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The association between cortical gyrification and sleep in adolescents and young adults

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Abstract

Study Objectives: Healthy sleep is important for adolescent neurodevelopment, and relationships between brain structure and sleep can vary in strength over this maturational window. Although cortical gyrification is increasingly considered a useful index for understanding cognitive and emotional outcomes in adolescence, and sleep is also a strong predictor of such outcomes, we know relatively little about associations between cortical gyrification and sleep. We aimed to identify developmentally invariant (stable across age) or developmentally specific (observed only during discrete age intervals) gyrification-sleep relationships in young people.

Methods: A total of 252 Neuroimaging and Pediatric Sleep Databank participants (9–26 years; 58.3% female) completed wrist actigraphy and a structural MRI scan. Local gyrification index (lGI) was estimated for 34 bilateral brain regions. Naturalistic sleep characteristics (duration, timing, continuity, and regularity) were estimated from wrist actigraphy. Regularized regression for feature selection was used to examine gyrification-sleep relationships.

Results: For most brain regions, greater lGI was associated with longer sleep duration, earlier sleep timing, lower variability in sleep regularity, and shorter time awake after sleep onset. lGI in frontoparietal network regions showed associations with sleep patterns that were stable across age. However, in default mode network regions, lGI was only associated with sleep patterns from late childhood through early-to-mid adolescence, a period of vulnerability for mental health disorders.

Conclusions: We detected both developmentally invariant and developmentally specific ties between local gyrification and naturalistic sleep patterns. Default mode network regions may be particularly susceptible to interventions promoting more optimal sleep during childhood and adolescence.

Key words: sleep; actigraphy; cortical gyrification; cortical folding; neuroimaging

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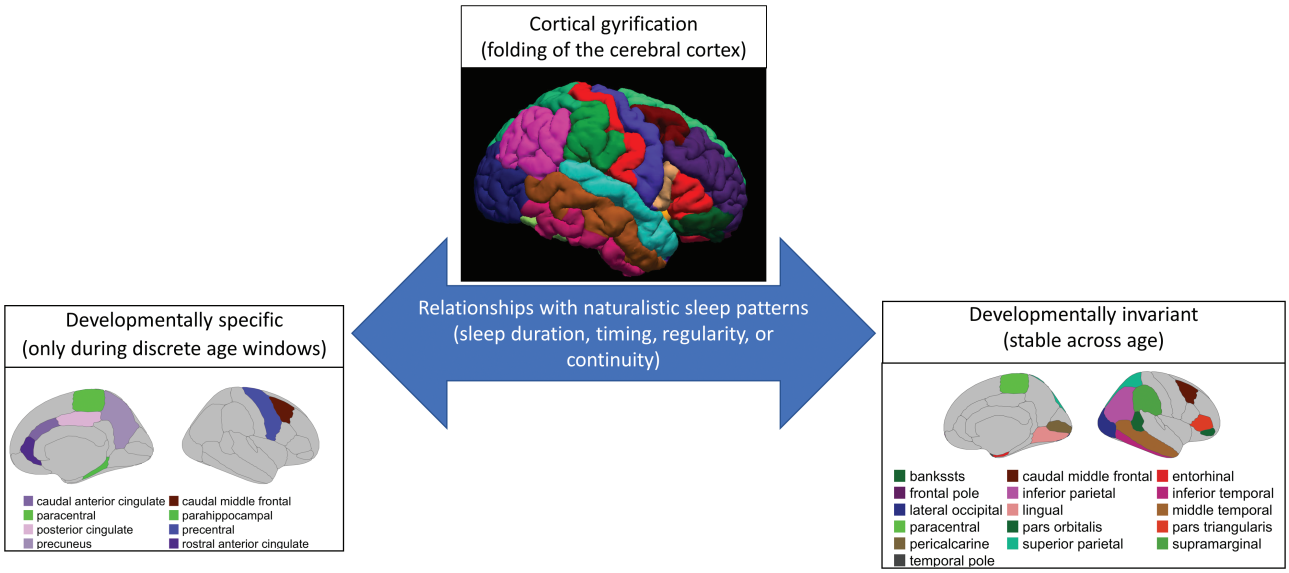
Graphical Abstract



Statement of Significance

Sleep is a behavior important for neurodevelopment and the relationships between brain and sleep may vary among developmental stages and among specific sleep characteristics. While other metrics of brain structure have been explored, little is known about the association between cortical gyrification (folding of the cerebral cortex) and sleep. Cortical gyrification is a useful index for understanding brain development and aging. Exploring the relationship between cortical gyrification and sleep in typically developing young people will provide new insights into the brain-sleep relationships during the transition from childhood to adulthood.

Introduction

Brain structure and sleep patterns undergo significant maturational changes over adolescence [1], and developmental shifts in these phenomena are each known to influence adolescent emotional, social, cognitive, and behavioral outcomes [2–4]. Data from animal models now demonstrates that sleep quality during the sensitive period of adolescence plays a causal role in adult behavioral outcomes via brain-based pathways [5]. Yet, our basic understanding of relationships between brain morphology and sleep patterns in human adolescents remains in the early stages. Although several studies have now explored relationships between gray matter structure (e.g. cortical thickness, cortical, and subcortical volume) and sleep in adolescence, we still know relatively little about associations between cortical gyrification and sleep [6]. Cortical gyrification (i.e. the folding of the cerebral cortex [7–9]) is a sensitive indicator of brain development [9, 10] and is emerging as an important predictor of positive adolescent health outcomes [11, 12]. Given that sleep is important for neuroprotection [13], synaptic plasticity [14], and neural reorganization [15, 16], processes which may be reflected in measures of cortical gyrification, exploring the relationship between cortical gyrification and sleep during adolescence will deepen our understanding of complex relationships between the brain and sleep during the transition from childhood to adulthood.

