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ORIGINAL ARTICLE

Sleepless Night and Day, the Plight of Progressive Supranuclear Palsy

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Objectives: To elucidate the unique sleep and waking characteristics in progressive supranuclear palsy (PSP), a neurodegenerative disease associated with motor deficits and dementia that largely affects the brainstem and thalamic regions.

Methods: A total of 20 PSP and 16 healthy older adult controls participated in this study. The participants underwent an overnight polysomnography and multiple sleep latency test (MSLT) the following day. Prior to the MSLT last trial, they were asked to complete the Stanford Sleepiness Scale. Data were assessed for measures of latency to sleep onset, sleep duration, waking, and sleep staging during the night. Mean sleep latency, a measure of daytime sleepiness, sleep onset rapid eye movement (REM) periods, and microsleeps were studied with the MSLT. Spectral analysis of wake electroencephalogram (EEG) was performed for 30-second periods at the start of each MSLT trial.

Results: PSP took significantly longer time to fall asleep ($p < .001$), slept less during the night ($p \leq .001$), and had more wake after sleep onset than controls ($p \leq .001$). PSP had less N2 sleep ($p < .05$) and N3 sleep ($p < .05$), and REM sleep ($p < .001$) than controls. During the MSLT, PSP took significantly longer to fall asleep ($p < .001$), did not have microsleeps when they remained awake throughout the assessment periods, but were subjectively sleepier than controls ($p < .05$). Gamma power was increased during wake EEG in PSP ($p < .01$).

Conclusions: Sleep/waking regulation and REM sleep regulation are disrupted in PSP, leading to profound sleep deprivation without recuperation. Our findings suggest a diminished homeostatic sleep drive in PSP. This hyperaroused state is unique and is a severely disabling feature of PSP.

Keywords: multiple sleep latency test, spectral analysis, hyperarousal, homeostatic sleep drive, neurodegenerative disease.

Statement of Significance

Sleep is often disrupted in neurodegenerative disease and dementia, and is typically a key stressor for patients and caregivers. Unique to progressive supranuclear palsy (PSP), a neurodegenerative disease, the neuroanatomical areas typically affected generally overlap with those that regulate sleep/wake behavior. This study highlights that PSP is associated with profound sleep/waking disturbance, disrupted rapid eye movement and slow wave sleep, and decreased homeostatic sleep drive across the 24-hour period. To date, our understanding of sleep/wake regulatory networks has been predominantly based on animal research; however, although our study is observational, our findings suggest that with further efforts, PSP could uniquely help elucidate the role of the brainstem and thalamic regulatory networks during sleep in humans. Furthermore, understanding sleep/wake physiology in PSP can help direct approaches for treating sleep disruption in this disorder.

INTRODUCTION

The overarching goal of this study is to establish the initial steps in a more thorough investigation of mechanisms of sleep/wake regulation in a neurodegenerative disease starting with progressive supranuclear palsy (PSP), which targets brainstem areas. The current sleep/wake regulation working model describes a network of feedback loops mostly centered on neurons and nuclei in the hypothalamic and brainstem regions (e.g., see Refs.[1] and[2]). This model has been developed largely through the study of animals, and there is often little opportunity to study the effects of altered structure/function relationships in these brain regions in humans. The reliably predictable brainstem neuroanatomy of PSP offers a unique opportunity to probe sleep in humans. PSP is a progressive neurodegenerative disease, characterized by slowed saccades, vertical supranuclear gaze palsy, postural instability, and increased falls.[3] PSP is a 4-repeat (4-R) tauopathy. Specifically relevant to sleep/waking regulation, brain imaging of PSP and neuropathology indicates selective vulnerability of the pons and midbrain.[4]

There is similar histopathology across the PSP subtypes[5] with neuronal loss observed in basal nucleus of Meynert, globus pallidus, subthalamic nucleus, thalamic intralaminar nuclei, and brainstem. More specifically, brainstem regions affected include superior colliculus, periaqueductal gray matter, oculomotor nuclei, substantia nigra, dorsal raphe nucleus, locus coeruleus, pedunculopontine nucleus, pontine nuclei, vestibular nuclei, medullary tegmentum, and inferior olives.[3,5–13] These same brain regions house much of the sleep/waking regulation system (e.g., see Ref.[1]), in particular, the ascending reticular activating system and a rapid eye movement (REM) sleep regulating system. Based on the overlapping anatomical regions between sleep and PSP, it is plausible that sleep/wake and REM sleep regulation would be altered in PSP.

Despite the common areas involved in sleep regulation and PSP degeneration, previous research on sleep in PSP is limited. Sleep disturbances, in particular, subjective insomnia and daytime sleepiness, have been described in 60% of PSP baseline assessments,[14] and we have found weaker rest-activity rhythms in PSP.[15] These studies might collectively suggest that weaker nighttime and daytime rhythms may result in increased sleep during the day and decreased sleep at night. To date, there have been only two overnight polysomnography (PSG) studies investigating sleep in

PSP compared with healthy controls.[16,17] These studies described disrupted sleep in PSP, with increased non-REM (NREM) stage (N)-1 sleep and decreased REM sleep.[16,17] Although both studies did a multiple sleep latency test (MSLT), they found widely varying results within their participants and neither study compared PSP with healthy controls. Although a few participants with PSP had short mean sleep latencies, most of the participants in both studies had normal or prolonged sleep latencies.

