

RESEARCH ARTICLE

Night-to-night variation in sleep associates with day-to-day variation in vigilance, cognition, memory, and behavioral problems in Alzheimer's disease

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Abstract

Introduction: Sleep disturbances are commonly reported in people living with Alzheimer's disease (AD), but it is currently unknown whether night-to-night variation in sleep predicts day-to-day variation in vigilance, cognition, mood, and behavior (daytime measures).

Methods: Subjective and objective sleep and daytime measures were collected daily for 2 weeks in 15 participants with mild AD, eight participants with mild cognitive impairment (MCI), and 22 participants with no cognitive impairment (NCI). Associations between daytime measures and four principal components of sleep (duration, quality, continuity, and latency) were quantified using mixed-model regression.

Results: Sleepiness, alertness, contentedness, everyday memory errors, serial subtraction, and behavioral problems were predicted by at least one of the components of sleep, and in particular sleep duration and continuity. Associations between variations in sleep and daytime measures were linear or quadratic and often different between participants with AD and those with NCI.

Discussion: These findings imply that daytime functioning in people with AD may be improved by interventions that target sleep continuity.

KEYWORDS

actigraphy, Alzheimer's disease, behavior, cognition, dementia, memory, mild cognitive impairment, mood, older adults, sleep, vigilance

1 | BACKGROUND

Sleep disturbances, quantified through self-report, carer report, actigraphy, or polysomnography, are highly prevalent in people living with mild cognitive impairment (MCI) and Alzheimer's disease (AD), and contribute to quality of life and caregiver burden.^{1,2} These sleep disturbances include early sleep timing, long sleep periods, frequent awakenings, nocturnal wandering, reduced rapid eye movement and slow wave sleep, sleep-related breathing disorders, and excessive daytime sleepi-

ness, as well as long naps.²⁻⁶ Cross-sectional and longitudinal studies indicate that sleep disturbances are predictive of AD before AD symptoms emerge and are associated with AD pathology.^{7,8} Based on these and other studies, a bidirectional link between sleep disturbances and cognitive decline has been suggested.^{9,10}

The extent to which sleep disturbances associate with AD symptoms on shorter timescales has received less attention.¹¹ Symptoms in AD vary from day-to-day and contribute to variation in caregiver burden.^{12,13} More variable sleep duration has been associated with

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increased risk for MCI¹⁴, night-to-night variations in subjective sleep quality have predicted daily variations in memory in amnesic MCI participants.¹⁵ However, how intraindividual variation of sleep relates to day-to-day variation in measures of daytime functioning (e.g., cognition, behavior, mood) in MCI and AD has not been investigated in detail.

Previous studies of the association between daytime function and sleep in AD often use standard clinical assessment tools, such as the Mini-Mental State Examination (MMSE),¹⁶ which cover a limited range of cognitive domains (see Bubu et al.¹⁷ for examples of these studies). Furthermore, to our knowledge, associations between sleep disturbances and cognitive and behavioral problems in AD have rarely been assessed in studies that include multiple, repeated assessments that are close temporally. The current study aimed to overcome these limitations and to determine whether (1) night-to-night sleep over 2 weeks differs in people living with AD and MCI, compared to older adults with no cognitive impairment (NCI), and (2) how variation in sleep relates to day-to-day measures of cognition, mood, vigilance, and behavior. Ultimately, insights into these associations may inform the development of sleep-based interventions to improve daytime functioning in people living with AD.

2 | METHODS

For extended details of the Methods see Document 1 in supporting information.

2.1 | Participants and ethics

The protocol was approved by the National Health Service Health Research Authority (REC ref: 16/NE/0339). Three groups of participants were recruited: probable mild AD ($n = 15$), MCI ($n = 8$), and NCI ($n = 24$). The AD and MCI groups were recruited from and diagnosed by UK Memory Assessment Services, in line with internationally agreed diagnostic guidelines.^{18,19} MCI diagnosis met core clinical criteria for the symptomatic predementia phase of AD, comprising prominent impairment in episodic memory, but excluded biomarker measures.¹⁸ Probable AD diagnosis met the following criteria: insidious onset of dementia with progression and exclusion of any other systemic or brain disease that could cause dementia (e.g., Parkinson's disease).¹⁹ The Addenbrooke's Cognitive Examination Revised was used by associated memory clinics to determine MCI and AD diagnoses.²⁰ MCI and AD participants were screened at time of recruitment via medical records and again through self-report from participant and caregiver, to ensure they met all inclusion criteria and no exclusion criteria. NCI participants, who were healthy older adults recruited from the community in response to an advertisement, were screened via self-report. Key inclusion criteria for all participants were 65 to 85 years of age, fluent in English, with access to a telephone, in reasonably good health, and able-bodied. Key exclusion criteria for all participants were: severe learning disabilities, acute psychiatric disorders, sleep disorder diagnosis (e.g., sleep apnea), or use of sleep medication. Participants with AD or MCI were only included if they had a relative or caregiver living with them

