

UC San Diego

UC San Diego Previously Published Works

Title

Home EEG sleep assessment shows reduced slow-wave sleep in mild-moderate Alzheimer's disease

Permalink

<https://escholarship.org/uc/item/1zm6b3rh>

Journal

Alzheimer's & Dementia: Translational Research & Clinical Interventions, 8(1)

ISSN

2352-8737

Authors

Kent, Brianne A
Casciola, Amelia A
Carlucci, Sebastiano K
et al.

Publication Date

2022

DOI

10.1002/trc2.12347

Peer reviewed

SHORT REPORT

Home EEG sleep assessment shows reduced slow-wave sleep in mild–moderate Alzheimer's disease

Brianne A. Kent^{1,2} | Amelia A. Casciola¹ | Sebastiano K. Carlucci¹ | Meghan Chen¹ | Sam Stager¹ | Maryam S. Mirian¹ | Penelope Slack¹ | Jason Valerio¹ | Martin J. McKeown¹ | Howard H. Feldman^{1,3} | Haakon B. Nygaard¹

¹Division of Neurology, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC V6T1Z3, Canada

²Department of Psychology, Simon Fraser University, Burnaby, BC V5A 1S6, Canada

³Department of Neurosciences, Alzheimer Disease Cooperative Study, University of California, La Jolla, California 92037, USA

Correspondence

Haakon B. Nygaard, Division of Neurology and Djavad Mowafaghian Centre for Brain Health, 2215 Wesbrook Mall, Vancouver, BC V6T1Z3, Canada.

E-mail: haakon.nygaard@ubc.ca

Abstract

Introduction: Sleep disturbances are common in Alzheimer's disease (AD), with estimates of prevalence as high as 65%. Recent work suggests that specific sleep stages, such as slow-wave sleep (SWS) and rapid eye movement (REM), may directly impact AD pathophysiology. A major limitation to sleep staging is the requirement for clinical polysomnography (PSG), which is often not well tolerated in patients with dementia. We have recently developed a deep learning model to reliably analyze lower quality electroencephalogram (EEG) data obtained from a simple, two-lead EEG headband. Here we assessed whether this methodology would allow for home EEG sleep staging in patients with mild–moderate AD.

Methods: A total of 26 mild–moderate AD patients and 24 age-matched, healthy control participants underwent home EEG sleep recordings as well as actigraphy and subjective sleep measures through the Pittsburgh Sleep Quality Index (PSQI). Each participant wore the EEG headband for up to three nights. Sleep was staged using a deep learning model previously developed by our group, and sleep stages were correlated with actigraphy measures as well as PSQI scores.

Results: We show that home EEG with a headband is feasible and well tolerated in patients with AD. Patients with mild–moderate AD were found to spend less time in SWS compared to healthy control participants. Other sleep stages were not different between the two groups. Actigraphy or the PSQI were not found to predict home EEG sleep stages.

Discussion: Our data show that home EEG is well tolerated, and can ascertain reduced SWS in patients with mild–moderate AD. Similar findings have previously been reported, but using clinical PSG not suitable for the home environment. Home EEG will be particularly useful in future clinical trials assessing potential interventions that may target specific sleep stages to alter the pathogenesis of AD.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

KEYWORDS

actigraphy, Alzheimer's disease, deep learning, home electroencephalogram, N3, polysomnography, Pittsburgh Sleep Quality Index, rapid eye movement, sleep staging, slow-wave sleep

Highlights

- Home electroencephalogram (EEG) sleep assessments are important for measuring sleep in patients with dementia because polysomnography is a limited resource not well tolerated in this patient population.
- Simplified at-home EEG for sleep assessment is feasible in patients with mild-moderate Alzheimer's disease (AD).
- Patients with mild-moderate AD exhibit less time spent in slow-wave sleep in the home environment, compared to healthy control participants.
- Compared to healthy control participants, patients with mild-moderate AD spend more time in bed, with decreased sleep efficiency, and more awakenings as measured by actigraphy, but these measures do not correlate with EEG sleep stages.

