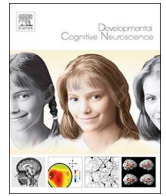




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## Neurophysiological differences in the adolescent brain following a single night of restricted sleep – A 7T fMRI study

Jennifer L. Robinson<sup>a,b,c,\*</sup>, Stephen A. Erath<sup>d</sup>, Rajesh K. Kana<sup>c,e</sup>, Mona El-Sheikh<sup>d</sup><sup>a</sup> Department of Psychology, Auburn University, Auburn, AL, 36849, USA<sup>b</sup> Auburn University MRI Research Center, Auburn University, Auburn, AL, 36849, USA<sup>c</sup> Alabama Advanced Imaging Consortium, USA<sup>d</sup> Department of Human Development and Family Studies, Auburn University, Auburn, AL, 36849, USA<sup>e</sup> Department of Psychology, University of Alabama-Birmingham, Birmingham, AL, 35294, USA

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## ABSTRACT

Sleep deprivation in youth has garnered international attention in recent years, as correlational studies have demonstrated significant relationships between lack of sleep and detrimental behavioral and academic outcomes. However, no study to date has systematically examined the neurophysiological consequences of a single night of sleep restriction (i.e., 4 h) in adolescents using ultra-high field functional neuroimaging. Much of what we know regarding the neural consequences of sleep deprivation has come from the adult literature, and among those studies, the majority use region of interest (ROI) approaches, thus disregarding the dynamic mechanisms that may subserve the behavioral effects of sleep restriction. Leveraging a crossover within-subjects design, we demonstrate that pivotal brain regions involved in the default mode and limbic regulatory centers have disrupted functioning following a night of restricted sleep compared to a night of “normal sleep”. Specifically, a normal night (i.e., 8 h) of sleep led to increased global and local efficiency of bilateral amygdala, and less efficiency in the posterior cingulate, as measured by graph theory, compared to a night of sleep restriction. Furthermore, aberrant functional connectivity patterns were identified in key fronto-limbic circuitry, suggesting a potential pathophysiological mechanism underlying the widespread effects of sleep deprivation in youth.

## 1. Introduction

Sleep deprivation in youth is a significant national and international problem (Mindell and Owens, 2010). As children transition into adolescence, they go to sleep later, obtain less sleep, and experience more sleepiness and poorer quality sleep (Carskadon et al., 2004; Smaldone et al., 2007), with up to 25% obtaining less than 6 h (National Sleep Foundation, 2006; Bartel et al., 2015; Becker et al., 2015). Meanwhile, rates of sleep-related behavioral and emotional disorders continue to rise during adolescence (Costello et al., 2011), as does the potential for negative consequences of sleep deprivation. In adolescence, hormonal effects on brain development create windows of vulnerability (Dahl and Lewin, 2002; Andersen and Teicher, 2004), and escalating social and academic demands may increase the need for the restorative and regulating functions of sleep (Dahl and Spear, 2004; Becker et al., 2015).

In studies conducted predominantly with adults, both prolonged sleep disturbances and short-term sleep restriction have been associated with distinct changes in the brain along both anatomical and functional dimensions, even in otherwise healthy populations. Furthermore,

behavioral data suggest powerful effects in cognitive and emotional domains, both following acute and chronic sleep deprivation and restriction. As a result, it is not surprising that disrupted limbic and cortical regions have been implicated as plausible pathophysiological mechanisms underlying the widespread cognitive and mental health disturbances associated with sleep disturbances.

Despite the documented effects of sleep deprivation, our understanding of the neurophysiological underpinnings of even a single night of sleep restriction in youth is limited. Sleep disturbances are thought to undermine control of regulatory centers in the brain and prime emotion or reward circuits (van der Helm and Walker, 2012; Mullin et al., 2013). Adolescents who reported relatively poor sleep over a 30-day period exhibited less recruitment of the dorsolateral prefrontal cortex (dlPFC) during cognitive control demands and greater insula activation during reward processing (Beebe et al., 2009; Telzer et al., 2013). Research conducted mostly with adults also suggests that sleep disturbances and mental health problems both may be related to “decoupling” of regulatory and reactive subsystems of the brain, such that strong emotions and impulses are under insufficient inhibitory control.

\* Corresponding author at: Department of Psychology, 226 Thach Hall, Auburn University, AL 36849-5214, USA.  
E-mail address: [jrobinson@auburn.edu](mailto:jrobinson@auburn.edu) (J.L. Robinson).

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The PFC has a reciprocal relationship with the amygdala, such that it can serve as a ‘braking system’ to the emotional brain (Delgado et al., 2008), exerting cognitive control over emotions in adaptive regulation of emotion and impulsivity. At least one study with adolescents (Telzer et al., 2013), and several studies with adults, have indicated that sleep disruptions may contribute to such a decoupling (Van der Helm and Walker, 2010; Killgore, 2013).

Affective dysregulation and reward sensitivity are not the only neurophysiological disruptions that manifest from poor, or lack of, sleep. Behavioral and psychiatric problems, neurobehavioral impairments, academic underachievement, autonomic dysregulation, and obesity have also been associated with sleep disturbances (El-Sheikh and Erath, 2011; Baum et al., 2014; Shochat et al., 2014; Rodríguez-Colón et al., 2015). Persistent sleep problems, even if only minor, can cause permanent neuronal cellular stress over time (Jan et al., 2010). Such effects may be more severe among youth, given the level of plasticity and rapid rate of development in young brains (Spruyt et al., 2005; Jan et al., 2010). This highlights the importance of examining neurophysiological disruptions associated with sleep restriction in youth.