RESEARCH IN CONTEXT

1. Systematic Review: A review of the literature on associations between sleep and symptoms of Alzheimer's disease (AD) showed that no study has investigated how night-to-night variation in objectively and subjectively assessed sleep covaries with day-to-day variation in symptoms of AD, such as memory errors and behavioral and cognitive problems.
2. Interpretation: Our findings demonstrate that, compared to age-matched healthy adults, there is more day-to-day variation in memory and other cognitive and behavioral problems in AD, and that these problems covary with night-to-night sleep parameters, specifically the continuity of sleep, which is inversely correlated with the duration of the nocturnal time in bed period and daytime naps.
3. Future Directions: Interventional studies, in which sleep continuity is enhanced, by, for example, optimizing the duration of time in bed, may elucidate to what extent symptoms in AD are causally related to sleep disturbance.

who agreed to be a study partner. Participants with AD were excluded if they were on an unstable dose of antedementia medication. NCI participants were excluded if they reported memory problems. All three participant groups were matched for age, sex, ethnicity, years of education, and IQ (all $ps > .05$; Table 1). Informed consent was obtained from all participants.

2.2 | Procedure and assessment schedule

The protocol consisted of baseline and end of study assessments and an approximately 2-week period during which assessments were obtained daily, except Sunday (see Figure S1 in supporting information). Measures of mood, cognition, and observed behavior were obtained daily through questionnaires, diaries, and cognitive tests that were administered by phone every morning. Sleep was assessed objectively by actigraphy and subjectively by sleep diaries during the 2-week period. The analyses reported here are based on approximately 500 participant-days of assessments.

2.3 | Assessments

2.3.1 | Baseline and end of study measures

At baseline, demographic information and medical history were collected and the Pittsburgh Sleep Quality Index (PSQI²¹) and the National Adult Reading Test-IQ (NART²²) were administered. At baseline and again at end of study, Montreal Cognitive Assessment

TABLE 1 Demographic characteristics and home visit measures within each group

	AD (n = 15)	MCI (n = 8)	NCI (n = 22)	P (group)
Age at baseline	75.87 ± 5.07	73.75 ± 5.44	73.59 ± 5.27	.409
Female	5 (33.33%)	5 (62.5%)	13 (59.1%)	.219
Ethnicity				
White British	15 (100%)	8 (100%)	21 (95%)	1.000
Asian/Asian British	–	–	1 (5%)	–
Education (years)	15.37 ± 3.09	12.94 ± 3.65	16.64 ± 3.84	.052
NART	117.79 IQR (111.59–123.98)	114.9 IQR (112.42–119.65)	123.16 IQR (120.47–125.02)	.072
Partner	15 (100%)	8 (100%) [†]	12 (55%) [†]	<.001
Well-being measure				
QOL	38.53 CI (35.88–41.19)	38.50 CI (34.86–42.14)	40.66 CI (38.47–42.85)	.389
Depression	1.69 CI (0.85–2.53)	3.00 CI (1.28–4.71)	2.14 CI (1.33–2.96)	.349
Anxiety	1.98 CI (0.99–2.97)	4.39 CI (1.94–6.84)	2.94 CI (1.86–4.02)	.117
Functional ability measure				
FAQ	7.40 CI (4.93–9.88)	5.96 CI (3.00–8.91) [‡]	1.15 CI (0.41–1.89) [§]	<.0001
Cognitive ability measure				
MoCA	19.48 CI (16.68–22.28) [*]	24.01 CI (21.68–26.33) [§]	28.26 CI (27.71–28.81) [§]	<.0001
PRMQ	45.30 CI (40.34–50.25)	38.25 CI (32.51–43.98)	32.21 CI (29.30–35.12) [§]	<.0001
Sleep quality measure				
PSQI	3.5 IQR (2–4.75)	6 IQR (2.5–8.25)	5 IQR (3.25–6.75)	.285

Abbreviations: AD, Alzheimer's disease participants; FAQ, Functional Activities Questionnaire; MCI, mild cognitive impairment participants; MoCA, Montreal Cognitive Assessment; NART, National Adult Reading Test IQ; NCI, no cognitive impairment participants; P (group), P-value for overall group effect; PRMQ, Prospective-Retrospective Memory Task; PSQI, Pittsburgh Sleep Quality Index; QOL, Quality of Life.

Notes: Values are expressed as number (%) for categorical variables, mean ± standard deviation for normally distributed continuous variables, and median and interquartile range (IQR) for skewed continuous variables. All well-being, functional ability, and cognitive ability are presented as a least squares mean of the two repeated measures taken at baseline and follow-up, along with 95% confidence intervals (CI). Missing values include one baseline FAQ in the MCI group, and one PSQI in the AD group. AD compared to MCI; MCI compared to NCI; NCI compared to AD.

*P < .05.

†P < .01.

‡P < .001.

§P < .0001.

(MoCA²³), Quality of Life in Alzheimer's Disease (QOL-AD²⁴), Hospital Anxiety and Depression Scale (HADS²⁵), Functional Activities Questionnaire (FAQ²⁶), and Prospective-Retrospective Memory Questionnaire (PRMQ²⁷; a self-report measure of prospective and retrospective memory slips in everyday life) were administered.