The overarching goal of this study was to utilize an observational study paradigm to elucidate sleep/wake regulation and sleep architecture characteristics in PSP compared with healthy controls. We pursued this by performing overnight PSG and MSLT the following day in PSP and healthy controls. Based on the previous literature and the brain areas affected in PSP, we predicted increased sleep disturbance in PSP and disrupted REM sleep. Furthermore, we hypothesized that PSP would have shorter mean sleep latencies on the MSLT compared with controls, as they worked to recover sleep loss. Therefore, in contrast to previous studies investigating sleep in PSP, following this study, we would better understand sleep propensity across the 24-hour period in PSP relative to healthy older adults. In particular, our study extends prior findings by comparing PSP with healthy controls on the MSLT, enriching our understanding of the sleep/wake disruption during the day paired with the prior night's sleep pattern in PSP. Finally, to help interpret the MSLT findings, we included a spectral analysis of wake electroencephalogram (EEG).

METHODS

Sample

Participants were recruited from ongoing studies at the University of California, San Francisco (UCSF) Memory and Aging Center's (MAC) longitudinal studies (Frontotemporal Dementia: Genes, Imaging and Emotions or 4 Repeat Tauopathy Neuroimaging Initiative, and UCSF Healthy Aging Cohort). As part of these longitudinal studies, participants underwent comprehensive evaluations, including a neurological examination, neuropsychological assessment, and an informant interview. Consensus diagnoses were made by a team of neurologists, nurses, neuropsychologists, and trained support staff at the MAC. Epilepsy, active neoplastic disease, and active substance abuse were exclusionary for both groups. Individuals with a diagnosis of possible or probable PSP diagnosis based on the Litvan criteria[3] were approached for this study. Recruitment for this study was from October 2013 until March 2016. Twenty individuals with a diagnosis of possible or probable PSP took part in this study; however, technical issues corrupted data for one participant, leaving a final total of 19 PSP (13 men and 6 women; mean age: 70.95 ± 5.3 years; the PSP clinical variants included were 15 Richardson's syndrome [PSP-RS], 2 progressive gait freezing [PSP-PGF], 1 Parkinsonism [PSP-P], and 1 postural instability [PSP-PI][18]).

Healthy older adults were identified as those individuals with no evidence of neurodegenerative disease and were recruited from the UCSF Healthy Aging Cohort. Participants were prescreened for an apnea hypopnea index (AHI) less than 10 measured using an Apnealink plus (ResMed) to optimize selection of healthy older adults with relatively healthy sleep and a low risk of sleep apnea. The demographics for the final healthy older adult control cohort for this study were 7 males and 9 females, with a mean age of 72.50 ± 3.8 years. This study was approved by the UCSF Institutional Review Board (IRB). All participants gave informed consent prior to starting the study.

Study Design

Participants completed a series of questionnaires and assessments through co-enrolled studies. Once enrolled in the current study, participants underwent an overnight PSG assessment and a MSLT the subsequent day in the Clinical Research Center at UCSF. Participants maintained their usual medication regimen throughout the 24-hour study.

Demographics: CDR, Self-reported Disease Duration, and PSP Rating Scale

Through the on-going co-enrolled studies and current study, measures of age, global cognition (Mini Mental State Examination, MMSE[19]), self-reported depression (30-item Geriatric Depression Scale, GDS[20]), and the clinical dementia rating scale (CDR[21]) were gathered and available for the majority of our participants. In individuals with PSP, both a subjective report of disease duration and the PSP rating scale (PSPRS[22]), a measure of disease severity, were acquired. The subjective report was gathered from the caregiver/informant(s) during the informant interview, available medical records, and the patient history during the neurological assessment. Informants were asked about when symptoms were observable and their approximate date of onset. The range of the PSPRS scale is between 0 and 100, where more severe disease symptoms are given a higher score.

Polysomnography

Nocturnal PSG and video were digitally recorded at 400 Hz using a portable sleep monitoring system (Beehive®Horizon, Grass Technologies) and, in a single case, an ambulatory recorder (Trea®Ambulatory; Grass Technologies) was used. Recording parameters consisted of six EEG (F3, F4, C3, C4, O1, and O2) referenced to contralateral mastoids (M1 and M2), six EOG (Fp1,Fp2, below, and lateral to E1/E2), three mentalis/submentalis EMG, four bilateral EMG on the anterior tibialis, four bilateral EMG on the extensor digitorum, a 2-point EKG, two respiratory effort belts using inductance plethysmography on the chest and abdomen, a thermistor and nasal cannula pressure transducer, and a pulse oximeter for detection of oxygen desaturation events.

