Title: Alzheimer's Disease phenotypes show different sleep architecture

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INTRODUCTION: Sleep-wake disturbances are a prominent feature of Alzheimer's Disease (AD). Atypical (non-amnestic) AD syndromes have a different pattern of cortical vulnerability to AD. We hypothesized that atypical AD also shows differential vulnerability in subcortical nuclei that will manifest as different sleep dysfunction pattern.

METHODS: Overnight-EEG monitoring on forty-eight subjects, including 15 amnestic, 19 atypical AD and 14 controls. AD was defined based on neuropathological or biomarker-confirmation. We compared sleep architecture by visual scoring and power spectral analysis in each group.

RESULTS: Overall, AD cases showed increased sleep fragmentation and N1 sleep than controls. Compared to atypical AD groups, typical AD showed worse N3 sleep dysfunction and relatively preserved REM sleep.

DISCUSSION: Results suggest differing effects of amnestic and atypical AD variants on slow wave versus REM sleep, respectively, corroborating the hypothesis of differential selective vulnerability patterns of the subcortical nuclei within variants. Optimal symptomatic treatment for sleep dysfunction in clinical phenotypes may differ.

Keywords: Sleep; Alzheimer's Disease; Selective vulnerability; Neuromodulatory Subcortical Systems, Locus Coeruleus.

1. Introduction

Sleep alterations such as nighttime awakenings or daytime sleepiness are widespread among Alzheimer's Disease (AD) patients[1]. Sleep dysfunction negatively affects the patient's wellbeing and likely leads to greater cognitive decline[2], making sleep disturbances a leading cause of caregiver burden and early institutionalization in AD[3]. Despite their significant negative impact, sleep disorders in AD are still often misdiagnosed and undertreated[4]. Furthermore, the most used pharmacological treatments are non-specific, frequently causing adverse effects, warranting research to understand the neuronal basis of sleep dysfunction and improve treatment strategies[5].

AD is a biological-based diagnosis requiring deposits of beta-amyloid plaques and neurofibrillary tangles in a particular disposition[6]. In most cases, individuals with AD neuropathology initially manifest short-term memory deficits that later evolve to include other cognitive domains (amnestic e or typical phenotype). However, AD neuropathology can display a predominance of language, visuospatial or behavioral impairment instead of memory at early clinical stages (non-amnestic or atypical variants)[7].

The brain control of the sleep cycle includes a series of subcortical structures specializing in wake-promoting, REM and non-REM sleep-promoting, and circadian clock regulating functions[8]. Most of these nuclei develop AD neuropathological changes[8]. In particular, key components of the arousal system: *locus coeruleus* (the primary source of brain noradrenaline), orexinergic neurons of the lateral hypothalamic areas, and histaminergic neurons of the tuberomammillary nucleus, develop AD-type tau changes and degeneration even before the disease start developing in cortical regions[9–11]. In a study combining unbiased quantitative pathology with polysomnography, we recently showed that AD-related neurodegeneration of wake-promoting nuclei correlated with sleep dysfunction[12]. In vivo studies also show a link

among locus coeruleus integrity, noradrenergic dysfunction, and disruption of the sleep-wake cycles[13–15].

Although the neuropathological patterns of typical, amnestic and atypical, non-amnestic AD show similarities, the cortical tau spread and atrophy patterns are presentation-specific[7,16,17]. We recently disclosed a distinct pattern of neuropsychiatric features between amnestic and atypical AD variants, which suggests that subcortical nuclei of the neuromodulatory subcortical system (NSS) also show a different pattern of degeneration in AD clinical variants[5,18]. Indeed, scarce data available suggest distinct sleep features among AD clinical variants, another manifestation of a likely specific pattern of NSS degeneration.

We aimed to shed light on possible differences in sleep architecture between AD clinical phenotypes (amnestic/typical vs. non-amnestic/atypical), by investigating objective sleep metrics obtained via overnight video-electroencephalography (video-EEG) in a cohort of longitudinally followed, well-characterized AD cases. Cohort strengths include enrichment for atypical/non-amnestic variants, biomarker/autopsy-proven AD cases, and clinical data allowing us to account for potential effects of sleep modifiers such as anticholinesterase inhibitors, Selective Serotonin Reuptake Inhibitors and silent epileptiform activity.

Optimal symptomatic treatment of sleep disturbances requires a deep understanding of its specific neurobiological basis to modulate the correct combination of neurotransmission systems. Uncovering the differences in sleep alterations across AD variants is of utmost importance. Clinically, it will inform customized treatment. Biologically, polysomnography is a tool that can be used to discover sleep clinical features associated with different patterns of neuronal vulnerability in AD phenotype that can ultimately provide insights into the disease pathogenesis[5].

