive decline associated with dementia.

The distinct nature of the effects of AD pathophysiology on the expression of local sleep features relative to those observed with advancing age hints at a distinction in underlying mechanisms, which may herald the emergence and progression of AD in its initial stages. Recent work highlights the mechanistic links between local sleep disturbance and AD pathophysiological features, which are examined in detail in the next section.

EMERGING LINKS BETWEEN LOCAL SLEEP AND AD PATHOPHYSIOLOGY

The Alzheimer's Disease Cascade—The Role of Amyloid (A), Tau (T), and Neurodegeneration (N)

Contemporary theories of AD pathogenesis describe the emergence of a biological cascade of pathological events which trigger a progressive degenerative process that ultimately results in the clinical and cognitive symptoms of dementia (Jack et al., 2010, 2013; Jagust, 2018; Marquez and Yassa, 2019). While there remains controversy over which pathological event emerges first (see Herrup, 2015; Musiek and Holtzman, 2015, for further details), what is clear is that the initial stages involve the build-up of cortical Aβ (A) and subcortical tau (T; **Figure 2**). As they converge and interact, tau begins to spread cortically and Aβ subcortically, triggering progressive and widespread neurodegeneration (N) which results in progressive cognitive and clinical dysfunction, and ultimately gross loss of basic functions (Jack et al., 2010, 2013, 2019).

The probability of onset and rate of progression of this neurodegenerative process is influenced by other biological factors which directly or indirectly influence this core biology of AD. For example, many of the known genetic risk factors for familial and sporadic AD, such as mutations in the amyloid precursor protein (APP), presinilin, and apolipoprotien E (APOE) genes, result in an acceleration of Aβ accumulation and the resulting neurodegeneration (Bagyinszky et al., 2014).

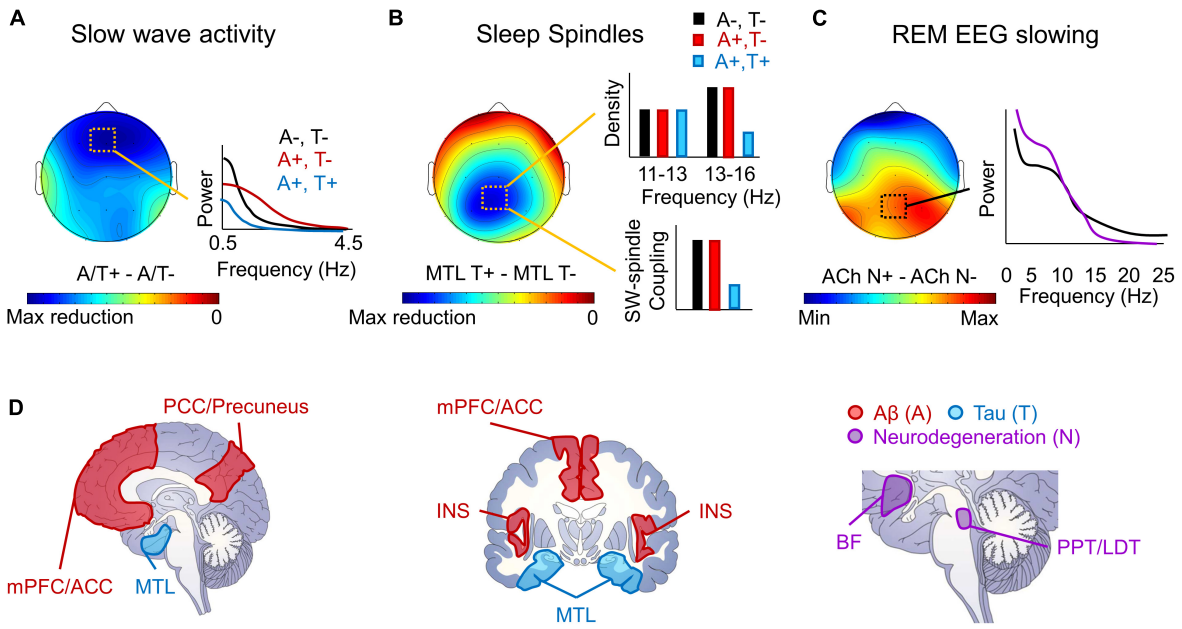

FIGURE 1 | Schematic depiction of local sleep features disrupted by AD pathophysiology. **(A)** A schematic topoplot of decreases in SWA during NREM sleep in individuals with Aβ (A +, red) and tau (T +, blue) pathology relative to those without pathology (A–, T–, black) is presented, with cooler colors reflecting the severity in the hypothesized reduction in SWA. A schematic of the effects of Aβ and tau pathology on SWA by frequency are plotted to the right. **(B)** A topoplot of decreases in sleep spindles in individuals with tau pathology, particularly in the medial temporal lobe (MTL) is presented, with cooler colors reflecting the severity of sleep spindle loss in individuals with tau pathology. Schematic bar graphs of the effects of both Aβ (red) and tau (blue) pathology on sleep spindle density and slow wave (SW)-sleep spindle coupling relative to those without AD pathology (black) are presented to the right. **(C)** A topoplot of the increase in REM sleep EEG slowing in those with cholinergic degeneration (ACh N +, purple) relative to those without significant cholinergic degeneration (ACh N–, black). A schematic frequency by spectral power plot of REM sleep is shown to the right, indicating increased low frequency power and decreased high frequency power in the presence of cholinergic degeneration. **(D)** Schematic of brain slices depicting the hypothesized locations of Aβ (A, red) and tau (T, blue) deposition, as well as neurodegeneration (N, purple), that lead to the observed local deficits in NREM and REM sleep. mPFC/ACC denotes medial prefrontal cortex and anterior cingulate cortex, PCC/Precuneus denotes posterior cingulate cortex and precuneus, MTL denotes the medial temporal lobe, INS denotes the insula cortex, BF denotes the cholinergic basal forebrain, and PPT/LDT denotes the cholinergic pedunculopontine and lateral dorsal tegmental nuclei.

Sex also influences AD, with women being at twofold greater risk for developing AD relative to men (Podcasy and Epperson, 2016). Recent evidence indicates that one potential reason for this is that the same degree of Aβ burden may facilitate a greater degree of accumulation of tau pathology in women relative to men (Buckley et al., 2019).

Emerging evidence indicates that chronic inflammation plays a critical role in mediating the interactions between multiple pathophysiologic features of AD, facilitating its progression (for in depth reviews see, Heppner et al., 2015; Spangenberg and Green, 2017; Wang et al., 2017). Microglia—glial cells supporting innate immunity within the central nervous system—are activated by Aβ through its interaction with the triggering receptor expressed on myeloid cells 2 (TREM2), resulting in the release of proinflammatory cytokines and chemokines, including interleukin-1 β (IL-1β), IL-6, tumor necrosis factor alpha (TNF-α), among others (Heppner et al., 2015; Spangenberg and Green, 2017). This activation, alongside activation of astrocytes, facilitates Aβ clearance through degradation and phagocytosis (Heppner et al., 2015; Spangenberg and Green, 2017). When Aβ plaques are formed, both astrocytes and microglia surround them to degrade and clear them from the central nervous system, as well as to form a barrier to minimize the toxic effects of Aβ on surrounding neural tissue (Heppner et al., 2015; Spangenberg and Green, 2017).

Unfortunately, Aβ also impairs microglial function, suppressing its ability to degrade and clear Aβ. This leads to the induction of a chronic inflammatory state, which facilitates microglial burn-out, astrocytic atrophy, sustained Aβ production, decreased Aβ clearance, disrupted tau-microtubule binding, neurofibrillary tangle (NFT) formation, and propagation of tau pathology (Heppner et al., 2015; Spangenberg and Green, 2017). Chronically activated microglia also contribute to neurodegeneration and cognitive decline through dysfunctional phagocytosis, which results in pathological stripping of synapses and facilitation of neuronal loss (Spangenberg et al., 2016), a process also observed following sleep deprivation (Bellesi et al., 2017). Indeed, the number of activated microglia have been shown to correlate with cognitive decline (Cagnin et al., 2001; Versijpt et al., 2003; Edison et al., 2008). These findings are supported by studies in humans showing that chronic systemic inflammatory conditions, such as rheumatoid arthritis, increase risk for developing AD through sustained increases in IL-1β, IL-6, TNF-α, and C-reactive protein (CRP) levels, which can cross the blood brain barrier and directly impact brain Aβ metabolism or impact Aβ in the periphery which

