



# Sleep and future cognitive decline

This scientific commentary refers to ‘Sleep and longitudinal cognitive performance in preclinical and early symptomatic Alzheimer disease’ by Lucey et al. (doi:10.1093/brain/awab272).

Recently described mechanisms point to physiological processes during sleep, particularly non-REM (slow wave) sleep, reducing Alzheimer’s-related proteins such as amyloid- $\beta_{42}$ .<sup>1</sup> Does this mean we should treat sleep to help prevent Alzheimer’s disease and, if so, for whom and when—before or after the onset of Alzheimer’s disease pathology or symptoms? Most previous work on sleep in dementia has used self-reported or actigraphy measures of sleep that do not tell us about non-REM physiology. In-laboratory overnight polysomnography provides neurophysiological sleep data, but is expensive and does not capture naturalistic sleep. Even where sleep is recorded in clinical cohorts, Alzheimer’s disease is often not well characterized and relies on a clinical diagnosis of dementia, which is generally late and relatively inaccurate.<sup>2</sup> So, we often do not really know whether people already have early Alzheimer’s disease at the time of sleep recordings. In their paper, Lucey and colleagues<sup>3</sup> combine molecular Alzheimer’s disease biomarker testing in a cognitively relatively healthy cohort with home EEG sleep recording and longitudinal cognitive follow-up.

Building on inverted U-shaped associations between sleep duration and cognition from epidemiological literature, Lucey and colleagues<sup>3</sup> test the hypothesis that cognitive function is non-linearly associated with sleep parameters in older adults. Neuropsychological tests were performed annually to detect cognitive change and all participants had at least 2 years of assessments. Cognitive tests included the Mini-Mental State Examination (MMSE), two tests of episodic memory and the Digit Symbol Substitution Test—combined to produce a Preclinical Alzheimer Cognitive Composite Score (PACC). Innovatively, sleep was measured at home over four to six nights using a single channel EEG device allowing for estimation of sleep stage and non-REM slow-wave activity (NREM SWA) in usual surroundings. Generalized additive mixed effects models corrected for Clinical Dementia Rating (CDR), CSF Alzheimer’s disease biomarkers, APOE status and demographic factors.

Twelve individuals were cognitively impaired (11 with mild cognitive impairment and one with mild dementia) and 88 were cognitively unimpaired. Both high and low values of total sleep time, N2/N3 sleep duration, REM sleep duration and both <1 Hz and 1–4.5 Hz NREM SWA were associated with a deteriorating PACC score. At the shortest to longest sleep time these effects ranged from a standardized score of –0.2 to –0.3—an effect on cognitive decline similar to age. Participants with intermediate values demonstrated stability in cognitive function.

This study benefits from several positive features. It is one of the first to draw together at-home sleep EEG and molecular

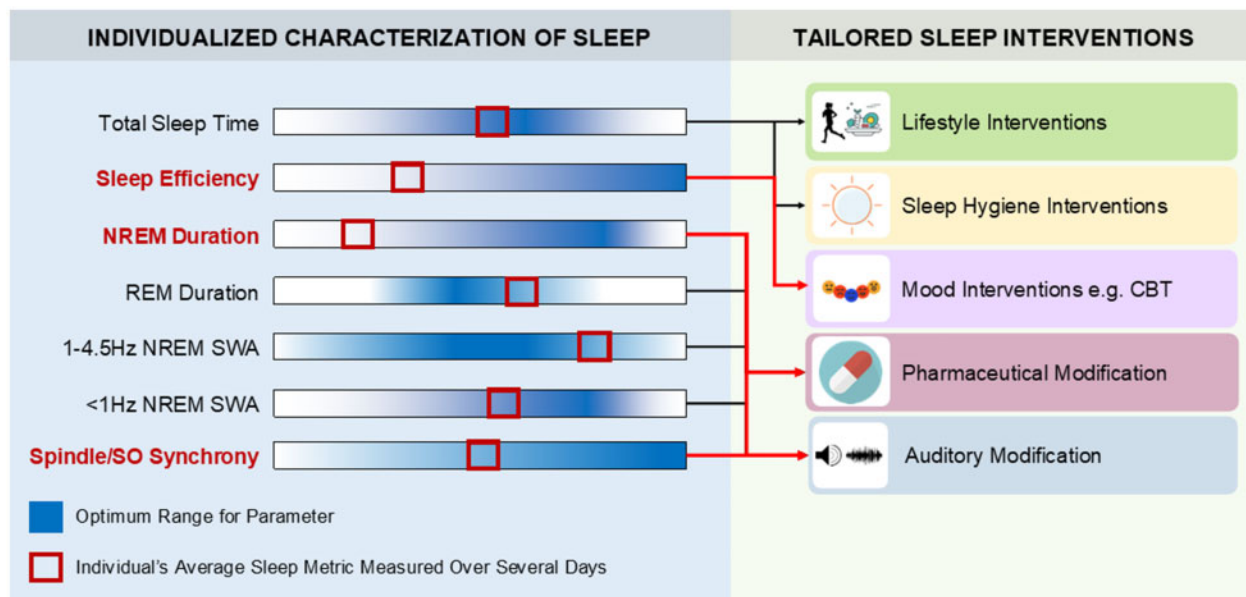
characterization of Alzheimer’s disease with longitudinal cognitive testing. Recording four to six nights of EEG compensates for first-night effects of wearing equipment while sleeping. The longitudinal design and detailed patient characterization allow the impact of pre-existing Alzheimer’s disease on the relationship between sleep and cognitive decline to be assessed.

