

# Nighttime Sleep Characteristics and White Matter Integrity in Young Adults

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**Purpose:** Sleep is essential for life and plays a key role for optimal physiology, brain functioning, and health. Evidence suggests a relation between sleep and cerebral white matter integrity. Human studies report that sleep duration shows a U-shaped association with brain functioning. We hypothesized that participants with longer or shorter sleep time in the nighttime period show altered microstructural white matter integrity.

**Participants and Methods:** Seventy-three young adult participants were evaluated. Sleep-wake cycle parameters were assessed objectively using actigraphy. Diffusion tensor imaging studies were performed to assess white matter integrity using fractional anisotropy and mean, axial, and radial diffusivities. Relations between white matter microstructure indexes and sleep parameters were investigated through tract-based spatial statistics. Participants were grouped according to their nocturnal total sleep time: 27 in the Reference sleep group (6.5–8.0 h), 23 in the Short sleep group (<6.5 h) and 23 in the Long sleep group (>8.0 h).

**Results:** Compared with the Reference sleep group, participants in the Long sleep group showed lower fractional anisotropy ( $p < 0.05$ ) and higher radial diffusivity ( $p < 0.05$ ) values in white matter tracts linked to sleep regulation (corona radiata, body of the corpus callosum, superior longitudinal fasciculus, and anterior thalamic radiation).

**Conclusion:** This pattern of reduced fractional anisotropy and increased radial diffusivity in the Long sleep group indicates an association between sleep duration and lower integrity of myelin sheaths. Because myelin is continuously remodeled in the brain, nighttime sleep characteristics appear to be a key player for its quality and maintenance.

**Keywords:** long sleep, brain, myelin, fractional anisotropy

## Introduction

The sleep-wake cycle (SWC) is consolidated by the interaction between homeostatic and circadian processes. The homeostatic process refers to a need for sleep that is accumulated throughout waking and dissipated during sleep. The circadian process is modulated by the internal circadian clock (located in suprachiasmatic nuclei) that is entrained to the light–dark cycle, promoting wake during an active phase of the cycle and allowing sleep during a rest phase of the cycle.<sup>1,2</sup> Sleep is essential for life and plays key roles for optimal physiology, brain functioning, and health.<sup>3–6</sup>

Cerebral white matter is composed of myelinated axons that connect neurons in different brain regions into functional circuits. Myelin is formed by oligodendrocytes and acts as an insulator, which allows high-speed electrical impulse transmission.<sup>7</sup> The myelin sheath consists of multiple layers along the axon with small gaps devoid of myelin called nodes of Ranvier.<sup>8,9</sup> The nodes are delimited at both sides by the paranode,<sup>10</sup> where these myelin layers terminate and form series of paranodal loops tightly attached to the axon.<sup>11</sup> Myelination continues until at least the third decade of age in humans.<sup>12</sup> Alterations in white matter can disrupt behavior, sensory, motor, and cognitive developmental processes.<sup>12–14</sup>

Studies in animals have suggested that chronic sleep loss reduces the proliferation of oligodendrocyte precursor cells,<sup>15</sup> inhibits the transcription of proteins related to myelination,<sup>16</sup> alters node length, and decreases myelin

thickness.<sup>17</sup> To form layers of myelin, the most external paranodal loop of myelin is continuous with the plasma membrane of the oligodendrocyte.<sup>18</sup> De Vivo and Bellesi<sup>8</sup> proposed that greater sleep restriction causes the outer paranodal loop to detach from the paranodal region and leads to increased node length in the axon followed by retraction into the oligodendrocyte, with consequent myelin sheath thinning.

