Abstract: STUDY OBJECTIVES Gains in cognitive test performance that occur during adolescence are associated with brain maturation. Cortical thinning and reduced sleep slow wave activity (SWA) are markers of such developmental changes. Here we investigate whether they mediate age-related improvements in cognition. METHODS 109 adolescents aged 15-19y (49 males) underwent magnetic resonance imaging, polysomnography (PSG) and a battery of cognitive tasks within a 2-month time window. Cognitive tasks assessed non-verbal intelligence, sustained attention, speed of processing and working memory and executive function. To minimize the effect of sleep history on SWA and cognitive performance, PSG and test batteries were administered only after at least 8 nights of 9-h time-in-bed (TIB) sleep opportunity. RESULTS Age-related improvements in speed of processing ($r = 0.33$, $p = 0.001$) and non-verbal intelligence ($r = 0.24$, $p = 0.01$) domains were observed. These cognitive changes were associated with reduced cortical thickness, particularly in bilateral temporoparietal regions ($r_s = -0.21$ to $-0.45$, $p < 0.05$), as well as SWA ($r = -0.35$, $p < 0.001$). Serial mediation models found that ROIs in the middle/superior temporal cortices, together with SWA mediated the age-related improvement observed on cognition. CONCLUSIONS During adolescence, age-related improvements in cognition are mediated by reductions in cortical thickness and sleep slow wave activity.

DOI: https://doi.org/10.1093/sleep/zsab206
Cortical thinning and sleep slow wave activity reductions mediate age-related improvements in cognition during mid-late adolescence

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Abstract

Study Objectives: Gains in cognitive test performance that occur during adolescence are associated with brain maturation. Cortical thinning and reduced sleep slow wave activity (SWA) are markers of such developmental changes. Here we investigate whether they mediate age-related improvements in cognition.

Methods: 109 adolescents aged 15–19 years (49 males) underwent magnetic resonance imaging, polysomnography (PSG), and a battery of cognitive tasks within a 2-month time window. Cognitive tasks assessed nonverbal intelligence, sustained attention, speed of processing and working memory and executive function. To minimize the effect of sleep history on SWA and cognitive performance, PSG and test batteries were administered only after at least 8 nights of 9-h time-in-bed (TIB) sleep opportunity.

Results: Age-related improvements in speed of processing (r = 0.33, p = 0.001) and nonverbal intelligence (r = 0.24, p = 0.01) domains were observed. These cognitive changes were associated with reduced cortical thickness, particularly in bilateral temporoparietal regions (rs = −0.21 to −0.45, ps < 0.05), as well as SWA (r = −0.35, p < 0.001). Serial mediation models found that ROIs in the middle/superior temporal cortices, together with SWA mediated the age-related improvement observed on cognition.

Conclusions: During adolescence, age-related improvements in cognition are mediated by reductions in cortical thickness and sleep SWA.

Statement of Significance

During adolescence, age-related improvements to cognition have been documented, alongside decreases in cortical gray matter and sleep slow wave activity (SWA). We investigated the links between these outward manifestations of neural refinement in a moderately large sample of 109 mid-late adolescents. We found that speed of processing and nonverbal intelligence significantly improved with age. These age-related improvements were mediated by reductions in cortical thickness in the middle/superior temporal cortices, as well as sleep SWA. These findings provide support for inter-relationships between sleep and brain structure/function during adolescence.

Key words: adolescence; cortical thickness; slow wave activity; cognitive function

Submitted: 5 May, 2021; Revised: 6 August, 2021
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Introduction

Adolescence is a period of rapid development where a myriad of biological, cognitive, psychological, and social changes occur, in preparation for adulthood [1-3]. Compared to a child, an older adolescent possesses superior executive functioning, cognitive flexibility, and logical reasoning abilities [4-6]. These gains in cognitive ability are associated with strikingly similar maturational trajectories of three brain measures—synaptic density, cerebral metabolism, and slow wave activity (SWA) during sleep [7]. In this work, we seek to clarify and extend links between advancement in cognition, SWA, and magnetic resonance imaging (MRI) measures of cortical thickness in a larger cohort, focusing on mid-late adolescence.