Despite the widespread effects of sleep disturbances, most studies have focused solely on *a priori* regions of interest inclusive of primarily the PFC and the amygdala. Enhancing the novelty of this study, we leveraged the advantages of ultra-high field functional neuroimaging (i.e., higher signal-to-noise ratio, higher spatial resolution, and increased sensitivity to the blood-oxygen-level-dependent signal), to examine neurophysiological changes associated with sleep restriction (compared to a ‘normal’ night of sleep) across the entire brain. Specifically, we hypothesized that differences would emerge in critical networks that modulate global processing (i.e., the default mode network) in the brain, and that involve regions that have been previously implicated in sleep disturbances. Furthermore, rather than focusing on activation patterns or specific levels of activation signal which limit the conclusions that can be drawn about the functional architecture of specific regions/networks, we focused on examining connectivity patterns. To this end, we expected to find differences not only within prefrontal and limbic regions, but also in regions that are commonly associated with a broader cognitive-affective network. Employing a within-subjects design, participants were scanned within two hours of waking up. Resting-state functional connectivity analyses and graph theory metrics were conducted to determine differential patterns of brain connectivity and function.

## 2. Methods

### 2.1. Participants

Participants were 18 healthy adolescents (9 female) aged 13–15 years old ( $M_{\text{age}} = 14.40 \text{ years} \pm 1.94 \text{ months}$ ) who were recruited from public schools and partook in a larger study of sleep and child development (Auburn University Sleep Study). Thirteen participants were European American and 5 were African American. Sixteen were right-handed.<sup>1</sup> A researcher contacted the participants’ parents via phone to determine eligibility for the study. Exclusion criteria included braces/metal in the body, medication use, ADHD, asthma, diagnosed sleep disorders based on mothers’ report (e.g., sleep apnea, restless leg syndrome), learning disabilities, concussion, seizures, claustrophobia, and chronic illnesses.

<sup>1</sup> ICA and graph theory analyses were performed with and without the left-handed individuals. Because no differences emerged between statistical maps, we included the individuals in all group analyses. Importantly, the functional neuroimaging analyses performed for this project did account for the within-subjects nature of the data.

### 2.2. Procedures

All procedures were approved by the Institutional Review Board at Auburn University. Written assent and consent were obtained from adolescents and their parents. All participants visited the Auburn University MRI Research Center (AUMRIRC) prior to giving written informed consent and, if interested in the study, were placed in the scanner to acclimate them to the study procedures and gauge their tolerability to the scanning environment. To reduce potential confounds, participation occurred during the regular school year, excluding holidays. Actigraphs were delivered to the participants.

Using a repeated measures design, adolescents participated in two experimental conditions (restricted sleep and ‘normal’ sleep) one week apart, each followed by an fMRI session. The order of the experimental conditions was counterbalanced across participants. Sleep manipulations were on Friday nights (to reduce the effects of weekday-weekend sleep schedule differences and sleep restriction during the school week), and fMRI assessments were on Saturday mornings during the academic year. To maintain consistency in the sleep environment, and given the young age of youth, all sleep assessments occurred in the adolescents’ homes.

To gauge participants’ regular sleep schedules and examine compliance, sleep was monitored with actigraphs for 6 nights total across two weeks (Wednesday-Friday prior to each scan). During the Wednesdays and Thursdays of these two weeks, participants were told to go to bed and to wake up at their usual times. For sleep restriction, youth were instructed to be in bed for 4 h on the Friday before the scan. Scheduled sleep times were either 2:00 a.m.–6:00 a.m. (for those scanned at 8:00 a.m.) or 3:00 a.m.–7:00 a.m. (for those scanned at 9:00 a.m.) depending on scheduled MRI time the following morning. To facilitate compliance, adolescents were called by researchers every 30 min from 10:00pm until 15 min prior to instructed bedtime to make sure they were awake. Researchers inquired about ongoing activities, fatigue, and provided suggestions for staying awake (e.g., get up and walk). In the morning, the researcher called the participants at the scheduled wake time to ensure compliance with the study protocol. For the ‘normal’ sleep condition, participants were told to remain in bed for at least eight hours: 10:00 p.m.–6:00 a.m. for those scanned at 8:00 a.m., or 11:00 p.m.–7:00 a.m. for those scanned at 9:00 a.m. Participants were called in the evening and instructed to go to bed at the scheduled time and were called in the morning at the scheduled wake time to make sure they did not oversleep. For both conditions, participants were instructed to avoid naps and caffeine throughout the day and to arrive at the AUMRIRC within 2 h of waking. Further, for all nights during which actigraphy data were collected, a research assistant called the participants every night to obtain sleep diary information from the previous night to facilitate the coding of actigraphy data and to remind the adolescents to wear the actigraph.

### 2.3. Actigraphy

Actigraphs were used to estimate sleep (Octagonal Basic Motionlogger, Ambulatory Monitoring, Inc., Ardsley, NY). Actigraphy has been validated with children and adolescents for the assessment of multiple sleep parameters and has good psychometric properties when compared to polysomnography (Sadeh et al., 1994; Sadeh et al., 1995). The actigraph recorded activity in 1-min epochs between bedtime and wake time. Data were downloaded using ACTme software and were scored using the Sadeh algorithm (Sadeh et al., 1994; Sadeh et al., 1995) and the Action W-2 analysis software (ActionW User’s Guide version 2.4, 2002). Established procedures for determining sleep/wake times were used (Acebo and Carskadon, 2001). Youth reported their bedtimes and four actigraphy-based variables were derived: (a) Sleep Onset Time; (b) Awakening Time; (c) Sleep Period (bedtime to awakening time and latency); and (d) Total Actual Sleep Minutes (from sleep onset to wake time excluding wake minutes after sleep onset).

## 2.4. fMRI scanning & data analysis

We performed ultra-high field, high-resolution resting state functional magnetic resonance imaging (rs-fMRI) to characterize differences in resting state networks between conditions. Participants were scanned using an EPI sequence, optimized in-house to reduce susceptibility artifacts (37 slices acquired parallel to the AC-PC line, 0.85 mm × 0.85 mm × 1.5 mm voxels, TR/TE: 3000/28 ms, 70° flip angle, base/phase resolution 234/100, A > P phase encode direction, iPAT GRAPPA acceleration factor = 3, interleaved acquisition, 100 time points, total acquisition time 5:00). Participants were asked to rest with their eyes closed for the duration of the scan. Data were acquired on the AUMRIRC Siemens 7 T MAGNETOM outfitted with a 32-channel head coil by Nova Medical (Wilmington, MA). A whole-brain high-resolution 3D MPRAGE image (256 slices, 0.70 mm<sup>3</sup> voxels, TR/TE: 2200/2.89 ms, 7° flip angle, base/phase resolution 256/100, A > P phase encode direction, iPAT GRAPPA acceleration factor = 2, total acquisition time 5:18) was also acquired for registration purposes. It is important to note that scanning utilized an ultra-high resolution sequence (i.e., submillimeter in-plane acquisition), which allows for greater sensitivity and delineation of anatomical features. This leads to improved pre-processing and registration to anatomical images, in addition to more accurate functional brain maps.

