The Importance of Sleep-Dependent Memory Testing in Positive Airway Pressure Treatment of Obstructive Sleep Apnea

Memory is classically divided into three phases: encoding of new experiences, offline processing or consolidation of this information, and recall. An abundance of evidence from the world of neurobiology suggests that sleep is crucial for the offline processing phase. This potentially occurs through sleep "replay" of the temporal firing pattern of neurons that occurred during prior wakefulness, strengthening of synapses for information marked as salient while weakening synapses for information marked as irrelevant, or distribution of information heavily encoded by one brain area during encoding to additional brain areas (so-called systems consolidation) (1–3). It therefore stands to reason that disruptions to sleep would most strongly impact this offline processing phase of memory. Obstructive sleep apnea (OSA), with its associated sleep fragmentation and intermittent hypoxia during sleep, likely represents the most common clinical disorder through which memory processing could be impacted. Although OSA can potentially also impact the encoding and recall phases of memory, perhaps through effects on sleepiness or attention, the ability to capture an effect of OSA on the offline processing phase can only occur using sleep-dependent memory paradigms, in which the encoding and recall of information are separated by a period of sleep that either does or does not contain OSA. Studies using such sleep-dependent memory paradigms have shown deleterious effects of OSA on the offline change in declarative (4), spatial navigational (5), and motor memories (6) in comparison with conditions lacking OSA. Unfortunately, the vast majority of studies on OSA and memory exclusively use tasks occurring during daytime testing with no offline processing phase, including APPLES (Apnea Positive Pressure Long-Term Efficacy Study) (7), one of the larger randomized controlled trials of positive airway pressure (PAP) on primary cognitive outcomes.

Thus, the research by Djonlagic and colleagues in this issue of the *Journal* (pp. 1188–1190) is an important contribution to the sleep apnea field, as the authors employ a sleep-dependent declarative verbal paired-associates task involving the encoding and recall of word pairs before and after sleep (8). The authors first demonstrated in a case–control design that individuals with OSA (apnea–hypopnea index [AHI] $\geq$ 5 events/h) display worse overnight retention of word pairs than individuals without OSA (AHI $<$ 5 events/h). Then, individuals with OSA were randomized to autotitrating PAP plus diet and exercise lifestyle modifications or diet and exercise modifications alone. Three months after the intervention onset, individuals from both groups returned for follow-up testing on the word-pair task as well as an in-laboratory polysomnogram. Although the sample size was relatively small, this is the first study to our knowledge that demonstrates a benefit of OSA treatment with PAP in a randomized controlled trial on a primary memory outcome. In fact, overnight retention of word pairs in those randomized to PAP was equivalent to that of control subjects without OSA. Crucially, there were no differences in evening encoding of word pairs and no differences in subjective measures of sleepiness during either the evening or morning in subjects randomized to PAP versus the control condition, suggesting that PAP treatment is most likely impacting the sleep-dependent processing phase of this memory.

Next, the authors performed regression modeling from the case–control portion of the study to identify sleep physiology factors predictive of the overnight change in memory and found that time spent in slow-wave sleep (e.g., non-REM stage 3) represented a significant predictor, whereas the oxygen saturation nadir, AHI, and arousal index did not. In addition, in the clinical trial portion of the study, the increase in slow-wave sleep on the PAP-treated night from the baseline night in those subjects randomized to PAP significantly correlated with the overnight improvements in word-pair retention. These findings are in agreement with observations suggesting that slow-wave sleep and slow-wave activity are important predictors of offline memory processing in individuals with (9) and without OSA (10, 11). Although the inverse relationship between OSA severity and measures of slow-wave sleep is likely to be nonlinear and age dependent (12), other aspects of sleep neurophysiology, such as sleep spindle density (13), spindle–slow oscillation coupling (14), aspects of REM sleep (5) (bout length and theta oscillations), and the sequential occurrence of non-REM and REM sleep (15) have been postulated to be important in the processing of different types of memories and may also be negatively impacted by OSA. Investigation of these other markers would only increase the significance of the present study.

Although we view the use of a sleep-dependent memory task as a key aspect of the success of the randomized controlled trial of PAP in this study, there are at least two other factors that likely also contributed. First, although no OSA severity inclusion criteria were listed, average OSA severity was reasonably high, with a mean AHI of 34.7 events/h and an oxygen saturation nadir of 78.5%. Second, PAP adherence in those randomized to the PAP treatment arm was quite high at an average of 5.68 hours per night. Because subjects were recruited from both the community and local sleep clinics, it is possible that subjects recruited from the clinic randomized to PAP had an incentive to use PAP that may not be present in populations recruited exclusively from the community with incidentally identified OSA.