2. Materials and methods

2.1 Participants:

Forty-eight subjects, including 15 amnestic AD, 19 non-amnestic AD (9 lvPPA, 10 PCA) and 14 healthy controls were recruited at the Memory and Aging Center, UCSF, from 2008 to 2015. All data for this cross-sectional study were collected from a preexisting dataset designed to study epileptiform activity in AD[19]. The study was approved by the UCSF Institutional Review Board, and all participants gave their written, informed consent.

Twenty-two patients met the National Institute on Aging and Alzheimer's Association Research Framework biomarker-based diagnostic criteria for AD (19 amyloid-PET, 3 CSF AD biomarkers). Another 12 had a confirmed postmortem diagnosis of AD[6,20]. Based on the clinical presentation and the neuropsychological profile, participants were classified as amnestic/typical or non-amnestic/atypical variants based on the predominant memory or non-memory cognitive domains impairment. Atypical phenotypes included predominant impairments in visuospatial (PCA) and language (lvPPA).

Controls were required to have a Mini-Mental State Examination (MMSE) score of ≥28, a Clinical Dementia Rating (CDR) Sum of Boxes (CDR-SOB) score of 0, no cognitive concerns reported by themselves or their informants, age-appropriate pattern on brain magnetic resonance imaging (MRI), and no neurological disorders.

2.2. Neuropathological evaluation

Neuropathological diagnoses (n=12) were based on an extensive dementia-oriented postmortem assessment at the UCSF/ Neurodegenerative Disease Brain Bank[21]. Twenty-six

tissue blocks covering dementia-related regions of interest were dissected from the fixed slabs, and hematoxylin and eosin and immunohistochemical stains were applied following standard diagnostic procedures developed for patients with dementia. Neuropathological diagnosis followed currently accepted guidelines[21]. Overall severity of AD Neuropathologic Change (ADNC) was assigned using the National Institute on Aging (NIA)–Reagan criteria and NIA–Alzheimer Association criteria for AD[6].

2.3. Overnight long-term monitoring by video-electroencephalography

The methods for clinical sleep assessments are previously described[12]. All participants were evaluated at the Clinical and Translational Science Institute Clinical Research Center at Moffitt Hospital. The monitoring included long-term recording using silver cup electrodes in the standard international 10-20 electrode array and additional leads to record electrocardiography. EEGs included video telemetry recordings. After initial setup, participants were asked to hyperventilate for 3 minutes then rest and breath normally for 7 minutes with eyes closed. EEG recordings then continued overnight. Throughout the assessment, participants continued their usual medication regimen.

The long-term EEG monitoring data were exported to European Data Format (EDF) using Persyst 14 software, and sleep staging was performed in PRANA Production Suite 15.2 (Phi Tools, Strasbourg, France) following the American Academy of Sleep Medicine (AASM) criteria[22]. All studies were manually scored and reviewed by an experienced polysomnographic technologist (LY) and a trained neurologist (NF).

Electrode sites A1 and A2 were not available for all recordings. Therefore, the sleep staging montage was modified and re-referenced to contralateral temporal sites (T3, T4) post-recording

to achieve standardization across all participants using six scalp electrodes (F3-T4, F4-T3, C3-T4, C4-T3, O1-T4, O2-T3) and two modified EOG (Fp1-T4, Fp2-T3). High-pass filters were set at 0.3 Hz and low-pass filters at 35 Hz for EEG and EOG. Raw data were visually scored in 30-s epochs into Wake, Stage N1, Stage N2, Stage N3, and REM sleep. A visual spectrogram was created to compare against the staging hypnogram using RemLogic 3.4 (Natus Medical, Inc.San Carlos, CA) as a confirmation of wake and sleep periods.

Measures of interest were total sleep time (TST, min), wake after sleep onset (WASO, min), REM latency (min), sleep maintenance (%), and percent time in Non-REM N1 sleep (%), N2 sleep (%), N3 sleep (%), and REM sleep (%), during sleep period time (SPT) and TST. Note that SPT refers to the duration of time from sleep onset to final awakening (including WASO), while TST refers to the total amount of sleep time scored, excluding awake time (WASO).

2.4. Electroencephalography data processing

Over-night video-EEG data were preprocessed using custom python scripts and functions from the YASA toolbox[23] to assess spectral power estimates and detect spindles and K complexes (*Supplementary Material 1*).

2.5. Statistical analyses

Statistical analyses were conducted using Stata/IC 16.1 (College Station, Texas, USA). Baseline characteristics by diagnostic groups are presented as means or frequencies. Differences between amnestic AD, atypical AD, and healthy controls in demographics, sleep parameters and spectral frequencies were analyzed by the non-parametric Dunn test. Additional

regression models were adjusted by the presence of silent epileptiform activity and prescription of anticholinesterase inhibitors treatment and antidepressants.

