

COMMENTARY

Fragmented Sleep and Cortical Thinning in Old Adults: Time to Wake Up?

Commentary on Lim et al. Regional neocortical gray matter structure and sleep fragmentation in older adults. *SLEEP* 2016;39(1):227–235.

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Retired older adults may have the freedom to sleep ad libitum, but this benefit can be offset by age-associated changes in sleep such as reduced duration, poorer subjective quality, increased fragmentation and/or altered macrostructure. Although sleep duration is probably the measure that has traditionally received the most attention,¹ there is accumulating evidence that sleep quality and sleep fragmentation in particular, can have deleterious effects on brain structure and cognition.^{2–5} A change in sleep pattern in late adulthood can foreshadow cognitive decline,⁶ perhaps as a result of accumulation of neurotoxic substances that are normally cleared during sleep.⁷ Magnetic resonance imaging of the brain is an attractive tool for studying how poor sleep affects the brain, which may then mediate cognitive changes. Alternatively, as will become apparent, variations in brain structure could also affect sleep. A challenge in interpreting how brain structure relates to degraded sleep quality (and vice versa) in older adults is the extent to which structural features putatively related to sleep variables can be differentiated from age-related changes that occur even in healthy, cognitively intact older adults.

In this issue of *SLEEP*, Lim and his colleagues⁸ report an association between fragmented sleep and thinning of the lateral orbitofrontal and inferior frontal cortex in healthy, cognitively intact, community-dwelling, old adults. This study is notable for its relatively large sample size and the care taken to account for factors that could obscure or confound sleep-brain structure associations. The recruitment of healthy and cognitively intact persons minimizes concerns that either sleep fragmentation or brain structural differences could have been secondary to either poor health or cognitive impairment. Sleep fragmentation was measured objectively with actigraphy, attenuating concerns about the reliability of self-reported sleep history. Interestingly, no association between self-reported sleep continuity and cortical thinning was found. The work additionally differentiated the association between brain structure and *objective* sleep fragmentation from associations with *self-reported* sleep duration, as the latter was not significantly associated with any of the 68 brain morphometric measures used in the study.

How localized are the structural features associated with sleep fragmentation? The multitude of brain morphometric measures used allowed the authors to definitively relate sleep fragmentation to lower gray matter volume in the cortical mantle sparing subcortical gray matter and white matter volumes. Impressively, reduced lateral orbitofrontal cortical thickness remained significant even after accounting for age effects on total gray matter volume, and correcting for multiple comparisons, strengthening the claim that the association between sleep fragmentation and cortical thinning was regionally specific. The use of cortical thickness as a measure of regional assessment of brain structure is

favored over the use of volumes by specialists in imaging genetics,^{9,10} and it is important to point out that just as there are different measures of sleep fragmentation, the different measures used to characterize brain structure may have different underpinnings.

How might the observed brain structural findings relate to sleep fragmentation? Reduced gray matter density within the lateral orbitofrontal cortex is a recurring finding in imaging studies of chronic insomnia.^{11,12} It has been associated with early morning awakening, which is in turn correlated with problems with sleep maintenance, but not with difficulty initiating sleep.¹³ The anterior insula, included in the region showing thinning, shows phasic increases in blood flow in association with the occurrence of both slow and fast spindles.¹⁴ In turn, spindles appear to insulate the sleeper from external sensory stimuli,¹⁵ so circumscribed gray matter thinning in this region could potentially increase a person's susceptibility to sleep disruption. Additionally, the onsets of slow oscillations that feature in slow wave sleep are coincident with transient increases in BOLD signal in the inferior frontal gyrus and medial prefrontal cortex.¹⁶ High-density EEG shows the insula to be a source of posteriorly propagating slow oscillations.¹⁷ Together these findings suggest a role for the lateral orbital/inferior frontal region in maintaining sleep. While future work will be required to confirm these links, they appear to be plausible mechanisms through which the brain structural changes could initiate or perpetuate sleep fragmentation.

