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Naturalistic sleep patterns are linked to global structural brain aging in adolescence

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Abstract

Purpose: We examined whether interindividual differences in naturalistic sleep patterns correlate with any deviations from typical brain aging.

Methods: Our sample consisted of 251 participants without current psychiatric diagnoses (9–25 years; mean(SD) = 17.4±4.52yr; 58% female) drawn from the Neuroimaging and Pediatric Sleep Databank. Participants completed a T1-weighted structural MRI scan (sMRI) and 5–7 days of wrist actigraphy to assess naturalistic sleep patterns (duration, timing, continuity, regularity). We estimated brain age from extracted sMRI indices, and calculated brain age gap (estimated brain age - chronological age). Robust regressions tested cross-sectional associations between brain age gap and sleep patterns. Exploratory models investigated moderating effects of age and biological sex and, in a subset of the sample, links between sleep, brain age gap, and depression severity (PROMIS Depression).

Results: Later sleep timing (midsleep) was associated with advanced brain aging (larger brain age gap), β=0.1575, p_{uncorr}=0.0042, p_{fdr}=0.0167. Exploratory models suggested that this effect may be driven by males, although the interaction of sex and brain age gap did not survive multiple comparison correction (β=0. 2459, p_{uncorr}=0.0336, p_{fdr}=0.1061). Sleep duration, continuity, and regularity were not significantly associated with brain age gap. Age did not moderate any brain age gap–sleep relationships. In this psychiatrically healthy sample, depression severity was also not associated with brain age gap or sleep.

Conclusions: Later midsleep may be one behavioral cause or correlate of advanced brain aging, particularly among males. Future studies should examine whether advanced brain aging and individual differences in sleep precede the onset of suboptimal cognitive-emotional outcomes in adolescents.

Keywords

Sleep; Adolescence; Brain Development

INTRODUCTION

The transition through adolescence and into young adulthood is a unique period of development (defined by the World Health Organization as the ages from 10–24 years) when structural brain changes continue to take place, setting the stage for adult trajectories. Sleep behavior also changes during adolescence, and individual differences in sleep behavior during adolescence have been linked to subsequent neurobehavioral outcomes in adulthood[1]. Deviations from a normative neuromaturational timetable may be linked to individual differences in sleep. Advancing our understanding of brain maturation and associated processes may help us identify early markers of vulnerability for later suboptimal outcomes. Linking brain measures to *modifiable* behaviors may allow us to intervene earlier in youth and prevent subsequent negative outcomes.

We recently reported that gray matter structure across numerous brain regions was associated with sleep patterns across adolescent development[2]. Given the wide range of brain regions implicated, multivariate approaches that quantify brain maturation may be a more parsimonious and powerful approach to linking neurodevelopment and sleep patterns. Disruptions to the timing, duration, continuity, and regularity of sleep are associated with a diverse range of mental, cognitive and physical health outcomes in adolescence[1]. Individual differences in sleep patterns are also related to the myriad brain regions supporting these health outcomes[2–5]. In the past five years, a multivariate measure known as "brain age" has gained in popularity[6]. Here, various machine learning approaches are used to identify brain regions that are the strongest predictors of chronological age. The derived model weights are then applied to individual brain regions to predict an individuals' chronological age (i.e., the "predicted brain age"). The individual's true chronological age is then subtracted from their predicted brain age, resulting in a measure known as the "brain age gap". If the predicted brain age is greater than the chronological age, this is typically perceived to reflect age-related brain alterations.

In adults, older brain age (i.e., a larger positive brain age gap) may reflect advanced "biological aging", indicative of neurotoxic processes, environmental insults, and/or genetic influences. A greater brain age gap (i.e., advanced brain age) has been associated with a wide range of poor outcomes, including increased mortality[7], lower cognitive abilities[8], unhealthy lifestyle factors[9], psychopathology[10], and dementia[11]. However, most prior studies have examined adults and focused on individuals with established disorders or impairments.