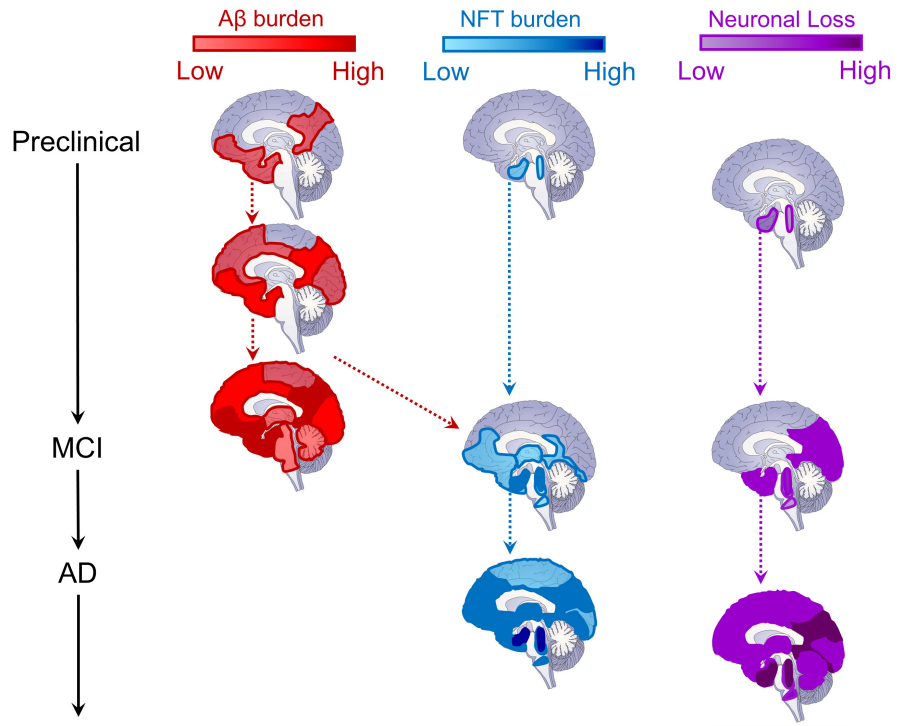

FIGURE 2 | Schematic depiction of the evolution of Alzheimer's disease biomarkers. Sagittal brain slices depicting the hypothesized locations of Aβ (red, left column) and tau (blue, middle column) deposition, as well as neurodegeneration (neuronal loss, purple, right column) across disease stages. For Aβ, deposition begins in medial prefrontal, cingulate, temporal, and precuneus regions, and progresses cortically and then subcortically until most of the brain contains amyloid plaques (Braak and Braak, 1991; Thal et al., 2002; Sepulcre et al., 2013; Palmqvist et al., 2017). The cortex is likely already saturated with amyloid plaques by the time most patients convert to MCI (Jack et al., 2010, 2013). For tau neurofibrillary tangles (NFT), deposition begins in the locus coeruleus and cholinergic brainstem nuclei in Braak stage 0, progressing into entorhinal cortex in the medial temporal lobe by stage I (Braak and Braak, 1991; Mesulam et al., 2004; Grudzien et al., 2007; Ehrenberg et al., 2017). NFTs remains largely constrained within the MTL until Braak stage III (Braak and Braak, 1991, 1995), when, through its interaction with Aβ pathology (red dashed arrow), tau pathology spreads throughout the brainstem, thalamus, MTL, inferior temporal cortex, and medial prefrontal and cingulate brain regions (Vogel et al., 2020). It is at this time that MCI conversion begins to be observed (Jack et al., 2010, 2013). In later Braak stages, tau pathology is observed throughout most of the cortex (Braak and Braak, 1991, 1995), triggering widespread cortical degeneration as its spreads (Jack et al., 2010, 2013). Regarding neurodegeneration (neuronal loss), as with NFTs, synaptic and neuronal loss begins within locus coeruleus, cholinergic brainstem nuclei, and the MTL (Mesulam et al., 2004; Grudzien et al., 2007; Whitwell, 2010). As MCI progresses into later stages, cortical atrophy is prevalent throughout the temporal, parietal, and occipital lobes (Whitwell, 2010). Ultimately, in later AD stages, cortical atrophy progresses through lateral frontal cortex and, eventually, throughout the entire brain, impacting neural regulation of even basic functions supporting life (Jack et al., 2010, 2013; Whitwell, 2010).

then interacts with central Aβ pools (Wang et al., 2017). Further, in addition to genetic mutations in genes impacting Aβ accumulation, genetic mutations in numerous genes affecting microglial function, such as mutations in TREM2, also increase AD risk (Spangenberg and Green, 2017). In addition, release of APOE by astrocytes is thought to critically support the capacity of microglia to clear Aβ (Terwel et al., 2011), and thus mutations in the APOE gene may impact Aβ in part through its impact on central immunity. It is important to note, however, that chronic inflammation can precede Aβ plaque deposition, and facilitate AD pathogenesis (Krstic et al., 2012), indicating that chronic inflammation may not only be an outcome of Aβ pathophysiology but also an initiating event. Thus, onset into and progression of AD depends on the interaction between two distinct pathologies, that of Aβ and tau, and the influence of other biological factors that affect them, their interaction, and potentially their impact on neuronal integrity and function.

Prior to widespread degeneration, Aβ and tau also influence neuronal function in distinct ways. A recent study implemented multiple rodent models and examined neuronal dysfunction resulting from them (Busche et al., 2019). In a model expressing only Aβ, neuronal hyperexcitability was predominant (Busche et al., 2019), mirroring the dysfunctional hippocampus and default mode network hyperactivation observed in early stages of MCI and Aβ positive but cognitively asymptomatic older adults (Sperling et al., 2009; Yassa et al., 2010b; Leal et al., 2017). This is also consistent with other studies reporting increased incidence of interictal spikes, particularly during sleep, in rodent models overexpressing Aβ pathology (Kam et al., 2016). In further support of this notion, recent studies have shown that antiepileptic drugs targeting this presumably Aβ-related hyperactivity resolved hippocampus-dependent memory impairments observed in early stages of amnestic MCI (Bakker et al., 2012, 2015). In contrast, rodent models expressing either tau alone or both Aβ and tau resulted

in neuronal silence (Busche et al., 2019), meaning that, when convergent, tau trumps the effects of Aβ on neuronal function. This finding supports the possibility that the form of neuronal dysfunction observed in AD, and the cognitive consequences of that dysfunction, may depend on the neural network examined and the relative abundance of both Aβ and tau pathology within that network. This theoretical model of AD offers critical insight into the mechanistic links between local NREM and REM sleep dysfunctions and AD (**Figure 1D**). It also highlights the potential of these local sleep dysfunctions to offer a window into AD stage and progression, and the cognitive consequences of their relationships, all of which are reviewed below.

β-Amyloid and Local Expression of Slow Wave Activity (A)

Aβ levels increase during wakefulness and decrease during sleep in the interstitial fluid (ISF) in rodents and CSF in humans, and subjective and objective measures of sleep duration and quality are associated with Aβ burden (Kang et al., 2009; Roh et al., 2012; Ju et al., 2013; Spira et al., 2013; Mander et al., 2015; Sprecher et al., 2015, 2017; Varga et al., 2016b), indicating that Aβ peptides are regulated by the sleep/wake cycle. Collectively, these studies show that NREM sleep loss is associated with greater Aβ burden while greater Aβ burden further disrupts NREM sleep, potentially triggering a vicious cycle fostering AD progression (Ju et al., 2014; Mander et al., 2016). The mechanisms for these bidirectional relationships remain unclear, though there are a few candidates highlighted by recent work. First and foremost considers how NREM sleep disruption may result in increased Aβ burden. Aβ burden increases with increasing neuronal activity (Li et al., 2013), and neurometabolic activity is higher in wake than in SWS (Buchsbaum et al., 1989; Braun et al., 1997; Dworak et al., 2010). Thus, reductions in SWS duration increases the duration of wakefulness which then results in increased net Aβ accumulation.

A second possible mechanism regards findings linking disruptions in slow oscillation expression in APP transgenic mice to Aβ plaque burden (Kastanenka et al., 2017, 2019). In APP transgenic mice, SWA is reduced specifically in the slow oscillation frequency range (<1 Hz) by 3 months of age, 2 months before Aβ plaques are apparent (Kastanenka et al., 2017). This is accompanied by reduced GABA levels and downregulation of $GABA_A$ and $GABA_B$ receptor expression, which directly impacted the expression of slow oscillations by disrupting neuronal synchrony. Slow oscillation expression was restored by both increasing GABA levels and by optogenetically enhancing neuronal synchrony, and this resulted in reduced Aβ plaque burden and intracellular calcium overload (Kastanenka et al., 2017). In contrast, doubling the frequency of the slow oscillation to >1 Hz resulted in increased Aβ production, increased intracellular calcium overload, and decreased dendritic spine density (Kastanenka et al., 2019).

Yet another possibility involves the recently discovered glymphatic system, which is a biological process in the brain that actively clears toxins and waste from the ISF by flushing the brain with CSF pulses (Jessen et al., 2015; Rasmussen et al., 2018). Two studies actively link this process to SWS. First, glymphatic flow is increased during SWS and results in increased clearance of Aβ proteins in rodents (Xie et al., 2013). Second, SWA peaks prior to and is phase locked to CSF flow through the brain in humans (Fultz et al., 2019). These findings suggest that it may not be NREM sleep, *per se*, but the expression of slow waves that is mechanistically linked to glymphatic clearance during sleep. If true, the efficacy of this system could depend on the integrity of astrocytic mechanisms regulating neuronal function. Astrocytes directly regulate the transition to and expression of slow oscillations, potentially through spatial K^+ buffering through the inwardly rectifying potassium channel Kir4.1 expressed in astrocytes in tripartite synapses (Fellin et al., 2009; Poskanzer and Yuste, 2016; Haydon, 2017; Cucchiara et al., 2020). Astrocytic function is also central to the expression of the glymphatic system (Nedergaard, 2013). However, high Aβ burden in AD results in loss of Kir4.1 potassium channels, as well as aquaporin 4 (AQP4) channels which are also hypothesized to be critical for glymphatic function (Wilcock et al., 2009; Nedergaard, 2013; Kress et al., 2014; Zeppenfeld et al., 2017). Hence, disruptions in slow waves during NREM sleep, associated with astrocytic dysfunction, may then decrease active clearance of AD pathology, also potentially yielding a net increase in Aβ accumulation. These possibilities are supported by recent studies showing significant associations between slow wave incidence and power and Aβ burden (Zhang et al., 2005; Mander et al., 2015; Varga et al., 2016b; Kastanenka et al., 2017; Kent et al., 2018). Directly addressing this possibility, a recent study showed that active suppression of SWA using acoustic stimulation resulted in increased CSF Aβ levels in middle-aged adults, indicating the potential for a causal relationship (Ju et al., 2017). However, it is important to note that the role of glymphatic clearance during SWS on Aβ protein levels has only been shown using injected radiolabeled Aβ proteins, and no study to date has shown direct evidence for endogenous clearance of Aβ via the glymphatic system during SWS (Smith and Verkman, 2018). This limitation is a critical caveat that must be addressed in future studies.

Lastly, it has been hypothesized that another potential pathway linking sleep deficits to increased Aβ pathology and AD risk is through an association with chronic inflammation (Irwin and Vitiello, 2019). Aging is coincidentally associated with chronic inflammation, SWS disruption, and increased AD risk (Ingiosi et al., 2013; Besedovsky et al., 2019). Sleep, and in particular SWS, has a complex bidirectional interaction with biological processes supporting immune function (for in depth reviews see, Besedovsky et al., 2019; Irwin, 2019). A recent meta-analysis of over 70 studies indicated that evidence of sleep disturbance, short sleep duration, and excessively long sleep duration was associated with elevated plasma levels of CRP and IL-6 (Irwin et al., 2016). Further, short sleep duration, greater wake after sleep onset (WASO), worse sleep efficiency, and greater of percentages of the sleep period with blood oxygen saturations below 90% are associated with increased IL-6, CRP, TNF-α, and interferon γ (INF- γ) in older adults and AD caregivers (Friedman et al., 2005; Von Kanel et al., 2006; Smagula et al., 2016). In addition, experimental sleep restriction to four hours increased nuclear factor κ-light-chain-enhancer of activated B cells (NF- κB) in plasma, which is a critical

factor regulating the inflammatory signal cascade (Irwin et al., 2008). Moreover, chronic sleep restriction to 4 h per night for 12 days resulted in increased IL-6 plasma levels in young adults (Haack et al., 2007).