In humans, white matter integrity is commonly assessed by diffusion tensor imaging (DTI), a magnetic resonance imaging (MRI)-based neuroimaging technique and non-invasive method.<sup>19</sup> The DTI parameters most commonly used are fractional anisotropy (FA) and mean diffusivity (MD). Greater FA indicates higher white matter integrity and reduced MD reflects heightened myelination.<sup>20</sup> In healthy adults, one night of sleep deprivation was related to decreased FA in the corpus callosum, the thalamus, and the brain stem.<sup>21</sup> Compared with self-reported moderate sleep (>6 to ≤8 h), short sleep duration (<6 h sleep) has also been related to increased MD values in the frontal, occipital, parietal, and temporal regions.<sup>22</sup> Using actigraphic recordings for objective SWC assessment, total sleep time (TST), lower sleep efficiency and increased duration of wake after sleep onset (WASO) have been associated with lower FA and greater MD in the thalamic radiation, corticospinal tract, uncinate fasciculus, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, cingulate, and the corpus callosum.<sup>23</sup> These findings suggest that sleep may contribute to the formation and maintenance of myelin in the axons and/or affect oligodendrocyte functioning.<sup>8</sup>

White matter alterations in middle-aged subjects are associated with the risk of dementia.<sup>24,25</sup> Moreover, sleep duration shows a U-shaped association with brain functioning<sup>26–28</sup> and increases the likelihood of cognitive impairment later in life.<sup>29–31</sup> In light of these findings, understanding the relation between white matter integrity and sleep-wake patterns is particularly relevant. In this study, we hypothesized that participants with long or short TST show altered microstructural white matter integrity.

## Materials and Methods

### Participants

All participants belong to an early infancy cohort of the behavioral and developmental effects of iron-deficiency anemia in infancy. The study design and findings during follow-ups have been published elsewhere.<sup>32–34</sup> Briefly, they were healthy term infants (birth weight ≥3.0 kg, without perinatal complications, and free of acute or chronic illnesses). Infants with iron-deficiency anemia at 6, 12, or 18 months of age were considered for neurophysiological evaluations. Those who were clearly non-anemic (venous Hb ≥115 g/L) were randomly invited to the control group. No participant had iron-deficiency anemia at subsequent ages.

In this cross-sectional study in adulthood, 77 young-adults within a narrow age range ( $22.5 \pm 0.2$  years) were assessed. Participants filled out the Epworth Sleepiness Scale<sup>35</sup> for daily sleepiness assessment, the Pittsburgh Sleep Quality Index<sup>36</sup> for a subjective measure of sleep quality, and a short questionnaire on sleeping and lifestyle habits. The inclusion criteria consisted of being between the ages of 20 and 30 years and having a regular sleep-work schedule. The exclusion criteria were pregnancy; contraindications to MRI; and history of sleep disorders, major medical and neurological disorders, psychiatric illness, and drug or alcohol dependency or abuse. All participants had actigraphic recordings and DTI studies, but from the initial sample, four were excluded from analysis: three for movement artifacts in the DTI study and one for technical differences in the DTI sequence. Excluded participants were no different in background characteristics.

Participants provided signed informed consent, according to the norms for Human Experimentation, Code of Ethics of the World Medical Association (Declaration of Helsinki, 1995). The original and follow-up protocols were approved and reviewed annually by the Institutional Review Boards of the University of Michigan, Ann Arbor, and the Institute of Nutrition and Food Technology, University of Chile, Santiago.

### Actigraphic Recordings

Participants wore waterproof actigraph devices (Actiwatch 2, Philips Respironics, Bend, OR, USA) continuously without removal for 1 week on their non-dominant wrist. Each 24-h interval was divided into nocturnal and diurnal periods. The nocturnal period began with the onset of the first sleep episode after 20:00 h that was followed for at least 30 consecutive

min of sustained sleep. This period ended with the transition to the diurnal period, which started with the first wake episode after 06:00 h lasting for at least 30 min of uninterrupted wakefulness. Actigraphic data were digitalized, stored for each successive 1-min interval, and processed on a minute-by-minute basis. We reassessed this first detection of sleep-wake episodes, to avoid the detection of short sleep and wake episodes, which are considered inaccurate and are a main source of errors in actigraphic recordings.<sup>37</sup> A locally developed automated procedure generated a new sequence of sleep and wake episodes lasting at least 5-min and incorporated them into the ongoing episode to generate a new sequence.<sup>38</sup> The following conventional sleep-wake parameters were assessed: wake-up and sleep onset times, nap episodes, time spent asleep in the nocturnal period (TST), time spent awake in the nocturnal period (WASO), the number of awakenings, mean wake episode duration, latency to the first wake episode, longest wake episode duration and its time placement, and sleep efficiency (proportion of the nocturnal period that is TST). These parameters were assessed in the overall nocturnal period, and WASO and awakenings were also analyzed by halves of the nocturnal period (Figure 1).<sup>39,40</sup> Participants also completed a diary of their SWC that provided data about bedtime, wake-up time, and time of eventual removal of the actigraph. Comparison groups were categorized according to the prior literature on TST: Reference sleep (6.5–8.0 h), Short sleep (<6.5 h), and Long sleep (>8.0 h) groups.<sup>41</sup>