The overnight PSG was used to identify the presence of sleep disorders, in particular, sleep apnea and periodic limb movements in sleep (PLMS). Further measures of interest were latency to sleep onset, arousal index and number of awakenings, wake after sleep onset, total sleep time, sleep efficiency, sleep maintenance, and percent time in N1 sleep, N2 sleep, N3 sleep, and REM sleep. To better understand possible differences in REM sleep, latency to REM sleep and the number of REM sleep episodes were also studied.

Multiple Sleep Latency Test

The MSLT assesses the propensity to fall asleep across the day and is typically used to identify the presence of narcolepsy, with short mean sleep latencies and the presence of sleep onset REM periods.[23] During the MSLT, participants laid in a dark, stimulus-free room for five 20-minute nap trials at 9 am, 11 am,

1 pm, 3 pm, and 5 pm. If a participant entered sleep for more than 15 seconds, the MSLT was extended an additional 15 minutes in order to detect sleep onset REM periods. No napping prior to the first trial or between trials was allowed. The measures of interest on the MSLT are mean latency to sleep onset and the number of REM sleep episodes during the nap period. On trials where participants did not fall asleep, the data were assessed for the presence of microsleeps (1–15 seconds of sleep). Prior to the final nap, the Stanford Sleepiness Scale (SSS[24]) was used to attain a subjective report of how sleepy the participant felt they were. The SSS is an 8-point scale with the participant selecting 1 if they are alert and wide awake, to 7 if they feel they are no longer fighting sleep or are having dream-like thoughts, with the lowest score (eighth point) for those who are asleep.

Spectral Analyses

A 30-second artefact-free epoch was selected during wake, eyes closed EEG during each MSLT trial to obtain the EEG spectral power analyses from channels F3, F4, C3, C4, O1, and O2 using polygraphic recording analyzer (PRANA, PhiTools) to visualize and process the data with DFT/FFT, 4-second Hanning window, and 50% overlap. The measures of interest for spectral analyses were power within delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–15 Hz), beta-1 (15–23 Hz), beta-2 (23–30 Hz), and gamma (30–45 Hz) energy bands.

Statistics

Within each measure of interest (e.g., total sleep time, or percent time spent in N1), an individual participant's data point was removed as an outlier if it was more than 3 standard deviations from the group's mean for that measure. Fisher's exact tests were used to test for group differences in gender, the incidence of sleep apnea, and both the periodic limb movement index (PLMI) and arousal index (AI). Effect sizes for Fisher's exact tests are reported as phi (ø). Otherwise, either Mann–Whitney *U* or Spearman's rho nonparametric analyses were used wherever appropriate. Nonparametric effect sizes were calculated for the Mann–Whitney test as *r* ($r = z/\sqrt{n}$), with the reported interpretation similar to Cohen's *d*.

To determine whether dopaminergic use contributed to the altered sleep/wake regulation in PSP, measures of increased wake or arousal were examined using dopaminergic use as a between-group measure. Monoamine oxidase (MAO) inhibitors can be associated with decreased REM sleep; thus, measures of REM sleep were reanalyzed excluding the individual PSP who used an MAO inhibitor, to ensure that the MAO inhibitor was not affecting the results. In general, antidepressants can alter the amount of REM sleep; therefore, we further analyzed the data comparing (i) PSP with and without antidepressants and (ii) PSP without antidepressants and healthy controls to ensure that our findings in REM sleep were not driven by antidepressant use.

RESULTS

Demographics

There were more males in the PSP cohort, but this difference was not significant ($p > .1$), and there were no significant age differences between the two groups (see Table 1). As expected, PSP had higher CDR values ($U = 0$, $[Z = -3.85]$, $p < .001$, $r = 0.77$), a lower MMSE ($U = 8.5$, $[Z = -4.63]$, $p < .001$, $r = 0.81$), and used more medications than healthy controls. Nine of the 19 PSP participants used dopaminergic medications, and one participant also used a MAO inhibitor (see Table 1). Ten PSP participants also used antidepressants/anxiolytics (five used a SSRI, one a tricyclic, four used other antidepressants, and one also used benzodiazepines during the day) and six used sleep medications (two used trazadone, three used benzodiazepines at night, and one used melatonin).

Identification of Sleep Disorders

Overall, PSP had more sleep disorders than healthy controls. The healthy controls were prescreened for an AHI less than 10 using an apnealink plus; however, two controls had AHI above 10 during the PSG, and four PSP (see Table 2). In addition, two PSP had previous diagnoses of sleep apnea and wore their CPAP during testing (AHI under 10 during testing). The incidence of PLMs ($p < .05$, Ø = 0.42) and abnormal arousal rates ($p < .01$, Ø=0.5) were increased in PSP as compared with controls.

Table 1—Demographics.