Consistent with adult studies, recent reports in adolescent samples find advanced brain aging in groups with elevated psychosis risk[12] and MDD diagnosis[13] relative to controls. Initial reports also demonstrate ties between advanced brain aging and dimensional psychopathology over adolescent development[14], although there have been non-replications[15]. While most studies tie advanced brain aging with negative health outcomes, one study found that youth with advanced brain age had faster cognitive processing speed[16], a positive cognitive outcome. However, others fail to observe a relationship between brain age and cognitive abilities[17]. Thus, it is unclear whether a "brain age gap" is a negative attribute in youth as well. Given more consistent ties between advanced brain aging and poor outcomes, understanding how brain age in youth relates to individual differences in modifiable behaviors – like sleep – could shed light on factors that protect healthy neurodevelopment. For example, in adults, more frequent engagement in healthy behaviors, like meditation and physical exercise[18,19], is linked to a smaller brain age gap.

Adolescent maturation of sleep-circadian bioregulatory systems (e.g., circadian rhythm delay) contributes to later sleep schedules[20], of which midsleep timing is a strong behavioral proxy[21]. This biological circadian shift converges with psychosocial factors, like school start times, to result in shorter sleep durations and, in some individuals, poorer continuity and regularity of sleep[20,22]. There is a strong biological contribution to sleep timing[20], however most sleep patterns have been linked to brain structure [e.g.,[2–5]], and thus it remains unclear which sleep patterns are associated with global structural brain aging.

Here we conducted a novel set of analyses looking at the relationships between brain age gap and naturalistic sleep patterns (sleep duration, timing, continuity, regularity) in a relatively large sample of healthy children, adolescents, and young adults. We hypothesized that a greater brain age gap would be associated with interindividual differences in sleep patterns. We also conducted exploratory analyses to investigate whether the relationships between brain age gap and sleep patterns were moderated by self-reported biological sex and/or age, as these effects have been observed for other outcomes[12,23]. In a subset of the sample with depression symptom ratings, associations between brain age, sleep, and subthreshold depression severity were explored.

METHODS

Participants

We utilized data from the Neuroimaging and Pediatric Sleep (NAPS) Databank, a large, harmonized cross-sectional databank comprised of healthy children, adolescents, and young adults drawn from eight University of Pittsburgh studies conducted between the years of 2009 to 2020. The NAPS databank was approved as a secondary data analysis protocol by the University of Pittsburgh Institutional Review Board. Participant consent or assent was collected at enrollment for each individual study included in NAPS and permitted sharing of de-identified data. Studies were considered for inclusion in NAPS if they included: a) baseline actigraphic sleep monitoring reflecting naturalistic sleep; b) a structural MRI scan; and c) participants aged 8.0–30.9 years-old (inclusive). Participant-level inclusion criteria for this study were: a) 9.0–25.9 years-old; b) absence of current psychiatric diagnosis based on clinical interview (i.e., KSADS, SCID); c) no current psychotropic or hypnotic medication use; d) ≥5 days of good quality actigraphic sleep monitoring composed of both weekday and weekend days; e) good quality MRI scan. Of the total 351 cases in NAPS, cases were excluded based on: removal of duplicate cases due to enrollment in multiple protocols (n=2), presence of a psychiatric diagnosis (n=24); poor quality or insufficient sleep tracking (n=6); poor quality MRI (n=40); age > 25 years-old (n=18). Demographics of the final analytic sample of N=251 are described in Table 1. Demographics by protocol are reported in eTables 1–2.

Neuroimaging Methods and Brain Age Calculation

sMRI protocol parameters for the individual studies have been previously published[2] and are reported in eTable 3. An automated MRIQC T1w-classifier determined individual scan quality based on a reference template. We used the software brainageR[7,24,25] to calculate the “estimated brain age” from the structural MRI images. In this software, structural MRI images from a large sample of healthy individuals (N=3,377; 18–90yr) were previously used to train a brain age model. T1-weighted MRI were segmented and normalized in SPM12. Normalized MRI images were loaded into R using the RNifti package[26]. Grey matter, white matter and CSF measures were vectorized and combined. Principal components analyses were conducted and 80 percent of the variance was retained, resulting in a total of 435 components. Gaussian processes regression (implemented in kernlab)[27] were used to predict chronological age. This trained brain age model was then tested in a hold-out sample (N=857). After all images were segmented and normalized in SPM12, the rotation matrix

of the principal components analysis from the discovery sample was applied to the holdout sample data and Gaussian Processes regression was used to predict an age value from the trained model. In the holdout test sample, there was a strong relationship between chronological age and brain-predicted age (r = 0.973, mean absolute error = 3.933 years). This model was also tested in an entirely independent sample of participants (CamCAN, N=611). Again, the creators of this software package observed a strong relationship between chronological age and brain-predicted age (r = 0.947, mean absolute error = 4.90 years).