Cortical synaptic density increases rapidly after birth, peaking at 1–2 years of age to approximately 150% of adult levels, before dropping sharply during adolescence and stabilizing in adulthood [8]. This could reflect a process of refinement for overall efficiency of brain networks—either through synaptic pruning by eliminating/weakening less active connections to strengthen active ones [9], or through synaptic remodeling by the reorganization of synapses and connections without change to their number or strength [10]. Paralleling these synaptic changes, are changes in MRI derived cortical gray matter volume and thickness [11, 12] that begin at the age of 5–7 years in primary motor and somatosensory regions, progressing to parietal, frontal, and temporal heteromodal association areas before culminating in the prefrontal cortex in the late twenties [12-15].

Alongside these brain structural changes, sleep architecture and physiology also undergo significant transformation in adolescence [16-19]. Of particular note, trajectories of SWA (0.5–4Hz), important for learning and memory consolidation reach a maximum before puberty and then decrease during adolescence and adulthood [20-23]. The developmental arc of cerebral glucose consumption reflects the waxing and waning of the energetically demanding nature of synaptic activity from childhood to adolescence [24]. Accompanying synaptic refinement and reduced daytime neural activity is reduced synaptic homeostasis during sleep and this is reflected in reduced SWA in adolescents compared to younger children [25, 26]. The decrease in SWA [27] was shown to be associated with gray matter reduction, with the strongest correlations occurring where maturational decreases are most prominent. These findings were subsequently extended by the finding of partial mediation of the direct age effect on SWA by frontal and parietal cortical thinning [28].

Cognitive development during adolescence is postulated to be mediated by these changes in brain structure and sleep physiology [20]. In adolescents aged 12–14 years, cortical thinning has been shown to be associated with better neuropsychological performance, particularly in the parietal association cortices [29].

In the present work, we extend prior findings by clarifying whether age-related SWA and cerebral gray matter changes in mid-late adolescence mediate adolescent cognitive development. To ensure our present effort yielded robust findings, we collected behavioral, polysomnography (PSG), and structural brain MR data from a relatively large group of 109 healthy adolescents aged 15–19 years. Baseline sleep history was controlled for a week prior to PSG so that the intensity of SWA measured was not tainted by prior sleep restriction [30]. Finally, we measured cognition three times in each participant using a cognitive test battery that evaluates cognitive domains known to improve with brain maturation.

Methods

One hundred twenty-nine participants from the series of Need for Sleep (NFS) studies [31-34] who agreed to undergo MRI scans were considered for this sub-study. Of this, 10 participants’ MRI scans were assessed to be of poor quality, while another 10 polysomnographic recordings were unusable due to device failures or electrode dropouts. The final sample consisted of 109 participants (49 males, mean age ± SD: 16.8 ± 1.07 years; Table 1). Participants reported no history of sleep disorders, neurological, or psychological illness, were not habitual short sleepers (< 6 h of actigraphically assessed average sleep with no sign of > 1 h extension on weekends) and had a BMI of ≤30. A detailed description of the inclusion criteria and experimental procedures used have been reported elsewhere [33]. All participants gave informed consent in accordance with protocols approved by the National University of Singapore’s Institutional Review Board.

During the screening period for this protocol, participants also completed a set of questionnaires: the Epworth Sleepiness Scale [35] (ESS) to assess levels of daytime sleepiness, the Pittsburgh Sleep Quality Index [36] (PSQI) to measure habitual sleep duration and quality, the Morningness-Eveningness questionnaire to examine chronotype [37], the Beck Depression Inventory [38] (BDI), and the Beck Anxiety Inventory [39] (BAI) which were used to assess levels of depression and anxiety respectively.

| Table 1. Characteristics of study sample (N = 109) |
|-----------------------------------------------|
| Mean   | SD   |
|-----------------|-----------------|
| Age (years)     | 16.77           | 1.07             |
| Sex (% male)    | 45.00           | —                |
| BMI (kg/m²)     | 20.62           | 2.65             |
| Epworth Sleepiness Scale score               | 7.72            | 3.38             |
| Pittsburgh Sleep Quality Index               |                 |
| Bedtime on weekdays (hh:mm)                  | 23:37           | 01:02            |
| Bedtime on weekends (hh:mm)                  | 00:06           | 01:03            |
| Waketime on weekdays (hh:mm)                 | 06:12           | 00:38            |
| Waketime on weekends (hh:mm)                 | 09:09           | 01:29            |
| TIB on weekdays, h                            | 6.59            | 1.06             |
| TIB on weekends, h                           | 9.03            | 1.16             |
| Global PSQI score                            | 4.87            | 2.16             |
| Morningness-Eveningness score                | 49.83           | 7.47             |
| Beck-Depression Inventory score              | 9.58            | 6.08             |
| Beck-Anxiety Inventory score                 | 9.92            | 7.00             |
| Cognitive Tasks                               |                 |
| Raven’s Progressive Matrices score (# correct) | 9.17            | 1.90             |
| 10-min Psychomotor Vigilance Task median     | 268             | 28               |
| reaction time (ms)*                          | 268             | 28               |
| 2-min Symbol Digit Modalities Task score     | 82.90           | 8.63             |
| (# correct)*                                 |                 |
| 4-min Mental Arithmetic Task score (# correct)* | 63.49           | 16.85            |
| 3-Back Working Memory Task score (A’)*       | 0.94            | 0.05             |