In addition to sleep disturbance triggering an inflammatory response, inflammation directly impacts sleep expression as well. However, the specifics of this effect depend on the duration and magnitude of inflammatory activation. While acute inflammation can induce SWS and enhance SWA, chronic inflammatory conditions are associated with fragmented sleep, alpha intrusions in NREM sleep, and reduced SWS, SWA, and REM sleep (Besedovsky et al., 2019; Irwin, 2019). Together these findings portray a complex interaction between inflammation and SWS in later life, with age-related increases in chronic inflammation potentially impairing SWS expression and overall sleep quality, ultimately resulting in greater systemic inflammation. Since chronic inflammation promotes Aβ accumulation (Krstic et al., 2012; Heppner et al., 2015; Spangenberg and Green, 2017), SWS deficits may increase Aβ burden through an interaction with markers of systemic and central inflammation. However, it should be noted that data linking either systemic or central inflammation markers to the local expression of any sleep oscillation is limited. Future work should examine this more closely to more fully address the hypothesis that slow wave deficits increase Aβ burden through interactions with inflammatory processes.

The second mechanistic question involves how Aβ burden may impact the expression of slow waves. NREM sleep is disrupted in rodent models over-expressing Aβ (Roh et al., 2012). Moreover, our recent work has shown that there is an association between SWA and cortical Aβ burden in cognitively asymptomatic older adults, but that this association is distinct from that due to age and age-related frontal cortical atrophy (Mander et al., 2015). Aβ was not associated with a global loss of slow waves or a global reduction in SWA, as is common in aging (Mander et al., 2017a), but instead showed a negative association with slow waves and SWA in the SO frequency range (0.6–1 Hz) and a positive association with slow waves and SWA in the delta frequency range (1–4 Hz), representing a shift in the slow wave distribution (**Figure 1A**) (Mander et al., 2015; Winer et al., 2019). If Aβ did not disrupt slow waves, but only was increased by slow wave disruption, than it would be expected that age-related changes in slow waves would predict increases in Aβ burden. This was not what we found. Instead, deficits associated with SWA were specific to Aβ and independent of age, indicating that Aβ may further disrupt slow wave expression independently of age-related changes. Interestingly, a similar effect on the SWA distribution was also observed in APP transgenic mice, a rodent model of AD selectively overexpressing Aβ pathology, with the loss of low frequency SO activity emerging as early is 3 months of age (Kastanenka et al., 2017). The mechanisms for how Aβ may disrupt slow wave expression is unknown, though there are some theoretical possibilities. One possibility is that Aβ may disrupt the generation and expression of slow waves as it accumulates in cortical slow wave generators (**Figures 1A,D**). Indeed, Aβ plaques initially deposit preferentially within many slow wave generating regions, including within the medial prefrontal cortex (mPFC) and anterior and posterior cingulate gyri (Buckner et al., 2005; Murphy et al., 2009; Sepulcre et al., 2013; Jagust, 2018). Supporting this possibility, the association between Aβ burden and SWA is not global, but peaks locally over midline and frontal derivations (Mander et al., 2015; Varga et al., 2016b). Further, source analysis confirmed that the strongest predictor of frontal SWA was Aβ burden within the same mPFC region where frontal slow waves were sourced (Mander et al., 2015). It remains to be determined exactly how Aβ burden could disrupt slow wave generation and expression. One hypothesis is that Aβ directly acts on the neurobiological mechanisms controlling slow wave expression (Mander et al., 2016). There is some evidence that Aβ disrupts GABA levels and GABA and NMDA receptor signaling (Kurup et al., 2010; Busche et al., 2015; Kastanenka et al., 2017), which are critical for SO expression (Steriade et al., 1993b). Another potential mechanism is the effect of Aβ on the inwardly rectifying potassium channel Kir4.1 in astrocytes (Wilcock et al., 2009). Astrocytes have been shown to impact slow oscillation expression through an impact on NMDA receptor activity in neurons (Fellin et al., 2009). Further, a recent report has linked a gain of function mutation in Kir4.1 channels in children expressing the Autism-Epilepsy Phenotype with a lengthening of the slow oscillation period during NREM sleep (Cucchiara et al., 2020). Since the presence of Aβ results in a loss of Kir4.1 channels (Wilcock et al., 2009), rather than a gain of function, it is likely that Aβ could trigger the opposite effect, i.e., a shortening of period and thus an increase in the mean slow oscillation frequency. This hypothesis remains to be tested and should be a focus of future studies. Yet another possibility is that Aβ burden triggers generalized cortical hyperexcitability, which then results in a shift toward a greater abundance of delta waves and a reduction in SO events as a consequence. Indeed, optogenetically doubling the slow oscillation frequency from 0.6 to 1.2 Hz in APP transgenic mice resulted in increased Aβ production, supporting the frequency specificity and bidirectional nature of this effect (Kastanenka et al., 2019). Lastly, since Aβ increases markers of inflammation and chronic inflammation can disrupt SWA expression, inflammation may also contribute to deficits in SWA associated with Aβ (Besedovsky et al., 2019; Irwin, 2019). Supporting the frequency specificity of this effect, relative to healthy controls, patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) exhibit reduced SWA in the SO frequency range and increased SWA in the delta frequency range, particularly over prefrontal cortex (Le Bon et al., 2012). This is notable, because central inflammation is a core component of ME/CFS (VanElzakker et al., 2019) and this frequency effect on SWA is highly consistent with the reported effects of Aβ (Mander et al., 2015; Winer et al., 2019). Regardless of the mechanism or the direction of causality, what is clear is that Aβ burden is associated with local disruptions in frontal slow waves, even prior to MCI diagnosis both cross-sectionally (Mander et al., 2015; Varga et al., 2016b; Winer et al., 2019) and longitudinally (Winer et al., 2020 in press). Some evidence also indicates that this effect of Aβ burden on local sleep may be specific to slow wave expression, as it does not appear to be associated with the REM sleep and spindle deficits observed in MCI and AD (Brazete et al., 2013, 2016;

Mander et al., 2015; Brayet et al., 2016; Gorgoni et al., 2016; Winer et al., 2019).

Tau Pathology and Local Sleep (T)

Habitual poor sleep and chronic sleep deprivation are associated with increased tau burden, tau hyperphosphorylation, and the spread of tau pathology across brainstem and hippocampal circuits, resulting in degeneration and memory impairment (Rothman et al., 2013; Di Meco et al., 2014; Ju et al., 2017; Zhu et al., 2018; Holth et al., 2019). Similar to the effects of sleep deprivation on Aβ, one recent finding indicated that ISF and CSF tau levels in rodents and humans also increase during wakefulness and decrease during sleep (Holth et al., 2019). Sleep deprivation exaggerated this wake-related increase, similar to its effects on Aβ, and chronic sleep deprivation increased the spread of tau pathology from the hippocampus to the locus coeruleus in the brainstem (Holth et al., 2019), a norepinephrine-expressing brain region known to accumulate tau pathology in the earliest stages of AD (Grudzien et al., 2007; Braak et al., 2011; Ehrenberg et al., 2017).

In addition to sleep deficits impacting tau pathology, more recent work shows that tau burden may be related to a number of distinct global and local sleep deficits observed in MCI and AD, each of which likely depends on the location of tau accumulation. Alongside the initial deposition of tau in the medial temporal lobe (MTL), tau also deposits in the brainstem, midbrain, and hypothalamus, preferentially within many sleep and wake-promoting nuclei (Oh et al., 2019), and this may decrease the consolidation of sleep and wakefulness which are regulated by these circuits (Lim et al., 2013a, 2014). Within the MTL, tau burden disrupts the GABA-regulated temporal synchrony of hippocampal ripple events during sleep and quiet wakefulness in a rodent model of tauopathy (Witton et al., 2016). Another rodent model of tauopathy identified the evolution of changes in sleep physiology, such that increases in NREM delta power and REM theta power in P301S tau transgenic mice relative to wild type mice at 6 and 9 months of age was followed by a decrease in NREM delta and REM theta power at 11 months (Holth et al., 2017). This finding indicated that, similar to the effect of MCI and AD on hippocampus activation, there may be a u-shaped curve in the expression of NREM and REM sleep oscillations as tau burden increases in the cortex.

In human studies, sleep spindle density and duration, but not SWA, are negatively associated with CSF-measured total and hyperphosphorylated tau levels in cognitively asymptomatic older adults (Kam et al., 2019). A similar finding was observed with slow wave-sleep spindle coupling strength, over frontal and parietal derivations, in relation to MTL tau burden in cognitively asymptomatic older adults (**Figures 1B,D**) (Winer et al., 2019). Similar to (Kam et al., 2019), this study did not find an association between SWA and MTL tau burden. In contrast, other reports showed that cortical tau was associated with a global loss of SWA across frequencies and prolonged duration of slow wave hyperpolarized down states (Menkes-Caspi et al., 2015; Lucey et al., 2019). However, these studies included patients with MCI (Lucey et al., 2019), and animal models that deposit tau in the cortex (Menkes-Caspi et al., 2015), which is not typical of early preclinical AD stages (Braak and Braak, 1996). It is possible that when tau remains confined to MTL and brainstem regions in early stages, SWA is not affected, while sleep features that depend on these structures are affected. Once tau begins to spread cortically, global deficits in SWA may begin to be apparent (**Figures 1A,D**), drowning out the hyperexcitability effects of Aβ (Busche et al., 2019). This hypothesis, which remains to be tested, would indicate that global and local sleep deficits due to AD pathophysiology are not static across disease stages, but instead evolve across disease stages as distinct AD pathophysiological features build up and spread throughout various cortical and subcortical brain circuits. If true, this would mean that a comprehensive picture of global and local sleep deficits may offer unique insight into how AD pathophysiology is progressing in a given individual, even in preclinical stages. Whether these tau effects on sleep are prior to or following tau-related neurodegeneration remain unclear, and should be distinguished in future studies.