What might underlie the circumscribed cortical thinning? The regression model used to assess if regionally specific thickness was associated with sleep fragmentation, considered age, gender, education, depression, peripheral-vascular, cardiovascular as well as cerebrovascular disease, smoking and hypnotic use—a comprehensive list of potential confounders. Unlike the hippocampus, which is exquisitely sensitive to a variety of insults,¹⁸ there is presently no clear evidence that orbitofrontal/inferior frontal thinning is triggered by exogenous factors. Instead, constitutional factors are likely to be relevant. Major depression could negatively affect orbitofrontal volume,¹⁹ but this was accounted for in Lim's study. Prefrontal cortical thickness exhibits a high degree of heritability,¹⁰ suggesting that a common heritable factor influences both sleep continuity in later life and orbitofrontal thickness.¹³ In chronic insomnia patients, reduction in orbitofrontal gray matter density did not correlate with the duration of insomnia,¹³ suggesting that the structural feature represents a preexisting vulnerability that gets unmasked with age. Might this have been the case in the present study?

Although Lim's study was not designed to evaluate the relationship between sleep fragmentation and cognitive decline, the advanced age of the participants begs the question of how

localized orbitofrontal/inferior frontal cortical thinning might impact cognition. The fact that participants in the study were cognitively intact despite having fragmented sleep suggests that the observed structural differences are unrelated to risk of cognitive decline. A direct comparison of structural imaging changes associated with healthy aging and Alzheimer disease indicates that insula thinning may be a morphological feature of healthy ageing rather than Alzheimer disease.²⁰ Further, while reduced sleep efficiency has been associated with β -amyloid accumulation in the brain,²¹ areas that accumulate β -amyloid the most are highly metabolically active and include the precuneus/midline parietal, temporal and cingulate areas relatively sparing the orbitofrontal region.²² To date, the sole work that evaluated longitudinal changes in brain structure in relation to self-reported sleep quality found that lower global sleep quality scores on the Pittsburgh Sleep Quality Index (PSQI) related to more rapid atrophy of several frontal, temporal, and inferior parietal areas.²³ However, as cognitive testing was not performed it is possible that the more extensive longitudinal changes observed in that study were influenced by inadvertent inclusion of cognitively impaired participants. Based on available evidence, the cognitive consequences of orbitofrontal thinning in otherwise cognitively intact older persons appears to be relatively benign.

One caveat before generalizing from the authors' findings is that the kRA metric²⁴ used to quantify sleep fragmentation is new and not yet widely used. The relationship between the brain findings and more conventional measures like sleep efficiency (SE) and wake after sleep onset (WASO) is unknown. Neither was the kRA related to the widely used PSQI measure of sleep quality. The kRA is moderately correlated (r around 0.4–0.6) with the aforesaid traditional measures, but as it measures the probability of a brief arousal within a 15-s window of sleep, it is likely to provide a finer grained, more sensitive marker of disturbance in sleep continuity and is likely to capture events that are not subjectively detected. Looking ahead, objectively measuring sleep with wrist actigraphy will become increasingly relevant with the growing adoption of mobile health trackers that have inbuilt motion sensors. Another noteworthy point is that participants were remarkably healthy and cognitively intact (MMSE \sim 29) despite being advanced in years (mean age = 82 years), suggesting they may have some protective factor to enable them to avoid the reported negative health effects of sleep fragmentation.

In summary, Lim et al. elegantly demonstrate how sleep fragmentation measured in a specific way may be associated with localized thinning of a brain region which may be important for maintaining sleep continuity and whose thinning has been linked to chronic insomnia. Future studies should clarify how different measures of sleep quality relate to various changes in brain structure and function and whether improving sleep quality can ameliorate or reverse either adverse structural or functional outcomes. For this to occur, the field should agree on a set of common sleep as well as brain measures so that findings can be compared across groups. Longitudinal studies would also be important in establishing the temporal and possibly casual relationships between localized brain atrophy, sleep disturbance, and cognitive change.²⁵

CITATION

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