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Can N3 Period Duration Serve as a Predictor of Cognitive Dysfunction?

To the Editor:

Obstructive sleep apnea (OSA) can cause cognitive impairment, affect the quality of life of patients, and increase the burden on families and society. It has attracted the attention of more and more researchers, and there are also studies that point out the cognitive function of OSA. Most of them are mainly mild damage, and the specific mechanism is still unclear (1).With interest, we read the paper by Djonlagic and colleagues (2), which indicates that 3 months of nocturnal continuous positive airway pressure (CPAP) treatment can increase N3 sleep proportionally to the level of the healthy control group, thereby alleviating the declarative memory deficits of patients with OSA. From the data in the study, it can be seen that apnea–hypopnea index has dropped from 34.7 $\pm$ 7.5 to 3.6 $\pm$ 0.7 events/h, which reduces arousal and increases the time of the deep sleep N3 phase (mainly slow-wave sleep). The increase of slow-wave sleep helps the recovery of the key memory system in the brain.

Djonlagic and colleagues (2) did not show whether declarative memory deficit is related to hypoxia, because the oxygen nadir of patients with OSA is lower than normal, and it increases after treatment. However, studies have shown that sleep deprivation in individuals without OSA can severely impair cognitive functions such as attention, memory, and decision-making, especially affecting the execution of tasks that require a high degree of concentration and rapid response (3). The study by Canessa and colleagues (4) found that before CPAP treatment, most areas of cognitive function of patients were impaired. These damages are related to the decrease in the volume of gray matter in the left hippocampus, left posterior parietal cortex, and right frontal gyrus. After 3 months of CPAP treatment, the patients' memory, attention, and executive functions improved significantly, which paralleled the increase in the volume of gray matter in the hippocampus and frontal lobe structure. It is believed that the cognitive impairment and brain structure damage in patients with OSA may be related to sleep deprivation and repeated intermittent hypoxemia at night, and these damages can be restored by continuous and thorough CPAP treatment. It provides an anatomical basis for OSA cognitive dysfunction and confirms the importance of early diagnosis and treatment of OSA. The possible mechanism is that sleep apnea in patients with OSA leads to hypoxia and changes in sleep structure, which disrupts the functional homeostasis of brain cells and changes the activity of neurons and glial cells in specific areas of the brain (such as frontal and temporal lobes) (5). Some scholars also believe that sleep fragmentation is one of the key mechanisms of OSA cognitive impairment (6).

These findings give us important hints that slow-wave sleep is very important for stabilizing and strengthening declarative memory traces. The question remains whether the duration of the N3 period in sleep monitoring can be used as a predictive indicator to assess the cognitive function of patients, the cutoff of which can be obtained by monitoring in a large sample of patients with and without cognitive dysfunction, so as to screen out high-risk cognitive dysfunction populations for further examination and then targeted treatment for the patients. With the aging of the population and the increasing incidence of cognitive dysfunction, early screening and early intervention are of great significance.

Based on the above points of view, although the sample size is small, the study by Djonlagic and colleagues (2) showed that the shortened N3 stage of sleep of patients with OSA leads to declarative memory deficit and that CPAP can be used to recover. Whether N3 sleep can be used as a predictor of early cognitive dysfunction is worth exploring. ■

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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).

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

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