3. Results

3.1 Sample characteristics

Details on demographic and clinical data are described in *Table 1*. Amnestic and typical AD groups showed similar age at EEG, gender, age at disease onset), disease duration, cognitive (MMSE), and functional status (CDR SoB) at EEG. The presence of silent epileptiform activity and the prescription of anticholinesterase treatments was also similar between AD groups. The control group was slightly older than the amnestic AD at EEG time. As expected, controls showed higher MMSE and lower CDR SoB scores than AD groups. In addition, controls had no silent epileptiform activity and were not using anticholinesterase inhibitors.

3.2. Sleep parameters over Sleep Period Time

Detailed results on sleep parameters over SPT are described in *Table 2* and *Fig. 1*. Total Sleep Time (TST) was similar among amnestic AD, atypical AD, and controls. Despite similar TST, when compared to controls, amnestic AD showed higher WASO(%) and N1(%) and lower sleep maintenance (%) and N3(%). In the same line, atypical AD showed a higher rate of N1(%). In contrast to amnestic AD, atypical AD had less REM(%), longer REM latency (min) and no differences in sleep maintenance, WASO, or N3 compared to controls. N3(%) was significantly lower in amnestic than in atypical AD. The distribution of sleep stages over SPT showed no difference between atypical non-amnestic/atypical variants (lvPPA, PCA) (*Supplementary Fig. 1*). Linear regression models adjusting by epileptiform activity and the prescription of anticholinesterase inhibitors and antidepressants did not modify the results.

3.4. Sleep parameters over Total Sleep Time

Detailed results on sleep parameters over TST are described in *Table 3, Figure 2*. Amnestic AD showed higher N1(%) and lower N3(%) compared to controls and non-amnestic/atypical. Non-amnestic/atypical AD showed higher N1(%) and lower REM(%) compared to controls and amnestics. Therefore, findings using TST and SPT were similar, aside from REM sleep, where non-amnestic AD had significantly less REM sleep as a percent of TST (excluding time awake after sleep onset) but not as a percent of SPT as compared to amnestics. The distribution of sleep stages over TPT showed no difference between atypical non-amnestic variants (lvPPA, PCA) (*Supplementary Fig. 2*).

3.5. Spectral analyses

Atypical AD had higher delta power during NREM stages 2 and 3 sleep as compared to both amnestic (Frontal SO P=0.02; Central SO P=0.01) and controls (Frontal SO P<0.01, Central SO P=0.03). There were no significant differences between amnestic AD and controls. Spindle and K-complex measures did now show any differences between groups (*Supplementary Table 1 and 2*).

4. Discussion

This cross-sectional overnight video-EEG study demonstrates that biomarker/postmortem-validated AD patients with amnestic and atypical phenotypes show different profiles for sleep architecture and power spectral analysis (i.e., the percentage of sleep stages, delta power). Despite having similar total sleep time to controls, amnestic AD shows a reduced N3 (slow-wave sleep -SWS) phase and atypical AD shows reduced REM stage and increased REM

latency, but similar N3 to controls. Delta power during N2 and N3 was higher in atypical than in amnestic AD. The discrepancy between N3 and REM is also significant when comparing amnestic to atypical AD. These differences remained significant after correcting for silent epileptiform activity, and the use of anticholinesterase inhibitors or antidepressants. In addition, the study confirmed a sleep fragmentation pattern consisting of more time spent awake (WASO) and also greater time in N1 sleep in AD overall compared to healthy controls.

Sleep fragmentation and difficulty reaching deeper sleep stages such as N3/SWS have been previously documented in AD. However, these studies mostly included late-onset amnestic cohorts[1,24–26]. Our study confirms that N3/SWS deficits are also a feature of sporadic EOAD, when the clinical manifestation is amnestic. However, the finding that atypical AD had a relatively preserved N3/SWS stage but significant deficits in REM is novel. Overall, it suggests a different pattern of subcortical degeneration of nuclei regulating REM versus NREM sleep between AD subtypes. These findings are intriguing, marrying models of AD/memory models and sleep/memory models. The prevailing AD /memory model attributes hippocampal formation degeneration as the main contributor to early short-term memory disturbances in AD[7,27,28]. Patients with amnestic AD show a disproportionately high burden of neurofibrillary tangles in the hippocampus than patients with atypical phenotypes[7,17]. In relation to models of sleep and memory: N3/SWS has been classically related to memory processing and consolidation in physiological conditions[29–31]. Prior studies showed that reduced NREM N3/SWS leads to an impaired overnight sleep-dependent memory retention in otherwise healthy elders. In contrast, naps, including NREM sleep periods, could increase memory performance[29]. Our results raise the question of whether a lower vulnerability of SWS-promoting neurons and subsequently less impaired N3 stage contributes to the relatively better memory scores seen in atypical AD as well as the broader question of how the SWS-

promoting generators interact with the hippocampal formation in affecting short-term memory function.