2.3.2 | Daily measures

Self-reports of sleep were obtained with the Karolinska Sleep Diary,²⁸ complemented by two items from the Consensus Sleep Diary²⁹ to document daytime naps. We analyzed self-reported time in bed (sTIB), total sleep time (sTST), sleep efficiency (sSE; sTST/sTIB), wake after sleep onset probability (sWASOprob) and duration (sWASO), number of awakenings (sNAW), a nocturnal sleep quality index (sSQI) defined as the average of four diary questions (how well did you sleep, easy to

fall asleep, restless sleep, wake up ahead of time), probability that the participant napped in the day (sNAP), and duration of naps (sNaptime).

Objective measures of sleep were obtained by actigraphy (CamNtech Ltd), which is considered a valid tool to assess sleep patterns in dementia.^{30,31} The actigraphy analysis algorithm was applied to the time in bed period as documented in the sleep diary. Parameters analyzed were sleep latency (aSleepLat), sleep period time (aSPT; interval between sleep start and wake time), total sleep time (aTST), sleep efficiency (aSE; actigraphy measured total sleep time/actigraphy measured time in bed), number of awakenings (aNAW), percentage of minutes immobile (almmo; number of minutes immobile/aSPT), and mean length of immobility periods.

Vigilance and cognitive measures assessed during a daily telephone session included sleepiness (Karolinska Sleepiness Scale [KSS]³²), prospective memory, immediate (IR) and delayed (DR) recall (10 words³³), attention and calculation (Serial 7s Subtraction Test [SS]³⁴), and verbal fluency category (VFC; Controlled Word Association Test³⁵).

We also performed evening assessments of mood, memory errors, and behavioral problems. Alertness, contentedness, and calmness scores were obtained from Bond–Lader Visual Analogue Mood Scales.³⁶ Every evening participants completed the Everyday Memory Error Questionnaire (EME).³⁷ A caregiver/study partner of the AD and MCI participants completed the Revised Memory and Behavior Checklist (RMBC)³⁸ to quantify observable behavioral problems (RMBC) and the caregivers' response to these (RMBC-CR).

3 | STATISTICAL ANALYSES

Group differences in baseline measures were explored using Student *t*-tests, Mann–Whitney tests, and Chi-squared/Fisher's exact tests. Differences between groups for the repeated measures at baseline and study-end and daily measures of vigilance, mood, cognition, behavior, and sleep were analyzed using a mixed-model approach with a random "subject" effect to account for correlations between outcomes in the same participant. Group estimates were presented as least squares means and differences.

To quantify intraindividual variability per group we computed the average of the within-participant coefficient of variation (CV) and the intraclass correlation (ICC).³⁹

Sleep variables were subjected to principal component analysis (PCA) using Proc Factor, using the principal method followed by varimax rotation.

For associations between principal components (PCs) of sleep and vigilance, cognition, behavior, and mood, a mixed model approach (participant as random effect) was used with vigilance, cognition, behavior, and mood measures as dependent variables, and PCs of sleep as independent variables. Models included group and group × PC interaction effects to allow for the degree of association to differ between groups. Linear and quadratic associations between PC and dependent variables were investigated. Where the quadratic term was not significant, we reported the linear term model only. Models were adjusted for age, sex, and years of education.

The α -level was set to 0.05 in all analyses and exact *P*-values have been reported. The only group comparisons made were AD–NCI and MCI–NCI.

Statistical analyses were undertaken using SAS version 9.4 or R version 4.01.

4 | RESULTS

4.1 | Participants and completeness of data

Of the 47 participants initially enrolled, 2 were excluded (scoring > 11 on HADS anxiety); thus, the dataset comprised 15 AD, 8 MCI, and 22 NCI participants.

Across all variables (except demographics), on average, 92.6% (standard deviation [SD] = 7.1%; range: 80.7% for actigraphy to 99.4% for verbal fluency) of scheduled assessments were successfully obtained.

4.2 | Baseline and end-of-study measures

The groups were well matched for age, sex, and education. NART-IQ, PSQI, composite measure of QOL-AD, Anxiety, and Depression did not vary significantly across groups. Estimates of FAQ, PRMQ, and MoCA all varied as expected across the groups, with AD performing worse, then MCI and NCI, respectively (Table 1) and were, in general, stable across the 2-week period (Table S1 in supporting information).

4.3 | Daily measures of vigilance, mood, cognition, everyday memory errors, and behavior

4.3.1 | Group effects

Vigilance and mood variables did not vary between groups (summarized in Figure 1; detail in Table S2 in supporting information). AD participants performed significantly worse on all cognitive measures and had more EMEs compared to NCI, with MCI intermediate between AD and NCI. RMBC problems were more frequent in AD than MCI, and AD caregivers reacted more strongly to RMBC problems than MCI caregivers.