Neurodegeneration and Local Sleep (N)

Similar to tau pathological burden, the influence of neurodegeneration on global and local sleep likely depends on the location of neurodegeneration. Moreover, the distinction between degeneration due to age-related processes and dementia is not always clear. In the context of global sleep, loss of galanin-expressing inhibitory neurons in the intermediate nucleus of the hypothalamus, a potential human homolog to the ventral lateral preoptic nucleus which regulates sleep maintenance, is associated with sleep fragmentation (Lim et al., 2014). In patients with AD, the loss of galanin neurons and sleep fragmentation were both more extreme, but the overall relationship remained unchanged. Hence, it is not clear whether galanin neuron degeneration was due to an AD-specific process that began early in preclinical stages, or whether it was primarily age-related. However, there was also a trend for neurofibrillary tau tangles to be more concentrated in those with greater sleep fragmentation, indicating that galanin neurodegeneration may be driven by tau pathological burden in the hypothalamus (Lim et al., 2014). New evidence may help begin to distinguish between the role of tau and tau-related neurodegeneration on sleep expression. A recent study conducted comprehensive histopathological analysis of tau inclusion, neurotransmitter synthesis, and neuronal loss in a series of brainstem wake-promoting nuclei in healthy controls and patients with a variety of tauopathies, including AD, corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP) (Oh et al., 2019). Increased tau inclusion and a decrease in neurons synthesizing neurotransmitters was apparent in all tauopathies relative to controls. However, it was only in AD that widespread neuronal loss was observed. Given these findings, it is therefore possible that distinct sleep phenotypes observed in distinct tauopathies is driven not by tau pathology, *per se*, but by the neurodegenerative effects of that pathology. For example, an extreme form of insomnia characterized by the inability to nap despite a profoundly shortened nighttime sleep duration (2–4 h per night) is consistently seen in PSP patients (Gagnon et al., 2008; Walsh et al., 2017), while sleep/wake instability is more typical in AD patients (Gagnon et al., 2008).

This makes sense if widespread neuronal loss in wake-promoting brainstem regions is observed in AD and not in PSP. The reason why tau-related neurodegeneration in the brainstem differs by tauopathy remains unclear, though one possible mechanism regards potential differences in interactions between central inflammation and tau pathology (Leyns and Holtzman, 2017).

Less is clear about the role of neurodegenerative processes in the expression of local sleep. While it has been shown that frontal atrophy is consistently associated with slow wave deficits and slow wave-sleep spindle coupling deficits (Mander, 2013; Varga et al., 2016a; Helfrich et al., 2018), and hippocampal atrophy and frontal white matter degeneration are associated with sleep spindle deficits (Fogel et al., 2017; Mander et al., 2017b), it is unclear if these are secondary to an AD process or generally related to aging. However, recent findings have linked deficits in subjective sleep duration and quality to cross sectional and longitudinal volumetric differences in signature cortical amnestic MCI and AD regions as well as overall ventricular enlargement (Lo et al., 2014; Spira et al., 2016; Alperin et al., 2019), though the directionality of these relationships remains unclear.

In terms of loss of EEG desynchrony during REM sleep in MCI and AD, a double blind placebo controlled clinical trial administering donepezil, an anticholinesterase inhibitor, in patients with AD showed that donepezil treatment for 6 months reduced REM sleep EEG slowing and increased REM sleep duration (Dos Santos Moraes et al., 2006). This indicates that REM sleep EEG slowing may be due to progressive loss of cholinergic activity in AD (**Figures 1C,D**). This is consistent with the fact that EEG desynchrony during REM sleep is critically dependent on brainstem and basal forebrain cholinergic inputs (Peever and Fuller, 2016; Scammell et al., 2017), and that basal forebrain cholinergic projections are selectively degenerated early in the AD pathophysiological process (Mufson et al., 1988; Mesulam et al., 2004; Oh et al., 2019). These findings support the hypothesis that REM sleep EEG slowing may be related to tau pathological burden, but only because of the tau-dependent degeneration of the cholinergic system (Oh et al., 2019). However, these hypotheses remain to be directly tested. Further, whether global and local REM sleep deficits are a biomarker of or directly related to cognitive deficits in AD is unknown.

Hence, new emerging evidence indicates that signature pathological features of AD (i.e., Aβ, tau, and neurodegeneration) are all associated with distinct effects on global and local sleep expression, and that the sleep deficits observed in AD are likely dependent on the location and relative severity of each of these processes and the manner in which they synergistically interact. However, much less is known about the direct and indirect roles these local sleep deficits may play in the cognitive decline associated with AD pathophysiology.

LOCAL SLEEP AND AD-RELATED MEMORY IMPAIRMENT

Critical components of a functioning MTL memory system include a network linking the entorhinal cortex (EC) layer II neurons to the dentate gyrus (DG) and cornu ammonis 3 (CA3) hippocampal subfields by way of the perforant path (Hyman et al., 1986; Witter, 2007). This network, which supports successful separation between similar yet distinct memories—i.e., pattern separation (Yassa et al., 2011b)—is highly sensitive to age and sleep loss, and is among the earliest and most dramatically affected in AD (Jagust, 2013; Leal and Yassa, 2013). Indeed, degeneration of this MTL circuit is a critical preclinical structural biomarker of MCI and AD (Desikan et al., 2012; Holland et al., 2012). Targeted studies have identified diminished pattern separation ability both in aging (Wilson et al., 2006; Stark et al., 2010, 2013; Yassa et al., 2011a,b) and following sleep deprivation (Saletin et al., 2016), and impaired pattern separation is even more dramatic in patients with amnestic MCI (Bakker et al., 2012, 2015). In aging and MCI, these deficits are associated with DG/CA3 region hyperactivity (Yassa et al., 2011a,b), EC thinning (Reagh et al., 2018), and perforant path degeneration (Yassa et al., 2010a, 2011b). Levetiracetam (LEV) is an anti-epileptic drug that modulates synaptic excitability by binding to synaptic vesicle protein SV2A, thus impacting action potential-dependent neurotransmitter release (Lynch et al., 2004). LEV administration in aMCI patients significantly reduces hyperactivity and enhances object pattern separation performance relative to placebo (Bakker et al., 2012, 2015), supporting the notion that this hyperactivity is dysfunctional rather than compensatory. Of note, in addition to its impact on functional hyperactivity and cognition during wakefulness, LEV has also been shown to consolidate SWS and increase its duration in healthy adults, suggesting that it may also influence SWS-related memory processing as well (Cicolin et al., 2006).

Beyond the MTL, cortical network dysfunction and impaired functional connectivity have been observed in the context of AD pathophysiology. In particular, breakdown of connectivity and disinhibition of activity within the default mode network (DMN) is associated with both hippocampus hyperactivity and cognitive impairment in individuals with AD pathologies (Pihlajamaki et al., 2008; Jacobs et al., 2013; Pereira et al., 2019). Disruptions in DMN functional connectivity are also observed following sleep deprivation (Gujar et al., 2010) and are associated with the extent of daytime sleepiness (Ward et al., 2013). This may be due, in part, to a deprivation or disruption of infraslow EEG oscillations during SWS that organize DMN expression supporting sleep-dependent memory consolidation (Picchioni et al., 2011). Together, these findings implicate widespread circuit dysfunction within frontal, parietal, and MTL networks, which are associated with memory impairments even prior to AD-related neurodegeneration. Further, dysfunction within this circuit has also been associated with sleep disturbance, including in disorders such as sleep apnea and attention deficit hyperactivity disorder (Gujar et al., 2010; Ward et al., 2013; Khazaie et al., 2017; Tashjian et al., 2017), indicating that sleep disturbance may also be related to the effects of AD pathophysiology on cortical brain function.

The role of AD pathology in this memory-related circuit dysfunction is still being investigated. However, it appears that MTL tau burden, microglial dysfunction, and related synaptic loss are more strongly associated with memory impairment than Aβ burden (Jack et al., 2010, 2013; Scholl et al., 2016; Spangenberg

et al., 2016; Pereira et al., 2019). This has led to the view that tau pathology is more directly linked with cognitive impairments in AD than Aβ, though the truth is likely more complicated (Bloom, 2014; Maass et al., 2018; Sperling et al., 2019). For example, while tau is more likely to deposit early in the MTL, the tau-related memory impairments observed may be more typical of age-related memory decline (Maass et al., 2018). Once tau spreads beyond the MTL, which may depend on the presence of Aβ (Bloom, 2014; Tosun et al., 2017; Sperling et al., 2019), AD-related cognitive decline may begin to emerge and progress (Tosun et al., 2017; Sperling et al., 2019). Regardless, the pathophysiology of the long-term trend in tau-related cognitive decline may be distinct from the memory impairments due to hippocampus hyperexcitability.

What role, if any, that local sleep dysfunction plays in AD-related memory impairment remains unclear, though there are multiple theoretical ways in which local sleep could interact with AD pathologies to disrupt a variety of memory functions. The state of the science supporting each of these possibilities is reviewed below.

Direct Effects

An established literature demonstrates a clear relationship between local sleep features and multiple forms of memory encoding and consolidation (Fischer et al., 2002; Walker et al., 2002; Marshall et al., 2004, 2006; Spencer et al., 2006, 2007; Mander et al., 2011, 2013, 2014, 2015, 2017a,b; Antonenko et al., 2013; Fogel et al., 2013, 2017; Westerberg et al., 2015; Lustenberger et al., 2016; Papalambros et al., 2017). Three, non-mutually exclusive core theories of sleep-dependent memory consolidation implicate specific synaptic and systemic processes that mechanistically support the role of sleep in the long-term retention of procedural and episodic memories. There is evidence that many of the neurobiological mechanisms supporting these process may be directly disrupted by AD pathophysiology.