One limitation of the study is that the memory outcomes in the clinical trial were evaluated at a single time point (3 mo), and whether PAP benefits memory over longer periods of time will be important to ascertain. The authors suggest that their findings may have implications for cognitive decline pertaining to neurodegenerative disease. Although this may be true, it is important to note that cognitive

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decline associated with dementia contains both the inability to form new memories prospectively (as tested here) and the deterioration of established memories. These are dissociable, and although evidence exists that OSA can negatively impact both (16), testing whether PAP treatment slows the deterioration of established memories will be challenging, may benefit from selection of at-risk individuals based on biomarkers, and will likely require years of follow-up. Nonetheless, establishing a benefit of PAP on the formation of new memories is an important and welcome first step. ■

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References

1. Puentes-Mestril C, Roach J, Niethard N, Zochowski M, Aton SJ. How rhythms of the sleeping brain tune memory and synaptic plasticity. *Sleep* 2019;42:zsz095.
2. Klinzing JG, Niethard N, Born J. Mechanisms of systems memory consolidation during sleep. *Nat Neurosci* 2019;22:1598–1610.
3. Ahuja S, Chen RK, Kam K, Pettibone WD, Osorio RS, Varga AW. Role of normal sleep and sleep apnea in human memory processing. *Nat Sci Sleep* 2018;10:255–269.
4. Kloepfer C, Riemann D, Nofzinger EA, Feige B, Unterrainer J, O'Hara R, *et al*. Memory before and after sleep in patients with moderate obstructive sleep apnea. *J Clin Sleep Med* 2009;5:540–548.
5. Varga AW, Kishi A, Mantua J, Lim J, Koushyk V, Leibert DP, *et al*. Apnea-induced rapid eye movement sleep disruption impairs human spatial navigational memory. *J Neurosci* 2014;34:14571–14577.
6. Djonlagic I, Saboisky J, Carusona A, Stickgold R, Malhotra A. Increased sleep fragmentation leads to impaired off-line consolidation of motor memories in humans. *PLoS One* 2012;7: e34106.
7. Kushida CA, Nichols DA, Holmes TH, Quan SF, Walsh JK, Gottlieb DJ, *et al*. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep* 2012;35: 1593–1602. [Published erratum appears in *Sleep* 39:1483.]
8. Djonlagic IE, Guo M, Igue M, Kishore D, Stickgold R, Malhotra A. Continuous positive airway pressure restores declarative memory deficit in obstructive sleep apnea. *Am J Respir Crit Care Med* 2021;203:1188–1190.
9. Mullins AE, Williams MK, Kam K, Parekh A, Bubu OM, Castillo B, *et al*. Effects of obstructive sleep apnea on human spatial navigational memory processing in cognitively normal older individuals. *J Clin Sleep Med* [online ahead of print] 5 Jan 2021; DOI: 10.5664/jcsm.9080.
10. Mander BA, Rao V, Lu B, Saletin JM, Lindquist JR, Ancoli-Israel S, *et al*. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nat Neurosci* 2013;16: 357–364.
11. Varga AW, Ducca EL, Kishi A, Fischer E, Parekh A, Koushyk V, *et al*. Effects of aging on slow-wave sleep dynamics and human spatial navigational memory consolidation. *Neurobiol Aging* 2016;42:142–149.
12. Mullins AE, Bagchi N, Parekh A, Kam K, Wang J, Williams MK, *et al*. Sex specific changes in sleep macro-structure with obstructive sleep apnea in a large clinical population of older adults. *Sleep* 2020;43: A319.
13. Kam K, Parekh A, Sharma RA, Andrade A, Lewin M, Castillo B, *et al*. Sleep oscillation-specific associations with Alzheimer's disease CSF biomarkers: novel roles for sleep spindles and tau. *Mol Neurodegener* 2019;14:10.
14. Helfrich RF, Mander BA, Jagust WJ, Knight RT, Walker MP. Old brains come uncoupled in sleep: slow wave-spindle synchrony, brain atrophy, and forgetting. *Neuron* 2018;97:221–230, e4.
15. Giuditta A, Ambrosini MV, Montagnese P, Mandile P, Cotugno M, Grassi Zucconi G, *et al*. The sequential hypothesis of the function of sleep. *Behav Brain Res* 1995;69:157–166.
16. Osorio RS, Gumb T, Pirraglia E, Varga AW, Lu SE, Lim J, *et al*.; Alzheimer's Disease Neuroimaging Initiative. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology* 2015; 84:1964–1971.

2020 American Thoracic Society BEAR Cage Winning Proposal: Collagen-targeted Positron Emission Tomography Imaging as a Novel Biomarker of Treatment Response in Idiopathic Pulmonary Fibrosis

Despite advances in the treatment of idiopathic pulmonary fibrosis (IPF), it remains a progressive and ultimately fatal disease. Barriers to expedited development of new treatments include costs, prolonged trial duration, and difficulty determining treatment response. Given the natural history of ongoing disease progression in IPF, deciphering treatment response for an individual patient is challenging if not impossible. Change in FVC over 12 months is the currently accepted efficacy endpoint for IPF clinical trials. Biomarkers of early treatment response are lacking. A validated measure of treatment response in IPF would *1*) improve clinical trial feasibility by enabling early determination of treatment efficacy, thereby decreasing overall trial duration; and *2*) improve patient care by enabling treatment plans to be tailored to an individual patient. The proposed use of collagen-targeted positron emission

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