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Research Letter

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Weekly sleep loss is associated with reduced cortical glutathione and antioxidant capacity in adolescents

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Introduction

Sleep is thought to play a crucial role in maintaining metabolic homeostasis in the brain as well as in peripheral tissues. While sleep loss has been linked to adverse cognitive and emotional outcomes [1], the specific neurophysiological factors mediating these outcomes are not yet fully understood. Many adolescents experience chronic sleep loss or curtailment due to a mismatch between their preferred later sleep schedules and early school start times. Given that adolescence is a critical period for developing mental health problems, it is particularly important for public health purposes to better understand neurophysiological changes associated with sleep abnormalities and to implement effective intervention strategies for this age group.

Increased oxidative stress is one of the possible mechanisms by which sleep loss causes metabolic burden and related neuronal dysfunction [2]. Oxidative stress is defined as an imbalance between the production of reactive oxygen species and their elimination by antioxidants. Several preclinical studies have demonstrated evidence of oxidative stress following sleep deprivation, including decreases in the levels of glutathione (GSH), the most abundant antioxidant in the brain [3], and alterations in cortical antioxidant enzyme activity, followed by increased anxiety-like behaviors [4]. However, in vivo imaging markers that could represent the state of sleep loss and that might be used to measure the physiological impact of sleep loss are largely unexplored possibly due to methodological challenges. Moreover, research on the neurophysiological effects of sleep loss has primarily focused on experimental sleep deprivation, leaving the impact of more common, naturally occurring sleep loss less understood.

This study investigated antioxidant capacity in the brain as a factor responsible for neurometabolic alterations imposed by sleep loss in young adolescents. We assessed weekly sleep loss based on Roenneberg et al. [5], defined as the amount of sleep loss accumulated on weekdays or weekends compared to individual sleep needs, determined by average weekly sleep duration. Higher values represent a greater sleep debt.

We employed a proton magnetic resonance spectroscopy (^{1}H-MRS) spectral editing technique for a reliable GSH quantification. We hypothesized that reduced GSH levels in the anterior cingulate cortex (ACC) would be correlated with more sleep loss. The ACC was selected as a region of interest, considering its key role in cognitive, emotional, and behavioral regulation and its functional alterations reported under sleep loss conditions [6, 7].

Materials and Methods

The participants of this study consist of a community sample of young adolescents ($N = 81$; 12–14 years; 39 [48.1%] females; see Supplementary Material for detailed sample information). The study protocol was approved by the institutional review board at the University of Utah. Parents provided written informed consent, and assent to participate was obtained from the adolescents.

^{1}H-MRS data in the ACC ($25 \times 25 \times 30$ mm^3, Figure 1A) were obtained using the Hadamard Encoding and Reconstruction of MEGA-edited Spectroscopy sequence [8] on a Siemens 3.0 T Scanner. The GSH levels were quantified relative to water (GSH [i.u.]) and creatine (GSH/Cr) using Gannet [9] (Figure 1B). We have further described ^{1}H-MRS data acquisition and analysis procedures in Supplementary Material (Table S1 and Figures S1 and S2).

We assessed sleep duration on weekdays and weekends (school-free days) using the Munich Chronotype Questionnaire [5]. Sleep loss across the week was calculated using the following