Data were analyzed using two techniques: 1) graph theory metrics and 2) independent component analysis. For graph theory analyses, we employed the ‘conn’ toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) (<https://www.nitrc.org/projects/conn/>) for MATLAB to calculate nodal measures such as local efficiency, clustering coefficient, and degree as well as global measures such as global efficiency, average path length, and betweenness centrality. In graph theory, a brain region is considered a node, and a connection between brain regions is considered an edge. These measures are indicative of how brain regions are interacting and integrating with other brain regions. Global and local efficiency measure the ability of a region to transmit information at the whole brain (i.e., global) or regional (i.e., local) level (Latora and Marchiori, 2001), while path length is a measure of integration as it accounts for the average shortest path length between all brain region pairs. Degree is an indication of the number of edges, or connections, emanating from a single brain region, while a clustering coefficient indicates how many of a region's neighbors are connected to one another. Graph theory metrics are used to characterize brain networks, and are a robust alternative to activation patterns as they provide more information about the nature of the network (i.e., how functionally integrated or segregated it may be) (Rubinov and Sporns, 2010). For all graph theory metrics, the adjacency matrix (composed of 85 atlas-based regions of interest) was formed by selecting a fixed percentile (15%) of the edges in each network (i.e., those with the highest correlation coefficient values, separately for each subject), using a two-sided threshold. Paired t-tests (between conditions) were conducted. All analyses surpassing a two-sided, FDR-corrected  $p < 0.05$  are reported. We also employed FSL's Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC), a spatial ICA-based approach to resting state data. Prior to analyses, standard resting state fMRI pre-processing steps (i.e., brain extraction, slice timing correction, Gaussian smoothing (3 mm FWHM), band-pass filtering (0.008–0.09), regression of motion and physiological artifacts (using CompCor), registration to anatomical space, and normalization to MNI standard space) were performed.

Finally, regional homogeneity (ReHo) analyses were performed on the data. ReHo evaluates the brain activity at the voxel level by measuring the similarity or synchronization between the time course of a given voxel and its nearest neighbors (Zang et al., 2004). The rationale and advantages of using ReHo are as follows: a) intrinsic brain activity is manifested in clusters of voxels rather than in a single voxel, and hence ReHo may be a more accurate measure; b) measuring local connectivity is important as it provides an index of specialization of

areas; c) local connectivity can induce alterations in remote functional connectivity (Deco et al., 2014); d) local connectivity can also determine the boundaries between functionally heterogeneous regions; and e) regional homogeneity can inform structure-function relationship in understanding the brain (Jiang and Zuo, 2016). Regional homogeneity implements Kendall's coefficient of concordance (KCC), which relies on rank correlations of time series to assess the homogeneity of a given center voxel and its neighboring voxels.

$$W = \frac{\sum (R_i)^2 - n(\bar{R})^2}{\frac{1}{12}K^2(n^3 - n)},$$

KCC within a given cluster of voxels is equal to the parameter  $W$  (ranging from 0 to 1), where  $R_i$  is the sum rank of the  $i$ th time point;  $\bar{R}$  is the mean of the  $R_i$ s;  $K$  is the number of time series within a selected cluster (7, 19, or 27 voxels), and  $n$  is the number of ranks, as determined by the number of time points. For this analysis, we used a cluster size of 27 voxels. To generate connectivity maps and be subjected to statistical analyses, ReHo maps were smoothed and then converted to z-scores. Contrasts were thresholded at  $p = 0.00001$ , cluster = 50 voxels, estimated through Monte Carlo simulations, which roughly corresponds to a familywise error (FWE) corrected threshold of  $p < 0.05$ .

## 2.5. Behavioral tasks

Participants completed two common neurocognitive tasks, known to elicit activation throughout the fronto-limbic network (Cazzell et al., 2012; Congdon et al., 2013; Robles et al., 2014; Rasmussen et al., 2016; Schmäser et al., 2016), and that have been used in sleep deprivation studies (Killgore et al., 2011). First, participants completed the balloon analogue risk task (BART) which is a computerized measure of risk-taking behavior. Adolescents were presented with a balloon that they could “blow up”. The balloon could “pop” at any time, and the more the balloon inflated, the more points they would earn. They could choose to stop inflating the balloon, and collect the points earned for that trial at any time. If the balloon popped, the points earned from that trial were lost. Youth were not informed about the balloon's breakpoints, which were random (Lejuez et al., 2002). The BART is sensitive in determining neural network differences in populations with varying levels of risk-sensitivity (Karen et al., 2014). For the BART, we examined the total amount of points earned over the 6-minutes they engaged in the task, the number of popped balloons, the average number of pumps per trial, the number of total trials and the number of successful trials, as well as reaction time. The second task was a Go/No-Go task, in which stimuli were presented in a continuous stream and youth performed a binary decision on each stimulus (e.g., is the stimulus in an alternating pattern with the previous stimulus?). Youth pressed a button if the stimulus met the criteria (go trial), or withheld their responses if it did not (no-go trial). There are more ‘go’ than ‘no-go’ trials, enticing the youth into a pattern of response, making the ‘no-go’ trials more difficult in people with poor impulse control (Roberts et al., 1994; Shibata et al., 1997; Braver et al., 2001; Rubia et al., 2001; Rubia et al., 2003). In this task, we examined the number of lure errors (i.e., how many times they responded when they shouldn't have), errors of omission (i.e., how many times they did not respond when they should have), total accuracy, and reaction time during correct trials.

## 3. Results

### 3.1. Actigraphy measures

Indicative of similarity in sleep schedule on the two nights (Wednesdays and Thursdays) preceding the normal and restricted sleep conditions, adolescents went to bed, fell asleep, and woke up at similar times during the two nights preceding each sleep manipulation

**Table 1**  
Means and standard errors for sleep schedule and period prior to and during the normal and restriction conditions.