In the human brain, gyrification starts in utero, leading to an increase in cortical surface area that fosters a marked increase in the number of neurons and neuronal connectivity without increasing overall brain volume [7–9, 17]. Gyrification peaks approximately 2 years after birth, and decreases across the lifespan [8, 9] in a non-linear trajectory [9], with childhood and adolescence showing more accelerated decreases over time relative to adulthood [9], most likely due to the maturational changes happening in the adolescent brain [17]. Overall, lower gyrification has been associated with worse outcomes in adults (e.g. poorer memory, attention, and executive function) [10, 18]. However, mixed anomalous patterns of cortical gyrification have been reported by studies focusing on major psychiatric disorders [8, 19–22]. Cortical gyrification is related to other structural MRI measures (e.g. volume, thickness, and surface area) [7, 18]; however, these measures only partially overlap [7]. Thus, cortical gyrification may provide unique information about brain-sleep relationships across neurodevelopment that has not been captured by other MRI measures.

Given the importance of sleep for many aspects of healthy development (e.g. mental health, cognition, and emotional regulation) [4, 23, 24], understanding whether the relationship between cortical gyrification and sleep is developmentally invariant (stable across age) or developmentally specific observed only during discrete age intervals or windows of development may offer new insights into windows of vulnerability to brain-based risk and windows of opportunity for early intervention promoting healthy development. We recently showed that, between 9 and 26 years, regional cortical thickness and subcortical volumes have both developmentally invariant and developmentally specific relationships with naturalistic sleep patterns (sleep duration, timing, continuity, and regularity) [1]. These findings suggest that neural mechanisms that underlie brain-sleep relationships have both stable and dynamic features [1], findings which have implications for targeted interventions and for understanding

neurobiological mechanisms of sleep. However, given the unique developmental trajectory of cortical gyrification, particularly in comparison to thickness and subcortical volumes [7], it is unclear whether gyrification will also exhibit developmentally specific associations with sleep during adolescence.

Our goal was to identify the relationships between cortical gyrification and actigraphy-assessed sleep characteristics in participants between 9 and 26 years, and to identify whether these relationships are stable over time (developmentally invariant) or present only during specific windows of development (developmentally specific). We used group-lasso regression [25, 26], an exploratory feature selection approach, to identify associations between regional gyrification and four key components of multidimensional sleep health (sleep duration, timing, continuity, and regularity) [2]. We hypothesized that cortical gyrification would show both developmentally invariant and developmentally specific associations with sleep, and that the latter would be more common during periods of increased brain development (childhood and/or adolescence).

Methods

Participants

The NAPS databank includes nine University of Pittsburgh studies that were conducted between 2009 and 2020 and includes baseline actigraphy sleep and structural MRI scan data for all participants (Supplementary Table 1). This databank was approved as a secondary data analysis protocol by the University of Pittsburgh Institutional Review Board. The initial sample in the databank consisted of 394 participants (for additional information about the inclusion criteria, see Supplementary Material). For these analyses, participants were selected if they were aged between 9 and 26 years old, had sleep and neuroimaging data available, had good quality MRI, and had no history of psychiatric disorders or psychotropic medications. The inclusion of participants between 9 and 26 years takes into account the broad definition of adolescence (10–24 years) [27]. The final sample included 252 (mean age [SD] = 17.37[4.53], age range = 9–26 years, 58.3% female) participants. Demographic and sleep information are detailed in Table 1.

Sleep data

Wrist actigraphy.

To behaviorally assess sleep, we used wrist actigraphy, a well-validated method for assessing naturalistic sleep characteristics in youth and adults [28, 29]. Participants wore actigraphs on their non-dominant wrist during a period of 5 or more consecutive days [30] and were asked to indicate the start and end of each sleep interval via button press. Wrist activity was sampled in 1-minute intervals (epochs). A combination of validated brand-specific sleep algorithms (Philips Respironics-Medium Threshold [PR]; Ambulatory Monitoring Incorporated [AMI]—Sadeh) and standardized visual editing procedures [31, 32] was used to estimate sleep characteristics. Actiware Software v6.0.9 was used for all PR devices and AMI Action 2 was used for AMI devices. Specific watch types are listed in Table 1 and by study in Supplementary Table 2

Sleep characteristics.

Four sleep characteristics were calculated based on actigraphic sleep data: (1) sleep duration (total sleep time in minutes), (2) timing (midpoint between sleep onset and offset in minutes from midnight), (3) continuity (minutes awake after sleep onset; WASO), and (4) regularity (intra-individual standard deviation of midpoint in minutes). The first three characteristics were averaged over the 5–7 tracking days most proximal to their MRI scan; regularity was calculated from the available days of recording. Sleep characteristics (duration, timing, continuity, and regularity) were natural log transformed to normalize distributions.

Neuroimaging data

Acquisition protocols for each study are described in Supplementary Table 3. Data usability was evaluated using an automated MRIQC T1w-classifier that determined individual scan quality based on a reference template [33]. T1 data were preprocessed using the FreeSurfer analysis software (v6.0) [34–37]. We implemented an additional quality assessment pipeline developed and used for the enhancing neuroimaging genetics through meta-analysis consortium [38–48].