*Mean of three test batteries (morning, afternoon, evening) conducted the day following the polysomnographic recording.

TIB, time in bed.
Brain imaging

High-resolution brain images were acquired on a 3T Siemens Prisma system (Siemens, Erlangen, Germany) using a T1-weighted MPRAGE sequence (TR = 2,300 ms, TI = 900 ms, flip angle = 8°, FOV 256 × 256 mm, isotropic voxel dimensions of 1.0 mm). 192 sagittal slices were acquired. Cortical thickness measures presumed to be sensitive to changes in synaptic density [8, 27], were obtained from the FreeSurfer 5.3.0 pipeline (http://surfer.nmr.mgh.harvard.edu/). Segmentation errors and tissue misclassifications during the cortical reconstruction process were visualized and manually corrected. Thickness measures represented the closest distance between the gray/white boundary to the pial surface at each vertex of the tessellated surface [40] and were calculated for each hemisphere (left: LH; right: RH) and lobe (frontal, parietal, temporal, occipital). Following significant lobar relationships, follow-up statistical analyses were performed on the regions-of-interest (ROIs) within each lobe following the Desikan-Killiany atlas [41].

Polysomnography

A 9-h time-in-bed (TIB) baseline sleep assessment was performed within 2 months of the brain scan, following a prescribed sleep schedule of 9-h TIB for at least 8 actigraphically monitored nights at home and one PSG adaptation night. During these nights, bedtimes and wake times were set at 23:00 and 08:00, respectively. Electroencephalography (EEG) was recorded using a SOMNOtouch recorder (SOMNOmedics GmbH, Randersacker, Germany) on two channels (C3 and C4) in the international 10–20 system, referenced to contralateral mastoids. Cz and Fpz were used as common reference and ground electrodes, respectively. All EEG electrodes were kept to an impedance of below 5 kΩ. Electrooculography (EOG) and submental electromyography were also performed with impedances kept below 10 kΩ. Pulse oximetry was measured on the first night to screen for undiagnosed sleep apnea.

Signals were sampled at 256 Hz and band-pass filtered between 0.2 and 35 Hz for EEG, and between 0.2 and 10 Hz for EOG. The Z3Score algorithm [42] (https://z3score.com) in conjunction with the FASST EEG toolbox [43], was used to automate sleep and artifact staging before they were visually checked by trained research staff following standards set by the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events [44].

SWA in the 0.6–4 Hz band was computed across all artifact-free NREM epochs on electrode C3/A2 following our prior work [45]. Power spectral density estimates were computed using Welch’s modified periodogram method [46] (Hamming window; 0.2 Hz bin resolution) on nonoverlapping 5 s epochs and integrated from 0.6 to 4 Hz using the trapezoidal rule for integral approximation to obtain SWA measures per epoch, which were then averaged across the whole night of sleep.

Assessment of cognition

Cognitive function across four main domains was assessed. Nonverbal intelligence was assessed during the screening period for study inclusion, while the latter three domains—sustained attention, speed of processing (SOP), and working memory were assessed using an average of three test battery assessments (morning, afternoon, evening) conducted the day following the polysomnographic recording when the participants were well-rested after at least nine nights of 9-h TIB. Subjective sleepiness was also measured with the Karolinska SleepINESS Scale [47] (KSS) prior to the test battery assessments to ensure effects were not driven by sleepiness levels.

Nonverbal intelligence. This was assessed using Raven’s Advanced Progressive Matrices [48] (APM) which is a test of observation and clear thinking ability, and is used as a nonverbal estimate of abstract reasoning or fluid intelligence. The number of correct responses out of a total of 12 questions was used as a measure of performance.