For the data in our sample, we followed the procedure applied to the test data described above to calculate the predicted brain age for each participant. We then subtracted chronological age from the predicted brain age to obtain the brain age gap. Because there is a known relationship between brain age and chronological age[16], we regressed out the effects of chronological age prior to running any statistical analyses.

To understand how well the publicly available brain age model (brainageR) performed when predicting chronological age in our own sample, we calculated and reported the following model performance metrics: correlation coefficient (r) between predicted and chronological age, the amount of variance in the predicted age that can be explained by chronological age (R^2), the square root of the average squared errors (RMSE), and the average of the absolute value of the residual (MAE). We used bootstrapping[28] of N=1000 models to calculate the uncertainty (standard error) for each metric. We report these metrics based on guidance from a recent methodological paper on brain age performance evaluation[29]. We performed these calculations before and after age-bias correction, due to the age-bias present in brain age calculation[29,30]: that brain age is typically over-estimated in younger participants, whilst it tends to be under-estimated in older individuals[31]. A power analysis was also performed to ensure that we were adequately powered for our main analyses (see eMethods, eResults, eTable 4).

Sleep Estimation with Wrist Actigraphy

Actigraphy is a well-validated and widely-used tool for objectively assessing naturalistic sleep in children, adolescents, and adults[32]. Participants continuously wore accelerometers on their non-dominant wrist during a monitoring period of 5 or more consecutive days. eTable 2 describes the number of participants who wore watches from Philips Respironics (PR; Actiwach-64, Actiwatch2, Spectrum series) or Ambulatory Monitoring, Inc. (AMI; Basic Octagonal Motionlogger). Wrist activity was sampled in 1-minute intervals (epochs). Participants were asked to indicate via button press the start and end of each rest interval.

We estimated sleep from wrist actigraphy using a combination of validated brand-specific sleep algorithms (PR Medium Threshold; AMI Sadeh) and standardized visual editing procedures[2]. Trained scorers blinded to neuroimaging data manually identified rest intervals based on a combination of event markers indicated by participants and clear changes in activity and (if available) environmental light level recorded by the device. Brand-specific sleep scoring algorithms estimated sleep within each rest interval[2]. We implemented additional semi-automated quality assurance procedures using in-house R scripts, including identification of the main rest interval (defined as the longest rest interval each day), removal of invalid sleep intervals containing ≥1 hour of off-wrist time or recording errors[33,34], time

adjustment for daylight savings time, and final visual inspection of sleep intervals on raster plots.

Sleep Outcomes

Primary actigraphy sleep outcomes were based on the main rest interval. We selected four sleep outcomes corresponding to key dimensions of sleep health[35]: sleep duration (total sleep time in minutes), timing (midpoint between sleep onset and offset in minutes from midnight), continuity (minutes awake after sleep onset; WASO), and variability (intra-individual standard deviation of midpoint in minutes). The first three outcomes were averaged over the 5–7 tracking days most proximal to their MRI scan; variability was calculated from the available days of recording.

Depression

Self-reported depression severity was collected in a subset of 178 participants using validated instruments: the Mood and Feelings Questionnaire[36] (MFQ) and Patient-Reported Outcomes Measurement Information System [PROMIS]-Depression Inventory[37]. MFQ-Short scores (n=142) were harmonized to a common metric, the PROMIS-Depression Inventory T-Score, using an established linking method[38,39]. The PROMIS scale is an advantageous common metric because it yields a T-Score centered to both pediatric and adult US general population; depression severity estimates are weighted to population age, sex, and education norms.

Statistical Analyses

We first conducted general additive models to confirm that the four sleep outcomes showed age-associated patterns consistent with prior research (eFigure 1). We observed the characteristic decline in sleep duration, delay in sleep timing, and increased sleep variability over adolescent development. Sleep continuity did not vary with age.