Much of the challenge in generalizing the data here stem from the fact that, given the number of variables, the sample size is fairly small ( $n = 100$ ). While CSF amyloid positivity ( $n = 43$ ) and negativity ( $n = 57$ ) are balanced, only a small number of people have cognitive impairment ( $CDR \geq 0.5$ ). In the context of neurodegeneration, even mild cognitive impairment on the measures used probably represents over a decade of progressive pathological change. As expected,  $CDR = 0$  versus  $0.5$  groups behaved differently with a trend towards MMSE and Delayed Recall scores improving amongst the  $CDR = 0$  participants but with substantial deteriorations seen in the  $CDR = 0.5$  group. This suggests that the cohort was heterogeneous in terms of manifestation of Alzheimer’s disease pathology at baseline.

Alzheimer’s disease sleep treatments are best targeted to the disease stage where sleep-related changes are thought to have most impact. It would be relevant to compare sleep at baseline and the association with future decline in those ostensibly free of Alzheimer’s disease at baseline ( $CDR = 0$  and CSF biomarkers normal) versus those who were in the early stages of Alzheimer’s disease ( $CDR 0$  or  $0.5$  with evidence of Alzheimer’s disease biomarkers). Although models are partially corrected, we are left not really knowing whether the impact of sleep differs at different stages of Alzheimer’s disease. It would have been interesting to see the analyses for just the cognitively unimpaired group—although CDR scores were obtained up to 2 years before or after sleep testing, which might limit the validity of grouping according to CDR.

The longitudinal outcome was cognitive, rather than molecular. Within the healthy group, pathological changes of Alzheimer’s disease may have reflected a more sensitive outcome measure than cognition given their known emergence well before symptomatology, but these data were not collected. It would also have been very interesting to know about affective symptoms. Anxiety and depression are more common in mild cognitive impairment<sup>4</sup> and are associated with both inadequate and excessive sleep. Subclinical depression moderates the relationship between sleep and cognitive performance in healthy older adults<sup>5</sup> and raises questions about the direction of causality.

Single electrode EEG offers flexibility for home use and is reasonably accurate for sleep staging. The authors have previously investigated its reliability compared to polysomnography. However, single electrode EEG gives less rich data than full-head EEG—for example N3 slow wave sleep measurement is




**Figure 1 Approach to tailoring sleep therapies in people at risk of Alzheimer's disease.** Theoretical characterization of sleep for an individual at risk of Alzheimer's disease. This individual has adequate total sleep time, REM duration and slow-wave activity (SWA) activity but insufficient sleep efficiency, NREM duration and spindle/slow oscillation (SO) synchrony. A potential tailored treatment programme is indicated by the red arrows.

concatenated with N2 and we did not see key parameters of interest, e.g. spindle characteristics and slow oscillation-spindle synchrony thought to be abnormal in mild cognitive impairment.<sup>6</sup> Slow wave frequencies below and over 1 Hz could be interrogated separately to explore the possibility that they predicted change independently. The rationale for considering <1 Hz and 1–4.5 Hz activity in non-REM separately is that reduced <1 Hz oscillations are associated with increased current amyloid deposition<sup>7</sup> and future amyloid accumulation<sup>8</sup> in humans, and optogenetic stimulation at 1.2 Hz (double the natural slow oscillation frequency in mice) increases slow oscillation frequency in mice and accelerates Alzheimer-related pathological changes (e.g. amyloid- $\beta$  production).<sup>9</sup> Here, <1 Hz slow oscillation activity was a more sensitive non-linear marker of future cognitive decline than 1–4.5 Hz activity. This is potentially in keeping with slow oscillation frequencies <1 Hz maintaining brain health. However, we are left asking why high levels of <1 Hz activity correlate with negative cognitive outcomes especially in healthy individuals. Possibly, given the outcome measures are cognitive, slow oscillation activity is reduced by Alzheimer's disease pathology, but in some people, or at early stages of disease, there is a compensatory increase e.g. at the onset of slow oscillation/sleep spindle dyssynchrony.

Assuming the findings are as they appear and the relationship between sleep and cognitive decline is non-linear, what does this really mean? On one level it seems obvious that sleep and cognition could never be entirely linearly positively related as this leads to the prediction that continuous sleep is associated with optimum cognition. Many biological processes have a normal range with negative consequences at high and low levels, e.g. blood glucose. The optimum range of, for example, sleep duration demonstrated in this paper is well within expected limits—around 5–7.5 h with even 8 h being associated with cognitive decline. But it is not clear whether this slightly longer sleep time is the result of pre-existing Alzheimer's disease or other conditions, or an independent risk factor for cognitive decline. The non-linear relationship remained even after adjustment for APOE status and t-tau/amyloid- $\beta_{42}$ —factors that might have been expected to explain the effect. Future understanding of the reasons for non-linearity and health implications is important.

So, if we do not really understand the implications of the non-linear relationship, why is it interesting? One argument against personalized sleep interventions is that, if everyone benefits and more sleep is generally better, then generalized population strategies to improve sleep can be employed. However, if there is truly a non-linear relationship for everyone or increasing a sleep parameter could either benefit or harm future cognition depending on disease-stage, age or other factors, then individualized sleep therapies are required (Fig. 1). Home sleep recording through wearable devices providing a deep characterization of sleep phenotype may help target treatments to the right patients at the right time.

The non-linear link between sleep and cognitive decline observed here is tantalizing and paves the way for larger cohort studies with molecular Alzheimer's disease characterization and sleep analysis to really understand how we could treat sleep to maintain brain health in later life.<sup>10</sup>

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## Competing interests

The authors report no competing interests.

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