1 | INTRODUCTION

Sleep disturbances are known to impact patients with Alzheimer's disease (AD), with one estimate indicating that up to 65% of those diagnosed with AD meet the criteria for a major sleep disorder.^{1,2} While most sleep disorders are addressed symptomatically, more recent studies are addressing biological links by which sleep disturbances directly impact AD pathophysiology, especially levels of brain amyloid beta ($A\beta$) and tau.³⁻⁷ A number of small studies using laboratory polysomnography (PSG) testing in AD have reported reduced slow-wave sleep (SWS) and rapid eye movement (REM) sleep,⁸ both of which are potential sleep therapeutic targets. As the gold standard, PSG affords the highest quality sleep staging information, but with the major drawbacks of high cost, limited availability, and the requirement to spend a night in a clinic bed, with inherent risks to persons with dementia who do not respond well to a change in environment. Simplified, home electroencephalogram (EEG) would address these limitations, and vastly expand access to sleep staging, while recognizing potential limitations to the quality of data acquisition as well as analysis. While several studies have explored one- to two-channel sleep-EEG in older individuals,^{7,9,10} to our knowledge no study to date has used such a setup in patients with a clinical diagnosis of AD. We recently validated a two-lead EEG headband for home sleep staging, using a deep learning data analysis approach.¹¹ Against the gold standard PSG, the headband had good accuracy for the quantification of N3 (SWS; 84%), making it especially suitable for AD studies.¹¹

Here we report on measures of sleep quality and quantity in patients with mild-moderate AD and healthy control participants using self-reporting, actigraphy, and home EEG. Our primary objectives were to establish the feasibility of home EEG monitoring in patients with AD, and to characterize the sleep architecture in this patient group in their home environment.

2 | MATERIALS AND METHODS**2.1 | Participants**

A total of 50 participants enrolled in the Medium Chain Triglyceride Intervention for Alzheimer's Disease study at the University of British Columbia (UBC; NCT02912936) were recruited for this EEG substudy. Three additional participants declined participation and were not enrolled. There were 26 participants with a diagnosis of mild-moderate AD, determined according to National Institute on Aging-Alzheimer's Association criteria,¹² with a Mini-Mental State Examination Score of 16-26 (inclusive), a Montreal Cognitive Assessment (MoCA) score of <26, a Geriatric Depression Scale¹³ <6, and a Modified Hachinski¹⁴ ≤ 4 . Cholinesterase inhibitors and stable psychiatric medications were allowed if stable for 12 weeks prior to the screening visit. There were 24 healthy control participants with no subjective cognitive symptoms, and a MoCA ≥ 26 (Table 1). All human

TABLE 1 Participant characteristics

	AD		Healthy control subjects		P
	Mean	SD	Mean	SD	
Sex (M/F)	16/10	-	8/16	-	-
APOE $\epsilon 4$ carrier	18/8	-	-	-	-
Age (y)	67.3	8.1	63.5	10.1	.150
Education (y)	14.3	2.7	16.0	2.3	.020
On AChE inhibitor	17/9	-	-	-	-
MoCA (/30)	15.3	4.0	28.4	1.5	<.0001
Global PSQI	3.8	2.8	4.9	3.4	.252

Abbreviations: AChE, acetylcholinesterase; AD, Alzheimer's disease; APOE, apolipoprotein E; MoCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.

RESEARCH IN CONTEXT

- 1. Systematic Review:** There is growing evidence of a direct link between sleep and Alzheimer's disease (AD) pathophysiology. Given the expense and limited availability of clinic-based polysomnography sleep assessments, and the added challenges and risks of studying persons with dementia overnight in a new environment, there is a strong need for accurate home electroencephalogram (EEG) for sleep staging in patients with dementia.
- 2. Interpretation:** Our findings demonstrate an effective protocol for staging sleep in the home environment using a two-channel EEG headband. Home EEG, coupled with a deep learning analysis model, showed that patients with AD had reduced slow-wave (N3) sleep stage compared to age-matched non-demented control participants.
- 3. Future Directions:** Home EEG sleep assessments will be particularly useful in future clinical trials assessing novel interventions to target specific sleep stages as a potential therapeutic intervention to alter the pathogenesis of AD.

participants provided informed consent, and the study was approved by the UBC Clinical Research Ethics Board (H15-02537).

2.1.1 | EEG acquisition

We used a commercially available EEG headband (Cognionics Inc.) customized for two-channel recordings, as previously described.¹¹ The headband was also made to use disposable clip-on Kendall Meditrace Mini adhesive hydrogel foam electrodes (Cardinal Health). Detailed picture instructions on where to attach the electrodes at home were given. Frontal electrodes were placed at an equal distance between the eyebrow and hairline, along a vertical line from the center of the eye. Each participant attempted to record for up to three nights. Data were recorded at a bandwidth of 0 to 131 Hz, 500 Hz sample rate, 6× amplifier gain, with a noise of 0.7 μ V. The fixed, two-channel montage is shown in Figure 1A.