First, one theory posits that the coordinated expression of cortical slow oscillations (0.5–1 Hz), cortico-thalamic sleep spindles (12–16 Hz), and hippocampal ripples (140–220 Hz) actively supports memory consolidation by triggering memory replay during SWS to transform memory traces to be more cortically-dependent (**Figure 3A**) (Steriade, 2006; Diekelmann and Born, 2010; Abel et al., 2013; Staresina et al., 2015; Mander et al., 2017a; Helfrich et al., 2018). This framework has been supported by studies demonstrating induction of LTP-related plasticity, coordinated replay of neuronal ensembles, and coordinated hippocampal-neocortical information transfer during this tripartite coupling of slow wave, sleep spindle, and ripple events (Rosanova and Ulrich, 2005; Wierzynski et al., 2009; Chauvette et al., 2012; Abel et al., 2013; Latchoumane et al., 2017; Helfrich et al., 2019). More specifically, it has been shown that the hyperpolarized downstate of the cortical slow oscillation induces the expression of sleep spindles in the thalamic reticular nucleus which are preferentially expressed during the rising phase toward the depolarizing upstate of the slow oscillation (Mak-McCully et al., 2017). In addition, hippocampal ripple expression is maximal during the excitatory troughs of sleep spindles (Staresina et al., 2015; Latchoumane et al., 2017). Recent closed-loop optogenetic evidence in rodents has demonstrated that this precise phase-relationship of coupling between sleep spindles with slow oscillations is essential for successful hippocampus-dependent memory consolidation (Latchoumane et al., 2017). Induction of sleep spindle expression in thalamic reticular neurons during the rising phase of the slow oscillation up-state increases phase locking of hippocampal ripples to spindle troughs and enhances memory consolidation, while suppression of sleep spindle expression during this SO phase impairs memory consolidation. Conversely, either inducing or suppressing sleep spindle expression outside of this SO rising up phase has no effect on memory consolidation. Prior studies offer mechanistic support for this effect of SO-sleep spindle coupling on memory consolidation. Sleep spindles have a local effect on neuroplasticity, but this depends on its coupling with slow oscillations. When sleep spindles are appropriately phase locked to slow oscillations local evidence of long term potentiation (LTP) is apparent, and when sleep spindles are expressed without slow oscillations long term depression (LTD) is instead observed (Rosanova and Ulrich, 2005). Another recent optogenetic study also demonstrated a causal role for SO events (<1 Hz slow waves) and not faster frequency delta waves (1–4 Hz slow waves) in memory retention (Kim et al., 2019). Hence, optogenetic manipulation of both SO and sleep spindle events directly impacts long-term memory retention, supporting their causal role in sleep-dependent memory consolidation. This model is further supported by studies that mechanistically enhance slow waves, sleep spindles, and slow wave-sleep spindle coupling through external electrical and auditory stimulation methods in humans, resulting in improved procedural and episodic memory, even in older adults and patients with MCI (Marshall et al., 2004, 2006; Westerberg et al., 2015; Lustenberger et al., 2016; Ladenbauer et al., 2017; Papalambros et al., 2017, 2019).

Theoretical depictions of this form of sleep-dependent memory describe a process by which hippocampal-neocortical neuronal ensembles which are primed by learning during prior wakefulness are reactivated during slow wave sleep in a temporally precise manner. This is supported by classic studies showing replay of coordinated place cell activity during slow wave sleep, and specifically during hippocampal ripples (Wilson and McNaughton, 1994; Ji and Wilson, 2007; Davidson et al., 2009). It has been hypothesized that this replay provides a window for information transfer from hippocampal nodes to neocortical nodes facilitating neuroplasticity in support of memory transformation and long-term memory retention (Buzsaki, 1998). This supposition has been supported by studies in rodents and intracranial EEG studies in humans describing evidence of information transfer from hippocampus to cortex during triple coupling of SOs, sleep spindles, and ripple events (Olcese et al., 2018; Helfrich et al., 2019), with this information transfer being particularly prominent in neuronal ensembles modulated by a memory task in prior waking periods (Olcese et al., 2018). Further support for the causal role of replay in memory consolidation is demonstrated by a series of studies implementing targeted memory reactivation (TMR) methods to trigger the replay of memories encoded prior to sleep during SWS. This approach implements pairing learning with external

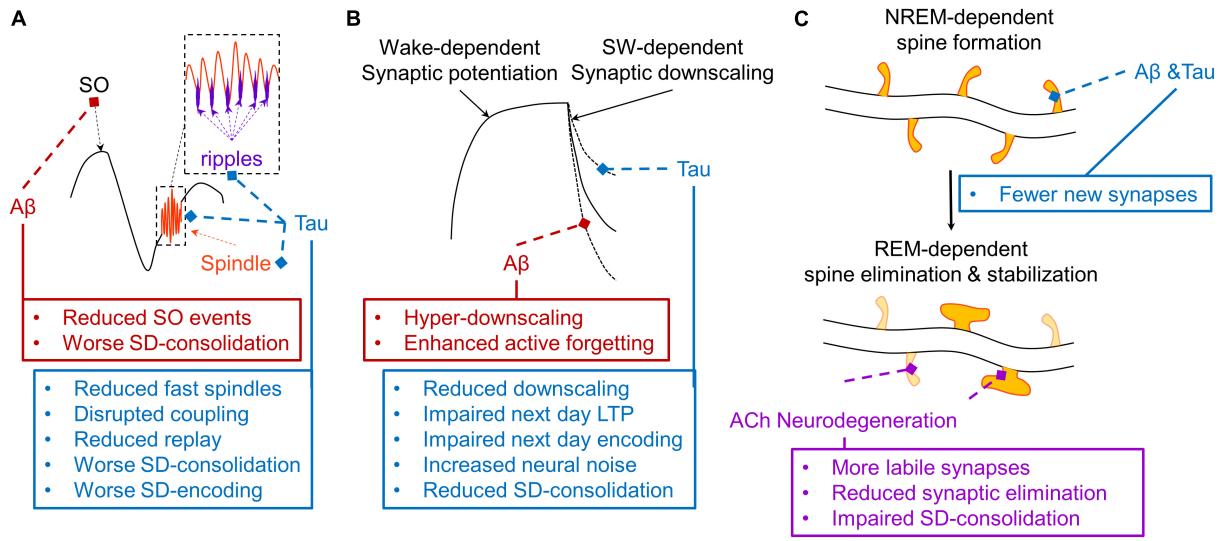

FIGURE 3 | Schematic depiction of hypothesized effects of AD pathophysiology on mechanisms of three models of sleep-dependent memory consolidation. **(A)** A theoretical depiction of the mechanisms supporting active systems consolidation (Steriade, 2006; Diekelmann and Born, 2010; Watson and Buzsaki, 2015). The thalamic sleep spindle (orange) is phase-locked to the depolarizing upstate of the slow oscillation (SO, black), and the hippocampal ripple is phase-locked to the troughs of the sleep spindle (purple), supporting coordinated replay of memory traces which triggers the cortical plasticity necessary for systems consolidation. Aβ (red) selectively disrupts SO expression, impairing sleep-dependent (SD) memory consolidation. Tau (blue) disrupts fast sleep spindle and ripple expression and their coupling with the SO, disrupting memory replay and related memory consolidation and subsequent encoding (Walker, 2009; Watson and Buzsaki, 2015; Mander et al., 2017a). **(B)** A theoretical depiction of the sleep homeostasis hypothesis (SHY), which posits that slow waves (SW) facilitate global synaptic downscaling in response to widespread synaptic potentiation following waking experience (Tononi and Cirelli, 2014). Aβ increases delta waves, which may increase the magnitude of synaptic downscaling, potentially overriding local signals protecting relevant synapses from long-term depression (LTD), ultimately exaggerating an active forgetting process. Tau reduces overall slow wave activity, which may weaken the process of synaptic downscaling, resulting in increased neural noise and impaired sleep-dependent memory consolidation. Another consequence could be a brain that remains more over-potentiated, thus limiting the capacity to induce long-term potentiation (LTP), resulting in impaired next day learning. **(C)** A theoretical depiction of a NREM-REM two-stage model of synaptic plasticity supporting sleep-dependent memory (Yang et al., 2014; Miyawaki and Diba, 2016; Li et al., 2017; Mizuseki and Miyawaki, 2017). In this model, NREM sleep facilitates the formation of a small number of dendritic spines on dendritic branches of neurons triggered by learning experiences during prior wakefulness. This is followed by a REM sleep-dependent process that eliminates most of these new labile dendritic spines, but stabilizes some that most support successful memory formation. Through their disruption of memory-relevant NREM sleep oscillations, both Aβ and tau could reduce the number of new dendritic spines formed following a learning experience. Through cholinergic degeneration (purple), and the resulting impairments in REM sleep physiology, this could be further compounded by impaired REM sleep-dependent elimination and stabilization of relevant dendritic spines. This could result in greater neural noise, faster memory trace decay, and a reduction in resistance to interference, exacerbating forgetting.

sensory stimulation, such as pairing odor cues with a memory task (Rasch et al., 2007) and auditory cues with individual memory trials (Rudoy et al., 2009; Antony et al., 2012; Van Dongen et al., 2012; Batterink et al., 2016; Berkers et al., 2018). These sensory cues are then replayed during sleep with memory performance being assessed in sensory cued versus un-cued trials in subsequent waking periods. These studies have shown that sensory cueing specifically during SWS enhances slow wave-sleep spindle coupling and memory performance (Rasch et al., 2007; Rudoy et al., 2009; Antony et al., 2012; Van Dongen et al., 2012; Feld and Diekelmann, 2015; Batterink et al., 2016; Berkers et al., 2018; Bar et al., 2020), with the efficacy of this effect depending on the phase of the slow wave during sensory cueing (Batterink et al., 2016; Goldi et al., 2019). Hence, these findings implicate a mechanism by which triple coupling of SO, sleep spindle, and ripple events coordinate replay of relevant neuronal ensembles supporting targeted neuroplasticity in facilitation of memory consolidation.

Cortical slow oscillations are diminished in the presence of both Aβ and tau pathology in the cortex (Mander et al., 2015; Lucey et al., 2019), and this effect is independent of gray matter atrophy (Mander et al., 2015). Furthermore, this effect of Aβ on SWA was correlated with retrieval-related hippocampus hyperactivation, which was negatively associated with sleep-dependent memory retention (Mander et al., 2015). Further supporting the importance of the <1 Hz SO, doubling the frequency of the SO from 0.6 to 1.2 Hz in APP transgenic mice resulted in reduced dendritic spine density, likely directly impacting memory functions (Kastanenka et al., 2019). In addition, MTL tau burden has been shown to disrupt hippocampal ripple expression and slow wave-sleep spindle coupling during NREM sleep (Witton et al., 2016; Winer et al., 2019). Hence, current evidence indicates that AD pathologies disrupt the expression and coupling of all three of the core sleep oscillations underlying sleep-dependent memory consolidation (**Figure 3A**). Beyond their direct effects on local sleep expression, AD pathophysiology could also disrupt cortical network structure and function in a way that diminishes the efficacy of local sleep expression to support consolidation across memory systems, as observed in aging (Mander et al., 2017a).

