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ARTICLE

Slow-Wave Sleep and MRI Markers of Brain Aging in a Community-Based Sample

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Abstract

Objective

To test the hypothesis that reduced slow-wave sleep, or N3 sleep, which is thought to underlie the restorative functions of sleep, is associated with MRI markers of brain aging, we evaluated this relationship in the community-based Framingham Heart Study Offspring cohort using polysomnography and brain MRI.

Methods

We studied 492 participants (age 58.8 ± 8.8 years, 49.4% male) free of neurological diseases who completed a brain MRI scan and in-home overnight polysomnography to assess slow-wave sleep (absolute duration and percentage of total sleep). Volumes of total brain, total cortical, frontal cortical, subcortical gray matter, hippocampus, and white matter hyperintensities were investigated as a percentage of intracranial volume, and the presence of covert brain infarcts was evaluated. Linear and logistic regression models were adjusted for age, age squared, sex, time interval between polysomnography and MRI (3.3 ± 1.0 years), *APOE* ε4 carrier status, stroke risk factors, sleeping pill use, body mass index, and depression.

Results

Less slow-wave sleep was associated with lower cortical brain volume (absolute duration, β [standard error] = 0.20 [0.08], $p = 0.015$; percentage, 0.16 [0.08], $p = 0.044$), lower subcortical brain volume (percentage, 0.03 [0.02], $p = 0.034$), and higher white matter hyperintensities volume (absolute duration, −0.12 [0.05], $p = 0.010$; percentage, −0.10 [0.04], $p = 0.033$). Slow-wave sleep duration was not associated with hippocampal volume or the presence of covert brain infarcts.

Conclusion

Loss of slow-wave sleep might facilitate accelerated brain aging, as evidence by its association with MRI markers suggestive of brain atrophy and injury. Alternatively, subtle injuries and accelerated aging might reduce the ability of the brain to produce slow-wave sleep.

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Glossary

Aβ = β-amyloid; **PSG** = polysomnography; **SWS** = slow-wave sleep.

Slow-wave sleep (SWS), also known as N3 sleep, is the deepest sleep stage measured by its macrostructure (duration, percentage of sleep time) and microstructure (slow oscillations, delta power, slow-wave activity). SWS is thought to underlie multiple restorative physiological functions of sleep, including memory consolidation, energy restoration, hormone release and regulation, immune function, and metabolite clearance from the CNS.[1] In a breakthrough study, sleep, especially slow-wave activity, was associated with increased cerebral glympathic clearance of β-amyloid (Aβ).[2] Subsequently, similar findings were observed for tau proteins.[3] Slow oscillations are coupled with CSF flow,[4] suggesting that SWS might underlie glymphatic clearance during sleep. Consistently, studies have found associations between less SWS and Aβ and tau levels that characterize Alzheimer disease pathology,[5–7] leading to the hypothesis that impaired SWS might underlie the association between sleep disturbances and poor neurocognitive outcomes.[1,8] Accordingly, SWS is reduced in both the elderly and patients with dementia or stroke.[1,9–11] However, the limited number of studies available have failed to observe associations between SWS and cognitive decline or impairment.[12–14] Conversely, microstructural aspects of SWS were associated with developmental and age-related changes in cortical structure and white matter integrity.[15–20] However, the relationship between the macrostructure of SWS (duration, proportion) and MRI markers of brain aging in the general community has not been previously reported.

We investigated the association between SWS macrostructure and MRI markers of brain aging and injury to clarify whether less SWS is associated with accelerated brain aging in a representative community-based sample.

Methods

Sample

This study included a subset of participants from the Framingham Heart Study Offspring cohort[21] who participated in the Sleep Heart Health Study and were evaluated with in-home polysomnography (PSG) between 1995 and 1998 at their sixth examination (n = 699). Participants who attended their seventh clinic examination were invited to complete a brain MRI scan (1999–2002). For the present study, we excluded participants without a brain MRI (n = 152) and those who had neurological conditions (e.g., dementia, stroke, epilepsy, Parkinson disease; n = 20). We excluded participants who had unsatisfactory PSG signals (n = 29), and because most age-related changes in brain volume occurs after early adulthood, we also excluded participants <40 years of age (n = 6) at their sixth examination. Thus, the final analysis sample included 492 participants.