Local gyrification index (lGI) was calculated using Freesurfer (-localGI flag; https://surfer.nmr.mgh.harvard.edu/fswiki/LGI). In this approach, local measurements of cortical gyrification were calculated using the ratio between the pial cortical surface (interface between the brain and meninges) and the perimeter of an outer smoothed surface tightly wrapping the pial surface [49]. Brain regions with increased folding show higher lGI, while brain regions with less folding show lower lGI. Given that we did not have any specific hypotheses about laterality, we averaged cortical gyrification across hemispheres for each region (Desikan–Killiany atlas) [50], generating 34 individual measures. This atlas is a widely used automatic labeling scheme that subdivides cortex into regions of interest [50]. To account for scanner effects, we used ComBat, a batch-effect correction tool that minimizes the variance introduced by different MRI protocols [51].

Statistical approach

To explore the association between cortical gyrification and sleep, we used the R package Group-LassoINTERaction-NET (GLINTERNET) [25, 26] to examine the main relationships between structural neuroimaging measures (lGI), as well as their interaction with age and sex, for each sleep characteristic (sleep duration, timing, continuity, and regularity). Group-lasso is a feature-selection method that identifies the strongest variables associated with an outcome and uses a shrinkage parameter to reduce the coefficient of non-relevant variables toward zero [25, 26]. This dimensionality reduction allows one to consider a large variable set simultaneously and avoid issues with multiple comparisons. In addition, this method allows for the inclusion of interactions between non-zero coefficients as potential predictors [26]. We also included multiple actigraphy covariates (i.e. tracking days, season, ratio of weekday to weekend days, and actigraph model) in the models. Similar to previous work [1], we repeated 10-fold cross-validation 100 times, using the penalty parameter (λ) one standard deviation away from the minimal cross-validation error (Lmin). The final model for each sleep characteristic was the Lmin model which was selected most often during cross-validation. In addition, variables of interest were standardized so the regression coefficients should be approximated by standardized betas, which can be used as an estimate for effect size.

To gain a better understanding of the final model, we followed up on main relationships identified in the above group-lasso models for each sleep characteristic (sleep duration, timing, continuity, and regularity) with multiple regression models. We computed R^2 estimate variance explained by each full model, as well as groups of measures (i.e. demographics, neuroimaging measures) [52–54]. We then assessed non-zero interactions between age and

Table 1. Demographic and Sleep Characteristics of the Sample Included in the Analyses

Variable	Mean or N (SD or %)
Sample *N*	252
Age (years)	17.37 (4.53)
Self-reported sex	
Female	147 (58.3%)
Male	105 (41.7%)
Ethnicity	
Non-Hispanic	236 (93.65%)
Hispanic	14 (5.56%)
Missing	2 (0.79%)
Race	
White	181 (71.83%)
Black	38 (15.08%)
Asian	9 (3.57%)
Multiple	21 (8.33%)
Unknown/missing	3 (1.19%)
Actigraphy model	
AMI Octagonal MotionLogger	35 (13.89%)
PR/MiniMitter Actiwatch64	25 (9.92%)
PR Actiwatch2	98 (38.89%)
PR Spectrum Series	94 (37.30%)
Tracking days	6.61 (0.83)
Weekdays	4.53 (0.91)
Weekend days	2.07 (0.51)
Season	
Spring	44 (17.46%)
Summer	106 (42.06%)
Fall	58 (23.02%)
Winter	44 (17.46%)
Sleep duration (minutes)	420.54 (62.15)
Wake after sleep onset (minutes)	56.45 (26.87)
Midsleep (minutes from midnight)	265.68 (76.44)
Midsleep variability (minutes)	64.81 (26.87)

Abbreviations: AMI, Ambulatory Monitoring Incorporated; PR, Philips Respironics.

neuroimaging measures using the Johnson-Neyman technique [55–57], which obtains parameter estimates and points of significance from the interaction between two continuous variables. In this study, the Johnson-Neyman technique helped identify the discrete age intervals (or windows) in which cortical gyrification and sleep component relationships are significant. Non-zero interactions between sex and neuroimaging measures were probed by comparing estimated marginal means [58]. Figures were generated using the R packages ggseg and ggplot2 [59, 60].

Results

All non-zero associations (main effects and their interactions) for the four sleep characteristics are described in Table 2–5. The relationship between cortical gyrification and sleep characteristics is shown in Figure 1. The stability of non-zero predictors and multiple regression models are detailed in Supplementary Tables 4 and 5. Each model is described below.

Cortical gyrification and age

Overall, there was a significant negative linear association between age and cortical gyrification ($p < 0.05$).

Sleep duration (total sleep time)

All features selected in this model explained 23% of the variability in sleep duration (Table 2). Shorter sleep duration was associated with older age and males had shorter sleep duration in comparison to females.

We observed several developmentally invariant relationships between lGI and sleep duration in frontal and temporal regions. Greater lGI in the pars orbitalis, a brain region implicated in reasoning and social processes [61], was associated with longer sleep duration. In addition, greater lGI in the inferior temporal region, which is involved in object recognition, visual and language processing [62–64], as well as the banks of the superior temporal sulcus, a brain region associated with audio–visual integration, motion processing, speech processing, and face processing [65], was associated with longer sleep duration in male participants only. While the regularized regression model indicated that sex moderated the association between other temporal regions and sleep duration, this moderation effect was not significant in the traditional regression model (Supplementary Table 6).