Second, the synaptic homeostasis hypothesis posits that slow waves act to globally downscale synapses to manage the growing energy demands of the brain following continuous learning and thus wide-spread synaptic potentiation (**Figure 3B**) (Tononi and Cirelli, 2014). In theory, memory is consolidated and enhanced by this process as it acts to enhance the signal to noise of neuronal ensembles related to a given memory trace. A series of studies across model systems support key tenants of this hypothesis. Synaptic potentiation is saturated following extended wakefulness, resulting in partial occlusion of long term potentiation (LTP) induction, which is refreshed following SWS (Vyazovskiy et al., 2011). This is mirrored in some human studies, with slow wave stimulation and sleep spindle expression both predicting restoration of memory encoding ability following sleep (Mander et al., 2011; Antonenko et al., 2013). Other studies have shown that memory tasks targeting localized brain networks result in local increases in SWA in subsequent sleep periods, with the intensity of SWA predicting the degree of motor learning (Huber et al., 2004, 2006). A recent optogenetic paper has showed that while SO events support memory retention, delta waves may support forgetting (Kim et al., 2019). This finding may support the presence of both hypothesized mechanisms in SWS, with an active process enhancing synaptic strength of a small number of neuronal ensembles directly relevant to triggered replay of specific prior waking experiences, while another globally downscales synapses to maintain energy homeostasis and reduce neural noise.

This latter mechanism may also be influenced by AD pathology (**Figure 3B**). While Aβ decreased SO events, it also increased delta waves (Mander et al., 2015). It is possible this shift in SO-delta wave balance may shift memory systems toward greater forgetting and lower memory retention (Kim et al., 2019). Indeed, while SO events were positively associated with sleep-dependent memory consolidation, delta events were negatively associated with sleep-dependent memory consolidation in older adults with Aβ pathology (Mander et al., 2015). In addition to this potential "hyper downscaling" in the presence of Aβ, cortical tau may impoverish the downscaling process altogether, indirectly impacting the ability of the brain to encode novel experiences in subsequent waking periods due to incomplete depotentiation of synapses (**Figure 3B**). Therefore, AD pathologies may either exaggerate a downscaling process or disrupt it altogether, impairing sleep-dependent memory consolidation and/or sleep-related memory encoding ability.

Lastly, another model concerns coordinated sequential synaptic remodeling across NREM-REM cycles (Yang et al., 2014; Miyawaki and Diba, 2016; Li et al., 2017; Mizuseki and Miyawaki, 2017). This theory is supported by animal work showing that NREM sleep can trigger a limited formation of new synapses following a learning experience in a dendritic branch-specific manner (Yang et al., 2014). REM sleep then eliminates many of these, but stabilizes the synapses not eliminated (Li et al., 2017). AD could impact this process, too, by disrupting the stability of NREM and REM sleep, shortening REM duration, and/or disrupting the EEG desynchrony characteristic of REM sleep. This would likely result in fewer new synapses formed following learning, all of which would be more labile and vulnerable to decay (**Figure 3C**). As with the other sleep-dependent memory models, this possibility has not been directly tested.

Each of the theoretical mechanisms proposed to support sleep-dependent memory encoding and consolidation are likely negatively influenced by AD pathophysiology (**Figure 3**), which would contribute to the memory impairments observed in AD. However, the impact of local sleep deficits on memory in AD is not necessarily limited to the effects of AD pathophysiology on sleep-dependent memory mechanisms.

Indirect Effects

There is also evidence that AD pathology interacts with sleep deficits to influence cognition. For example, the interaction between Aβ and sleep efficiency predicts cognitive deficits on cognitive tasks, such that poor sleep quality results in impaired memory to a greater extent when an individual has AD pathology in their brain (Molano et al., 2017). Moreover, the influence of APOE genotype—the strongest genetic risk factor for late onset, sporadic AD (O'Donoghue et al., 2018)—on cognition depended on the quality of sleep, with APOE genotype having minimal impact in those with high quality sleep and substantial impact on those with low quality sleep (Lim et al., 2013b). This indicates that sleep may be related to a neural reserve factor making the brain more or less vulnerable to the presence of AD pathology or risk factors. Indeed, there is a literature that indicates that deficits in sleep quantity and quality result in cortical brain atrophy (Spira et al., 2016; Alperin et al., 2019) and overall ventricular enlargement even over the course of 2 years in healthy older adults (Lo et al., 2014), which would likely diminish neural reserves to compensate for AD pathophysiology.

Another possibility is that sleep may be related to cognitive impairment independently of sleep-dependent memory processes through its direct effects on AD pathophysiology. Growing evidence indicates the bidirectional relationship between slow waves and Aβ and tau pathology (Zhang et al., 2005; Xie et al., 2013; Mander et al., 2015, 2016; Menkes-Caspi et al., 2015; Varga et al., 2016b; Ju et al., 2017; Kastanenka et al., 2017, 2019; Kent et al., 2018; Fultz et al., 2019; Lucey et al., 2019). More specifically, slow wave deficits and sleep/wake instability appear to foster greater production and lower clearance of both Aβ and tau pathology (Zhang et al., 2005; Mander et al., 2015; Varga et al., 2016b; Ju et al., 2017; Kastanenka et al., 2017, 2019; Kent et al., 2018; Musiek et al., 2018; Lucey et al., 2019), which may then exacerbate central inflammation and MTL-related neurodegeneration, thus accelerating memory decline (Jack et al., 2010, 2013, 2019; Yassa et al., 2010b, 2011b; Desikan et al., 2012; Holland et al., 2012; Jagust, 2013; Leal and Yassa, 2013; Scholl et al., 2016; Spangenberg et al., 2016; Leal et al., 2017; Spangenberg and Green, 2017; Reagh et al., 2018; Pereira et al., 2019).

Hence, in addition to the disruption of local sleep processes related to sleep-dependent memory encoding and consolidation, sleep disruption may further accelerate AD pathophysiology or make the brain more vulnerable to it. Each of these could contribute to AD-related cognitive decline, and could do so at distinct stages. For example, sleep-dependent memory deficits may emerge as soon as local sleep deficits emerge in

the initial stages of AD pathogenesis (Mander et al., 2015), while deficits associated with neural reserve or AD-related neurodegeneration may emerge later once AD pathological burden has reached a tipping point or degeneration has progressed sufficiently to result in clinical symptoms (Westerberg et al., 2012; Lim et al., 2013b; Liguori et al., 2014). This would indicate that the role of sleep in AD-related cognitive decline may also be multifaceted and evolve across AD pathophysiological stages.

CONCLUSION AND FUTURE DIRECTIONS

Evidence continues to mount in support of the relationship between local sleep processes and AD pathophysiology. Recent studies have established that Aβ, tau, and neurodegeneration, defining pathological components of AD, all result in specific deficits in local and global sleep expression that depend on the underlying brain regions impacted (**Figure 1**). Pathological accumulation and degeneration within brainstem and hypothalamic sleep/wake regulatory centers fosters sleep state instability, pathology and degeneration in the MTL impacts ripple and spindle expression, cortical deposition and degeneration alters slow wave expression, and AD-related cholinergic degeneration likely disrupts REM sleep expression. These deficits are likely not static, but evolve as AD pathophysiology progresses through brain networks and across disease stages. For example, the slow wave deficits due to Aβ may differ from those observed with tau (**Figure 1A**). In some cases, these deficits may actively contribute to the progression of the disease, especially as they relate to the facilitation of Aβ and tau accumulation and neurodegeneration of circuits vulnerable to these pathologies (e.g., disruption of glymphatic clearance of AD pathologies). There is some evidence that these associations between AD pathophysiology and local sleep expression may be relevant for the memory impairments observed in the context of AD, though mechanisms of these relationships remain hypothetical.

The current state of the science indicates that there are more questions that remain than answers, both at mechanistic and therapeutic levels. At the mechanistic level, a clearer understanding of how local sleep is influenced by AD pathophysiology at each stage of the disease process is warranted. This means conducting larger scale studies that can implement the ATN framework to understand how the presence and absence and relative burdens of different AD pathologies at different AD stages may impact local sleep. This will also require examining other mechanisms, including metabolic dysfunction, chronic inflammation, and HPA-axis dysregulation, all of which contribute to AD pathophysiology and are related to sleep disturbance (Heppner et al., 2015; Spangenberg and Green, 2017; Caruso et al., 2018; Carroll and Macauley, 2019; Irwin and Vitiello, 2019; Chappel-Farley et al., 2020). Chronic inflammation, in particular, is a promising target for future research, because of its known independent interactions with sleep expression and multiple aspects of AD pathophysiology, as well as the paucity of data addressing its links with age-related deficits in local sleep expression. Further, targeted studies examining how the flow of CSF in the brain that is phase-locked to SWA (Fultz et al., 2019) may change with age and in relation to endogenously generated pathological features of AD will critically advance our understanding of the importance of the glymphatic system in AD pathogenesis. A greater understanding of the intersection between sleep disorders and local sleep, and their relationship with AD pathophysiological progression is needed, to better understand how various forms of sleep disturbance impact AD risk. Studies examining how local sleep differs across forms of dementia or kinds of AD will be informative both in terms of understanding mechanisms and the utility of local sleep to aid differential diagnosis. Longitudinal studies incorporating local sleep measures alongside AD biomarkers are of great need to determine the time course of sleep changes in relation to AD pathophysiology. Lastly, a comprehensive examination of how local sleep disruption is related to various forms of impairment in sleep-dependent and sleep-independent cognitive processes in relation to AD pathophysiology will help unpack the role(s) sleep plays in AD-related cognitive decline across disease severity. This will necessarily include examination of the influence of MCI, AD, and AD pathophysiology on ripple expression and memory replay, as well as the efficacy of targeted memory reactivation paradigms to facilitate memory transformation and consolidation.

Alongside these efforts, an emphasis on large-scale studies implementing sleep interventions must be considered. At present, it is not clear whether local sleep deficits are a biomarker of AD progression, or are active contributors to AD pathophysiology or related cognitive decline. The utility of sleep interventions, both targeting global sleep and local sleep, to address AD pathophysiological progression remains entirely unknown. While there are some data that suggest that treating sleep disorders may impact AD biomarkers (Osorio et al., 2015; Liguori et al., 2017a,b), large scale studies are lacking. Further, while a few reports show that enhancing local sleep in older adults and patients with MCI will improve overnight memory consolidation (Ladenbauer et al., 2017; Papalambros et al., 2019), the efficacy of this type of intervention, even for more than one night, is unknown. As important is an examination of the impact of AD disease stage on the efficacy of sleep interventions to impact AD pathophysiology and related cognitive impairments. Will sleep interventions help preclinical, MCI, or AD patients equally, or will sleep interventions have diminishing returns as the disease progresses, or affect distinct outcomes? This will be a critical question to answer, as it will help guide expectations related to disease management and identify the appropriate therapeutic targets based on the disease stage.