Sustained attention. The 10-min Psychomotor Vigilance Task [49] (PVT) was used to measure sustained attention. Between intervals of 2–10 s, a counter on the computer screen would randomly start, and participants were instructed to respond as quickly as possible by pressing a key. An alarm would sound if no response was detected 10 s after stimulus onset. Median reaction time (ms) across all trials was used as the primary measure of sustained attention, while exploratory associations with mean reaction time, average lapses, fastest 10%, slowest 10%, and speed are provided in the Supplementary Material.

Speed of processing. This domain was assessed using two tasks. In the Symbol Digit Modalities Task [50] (SDMT), a key comprising nine pairs of symbols and digits (1–9) was presented. Participants were required to input the corresponding digit pair to each symbol that was presented as quickly as possible. An alarm was sounded if no response was detected after 15 s. The total number of trials correctly responded to within 2 min was used as a measure of performance. In the Mental Arithmetic Task [51] (MAT), participants were instructed to sum pairs of two-digit numbers as quickly as possible within 4 min. An alarm was presented if no response was detected after 15 s. The total number of correct trials was used as a measure of performance. The scores of these two tasks underwent T-score conversion (T-score = (z-score × 10) + 50) separately and were then averaged to obtain a domain-specific T-score.

Working memory and executive functions. Working memory and executive functioning was assessed using the verbal 3-Back [52] task. Letters were presented for 1 s each with a 3 s inter-stimulus interval. Participants had to indicate with “Y” or “N” on the keyboard whether or not the current letter matched the one shown three items ago. The match to mismatch ratio was 8:24. The A’ measure of discriminability was used as a performance measure.

Statistical analyses

Statistical analyses were performed with SPSS 26.0 (IBM, Chicago, USA) to examine associations among age, brain, sleep, and cognitive measures. Partial correlations, controlled for sex, were employed to investigate age-related associations on brain, sleep, and cognitive measures. To investigate potential mediating effects of age on cognition by cortical thickness and SWA measures, FreeSurfer’s mri_glmfit was first used to identify brain regions that were separately associated with...
age, SWA, and cognitive domains of SOP and nonverbal intelligence (i.e. those that showed significant age associations). General Linear Models (GLMs) were conducted on all vertices of the cortical morphometric data, controlling for the effects of sex. Intersecting regions that were greater than 50 mm² from the conjunction of these three separate significance maps were then extracted. ROIs that were no longer significant in regression models predicting cognition from age, brain ROIs and SWA measures were excluded, and the remaining ROIs were then considered in further serial mediation analyses [53].

SWA measures were log-transformed prior to analyses to improve normality (p > 0.05 on Kolmogorov-Smirnov and Shapiro-Wilk tests after log-transformation), while serial mediation analyses were conducted using the PROCESS function in SPSS (v3.5, Hayes Model 6 [54]). The indirect effect was tested using 5,000 bootstrap samples and a 95% confidence interval (bias-corrected). Sex was included as a covariate in all models, but as it did not interact with any of the other variables inspected, interaction terms were not included in the final models.

Results

Characteristics of participants included in the final sample, along with scores on the cognitive tasks performed are provided in Table 1.

Cortical thickness and EEG SWA decline with age

Accompanying age-related increases observed in cognition, was cortical thinning of both cerebral hemispheres with age (Figure 2A and B). Partial correlations controlled for sex showed significant negative associations between age and cortical thickness (left hemisphere r = −0.32, p = 0.001; right hemisphere r = −0.32, p = 0.001). Further inspection of the four lobes revealed that this association was steepest in the temporoparietal regions (LH parietal: r = −0.34, p < 0.001, RH parietal: r = −0.36, p < 0.001; LH temporal: r = −0.46, p < 0.001, RH temporal: r = −0.43, p < 0.001), and to a lesser extent in the occipital regions (LH occipital: r = −0.20, p = 0.04). Follow-up analyses in these lobes identified specific ROIs within each lobe that exhibited these negative correlations with age (Table 2). In addition, there was also a negative correlation between EEG SWA (0.6–4 Hz) and age (r = −0.35, p < 0.001; Figure 2C), and a positive correlation between SWA and cortical thickness (Table 2), suggesting inter-relationships between these measures.