Participants in the Framingham Heart Study are followed up rigorously regarding their cognitive status. At every examination (every ≈4 years), participants are tested with the Folstein Mini-Mental State Examination. In addition, at selected examinations, including the seventh offspring cohort examination, participants complete a comprehensive neuropsychological test battery. Participants are flagged for possible cognitive impairment if their Mini-Mental State Examination score drops below the education-specific cutoff, by ≥3 points between 2 continuous examinations, or by ≥5 points compared to their previous highest score at any examination. Participants are also flagged for suspected cognitive impairment if their neuropsychological assessment suggests cognitive impairment; hospitalization records or health status updates suggest diagnosed or undiagnosed cognitive impairment; or a physician, staff, family, or the participant raised concerns regarding the participant's cognitive function. When participants are flagged for possible cognitive impairment, they are followed up annually with comprehensive neuropsychological and neurological evaluations until they are adjudicated to have dementia or to be cognitively normal. Flagged participants are reviewed by the study Dementia Review Committee, comprising at least 1 neuropsychologist and neurologist, who adjudicate a diagnosis of mild cognitive impairment[22] or dementia.[23] Moreover, medical records, health status updates, and neurological evaluations are used to identify other neurological conditions such as stroke, epilepsy, and Parkinson disease. For this article, we excluded participants with neurological conditions or dementia according to our strict and rigorous cognitive surveillance procedure.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants gave their written informed consent before the study. The institutional review board at Boston University Medical Center approved the study with human participants.

PSG Recording and SWS

The in-home portable PSG system included EEGs, electrooculograms, ECGs (C3/A1 and C4/A2), chin EMG, oximetry, chest wall and abdomen inductance plethysmonography, and nasal/oral airflow (thermistry). Scoring criteria and procedures were published previously.[24–26] The primary variable of interest was SWS (N3 sleep stage), which was assessed both in absolute duration and as a percentage of the total sleep time. Moreover, we also investigated REM sleep as absolute duration and percentage of total sleep time.

MRI-Based Markers

MRI markers of brain aging and injury were measured with a brain-dedicated Siemens Magnetom MRI (1.5T; Siemens, Munich, Germany) with parameters and sequences described previously.[27] Structural MRIs were processed to remove the skull

using an atlas-based method.[28] Segmentation of white matter hyperintensities, hippocampus, cortical, frontal cortical, and subcortical gray matter as well as total brain volume was performed from fluid-attenuated inversion recovery and T1-weighted images by automated procedures described previously and that demonstrate high interrater reliability.[29–31] Volumes were computed as a percentage of the total intracranial volume to remove any effect of head size. Covert brain infarcts were inspected visually by 3 raters. Lesions ≥3 mm were considered and were coded according to their presence or absence.[27]

Statistical Analyses

Statistical analyses were performed with SAS software version 9.4 (SAS Institute Cary, NC). We used multivariable linear and logistic regression models to model the associations between SWS and each MRI-based marker. In initial models, age, age squared (given the nonlinear association between age and MRI-based markers), sex, and the time interval between the PSG and MRI were included as covariates (model 1). Subsequent models included additional adjustments for *APOE* ε4 allele carrier status, body mass index, regular use of sleeping pills, depressive symptoms (Center for Epidemiologic Studies Depression Scale score ≥16 or antidepressant use), and the Revised Framingham Stroke Risk Profile score (a clinical risk prediction tool for the 10-year risk of incident stroke using clinical information, including age, smoking status, prevalent cardiovascular diseases, atrial fibrillation, diabetes mellitus, and hypertension) (model 2).[32] Finally, the last models additionally adjusted for education levels and the apnea-hypopnea index to account for an obstructive sleep apnea effect (model 3). These covariates were selected because of their association with either cognitive brain aging or sleep. To achieve normality and to facilitate comparison, square root transformations and standardization were applied to SWS duration and percentage, and natural log transformations were applied to white matter hyperintensities volume and body mass index. Participants with missing data were removed on an analysis-by-analysis basis. The same analyses were also performed for REM sleep absolute duration and percentage. To provide a comparison with brain aging, we regressed each MRI marker on age and compared standardized coefficients with those of significant findings with SWS. As a sensitivity analysis, we performed all statistical models again after excluding participants with mild cognitive impairment. Results were considered significant if $p < 0.05$.

