EDITORIAL

Is Cognitive Aging Associated with Levels of REM Sleep or Slow Wave Sleep?

Commentary on Song et al. Relationships between sleep stages and changes in cognitive function in older men: the MrOS Sleep Study. SLEEP 2015;38:411–421.

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Approximately 200 scientific reports have been published at the intersection of sleep, cognition, and aging.[1] These papers range from population-based cross-sectional studies that subjectively measured both sleep quality and cognitive vitality with large sample sizes (N > 100,000 in Sternberg et al.[2]) to small-sample experimental studies that manipulated PSG-defined sleep and objectively measured cognitive performance.[3,4] What is missing from this extensive literature is a longitudinal, population-based PSG and cognition study in aging adults with substantial statistical power. In this issue of *SLEEP*, Song et al.[5] addressed this gap in the literature by capitalizing on the Osteoporotic Fractures in Men (MrOS) Study. They obtained one night of at-home PSG recordings in a large group of older adults who did not have a dementia diagnosis (N = 2,601) and evaluated cognitive performance using the Trail Making Test Part B and the Modified Mini-Mental State Examination at the baseline sleep visit and again 3–4 years later. Their most impressive findings were that after adjusting for 15 potentially confounding variables (e.g., age, depression, hypertension), men with the lowest quartile of REM sleep (< 15%) and the highest quartile of N1 sleep (≥ 8.52%) showed an accelerated rate of cognitive decline relative to those in the upper quartile of REM sleep (≥ 23.7%) and lowest quartile of N1 sleep (< 3.98%), respectively.

The findings of Song et al. are bolstered by a long history of related studies that also implicated diminished REM sleep in cognitive aging. Nearly a half-century ago, Feinberg and colleagues[6] conducted the first PSG and cognition correlational study in healthy older adults, and one of their primary findings was that low REM activity in healthy older adults was associated with lower performance on psychometric tests. Furthermore, from 1976 to 1990, Spiegel and colleagues evaluated cognitive performance (e.g., mini-mental state examination) in a group of 57 older adults who had baseline PSG data.[7,8] They found that low REM density predicted speedier decline on some cognitive tests. More recently, REM sleep in older adults has been associated in cross-sectional studies with a variety of cognitive measures including episodic memory.[9–11] Similar findings between cognitive function and REM sleep have emerged in aged rodent studies.[12,13] The above findings, however, belie the inconsistent associations involving PSG in the literature,[1] which perhaps reflect small sample sizes (Ns < 20) that do not generalize to the population and increase risk for type I and type II errors.[14] Song et al.'s report,[5] which included the largest and most generalizable sample for a longitudinal PSG and cognitive aging study, provides the most convincing evidence to-date for low REM sleep (and high N1 sleep) being a predictor of declining cognitive functions with aging.

The null findings in Song et al.[5] are perhaps equally interesting. Much of the current work on sleep, aging, and cognition—often inspired by results emanating from memory consolidation research[15,16]—has focused on the role of slow wave sleep (SWS) and whether the changes observed in slow wave activity across the lifespan[17,18] presage declining cognition.[19–23] Yet, most PSG and cognitive aging studies indicate that SWS measures are not associated with cognitive measures in healthy older adults. A few studies have reported positive cognitive correlations with SWS or EEG sleep delta activity in older adults, but there may be nearly as many negative associations in the literature.[1] The finding of Song et al.[5] that duration and percent of SWS at baseline did not predict cognitive decline over 3–4 years is consistent with this negative literature. An important caveat is that the MrOS study lacked a measure of episodic memory, which might be more likely to correlate with SWS (or delta band power[22] or spindle density[10]).

The longitudinal design used by Song et al.[5] makes it tempting to conclude that low REM and high N1 in advanced age *cause* cognitive function to decline. The reverse explanation—that lower cognitive function or effort leads to decreased REM sleep or sleep continuity—seems unintuitive but requires careful consideration. First, two longitudinal studies in humans found that lower cognitive performance at baseline was a predictor of subsequently lesser REM sleep duration[24] and lower sleep efficiency[25] years later. Similar findings for impaired memory predicting shorter duration of paradoxical sleep bouts have been observed in rats as well.[26] Second, in MrOS's "sister study" (the Study of Osteoporotic Fractures), women whose mini-mental state examination scores declined over the preceding 15 years were more likely than non-decliners to show lower actigraphy-defined sleep efficiency.[27] Third, experimental evidence also converges with the account that cognitive function, use, and/or effort impacts sleep in older adults. Interventional "cognitive training" studies have noted that after nearly two months of repeated training on cognitive tasks, subjective and actigraphy-defined measures of sleep improved.[28–30] Such findings might be subsumed under synaptic downscaling theory that predicts that the amount of learning that occurs during the day directly impacts sleep quality that

Submitted for publication January, 2015
Accepted for publication January, 2015
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night[31,32]; however, synaptic downscaling theory has tended to focus more on the impact on SWS rather than REM sleep or sleep continuity.

Sleep decline and cognitive decline could also be epiphenomenal in older age, and be better explained by diminishing general health. The study of Song et al.[5] discourages this explanation because they controlled for many health variables. However, the health variables were often self-reported, thereby possibly lacking in precision. A possible explanation for correlations between REM sleep and cognitive function in old age is central cholinergic dysfunction. Cholinergic innervation is critical to eliciting REM sleep[33]; cholinergic dysfunction has consistently been associated with cognitive deficits[34]; and reduced cholinergic innervation is observed in many older adults, particularly those with the early stages of Alzheimer disease.[35] It is therefore noteworthy that when researchers manipulated REM sleep in older adults via REM deprivation, REM rebound, and with an acetylcholinesterase inhibitor, that only the cholinergic medication had an effect on cognitive functioning.[36]

The well-designed study of Song et al.[5] is a valuable reminder that REM sleep has historically been more consistently connected with cognitive measures than has SWS in older adults. Whether low REM sleep causes cognitive function to decline is a hypothesis that requires further investigation, with particular attention paid to the possibility that a common substrate (e.g., decreased cholinergic neurotransmission) may explain declines in both cognitive function and REM activity.

CITATION

Scullin MK, Bliwise DL. Is cognitive aging associated with levels of rem sleep or slow wave sleep? *SLEEP* 2015;38(3):335–336.

DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.

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