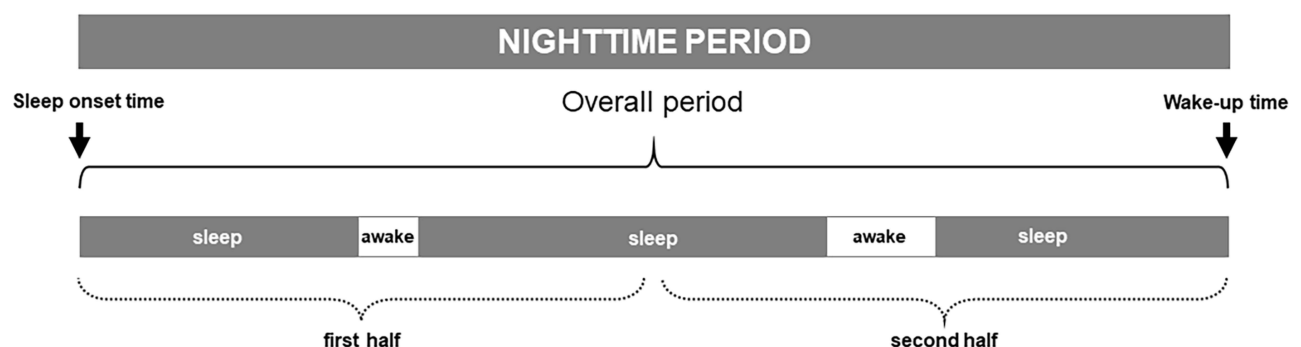
## DTI Studies

Studies were performed with a 3-Tesla scanner (Siemens MAGNETOM Skyra System, Siemens Healthcare, Erlangen, Germany). DTI data were acquired using a single shot EPI sequence (TE = 91 ms; TR = 9900 ms; FOV: 256 mm; slices: 72, slice thickness: 2 mm; slice gap: 0 mm; 30 gradient directions with  $b = 1000 \text{ s/mm}^2$  and 1 with  $b = 0 \text{ s/mm}^2$ ).

Preprocessing was carried out in FMRIB Software Library (FSL, version 5.04).<sup>42</sup> The steps were eddy current correction, head motion correction, and brain masking. The diffusion tensor model was then fit at each voxel to obtain maps of FA, MD, axial diffusivity (AD), and radial diffusivity (RD).

Using Tract-Based Spatial Statistics (TBSS, a toolbox of FSL), we performed voxel-wise analysis.<sup>43</sup> Running the nonlinear registration (FNIRT), FA images were aligned to the FMRIB58\_FA template and affine transformed into Montreal Neurological Institute MNI standard space. FA images were merged, creating a mean FA image, and a skeleton was then generated. A threshold of 0.2 was applied to the FA skeleton to consider only white matter. The aligned FA map of each participant was then projected onto the skeleton. The MD, RD, and AD maps were also projected onto this skeleton.

The microstructural integrity of white matter was indexed by the main parameters of DTI: FA, MD, AD, and RD. Briefly, FA is a quantitative index of the orientation of water diffusion coherence, MD is the average rate of water diffusion, AD measures diffusivity along the primary axis (eigenvalue  $\lambda_1$ ), and RD is the average diffusivity of the two minor axes (eigenvalues  $\lambda_2$  and  $\lambda_3$ ), that is, measuring diffusivity perpendicular to the major axis,<sup>44</sup> and is related to myelin damage.<sup>45</sup>



**Figure 1** Illustration of a representative actigraphic nighttime period. Standard parameters of the sleep wake-cycle (eg, wake-up and sleep onset times, duration of sleep and wake episodes) were assessed for the overall nighttime period. Wake episode frequency, duration, distribution, and localization were computed by halves of the nighttime period.