Cortical thinning and SWA reductions mediate age-related improvements in cognition

Given the significant associations of age with cortical thickness, SWA, and two cognitive domains, we next sought to determine whether age-related improvements in cognition were statistically mediated by reduction in cortical thickness and SWA in a serial mediation model. To identify ROIs that were simultaneously associated with all three variables of interest—age (Figure 3A), SWA (Figure 3B), and cognition averaged across speed of processing and nonverbal intelligence domains (Figure 3, C and D), a conjunction of three vertex-wise analyses (controlled for sex) in Freesurfer (Figure 3, E and F) was conducted. ROIs that were no longer significant in regression models predicting cognition from age, brain ROIs and SWA measures were excluded. Finally, serial mediation models controlled for sex on the remaining ROIs showed that the age-related improvements in both speed of processing and nonverbal intelligence domains were mediated by cortical thickness in these brain ROIs and SWA measures (speed of processing—Figure 4A:...
left superior temporal region; indirect effect $b = 0.141, SE = 0.090$, 95% CI = [0.0057; 0.3478]; Figure 4B: right middle temporal region; indirect effect $b = 0.2078, SE = 0.1314$, 95% CI = [0.0275; 0.5245]; nonverbal intelligence—Figure 4C: left middle temporal region; indirect effect $b = 0.0317, SE = 0.0236$, 95% CI = [0.0003; 0.0888]; Figure 4D: right middle temporal region; indirect effect $b = 0.0313, SE = 0.0220$, 95% CI = [0.0024; 0.0833]). Results also indicated full mediation of the age-related improvement effect on cognition, as direct effects were no longer significant after inclusion of SWA and cortical thickness measures as mediators. The proportion of variance explained by the model with stepwise inclusion of cortical thickness followed by SWA increased significantly in all models considered (speed of processing: from 11% to 18% and 33% in the left hemisphere, and to 18% and 26% in the right hemisphere; nonverbal intelligence: from 7% to 15% and 20% in the left hemisphere, and to 15% and 18% in the right hemisphere; all $p$s < 0.05), suggesting independent contributions of both serial mediators to cognition.

**Discussion**

In the present work, we observed age-related improvements in cognitive abilities across mid-late adolescence, alongside reductions in cortical thickness and SWA measures, congruent with findings obtained over a broader childhood-adolescent age range [27, 28]. In addition, we expand on these findings by demonstrating that the extent of cortical thinning—particularly in the middle/superior temporal regions, and reduction in SWA mediated the age-related improvements on cognition. This solidifies evidence for cross-linkages involving brain development, sleep, and cognitive functioning.
We found that cognition, particularly in the speed of processing and nonverbal intelligence domains, improved with age. Given that sleep history was carefully controlled and that there was no association between average KSS scores and cognitive performance, these results could not be explained by differences in sleepiness levels. Compared to simple reaction time tasks that reach maturity in early adolescence [55], cognitive tasks that recruit higher-order executive processes such as information integration, reasoning, and problem solving are more reliant on heteromodal association areas that develop in late adolescence.

The temporoparietal areas which show the strongest associations with age, SWA, and cognition in the present work are involved in higher order cognitive processes such as semantic processing, language, and cross-sensory modality integration of information [11].

Prior work has shown associations between age, cortical thinning, and SWA reduction during adolescence over a wider age window (8–19 years [27] and 12–21 years [28]). Even within a narrow age window of 4 years during mid-late adolescence (15–19 years), we found significant age/SWA-related cortical thinning; although this was observed mainly in the temporal...
lobe rather than in frontal cortices described previously [27, 28]. This may be because temporal lobe gray matter volume peaks at around 16.6 years—the midpoint of the present sample's age-range, compared to 10–11 years in the parietal lobes and 11–12 years in the frontal lobes [13]—with development of the prefrontal cortex continuing well into early adulthood [56–58].

Figure 4. The serial mediating effect of cortical thickness measures in middle/superior temporal brain regions as well as sleep slow wave activity in the relationship between age and cognitive domains of speed of processing (A, B) and nonverbal intelligence (C, D) (*p < 0.05, **p < 0.01, ***p < 0.001). All effects are unstandardized; a represents effects of age on cortical thickness measures and SWA as mediators; b represents the effect of these mediators on cognition; c and c' represent direct and total effects of age on cognition; d is effect of cortical thickness in the right and left middle/superior temporal regions on SWA. All models were controlled for sex (male = 0). Results indicated full mediation of the age-related improvement effect on cognition, as direct effects were no longer significant after inclusion of SWA and cortical thickness measures as mediators.