Sleep Schedule and Period	Sleep	Condition	t-value
	Normal	Restriction	
<b>Wednesday &amp; Thursday</b>			
Reported Bedtime	10:00 p.m. ± 13.04	10:08 p.m. ± 9.59	-0.70
Sleep Onset Time	10:39 p.m. ± 12.73	10:47 p.m. ± 13.27	-0.75
Total Sleep Minutes	413.75 ± 14.18	380.31 ± 13.69	3.26**
Wake Minutes	31.72 ± 5.02	40.83 ± 6.80	-2.39*
Awakening Time	6:04 a.m. ± 11.62	5:51 a.m. ± 15.13	1.54
Sleep Period	455.03 ± 13.86	439.67 ± 17.53	0.12
<b>Friday – Manipulation (Fri)</b>			
Awakening Time	6:09 a.m. ± 13.29	6:06 a.m. ± 14.80	1.46
<b>Reported Bedtime</b>			
10:00 pm / 2:00 am	9:55 p.m. ± 7.14	1:54 a.m. ± 7.88	-61.43***
11:00 pm / 3:00 am	11:13 p.m. ± 8.81	3:13 a.m. ± 8.81	-19.24***
<b>Sleep Onset Time</b>			
10:00 pm / 2:00 am	10:31 p.m. ± 11.35	1:59 a.m. ± 7.47	-15.28***
11:00 pm / 3:00 am	11:38 p.m. ± 14.86	3:13 a.m. ± 9.85	-19.33***
Total Sleep Minutes	401.67 ± 12.32	209.39 ± 8.44	20.06***
Wake Minutes	38.61 ± 5.46	16.94 ± 5.28	3.58**
<b>Awakening Time (Sat)</b>			
6:00 am	5:48 a.m. ± 8.08	5:52 a.m. ± 7.25	-0.75
7:00 am	7:01 a.m. ± 12.42	6:55 a.m. ± 11.42	0.45
Sleep Period	449.83 ± 8.41	239.78 ± 5.43	26.67***

Note: Sleep period refers to time in bed (bedtime to awakening time). Total sleep minutes refer to actual sleep between sleep onset and wake time excluding minutes awake after sleep onset.  $df = 17$ . \*  $p < 0.05$ , \*\*  $p < 0.01$ , two-tailed. \*\*\*  $p < 0.001$ , two-tailed.

(Table 1). Further, adolescents woke up at similar times on the Fridays of the two sleep conditions. The sleep manipulations were effective (see Table 1), and both bedtimes and sleep onset times were later during the sleep restriction in comparison to the normal sleep condition. The sleep period (overall time in bed) and actual sleep minutes were shorter during the night of sleep restriction in comparison to that of normal sleep (Table 1). On average, participants had a difference of 3.5 h of actual sleep minutes between conditions. Descriptive information regarding sleep schedule during the normal and restriction conditions is compiled in Table 1.

### 3.2. Graph theory metrics

In comparison to a night of restricted sleep, a normal night of sleep was associated with greater local and global efficiency in bilateral amygdala and left posterior fusiform gyrus. Additionally, the left amygdala exhibited a significantly greater clustering coefficient along with the left anterior parahippocampus following a normal night of sleep in comparison to sleep restriction. Limbic circuitry inclusive of bilateral amygdala, fusiform, thalamus, and right nucleus accumbens had higher degree following normal compared to restricted sleep. In contrast, the posterior cingulate cortex (PCC) and left superior portions of the lateral occipital cortex demonstrated greater local and global efficiency, while other sensory processing/integration regions also exhibited greater global efficiency (i.e., left angular gyrus, precuneus, bilateral anterior supramarginal gyri, and right superior parietal lobule) following a night of sleep restriction. Differences in average path length were also noted such that increases in sensory processing networks were observed following a normal night of sleep, while greater path lengths were exhibited in the left thalamus and fusiform regions following a night of sleep restriction (Fig. 1, Table 2).

### 3.3. Independent component analysis: functional networks

Our data demonstrate hyperactive nodes within the default mode network (i.e., the anterior cingulate cortex (ACC; BA24/32), PCC (BA30), and the inferior/middle frontal gyri (BA9/46)) associated with sleep restriction, along with hypoactive regions of the dorsolateral prefrontal cortex (dlPFC). Although not significant, it is noteworthy that differences between conditions within the limbic network approached significance, with normal sleep demonstrating greater activity (Fig. 2).

### 3.4. Regional homogeneity (ReHo)

Statistically significant differences in ReHo were found with increased local connectivity in participants following normal sleep compared to restricted sleep. Local connectivity differences were identified primarily throughout the right hemisphere inclusive of the supramarginal gyrus, posterior cingulate, precuneus, medial prefrontal cortex (MPFC), and middle cingulate gyrus (Fig. 3, Table 3). Only one local connectivity difference was noted in the left hemisphere (inferior parietal lobule). No significant increases in connectivity were identified in the sleep restriction > normal sleep contrast.

### 3.5. Behavioral results

For the BART, one-tailed, paired t-tests revealed significant effects for the average number of pumps per trial ( $M \pm SEM$ :  $M_{\text{restriction}} = 4.81 \pm 0.18$ ,  $M_{\text{normal}} = 4.55 \pm 0.22$ ,  $t(17) = 1.796$ ,  $p < 0.05$ ), the number of successful trials ( $M_{\text{restriction}} = 14.78 \pm 1.18$ ,  $M_{\text{normal}} = 17.78 \pm 1.41$ ,  $t(17) = -3.956$ ,  $p < 0.001$ ), and the number of blocks ( $M_{\text{restriction}} = 22.06 \pm 0.84$ ,  $M_{\text{normal}} = 23.94 \pm 1.07$ ,  $t(17) = -2.058$ ,  $p < 0.03$ ). The number of popped balloons approached significance ( $M_{\text{restriction}} = 7.28 \pm 0.71$ ,  $M_{\text{normal}} = 6.17 \pm 0.53$ ,  $t(17) = 1.668$ ,  $p = 0.057$ ). For the Go/NoGo task, sleep restriction led to more errors of omission ( $M_{\text{restriction}} = 15.11 \pm 4.72$ ,  $M_{\text{normal}} = 7.00 \pm 1.49$ ,  $t(17) = 1.739$ ,  $p < 0.05$ ), greater reaction times ( $M_{\text{restriction}} = 327.40 \pm 13.77$  ms,  $M_{\text{normal}} = 302.14 \pm 10.27$  ms,  $t(17) = 2.072$ ,  $p < 0.03$ ), and less accuracy ( $M_{\text{restriction}} = 206.44 \pm 5.38$ ,  $M_{\text{normal}} = 215.44 \pm 1.62$ ,  $t(17) = -1.771$ ,  $p < 0.05$ ). These results suggest that across tasks, the sleep restriction condition led to greater risk-taking behavior, and less accurate responding.