## Data Analysis

General linear models were calculated to explore the differences in SWC and DTI indices (FA, MD, RD, and AD) among the groups. We utilized non-parametric permutation-based statistics with the “randomise” tool ( $p < 0.05$ ) in FSL.<sup>46</sup> Five thousand permutations were performed, and threshold-free cluster enhancement (TFCE) was applied to correct for multiple comparisons.<sup>47</sup> JHU ICBM-DTI-81 White-Matter Labels and the JHU White-Matter Tractography Atlas were used to identify the location of significant clusters.<sup>48,49</sup> All analyses were adjusted for sex and WASO. The Bonferroni correction method was applied. A  $p$ -value  $< 0.05$  (corrected for multiple comparisons) was considered statistically significant. Statistical analyses were conducted with SAS<sup>®</sup> Studio (SAS Institute Inc. Cary, NC, USA.).

## Results

The mean age of the participants was  $22.5 \pm 0.2$  years and 48% were female. The sleep groups were similar in all background characteristics (Table 1).

## Sleep-Wake Parameters

By definition, the groups differed in TST (Table 2). Compared with the Reference sleep group, the Short sleep group showed lower sleep efficiency in the overall nocturnal period and greater WASO in the second half of the night. The Long sleep group showed greater WASO and lower sleep efficiency than the Reference group in the overall nocturnal period. The number of wake episodes and WASO were also higher during the second half of the nocturnal period in the Long sleep group compared with the Reference group (Table 2).

**Table 1** Background Characteristics of Study Participants

	Reference Sleep (n = 27)	Short Sleep (n = 23)	Long Sleep (n = 23)	p-value
Female n (%) <sup>a</sup>	11 (41%)	9 (39%)	15 (65%)	0.134
Birth weight (kg)	$3.5 \pm 0.1$	$3.5 \pm 0.1$	$3.5 \pm 0.1$	0.976
Birth height (cm)	$50.7 \pm 0.3$	$50.6 \pm 0.3$	$50.5 \pm 0.3$	0.948
Gestational age (weeks)	$39.4 \pm 0.2$	$39.3 \pm 0.2$	$39.4 \pm 0.2$	0.938
IDA in infancy n (%) <sup>a</sup>	14 (52%)	13 (57%)	10 (43%)	0.575
Intelligence quotient <sup>b,c</sup>	$90.2 \pm 2.5$	$91.8 \pm 1.6$	$91.9 \pm 2.0$	0.801
Socioeconomic status <sup>b,d</sup>	$34.3 \pm 1.3$	$33.8 \pm 1.1$	$32.0 \pm 1.4$	0.443
Maternal education (years)	$9.1 \pm 0.6$	$9.6 \pm 0.4$	$9.9 \pm 0.5$	0.601
Age at test (years)	$22.4 \pm 0.3$	$22.4 \pm 0.2$	$22.7 \pm 0.3$	0.771
Formal education (years)	$11.5 \pm 0.2$	$11.8 \pm 0.2$	$11.1 \pm 0.3$	0.151
High school graduation n (%) <sup>a</sup>	22 (81%)	20 (87%)	16 (70%)	0.106
BMI at test ( $\text{kg}/\text{m}^2$ )	$26.8 \pm 1.0$	$27.0 \pm 0.9$	$26.9 \pm 0.9$	0.981
Smoking n (%) <sup>a</sup>	12 (44%)	11 (48%)	10 (43%)	0.952
Snoring self-reported n (%) <sup>a</sup>	11 (65%)	9 (39%)	13 (56%)	0.417
Epworth Sleepiness Scale (score)	$7.6 \pm 0.6$	$8.9 \pm 0.8$	$8.6 \pm 0.9$	0.478
Pittsburgh Sleep Quality Index	$5.4 \pm 0.6$	$6.4 \pm 0.7$	$4.9 \pm 0.4$	0.200

**Notes:** Values are expressed as mean  $\pm$  standard error. One-way analysis of variance. <sup>a</sup>Chi square test or adjusted chi-square test. <sup>b</sup>At age 10 years. <sup>c</sup>Wechsler Intelligence Scale for Children Revised. <sup>d</sup>Modified Graffar index.