We also found developmentally specific relationships between the caudal middle frontal (a brain region associated with attention and working memory) [66] and precentral (a brain region involved with motor functions) [67] lGI and sleep duration (Figure 2A), with Johnson-Neyman analyses showing that greater lGI was associated with longer sleep duration in participants 9–16 years old, but not in individuals 16–26 years old (Supplementary Table 7).

Sleep timing (midsleep)

Features selected in this model explained 15% of the variability in sleep timing (Table 3). Later midsleep was associated with older age and being male.

We identified developmentally invariant relationships in frontal, temporal, parietal, and occipital regions. Greater lGI in brain regions involved with sensory processing (i.e. lateral occipital) [68] and memory, language, and semantic processing (i.e. middle temporal gyrus) [69–73] was associated with later sleep timing. In addition, greater lGI in brain regions implicated in myriad cognitive functions (i.e. entorhinal and superior parietal) [74, 75] was associated with earlier sleep timing. In female participants only, greater lGI in the caudal middle frontal region, was associated with earlier sleep timing. In male participants only, greater lGI in the entorhinal cortex, a brain region that mediates interactions between the hippocampus and the neocortex [76], was associated with earlier sleep timing. While the regularized regression model indicated that sex moderated the association between occipital regions and sleep timing, this moderation effect was not significant in the regression model (Supplementary Table 6).

Developmentally specific relationships were observed in brain regions involved with motor (i.e. paracentral) [77] and cognitive functions (i.e. posterior cingulate, a brain region part of the default mode network—DMN) [78](Figure 2B). Greater lGI in these regions was associated with earlier sleep timing in participants 9–15 years old, but not in older adolescents and young adults (16–26 years old; Supplementary Table 7).

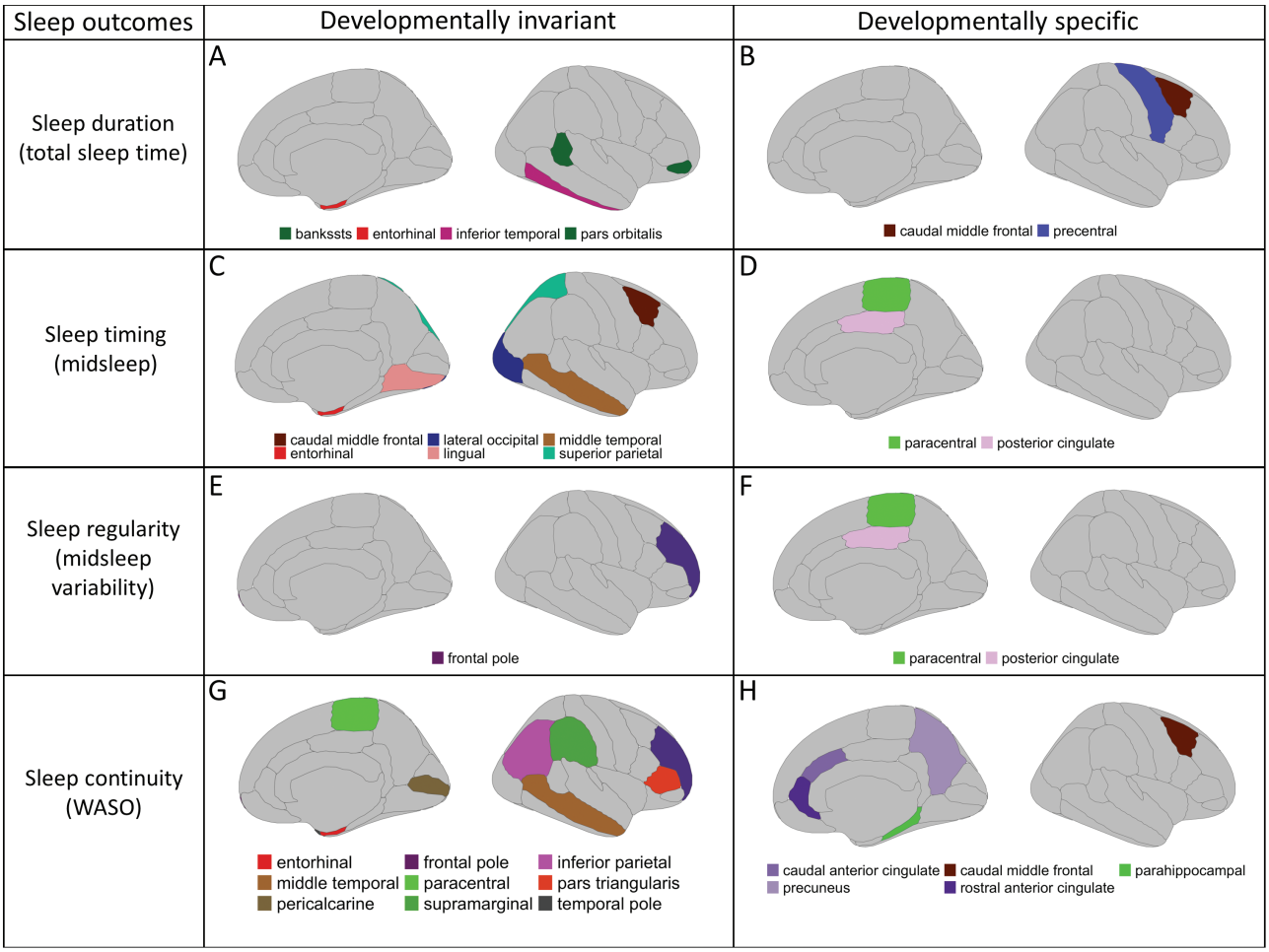


Figure 1. Developmentally invariant and specific relationships between sleep patterns and cortical gyrification. Figure 1 shows brain regions with developmentally invariant or specific relationships between sleep patterns and cortical gyrification. Panels A–B show sleep duration relationships, panels C–D show sleep timing relationships, panels E–F show sleep regularity relationships, and panels G–H show sleep continuity relationships. Each panel contains a legend with colors for the brain regions with non-zero coefficients identified with GLINTERNET.