2.1.2 | EEG sleep staging analysis

Raw EEG data were first converted to a European Data Format, and visually inspected for overall inclusion. A finite impulse response band-pass filter with cutoff frequencies of 0.5 and 12 Hz was applied, and the data down-sampled to 25 Hz and separated into non-overlapping 30-second epochs. To remove the corrupted data, we filtered epochs where the correlation between signals from channels 1 and 2 was below 0.9, and the mean amplitude of at least one channel was above 40 μ V. We removed data only in the corrupted channel, duplicating the

valid channel in its place. We then passed the EEG into 12 deep learning models, previously described,¹¹ each trained on a different overlapping subset of labelled data. Majority voting was used to predict the 12 models, keeping the majority prediction for epochs in which ≥ 7 models agreed, labelling epochs for which the majority of the models did not agree as “unknown.”

2.2 | Self-reported sleep

Participants completed the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire validated in older adults, assessing sleep quality and disturbances over a 1-month period.¹⁵

2.3 | Actigraphy

Participants continuously wore an ActTrust (Condor Instruments) actigraphy device, and 5 days of data were analyzed for this report using ActStudio (Condor Instruments) and Clocklab (Actimetrics).

2.4 | Statistical analysis

Data were analyzed using a two-tailed Student's *t*-test where indicated. Pearson correlation was used for actigraphy-sleep stage comparisons. Cohen's *d* was calculated as the difference between two means divided by the pooled standard deviation. Prism (GraphPad Software) was used for all analyses.

3 | RESULTS

3.1 | At-home sleep EEG is feasible and well tolerated in patients with AD

Overall, setting up and sleeping with an EEG headband was well tolerated in patients with mild-moderate AD, given a caregiver was available to help with electrode placements and the recording device. Most participants completed at least one night of home EEG (control 21/24 participants; AD 22/26 participants). Overall, 79% of attempted nights of home EEG recording in enrolled AD participants provided useful data, with 82% in healthy controls (Table S1 in supporting information). Reasons for excluding home EEG data were varied, and are listed in Table S1.

3.2 | Slow-wave sleep is reduced in mild-moderate AD using two-lead home EEG

Alzheimer's disease patients were found to have significantly reduced SWS (N3; 3.4% of total sleep in AD vs. 10.8% in healthy controls, $P = .001$, Cohen's $d = 1.039$), without differences in other sleep stages