Within the R package MASS[40], we used robust regression[41,42] to estimate associations between brain age gap and four sleep characteristics (sleep duration, midsleep, midsleep variability, wake after sleep onset). Robust regression was selected over ordinary least squares regression due to the presence of potentially meaningful outliers in our sleep outcomes. Robust regression is a form of linear regression that de-weights high-leverage outliers based on the distribution of the outcome data, making it a more conservative model and less sensitive to outliers than ordinary least squares regression. Robust linear regression analyses were performed in R (using *rlm* function from the MASS package, Huber weights) and p-values estimated using robust F-tests (*f.robftest* function from the sfmisc package). The following covariates were included in all models: age, sex, season, study (as a factor), lag in days between actigraphy tracking and MRI scan, number of actigraphy tracking days, proportion of weekday to weekend days during actigraphy tracking. To ensure that the beta weights were interpretable, all continuous independent and outcome variables were normalized to mean of zero and a standard deviation of one.

To check the robustness of our primary analyses, we performed “leave-one-out analyses” to evaluate the extent to which any one study influences associations between brain age

gap and our sleep outcomes. We re-ran robust regression models for each sleep outcome 9 times, each time omitting all data from a different study. Second, based on recent evidence indicating that linear mixed-effects random-intercept models may outperform the ability of linear regression models to account for cohort differences in multi-cohort analyses[43], we performed sensitivity analyses using this alternative analytic method (see eMethods).

We conducted two sets of exploratory analyses. First, we ran robust regression models to probe whether age or sex moderated relationships between brain age gap and sleep outcomes. Specifically, we included an interaction term (e.g., βsex*sleep outcome) as an additional parameter to the primary models. Second, we examined whether sleep outcomes or brain age gap was associated with depression severity in the subset of the sample with depression ratings.

RESULTS

Sample characteristics

Table 1 depicts participant characteristics. Most sleep variables exhibited small intercorrelations. Shorter sleep duration was associated with later midsleep ($r = -0.17$, p=.0055), greater day-to-day midsleep variability ($r = -0.20$, p=.0012), and greater time spent awake after sleep onset ($r = -0.13$, p=.0305). Later midsleep timing was strongly correlated with greater midsleep variability ($r = 0.40$, p=$3e^{-11}$) and longer time spent awake after sleep onset ($r = -0.22$, p=.0005). Midsleep variability and wake after sleep onset were uncorrelated (r=0.05, p=0.4313).

Brain Age Performance Metrics

Brain age performance metrics before and after age-bias correction are reported in eTable 5. Correlation plots between chronological and predicted brain age (before and after age correction) are presented in eFigure 2. Both r and R^2 increased when age-bias correction was performed (r_{before}=0.54, r_{after}=0.62; R^2_{before}=0.28, R^2_{after}=0.39) However, MAE and RMSE remained similar before and after age-bias correction ($RMSE_{before}$=5.7 years, $RMSE_{after}$=6.4 years; MAE_{before}=4.6 years; ME_{after}=5.2 years).

Brain age gap was associated with midsleep timing, but not other sleep outcomes

Results of primary analyses are reported in Table 2. After correcting for multiple comparisons, there was a statistically significant association between brain age gap and midsleep timing ($\beta = 0.1575$, $p_{uncorr} = 0.0042$, $p_{fdr} = 0.0167$; Figure 1A), such that a larger brain age gap (i.e., older predicted brain age relative to chronological age) was associated with later sleep timing. Larger brain age gap was also associated with greater day-to-day midsleep variability, but this result did not survive multiple comparison correction ($\beta = 0.0721$, $p_{uncorr} = 0.0474$, $p_{fdr} = 0.0948$; Figure 1B). Brain age gap was not significantly associated with sleep duration ($\beta = 0.0296$, $p_{uncorr} = 0.5602$) or minutes wake after sleep onset ($\beta = 0.0203$, $p_{uncorr} = 0.6907$). We obtained similar results when we conducted robust linear mixed-effects model sensitivity analyses (eResults, eTable 6), highlighting the robustness of our findings.

Relationship Between Midsleep Timing and Brain Age Gap Was Not Driven by an Individual Study

Table 3 shows results of the leave-one-out analyses. Findings across iterations were largely consistent for significant positive associations between brain age gap and midsleep timing (p-values < 0.05), with just one of nine models failing to reach statistical significance (p = 0.055). For associations between brain age gap and midsleep variability, results were more inconsistent and ranged from non-significant (p-values > 0.1, 2 models) to trend level (p-values 0.05–0.1, 5 models) to significant (p-values < 0.05, 2 models). Thus, results for midsleep variability were more strongly influenced by the composition of specific samples. As in our primary analysis, brain age gap was not significantly associated with sleep duration or wake after sleep onset in all nine models (all p-values > 0.1).