It is undisputed that impairment of sleep-wake cycles in AD is associated with greater cognitive decline, negatively impacting the quality of life, increasing caregiver burden, and causing early institutionalization[2,4,26]. Although a full picture of the mechanisms explaining the association between poor sleep and greater cognitive decline in AD remains under investigation, the specific neurobiological mechanisms driving these AD -related sleep alterations are being explored. For instance, growing evidence has suggested that early tau accumulation within the neuromodulatory subcortical systems could play a central role[32,33]. In this line, the noradrenergic *locus coeruleus*, one of the first sites of tau-related neurodegeneration in AD (from Braak I-II already), has arisen as a main driver of sleep-wake dysfunction in AD patients. Prior neuropathological studies have demonstrated that LC early neuronal loss due to tau deposition is specific for AD compared to other tauopathies, suggesting a selective vulnerability pattern of the LC wake-promoting neurons[9,12,34]. Moreover, LC degeneration has been associated with higher odds for presenting with symptomatic sleep disruption as well as other neuropsychiatric symptoms in early stages, even before tau spread reaches cortical areas (i.e., hippocampus) and leads to cognitive dysfunction[10,35]. Our results showing a pattern of sleep disruption (higher awakenings, N1 and lower sleep maintenance) in a cohort enriched with early-onset presentations, suggests a dysfunctional arousal system driven by LC wake-promoting neurons. Work by our group studying the direct correlates of night time sleep metrics and wake promoting nuclei (orexinergic lateral hypothalamic area (LHA), the histaminergic tuberomammillary nucleus (TMN) and the noradrenergic LC), found that wake promoting nuclei were associated with increased sleep disruption[12]. Indeed, the fact that EOAD manifests with a higher burden of behavioral and sleep disturbances in addition to the higher LC degeneration found on postmortem AD brain

tissue, could indicate that vulnerability of the LC is even higher in early- than late-onset presentations[9,18,35]. Our previous work also highlighted that greater TMN was associated with less REM sleep and greater LC with prolonged latency to REM sleep an association[12]. Together with this current work, it suggests further augmented function of the LC in non-amnestic/atypical EOAD with diminished REM sleep compared to amnestic EOAD. Further work is necessary on both the wake and sleep promoting nuclei in these cohorts to confirm these hypotheses.

The specific areas driving such NREM impairment in AD (and particularly in amnestic AD) are unclear, especially since the physiological sleep-wake circuitry in the human brain remains under discussion given significant differences with the rodent model[8]. The classical N3/SWS regulation model suggested a reciprocal relationship between the sleep-promoting neurons on the intermediate nucleus and a network of the brainstem and hypothalamic neurons being attributed to an overall wake-promoting role. In this model these sleep-wake interconnected networks would interact in an 'on/off switch' manner, modulated by the circadian pacemaker in the suprachiasmatic nucleus. Nevertheless, recent animal investigations challenged this idea/model by highlighting brainstem areas such as the nucleus accumbens (NAc), the lateral hypothalamic area (LHA), and the medullary parafacial zone (PZ) as an N3-SWS generator[36–38]. In this line, the elevated adenosine levels on the NAc, the activation of neurons containing melanin-concentrating hormone in the LHA, and the GABAergic control of the PZ induce N3/SWS, whereas their inhibition suppresses sleep[36,38,39]. These interconnected areas hierarchically modulate thalamocortical synchronization and oscillation, resulting in the sleep/wake cycle. Despite that the current sleep/wake regulation conceptual paradigm has been mainly elucidated by animal studies, it also couples with recent human findings demonstrating the regulation of sleep stages is complex, implying several sleep-wake promoting centers[8,12]. In consequence, our study findings showing that the sleep dysfunction

in amnestic AD relates mostly on lower NREM-N3/SWS sleep periods, we could infer that amnestics may present a specific pattern of tau-driven degeneration predominantly affecting these NREM sleep-wake interplaying areas.

