Hypotrophy versus Hypertrophy: It's Not Black or White with Gray Matter

Obstructive sleep apnea (OSA) is commonly associated with cognitive deficits, including impairments in episodic and semantic memory, working memory, and executive function (1–4). OSA also impacts attention and vigilance; however, when these are controlled, few consistent memory deficits have been found. Moreover, OSA is common in older people, and the mechanism of how OSA-related deficits increase the risk of cognitive decline and dementia in older people is not yet understood (5). A recent quantitative metaanalysis suggests that up to half of patients with Alzheimer's disease have (or develop) OSA after their diagnosis (6), which may in turn exacerbate the cognitive decline and progression of the Alzheimer's disease. This is of relevance, as it has been predicted that, by 2050, the number of people aged 65 and older with Alzheimer's disease could triple, from 5.2 million to a projected 13.8 million, barring the development of medical breakthroughs to prevent or cure the disease (7). Recent statistics also suggested that the estimated cost of caring for patients with Alzheimer's disease in the United States in 2016 was around $236 billion, with patients with Alzheimer's disease being hospitalized three times more often than seniors without Alzheimer's disease (7).

The link between OSA and dementias appears to be supported by several recent studies (8–10), and if future prospective studies bear out this association, it will follow that any treatment of OSA that can produce improvements in quality of life, or slow cognitive decline in older patients, will have a significant impact on the health care burden of countries with an aging population. The estimated global cost of Alzheimer's disease and dementia is a staggering $605 billion, which is equivalent to 1% of the entire world's gross domestic product (7).

It has been 15 years since the first report of widespread changes in cerebral gray matter structure of patients with OSA (11). Since then, there has been an almost continuous debate about the extent of any structural brain changes in patients with OSA (12–14), the relationship between the structural and functional deficits, and the reversibility of any changes (15, 16). The inconsistency of the findings may in part be due to different patient groups studied (e.g., variability in disease severity and duration of exposure, comorbidity, cognitive reserve, etc.) and/or the development of methods of neuroimaging and analysis (e.g., statistical thresholds and statistical parametric mapping version number, etc.) (13, 17, 18). A recent quantitative metaanalysis of structural and functional brain magnetic resonance data in patients with OSA highlighted changes in the right amygdala/hippocampus complex and the insular cortex (19). Both areas have important roles in the cognitive and affective circuitry, as part of a network comprising the anterior insula, posterior-medial frontal cortex, and thalamus (19). Overall, these and other neurophysiological findings (20, 21) suggest that OSA has a significant impact on the thalamocortical oscillator, with involvement of the hippocampal formation (16, 22). It is notable, however, that almost none of these studies included older people, with the mean age of the patients with OSA included in the studies being 46.6 years (19).

In this issue of the *Journal*, the study by Baril and colleagues (pp. 1509–1518) investigates the impact of OSA gray matter changes in a large number of middle-aged and older patients with OSA, examining both structural changes and cortical thickness in association with severity of the OSA as defined by three respiratory and sleep variables, namely hypoxemia, respiratory disturbances, and sleep fragmentation (23). In this study, 71 participants (mean age, 65.3 $\pm$ 5.6 yr) ranging from healthy volunteers to those with severe OSA were studied (23). Patients with OSA were found to have increased volume and thickness of the left lateral prefrontal region plus increased thickness of the right frontal pole, right lateral parietal, and left posterior cingulate regions of the cortex. Those patients with a higher respiratory disturbance index had an enlarged amygdala, and fragmented sleep was correlated to a thicker inferior frontal gyrus. This is not the first study to report an increase in gray matter in patients with OSA, either at baseline or after the treatment (15, 16, 24), and the relationship between adaptive and maladaptive pathways in response to sleep and hypoxic disturbances has been debated previously (25, 26). However, several findings and methodical approaches in this study are novel and should be highlighted.

First, this study emphasizes the potential sensitivity differences between various neuroimaging analysis methods. For example, traditionally in respiratory sleep research, voxel-based morphometry analysis has been most commonly used (13). More recently, the newer FreeSurfer analysis has been used (16, 24). The study of Baril and colleagues has added to the field by showing that differential neuropathological changes can be found using different techniques (23). Second, the finding of neural hypertrophy in older patients with OSA is novel, and the authors argue several adaptive and maladaptive mechanisms, such as cerebral edema, reactive gliosis, neural branching, and increased β-amyloid may underlie this ultrastructurally (23).