Data Availability

The Framingham Heart Study makes phenotypic and genetic data available through the online repositories BioLINCC and dbGap, respectively. Sleep data are available via the National Sleep Research Resource.

Results

Sample characteristics for the 492 included participants are presented in table 1. Brain MRI was performed on average 3 years after the PSG. The mean age of the sample was 59 years with a nearly equal representation of men and women. A low proportion of the sample presented with confounding diseases that could affect brain integrity such as prevalent cardiovascular disease, diabetes, or depression. However, over a fifth of the sample were treated for hypertension or were carriers of the *APOE* ε4 allele. Around 10% of the sample had covert brain infarcts. Although no participants had mild cognitive impairment at the time of the PSG, 8 participants developed mild cognitive impairment at the time of the MRI.

Table 2 shows the associations between SWS absolute duration or percentage and MRI outcomes. Shorter SWS absolute duration and lower SWS percentage were associated with lower cortical gray matter volumes and higher white matter hyperintensity volumes. A 1-SD unit loss in the square root of SWS duration was associated with 2.86 years of brain aging as defined as lower cortical gray matter volume and with 2.4 years of brain aging as defined by higher white matter hyperintensities volume (model 2).

Lower SWS percentage was associated with lower subcortical gray matter volume when adjusting for model 1 and 2 covariates. Shorter SWS absolute duration was associated with lower total brain volume when adjusting for model 1 covariates; although not statistically significant, similar effect sizes were observed when adjusting for model 2 covariates and when examining SWS percentage rather than absolute duration. No association was observed between SWS and hippocampal volume, covert brain infarcts, or frontal cortical gray matter volume. No MRI-based markers were associated with REM duration or percentage. Results were unchanged when we excluded those with mild cognitive impairment (n = 8) or missing cognitive follow-up data (n = 11) from analyses (data not shown).

Discussion

To the best of our knowledge, this is the largest study to investigate SWS in relation to brain MRI metrics in a community-based sample. We found that less SWS was associated with MRI markers of brain aging independently of multiple dementia risk factors and potential confounders associated with sleep. More specifically, lower SWS absolute duration and percentage correlated with lower cortical gray matter volume and higher white matter hyperintensities volume and, to a lesser extent, lower total brain volume and subcortical gray matter volume. Our novel findings support the hypothesis that altered SWS might relate to accelerated brain aging, since gray matter atrophy and white matter hyperintensity burden are associated with a brain that ages faster than chronological aging in both cognitively normal and pathological states.[33] Our findings are also of interest because lower brain volumes and greater white matter disease on MRI are strong risk factors for incident dementia[34,35] and are associated with histopathologic findings of Alzheimer disease