**Abbreviation:** IDA, iron-deficiency anemia.

**Table 2** Sleep-Wake Cycle Parameters By Groups

	Reference Sleep Group (n = 27)	Short Sleep Group (n = 23)	Long Sleep Group (n = 23)	p-value		
				Short vs Reference	Long vs Reference	Short vs Long
<i>Overall nocturnal period</i>						
Wake-up time (h:min ± min)‡	8:55 ± 0.3	8:07 ± 0.3	9:41 ± 0.3	0.346	0.258	0.008
Nap episodes (number)	3.2 ± 0.3	3.1 ± 0.4	3.7 ± 0.4	0.997	0.724	0.714
Nap episodes mean duration (h) <sup>†</sup>	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.996	0.996	0.989
Sleep onset time (h:min ± min)‡	01:08 ± 0.3	01:28 ± 0.3	00:38 ± 0.3	0.790	0.654	0.253
Total sleep time (h)	7.4 ± 0.1	6.0 ± 0.1	8.8 ± 0.1	< 0.001	< 0.001	< 0.001
Wake after sleep onset (h)	0.3 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	0.281	0.002	0.290
Wake episodes (number)	1.5 ± 0.2	2.1 ± 0.3	2.4 ± 0.3	0.198	0.088	0.837
Wake episodes mean duration (h) <sup>†</sup>	0.2 ± 0.1	0.2 ± 0.2	0.2 ± 0.1	0.996	0.741	0.887
Latency to first wake episode (h)	3.9 ± 0.4	2.6 ± 0.4	3.7 ± 0.4	0.095	0.981	0.134
Longest wake episode duration (h) <sup>†</sup>	0.3 ± 0.3	0.4 ± 0.3	0.3 ± 0.3	0.089	0.373	0.753
Sleep efficiency (%)	96.5 ± 0.8	92.9 ± 0.9	93.7 ± 0.9	0.008	0.041	0.822
<i>First half of the nocturnal period</i>						
Wake after sleep onset (h) <sup>†</sup>	0.1 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.357	0.092	0.927
Wake percent after sleep onset	5.7 ± 1.2	9.9 ± 1.3	6.8 ± 1.2	0.109	0.923	0.389
Wake episodes (number)	0.8 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	0.872	0.215	0.927
Longest wake episode localization (%)	37.7 ± 9.7	36.9 ± 9.8	24.6 ± 8.9	0.998	0.727	0.698
<i>Second half of the nocturnal period</i>						
Wake after sleep onset (h) <sup>†</sup>	0.2 ± 0.4	0.4 ± 0.5	0.4 ± 0.4	0.044	0.005	0.998
Wake percent after sleep onset	7.7 ± 1.0	13.9 ± 1.2	10.9 ± 1.1	< 0.001	0.036	0.283
Wake episodes (number)	1.3 ± 0.1	1.7 ± 0.2	1.9 ± 0.2	0.218	0.002	0.388
Longest wake episode localization (%)	62.3 ± 10.2	63.1 ± 9.6	75.4 ± 8.1	0.997	0.731	0.689

**Notes:** Values are expressed as mean ± standard error. Bonferroni adjusted p-values. General linear model.<sup>†</sup> SE × 10<sup>1-‡</sup> Clock time.

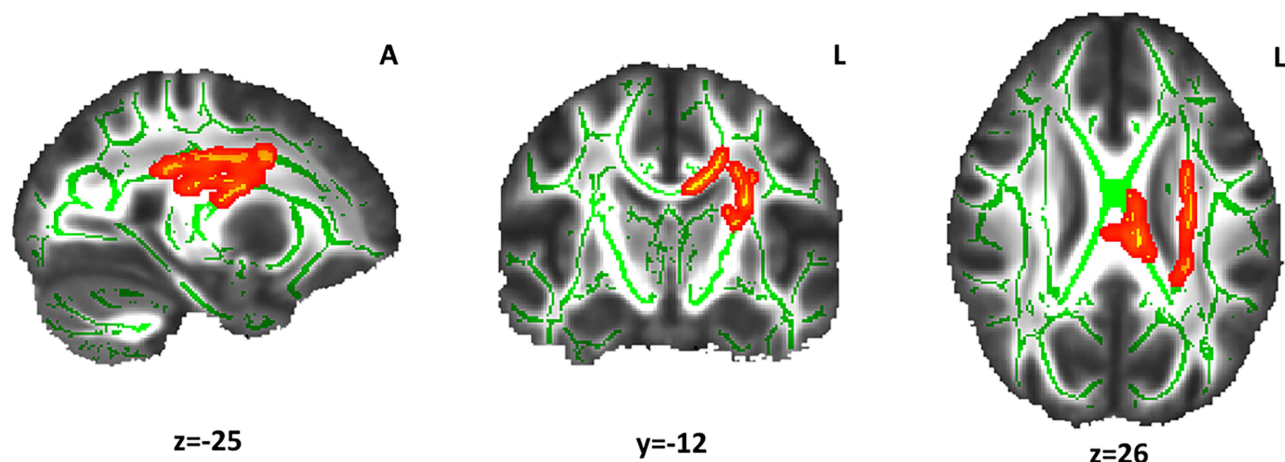
## White Matter Integrity and Total Sleep Time