While much remains unknown, it is clear that local sleep processes are intricately intertwined with AD pathophysiology, likely in a bidirectional manner and through multiple mechanisms. These findings also open up the possibility that local sleep may offer a unique and sensitive window into

circuit level dysfunction across different forms of dementia, aiding early efforts in differential diagnosis of dementia risk. As different forms of dementia target distinct neural networks, the profile of deficits in local and global sleep appear to differ as well (Petit et al., 2004; Gagnon et al., 2008; Oh et al., 2019). Ultimately, the importance of local sleep for the optimal functioning of the brain means that local sleep disruption will likely be a crucial factor in the progression of all dementias, whether as a biomarker of a diseased brain, a contributor to disease pathogenesis, or an independent factor influencing the brain's resiliency or vulnerability to dementia. Uncovering the specific roles of local sleep in dementias such as AD will thus offer new opportunities to target interventions to offer symptomatic relief, impact disease progression and risk, and slow affiliated cognitive decline.

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The author confirms being the sole contributor of this work and has approved it for publication.

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Circadian and Sleep Dysfunctions in Neurodegenerative Disorders—An Update

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Disruptions of sleep and circadian rhythms are among the most debilitating symptoms in patients with neurodegenerative diseases. Their underlying pathophysiology is multilayered and multifactorial. Recent evidence suggests that sleep and circadian disturbances may influence the neurodegenerative processes as well as be their consequence. In this perspective, we provide an update of the current understanding of sleep and circadian dysregulation in Alzheimer's, Parkinson's, and Huntington's diseases.

Keywords: Alzheimer, Parkinson, Huntington, sleep, circadian system

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INTRODUCTION

Neurodegenerative disorders are characterized by a constellation of multiple impairments in diverse functional domains (Jucker and Walker, 2013). In addition to the primary symptoms characterizing each neurodegenerative disease [i.e., memory dysfunction in Alzheimer's disease (AD) and motor disorders in Parkinson's disease (PD), and Huntington's disease (HD)], several physiological functions deteriorate over disease progression and will ultimately dominate the clinical picture at advanced stages of the diseases (Bates et al., 2015; Masters et al., 2015; Poewe et al., 2017; Long and Holtzman, 2019). The primary neurodegenerative processes affect regions involved in the regulation of sleep, alertness and circadian rhythms, leading to disrupted sleep-wake cycles and circadian dysregulation (Coogan et al., 2013; Videnovic and Golombek, 2013, 2017; Videnovic et al., 2014a,b; Mattis and Sehgal, 2016; Musiek and Holtzman, 2016; Videnovic and Willis, 2016; De Pablo-Fernández et al., 2017; Fifel, 2017; La Morgia et al., 2017; Li et al., 2017; De Lazzari et al., 2018; Leng et al., 2019; Duncan, 2020). Increasing evidence points to deleterious effects of disrupted sleep and circadian homeostasis on the biological processes that underlie neurodegeneration. This bi-directional relationship between neurodegeneration and sleep and circadian systems opens immense opportunities for the development of novel treatment approaches for these disorders (Musiek and Holtzman, 2016; Leng et al., 2019). In this perspective, we summarize the symptomatology of sleep and circadian rhythms in neurodegenerative disorders, with an emphasis on the most common neurodegenerative disorders—AD, PD, and HD. Mechanistic insights mediating sleep and circadian dysfunction in these neurodegenerative diseases are highlighted as

well. We have focused on human clinical investigations with occasional referral to animal studies for mechanistic insights.

CIRCADIAN DYSFUNCTION IN NEURODEGENERATIVE DISORDERS

Circadian organization of biological processes is manifest, and plays a paramount role, at every level of organization from gene expression and cellular redox state regulation to intra- and inter-organ physiological coordination (Bass and Lazar, 2016; Patke et al., 2020). Given this complex and hierarchical organization of circadian biology, it is not a surprise that chronic breakdown of circadian rhythms is a significant risk factor for a range of diseases, including cancer, metabolic disorders, psychiatric disturbances, and neurodegenerative diseases (Bass and Lazar, 2016; Patke et al., 2020). In neurodegenerative disorders, three types of circadian alterations can be defined: behavioral, physiological and molecular alterations.

The most evident and extensively studied overt behavioral circadian disturbance in patients with neurodegenerative diseases is the alteration of sleep/wake behavior. Given the complex and widespread neuronal centers governing the quality and quantity of sleep/wake cycle (Saper et al., 2005) and the widespread nature of neurodegeneration and neural dysfunction in patients with neurodegenerative disorders (Jucker and Walker, 2013), sleep disruption usually precedes respective clinical diagnoses by several years and contribute significantly to the deterioration of the patients' quality of life. Some of the sleep alterations in neurodegenerative diseases are exaggerated forms of age-related sleep alterations (Mander et al., 2017). A typical example of this in AD, PD, and HD patients is the progressive fragmentation of sleep cycle over time. A more detailed discussion of sleep disorders in AD, PD, and HD diseases will follow in the next section. Other studies have capitalized on actigraphy to continuously monitor the progression of rest/activity rhythms in community-dwelling patients with neurodegenerative diseases (Leng et al., 2019). These studies have shown several alterations including frequent daytime naps, altered phase angles as evident by shifts in both bedtime and wake times, rest/activity fragmentation, and reduced amplitudes (Ortiz-Tudela et al., 2014; Hooghiemstra et al., 2015; Wang et al., 2015; Weissova et al., 2016). Interestingly, four recent studies have revealed robust association between weakened rest/activity rhythmicity and the subsequent development of AD and PD years later (Musiek et al., 2018; Lysen et al., 2019; Leng et al., 2020; Li et al., 2020). Circadian disturbances could therefore act as independent risk factor for the development of neurodegenerative diseases. Future studies should investigate the mechanisms behind these associations. Further, circadian rhythms could be a promising therapeutic target for the prevention and management of neurodegenerative diseases.

Alterations of additional physiological processes that are under the regulation of the circadian pacemaker, the suprachiasmatic nucleus (SCN) have been reported in these neurodegenerative disorders (Fifel, 2017; Fifel and DeBoer, 2020; Fifel and Videnovic, 2020). Several investigations in AD, PD and HD patients have revealed alterations of the circadian amplitude of cortisol rhythm (Hartmann et al., 1997; Hatfield et al., 2004; Aziz et al., 2009a; Adamczak-Ratajczak et al., 2017), reversal or complete loss of nychthemeral modulation of blood pressure and heart rate variability (Ejaz et al., 2006; Chen et al., 2013; Vetrano et al., 2015; Diago et al., 2018; Baschieri and Cortelli, 2019), phase desynchrony and amplitude disruption of melatonin-release cycle (Skene and Swaab, 2003; Aziz et al., 2009b; Kalliolia et al., 2014; Adamczak-Ratajczak et al., 2017; Fifel, 2017), dampening or reversal of the diurnal pattern of urine excretion (Hineno et al., 1994; Ouslander et al., 1998) and impaired body temperature (Raupach et al., 2019). Collectively these alterations demonstrate that patients with neurodegenerative diseases exhibit a global circadian desynchrony. This state of systemic desynchrony is known to precipitate deleterious impact on global health that is worse than having a dysfunctional SCN clock (Fernandez et al., 2014) and is therefore expected to causally contribute to health impairment in patients with neurodegenerative diseases.

The additional body of evidence linking circadian disturbances with neurodegenerative disorders comes from studies investigating circadian molecular markers in patients with neurodegenerative diseases. In PD patients, although all clock genes were not affected, significant alterations of the timing and amplitude of core clock genes such as Bmal1, Bmal2, Per2, and Rev-erbα were reported (Cai et al., 2010; Breen et al., 2014). Breen et al. reported a loss of the circadian expression of Bmal1 in peripheral mononuclear cells of PD patients (Breen et al., 2014). Few studies have also examined the contribution of circadian dysfunction to health impairments in PD patients by exploring the associations between single-nucleotide polymorphism of several clock-related genes and motor and non-motor symptoms of PD (Ding et al., 2011; Hua et al., 2012; Gu et al., 2015; Lou et al., 2018; Mao et al., 2018). Polymorphisms in clock-related genes such as ARNTL, thyrotroph embryonic factor gene, Clock, were proposed as independent risk factors for motor, depression-related and sleep disorders in PD (Gu et al., 2015). These studies suggest that the molecular mechanisms of the clock in peripheral organs of PD patients are altered and could contribute to the behavioral and physiological desynchronization observed in patients with PD (Fifel, 2017). Similar studies centered on clock genes expression in AD and HD are scant. However, few pathological studies using post-mortem brain tissue have shown a loss of the diurnal profile of clock genes (Bmal1, Cry1, Per1) in the pineal gland of patients with preclinical and manifest AD (Wu et al., 2006). Similarly, by examining the expression of clock genes per1, per2 and bmal1 in several brain structures, Cermakian et al. (2011) reported a dyssynchronous expression of several clock genes in different brain structures. In addition to altered clock gene expression, the expression of key SCN neuropeptides such as vasopressin, AVP and VIP, is significantly decreased in patients with AD and HD (Zhou et al., 1995; Liu et al., 2000; Wu et al., 2007; van Wamelen et al., 2013). Collectively, the behavioral, physiological and molecular alterations of the circadian system strongly implicate their involvement as a significant causal factor in the impairment of the quality of life in patients with neurodegenerative diseases.

Similar to the underlying mechanisms of sleep disturbances, the mechanisms of circadian alterations are also multifactorial involving the interactions between several intrinsic neurodegenerative processes (i.e., inflammation, oxidative stress) as well as a dysfunctional communication between central and peripheral clocks (Musiek and Holtzman, 2016; Chauhan et al., 2017). Recently, several molecular pathways linking multiple neurodegenerative processes with the genetic machinery of the circadian clock have been identified (Musiek and Holtzman, 2016; Sharma et al., 2020). However, translational insights from these mechanistic studies aimed at restoring a robust, yet flexible, circadian rhythms in patients with neurodegenerative disorders have not yet materialized.

From a neural network perspective, circadian rhythms are generated by a well-coordinated communication between peripheral clocks and the central clock in the SCN. This is achieved by both neural connections and humoral signals (Hastings et al., 2003; Bass and Lazar, 2016). In neurodegenerative diseases, significant impairments in different parts of this circadian neuronal network have been documented and have been recently reviewed elsewhere (Chauhan et al., 2017; Fifel, 2017; Fifel and DeBoer, 2020; Fifel and Videnovic, 2020). This knowledge is of a paramount importance for future attempts to develop specific network-based therapies for circadian and sleep symptoms in neurodegenerative diseases.