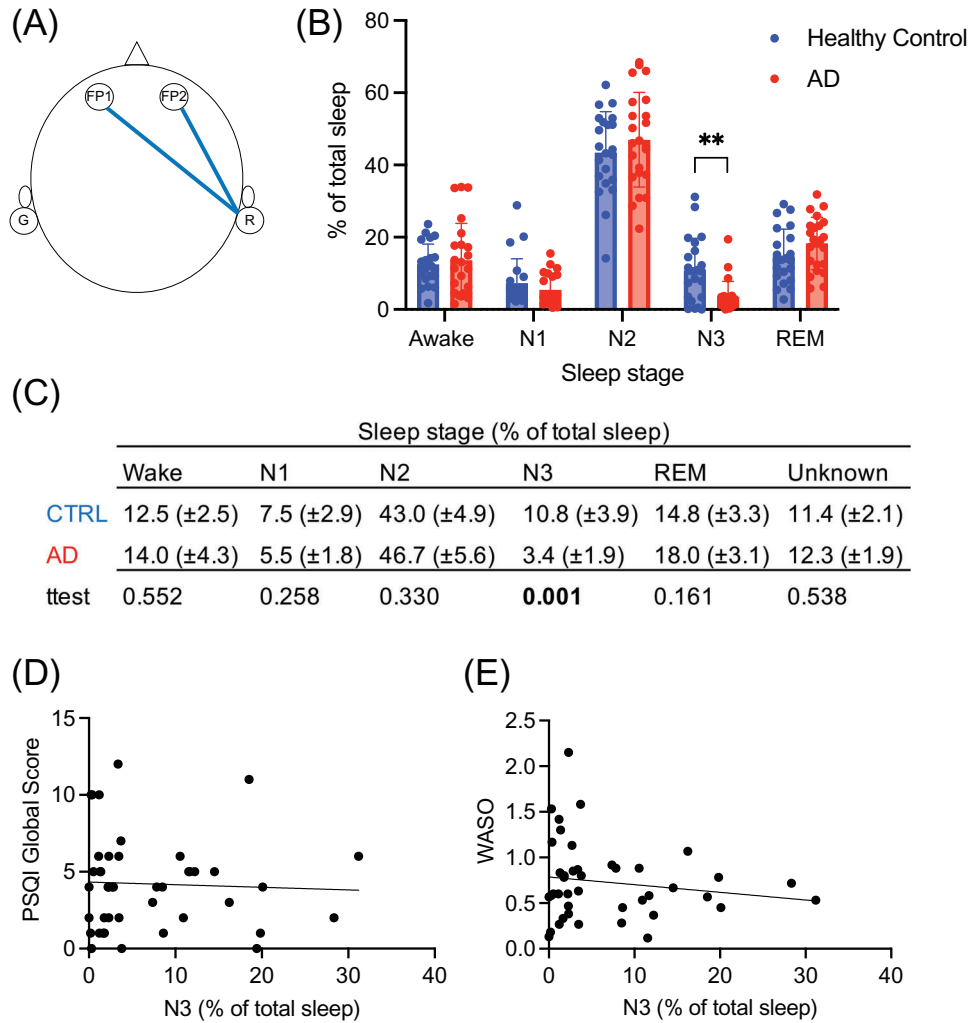


FIGURE 1 Home EEG shows reduced SWS sleep in AD. The simplified home EEG montage is shown in (A). Patients with AD have less SWS (N3) sleep compared to healthy control participants ($P = .001$, Student's t -test), with no differences seen in other sleep stages (B, C). Subjective sleep scoring using the PSQI or the actigraphy measure WASO do not predict home EEG sleep staging (D, E). AD, Alzheimer's disease; CTRL, control; EEG, electroencephalogram; FP1, left frontal pole electrode; FP2, right frontal pole electrode; G, ground electrode; N3, slow-wave sleep stage (SWS); PSQI, Pittsburgh Sleep Quality Index; R, reference electrode; REM, rapid eye movement; WASO, wake after sleep onset

(Figure 1B,C). These findings allowed us to estimate the sample size needed with SWS as an outcome measure in future clinical trials. Assuming a predicted, absolute increase in SWS of 1.7% (50% relative increase), with an alpha of 0.05 and 80% power, a total cohort of 218 participants with AD would be required. A more ambitious target of a 100% relative SWS increase reduces the total cohort size to 54.

3.3 | Self-reported sleep or actigraphy do not correlate with SWS or REM sleep

On PSQI subsections, AD patients reported greater total sleep time ($P = .0053$), and a later wake-up time ($P = .0131$) compared to healthy control participants (Table S2 in supporting information). Patients with mild-moderate AD also showed changes in several actigraphy mea-

asures, including longer time spent in bed ($P = .0127$), lower sleep efficiency ($P = .0156$), and longer wake after sleep onset ($P = .0030$; Table S2). We next assessed whether any measure of self-reported sleep or actigraphy correlated with SWS or REM sleep stages. Using a correlation matrix, we found that neither self-reported sleep nor actigraphy correlated with SWS or REM, exemplified by the PSQI and wake after sleep onset versus SWS (N3; Figure 1D,E; Table S2).

4 | DISCUSSION

The main finding of this study is that at-home sleep staging in patients with AD is feasible using a simplified two-lead EEG headband, coupled with deep learning data analysis. For patients with mild-moderate AD, with the support of a study partner for placement of the headband and

electrodes, successful recordings were obtained in approximately 79%. This was comparable to those who were cognitively normal. Corroborating the consensus findings in AD,⁸ we show that SWS is reduced in AD patients, but without seeing reductions in REM. Our findings address the limitations of PSG, especially cost, availability, and the need to spend a night in a hospital bed, while also addressing the main limitation of home EEG related to increased variability in data quality in the less controlled home environment. We note that one limitation of our approach is the inability to assess for sleep apnea, a possible confounder. Further, while our deep learning model has good accuracy for N3 (SWS), other sleep stages, especially N1, are less accurate,¹¹ and our results must be viewed in this context. Finally, we find that while our actigraphy measures in AD are similar to previous reports,^{16,17} these measures cannot substitute EEG for sleep staging.

To our knowledge, a simplified, home EEG headband has not previously been tested in AD. Numerous studies have shown that EEG headbands compare favorably to PSG, some of which are referenced here.^{7,10,18–20} A relatively large study used home EEG in older patients with a Clinical Dementia Rating scale up to 0.5, finding a correlation between reduced single-lead EEG power in the lower frequency range and AD pathology.⁷ However, the same study did not find any correlation between traditional sleep stages and AD pathology, perhaps highlighting limitations in manual scoring or the less impaired study population in those without dementia.

In conclusion, our data suggest that home EEG with a headband has excellent potential for sleep staging in AD. This approach will be particularly useful in future clinical trials assessing novel approaches targeting specific sleep stages as a potential disease-modifying therapy for AD.