Sleep regularity (midsleep variability)

All features selected in this model explained 7% of the variability in sleep regularity (Table 4). Greater variability in sleep regularity was associated with older age and being male.

A developmentally invariant relationship was identified in the frontal pole, a brain region implicated in working memory and affective processing [79, 80]. Greater lGI in this region was associated with lower variability in sleep regularity. There were no non-zero interactions between sex and lGI on sleep regularity.

Paracentral and posterior cingulate regions showed developmentally specific relationships with sleep regularity (Figure 2C). In these regions, greater lGI was associated with lower sleep variability in participants 9–16 years old, but not in individuals older than 16 (Supplementary Table 7).

Sleep continuity (WASO)

Features selected in this model explained 15% of the variability in sleep continuity (Table 5).

Several developmentally invariant relationships were identified. Greater lGI in the entorhinal, inferior parietal, middle temporal, and supramarginal regions was associated with longer WASO, while greater lGI in the frontal pole, pars triangularis, and pericalcarine regions was associated with shorter WASO (i.e. better sleep continuity). The pars triangularis is a brain region implicated with language processing [81] and the pericalcarine is a brain region involved with visual processing [82]. In male participants only, greater lGI in the paracentral regions was associated with shorter WASO. While the group-lasso model indicated that sex moderated the association between WASO and caudal anterior cingulate, middle temporal, and supramarginal lGI, these moderation effects were not significant in the linear regression models (Supplementary Table 5).

The precuneus and caudal middle frontal regions showed distinct intervals and opposite developmentally specific relationships. Greater lGI in the precuneus was associated with shorter WASO in participants 9–16 years old only, while greater lGI in the caudal middle frontal region was associated with greater WASO in participants 19–26 years old only. As mentioned before, the caudal middle frontal region is implicated with attention and working memory [66]. The precuneus is a brain region involved with working memory and self-referential processes [83]. Interestingly, the rostral and caudal anterior cingulate showed more than one interval for the relationships with sleep continuity: greater lGI was associated with shorter WASO in participants 9–14 years old and with longer WASO in participants 21–26 years old (Figure 2D; Supplementary Table 7). The anterior cingulate is associated with a broad range of emotional and cognitive functions, with the

Table 2. Main Effects and Interactions Associated With Sleep Outcomes: Sleep Duration (Total Sleep Time)

Sleep duration (total sleep time)			
Type of variable		**Variable**	**Predictor weight**
Demographic		Age	–0.1515
		Sex[a]	0.0832
Neuroimaging	Local gyrification indexes	Banks of the superior temporal sulcus	0.0009
		Caudal middle frontal	0.0210
		Entorhinal	–0.0005
		Inferior temporal	0.0153
		Pars orbitalis	0.0326
		Precentral	0.0366
	Interaction with age	Age by caudal middle frontal	–0.0294
		Age by precentral	–0.0498
	Interaction with sex	Sex[a] by banks of the superior temporal sulcus	–0.0037
		Sex[a] by entorhinal	–0.0149
		Sex[a] by inferior temporal	–0.0205
Covariates		Age by wrist actigraphy (brand-model) [b]	–0.0372
		Season[c]	–0.0298
		Sex[a] by weekend:weekday ratio	0.0356
		Tracking days	–0.1556
		Weekend:weekday ratio	–0.0137
		Wrist actigraphy (brand-model) [b]	0.0290
Adjusted $R^2 = 0.23$			
Variance accounted for by demographic measures only: adjusted $R^2 = 0.15$			
Variance accounted for by neuroimaging and demographic measures, and their interactions: adjusted $R^2 = 0.19$			

[a]Coefficient represents the effect of being female (dummy codes for Sex: 0 = male, 1 = female).
[b]Coefficient represents the effect of AMI brand (dummy codes for watch: 0 = PR model, 1 = AMI model).
[c]Coefficient represents the effect of winter season (dummy codes for season: 0 = winter, 1 = spring, 2 = summer, 3 = fall).

rostral areas involved in more "emotion-related" processes and the caudal areas involved in "cognitive-related" processes [84].

Discussion

We examined how measures of cortical gyrification were related to sleep characteristics and tested the extent to which these relationships were stable over age (developmentally invariant) or present only during specific windows of development (developmentally specific) in typically developing young people. Findings showed that cortical gyrification in diverse brain regions was associated with all investigated sleep characteristics. In most cases, greater cortical gyrification was associated with longer sleep duration, earlier sleep timing, lower variability in sleep regularity, and shorter time awake after sleep onset. These sleep characteristics are generally associated with "better" sleep. Additionally, and in line with our hypotheses, developmentally specific associations were present and more common during late childhood through early-to-mid adolescence.