4.3.2 | Intra-individual variability

Intraindividual variability in EME is illustrated in Figure 2A–B (EMEs) and the coefficient of variation of all measures is illustrated in Figure 3 (see Table S2 for 1-ICC). Intraindividual variability varied across measures and groups. Day-to-day variability in measures of memory was considerable and significantly larger in AD than in NCI (Figure 3A). Variability in SS and VFc was small but was significantly greater in AD than in NCI. Interday variability for the RMBC and the RMBC-CR was larger in MCI than in AD. Day-to-day variation for the KSS was significantly larger in AD than NCI (Figure 3A).

4.4 | Subjective and objective daily measures of sleep

4.4.1 | Group effects

AD participants reported earlier bedtimes than in NCI, and both AD and MCI participants reported significantly longer sTIB than NCIs. sNAW was lowest in AD. The only objective measures of sleep that varied between groups were aSPT and aSleepLat, both being longer in AD than NCI (Figure 1; Table S2).

4.4.2 | Intraindividual variability

Variability was large for sNapTime, sSleepLat, sWASO, and sNAW in all groups; only sNAW varied significantly across groups, being larger in AD than in NCI (Figure 3B). Variability in the sSQI was

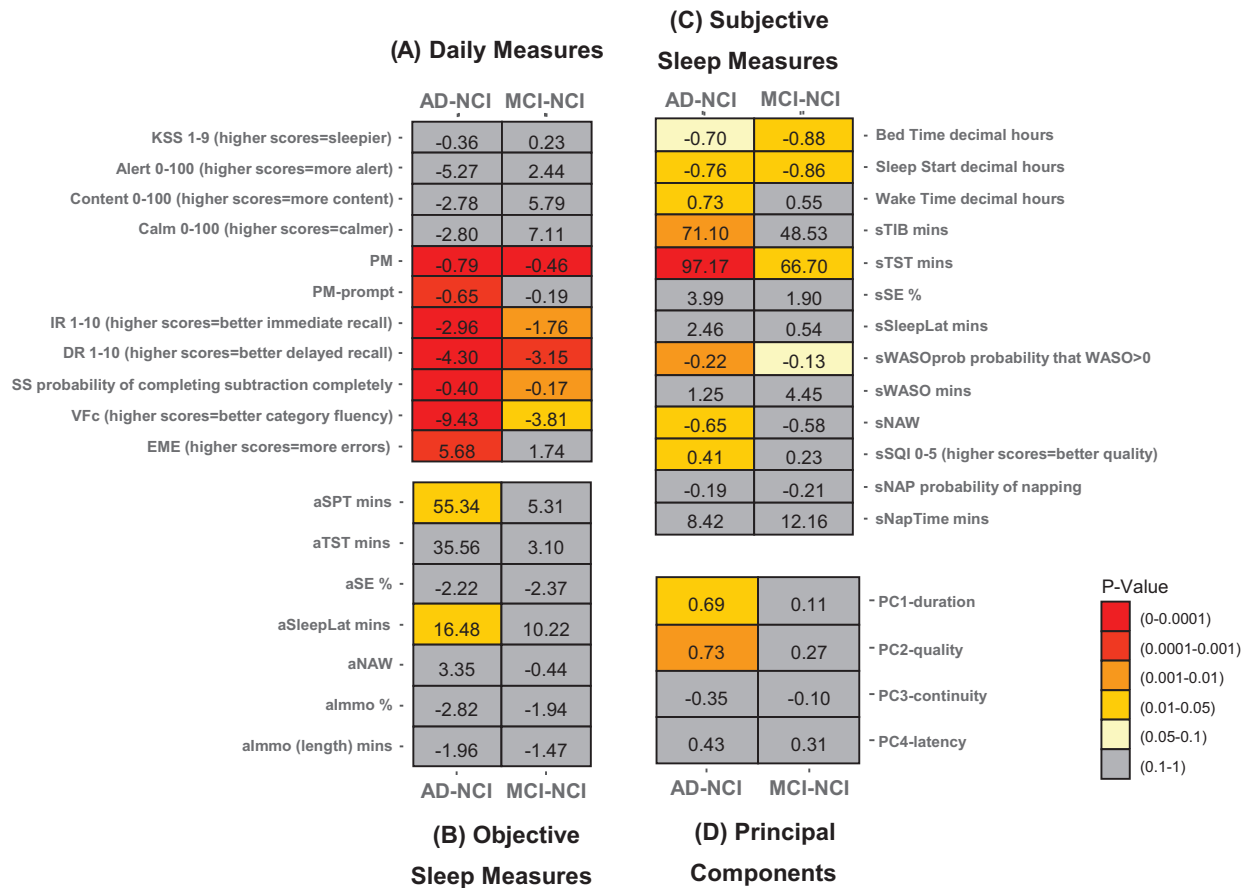


FIGURE 1 Heatmap of differences between AD versus NCI and MCI versus NCI for the (A) daily measures, (B) objective sleep measures, (C) subjective sleep measures, and the (D) sleep principal components. Pale yellow to dark red indicates increasing levels of significance. *Note 1.* PM, PM-prompt, and SS are predictive probabilities. All other differences are in the original units of the variables/tests. *Note 2.* Negative numbers (AD-NCI, MCI-NCI) indicate that the values were larger in NCI. AD, Alzheimer's disease; DR, delayed recall; EME, everyday memory errors; IR, immediate recall; KSS, Karolinska Sleepiness Scale; MCI, mild cognitive impairment; NAP, napped in the day; NAW, number of awakenings; NCI, no cognitive impairment; PC, principal components; PM, prospective memory; SE, sleep efficiency; SQI, sleep quality index; SS, Serial 7s Subtraction Test; TIB, time in bed; TST, total sleep time; VFc, verbal fluency category; WASO, wake after sleep onset

significantly smaller in AD than in NCI. Within the objective sleep measures, aSleepLat had the most variability, but there were no significant group differences for any of these measures (Figure 3C).