Table 1 Sample Characteristics

Characteristics	Mean (SD) or n (%)
Age, y	58.8 (8.8)
Male, n (%)	243 (49.4)
Time between PSG to MRI, y	3.3 (1.0)
Systolic blood pressure, mm Hg	125.8 (17.2)
Antihypertensive medication, n (%)	112 (22.8)
Revised Framingham Stroke Risk Profile, score units	0.03 (0.04)
Body mass index, kg/m^2	28.0 (4.9)
Current smoking, n (%)	69 (14.0)
Prevalent cardiovascular disease, n (%)	33 (6.7)
Diabetes, n (%)	47 (9.6)
APOE ε4 allele carriers, n (%)	104 (21.6)
Regular use of sleeping pills, n (%)	86 (17.8)
Depression, n (%)	57 (11.6)
Antidepressant medication, n (%)	29 (5.9)
Anticonvulsants medication, n (%)	4 (0.81)
Education, n (%)	
No high school degree	20 (4.1)
High school degree	146 (29.7)
College without graduating	155 (31.5)
College graduate	171 (34.8)
SWS duration, min	69.9 (41.9)
SWS, % of total sleep time	18.5 (10.8)
REM duration, min	80.0 (27.1)
REM, % of total sleep time	20.9 (5.9)
Apnea-hypopnea index, events/h	8.8 (12.7)
No obstructive sleep apnea (<5), n (%)	244 (53.2)
Mild obstructive sleep apnea (5–15), n (%)	132 (28.8)
Moderate obstructive sleep apnea (15–30), n (%)	58 (12.6)
Severe obstructive sleep apnea (>30), n (%)	25 (5.5)
Total brain volume, % of ICV	77.5 (2.4)
Cortical gray matter volume, % of ICV	37.3 (1.7)
Frontal cortical gray matter volume, % of ICV	14.4 (0.8)
Subcortical gray matter volume, % of ICV	3.1 (0.3)
Hippocampal volume, % of ICV	0.54 (0.04)
White matter hyperintensities, % of ICV	0.04 (2.70)
Covert brain infarcts, n (%)	47 (9.6)

Abbreviations: ICV = intracranial volume; PSG = polysomnography; SWS = slow-wave sleep.

and other dementias, including neurofibrillary tangles, neuritic plaques, demyelination, and gliosis.[36,37]

Our findings are consistent with the few studies that evaluated the relationship of SWS macrostructure, that is, absolute duration or percentage of total sleep time, with gray matter structure. Lower SWS percentage was previously associated with thalamic atrophy in 33 patients with neuromyelitis.[38] In the current study, we also observed that SWS percentage correlated with subcortical gray matter volume in our healthy community-based sample. In 167 participants followed up longitudinally, shorter SWS duration was associated with generalized atrophy at autopsy,[39] which is similar to our finding linking shorter SWS to lower total brain and cortical gray matter volume. Here, we also show that more SWS was associated with lower white matter hyperintensity volume, which, to the best of our knowledge, has not previously been investigated. Previous neuroimaging studies showed that microarchitectural SWS characteristics, that is, slow oscillations and slow-wave activity, are associated with brain structure.[15–20,40,41] Our results add to the literature by showing that, in addition to SWS microstructure, the macrostructure of SWS, that is, the absolute duration and percentage of total sleep time, is associated as well with MRI markers of brain aging. From the perspective of identifying dementia prediction biomarkers, this is an important finding because sleep stages can be scored according to standard criteria[42] and thus can be more easily quantified than microarchitectural SWS characteristics, which need more extensive EEG processing.

SWS is characterized by oscillations of high voltage and low frequency, and thus, the slow EEG signal of this sleep stage reflects a high synchrony of cortical neurons.[1] Decreases in SWS duration and the density of these slow oscillations over the lifespan are the strongest and most consistent change in sleep with aging.[1] Although the reason for this decrease is still unknown, it has been hypothesized that because highly synchronized cortical activity necessitates strong and healthy networks, neuronal and synaptic loss and altered glia function in aging might underlie this decrease.[1] This hypothesis is supported by studies modeling brain structure and SWS across different age groups, in which the association between age and slow-wave activity or slow oscillations is explained by the mediating effect of cortical volume.[17,18,20,40] In fact, these models suggest that development and aging are associated with reductions in gray matter volume, which then explain the age-dependent reductions in slow-wave activity or slow oscillations. In our age-adjusted analyses, the positive association between more SWS and MRI-based markers of brain health could reflect how interindividual variations in gray and white matter structure might influence the capacity to produce SWS. Consistent with this notion, after a traumatic brain injury leading to extensive cerebral damage, lower white matter integrity was strongly associated with changes in the morphology of slow oscillations,[19] suggesting that structural brain deterioration might result in an altered ability to generate SWS. Reduced SWS duration is also observed in other conditions in which extensive brain damage is