On the other hand, the decreased amount of REM sleep and delayed REM latency in non-amnestic/atypical AD suggest a predominance of REM sleep dysfunction in atypical phenotypes. The neural network that generates REM sleep consists of a large number of anatomic structures located in the brainstem, limbic system, thalamus, hypothalamus and cortex[40,41]. The critical REM-controlling areas are located in the mesopontine tegmentum and in the ventral medial medulla. Several monoaminergic and non-cholinergic structures in the mesopontine tegmentum act as REM-on and REM-off structures with reciprocal inhibitory projections acting as a flip-flop switch, and therefore transitioning from REM sleep to NREM sleep and back[42]. For instance, the noradrenergic locus coeruleus, orexigenic LHA, cholinergic neurons of the pedunculopontine nucleus (PPT), and the nucleus basalis of Meynert or GABAergic sublaterodorsal nucleus seem to promote REM sleep. In contrast, others, like the serotonergic dorsal raphe nucleus (DRN), inhibit REM sleep states[8]. These regions send projections inhibiting or activating nearby nuclei in the brainstem or other distant brain regions. Acting as REM sleep modulators, the decreased activity of noradrenergic LC, serotonergic DRN, histaminergic TMN and orexinergic LHA, allow the final REM sleep cortical activation. Previous findings from our group working with Progressive Supranuclear Palsy, a tauopathy neurodegenerative disease associated with executive dysfunction, which serves as a naturalistic model for extensive degeneration/vulnerability of the brainstem, found REM sleep deficits and profound sleep disruption[43]. In light of this and our current results, we could hypothesize that the interplay between these REM sleep-regulating areas might be more affected in neurodegenerative diseases associated with cognitive deficits other than memory earlier in disease progression, such as non-amnestic AD. Thus, this study suggests a selective

vulnerability pattern of tau-derived neurodegeneration between AD variants with amnestics associated with NREM generators and non-amnestics with REM sleep generators. In this line, the LC changes have been particularly associated with REM dysfunction, as recently reported by Oh et al.[12]. A more severe degeneration of REM-promoting neurons (and preservations on REM-off structures such as LC) in non-amnestic AD could underly the more significant REM dysfunction in this group. It could be argued that the lower REM sleep in non-amnestic *vs* amnestic AD could be affected through typical treatment of anticholinesterase inhibitors for AD which may be prescribed more readily for amnestic than non-amnestic patients. Use of these medications were controlled for in our analyses, though further investigation to the effect of a prolonged altered cholinergic system in AD and REM sleep is warranted. In addition, further research assessing tau degeneration in these nuclei within the AD spectrum is needed to confirm this hypothesis.

There is a possibility that co-pathologies might also contribute to defining these differences in sleep architecture between amnestic and non-amnestic AD. Our cohort is enriched with EOAD presentations, theoretically reducing the odds for overall co-pathologies. However, a particular non- AD pathological change, Lewy Body Disease (LBD), co-exists frequently in EOAD, as described recently by Spina et al., 2021[21]. LBD co-pathology in AD significantly worsens the clinical severity and modifies clinical presentations[44–47]. Some studies report up to 27% of REM sleep Behavior Disorder (RBD) prevalence in patients with AD -type dementia[48,49], which is likely a consequence of LBD co-pathology. Considering the high prevalence of LBD comorbidity in AD, it is probable that LBD is accentuating LBD -like symptoms in AD such as RBD, which could explain the REM sleep impairment found in non-amnestic/atypical EOAD in our study. However, this hypothesis remains untested, and further studies evaluating the association between RBD in AD and underlying LBD co-pathology are warranted.

This study's strengths include the inclusion of autopsy-proven or biomarker-based AD cases – which had clinical and sleep data obtained using standardized methods by the same experts, a predominant early onset AD (EOAD) cohort, which reduces the odds of severe co-pathologies, enrichment of non-amnestic patients, and the inclusion of known sleep modifiers (i.e: anticholinesterase inhibitors, antidepressants, silent epileptiform activity) in the analytical models.

Nevertheless, our study has some limitations. The use of overnight EEG telemetry recordings prevented us from characterizing specific sleep conditions such as obstructive sleep apnea, RBD, or periodic limb movements syndrome. Further studies using polysomnography are needed to clarify the influence of these factors on AD phenotype-associated differences in sleep patterns. Also, we do not have EEG measures of the wake-period, which is a limitation as the wake-promoting nuclei degenerate early in AD and alpha waves correlate with cortical tau burden atypical AD cases have a disproportional higher cortical tau burden than amnestics [7,17,50]. Lastly, though our study attempted to recruit from a broad population, those who agreed to participate in our study were predominantly Caucasian.

In conclusion, sleep architecture in AD is not merely an exacerbation of age-related sleep changes but shows specific features across clinical variants. In line with prior literature, amnestic AD shows decreased N3 sleep. However, non-amnestic variants show a specific pattern consisting of predominant REM sleep dysfunction. The existence of specific sleep-wake profiles between variants suggests differential degenerative patterns of the sleep and wake-promoting systems within AD phenotypes, which would open the door to uncover the selective vulnerability on subcortical structures. Better understanding of the neurobiological changes underlying sleep differences between variants would promote tailored treatment avenues for sleep disorders in AD.

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Competing interests

The authors report no competing interests.

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Figure legends

Figure 1. Distribution of sleep stages over sleep period time (SPT) in amnestic, atypical Alzheimer's Disease and controls. Fig. 1 Shows the amount of each sleep stage (percentages, %) across groups. Note that the percentage of N3 is reduced in amnestics and REM sleep is reduced in atypical Alzheimer's Disease. WASO and N1 are increased in Alzheimer's Disease groups.

