GUEST EDITORIAL

Sleep disturbance: an emerging opportunity for Alzheimer's disease prevention?

As the older segment of our population grows, cognitive decline and dementia will increase in prevalence, with Alzheimer's disease (AD) as the cause in most cases. Until a cure exists, prevention through the identification and manipulation of modifiable risk factors for dementia, in general, or AD, in particular, will be our only means of reducing dementia prevalence or delaying its onset. Furthermore, it is likely that eventual treatments for AD, when available, will depend on the ability to identify individuals at greatest risk for developing AD. Sleep disturbances are common in later life – roughly half of older adults experience regular insomnia (Ohayon, 2002) and about as many have some degree of sleep-disordered breathing (SDB) (Ancoli-Israel *et al.*, 1991) – and accumulating evidence suggests they may contribute to cognitive decline, at least in part, by promoting the development of AD pathology (Spira *et al.*, 2014). Because they are treatable, sleep disturbances are an important potential target for ongoing study in AD prevention. Moreover, understanding the mechanisms underlying an effect of sleep on subsequent cognitive decline and AD would allow for better identification of opportunities and optimal timing for treatment of sleep disorders, and ultimately perhaps, AD prevention.

Research into the mechanisms that might underlie associations between sleep loss and cognition was energized in 2009 by a seminal paper showing in an AD mouse model that during wake there are increases, and during sleep there are decreases in β-amyloid (Aβ) protein in brain interstitial fluid (Kang *et al.*, 2009). The authors showed similar sleep-dependent changes in the cerebrospinal fluid of young healthy humans, and most importantly, that sleep deprivation increased brain amyloid deposition in the mouse model. Since then, observational studies have linked poor sleep to AD biomarkers in humans, including cerebrospinal fluid and positron emission tomography measures of Aβ; a randomized trial showed that sleep deprivation altered Aβ dynamics in healthy middle-aged humans (Spira *et al.*, 2014), and research in a *Drosophila* model of AD demonstrated that sleep deprivation led to substantially greater Aβ deposition (Tabuchi *et al.*, 2015). Taken together,

these and related findings have raised interest in further investigating sleep's status as a means of preventing AD.

Two main physiological mechanisms have been proposed to explain how sleep loss leads to AD. The first is based on the observations that increased neuronal firing promotes Aβ production, that this firing is reduced during slow-wave sleep relative to wake, and that sleep loss consequently leads to net increases in neuronal activity and a resultant increase in Aβ production (Ju *et al.*, 2014). The second mechanism is based on recent research showing that, during slow-wave sleep, the brain can more efficiently clear metabolic waste, and that Aβ can also be cleared more effectively during this state (Xie *et al.*, 2013). Moreover, the two main consequences of SDB are sleep fragmentation and chronic intermittent hypoxia. SDB-induced sleep fragmentation could increase Aβ production through the mechanisms just described, and hypoxia could do so by affecting APP production and related processes (Daulatzai, 2012).

Although physiologic data support a possible mechanistic association between disturbed sleep and AD, the notion that disturbed sleep promotes AD or other poor brain health outcomes strikes many as surprising or counterintuitive, at least initially, and this may be why it is only now gaining recognition as a potential AD risk factor. Indeed, the salience of sleep disturbance observed in older adults with AD may have oriented us to think of disturbed sleep as a consequence of AD, rather than a cause. Over the last 15 years or so, however, many studies have linked self-report or objective measures of different sleep parameters (e.g. sleep quality, duration, and onset latency) or indices of SDB to lower performance or decline in measures of global cognitive function or particular cognitive domains in the general population of older adults, suggesting that sleep loss may increase the risk of poor cognitive outcomes (Scullin and Bliwise, 2015). This focus on relatively healthy populations and on sleep as a risk factor for subsequent cognitive decline is a shift from earlier studies in already-impaired older adults.