## 4. Discussion

The extant literature has attempted to understand the neuropathophysiological mechanisms underlying sleep deprivation by focusing on the obvious targets of affective processing – namely, fronto-limbic and fronto-striatal connections – predominantly with adult samples. Using whole-brain analyses (i.e., as opposed to seed-based or ROI-based approaches), strong methodology (i.e., a within-subjects crossover design), novel analytic methods (i.e., graph theory and regional homogeneity), and a 7T scanner, we identify additional neural components that may contribute to the system-wide effects of a single night of sleep restriction during mid-adolescence.

Our data support previous findings of disrupted striatal and limbic circuitry in adults (De Havas et al., 2012; Mullin et al., 2013), and extend them to youth. Building on the literature, we used graph theory metrics to explicate the neural environment resulting from a night of sleep restriction (4 h in bed) and a night of normal sleep (8 h in bed). Specifically, we found that following normal sleep, key limbic structures (i.e., bilateral amygdala) appear to have greater local efficiency (e.g., greater average path connecting all neighbors of a given node) and global efficiency (e.g., the inverse of the average shortest path length between all node pairs), as well as a higher degree (e.g., the number of edges originating from a single node). These results suggest

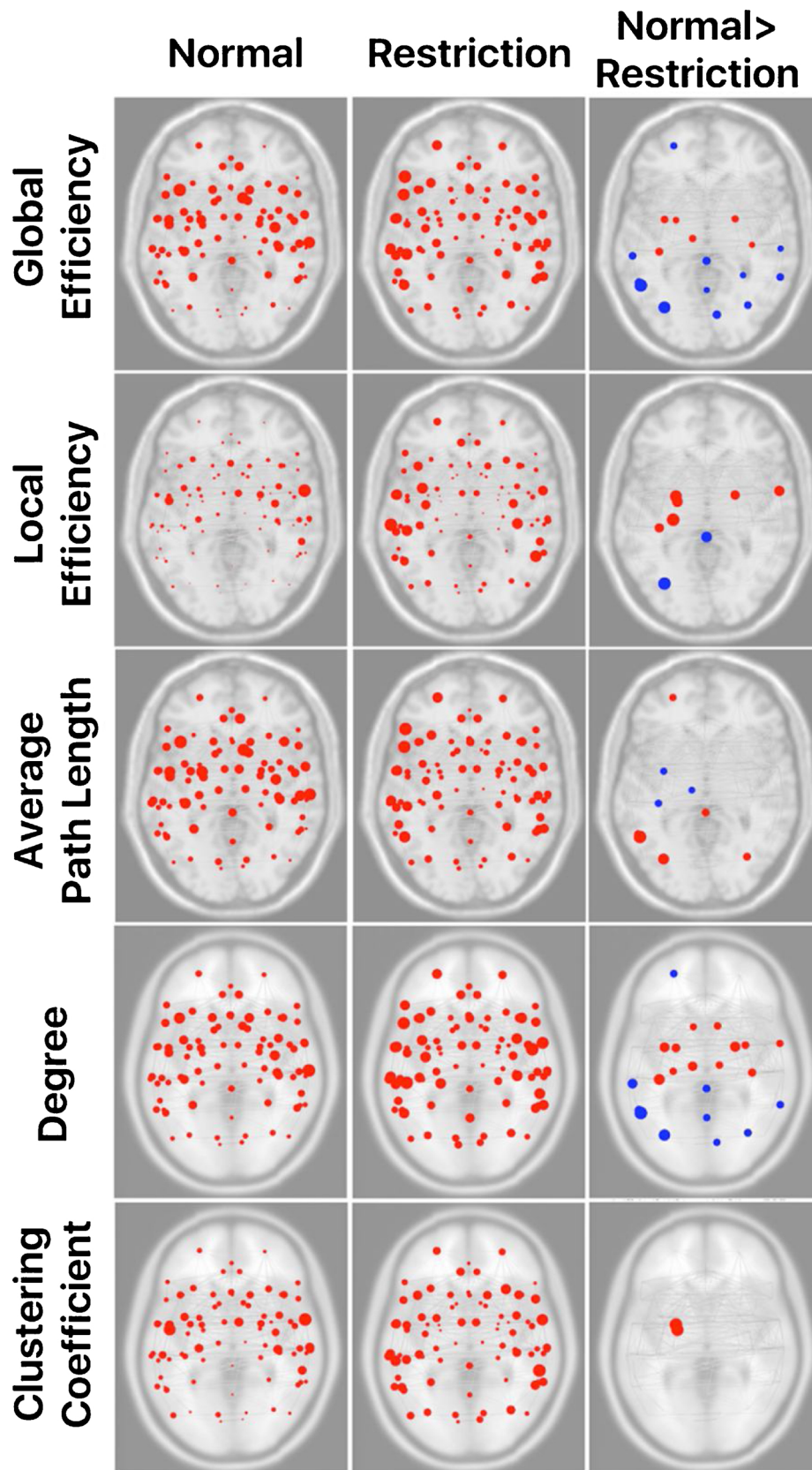


Fig. 1. Significant differences across graph theory metrics between normal and restricted sleep conditions. Red dots indicate regions where normal > restriction, and blue dots indicate regions where restriction > normal. Dot size is an indication of the magnitude ( $t$ -value). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