4.5 | Independence of daytime measures

To assess independence between measures we computed the correlations across standardized variables (Figure 4A). For most daytime measures, correlations were small. Substantial positive correlations of a moderate ($r > 0.3$) to large ($r > 0.5$) effect size were only observed between mood variables, between IR and DR, and between RMBC and RMBC-CR.

4.6 | Interdependence of sleep measures

Multiple significant correlations were observed both within and across the objective and subjective sleep measures (Figure 4B). Of interest are

the significant positive correlations between sSQI and objective actigraphy measures (aTST, aSE, and almmo).

4.7 | Principal component analysis of sleep measures

The sleep variables were summarized by PCA identifying four components with an eigenvalue greater than 1, which accounted for 75% of the variance (Figure 4C). Component 1 was dominated by objective and subjective sleep duration measures (PC1-duration); Component 2 by subjective sleep measures including sleep quality (PC2-quality); Component 3 by objective sleep continuity measures and shorter sTIB (PC3-continuity); and Component 4 primarily by longer objective sleep latency, lower objective sleep efficiency, and longer nap duration. PC4 was named "Objective Latency to Sleep" (PC4-latency), although the interpretation of this PC is somewhat ambiguous and could also be interpreted as reflecting "Low Sleep Pressure" (see Figure 4C).