Perhaps, however, disturbed sleep should have been a more obvious suspect as a modifiable risk factor for AD, given it has itself been linked to multiple identified modifiable AD risk factors (Barnes and Yaffe, 2011), including diabetes, hypertension, depression, obesity, and smoking (Daulatzai, 2012), reduced physical activity (Schmid et al., 2009), and low educational levels (Grandner et al., 2010). Moreover, age and the apolipoprotein E (APOE) ε4 allele are not only among the most robust AD risk factors but have both been tied to an increased risk of SDB (Kadotani et al., 2001; Daulatzai, 2012). Thus, even without a putative mechanism to explain how disturbed sleep might actually promote AD pathology, its association with these established risk factors suggests that it plays an important role. It may be that knowledge of the importance of the critical timing of measuring and treating these more traditional risk factors needs to be applied to the sleep field; midlife hypertension appears most important in subsequent dementia risk (Iadecola et al., 2016), and it is worth exploring whether similar patterns exist for disturbed sleep and SDB. Furthermore, establishing whether sleep's effect on cognitive decline and AD is additive beyond the potential effect on these shared risk factors would be important to the optimization of treatment and prevention strategies.

Although treating sleep disturbance or optimizing sleep may ultimately turn out to be effective avenues for AD prevention, further evidence is needed before we embrace them as such. The most immediate need is for longitudinal studies with objective sleep measures and with AD biomarkers, to complement existing studies, many of which are cross sectional or rely solely on self-report sleep measures. Although people's subjective report of their sleep quality, duration, and other sleep parameters provides valuable information about their perceptions, self-report measures do not necessarily reflect how people are actually sleeping. Objective sleep measures include polysomnography (an overnight sleep study, either in the sleep lab or in participants' homes) and wrist actigraphy, which involves the recording of movement at the wrist over sequential 24-h intervals using an accelerometer. Algorithms developed in validation studies with polysomnography as the criterion are applied to the actigraphy data, producing sleep parameters comparable to those obtained by polysomnography (Ancoli-Israel et al., 2015). An advantage of actigraphy is that it is far less expensive than polysomnography and can therefore be used in large cohort studies to obtain an objective sleep measure at relatively low costs. Downsides are that actigraphy cannot definitively discriminate between a person who is asleep and one who is simply lying very still, and it cannot yet be used to quantify SDB. Another limitation of existing studies linking sleep to AD is that they have relied almost exclusively on cognitive measures as outcomes. Although cognitive outcomes are of critical clinical importance, biomarkers provide important complementary information regarding etiology. Fortunately, studies of sleep and AD biomarkers are being published with greater frequency.

A separate important question is how to proceed if evidence accumulates to the point that clinical guidelines support addressing sleep for AD prevention. For example, in the case of insomnia, sedative-hypnotic medications are risky – especially among older adults – and are short-term solutions in the best case, and although we have highly effective behavioral treatments (e.g. cognitive-behavioral therapy for insomnia), we have inadequate numbers of qualified providers to meet the hypothetical treatment need. In addition to increasing the availability of skilled practitioners in the clinic, another solution is to develop community-based interventions to prevent or treat insomnia that are both accessible and scalable (Black et al., 2015). For example, a recent randomized trial showed that a mindfulness meditation intervention improved sleep in older adults with moderate sleep complaints (Black et al., 2015). Additional interventions like this are needed that can be delivered in the community-by-community members, rather than by professionals in clinical settings. Because no one community-based intervention will appeal to all older adults, a range of effective options is needed (Spira, 2015). Volunteering may be another example of a community-based "intervention," and may improve sleep by increasing physical, cognitive, and social activity (Spira, 2015). However, this possibility requires further study. With respect to SDB, continuous positive airway pressure therapy is a highly effective treatment, but adherence is commonly a challenge and scalable community-based interventions to address SDB are not readily apparent.

In sum, these are exciting times for those of us with an interest in sleep, AD, and AD prevention, but much research with longitudinal study designs and more rigorous sleep measures is needed. If findings continue to identify sleep as a modifiable risk factor for AD, we will have to think creatively to disseminate existing safe and effective clinical interventions and to develop community-based approaches to maximize sleep health that will reach the large numbers of people who will need them.

Conflict of interest

Acknowledgment

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