	Controls	PSP	*p*
N	16	19	
Gender (male, *n*)	7	13	.18
Age (years)	72.50 ± 1	70.94 ± 1	.57
MMSE	29.27 ± 0.3	23.06 ± 0.9	<.001
CDR Box score	0	3.67 ± 0.6	<.001
PSPRS	–	39.9 ± 4	
Estimated disease duration ≤5 years (*n*)	–	6	
Dopaminergic (*n*)	0	9	
Antidepressants (*n*)	0	10	
Sedative (*n*)	0	6	

Data are presented as mean ± SEM, unless otherwise indicated. A dash indicates that the measure was not assessed in that cohort. Estimated disease duration is reported as the number of individuals whose informant(s) reported possible symptoms starting in the past 5 years.

Table 2—Incidence of Sleep Disorders.

	Controls	PSP	*p*
Sleep apnea (AHI ≥ 10)	2/16 (12.5%)	6/19[a] (32%)	.43
Periodic limb movements index (PLMI ≥ 25)	2/16 (12.5%)	10/19 (52.6%)	<.05
Arousal index (AI ≥ 28)	0/16 (0%)	7/19 (36.8%)	<.01

Data are presented as the number and ratio of individuals within the group who presented with the sleep disorder at the indicated cutoff. [a]In addition to the four individuals with PSP that we detected had sleep apnea, two additional individuals had previous diagnoses of sleep apnea and wore their CPAP like all other nights, during PSG testing.

Sleep Staging from Overnight PSG

Overall compared with controls (Con), PSP has disrupted sleep/wake regulation with decreased sleep efficiency (Con 76.00 ± 3.5%, PSP 50.78 ± 4.3%, $U = 32$, $Z = -3.83$, $p < .001$, $r = 0.66$) and sleep maintenance (Con 78.33 ± 3.3%, PSP 57.81 ± 4.3%, $U = 48$, $Z = -3.44$, $p < .001$, $r = 0.58$). PSP patients took significantly longer to fall asleep ($U = 37$, $Z = -3.55$, $p < .001$, $r = 0.62$, see Figure 1), were awake longer during the night (minutes $U = 56.5$, $Z = -2.86$, $p < .01$, $r = 0.50$, percent of the sleep period time [SPT] $U = 43$, $Z = -3.20$, $p \leq .001$, $r = 0.67$), and had less total sleep time during the night ($U = 46$, $Z = -3.24$, $p = .001$, $r = 0.56$) as compared with healthy older adult controls. This suggests that overnight sleep/wake regulation is disrupted in PSP.

When asleep, there was no difference in the amount of N1 sleep (see Figure 2 and Table 3); however, PSP had significantly less time in N2 sleep (minutes $U = 68$, $Z = -2.45$, $p < .05$, $r = 0.43$, percent of SPT $U = 87$, $Z = -2.15$, $p < .05$, $r = 0.36$) and less time in N3 sleep (minutes $U = 74$, $Z = -2.23$, $p < .05$, $r = 0.39$, percent of SPT $U = 98.5$, $Z = -1.77$, $p < .1$). PSP appears to have disrupted REM sleep regulation. PSP took longer to enter REM sleep ($U = 45$, $Z = -3.12$, $p \leq .001$, $r = 0.55$), had fewer REM sleep episodes ($U = 52$, $Z = -3.09$, $p < .01$, $r = 0.54$), and overall less time in REM sleep (minutes $U = 25$, [$Z = -3.88$], $p < .001$, $r = 0.69$, percent of SPT $U = 47$, $Z = -3.48$, $p < .001$, $r = 0.59$) compared with healthy controls (when the individual with PSP-PI was removed from the PSP cohort, our findings remained). Removal of the individual using an MAO inhibitor did not alter the REM sleep findings. We found no statistical differences in measures of REM sleep comparing PSP using antidepressants and PSP not using antidepressants. Furthermore, when only PSP not using antidepressants were compared with healthy controls, the finding of decreased REM sleep in PSP was not altered.

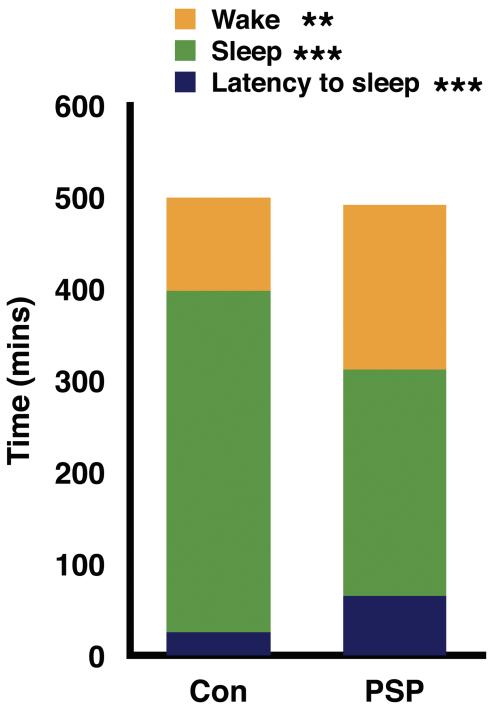

Figure 1—PSP have difficulty sleeping during the night. The number of minutes it took both healthy older adult controls (Con) and PSP to fall asleep (blue), total sleep time (green) and wake during the sleep period time (orange) is shown in minutes. **$p \leq .01$, ***$p \leq .001$.

