4. Pi H, Kosanovich CM, Handen A, Tao M, Visina J, Vanspeybroeck G, *et al.* Outcomes of pulmonary arterial hypertension are improved in a specialty care center. *Chest* 2020;158:330–340.
5. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, *et al.*; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009;53:1573–1619.
6. Pulmonary Hypertension Association. PH care centers: accredited centers. [accessed 2025 Feb 27]. Available from: https://phassociation.org/phcarecenters/accredited-centers/.
7. Leary PJ, Le RJ, Panjabi S, Hartney J, Goyal A, Ward C, *et al.* Location of care delivery for pulmonary arterial hypertension in the United States. *Am J Respir Crit Care Med* 2025;211:619–627.
8. Gillmeyer KR, Lee M-M, Link AP, Klings ES, Rinne ST, Wiener RS. Accuracy of algorithms to identify pulmonary arterial hypertension in administrative data: a systematic review. *Chest* 2019;155:680–688.
9. Kovacs G, Bartolome S, Denton CP, Gatzoulis MA, Gu S, Khanna D, *et al.* Definition, classification and diagnosis of pulmonary hypertension. *Eur Respir J* 2024;64:2401324.
10. Deano RC, Glassner-Kolmin C, Rubenfire M, Frost A, Visovatti S, McLaughlin VV, *et al.* Referral of patients with pulmonary hypertension diagnoses to tertiary pulmonary hypertension centers: the multicenter RePHerral study. *JAMA Intern Med* 2013;173:887–893.
11. Gillmeyer KR, Rinne ST, Qian SX, Maron BA, Johnson SW, Klings ES, *et al.* Socioeconomically disadvantaged veterans experience treatment delays for pulmonary arterial hypertension. *Pulm Circ* 2022;12:e12171.
12. Issa R, Minhas AMK, Issa R, Ariss RW, Nazir S, Satti DI, *et al.* Urban-rural disparities in pulmonary hypertension-related mortality between 2004 and 2019: a call to improve access to specialty care centers for rural residents in the United States. *Curr Probl Cardiol* 2023;48:101623.
13. Pulmonary Hypertension Association. Pulmonary vascular disease fellowship programs. [accessed 2025 Feb 27]. Available from: https://phassociation.org/education-programs/pvdfellowships/.
14. Chambers HE, Reinschmidt K, Smith G, Agudelo E, Brodahl K, Herriman E, *et al.* Examining the critical role of advanced practice providers on a multidisciplinary transplant team. *Am J Transplant* 2021;21:3840–3846.
15. Benza RL, Doyle M, Lasorda D, Parikh KS, Correa-Jaque P, Badie N, *et al.* Monitoring pulmonary arterial hypertension using an implantable hemodynamic sensor. *Chest* 2019;156:1176–1186.
16. Elrod JK, Fortenberry JL. The hub-and-spoke organization design: an avenue for serving patients well. *BMC Health Serv Res* 2017;17:457.
17. Furukawa MF, Kimmey L, Jones DJ, Machta RM, Guo J, Rich EC. Consolidation of providers into health systems increased substantially, 2016-18. *Health Aff (Millwood)* 2020;39:1321–1325.

Obstructive Sleep Apnea Treatment for Brain Health: Improvement in Connectivity but Not Measurable Function?

Obstructive sleep apnea (OSA) is increasingly recognized as a risk factor for cognitive impairment. The default mode network (DMN), which includes nodes across the frontal, temporal, and parietal lobes of the brain, is crucial for integrating memories for events across time (episodic memory) and emotional experiences (1). Nodes receiving simultaneous blood flow at rest, believed to reflect simultaneous neural firing, is what defines functional connectivity (FC). Reduced FC within the DMN is linked to cognitive impairments in patients with OSA, possibly related to hypoxemia more than sleep fragmentation (2). Therefore, multimodal assessments of brain structure (T1 structural magnetic resonance imaging [MRI]), connectivity (resting-state blood oxygen level–dependent functional MRI), and function (cognitive testing) with continuous positive airway pressure (CPAP) treatment are important to evaluate.

In this issue of the *Journal*, Xu and colleagues (pp. 628–636) conducted a multicenter randomized controlled trial to evaluate the effects of CPAP treatment on brain connectivity, structure, and function in middle-aged patients with OSA and normal cognition (3). The study involved 148 participants with an apnea–hypopnea index (AHI3A) ⩾15 events/h recruited from five hospitals and randomly assigned to two groups: CPAP with best supportive care (BSC) versus BSC alone. The primary endpoint was the Montreal Cognitive Assessment (MoCA) score at 6 months, and secondary endpoints included intranetwork FC of the DMN and cortical thickness assessed by structural MRI at 3, 6, and 12 months. The results showed no significant difference in MoCA scores at 6 months between the CPAP and BSC groups. However, significant differences in FC of the DMN and cortical thickness were observed between the CPAP and BSC groups at 6 months, suggesting that OSA interventions may improve brain structure and function in patients with normal cognition.