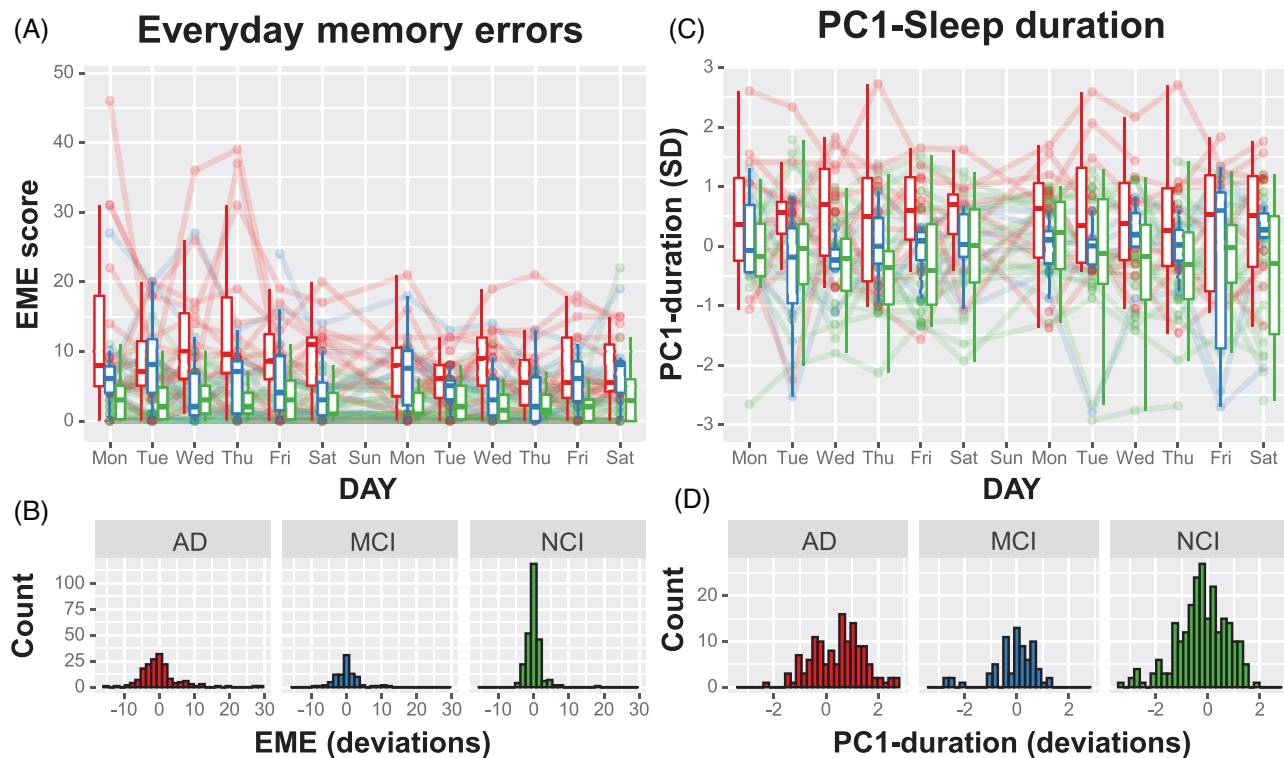


FIGURE 2 Variation in everyday memory errors score (EME) (A, B) and sleep duration principal component (PC1-duration) standard deviations (SD) (C, D). Boxplots (A, C) illustrate the distributions for the data for each group each day. Boxplots include median (horizontal line), interquartile range (IQR; lower and upper hinges), the range no further than $1.5 \times$ IQR from the hinges (whiskers). Data beyond the whiskers are classified as outliers and are hidden in the plot. Lines represent values per participant. Frequency histograms (B, D) illustrate the distribution of the daily observation expressed as deviation from each participant's average. *Note:* Larger variation in mild cognitive impairment (MCI) and Alzheimer's disease (AD) compared to no cognitive impairment (NCI) for EME, but similar variation across groups for PC1-duration

PC1-duration marginally varied across the three groups ($p = .053$) and was significantly longer in AD versus NCI (Figure 1 and Table S2). PC2-quality also varied across the three groups ($p = .018$) and was significantly better in AD versus NCI. PC3-continuity and PC4-latency did not vary across the three groups.

Night-to-night variability was substantial for PC1-duration and PC2-quality, but there were no group differences in the variability of any of the PCs (Figure 3 and 1-ICCs in Table S2).

4.8 | Associations between nightly variations in principal components of sleep and next day vigilance, cognition, behavior, and mood

4.8.1 | Sleep duration (PC1)

Alertness assessed in the evening was positively and linearly associated with PC1-duration in the previous night, and similarly so in all three groups (Figure 5A, Figure S2 in supporting information). For SS and EME, both the quadratic term and the interaction between PC1-duration and group were significant. For SS both shorter and longer sleep associated with poorer performance in this task for AD. For MCI, longer sleep duration associated with poorer performance in SS.

For EME, both the quadratic term and the interaction between PC1-duration and group were significant. In AD the association between PC1-duration and EME showed an inverted U, while for MCI and NCI, the association was U-shaped. The results imply that both shorter and longer sleep duration associates with fewer memory errors in AD.

4.8.2 | Subjective sleep quality (PC2)

Better PC2-quality significantly associated with KSS, Contentedness, and RMBC, and significantly interacted with group for all three daytime measures. KSS showed a U-shaped relationship in AD and MCI, whereas in NCI sleepiness decreased with increasing sleep quality. The quadratic effect in AD was significantly different than the effect in NCI. In the AD group, better sleep quality significantly associated with fewer reported RMBC problems, but in MCI, there was a positive association between PC2 and RMBC.

4.8.3 | Objective sleep continuity (PC3)

PC3 was linearly associated with KSS, Alertness, SS, EME, and RMBC. There was a significant interaction of PC3 and group for Alertness