Across typically developing young people, increased cortical gyrification in a wide range of cortical regions was associated with characteristics generally associated with better sleep. These regions are involved in a number of functions including affective processing (frontal pole) [79], language processing (inferior temporal gyrus) [62, 63], memory (middle temporal gyrus) [69, 70], visual processing (inferior temporal gyrus) [62], and working memory (frontal pole) [79, 80]. In line with these findings, other macrostructural properties of the adolescent brain, such as volume and cortical thickness, have been associated with sleep [1, 85–87]. Some of these developmentally invariant relationships involved regions (e.g. middle frontal, supramarginal, and parietal regions) commonly associated with the frontoparietal network (FPN), a brain network implicated with executive control and complex cognitive functions [88]. Previous studies have shown that poor sleep during brain development is detrimental to FPN function [89] and connectivity between FPN and other networks (e.g. limbic network) [90]. However, no study has shown a link between cortical gyrification of regions within the FPN and sleep characteristics, and our findings show this relationship is present throughout all stages of brain development. Considering that cortical gyrification has been associated with age- and cognition-related decline later in life [10, 18], our findings suggest that better sleep may be an important factor for brain-cognition relationships observed across the lifespan and that maintaining better sleep since early age may promote better cognitive functioning later in life.

Our findings also add to an existing literature demonstrating that cortical gyrification across lifespan may be associated with modifiable lifestyle behaviors, such as physical activity [91], dietary patterns [92], and substance use (e.g. tobacco, and alcohol) [91]. For example, in one of these studies [91], a composite "lifestyle risk" factor was calculated based on alcohol consumption, smoking, physical activity, and social integration in older adults. The researchers demonstrated that more optimal health behaviors were associated

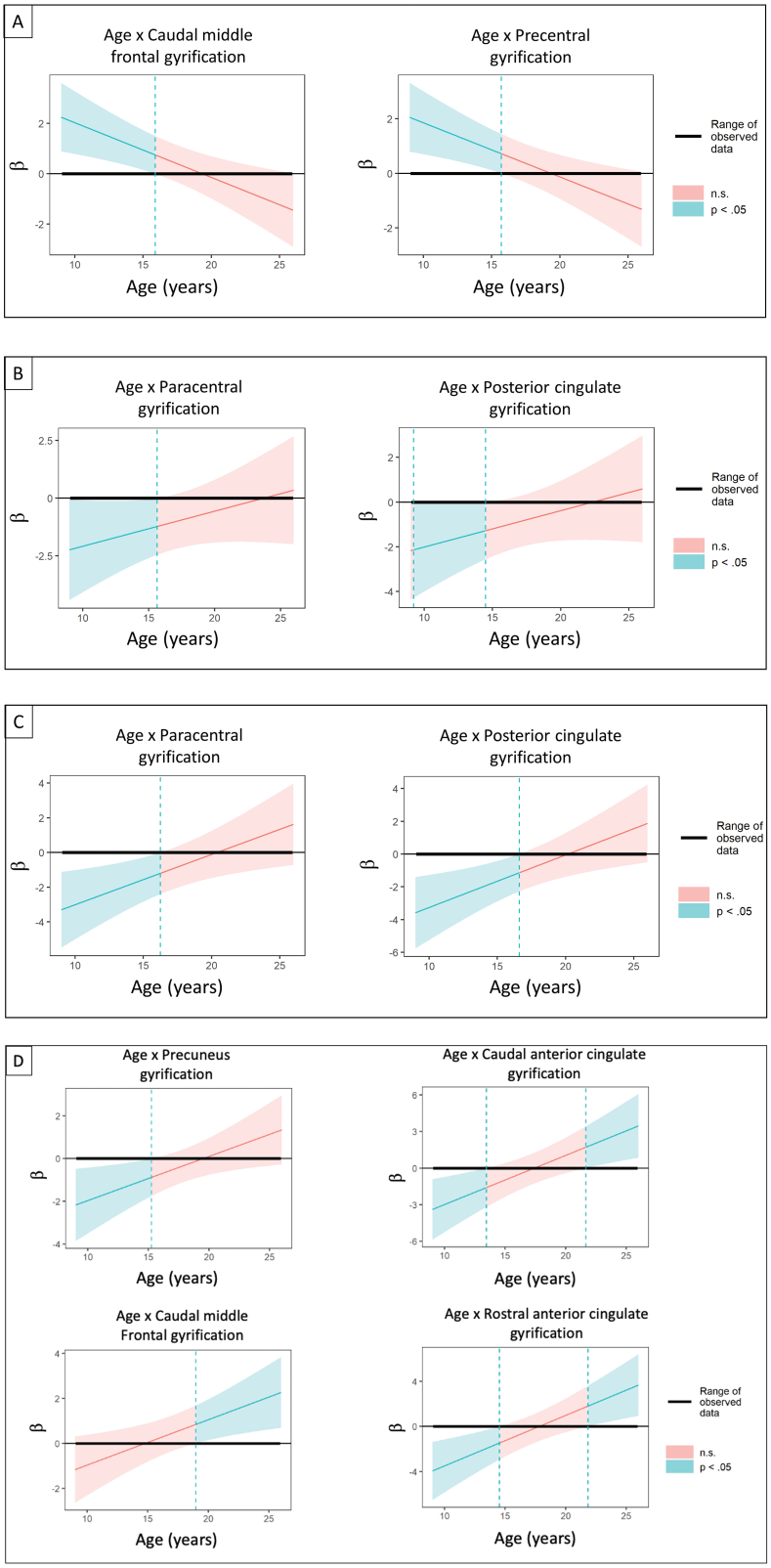


Figure 2. Johnson-Neyman plots for developmentally specific relationships. Figure 2 shows Johnson-Neyman plots for developmentally specific relationships (only during specific windows of development). Panel A shows sleep duration relationships, panel B shows sleep timing relationships, panel C shows sleep regularity relationships, and panel D shows sleep continuity relationships. In each plot, the X-axis shows the moderator (age—years) and the Y-axis shows the conditional association between sleep and cortical gyrification. Statistically significant relationships are reported in Supplementary Table 7..