Participants of the Long sleep group showed lower FA (Figure 2) and higher RD values (Figure 3) compared with the Reference sleep group. Of note, not all RD results reached statistical significance. There were significantly lower FA values in the Long sleep group in the body of the corpus callosum and regions of the left hemisphere (Table 3). Overlapping but much more restricted clusters were obtained for RD (Table 4). There were no other significant differences when comparing the Reference and Short sleep groups, or in MD and AD values in any group comparisons.

## Discussion

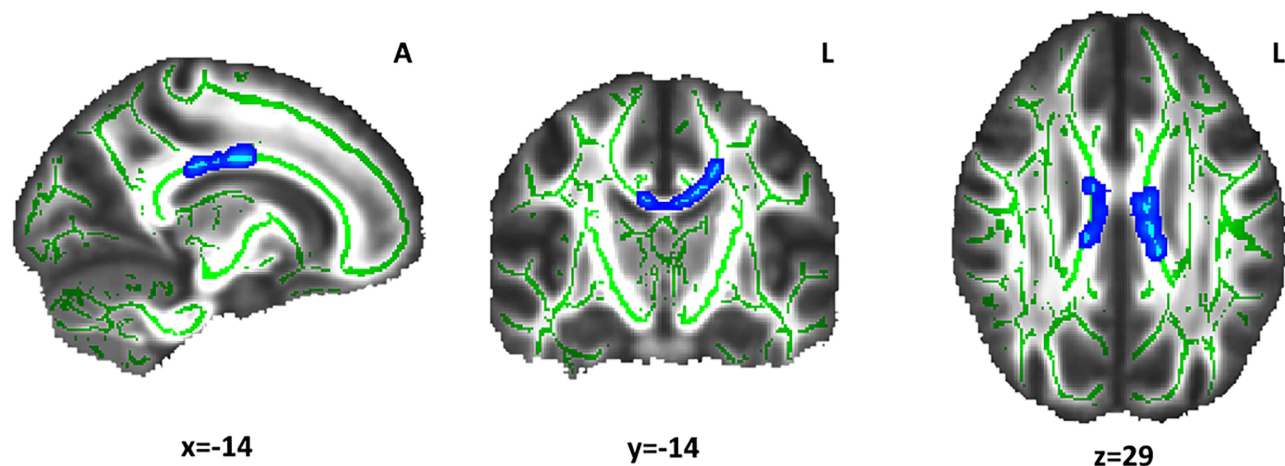
This study provides evidence regarding white matter microstructure characteristics in relation to sleep amount in young adults. Compared with the Reference sleep group (6.5–8.0 h), the Long sleep group (>8 h) showed lower white matter





**Figure 2** Fractional anisotropy differences between the Long and Reference sleep groups. The red-yellow color indicates the white matter clusters that showed lower fractional anisotropy values ( $\alpha < 0.05$ , threshold-free cluster enhancement and family-wise error correction) in the Long sleep group compared with the Reference sleep group (at the indicated coordinates). The mean skeleton of fractional anisotropy is shown in green. The white matter tracts include the superior Corona radiata and the body of the corpus callosum. The coordinates are presented in Montreal Neurological Institute (MNI) template space.