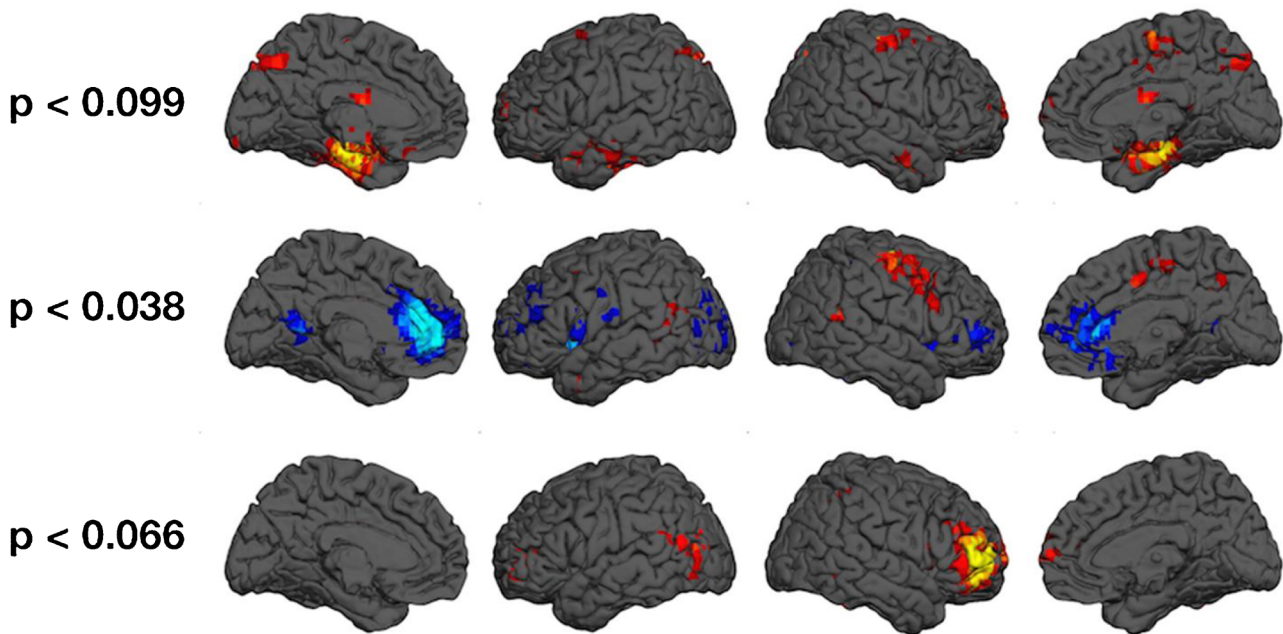
**Table 2**  
Regions of significant difference as a result of acute sleep restriction.

Graph Theory Results				
Global Efficiency Differences				
Contrast	Region	t-value	p-FDR corrected	
Normal > Restriction	Left Amygdala	3.15	0.035	
	Left Anterior Temporal Fusiform Cortex	3.62	0.018	
	Left Posterior Temporal Fusiform Cortex	3.80	0.018	
	Left Thalamus	3.47	0.020	
	Right Amygdala	3.46	0.020	
	Right Posterior Temporal Fusiform Cortex	2.97	0.040	
Restriction > Normal	Left Angular Gyrus	-5.92	0.001	
	Left Anterior Supramarginal Gyrus	-3.64	0.018	
	Left Frontal Pole	-3.45	0.020	
	Left Inferior Temporal Gyrus (temporooccipital part)	-3.99	0.018	
	Left Superior Lateral Occipital Cortex	-5.61	0.001	
	Posterior Cingulate	-3.86	0.018	
	Precuneous	-2.98	0.040	
	Right Anterior Supramarginal Gyrus	-2.98	0.040	
	Right Cuneal Cortex	-4.06	0.018	
	Right Middle Temporal Gyrus (temporooccipital part)	-3.66	0.018	
	Right Superior Lateral Occipital Cortex	-3.67	0.018	
	Right Superior Parietal Lobule	-3.03	0.040	
	Local Efficiency			
	Normal > Restriction	Left Amygdala	4.21	0.019
Left Anterior Parahippocampal Cortex		3.81	0.028	
Left Hippocampus		4.44	0.018	
Left Posterior Temporal Fusiform Cortex		3.31	0.047	
Right Amygdala		3.33	0.047	
Right Anterior Superior Temporal Gyrus		3.65	0.028	
Restriction > Normal	Left Superior Lateral Occipital Cortex	-4.37	0.018	
	Posterior Cingulate	-3.74	0.028	
Average Path Length				
Normal > Restriction	Left Angular Gyrus	5.88	0.002	
	Left Frontal Pole	3.47	0.035	
	Left Inferior Temporal Gyrus (temporooccipital part)	3.64	0.034	
	Left Superior Lateral Occipital Cortex	5.13	0.004	
	Posterior Cingulate	3.70	0.034	
	Right Superior Lateral Occipital Cortex	3.75	0.034	
Restriction > Normal	Left Anterior Temporal Fusiform Cortex	-3.36	0.039	
	Left Posterior Temporal Fusiform Cortex	-3.50	0.035	
	Left Thalamus	-3.21	0.048	
Degree				
Normal > Restriction	Left Posterior Temporal Fusiform Cortex	4.33	0.013	
	Left Accumbens	2.87	0.041	
	Left Amygdala	3.53	0.028	
	Left Anterior Temporal Fusiform Cortex	3.94	0.016	
	Left Hippocampus	3.02	0.035	
	Left Thalamus	3.77	0.018	
	Right Accumbens	3.04	0.035	
	Right Amygdala	4.12	0.015	
	Right Anterior Middle Temporal Gyrus	2.98	0.035	
	Right Anterior Temporal Fusiform Cortex	3.16	0.035	
	Right Posterior Temporal Fusiform Cortex	3.31	0.035	
	Right Thalamus	3.05	0.035	
	Restriction > Normal	Left Angular Gyrus	-5.04	0.009
		Left Anterior Supramarginal Gyrus	-3.90	0.016
Left Frontal Pole		-3.06	0.035	
Left Inferior Temporal Gyrus (temporooccipital part)		-3.45	0.029	
Left Superior Lateral Occipital Cortex		-4.56	0.012	
Posterior Cingulate		-3.19	0.035	
Precuneous		-3.00	0.035	
Right Cuneal		-3.00	0.035	
Right Middle Temporal Gyrus (temporooccipital part)		-3.08	0.035	
Right Superior Lateral Occipital Cortex		-2.95	0.036	
Clustering Coefficient				
Normal > Restriction	Left Amygdala	4.80	0.010	
	Left Anterior Parahippocampal Cortex	4.69	0.010	

that the functional integrity of the amygdala may break down following sleep restriction, resulting in less efficient processing. Similar patterns were observed for the accumbens and left hippocampus. Of note is that

our graph theory metrics did not highlight many PFC regions, as one would expect, with the exception of the frontal pole, which had greater global efficiency and degree in the sleep restriction condition. We