Exploratory Age and Sex Moderation Analyses

Table 4 describes the results of exploratory brain age gap × age and brain age gap × sex robust regression moderation models. Age did not moderate the association between brain age gap and any of the sleep outcomes (all p-values > 0.05). Sex moderated the association between brain age gap and midsleep (β = 0. 2459, p_{uncorr} = 0.0336, but this result did not survive multiple comparison correction (p_{fdr} = 0.1061). Post-hoc examination of sex-specific simple slopes (Figure 1C) suggest that ties between accelerated brain age and later midsleep timing may be driven by males (β = 0.263, p_{uncorr}=0.005) but not females (β = 0.038, p_{uncorr}=0.615). Sex did not moderate associations between brain age gap and sleep duration, midsleep variability, or minutes wake after sleep onset (all p-values > 0.05).

Exploratory Sleep, Brain Age, and Depression Analyses

PROMIS-depression severity T-score in the subsample of n=178 was 43.8±6.6 on average (T=50 reflects an age, sex, education-normed population average) and 87% of the sample had a T-score < 50, indicating that this sample had below-average depression severity. Neither brain age gap nor any of the four sleep outcomes were associated with depression severity (all p-values > 0.05; eTable 7).

DISCUSSION

Using a large sample of typical adolescent development (9.0–25.9 years), we identified relationships between individual differences in global structural brain age and naturalistic sleep patterns. Across adolescent development, later sleep timing was associated with a greater brain age gap, or “older brain age”. These results were not driven by sample characteristics or potential confounds (e.g., season, actigraph brand). Our results provide a novel view of brain-sleep structure relationships, highlighting the importance of using a neuroimaging summary score to identify relationships between brain structure and individual differences, as opposed to focusing on individual brain regions.

The selective relationship between brain age gap and midsleep is intriguing. Sleep timing and timing preference (chronotype) have been consistently associated with gray matter structure across diverse brain regions in adults (for example,[3,4]). Our result extends these findings by providing a more parsimonious interpretation that sleep timing is tied to global

brain age. Midsleep is a good proxy for endogenous circadian phase (timing)[21]. Midsleep time and the phase of the circadian clock become increasingly delayed over adolescent development[22]. Developmental changes in midsleep and circadian phase parallel, and may be guided by, pubertal maturation[44,45]. Age and puberty are highly correlated with one another, and the most prominent age-associated changes in sleep are typically observed in measures of sleep timing[46,47]. Furthermore, given our preliminary finding that the relationship between midsleep and brain age gap is stronger in males, it is possible that the effect of sex may be driven by differences in pubertal maturation. Males tend to undergo pubertal maturation later than females[48]. Future studies should examine 1) the common and unique influences of age and puberty on sleep and global brain maturation and 2) test the strength of the potential sex moderation effects on brain age gap in a larger sample. Another possibility is that lifestyle factors associated with later sleep timing and older brain age (e.g., alcohol use, smoking[49,50]) could underlie the observed relationship between sleep timing and brain aging. For next stage mechanistic studies, it will be important to distinguish whether it is a sleep-circadian process or a downstream lifestyle behavior driving the associations between sleep timing and structural brain aging.

The relationship between midsleep and brain age gap was not moderated by age. This finding suggests that this relationship remains consistent across a dynamic period of development. We did previously observe developmentally specific relationships (present in one age group but not another) between sleep and gray matter structure in our most recent paper from the same dataset[2]. This finding suggests that those developmentally specific associations may be restricted to discrete brain regions, and not more global neuromaturation.

Though midsleep variability was also associated with a greater brain age gap, this finding did not survive multiple comparison correction and appeared to be more strongly influenced by the sample composition. Thus, variable sleep patterns could be tied to brain age gap, as well as the sample characteristics for capturing this association. Sleep variability is inherently impacted by schedule constraints which may vary by social commitments, such as school, work, hobbies, or family responsibilities. Given that we utilized an archival data set, the sample composition varied greatly and were originally chosen for different reasons. Future studies should test the ability to replicate this relationship in a more homogenous sample and/or examine possible moderators of this relationship in a larger community sample (i.e., school/work schedule, parental-set sleep timing, season, etc.).