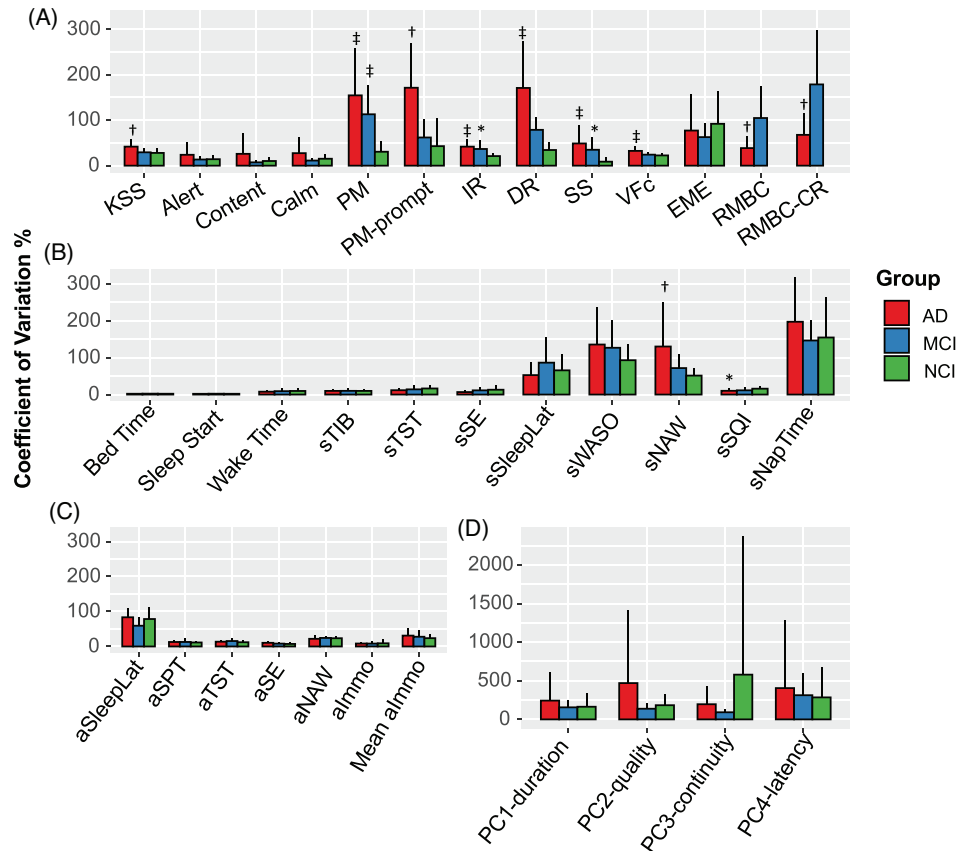


FIGURE 3 Intraindividual variability for daytime measures (A), subjective sleep measures (B), objective sleep measures, and (D) principal components. Variability is expressed as coefficient of variation (CV) computed as the average of CVs per participant in each group. Error bars indicate standard deviations. Significant differences between AD versus NCI and MCI versus NCI groups are indicated with * $p < .05$, † $p < .01$, ‡ $p < .001$, § $p < .0001$. Note: For RMBC and RMBC-CR, comparisons are between AD and MCI only, because this measure was considered irrelevant for the NCI group and no data were collected. AD, Alzheimer's disease; DR, delayed recall; EME, everyday memory errors; IR, immediate recall; KSS, Karolinska Sleepiness Scale; MCI, mild cognitive impairment; NAP, napped in the day; NAW, number of awakenings; NCI, no cognitive impairment; PC, principal components; PM, prospective memory; RMBC, Revised Memory and Behavior Checklist; RMBC-CR, Revised Memory and Behavior Checklist, caregiver's response; SE, sleep efficiency; SQI, sleep quality index; SS, Serial 7s Subtraction Test; TIB, time in bed; TST, total sleep time; VFc, verbal fluency category; WASO, wake after sleep onset

and EME. Higher PC3-continuity associated linearly with lower KSS (i.e., reduced sleepiness; Figure 5B) and similarly so in all three groups. PC3 associated with improved evening Alertness in AD only. Performance on the SS was poorer after nights with high PC3 for all three groups. ADs reported fewer EMEs after nights with high PC3-continuity (Figure 5C) and this effect was significantly different from the effects in NCI in which EME was not markedly affected by PC3. Caregivers reported fewer RMBC problems after nights with higher PC3 for both MCI and AD.

4.8.4 | Latency to sleep onset (PC4)

There was a significant quadratic association between PC4-latency and calmness and the PC4 by group interaction was significant: In AD and MCI, the association was an inverted U-shape and in NCI the association was U-shaped. Higher values on PC4 were associated with better performance on SS in AD and this effect was significantly different from NCI.

5 | DISCUSSION

Daily assessments of cognition, mood, and behavior in parallel with self-reported and objective assessments of sleep demonstrated that night-to-night variation in sleep associates with the substantial intraindividual day-to-day variation in cognition, mood, and behavior in AD, MCI, and NCI. The data also imply that waking function in AD is more affected by sleep disturbance than waking function in NCI. The findings demonstrate that also on a very short time-scale sleep modulates relevant waking functions, such as everyday memory errors and vigilance in AD. These findings have implications for targeting sleep disturbance for interventions to reduce symptoms.

5.1 | Validity and robustness of the approach

This mild AD group differed from NCI on all relevant measures of daytime function and MCI performance was mostly in between AD and

MCI. The groups did not differ with respect to potential confounders, such as depression and anxiety. The earlier bedtime and longer time in bed were among the most prominent features of sleep disturbance in AD in this study, in accordance with previous reports.⁶ The successful reduction of the many objective and subjective sleep measures to four meaningful principal components (duration, quality, continuity, and latency to sleep) represents a novel approach. The validity and sensitivity of this approach is illustrated by the associations between daily variations in vigilance (KSS, Alertness) and nightly variations in the principal components of subjective and objective measures of sleep. Sleepiness and alertness have repeatedly been shown to be very sensitive to experimental changes in sleep duration and sleep continuity^{40,41} and here we find that this also holds when we analyze spontaneous variation in PCs in AD, MCI, and NCI. These associations represent solid evidence for the significance of nightly variation in sleep duration and continuity for next-day function, because participants had no knowledge of their objective sleep measures when they reported their subjective alertness or sleepiness.

5.2 | Intraindividual variation in sleep and daytime measures and their association

The considerable day-to-day variation in measures of performance, mood, and memory, which was particularly prominent in AD, points to the importance of repeated assessments on a short time scale. The variability of the sleep measures, either at the individual item level or PCs, did not differ between groups, except self-reported awakenings, which was larger in AD, and self-reported sleep quality, which was smaller in AD. In line with previous reports on associations between sleep and outcome measures including sleep duration and dementia risk and other adverse health outcomes,^{42–44} we observed linear and quadratic (i.e., U or inverse U-shaped) associations between variation in sleep and variation in daytime measures. Quadratic associations were observed in some sleep measures in AD only (e.g., sleep quality vs. vigilance). One interpretation of these quadratic associations is that there appears to be an optimal level of sleep on cognition and other daytime measures,⁴² which is in accordance with recent studies.⁴⁵ Our observation that objective sleep continuity associated with improved vigilance and alertness, and reduced everyday memory errors, particularly in AD, is reminiscent of studies in which reduced sleep continuity has invariably been associated with increased dementia risk.^{8,46}