Figure 2. Distribution of sleep stages over TST in amnestic, atypical Alzheimer's Disease and controls. Fig 2. Shows the amount of each sleep stage across groups. Note that the percentage of N3 is reduced in amnestics and, REM sleep is reduced in atypical Alzheimer's Disease. N1 is increased in both Alzheimer's Disease groups.

Figure 1

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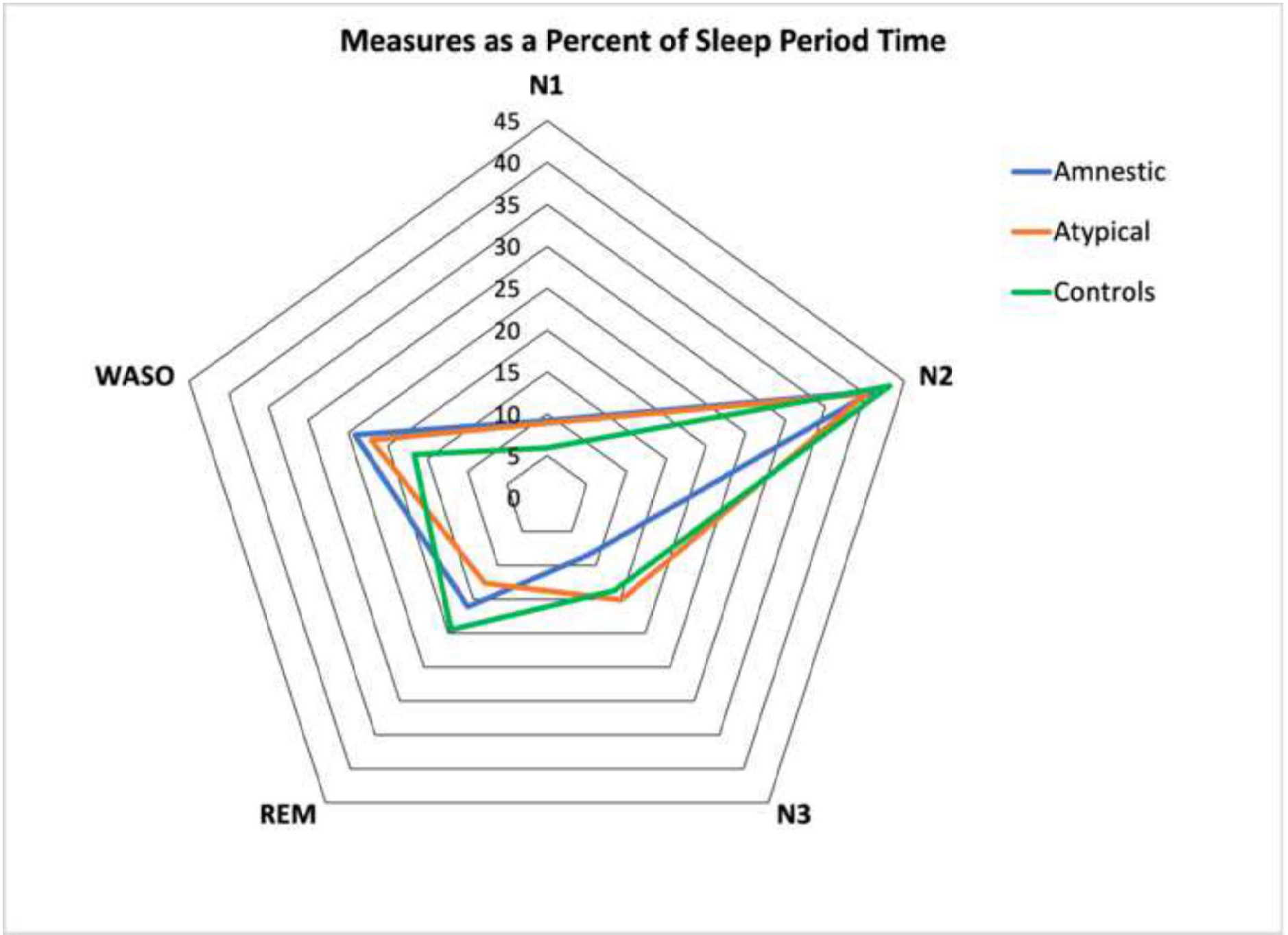