**Abbreviations:** A, anterior; L, left.



**Figure 3** Radial diffusivity differences between the Long and Reference sleep groups. The light-blue color indicates the white matter clusters that showed higher radial diffusivity values ( $\alpha \leq 0.05$ , threshold-free cluster enhancement and family-wise error correction) in the Long sleep group compared with the Reference sleep group (at the indicated coordinates). The mean skeleton of FA is shown in green. The white matter tract includes the body of corpus callosum. Coordinates are presented in Montreal Neurological Institute (MNI) template space.

**Abbreviations:** A, anterior; L, left.

integrity. This group also presented reduced sleep consolidation (higher WASO). The pattern of reduced FA and increased RD with longer TST suggests an association between longer sleep and lower integrity of myelin sheaths.

Relative to the Reference sleep group, the Long sleep group showed lower white matter integrity in tracts linked to sleep regulation. In this regard, the corona radiata contains ascending and descending fibers that transmit neural information to and from the cerebral cortex that relates to SWC patterns,<sup>50,51</sup> and is also involved with emotional processing,<sup>51</sup> attention, and cognitive control.<sup>50</sup> This major white matter tract is interconnected in the hemispheres via the corpus callosum.<sup>52</sup> This tract—the largest brain pathway to transfer interhemispheric electrical activity—is a key player in the regulation of ultradian rhythms, sleep initiation and maintenance,<sup>53</sup> rapid-eye-movement (REM) sleep,<sup>54</sup> and sleep electroencephalographic (EEG) activity,<sup>55</sup> including slow wave propagation within the deep stage (N3) of non-REM sleep.<sup>56,57</sup> Some studies have proposed that the corpus callosum white matter integrity might be sensitive to poor sleep quality.<sup>58,59</sup> The superior longitudinal fasciculus is constituted by fibers that connect the frontal lobe to the parietal,

**Table 3** Cluster of White Matter Tracts With Lower Fractional Anisotropy Values in the Long Versus Reference Sleep Groups

Cluster	Cluster Extension	Cluster Size (Voxels)	MNI Coordinates of the Peak Voxel			Z Score
			x	y	z	
1	Superior corona radiata L, body of corpus callosum, posterior corona radiata L, superior longitudinal fasciculus L, anterior thalamic radiation L	1398	-27	-5	27	0.034

**Notes:** Montreal Neurological Institute (MNI) template coordinates (x, y, z) and Z score refer to the voxel in the cluster with maximum probability.

**Abbreviation:** L, Left hemisphere.

**Table 4** Clusters of White Matter Tracts With Higher Radial Diffusivity Values in the Long Versus Reference Sleep Groups

Cluster	Cluster Extension	Cluster Size (Voxels)	MNI Coordinates of the Peak Voxel			Z Score
			x	y	z	
1	Body of corpus callosum	510	-14	-12	32	0.046
2	Body of corpus callosum, superior corona radiata L	306	10	-23	27	0.051

**Notes:** Montreal Neurological Institute (MNI) template coordinates (x, y, z) and Z score refer to the voxel in the cluster with maximum probability.

**Abbreviation:** L, Left hemisphere.

temporal, and occipital lobes<sup>60</sup> and is involved in the relation between sleep and cognitive performance.<sup>61,62</sup> Abnormalities in white matter integrity of this tract have been identified in patients with primary insomnia<sup>63,64</sup> and associated with disrupted sleep patterns.<sup>58,65</sup> Alterations in the white matter of the anterior thalamic radiation, which connects the thalamus and the frontal lobe,<sup>66</sup> have been linked to poor sleep quality,<sup>67</sup> sleep deprivation,<sup>68</sup> and sleep spindles activity.<sup>69</sup>

Because sleep fragmentation in the Long sleep group occurred mainly in the second half of the night, we suggest that REM sleep<sup>70,71</sup> is involved in the reduced integrity of white matter microstructure.<sup>54</sup> Even though higher WASO has already been related to reduce white matter microstructure,<sup>23,72</sup> particularly in the corpus callosum,<sup>23</sup> the location of sleep interruptions within the nighttime sleep could provide insights regarding the role of specific sleep stages in white matter. Time spent in REM sleep is positively associated with white matter integrity,<sup>54</sup> which could be explained by the fact that the proliferation of oligodendrocyte precursor cells, which form new myelin, is related to time spent in this sleep stage.<sup>15</sup>