Table 3. Main Effects and Interactions Associated With Sleep Outcomes: Sleep Timing (Midsleep)

Sleep timing (midsleep)			
Type of variable		**Variable**	**Predictor weight**
Demographic		Age	0.1874
		Sex[a]	–0.1174
Neuroimaging	Local gyrification indexes	Caudal middle frontal	0.0011
		Entorhinal	–0.0072
		Lateral occipital	0.0016
		Lingual gyrus	–0.0452
		Middle temporal	0.0575
		Paracentral	–0.0919
		Posterior cingulate	–0.0094
		Superior parietal	–0.0378
	Interaction with age	Age by paracentral	0.0273
		Age by posterior cingulate	0.0109
	Interaction with sex	Sex[a] by caudal middle frontal	–0.0134
		Sex[a] by entorhinal	0.1061
		Sex[a] by lateral occipital	–0.0065
Covariates		Age by season[c]	0.0875
		Age by wrist actigraphy (brand-model) [b]	0.0410
		Season[c]	0.0195
		Sex[a] by season[c]	0.0529
		Sex[a] by wrist actigraphy (brand-model) [b]	0.0054
		Wrist Actigraphy (brand-model) [b]	–0.0183
Adjusted $R^2 = 0.15$			
Variance accounted for by demographic measures only: $R^2 = 0.06$			
Variance accounted for by neuroimaging and demographic measures, and their interactions: $R^2 = 0.15$			

[a]Coefficient represents the effect of being female (dummy codes for Sex: 0 = male, 1 = female).
[b]Coefficient represents the effect of AMI brand (dummy codes for watch: 0 = PR model, 1 = AMI model).
[c]Coefficient represents the effect of winter season (dummy codes for season: 0 = winter, 1 = spring, 2 = summer, 3 = fall).

Table 4. Main Effects and Interactions Associated With Sleep Outcomes: Sleep Regularity (Midsleep Variability)

Sleep regularity (midsleep variability)			
Type of variable		**Variable**	**Predictor weight**
Demographic		Age	0.0507
		Sex[a]	–0.0053
Neuroimaging	Local gyrification indexes	Frontal pole	–0.0049
		Paracentral	–0.0040
		Posterior cingulate	–0.0548
	Interaction with age	Age by Paracentral	0.0048
		Age by Posterior cingulate	0.0738
Covariates		Season[c]	0.0122
		Sex[a] by Season[c]	0.0615
Adjusted $R^2 = 0.07$			
Variance accounted for by demographic measures only: $R^2 = 0.01$			
Variance accounted for by neuroimaging and demographic measures, and their interactions: $R^2 = 0.04$			

[a]Coefficient represents the effect of being female (dummy codes for Sex: 0 = male, 1 = female).
[b]Coefficient represents the effect of AMI brand (dummy codes for watch: 0 = PR model, 1 = AMI model).
[c]Coefficient represents the effect of winter season (dummy codes for season: 0 = winter, 1 = spring, 2 = summer, 3 = fall).

Table 5. Main Effects and Interactions Associated With Sleep Outcomes: Sleep Continuity (WASO)

Sleep continuity (WASO)			
Type of effect		**Variable**	**Predictor weight**
Demographic variables		Age	–0.1435
		Sex[a]	0.1081
Neuroimaging	Local gyrification indexes	Caudal anterior cingulate	–0.0017
		Caudal middle frontal	0.0187
		Entorhinal	0.0572
		Frontal pole	–0.0243
		Inferior parietal	0.0238
		Middle temporal	0.0123
		Paracentral	–0.0371
		Parahippocampal	0.0965
		Pars triangularis	–0.0181
		Pericalcarine	–0.0706
		Precuneus	–0.0310
		Rostral anterior cingulate	–0.0062
		Supramarginal	0.0280
		Temporal pole	–0.1089
	Interaction with age	Age by caudal anterior cingulate	0.0292
		Age by caudal middle frontal	0.0213
		Age by parahippocampal	–0.0655
		Age by precuneus	0.0459
		Age by rostral anterior cingulate	0.0987
	Interaction with sex	Sex[a] by caudal anterior cingulate	0.0253
		Sex[a] by middle temporal	0.0155
		Sex[a] by paracentral	0.0285
		Sex[a] by supramarginal	0.0138
Covariates		Age by season[c]	–0.0299
		Age by wrist actigraphy (brand-model)[b]	0.2033
		Season[c]	0.1007
		Sex[a] by season[c]	0.0346
		Sex[a] by tracking days	0.0581
		Tracking days	–0.0307
		Weekend:weekday ratio	–0.0213
		Wrist actigraphy (brand-model)[b]	–0.1277
Adjusted $R^2 = 0.15$			
Variance accounted for by demographic measures only: $R^2 = 0.03$			
Variance accounted for by neuroimaging and demographic measures, and their interactions: $R^2 = 0.14$			

[a]Coefficient represents the effect of being female (dummy codes for Sex: 0 = male, 1 = female).
[b]Coefficient represents the effect of AMI brand (dummy codes for watch: 0 = PR model, 1 = AMI model).
[c]Coefficient represents the effect of winter season (dummy codes for season: 0 = winter, 1 = spring, 2 = summer, 3 = fall).

with increased cortical gyrification (which is typically viewed as "healthier") and decelerated decline in multiple brain regions [91]. Given that, overall, gyrification has shown a positive relationship with cognitive functions in adults [10, 18], these findings suggest a potential mechanism by which lifestyle factors may impact cognition later in life. The multiple dimensions of sleep studied here—such as sleep duration, timing, regularity, and continuity—are amenable to efficacious behavioral interventions, providing an avenue for understanding and promoting healthy development. The period of adolescence and young adulthood is particularly important because of its foundational role in adaptive functioning during adulthood. Our findings of the association between gyrification and sleep characteristics provide clues to optimizing brain development. Future studies evaluating the effect of lifestyle risk factors on cortical gyrification, or other macrostructural properties of the brain should also consider the role of sleep.