Figure 2

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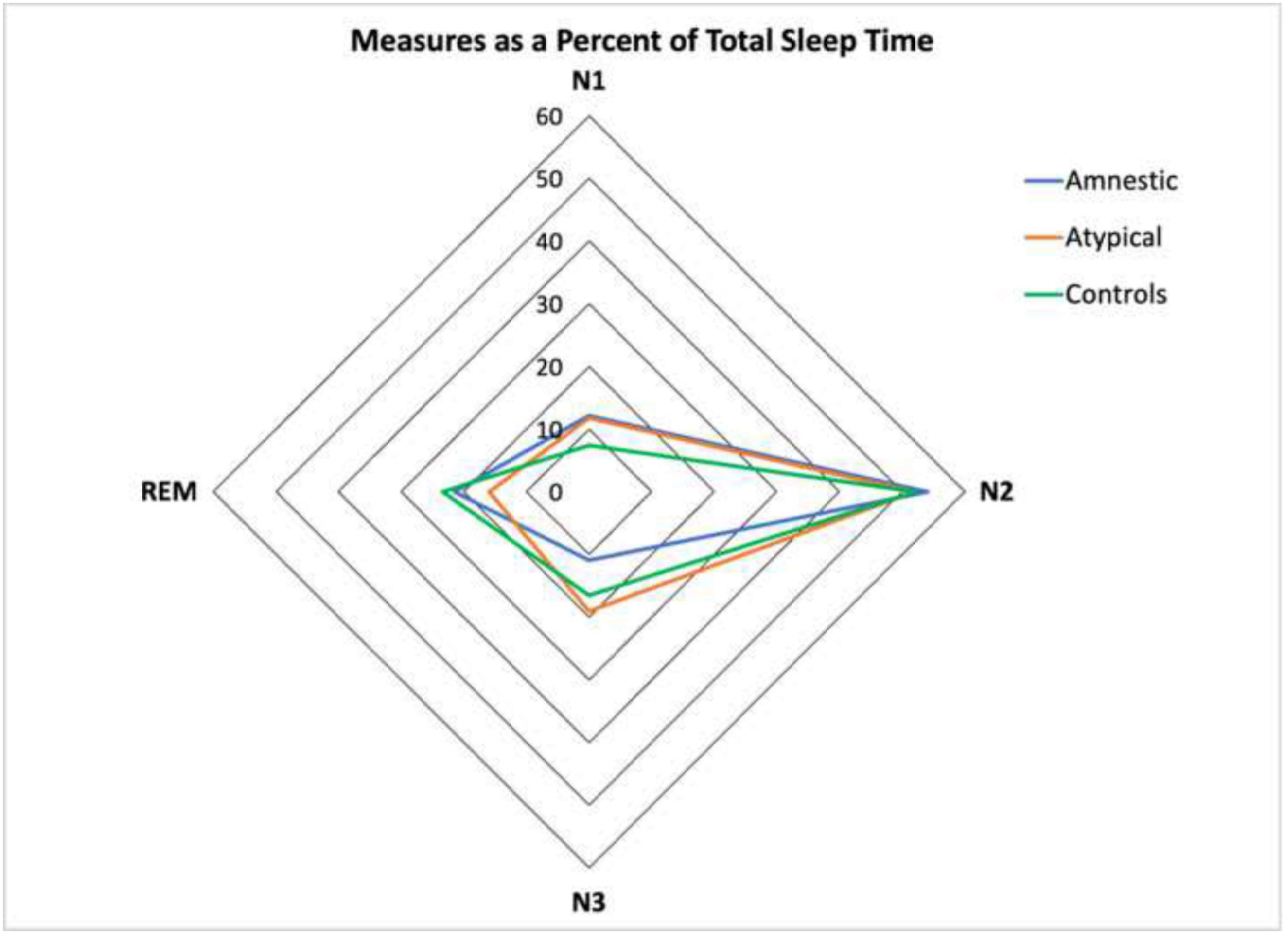

Table 1

Table 1. Demographics and clinical data

	Amnestic AD (n=15)	**Non-amnestic AD** (n=19)	**Controls** (n=14)	Amnestic *vs* controls	Non-amnestic *vs* controls	Amnestic *vs* non-amnestic
Age at onset (years)	56.1 ± 9.0	55.7 ± 7.5	N/A	N/A	N/A	ns
Age at EEG (years)	60.6 ± 9.7	60.5 ± 6.7	64.5 ± 5.6	*	ns	ns
Disease duration (years)	5.1 ± 2.4	5.3 ± 1.9	N/A	N/A	N/A	ns
Female (%)	64.3	57.9	64.3	ns	ns	ns
Education (years)	15.9 ± 2.5	16.5 ± 2.8	17.4 ± 1.9	ns	ns	ns
CDR at EEG time (%)	0.86 ± 0.4	0.84 ± 0.4	0 ± 0	**	**	ns
Normal	0	0	100	N/A	N/A	N/A
MCI	43	36.9	0	N/A	N/A	N/A
Mild dementia	50	57.9	0	N/A	N/A	N/A
Moderate dementia	7	5.2	0	N/A	N/A	N/A
CDR SoB at EEG time	5.4 ± 2.3	4.6 ± 2.3	0 ± 0	**	**	ns
MMSE at EEG time	21.1 ± 5.7	22. ± 4.5	29.5 ± 0.8	**	**	ns
Anticholinesterase Inhibitors (%)	80	89.5	0	**	**	ns
SSRI Antidepressants (%)	46.7	42.1	7.1	*	*	ns