Daytime Sleepiness Assessment

Two PSP and one control subject did not have one of the five nap recordings due to technical difficulties or participant factors. During the MSLT, all controls (14/14) fell asleep during the nap opportunities, with only two individuals remaining awake across four of the assessment periods. In contrast, 36% of the participants with PSP (5/14) remained awake across at least four of the nap opportunities provided. Therefore, overall, PSP took longer to fall asleep as compared with controls ($U = 23$, $Z = -3.45$, $p < .001$, $r = 0.65$, see Figure 3 and Table 3). Even after removing those that remained awake throughout the MSLT assessment, the remaining PSP group still took significantly longer to fall asleep ($U = 23$, $Z = -2.75$, $p < .01$, $r = 0.56$) (when the individual with PSP-PI was removed from the PSP cohort, our findings remained). Of those that fell asleep, 2/10 PSP had two REM sleep periods during the nap trials. In those individuals that did not fall asleep during any of the MSLT trials, no microsleeps were detected upon inspection of the waking profiles. In contrast to the MSLT findings, PSP reported higher levels of sleepiness based on the SSS on the MSLT day ($n = 11$, 3.82 ± 0.4 units) as compared with controls ($n = 14$, 2.46 ± 0.2 units, $U = 37.5$, $Z = -2.24$, $p < .05$, $r = 0.45$). The SSS was assessed immediately prior to the last MSLT trial, during which no PSP fell asleep.

Daytime Spectral Analysis of Wake Eyes Closed EEG

During the average wake eyes closed EEG across the testing periods, healthy older adults had higher delta power on central

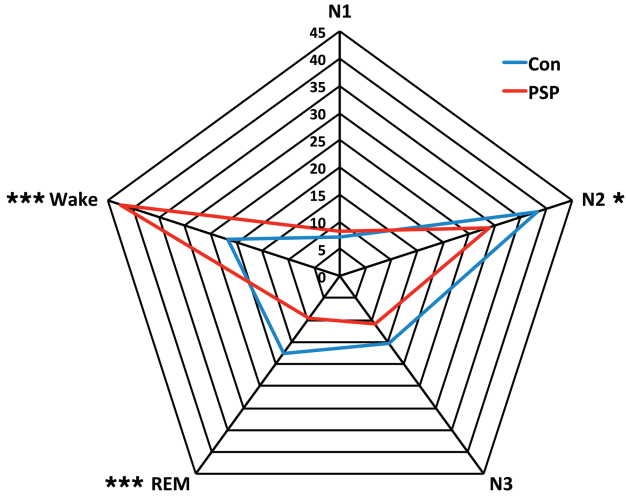

Figure 2—Percent time in sleep and wake during the sleep period time. The time of each sleep stage (N1, N2, N3, and REM) and waking (Wake) is shown as a percent of the sleep period time (time of the start of the first sleep stage to the end of the last sleep stage). Data are shown as the mean for Con (blue) and PSP (red). *$p < .05$, ***$p \leq .001$.

Table 3—Measures of Sleep and Waking During the PSG and MSLT.

	Controls	PSP	*p*
Sleep efficiency	77.11 ± 13.4	50.76 ± 18.8	<.001
Sleep maintenance	78.33 ± 13.1	57.81 ± 18.7	<.001
Sleep latency (minutes)	10.2 ± 8.0	56.39 ± 58.8	<.001
Total sleep time (minutes)	371.75 ± 80.0	247.00 ± 103.04	≤.001
Wake (minutes)	117.81 ± 70.4	250.62 ± 113.0	<.001
Wake during sleep period time (minutes)	102.06 ± 62.1	179.32 ± 91.4	<.01
N1 (minutes)	34.06 ± 14.4	37.18 ± 18.3	.87
N2 (minutes)	182.84 ± 56.8	121.82 ± 69.9	<.05
N3 (minutes)	71.31 ± 29.9	47.0 ± 34.4	<.05
REM (minutes)	83.53 ± 32.4	37.47 ± 18.0	<.001
Latency to REM (minutes)	71.07 ± 21.9	149.18 ± 100.8	≤.001
REM episodes (count)	4.25 ± 1.5	2.71 ± 1.3	<.01
MSLT (minutes)	11.66 ± 4.8	17.63 ± 2.1	<.001
SOREMs (count)	0	2/14 participants had two episodes	

Data are presented as mean ± SD, unless otherwise indicated.