## Normal Sleep > Sleep Restriction



## Sleep Restriction > Normal Sleep

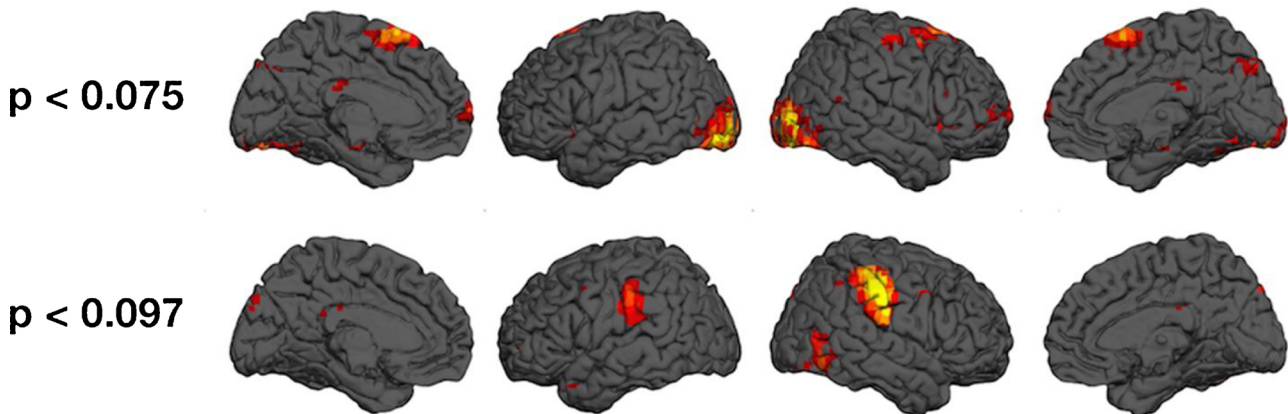


Fig. 2. Neurophysiological differences between normal and restricted sleep as evidenced by independent component analyses of task-independent fMRI.

did note that the default mode network, inclusive of the dlPFC and regions critically involved in a host of affective and cognitive processes (i.e., ACC and PCC), were significantly different between conditions. Together, these data confirm and extend findings regarding the coupling of limbic and cognitive control centers (Shao et al., 2014).

Across analyses, however, we observed convergent evidence for significant aberrations in PCC function associated with sleep restriction. Specifically, we found differences in the default mode network, inclusive of the ACC and PCC, along with greater local and global efficiency in the PCC concomitant with shorter average path lengths following a night of sleep restriction. We also demonstrated regional homogeneity differences. This result is intriguing because of the vast array of processes that the PCC is involved in, including reward prediction, learning, attention, memory, emotion, nociception, and interoception (Johnson et al., 2006; Vogt et al., 2006; Pearson et al., 2011; Leech and Sharp, 2014). Furthermore, the precuneus/PCC node is considered the core of the default mode network (DMN) with vital neurofunctional roles in task positive and task negative networks

(Utevsky et al., 2014). Therefore, sleep restricted participants who showed weaker local connectivity of this region may have poor flexibility in cognitive processes compared to participants who had normal sleep. We demonstrate behavioral indices suggesting that sleep restriction lead to less accuracy and increased reaction time on a task of inhibitory control and increased risky choice behavior on the BART (i.e., greater average number of balloon pumps, but less success). Given the functional connectedness and vast structural connectivity (Vogt et al., 2006), these data suggest that the PCC may be a neural hub at the center of sleep restriction or deprivation. Indeed, recent studies in adults have noted functional connectivity differences within the PCC as a result of sleep alterations (De Havas et al., 2012; Killgore et al., 2012; Shao et al., 2014). With such extensive system-wide effects resulting from a single night of sleep restriction, it is plausible that the PCC may be causing the downstream effects within fronto-limbic and fronto-striatal circuitry commonly associated with sleep disruptions.

Additionally, it should be noted that the main clusters of local connectivity differences (as determined by ReHo analyses) between the