In addition, for some of these developmentally invariant relationships, sex played a moderating role, with males showing

stronger relationships between cortical gyrification and sleep than females in areas implicated with memory, visual, and language processing. Sex differences play an important role in many neural and behavioral functions in typically developing young people, and these differences have been linked to the cascade of maturational changes (e.g. physical, psychological, and social) happening during this period [93, 94]. Previous studies have shown sex differences in sleep physiology [95], secondary clinical outcomes of sleep problems [96], and cortical gyrification of typically developing young people [97]. Our findings build upon the existing literature to show that sex differences are also present in the relationship between sleep and brain and suggest that cortical gyrification could be a structural component that contributes to sex differences found in the relationship between sleep and cognition [98, 99].

We found an association between increased cortical gyrification and more optimal sleep in late childhood through early-to-mid adolescence. In line with these findings, we have recently shown that other macrostructural properties of the brain (e.g. subcortical volume and cortical thickness) also present developmentally specific relationships with sleep from late childhood to mid-adolescence [1], reinforcing the importance of sleep during this period of brain development. The transition from childhood to adulthood represents a period of development marked by several physical, cognitive, and social changes, with early-to-mid adolescence being particularly associated with important maturational changes in the organization of brain networks [100, 101]. Studies have shown that abnormalities in this tuning process are associated with mental health issues later in life [102]. Our findings showed a developmentally specific relationship in frontal-parietal-limbic brain regions, including those typically associated with the DMN (e.g. anterior cingulate, posterior cingulate, and precuneus). The DMN is implicated with emotional and episodic memory processing and undergoes important strengthening of functional connectivity between its regions during late childhood through early-to-mid adolescence (7–15 years old) [103–105]. In addition, previous studies have shown that more optimal sleep is associated with increased network connectivity in DMN regions of adolescents and young adults [106, 107]. Our findings show a strong relationship between sleep patterns and regions associated with DMN, particularly during an important period for their development. More importantly, they also suggest early adolescence as a window of vulnerability for the effects of less optimal sleep and as a window of opportunity for early interventions aiming to improve trajectories for positive development.

There were limitations in this study. While this study raised important questions relevant to the relationship between sleep and brain, future prospective longitudinal studies would benefit from even bigger samples that included larger age ranges, different populations at risk, more racial and ethnic diversity, and other possible individual factors affecting this relationship during brain development (e.g. pubertal development, sex hormones, socioeconomic status). Disentangling the effects of chronological age, sex, and pubertal development will be particularly important for future research given that these factors all play important roles during brain development. The variance in sleep explained by the combined brain regions and their interactions accounted for roughly 4–19 percent of the variance in sleep measures (Table 2). As seen in this table, effect sizes contributions from individual brain regions were small, with regional contributions typically accounting for <0.5% of the variance in a sleep measure, which calls for caution in their interpretation and in making broad conclusions. Recent work shows that one can increase the amount of variance accounted for a particular phenotype by combining information from multiple regions and deriving a single neuroimaging summary score. This score can then be linked to individual differences in behavior [108]. This may be a useful approach when considering relationships between sleep and brain in the future, given the small effect sizes observed. Although group-lasso is a strong feature selection method that can identify even small effects important for the for tested models, non-zero coefficients identified with these methods do not always translate to significance in standard regression models. While LASSO regularization includes all potential variables and uses a shrinkage parameter to reduce the coefficient of non-relevant variables toward zero, standard regression models test a null hypothesis using pre-selected variables. Therefore, future studies using methods other than standard regression are needed to further explore non-zero coefficients. In addition, LASSO reduces the coefficients of highly correlated variables, leading to the possible exclusion of gyrification measures that are associated with sleep behavior (and correlated with other selected variability). Given that cortical gyrification measures show high correlation (Supplementary Figure 1), in the future, we may want to consider additional methods to best account for this covariance. Finally, this study explored linear relationships between sleep and cortical gyrification. Future studies should also explore potential non-linear relationships since many changes during adolescence follow both linear and non-linear trajectories.

We have, for the first time, established associations between cortical gyrification and naturalistic sleep patterns in young people. Consistent with prior work, several associations are stronger in late childhood and early adolescence, particularly in regions traditionally associated with the DMN. Future studies should evaluate relationships between cortical gyrification and sleep longitudinally within person to better understand shifts in the strength and directionality of these relationships across adolescence. Such studies would shed further light on the nuanced associations between sleep and brain structure over development and set the stage for sleep interventions designed to optimize brain-based outcomes.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Data Availability

The datasets included in the current work are not available for use outside of the University of Pittsburgh at this time, due to the nature of the ethics board approvals and possible risk(s) to study participants as well as the confidentiality promised to them. Data may be made available from the corresponding author on reasonable request with permission of NAPS investigators and ethics board approval.

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