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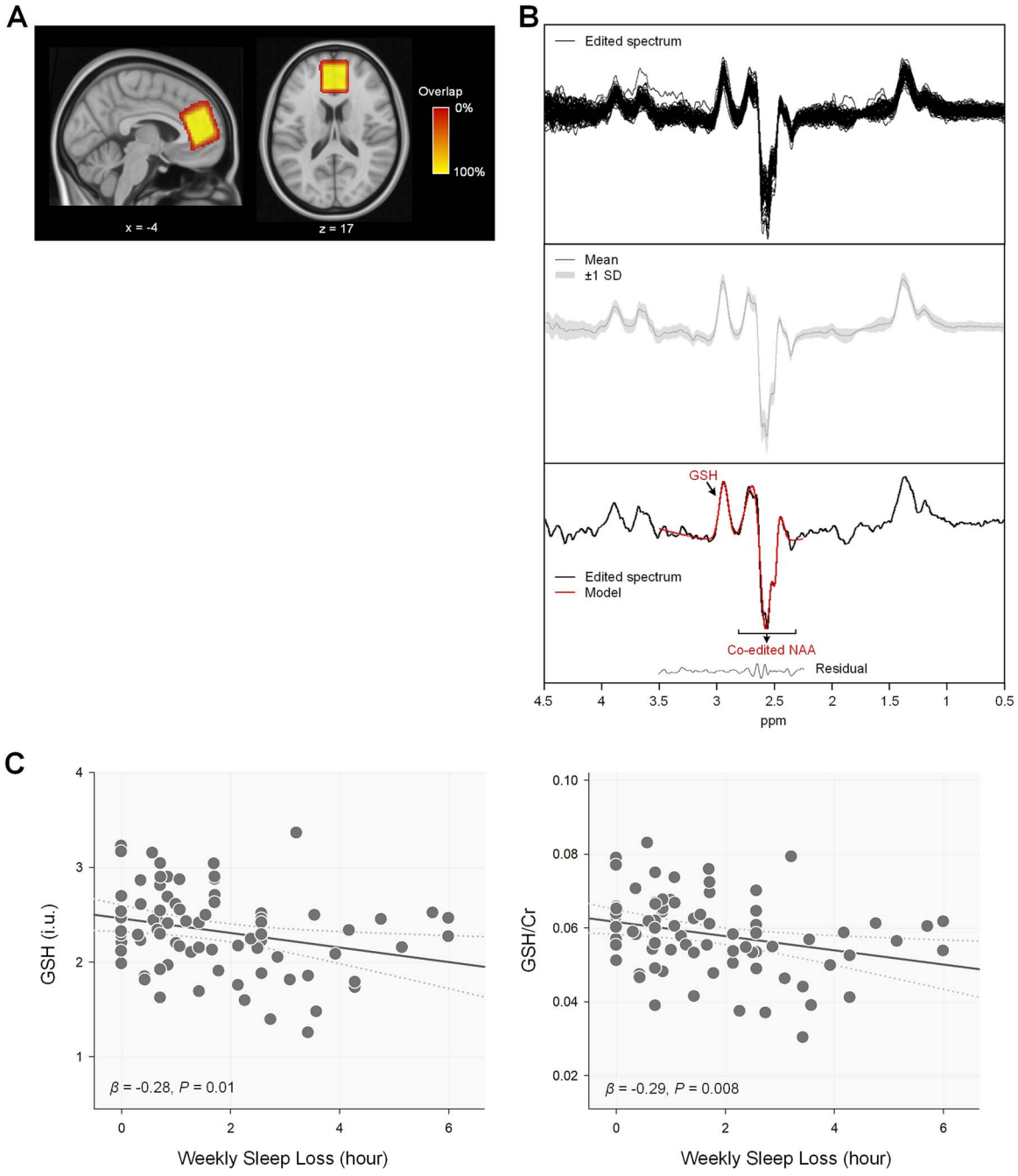

Figure 1. (A) Location of the magnetic resonance spectroscopy (MRS) voxel. To show anatomical overlap in voxel placement across participants, each participant's binary voxel mask was normalized to a standard Montreal Neurological Institute (MNI) space and overlaid on a standard brain template (the MNI-152 template). (B) Edited spectra of all participants (upper), mean of these spectra (middle), and sample edited spectrum and model fit generated using Gannet (lower). The edited spectra were modeled between 2.25 and 3.5 ppm using a five-Gaussian model, with one Gaussian modeling the GSH cysteinyl β-CH_2 signal at 2.95 ppm and the remainder modeling the co-edited *N*-acetyl aspartate peaks around 2.3–2.8 ppm. (C) Associations between weekly sleep loss and the GSH levels. The solid line represents the linear regression line, and the dotted lines indicate the 95% confidence intervals for the linear regression line. GSH, glutathione; i.u., institutional unit; Cr, creatine.

formula suggested by Roenneberg et al. [5]: if sleep duration during the weekdays (SD_w) was shorter than the mean sleep duration for the whole week (SD_{week}), ($SD_{week} - SD_w$) × number of weekdays. If sleep duration during school-free days (SD_f) was shorter than SD_{week}, the formula was: ($SD_{week} - SD_f$) × number of school-free days.