The study's strengths include its multimodal neuroimaging techniques and randomized controlled trial design, with a relatively long intervention period. The study had high retention rates (86% and 84% at 6 and 12 mo, respectively) and modest CPAP adherence (53% and 51% >4 h CPAP use/night at 6 and 12 mo, respectively). The study also had three follow-up assessments at 3, 6, and 12 months for other secondary and exploratory outcomes. Most prior studies of effects of CPAP on cognition have been observational, and few have combined the multiple brain imaging metrics employed here. In addition, the variability in patient selection, duration of OSA status, and methodology

Supported by NIH grants K23AG068534, R01AG082278, and RF1AG083975; Alzheimer's Association grant AARG-21-848397; and BrightFocus Foundation grant A2022033S (O.M.B.) and by NIH grants R01AG066870 and R01AG080609 and Alzheimer's Association grant AARG-22-928739 (A.W.V.). The funders had no role in the conception or preparation of the manuscript.

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202501-0057ED on February 28, 2025

in prior studies has made it difficult to identify clear patterns of gray matter changes in patients with OSA and treatment response (4, 5). Therefore, the randomized controlled trial by Xu and colleagues using multimodal assessments of brain structure, connectivity, and function is valuable for understanding the potential effects of adequate OSA treatment on cognitive function and brain imaging changes.

Although cognition is an undeniably important outcome, future studies may want to consider alternatives to the MoCA as the primary cognitive endpoint. The MoCA is primarily a screening tool for cognitive decline rather than overall cognition, which requires extensive evaluation with multiple neuropsychological tests. The study participants had normal cognition and were relatively young at an average age of ∼46 years, making it unlikely that they would decline over 3 to 12 months. Although longer study durations may be challenging, 2 years have been shown to be sufficient to observe cognitive changes related to OSA in older populations (6, 7). The authors observed relative increases in cognitive performance over time in both groups, which may reflect a practice effect from repeated assessments. The study's examination of OSA's role in cognitive memory exclusively employed daytime tests, which do not provide opportunities for sleep-dependent consolidation (8). Adjusting for sleep variables, such as sleep duration, might have been beneficial, because individuals with shorter habitual sleep duration may have less to gain from CPAP therapy. Pairing cognitive testing with assessment of Alzheimer's disease (AD) fluid or imaging biomarkers for amyloid (the primary component of neuritic plaques), phosphorylated tau (the primary component of neurofibrillary tangles), or neurodegeneration may be useful because OSA has been associated with such AD biomarkers even in cognitively normal older adults (7, 9, 10).

Despite the null findings in the primary cognitive outcome, Xu and colleagues observed significant differences in FC of the DMN and cortical thickness between the CPAP and BSC groups at 6 months, particularly in the left hemisphere. The exclusion of left-handed participants may have contributed to the observed lateralized effects. The cortical thickness observations in particular deserve contextualization. First, the magnitude of the difference in cortical thickness between the treatment and control groups at 6 months was 0.06 mm (60 μm), which is the approximate width of a human hair. At 3T, MRI voxel resolution is on the order of 1 mm, suggesting the differences are within the measurement error of the tool used. Second, although other observational studies have also noted gray matter increases after CPAP treatment (11), what this reflects on a cellular level is unclear. It seems very unlikely to represent neurogenesis because adult neurogenesis has only been observed in the dentate gyrus and olfactory bulb. The authors speculate that this could reflect an inflammatory process, but this would seem at odds with the observation that OSA has proinflammatory consequences that increase with OSA severity (12), suggesting that reduced inflammation might be expected with OSA treatment. Magnetic resonance spectroscopy measurements of key brain metabolites, which could assess brain metabolic changes and neuronal health, could help resolve some of these uncertainties. Future work that includes a healthy control group would aid in direct comparisons of baseline cortical thickness and DMN connectivity with a non-OSA population.

The authors couch their neuroimaging findings as being potentially relevant to AD risk. Consistent patterns of reduced cortical thickness and hippocampal subfield volumes have been identified in early AD (13); however, whether CPAP treatment slows this expected trajectory in those destined for AD may require longer observation durations in older populations. Functional DMN connectivity may differentiate patients with AD from healthy control subjects independently of age (14). Accumulation of established AD biomarkers, such as tau, may lead to impaired DMN connectivity and promote neurodegeneration (13, 14). Low resting-state brain activity may contribute to early amyloid-β deposition within the DMN, disrupting network connectivity (15). At face value, improved DMN connectivity as a function of CPAP therapy would seem to be of benefit and, notably, may be useful in creativity and forms of memory (e.g., autobiographical memory) (16) not captured by the MoCA. But, as with cortical volumes, whether this protects the deterioration of established memories may take longer periods of time in older individuals at greater AD risk.