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The provision of 9-h TIB for over a week prior to PSG assessment was designed to obviate the influence of sleep restriction on SWA. Adolescents in this age group often curtail sleep [59] and this can elevate early-night SWA on subsequent nights [45, 60, 61]. Whether chronic insufficient sleep in childhood and adolescence alters the generators of slow waves is an important unanswered question. Alteration of sleep homeostasis has not been observed following up to five nights of sleep restriction to 5-h TIB in human adolescents [62] but the effect of consistent short sleep over months or even years has not been evaluated. Changes to sleep homeostasis with a relatively short sleep restriction of five nights have been shown in rodents [63], suggesting the need for longitudinal studies on populations such as ours where nocturnal sleep durations are habitually below what is recommended [64]. It is thus important to evaluate the potential effects of habitual sleep duration on brain maturation. “Overpruning” during adolescence has been linked to schizophrenia, [9] mood disorders, [65] autism [66], and intellectual disability [67]. In addition, due to age-related SWA reductions and cortical thinning measures in typically developing adolescents, it would be imperative to control for age or include an age-matched control group when analyzing sleep EEG data involving children/adolescents even within a very small age range, for example, when investigating the role of SWA on memory consolidation/encoding.

**Limitations**

Cross-sectional data precludes tests for causal relationships between the variables examined. Future work should investigate longitudinal sleep–brain relationships, which would help assess whether SWA simply mirrors reductions in synaptic density or cortical thickness or whether it could be actively involved in synaptic refinement processes [68]. Although cross-sectional studies suggest that the peak of synaptic pruning occurs earlier than SWA [69], they could also bidirectionally influence each other. For example, chronic short sleep at an early age could alter SWA levels later on in life.

A longitudinal investigation will also enable better control over variation in peak thickness across individuals. Cortical thickness measures have been shown to exhibit moderate to strong heritability [70, 71] particularly in association areas between the ages of 12 and 17 [72]. These would be important to disentangle from cultural or environmental influences that could similarly impact developmental trajectories. Cortical thickness trajectories themselves could be more informative than point measurements. For example, children with superior intelligence exhibited a higher rate of cortical thinning than those with average intelligence [73]. Students in our sample were also recruited from among better-performing schools and typically have well-practiced cognitive abilities from an early age [74, 75].

In addition, age-related increases in intracortical myelination that affect gray-white tissue contrast as well as changes to cortical morphology during development can also result in apparent cortical thinning [76], while white matter microstructure can influence SWA [77, 78] and cognition [79]. Further work is needed to disentangle these developmental mechanisms with multimodal techniques as well as investigate the potential contribution of other EEG microstructural features to cognition, for example, sleep spindle characteristics—number, density, duration, and its temporal coordination with slow oscillations, which have also been known to mature with age [80, 81]. Our findings were limited to analysis of a single central electrode. Frontal SWA may be more sensitive to age-related changes in late adolescence [82] and should be considered in future studies. Finally, these results relate to East Asian adolescents. Future work should investigate whether developmental trajectories and relationships with sleep and cognition differ across race and cultures. One study in children between 8 and 16 years of age found regional differences in brain morphological development between Chinese and Caucasian children [83].

**Conclusions**

In summary, our findings show that age-related improvements in cognition during mid-late adolescence are mediated by cortical thinning and reductions in SWA, particularly in the middle/superior temporal regions—which undergo the most maturational change in this age range. These findings affirm prior work showing neural refinement for learning efficiency still taking place in late adolescence. Future work should investigate multimodal associations of brain, sleep, and cognitive development longitudinally and explore the impact of brain insults or sleep habit changes during specific developmental periods.

**Supplementary Material**

Supplementary material is available at SLEEP online.

**Funding**

This work was supported by grants from the National Medical Research Council, Singapore (NMRC/STaR/015/2013), National Research Foundation (NRF2016-SOL002-001), and the Far East Organization awarded to Michael W.L. Chee.

**Acknowledgments**

The authors would like to thank Alyssa Ng, Andrew Dicom, Christina Chen, Xin Yu Chua, Ksenia Vinogradova, Zhengbao Fu, Shohreh Ghorbani, Hosein Golkashani, Teck Boon Teo, Te Yang Lau, Brian Teo, Tiffany Koa, Jessica Lee, James Teng, Xian Wong, Zaven Leow, Litali Mohapatra, Caryn Yuen, Yuvan C, and Karthika Muthiah for assistance in data collection and sleep scoring.

**Disclosure Statements**

**Financial Disclosure:** There are no financial conflicts of interest.

**Nonfinancial Disclosure:** Michael Chee and Ju Lynn Ong have a patent for the Z3-score framework. Michael Chee consults for AIA (a health insurance company) on sleep-related matters and Quantactions (smartphone tap analysis).

**Data Availability Statement**

Summary data are available upon reasonable request to the author.
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