ACKNOWLEDGMENTS

The study was funded through a philanthropic gift to the University of British Columbia. H.B.N. was funded by Michael Smith Foundation for Health Research Scholar. B.A.K. was funded by Michael Smith Foundation for Health Research, Killam Trusts, and Canadian Institutes of Health Research Banting. The deep learning source code on which this study is based is freely available.¹¹

CONFLICTS OF INTEREST

H.B.N. serves as a paid, independent consultant for Hoffman-La Roche and Biogen. H.H.F. reports grant funding from Annovis (QR Pharma), Vivoryon (Probiobdrug), AC Immune, and LuMind; service agreements for consulting activities with Genentech (DSMB), Roche/Banner (DMC), Tau Consortium (SAB), Samus Therapeutics, Biosplice Therapeutics, Axon Neurosciences, Novo Nordisk Inc., and Janssen Research & Development LLC; and travel funding from World Events Forum (ADDF) with no personal funds received and all payments to UCSD, a philanthropic donation from the Epstein Family Alzheimer's Disease Collaboration for therapeutic research in AD with no personal funds received and all payments to UCSD. All other authors report no relevant conflicts of interest. Author disclosures are available in the [supporting information](#).

REFERENCES

- Guarnieri B, Adorni F, Musicco M, et al. Prevalence of sleep disturbances in mild cognitive impairment and dementing disorders: a multicenter Italian clinical cross-sectional study on 431 patients. *Dement Geriatr Cogn Disord*. 2012;33:50-58.
- Kent BA, Feldman HH, Nygaard HB. Sleep and its regulation: an emerging pathogenic and treatment frontier in Alzheimer's disease. *Prog Neurobiol*. 2021;197:101902.
- Spira AP, Gamaldo AA, An Y, et al. Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. *JAMA Neurol*. 2013;70:1537-1543.
- Kang JE, Lim MM, Bateman RJ, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science*. 2009;326:1005-1007.
- Iliff JJ, Wang, M., Liao, Y., et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Sci Transl Med*. 2012;4:147ra11-11.
- Jagirdar R, Fu CH, Park J, et al. Restoring activity in the thalamic reticular nucleus improves sleep architecture and reduces Abeta accumulation in mice. *Sci Transl Med*. 2021;13:eabh4284.
- Lucey BP, McCullough A, Landsness EC, et al. Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Sci Transl Med*. 2019;11:eaau6550.
- Zhang Y, Ren R, Yang L, et al. Sleep in Alzheimer's disease: a systematic review and meta-analysis of polysomnographic findings. *Transl Psychiatry*. 2022;12:136.
- Chou CA, Toedebusch CD, Redrick T, et al. Comparison of single-channel EEG, actigraphy, and sleep diary in cognitively normal and mildly impaired older adults. *Sleep Adv*. 2020;1:zpa006.
- Lucey BP, McLeland JS, Toedebusch CD, et al. Comparison of a single-channel EEG sleep study to polysomnography. *J Sleep Res*. 2016;25:625-635.
- Casciola AA, Carlucci SK, Kent BA, et al. A deep learning strategy for automatic sleep staging based on two-channel EEG headband data. *Sensors (Basel)*. 2021;21:3316.
- Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:270-279.
- Sheikh J, Yesavage J. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. In: Brind TL, ed. *Clinical Gerontology: A Guide to Assessment and Intervention*. New York: Haworth Press; 1986:165-173.
- Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. *Ann Neurol*. 1980;7:486-488.
- Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. *Sleep Med Rev*. 2016;25:52-73.
- Hatfield CF, Herbert J, van Someren EJ, Hodges JR, Hastings MH. Disrupted daily activity/rest cycles in relation to daily cortisol rhythms of home-dwelling patients with early Alzheimer's dementia. *Brain*. 2004;127:1061-1074.
- Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep*. 2013;36:1027-1032.
- Finan PH, Richards JM, Gamaldo CE, et al. Validation of a wireless, self-application, ambulatory electroencephalographic sleep monitoring device in healthy volunteers. *J Clin Sleep Med*. 2016;12:1443-1451.
- Popovic D, Khoo M, Westbrook P. Automatic scoring of sleep stages and cortical arousals using two electrodes on the forehead: validation in healthy adults. *J Sleep Res*. 2014;23:211-221.

20. Stepnowsky C, Levendowski D, Popovic D, Ayappa I, Rapoport DM. Scoring accuracy of automated sleep staging from a bipolar electroocular recording compared to manual scoring by multiple raters. *Sleep Med.* 2013;14:1199-1207.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kent BA, Casciola AA, Carlucci SK, et al. Home EEG sleep assessment shows reduced slow-wave sleep in mild–moderate Alzheimer's disease. *Alzheimer's Dement.* 2022;8:e12347. <https://doi.org/10.1002/trc2.12347>