It is important to highlight that Xu and colleagues provide valuable new data on the role of OSA treatment on brain connectivity and structure, even if disentangled from any relationship to AD risk. Like any good study, this one opens new questions, such as on the histological meaning of gray matter volume increases and the cognitive correlates of enhanced DMN connectivity. Given that race- and sex-specific differences exist for both OSA (17) and AD (18), it will be interesting to interrogate the consistency of these findings across diverse populations. Future studies could consider employing extensive cognitive evaluations with both standard neuropsychological tests and sleep-dependent tasks in which encoding and recall are separated by sleep. Using established biomarkers of AD pathology, characterizing OSA using endophenotypes and novel measures of severity, adjusting for potential confounding sleep variables, and implementing longer follow-up periods represent additional worthy endeavors. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Omonigho M. Bubu, M.D., Ph.D., M.P.H.
Departments of Psychiatry, Population Health, and Neurology
New York University Grossman School of Medicine
New York, New York

Andrew W. Varga, M.D., Ph.D.
Division of Pulmonary, Critical Care and Sleep Medicine and Friedman Brain Institute
Icahn School of Medicine at Mount Sinai
New York, New York

ORCID IDs: 0000-0001-7438-2628 (O.M.B.); 0000-0002-3668-3371 (A.W.V.).

References

1. Smallwood J, Bernhardt BC, Leech R, Bzdok D, Jefferies E, Margulies DS. The default mode network in cognition: a topographical perspective. *Nat Rev Neurosci* 2021;22:503–513.
2. Chang Y-T, Chen Y-C, Chen Y-L, Hsu S-W, Yang F-Y, Lee C-C, *et al.* Functional connectivity in default mode network correlates with severity of hypoxemia in obstructive sleep apnea. *Brain Behav* 2020; 10:e01889.
3. Xu H, Liu Y, Li C, Li X, Shen L, Wang H, *et al.* Effects of continuous positive airway pressure on neuroimaging biomarkers and cognition in adult obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med* 2025;211:628–636.
4. Celle S, Delon-Martin C, Roche F, Barthélémy J-C, Pépin J-L, Dojat M. Desperately seeking grey matter volume changes in sleep apnea: a

methodological review of magnetic resonance brain voxel-based morphometry studies. *Sleep Med Rev* 2016;25:112–120.
5. Mullins AE, Kam K, Parekh A, Bubu OM, Osorio RS, Varga AW. Obstructive sleep apnea and its treatment in aging: effects on Alzheimer's disease biomarkers, cognition, brain structure and neurophysiology. *Neurobiol Dis* 2020;145:105054.
6. Bubu OM, Kaur SS, Mbah AK, Umasabor-Bubu OQ, Cejudo JR, Debure L, *et al.* Obstructive sleep apnea and hypertension with longitudinal amyloid-β burden and cognitive changes. *Am J Respir Crit Care Med* 2022;206:632–636.
7. Bubu OM, Umasabor-Bubu OQ, Turner AD, Parekh A, Mullins AE, Kam K, *et al.*; Alzheimer's Disease Neuroimaging Initiative. Self-reported obstructive sleep apnea, amyloid and tau burden, and Alzheimer's disease time-dependent progression. *Alzheimers Dement* 2021;17: 226–245.
8. Varga AW, Kam K. The importance of sleep-dependent memory testing in positive airway pressure treatment of obstructive sleep apnea. *Am J Respir Crit Care Med* 2021;203:1064–1065.
9. Sharma RA, Varga AW, Bubu OM, Pirraglia E, Kam K, Parekh A, *et al.* Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly. A longitudinal study. *Am J Respir Crit Care Med* 2018; 197:933–943.
10. Carvalho DZ, Kremen V, Mivalt F, St Louis EK, McCarter SJ, Bukartyk J, *et al.* Non-rapid eye movement sleep slow-wave activity features are associated with amyloid accumulation in older adults with obstructive sleep apnoea. *Brain Commun* 2024;6:fcae354.
11. Canessa N, Castronovo V, Cappa SF, Aloia MS, Marelli S, Falini A, *et al.* Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. *Am J Respir Crit Care Med* 2011; 183:1419–1426.
12. McNicholas WT. Obstructive sleep apnea and inflammation. *Prog Cardiovasc Dis* 2009;51:392–399.
13. Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, *et al.* The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex* 2009;19:497–510.
14. Mohtasib R, Alghamdi J, Jobeir A, Masawi A, Pedrosa de Barros N, Billiet T, *et al.* MRI biomarkers for Alzheimer's disease: the impact of functional connectivity in the default mode network and structural connectivity between lobes on diagnostic accuracy. *Heliyon* 2022;8: e08901.
15. Han F, Liu X, Mailman RB, Huang X, Liu X. Resting-state global brain activity affects early β-amyloid accumulation in default mode network. *Nat Commun* 2023;14:7788.
16. Menon V. 20 years of the default mode network: a review and synthesis. *Neuron* 2023;111:2469–2487.
17. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, *et al.* Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7: 687–698.
18. Belloy ME, Andrews SJ, Le Guen Y, Cuccaro M, Farrer LA, Napolioni V, *et al.* APOE genotype and Alzheimer disease risk across age, sex, and population ancestry. *JAMA Neurol* 2023;80:1284–1294.