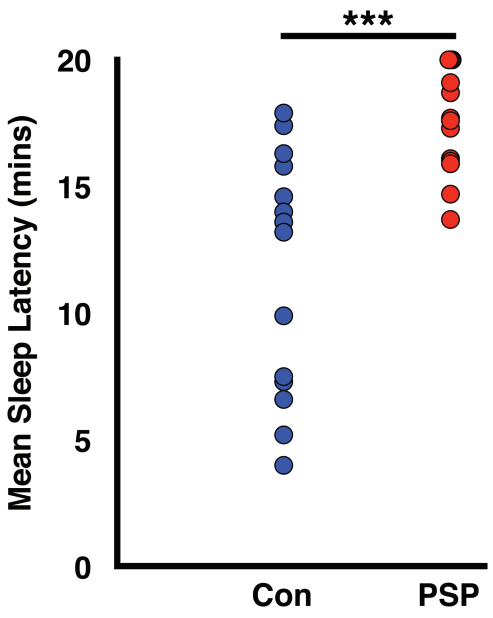

Figure 3—Average latency to sleep during the MSLT. The average time to fall asleep across the MSLT trials is shown in minutes for each individual of both the Con (blue) and PSP (red) groups. ***$p < .001$.

($U = 10$, $Z = -2.81$, $p < .01$, $r = 0.63$), frontal ($U = 16$, $Z = -2.61$, $p < .01$, $r = 0.57$, see Figure 4), and occipital ($U = 17$, $Z = -2.39$, $p < .05$, $r = 0.53$) channels as compared with PSP. Furthermore, gamma power was increased in PSP as compared with older adults on both central ($U = 6$, $Z = -2.83$, $p < .01$, $r = 0.69$) and frontal ($U = 3$, $Z = -3.18$, $p = .001$, $r = 0.77$) channels, and higher beta-2 power was present in PSP as compared with older adults on the occipital ($U = 22$, $Z = -2.09$, $p < .05$, $r = 0.47$) channels. There was no group × time interaction indicative of an assessment effect involving power. Average delta power was negatively correlated with the average mean sleep latency (rho: −0.507, $p < .05$ on central channels, rho: −0.594, $p < .01$ on occipital channels), whereas average gamma power was positively correlated with the average mean sleep latency (rho: 0.546, $p < .05$ on central channels, rho: 0.683, $p < .01$ on frontal channels).

Assessing the Potential Influence of Dopaminergic Use on Arousal in PSP

PSP participants were divided into two cohorts via dopamine agonist use. The two groups ($n = 9$ for use, $n = 10$ for nonusers) were compared on measures indicating increased arousal, specifically: sleep onset latency, total sleep time, wake after sleep onset, sleep efficiency, mean sleep latency during the MSLT trials, and gamma power during daytime wake eyes closed EEG. No group differences were observed for any comparison reported ($p \geq .67$ for all measures), suggesting that use of dopaminergic medications did not exacerbate or increase arousal in the PSP cohort tested here.

DISCUSSION

The present findings demonstrate greater overnight sleep disruption, with profoundly diminished total sleep times in PSP compared with controls with respect to both difficulties falling and remaining asleep. Contrary to our initial hypotheses, PSP patients did not sleep during the day and did not show prolonged latency to sleep on the MSLT compared with controls. MSLT findings were incongruent with subjective sleepiness but were positively associated with wake EEG gamma levels.

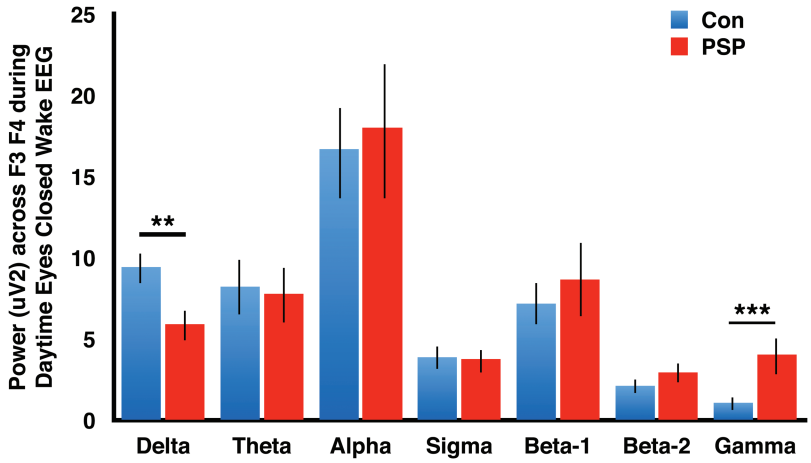

Figure 4—Spectral analysis of frontal channels during wake EEG. Power within each energy bandwidth of interest is shown as mean ± SEM for both Con (blue) and PSP (red). $^{**}p < .01$, $^{***}p < .001$.

Together, the daytime and nighttime data indicate that sleep/wake regulation mechanisms are profoundly disrupted in PSP. In particular, PSP did not appropriately respond to the accrued overnight sleep debt during the daytime nap opportunities raising the question about retained sensitivity to the homeostatic sleep drive. The homeostatic sleep drive is a term used to describe an increase in pressure to sleep during wakefulness; therefore, the longer someone is awake, the stronger the drive or pressure to sleep is (for review of how the homeostatic sleep drive, circadian system, and sleep regulatory systems work together, see Ref.[25]). REM sleep regulation was also disrupted in PSP as compared with controls during overnight sleep, and in some cases also during the daytime MSLT with the occurrence of REM sleep periods during the nap opportunities.

