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Reply to Zheng et al.

From the Authors:

We thank Zheng and colleagues for their comments regarding our research study, which demonstrated that 3 months of continuous positive airway pressure (CPAP) therapy can restore declarative memory deficits by augmenting slow-wave sleep (N3) (1).

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One question raised was which aspect of sleep disturbance from obstructive sleep apnea (OSA)—sleep fragmentation/deprivation versus hypoxia—is most pivotal in the development of cognitive deficits. OSA-related sleep fragmentation and intermittent hypoxemia have both been associated with cerebral blood flow, neurovascular and neurotransmitter changes, and a reduction of white matter (WM) fiber integrity.

Although Yaffe and colleagues showed in older women with untreated OSA that only hypoxemia measures were consistently associated with mild cognitive impairment or dementia, our previous research as well as animal studies have pointed to sleep fragmentation having a more detrimental effect on memory consolidation compared with intermittent hypoxemia (2, 3).

We presume that by treating OSA, individuals are able to generate more slow-wave sleep, which restores the hippocampal–medial prefrontal cortex interplay, enabling sleep-dependent stabilization of fragile memory traces and resulting in better retention of declarative memories (4). It is possible that the effects of sleep fragmentation and hypoxia on memory consolidation change across the lifespan. Given that nocturnal arousals become more prevalent with normal aging, the effects of sleep fragmentation on memory consolidation may theoretically be more detrimental in younger than in older people, who naturally have more fragmented sleep.

Previous studies investigating the effects of CPAP on cognitive recovery have applied CPAP for up to 12 months. Examining WM integrity by diffusion tensor imaging, Castronovo and colleagues demonstrated limited WM recovery after 3 months of CPAP therapy but “almost complete reversal of WM abnormalities” in multiple previously affected areas after 12 months, changes that were accompanied by improvements in memory, attention, and executive functioning (5).

We also point out that our group of patients with OSA did not report excessive daytime sleepiness (average Epworth score was below 10 and not different from healthy control subjects) and did not demonstrate a deficit in attention or vigilance, based on psychomotor vigilance task assessments in the evening and morning, yet clearly showed a deficit in sleep-related declarative memory consolidation, which was subsequently restored by CPAP therapy. These results would argue against using daytime sleepiness as a surrogate marker to differentiate between individuals with or without a deficit in memory function and support the independence of brain networks underlying these cognitive processes and their susceptibility to OSA-related sleep fragmentation. Moreover, we believe that many people identified as having “asymptomatic” OSA based on Epworth scores are being mislabeled.

The absence of a deficit in attention and vigilance in the evening and morning before the verbal pairs task test sessions also makes it unlikely that the deficit in sleep-related memory enhancement was due to circadian effects or sleep inertia differences between groups.

Finally, although looking at the duration or percentage of N3 sleep to predict cognitive function would seem reasonable on the basis of these findings, it is not feasible owing to the complexity of the EEG signal. EEG delta waves, which are the dominant rhythm during slow-wave sleep, vary highly between individuals and sexes, across the lifespan, and even from night to night. At this point, there are insufficient normative EEG data and as such we generally do not think in terms of “too much” or

“too little” N3 sleep. We might find more answers using sleep’s EEG microarchitecture as a more sensitive tool for identifying specific features that could help identify individuals at risk of neurocognitive deficits/decline (6). ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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