We used a mixed-effect regression model to examine the correlation between ACC GSH levels and weekly sleep loss, including age and sex as covariates. Family membership was also included in the model as a random effect to account for the clustering caused by siblings (2.5%) who were enrolled in the study from the same family. Statistical analyses were conducted using Stata SE version 18.0. The significance level was set at $p < .05$ for all analyses.

Results

The mean weekly sleep duration was 9.3 ± 0.9 h (sleep duration on weekdays, 9.0 ± 1.0 h; sleep duration on school-free days,

9.8 ± 1.3 h), and the mean weekly sleep loss of the sample was 1.7 ± 1.5 h (range = 0–6 h).

We found that greater weekly sleep loss was associated with lower GSH levels in the ACC (GSH [i.u.], $\beta = -0.28$, $z = -2.5$, $p = .01$; GSH/Cr, $\beta = -0.29$, $z = -2.7$, $p = .008$; Figure 1C). These correlations remained significant even after removing three moderate outliers (i.e., weekly sleep loss values beyond 1.5 × interquartile range from the lower and upper quartiles) (GSH [i.u.], $\beta = -0.36$, $z = -3.3$, $p < .001$; GSH/Cr, $\beta = -0.34$, $z = -3.1$, $p = .002$). Seventeen adolescents reported sleeping longer on weekdays than on school-free days. To ensure that this subset of adolescents did not influence our result, we repeated the analysis, including only 64 individuals with sleep loss on weekdays only, and found that the relationships were still significant (GSH [i.u.], $\beta = -0.26$, $z = -2.1$, $p = .04$; GSH/Cr, $\beta = -0.27$, $z = -2.2$, $p = .03$).

SD_{week} was not associated with ACC GSH levels ($p > .1$).

Age and sex were not associated with ACC GSH levels ($p > .4$). A sensitivity analysis additionally controlling for pubertal stage yielded similar results (Supplementary Material, Table S2).

Discussion

To the best of our knowledge, the current study provides the first in vivo evidence that sleep loss is associated with decreased GSH thought to reflect reduced antioxidant capacity in the brain of young adolescents. Our finding of the relationship between weekly sleep loss and reduced GSH in the ACC supports previous studies indicating that sleep has an antioxidative function and that altered sleep homeostasis could precipitate allostatic load resulting from oxidative stress and other metabolic mediators in the brain [2, 10]. It is of note that alterations in biomarkers related to oxidative stress have been studied mainly in experimental sleep deprivation, but this study suggests that a relative deficit in the antioxidant defense system could also be identified in naturally experienced sleep loss.

The current study findings can provide valuable insights for public health and clinical investigators, as early adolescence is a critical period for brain maturation and later mental health risks. Oxidative stress is a central mediator of metabolic disturbances, inflammatory responses, and neurotrophin dysfunction, all of which play a role in modulating neuronal development and function [2]. Previous studies have suggested that increased oxidative stress following sleep deprivation may underlie neurocognitive/behavioral alterations imposed by sleep loss [2]. Furthermore, the ACC is a key region implicated in sleep loss-associated cognitive/emotional dysregulations [7]. Together, reduced antioxidant capacity in the ACC might contribute to adverse mental health outcomes associated with sleep loss, thus could be utilized as a treatment target to preserve brain health against adolescent sleep loss.

This study has several limitations. While we used questionnaire-based data to assess sleep schedules on weekdays and weekends, other measures, such as actigraphy or sleep diaries, could provide more detailed information about sleep duration regularity. Also, our sample was a community sample of predominantly Caucasian youth (87.7%), limiting the generalization of our findings to other races/ethnicities and clinical samples. It is important to note that the ^{1H}-MRS scans were acquired between 10 a.m.–6 p.m.; however, our results remained significant after adjusting for the time of day of the ^{1H}-MRS scan (Supplementary Material, Table S3). Additionally, our cross-sectional findings encourage further longitudinal/experimental studies to unravel dynamic changes in brain GSH levels as sleep loss accumulates or is relieved. Finally, this study warrants further investigations in terms of the regional specificity of oxidative stress.

In summary, this study demonstrated the sleep loss-associated GSH alterations in young adolescents, detected by advanced ^{1}H-MRS. The findings provide a plausible neurobiological account for why maintaining a regular sleep duration during the week and minimizing sleep debt is beneficial for brain health in this age group.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Disclosure statement

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