We failed to observe relationships between brain age gap and sleep duration and wake after sleep onset. Though these sleep behaviors were related to multiple brain regions in our previous paper, our findings suggest that perhaps these relationships are best understood by cortical thickness and subcortical volume in these discrete regions, not a more global phenomenon. This lack of a relationship may be because sleep duration and wake after sleep onset are not as strongly driven by a developmental process, like midsleep[22,46]. While sleep duration declines over adolescence, is sometimes conceptualized as secondary to changes in circadian timing in combination with school start times[20].

We also did not detect associations between depression and brain age gap or sleep outcomes in exploratory models conducted in a subset of our sample. Both null results may be due to our healthy, psychopathology-free sample. One exciting possibility is that brain age-sleep associations are evident prior to the emergence of impairing depressive symptoms and their tie to global brain age. Based on our results, later midsleep in particular may reflect advanced brain aging before clinically significant depression symptoms manifest. This interpretation is consistent with the conceptualization of sleep as a precursor or prodrome of psychopathology[1].

There are several limitations to our study. First, the original brain age model was trained and tested on individuals 18–90 years old, and our sample encompassed individuals 9–25 years old. It has not yet been established if the same individual brain weights are the best at predicting chronological age in children and adults; however, other consortia are currently working on this issue[51]. Because there is evidence that age-related structural brain changes differ between childhood/adolescence and adulthood[52–54], the brainageR model may not adequately capture typical adolescent brain development and future studies should explore how sleep is related to a brain age model developed specifically for youth. Though several other studies have developed brain age models in youth[12,14,55], these models have not been validated in independent samples and the model we used has been rigorously tested in multiple samples. There are critiques against brain age calculations because it is a global measure. However, predicted brain age is heritable[25] suggesting that this summary score is still capturing valuable, meaningful biological information. The age gap score we used did not include other bodily system ‘ages’ (e.g., metabolic measures, epigenetic markers[56,57]). Given that sleep patterns are related to a diverse array of bodily systems, it will be informative to test how incorporating a more comprehensive assessment of biological brain age may improve our ability to account for variability in naturalistic sleep patterns. Another potential limitation is the generalizability of our findings due the sample composition and sleep measurement method. Our sample was comprised of multiple studies conducted in the Pittsburgh, Pennsylvania area, and thus is not a nationally representative sample. Further, actigraphy estimates sleep based on low activity levels, which could also reflect rested wakefulness. It will be important to replicate these findings in larger, nationally representative cohorts that incorporate objective sleep estimation methods, like polysomnography. Finally, because our analyses were cross-sectional across a range of ages, rather than longitudinal within participants, it is unclear whether sleep patterns are a cause, correlate, or consequence of global brain age. Advanced brain aging is most consistently associated with negative outcomes, as is later midsleep. Thus, it is possible that midsleep could contribute to or result from advanced brain aging. Future, prospective longitudinal studies are necessary to disambiguate directionality of relationships between sleep timing and brain aging.

A larger brain age gap may also serve as an early marker of risk for multiple suboptimal outcomes in youth. Brain age gap is an individual, parsimonious measure that may be more easily applied in a clinical setting. Later midsleep may be one behavioral indicator of, or contributor to, advanced brain age, particularly among males. Future studies should test the hypothesis that advanced brain age gap and individual differences in sleep patterns precede the onset of suboptimal outcomes, such as psychopathology. If sleep timing contributes

to advanced brain maturation, interventions that normalize sleep timing have potential to improve brain maturational trajectories over adolescence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest:

Dr. Goldstein reports receiving royalties from Guilford Press. Dr. Ryan is on the Scientific Advisory Committee for Axsome Therapeutics.

Dr. Buysse has served as a paid consultant to Bayer, BeHealth Solutions, Cereve/Ebb Therapeutics, Emmi Solutions, National Cancer Institute, Pear Therapeutics, Philips Respironics, Sleep Number, and Weight Watchers International. He has served as a paid consultant for professional educational programs developed by the American Academy of Physician Assistants and CME Institute, and received payment for a professional education program sponsored by Eisai (content developed exclusively by Dr. Buysse). Dr. Buysse is an author of the Pittsburgh Sleep Quality Index, Pittsburgh Sleep Quality Index Addendum for PTSD (PSQI-A), Brief Pittsburgh Sleep Quality Index (B-PSQI), Daytime Insomnia Symptoms Scale, Pittsburgh Sleep Diary, Insomnia Symptom Questionnaire, and RU_SATED (copyright held by University of Pittsburgh). These instruments have been licensed to commercial entities for fees. He is also co-author of the Consensus Sleep Diary (copyright held by Ryerson University), which is licensed to commercial entities for a fee.