Table 2 Regression Models Between SWS and MRI-Based Markers of Brain Aging

	Absolute SWS Duration		SWS Percentage	
	β (SE) or OR (95% CI)	*p* Value	β (SE) or OR (95% CI)	*p* Value
Total brain volume, % of ICV				
Model 1	0.21 (0.09)	0.017	0.17 (0.09)	0.056
Model 2	0.18 (0.09)	0.051	0.13 (0.09)	0.167
Model 3	0.07 (0.04)	0.068	0.09 (0.07)	0.195
Cortical gray matter volume, % of ICV				
Model 1	0.23 (0.08)	0.003	0.21 (0.08)	0.008
Model 2	0.20 (0.08)	0.015	0.16 (0.08)	0.044
Model 3	0.07 (0.03)	0.025	0.11 (0.06)	0.072
Frontal cortical gray matter volume, % of ICV				
Model 1	0.02 (0.01)	0.072	0.03 (0.03)	0.192
Model 2	0.02 (0.01)	0.172	0.02 (0.03)	0.385
Model 3	0.02 (0.02)	0.146	0.03 (0.03)	0.331
Subcortical gray matter volume, % of ICV				
Model 1	0.03 (0.02)	0.082	0.03 (0.01)	0.047
Model 2	0.03 (0.02)	0.053	0.03 (0.02)	0.034
Model 3	0.01 (0.01)	0.138	0.02 (0.01)	0.129
Hippocampal volume, % of ICV				
Model 1	−0.001 (0.002)	0.590	−0.002 (0.002)	0.465
Model 2	−0.001 (0.002)	0.610	−0.001 (0.002)	0.580
Model 3	0.00003 (0.0009)	0.975	−0.0004 (0.002)	0.823
White matter hyperintensities volume, % of ICV				
Model 1	−0.14 (0.04)	0.002	−0.11 (0.04)	0.010
Model 2	−0.12 (0.05)	0.010	−0.10 (0.04)	0.033
Model 3	−0.05 (0.02)	0.005	−0.08 (0.03)	0.017
Covert brain infarcts, n				
Model 1	1.00 (0.89–1.13)	0.998	0.99 (0.79–1.26)	0.994
Model 2	0.99 (0.87–1.11)	0.806	0.98 (0.76–1.24)	0.866
Model 3	0.98 (0.86–1.11)	0.694	0.96 (0.75–1.23)	0.754

Abbreviations: CI = confidence intervals; ICV = intracranial volume; OR = odds ratio; SE = standard error; SWS = slow-wave sleep.
A square root transformation and standardization were applied to SWS absolute duration and percentage. A natural log transformation was applied to white matter hyperintensities volume. All MRI-based markers are presented as a percentage of ICV. Model 1: adjusted for age, age squared, sex, and time between polysomnography and MRI. Model 2: adjusted for model 1 variables, *APOE* ε4 allele carriers, body mass index, sleeping pills, depression, and revised Framingham Stroke Risk Profile score. Model 3: adjusted for model 2 variables and the apnea-hypopnea index and education.

observed, including in dementia and stroke.[9,10] In amyloid precursor protein transgenic mice, increasing Aβ levels were found to play a causal role in sleep-wake disruptions and reduced SWS.[43] Therefore, reduced SWS may be a marker of cerebral dysfunctions and damage.

Alternatively, because SWS is involved in so many indispensable physiological functions such as synaptic plasticity and memory, energy and metabolism, immune response, and the clearance of cerebral metabolites,[1–4] our findings are also consistent with the interpretation of a causal relationship between reduced SWS and brain structure. In a previous study, the experimental disruption of SWS led to an increase in CSF levels of Aβ compared to a sham condition in the same participants.[5] Moreover, in a rodent model of traumatic brain injury, sleep modulation that increased slow-wave activity led

to improvement in histologic markers of diffuse axonal injuries and memory performance.[44] Taken together, these findings suggest that better and longer SWS might be a protective factor that promotes brain integrity.