Epileptiform activity (%)	20	26.3	0	*P*=0.07	*	ns

Data are shown as mean ± SD

Significance *$P<0.05$, **$P<0.01$; ns, non-significant; N/A, not applicable

Abbreviations: CDR, Clinical Dementia rating; CDR-SoB, CDR Sum of Boxes; MMSE, Mini Mental State Examination; SSRI, Selective serotonin reuptake inhibitors

Table 2

Table 2. Sleep parameters over SPT

	Amnestic AD	**Non-amnestic AD**	**Controls**	Amnestic *vs* controls	Non-amnestic *vs* controls	Amnestic *vs* non-amnestic
TST (min)	372.8 ± 80.4	392.7 ± 79	390.6 ± 81.1	ns	ns	ns
WASO (min)	118.8 ± 67	109.7 ± 57.4	79.93 ± 54.1	*	*	ns
N1 (min)	45.2 ± 20.9	44.8 ± 26.4	28.11 ± 13.9	**	*	ns
N2 (min)	202.3 ± 57.9	201.9 ± 53.9	202 ± 49.7	ns	ns	ns
N3 (min)	41.2 ± 24	74.9 ± 39.1	63.4 ± 32.6	*	ns	**
REM (min)	78.87 ± 31.5	65 ± 31	91.3 ± 35.7	ns	*	ns
Sleep Maintenance (%)	75.9 ± 12.6	78 ± 12	83.3 ± 10.0	*	ns	ns
WASO (%)	24.1 ± 12.6	22.1 ± 12.1	16.6 ± 10.0	*	ns	ns
N1 (%)	9.2 ± 4.1	8.9 ± 5	5.9 ± 2.8	**	*	ns
N2 (%)	41 ± 10	40.2 ± 9.2	43.1 ± 8.2	ns	ns	ns
N3 (%)	8.5 ± 5.4	15.1 ± 8.3	13.7 ± 6.8	*	ns	**
REM (%)	16.1 ± 6	12.6 ± 5.6	19.5 ± 6.5	ns	**	ns
REM Latency (min)	101.5 ± 58.1	133.7 ± 69	88.2 ± 32.8	ns	*	ns

Significance *P<0.05, **P<0.01

ns, non-significant

Abbreviations: TST, Total Sleep Time; WASO, Wake after sleep onset

Table 3. Sleep parameters over TST

	Amnestic AD	**Non-amnestic AD**	**Controls**	Amnestic *vs* controls	Non-amnestic *vs* controls	Amnestic *vs* non-amnestic
N1 (%)	12.1 ± 5.2	11.7 ± 6.8	7.4 ± 4.1	**	*	ns
N2 (%)	54.0 ± 9.0	52.0 ± 12.7	52.2 ± 9.4	ns	ns	ns
N3 (%)	10.9 ± 5.8	19.1 ± 10.1	16.5 ± 7.8	*	ns	**
REM (%)	21.5 ± 7.4	15.9 ± 7.2	23.4 ± 6.1	ns	**	**

Significance *P<0.05, **P<0.01

ns, non-significant

Highlights

-Alzheimer's Disease (AD) variants show distinct patterns of sleep impairment.

-Amnestic/typical AD has worse impairment of N3 - Slow Wave Sleep (SWS) than atypical AD.

-Atypical AD show more REM deficits than typical AD.

-Selective vulnerability patterns in subcortical areas may underly sleep differences.

-Relatively preserved SWS may explain better memory scores in atypical vs. typical AD.

Research in context:

Systematic Review: The authors thoroughly reviewed the literature using PubMed and cited appropriate articles. Polysomnography studies previously analyzed the sleep pattern in Alzheimer's Disease; however, most of the prior literature focuses on late-onset typical/amnestic AD. Very little is known about early-onset presentations with a predominance of atypical/non-amnestic syndromes.

Interpretation: Our study provides compelling evidence that sleep patterns differ across variants. Beyond the sleep fragmentation, amnestic AD shows a worse NREM N3/Slow-wave sleep impairment; conversely, the atypical/non-amnestic variants show a higher REM sleep dysfunction. Our study corroborates the hypothesis of differential selective vulnerability patterns of the subcortical nuclei within variants.

Future Directions: Development of targeted treatments for sleep dysfunction may be needed across variants. Studies investigating the neurobiological basis of sleep dysfunction in AD spectrum may provide insight for deciphering the selective vulnerability of the neuromodulatory subcortical system. Further understanding of preserved N3/SWS as a mechanism of preserved memory is warranted.