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Drs. Jalbrzikowski, Hayes, Franzen, Hasler, Siegle, Dahl, Ladouceur, McMakin, Silk, and Soehner, have no relevant financial interests, activities, relationships, or affiliations to report.

Abbreviations:

NAPS	Neuroimaging and Pediatric Sleep
KSADS	Kiddie Schedule for Affective Disorders and Schizophrenia
SCID	Structured Clinical Interview for DSM
T1w	T1-weighted magnetic resonance imaging
MRI	magnetic resonance imaging
CSF	cerebrospinal fluid
sMRI	structural magnetic resonance imaging
MFQ	Mood and Feelings Questionnaire
PROMIS	Patient-Reported Outcomes Measurement Information System-Depression Inventory
WASO	wake after sleep onset

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IMPLICATIONS AND CONTRIBUTION

Our findings link a developmentally-driven sleep characteristic – later sleep timing – with advanced brain aging over typical adolescent development, particularly among males. Herein, ties between sleep timing and brain age predate the emergence of suboptimal cognitive-emotional outcomes, implicating late sleep timing as a prodrome or risk factor for altered brain development.

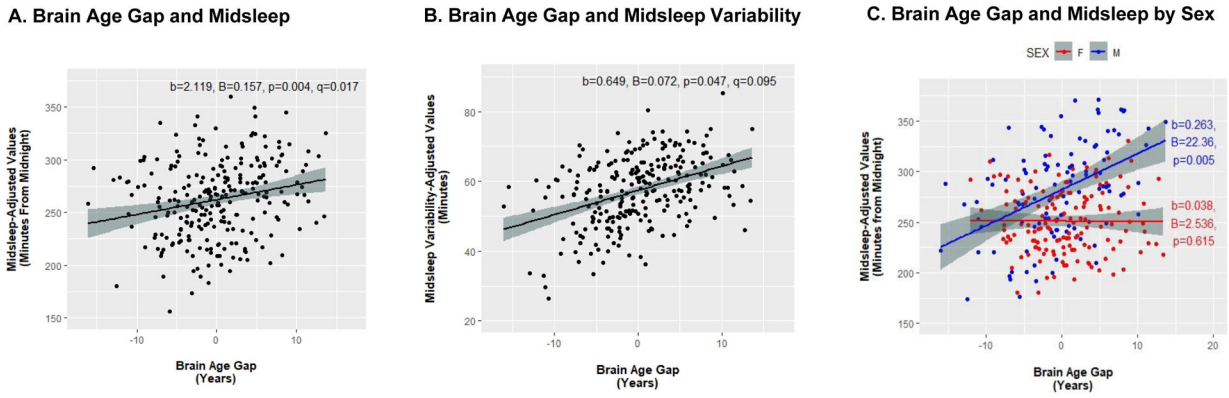

Figure 1: Associations between brain age gap and actigraphy-based midsleep

All regression models examining associations between brain age gap and sleep outcomes were adjusted for age, sex (except Fig. 1C), season, study, lag in days between actigraphy tracking and MRI scan, number of actigraphy tracking days, proportion of weekday to weekend days during actigraphy tracking in robust regression models). Linear best fit line with 95% confidence interval is plotted. Linear best fit line with 95% confidence interval is plotted. **A.** Brain age gap (years) plotted versus midsleep (minutes from midnight) in the NAPS sample (N=251). **B.** Brain age gap (years) plotted versus midsleep variability (minutes) in the whole NAPS sample (N=251). **C.** Brain age gap (years) plotted versus midsleep (minutes from midnight) for males (n=106; blue) and females (n=145; red).