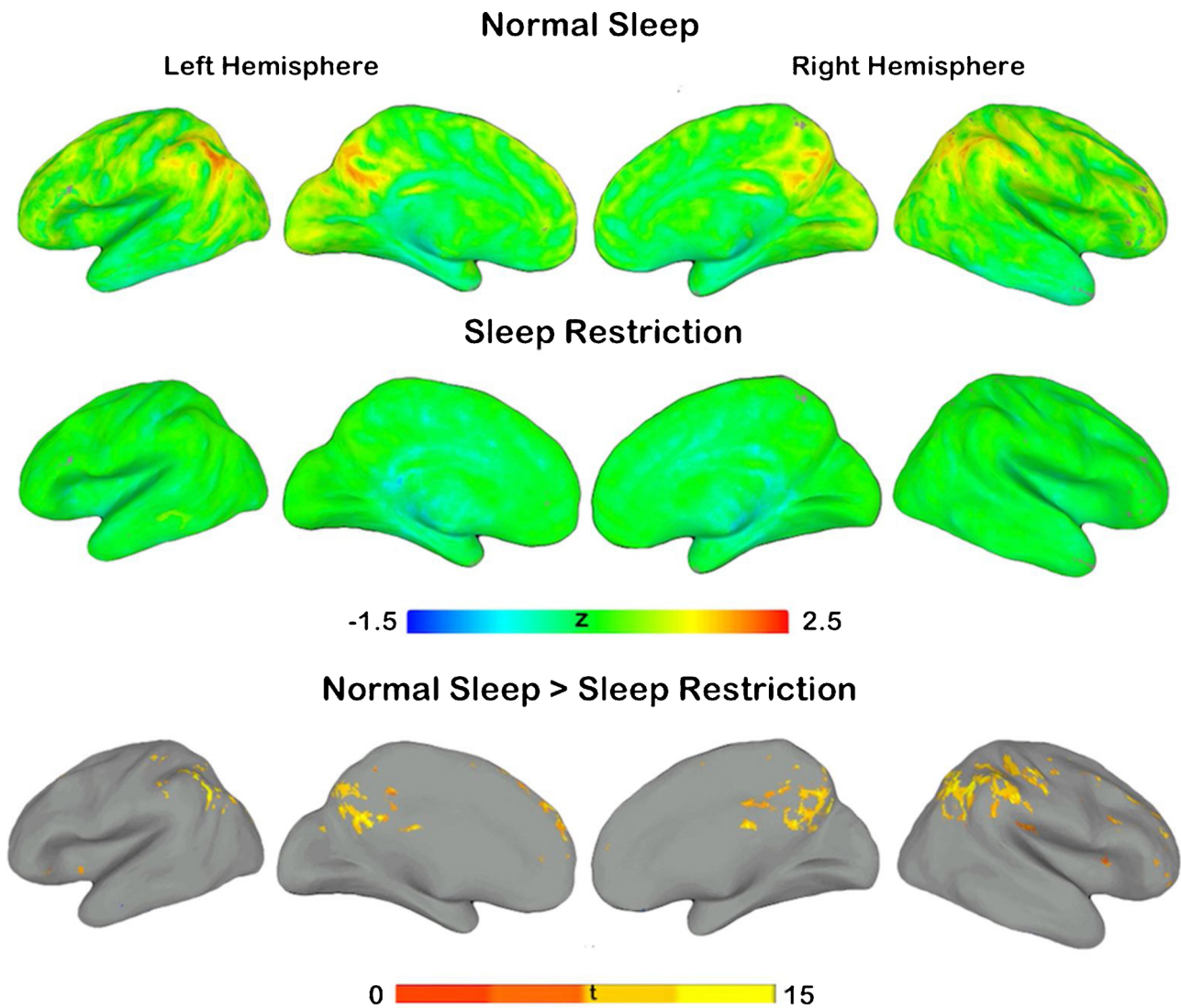


Fig. 3. Regional homogeneity (ReHo) differences between normal sleep and sleep restriction.

**Table 3**  
Significant differences in regional homogeneity between normal sleep and sleep restriction conditions. Data were thresholded at  $p < 0.0001$ .

Regional Homogeneity (Normal Sleep > Sleep Restriction)					
Region	Cluster size (in voxels)	Peak Coordinates (MNI)			
		x	y	z	t
Right Supramarginal Gyrus	2021	62	-46	32	14.77
Right Precuneus/Posterior Cingulate	1069	6	-50	38	12.49
Right Superior Medial Gyrus	467	2	56	10	11.46
Left Inferior Parietal Lobule	421	-50	-52	50	11.83
Right Middle Cingulate Cortex	233	2	-20	32	11.42
Right Middle Frontal Gyrus	195	50	14	44	11.86
Right Middle Frontal Gyrus	141	24	52	26	11.60
Right Middle Frontal Gyrus	85	38	56	16	11.34
Right Middle Frontal Gyrus	69	44	30	38	15.19
Right Rolandic Operculum	51	50	-24	18	14.14

two conditions were largely throughout the parietal cortex, comprising of the inferior parietal lobule, precuneus/PCC, and supramarginal gyrus, consistent with the results of the ICA analysis. These regions are involved in several different cognitive processes, such as visual

attention (Chambers et al., 2004; Stevens et al., 2005), working memory (Uncapher and Wagner, 2009), and semantic processing (Binder et al., 2009). Weaker local connectivity of these regions in sleep deprived participants in our study may reflect the impact of sleep on these cognitive functions.

Together, these complementary analytic approaches may suggest that following sleep restriction, there are concomitant network changes such that the amygdala-dlPFC relationship becomes altered via less efficient local and global processing. Furthermore, the PCC becomes more engaged and may mediate the cognitive, emotional, and interoceptive effects commonly described in sleep deprivation studies. Lastly, trends toward greater activity throughout occipital and parietal networks may suggest heightened sensory processing, or hypervigilant states. These data highlight the importance of whole-brain analyses to better understand the neurodynamics underlying sleep restriction, which may inform our understanding of sleep deprivation.

It should be noted that this study has limitations. First, while we collected two days of sleep actigraphy data prior to the manipulation, this does not account for potential habitual sleep patterns leading up to the study. As such, it is possible that participants may have already been operating under abnormal sleep patterns, which could have affected the results of the study. For example, our two groups differed in total sleep minutes for the two nights preceding the manipulation, despite going to bed, falling asleep, and waking up at similar times. We



did not account for these differences in our analyses, so it may be possible that the results are indicative of differences that emerge from a more chronic, rather than acute, sleep restriction. Second, while the use of ultra-high field functional neuroimaging is novel, the field is relatively new, and it is possible that there are limitations in using this methodology (i.e., greater artifacts).

To our knowledge, these data are the first ultra-high field sub-millimeter functional neuroimaging data to emerge in an adolescent sample. The neurofunctional consequences of one night of sleep restriction are largely unknown in this population, and utilizing a 7 T magnet may have afforded greater sensitivity to detect subtle network disruptions. Additionally, it is possible that the added signal-to-noise ratio of the 7 T, which is primarily driving the increased BOLD sensitivity, coupled with the increased spatial resolution, provided an opportunity to identify regions that are involved in neural circuitry that would not otherwise be detected at lower field strengths. Thus, future studies should be employed to deconstruct the contributions of regions that have been largely overlooked in the sleep deprivation literature (i.e., ACC, PCC, and sensory processing regions).

### Conflict of Interest

None.

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