This study replicates and extends the findings of previous reports on sleep in PSP compared with healthy older adults.[16,17] The total sleep time and sleep efficiency reported in our study are near identical to that reported in the study of Montplaisir et al.[16] and were more disrupted compared with the study of Arnulf et al.[17] Similar to our study, Arnulf et al.[17] also described an increased incidence of sleep disorders, in particular, increased AHI, PLMI, and AI in PSP as compared with controls.

Individuals with PSP had profound difficulties sleeping at night. To put their impairments into perspective, their observed sleep measures (sleep efficiency, sleep latency, total sleep time, and wake after sleep onset [WASO]) were more negatively impacted than those generated from an insomnia-based meta-analysis.[26] It is possible that the disrupted sleep patterns observed in PSP are not directly due to the impact of PSP on neuroanatomical areas controlling sleep, but the indirect effect of both motor and non-motor PSP symptoms disrupting sleep. It is also possible that sleep in PSP is not as disrupted as it appears on overnight PSG assessment, and that PSP has a delayed circadian rhythm, thus reducing their drive for sleep during the actual PSG assessment period. We recently described weaker circadian rhythms with unaltered circadian phase between PSP and healthy older adult controls,[15] suggesting that the previous interpretation is not valid, and that a phase difference did not contribute to the lack of sleep observed on testing. To account for possible circadian effects, we intentionally maintained the typical lights-off period for each individual participating in the current PSG study. This approach was intended to reduce any circadian effect at the start of the study. Therefore, our study highlights the profound sleep deprivation that individuals with PSP undergo.

Our study described MSLT findings in both PSP and controls. As compared with the expected values for MSLT mean sleep latencies (11.6 ± 5.2 minutes),[27] some of the healthy older adults assessed in this study entered sleep faster than expected. However, as noted by both Littner et al.[27] and Levine et al.,[28] MSLT values can be affected by age. The expected "normal" values currently used were established using an age cohort of 18–80 years. Furthermore, healthy individuals with no signs of excessive daytime sleepiness can fall asleep within 5 minutes during the MSLT.[28,29] Therefore, given that our healthy older adult cohort had an age range of 68–80 years, at the upper age limit of the cohort used to establish the expected normal values, it is possible that the faster mean sleep latencies observed in some of our healthy older adult cohorts is not indicative of a pathological finding. Therefore, our results comparing MSLT in PSP with healthy older adults emphasize the overall lack of sensitivity to sleep debt and disrupted homeostatic sleep drive. This is demonstrated in PSP with prolonged mean sleep latencies during the day following relatively disrupted sleep at night. With an intact homeostatic sleep drive, the pressure to sleep or recuperate sleep debt when given nap opportunities during the day should result in shorter mean sleep latencies. In addition, however, to the prolonged latency to sleep during the day, about 30% of our PSP participants remained awake the entire five 20-minute trials, in contrast to 0% of the controls. To determine whether we were missing small bouts of sleep during the MSLT, we looked for the presence of microsleeps during the MSLT trials for those who remained awake throughout the assessments and found none. This was further indication that some of the PSP cohorts were not attempting to recuperate lost sleep.

The increase in gamma power during the task-free 6-channel EEG measurement was unexpected due to both the disrupted sleep the previous night in PSP and prior reports in Parkinson's

disease showing increased theta power and decreased beta power, with decreased gamma in those with dementia.[30–32] However, our findings showed decreased delta power and increased gamma power in PSP, reflecting a shift of the spectral power to the right in PSP (see Figure 4). It is possible that the differences described in the literature and our study are disease or methodology-specific. This increased gamma power in wake EEG along with the prolonged mean sleep latencies in PSP could suggest that increased arousal interfered with sleep. It is possible that the presence of the increased gamma power during wake EEG, described in our study, over-rides the participant's subjective sleepiness, inhibiting them from sleeping. Although a positive association between gamma power and average mean sleep latency was described, it does not indicate a causative but a correlative association. In a study of insomniacs,[33] they also reported incongruent findings between the SSS and nap length, and suggested that hyperarousal overtook fatigue or subjective sleepiness. In our cohort, increased arousal or hyperarousal appears to persist across the 24-hour period and is likely an effect of altered homeostatic sleep drive.[34]

Beyond the disruption in sleep/wake regulation in PSP, and apparently altered homeostatic sleep drive, we also found differences in the sleep stages themselves. Specifically, we found disruption in REM sleep regulation, similar to previous reports.[16,17] In contrast to the other two studies, we also described decreased N2 and N3 sleep in PSP. It is unclear whether the diminished NREM sleep results from the interplay of both the disrupted sleep/wake and REM sleep regulatory systems, or if a regulatory system specific to NREM sleep is affected in PSP.