A major barrier to mapping and unlocking the mechanistic pathways in OSA is that the duration of disease is generally unknown. In animal models, adaptive responses to intermittent hypoxia occur relatively quickly (within days) (27). Of note is that a significant proportion of patients in the study by Baril and colleagues (42%) had milder OSA, with minimal neurocognitive deficits, and hence were considered to be in a presymptomatic stage of the illness (23). Therefore, it is possible that at least some of the observed hypertrophic changes were functional and adaptive. Interestingly, Lavie and Lavie have long argued that sleep apnea in the elderly may offer a survival advantage through instigation of adaptive mechanisms (28).

Last, the authors of this study have tried to address another unsolved question in the field, the impact of sleep fragmentation

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versus that of hypoxemia or arousals, by using a principal component analysis of respiratory and sleep variables. Although this approach is limited, and no robust conclusions on this issue may be implied, some interesting correlations and differential vulnerabilities of intrinsic brain circuitries have been highlighted. For example, the severity of OSA, defined by the level of hypoxemia, was correlated with changes in posterior default mode network and changes in the frontoparietal network (23). This is of note, as the major task of this network is in attentional selection of the relevant stimuli. Any disturbance in this network and/or its connectivity with other networks, such as a posterior default mode network, is likely to have a dramatic effect (29). Conversely, possible functional changes in salience network were implied by correlation between respiratory disturbances and amygdala changes. The salience network has key nodes in the insular cortices (19), and it has a central role in the detection of behaviorally relevant stimuli and the coordination of neural resources (29). The functional importance of these differences is yet to be understood, but they nonetheless raise questions about the validity of phenotypic profiling of patients and more specific therapeutic targeting of various aspects of OSA. Finally, in light of links with Alzheimer's disease, the unraveling of the exact neuropathohistological nature of the observed hypertrophic changes should be of particular importance, and future multimodal neuroimaging, physiological, and genetic studies are urgently needed to address this. Increased and prolonged neuronal firing has been implicated in neuroinflammatory responses, increased production of β-amyloid, and likely decreased functioning of the detoxifying glymphatics system in the brain, all of which is important for the instigation and development of the neurodegenerative process in the genesis of the Alzheimer's disease (30).

In conclusion, it is likely that at any given point in time, depending on the stage of OSA, its severity, and individual idiosyncratic vulnerability, a set of polymorphic and mixed adaptive and maladaptive responses might be at play (22). A key finding of the study featured in this editorial was that even mild OSA was associated with hypertrophic changes in gray matter structure (23). Clinically, this may be important, as older people often develop milder OSA due to age-related changes in the upper airway. The effects of moderate and severe OSA are well documented, and effective treatment with continuous positive airway pressure has been shown to improve symptoms and reduce health risks in these patients. Whether or not mild OSA warrants early treatment is less clear (31). We do know that treatment for OSA in symptomatic older people produces a benefit that is cost effective (32, 33), and there are also suggestions that it can improve sleep in Alzheimer's disease (34). ■

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Investigating the Pathogen Genomic Determinants of Tuberculosis Transmission

In this issue of the *Journal*, the article by Nebenzahl-Guimaraes and colleagues (pp. 1519–1527) is a novel look at the whole-genome determinants of *Mycobacterium tuberculosis* transmission (1). Relative to many other bacterial species, *M. tuberculosis* has comparatively little sequence diversity (2). This lack of diversity has limited findings from genotype–phenotype association studies that have used low resolution genotyping techniques.

Existing evidence suggests a *M. tuberculosis* lineage-specific effect on virulence (3–5), mutation rate (6), immune response (7), and transmissibility (8), although the findings vary by setting and are limited when comparison is made with control strains that have been passaged in the laboratory.

Many studies have examined the host and environmental factors that influence transmission and second cases of disease (9, 10). For example, it is well documented that smear-positive index cases (11, 12), those with cavitation (13, 14), and index cases with HIV-positive contacts give rise to more secondary cases of disease (15). However, the genotypic determinants of *M. tuberculosis* transmission remain poorly understood.

Transmission is conventionally deemed to have occurred when a previously skin test–negative contact of tuberculosis disease becomes skin test–positive after exposure to an index case. It is important to clarify that this study examines the association with second cases of tuberculosis disease and not transmission as it is conventionally defined. Understanding which tuberculosis index cases give rise to a second case of tuberculosis disease is arguably more important than understanding which individuals give rise to an infection that may never cause disease.

The behavioral aspects of transmission, such as abandoning treatment, inadequate nutrition, and index-contact mixing, are difficult to predict. However, the genome of *M. tuberculosis* is a relatively fixed entity with a mutation rate of approximately 0.5 single nucleotide polymorphisms per genome per year (16). Therefore, better understanding of the genetic determinants of transmission could enable clinicians and public health professionals to identify individuals at high risk of transmission, independent of other factors. If pathogen genetic factors can be shown to influence transmission, the possibility of isolating the

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