Other studies have reported robust relations between long sleep duration and several unhealthy outcomes, including cognitive performance, diabetes mellitus, cardiovascular disease, stroke, coronary heart disease, obesity, and all-cause mortality.<sup>65,73,74</sup> It has been proposed that long sleep duration could be secondary or occur in conjunction with factors like age, gender, socioeconomic status, and sleep disorders.<sup>75</sup> However, the relations between long sleep and health outcomes remained significant after adjustment of these confounders in large studies.<sup>76</sup> To the best of our knowledge, this is the first study to show differences in white matter integrity in young adults who are long sleepers. In our study, the groups were similar in background characteristics, and our results could provide insight into possible mechanisms (white matter integrity) that might help explain these relations.

Long sleep is related to poor sleep quality.<sup>77</sup> Although our sleep groups did not show significant differences in the Pittsburgh Sleep Quality Index, it is known that lower self-reported sleep quality in adults is explained mainly by insomnia, anxiety, and depressive symptoms, rather than by actigraphic variables of sleep.<sup>78</sup> Moreover, perception of good sleep is related to age and objective measures of increase N2 stage time, higher sleep efficiency, and lower sleep fragmentation.<sup>79,80</sup> In this study, the Long sleep group had higher sleep fragmentation in the nocturnal period than the Reference group, which could suggest the fact that sleep quality is a key factor in the maintenance of brain microstructure.

In contrast to other studies,<sup>21,65,68</sup> we did not identify differences in white matter indices between the Short and Reference sleep groups. With regard to this result, it is relevant to note that other reports did not find a significant relation between sleep and white matter integrity.<sup>58,81</sup> Some studies showing an association between white matter integrity and short sleep duration had been performed by using self-reported sleep data,<sup>22,64,82,83</sup> comparing only short and long sleep groups,<sup>50</sup> and included participants with mood disorders<sup>28,58,84</sup> and wider age ranges or older participants relative to our study.<sup>22,23,82,83</sup> Even though our participants are young adults in a narrow age range, with similar characteristics (Tables 1 and 2) and have been assessed with an objective method, our hypothesized differences in white matter microstructure between the Short and Reference sleep groups were not apparent.

Excluding the corpus callosum, the brain regions with lower white matter integrity are located in the left hemisphere, another unexpected result. Some studies suggest a left hemisphere dominance in the waking state<sup>85</sup> such that in situations of increased sleep pressure (sleep restriction/deprivation), a resetting mechanism regulated by prefrontal connectivity in this hemisphere might play a role in brain activity regulation.<sup>86</sup> In a study of white matter microstructure of the circadian tract (connecting the suprachiasmatic nucleus and lateral medulla) in the left hemisphere, Koller et al<sup>87</sup> found that daytime sleepiness correlated strongly with FA of this pathway. Moreover, lower levels of FA in the left superior longitudinal fasciculus have been related to reduced resistance to sleep deprivation (psychomotor vigilance performance monitoring).<sup>62</sup> In light of this information, we suggest that lower white matter integrity in the left hemisphere could relate to more fragmented sleep, greater sleep debt, and, therefore, increased daytime sleepiness. However, it is important to note that increased somnolence was not apparent in the Short sleep group based on the Epworth Sleepiness Scale results.

The limitations of our study include its cross-sectional nature, which precludes inferences regarding causality. We did not include information about other health variables or behaviors (physical activity, substance abuse, inflammation markers, etc.) that could affect white matter composition or sleep-wake characteristics. Regarding the strengths, we highlight the sample size with a narrow age range and the application of appropriate actigraphic recordings and neuroimaging studies (DTI). Our results require replication studies with larger samples.

## Conclusion

To conclude, our findings suggest an association between long sleep duration and decreased integrity of white matter microstructure. This group also had increased WASO in the overall period and a higher number of wake episodes in the second half of the night, suggesting lower sleep quality. Taking into account that myelin is continuously remodeled in the brain,<sup>8</sup> SWC may be a key factor involved in its formation and maintenance. Further, considering the growing prevalence of sleep problems worldwide, the present study provides support to the relevance of nighttime sleep-wake patterns for healthy brain structure and functioning.

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## Disclosure

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