SLEEP DYSFUNCTION IN NEURODEGENERATIVE DISORDERS

Disturbances of sleep and alertness are common in neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases. Despite its common presence, sleep disruption is frequently under-reported by patients and their caregivers and under-diagnosed by healthcare professionals. Disrupted sleep negatively affects the quality of life and may impact the safety of patients. Increasingly manifested as these disorders progress, sleep dysfunctions may also predate their onset by years, even decades. For example, REM Sleep Behavior Disorder represents the most significant prodromal manifestation of a synuclein-specific neurodegenerative disorder, and excessive daytime sleepiness has been linked with the development of Parkinson's disease (Abbott et al., 2005; Hogl et al., 2018).

Alzheimer's Disease

Alzheimer's disease (AD), the most common neurodegenerative disorder, has been associated with sleep and circadian disturbances for a long time. Recent evidence strongly suggests a bi-directional relationship between AD and sleep/circadian disruption (Wang and Holtzman, 2020). Sleep changes that accompany aging are accentuated among individuals affected by AD. In AD, sleep becomes fragmented leading to shorter total sleep time, excessive sleepiness may develop with subsequent frequent napping, and sundowning is often associated with behavioral changes and agitation. These changes affect not only patients but may cause a significant strain on their caregivers (Terum et al., 2017). Alterations in sleep architecture in AD encompass less frequent and poorly formed spindles and K complexes, reduced slow-wave sleep, and changes in the spectral properties of REM sleep (Vitiello et al., 1990; Petit et al., 2004; Guarnieri et al., 2020). Recently the contribution of Obstructive sleep apnea to cognitive impairments in AD patients has been recognized (Bubu et al., 2020; Liguori et al., 2020). Burgeoning evidence demonstrates an increased risk of developing AD in individuals with a long-standing history of disturbed sleep (Virta et al., 2013; Pase et al., 2017). Several recently published meta-analyses reported that individuals with sleep problems had up to 4 times higher risk of AD, cognitive impairment, and preclinical AD (Bubu et al., 2017; Shi et al., 2018). Advance in biomarkers of AD have allowed more sophisticated analysis of the relationship between sleep and AD. Disruption of slow-wave sleep is associated with increased levels of beta-amyloid, whose deposition may impair slow-wave sleep (Ju et al., 2017). Tau aggregation and spreading is known to drive AD neurodegeneration (Holth et al., 2019; Long and Holtzman, 2019). Recent investigations both in mice and humans have shown that not only beta-amyloid, but also tau aggregation is regulated by sleep/wake cycle (Holth et al., 2019). More specifically, recent longitudinal studies have identified changes in NREM slow-wave activity, especially at 1–2 Hz, as specific and reliable EEG markers in forecasting the rate of Aβ accumulation over several subsequent years (Lucey et al., 2019; Winer et al., 2020). Changes in REM sleep, such as reduced REM sleep and prolonged REM latency have also been linked with the development of dementia (Pase et al., 2017). Another mechanism implicating sleep in the progression of AD pathology is related to the glymphatic system. This system, which clears the brain of protein waste products, is mostly active during sleep and suppressed during wakefulness (Xie et al., 2013). Clearance of amyloid or tau proteins by the glymphatic system may therefore be reduced on a background of disrupted sleep (Rasmussen et al., 2018; Nedergaard and Goldman, 2020).

Proper assessment of disturbed sleep in AD necessitate that caregivers be interviewed, as patients may not be aware of these sleep disturbances. From an evidence-based perspective, employing good sleep hygiene, and trazodone seem beneficial for improving sleep quality (McCleery et al., 2014). Trazodone may exhibit additional benefits on cognition with long-term use (reviewed in Ferini-Strambi et al., 2020). Several studies that examined the role of melatonin in managing poor sleep associated with AD found no beneficial effects of several sleep metrics (McCleery et al., 2014).

Parkinson's Disease

James Parkinson reported on disrupted sleep in his initial clinical depiction of PD in 1817. The impact of disturbed sleep and alertness, however, has only been systematically examined over the past several decades. Excessive daytime sleepiness and/or disrupted nighttime sleep affect the majority of patients during the lifetime of their PD (Chahine et al., 2017). Fragmented sleep is the most prevalent sleep problem in the PD population (Chahine et al., 2017). Up to 80% of PD patients report poor sleep, which has been characterized by lower sleep times and

sleep efficiency on polysomnography (Yong et al., 2011). The multifactorial etiology of poor sleep encompasses co-existent sleep and psychiatric disorders, overnight re-emergence of PD symptoms, effects of antiparkinsonian medications on sleep, autonomic dysfunction as well as neurodegeneration of brain regions responsible for the regulation of the sleep-wake cycle.

Primary sleep disorders have some unique features when co-expressed with PD. REM Sleep Behavior Disorder (RBD), a parasomnia characterized by loss of muscle atonia during REM sleep and dream enactment behavior, affects up to 60% of patients with PD (Sixel-Doring et al., 2016). RBD is of special significance for PD as it represents the most significant prodromal manifestation of an evolving PD and other synucleinopathies—dementia with Lewy bodies and multiple system atrophy. Dream enactment behaviors of RBD pose a substantial risk for injuries of patients and their bed partners. Restless Legs Syndrome (RLS) is another primary sleep disorder frequently associated with PD. In contrast to RBD, whether RLS is also a risk factor for subsequent development of PD is still a subject of debate (Alonso-Navarro et al., 2019; You et al., 2019). True prevalence of RLS in PD is not well established as many mimickers of RLS frequently affect PD patients, such as akathisia, rigidity, and leg cramps (You et al., 2019). While both RLS and PD respond favorably to dopaminergic medications and are worsened by the administration of dopamine blocking medications, there are sharp differences from a neuropathological standpoint. Dopaminergic neuronal loss with co-existent increased iron in substantia nigra PD is in contrast to the absence of neuronal loss and reduced iron content in RLS (Ferini-Strambi et al., 2018). Initially reported within the context of parkinsonism during the 1918 Spanish flu pandemic, sleep disordered breathing seem to have similar prevalence in the PD and general populations (Cochen De Cock et al., 2010). Important differentiators include a higher proportion of central and mixed apneas among PD patients, and a lack of strong associations between elevated body mass index and sleep disordered breathing in the PD population (Lajoie et al., 2020). Excessive daytime sleepiness (EDS) became a focus of medical attention in early the 1990s when reports of EDS and "sleep attacks" in association with the use of dopamine agonists were published (Frucht et al., 1999). The prevalence of EDS in pivotal clinical trials of major dopaminergic medications was 15–30%; Treatment with dopamine agonists carries the highest risk of EDS, followed by the combination therapy with levodopa and dopamine agonist, and levodopa monotherapy (extensively reviewed by Chahine et al., 2017). EDS is more prevalent in PD compared with other chronic diseases (Tandberg et al., 1999). While poor alertness and disturbed sleep share causative factors, there are unique mechanisms underlying disturbed alertness in PD. These include loss of hypocretin neurons in the hypothalamus, neurodegeneration of wake-promoting centers and its projections within the brainstem, and circadian disruption discussed in other segments of this article (Fronczek et al., 2007; Fifel and Videnovic, 2020).

In summary, the landscape of disturbed sleep and alertness in PD is quite rich. The diagnosis and treatment approaches for disturbances of sleep and wake cycles have been presented in several well-written reviews (Amara et al., 2017; Loddo et al., 2017). It is worth emphasizing that further work is needed to develop new and optimize existing PD-specific diagnostic tools for disorders of sleep and wake. There is an overwhelming lack of effective, evidence-based treatments of sleep dysfunction in PD (Seppi et al., 2019). This dictates the need for clinical investigations of sleep therapeutics in PD. Sleep may be an important therapeutic target for alleviating both motor and non-motor manifestations of PD. These approaches may also have favorable effects on the disease progression itself.

Huntington's Disease

Huntington's disease (HD) is a progressive neurodegenerative disease characterized by movement deficits, cognitive deterioration, and psychiatric symptoms. Sleep disturbances are common in HD and affect up to 90% of patients. Despite its common occurrence in HD, sleep disorders have not been so thoroughly investigated as in other neurodegenerative disorders (Zhang et al., 2019). Although disturbed sleep in HD correlated with its severity and duration of illness, poor sleep has been reported in the early stages of the disease, even among asymptomatic carriers of the HD mutation (Arnulf et al., 2008; Lazar et al., 2015). Polysomnography in HD reveals fragmented sleep with reduced N3 stage and increased sleep spindle density (Wiegand et al., 1991). REM sleep appears to be reduced in HD, although this finding has been not replicated in all studies (Hansotia et al., 1985; Wiegand et al., 1991). RBD has been reported in HD (Videnovic et al., 2009). Poor sleep may be associated with depression and other neuropsychiatric manifestations of the disease (Videnovic et al., 2009). This emphasizes the need for timely diagnosis and aggressive treatment of disturbed sleep in patients with HD.

Diagnosis of disorders of sleep and wake in the HD population relies on instruments and tests used in general sleep medicine. Complexities of HD that influence sleep patterns in this population necessitate the development of novel assessment methods for sleep and alertness in HD. There is a paucity of therapeutic studies that focused on disturbed sleep in HD. Managing sleep disfunction is further complicated by complex medication regimens that include medications that may negatively impact sleep and/or daytime alertness. Non-pharmacological strategies such as physical exercise may be a promising approach in the management of sleep dysfunction in HD (Mueller et al., 2019).

CONCLUSION AND PERSPECTIVES

Sleep and circadian rhythms are interconnected and all-encompassing physiological systems that affect virtually all biological functions. Unsurprisingly, circadian disruption can precipitate considerable impairments on human health. In neurogenerative diseases, although it is well established that sleep and circadian dysfunctions are both a consequence of and a causal factor of neurodegenerative processes, holistic

investigation of clocks, sleep and neurodegeneration is still in its infancy. The extent of neuropathological dysfunctions in sleep and circadian neural centers is still not fully understood. Additionally, the exact role of clock genes in the regulation of cellular function in different brain structures and peripheral organs is unknown. The accelerating progress in this field is holding promising insights into the development of efficient therapies for improving health condition in patients with neurodegenerative diseases. Chronotherapies such as the use of timed bright light therapy is a recent example of how fundamental research in this field have yielded positive outcomes in patients with neurodegenerative disorders (Fifel and Videnovic, 2018, 2019).

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Both authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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