These alternative interpretations are not mutually exclusive, however, because the relationship between brain structure and SWS duration is likely bidirectional. The relationship between reduced SWS and accelerating brain aging might be a vicious circle: interindividual variability and damage to brain structure might reduce SWS, which in turn may cause altered physiological functions and the accumulation of neuropathology leading to further neurodegeneration.

In the present study, although shorter SWS duration was associated with a higher volume of white matter hyperintensities, it was not found to be associated with the presence of covert brain infarcts. White matter hyperintensities are often linked to ischemic injuries and small vessel disease but are also associated with other etiologies, including Alzheimer disease.[37,45] Therefore, the association that we observed between shorter SWS and white matter hyperintensities burden might be independent of vascular damage, especially because we adjusted for clinical stroke risk factors. Alternatively, the association between white matter hyperintensities and SWS might be explained by elevated nocturnal blood pressure, given the known association between poor SWS and incident hypertension.[46] On the other hand, only 9.6% of our sample had covert brain infarcts, and thus, our study might be underpowered to identify a potential association between altered SWS and silent ischemic strokes.

We also did not observe associations between SWS and hippocampal volume. Given the role of SWS in hippocampus-dependent memory consolidation,[1,47] this finding may suggest a functional rather than a structural effect of SWS on memory consolidation. The lack of association between SWS and hippocampal volume is consistent with previous studies showing that slow-wave activity or slow oscillations were associated mostly with the integrity of the frontal, parietal, temporal, medial cortical, and thalamic regions and white matter tracts projecting to and from these structures.[16,17,19,20,38,44] Surprisingly, although strong associations between total cortical gray matter volume and SWS were observed, we did not observe significant associations with frontal cortical gray matter volume. According to our interpretation that lower gray matter volumes might result in an impaired ability to produce SWS, this lack of association with the frontal cortex could highlight the importance of other cortical structures previously identified in the generation and propagation of slow waves, including the insula, cingulate, and precuneus.[48] Supporting our alternative interpretation of reduced SWS as a potential causative factor in accelerated brain aging through mechanisms such as reduced glymphatic clearance, damages to the brain might be more widespread to other cortical and subcortical regions and not focused on the frontal cortex especially, explaining our lack of strong association with this region.

Because a previous study from our group at the Framingham Heart Study found that shorter REM sleep in elderly participants, but not SWS duration, was associated with increased dementia risk on average 12 years later,[13] it is surprising that REM sleep duration or percentage did not associate with any markers of brain aging in the present study in participants >40 years of age. SWS and REM sleep have different trajectories with age[49]: the quantity of SWS starts dropping steadily from early adulthood to midlife and thus might be associated more closely with brain structure in our cohort that includes middle-aged adults. On the other hand, REM sleep duration starts to show reductions after 50 years of age and thus might be linked to subsequent brain volume loss later in life. In fact, it was argued that both SWS and REM sleep have a sequential and dynamic impact on cognitive and cerebral aging, with REM sleep effectively or ineffectively compensating later in life for the earlier SWS decline.[50] Future longitudinal studies with multiple time points of both PSG and MRI should investigate the differential relationships of REM sleep and SWS duration on brain structure and clinical expression of cognitive decline across the lifespan.

To the best of our knowledge, this is the largest study to investigate the associations between brain structure and SWS and the only study to evaluate various MRI markers of accelerated aging such as gray matter atrophy, white matter hyperintensities, and covert brain infarcts. However, due to the observational design, we cannot exclude the possibility of residual confounding, and our ability to draw inferences regarding the causal relationship between SWS and alterations in brain structure is limited. Moreover, few participants were taking medications that can alter SWS or REM sleep (e.g., antidepressants, certain anticonvulsants) in our sample, which precluded an investigation of whether they could affect the relationship between MRI markers and sleep stages.

Experimental enhancement of slow oscillations through multiple techniques, including phase-locked acoustic cues, suggests that increasing SWS duration might result in better memory performance.[1,51] Further studies could extend this line of research to evaluate whether inducing SWS minimizes neurodegenerative processes and slows brain aging.

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Disclosure

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