This study highlights the profound sleep loss in PSP; however, it remains unclear what the specific neuroanatomical changes are in PSP that result in the altered homeostatic sleep drive we observed. Further research is needed to link the observed clinical sleep changes with the affected nuclei through pathological investigation. Based on our findings and the current understanding of sleep/wake regulation systems, we propose the following mechanistic interpretation of the current sleep model: monoaminergic loss in the locus coeruleus, dorsal raphe, and tuberomammillary nucleus, and cholinergic loss in the magnocellular nucleus leads to decreased slow-wave activity,[35] a primary measure of homeostatic sleep drive; basal forebrain cholinergic loss will be associated with diminished homeostatic sleep drive,[36] in particular, the depletion of delta power[37]; galaninergic neuronal loss within the intermediate nucleus (human VLPO homologue) and gabaergic/glycinergic loss in the parafacial zone[38,39] will be associated with an increased wake after sleep onset.

Possible limitations of the study include the screening out of significant sleep apnea prior to PSG in the control group and the continued use of the participants usual medications. We did not exclude apnea in the PSP cohort because we considered that apnea could be causally related to the neurodegenerative process. We contend that the prolonged sleep latencies on the MSLT and evidence for EEG hyperarousal in PSP are all the more remarkable, given the higher prevalence of apnea in this group. Furthermore, many of the medications used in the PSP cohort would probably improve overall sleep time and promote daytime somnolence, which is directly in contrast to the observed findings. The clear exception is dopaminergic medications, which are frequently prescribed to clinical populations, whom also have pronounced sleep disruptions such as individuals with Parkinson's disease (cf. Ref.[40]) or multiple system atrophy (cf. Refs.[41] and[42]). However, the mechanism(s) of such medications in these groups remains unclear, as they may reduce sleep disruption through the management of motor disturbances or increase nighttime arousal and daytime somnolence.[43,44] Our subgroup analysis revealed that dopaminergic use did not affect the hyperarousal measures. It is possible that patients who have been able to remain on dopaminergics may be more tolerant to the effects of these drugs on sleep-wake measures. Investigation to determine whether using a MAO inhibitor contributed to the observed reduced REM sleep showed that the individual using this medication did not contribute to the reported PSP versus control differences in REM sleep. Furthermore, we continued to find the decreased REM sleep in PSP when comparing PSP not using antidepressants with healthy controls. This indicates that the disrupted REM sleep was disease related as opposed to the influence of antidepressant use. Therefore, overall, the results reported in this study were not driven by drug-related interactions within the PSP cohort.

The profound sleep issues observed in PSP may occur prior to diagnosis, given the overlap between sleep regulating regions and those areas affected early in PSP. Prior research has indicated that PSP patients do not appear to have insight into the level of sleep disturbance they have when providing subjective reports on their sleep.[45] Therefore, solely relying on asking a PSP patient about the level of sleep disturbance, they have or had in the past will probably result in under-reported sleep disturbance. The incorporation of a follow-up annual assessment to determine how objective sleep patterns change with disease progression appears to be warranted. Understanding this may help identify the key markers of hyperarousal that can be used as outcome measures to determine whether an intervention is altering the symptoms of disease. It is possible that improving sleep duration and continuity at night may improve disease symptoms and possibly even stave off or slow disease progression. Furthermore, better understanding the progression of the PSP related sleep/waking patterns and when they first occur could indorse screening for this marker of PSP in insomniac populations. Lastly, our data may offer translational significance, with further investigation to identify the neural substrates associated with specific sleep markers; the clinical sleep changes may highlight therapeutic avenues in optimally treating PSP sleep disruption through targeted interventions. For example, if gabaergic neuronal loss in the parafacial zone is noted in clinicopathological comparisons to be associated with premortem increased wake after sleep onset, then this might inform the use of gabaergic drugs in this disorder. Re-engaging the homeostatic sleep drive and establishing stable sleep/wake cycles may improve both patients' and caregivers' quality of life.

SUMMARY

Similar to previous studies, we describe disrupted sleep/wake regulation and disrupted REM and slow wave sleep regulation during the night in PSP. We extended this field by describing prolonged latencies on MSLT, despite decreased nocturnal sleep time, and increased high frequency power during daytime EEG. Our novel findings suggest diminished homeostatic sleep

drive with increased arousal across the 24-hour period in PSP. Improving our understanding of how sleep/waking is affected in PSP may provide insight into possible regulatory mechanisms for this network in humans. Furthermore, understanding the particulars of altered sleep patterns in PSP may help develop interventions to stave off or delay disease progression, in particular, in light of the fourfold increase in death hazard associated with the presence of sleep disturbance at baseline presentation in PSP.[14] Future research is required to determine whether our findings are specific to PSP or generalize across 4-R tauopathy diseases. Based on our findings and the predicted neuroanatomical underpinnings, we would expect our findings to be specific to PSP. Our study further highlights the need for clinicopathological studies focused on PSP to help elucidate/support the predominantly animal-based model of sleep–wake regulation in humans.

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