Table 1:

NAPS sample characteristics

Variable	Mean or n	sd or %
Sample N	251	
Age (Years)	17.4	4.52
Self-reported Sex at Birth		
Female	145	58%
Male	106	42%
Ethnicity		
Non-Hispanic	237	94%
Hispanic	14	6%
Race		
Asian	9	4%
Black	39	16%
Multiple	21	8%
White	179	71%
Unknown/Missing	3	1%
Wrist Actigraph Type		
AMI Octagonal MotionLogger	36	14%
PR/MiniMitter Actiwatch64	25	10%
PR Actiwatch2	93	37%
PR Spectrum Series	97	39%
Tracking Days	6.6	0.84
Weekdays	4.53	0.91
Weekend Days	2.07	0.51
Season		
Spring	43	17%
Summer	106	42%
Fall	58	23%
Winter	44	18%
Sleep Duration (min)	420.53	62.41
Wake After Sleep Onset (minutes)	56.5	26.93
Midsleep (minutes from midnight)	266.69	76.39
Midsleep Variability (minutes)	64.87	51.14
Actigraphy-MRI Scan Lag (days)	3.29	7.17

Note: PR = Philips-Respironics; AMI = Ambulatory Monitoring Inc.

Table 2.

Robust regression models for actigraphy-assessed sleep outcomes, brain age gap coefficient estimates

Outcome	Brain Age Gap Beta (se)	Uncorrected p-value	FDR-corrected p-value
Sleep Duration	0.0296 (0.0509)	0.5602	0.6907
Midsleep	0.1575 (0.0546)	**0.0042**	**0.0167**
Midsleep Variability	0.0721 (0.0364)	**0.0474**	0.0948
Wake After Sleep Onset	0.0203 (0.0509)	0.6907	0.6907

Note: All models adjusted for age, sex, season, study, lag in days between actigraphy tracking and MRI scan, number of actigraphy tracking days, proportion of weekday to weekend days during actigraphy tracking

Table 3.

Leave-one out models

Left Out Study			Sleep Duration		Midsleep		Midsleep Variability		Wake after Sleep Onset	
Name	***N***	***Age Range***	***Beta***	***p-value***	***Beta***	***p-value***	***Beta***	***p-value***	***Beta***	***p-value***
Study 1	23	13–17	0.045	0.384	0.138	**0.019**	0.069	0.069	0.037	0.493
Study 2	20	13–23	0.013	0.805	0.158	**0.006**	0.068	0.067	0.010	0.843
Study 3	19	14–18	0.014	0.791	0.173	**0.003**	0.060	0.128	0.012	0.817
Study 4	36	9–14	0.025	0.672	0.183	**0.003**	0.072	0.058	−0.015	0.787
Study 5	37	11–14	0.020	0.710	0.168	**0.004**	0.068	0.093	0.044	0.440
Study 6	24	18–22	0.024	0.650	0.169	**0.003**	0.083	**0.022**	0.038	0.467
Study 7	25	18–25	0.031	0.558	0.137	**0.019**	0.061	0.118	0.029	0.590
Study 8	36	19–25	0.086	0.136	0.111	0.055	0.067	0.079	0.023	0.681
Study 9	31	12–19	0.018	0.731	0.187	**0.002**	0.093	**0.024**	0.003	0.951

Note: All models adjusted for age, sex, season, study, lag in days between actigraphy tracking and MRI scan, number of actigraphy tracking days, proportion of weekday to weekend days during actigraphy tracking. All continuous variables were scaled.

Table 4.

Exploratory robust regression moderation models

Outcome	Brain Age Gap Beta (se)	Uncorrected p-value
Brain Age Gap* × *Age		
Age × Sleep Duration	−0.0398 (0.0539)	0.4595
Age × Midsleep	0.0579 (0.0574)	0.3135
Age × Midsleep Variability	0.0041 (0.0385)	0.1077
Age × Wake After Sleep Onset	−0.0867 (0.0535)	0.1061
Brain Age Gap* × *Sex		
Sex × Sleep Duration	−0.0732 (0.1037)	0.4804
Sex × Midsleep	0.2459 (0.1150)	**0.0336**
Sex × Midsleep Variability	0.1393 (0.0726)	0.0563
Sex × Wake After Sleep Onset	0.1797 (0.1019)	0.0796

Note: All models adjusted for age, sex, season, study, lag in days between actigraphy tracking and MRI scan, number of actigraphy tracking days, proportion of weekday to weekend days during actigraphy tracking