Some of the counterintuitive observations (shorter sleep duration associated with fewer everyday memory errors; longer sleep latency related to better serial calculation the next morning) are in line with previous cross-sectional studies: A meta-analysis found short sleep durations were related to better cognition in older adults.⁴⁷

Daytime measures in AD participants were not only sensitive to changes in sleep but often also more sensitive to this night-to-night variation than NCI. The sensitivity to variation in sleep on a very short time scale complements previous cross-sectional and longitudinal studies that demonstrated associations between sleep and AD risk.^{17,48,49} Future research should explore the development of sleep-

based strategies and their impact on daytime functioning, particularly determining an optimal amount of sleep to maximize sleep continuity. Our results show that both sleep continuity and sleep duration are predictors of next day waking functions. Sleep continuity is negatively associated with long time in bed periods and the duration of daytime naps (see Figure 4). From this, it follows that avoiding long nocturnal time in bed periods and avoiding daytime naps, which should lead to better sleep continuity, are potential interventions.

Our study had several limitations: The sample size was small, although the repeated measures design of the study somewhat mitigated this problem. Furthermore, we treated AD and MCI as separate groups, although they can be considered to represent a continuum. To investigate whether the small group sizes may have driven some of the interactions between sleep measures and group and whether an approach in which AD and MCI were treated as one group would still reveal significant associations, we repeated the main analyses but now with AD and MCI combined. The results of this sensitivity analysis were rather similar to those presented in Figure 5A and Table S3 in supporting information. Administering cognitive measures over the telephone presents a number of challenges, for example, hearing difficulties, lack of control over the participants' environment, potential use of aids during the tests, and incompatibility of some cognitive tasks to phone testing, limiting the types of cognitive measures. The test were administered in the morning and we cannot exclude that some of the observations were affected by sleep inertia.⁵⁰ We recognize that although we attempted to control for sleep disorders through medical history and PSQI, the lack of a clinical polysomnography means that some sleep disorders, such as sleep apnea, may have gone undetected. Although the use of clinical and cognitive evaluation is a reliable and valid method of diagnosing MCI due to AD,¹⁸ inclusion of biomarker measures could have solidified the etiology of MCI.

Notwithstanding these limitations, the successful simultaneous collection of sleep and waking function over a 2-week period demonstrated that there is substantial day-to-day variation in measures of vigilance and cognition in AD, MCI, and NCI and that this variation correlates with night-to-night variation in subjectively and objectively assessed sleep measures. These associations vary across cognitive domains and across AD, MCI, and NCI, and suggest sleep intervention strategies to reduce symptoms.

ACKNOWLEDGMENTS

The authors are grateful to all the participants and their families who dedicated their time to this study. They thank Dr Nayantara Santhi for providing training and expertise for the acquisition of actigraphy data, Dr Jeewaka Mendis for advice on SAS programming, Dr Richard Hoile for help with data collection, and Miss Abbie Harris for help with data entry. The conduct of the study was supported by the Centre for Dementia Studies, Brighton & Sussex Medical School (BSMS), and Sussex Partnership NHS Foundation Trust. SB was funded by the Centre for Dementia Studies, BSMS, to carry out the research in a Dementia Research Fellowship role. The analysis was supported by the UK Dementia Research Institute Care and Research Technology Centre at Imperial College London and the University of Surrey, Guildford, UK.

CONFLICTS OF INTEREST

DJD served as a paid consultant to and/or received research support from F. Hoffmann La Roche Ltd, Pfizer Inc., Eli Lilly and Company, Novo Nordisk A/S, Ono Pharma UK Ltd, Janssen Research & Development LLC, Eli Lilly and Company, and GW Pharma, Phillips Lighting, H Lundbeck A/S, Merck Inc, Vanda Pharmaceuticals, Cephalon Inc., Servier, UCB, Procter & Gamble, Ferring Pharmaceuticals A/S. NT received advisory and speaker honorarium, and research funding from Novo Nordisk, Roche, Eli Lilly, Novartis, Eisai, and Lundbeck. SS previously received research support from Pfizer Inc. and Astra Zeneca Plc. SB, DAD, and JR have no declarations of interest.

AUTHOR CONTRIBUTIONS

The study was conceived by SB, DJD, and NT. The protocol was finalized by SB, NT, and JR. Ethical approval negotiations, recruitment, data collection, and data management were all conducted by SB. Actigraphy analyses were conducted by DJD. Statistical analyses were conducted by DAD and directed by SS and DJD. The manuscript was drafted by DJD and SB and reviewed and edited by all authors.

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SUPPORTING INFORMATION

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How to cite this article: Balouch S, Dijk DAD, Rusted J, Skene SS, Tabet N, Dijk D-J. Night-to-night variation in sleep associates with day-to-day variation in vigilance, cognition, memory, and behavioral problems in Alzheimer's disease. *Alzheimer's Dement*. 2022;14:e12303. <https://doi.org/10.1002/dad2.12303>