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The adolescent decline of NREM delta, an indicator of brain maturation, is linked to age and sex but not to pubertal stage

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Abstract

Two dramatic phenomena of human adolescence are sexual maturation and a steep decline in the delta EEG of non-rapid eye movement (NREM) sleep. It has long been speculated that these developmental changes are causally related. Here, we present the first longitudinal data on this issue. Cohorts of 9- and 12-year-old children ($n = 31, 38$) were studied with in-home sleep EEG recordings at 6-mo intervals over 2 years. Pubertal (Tanner) stage, height, and weight were obtained at each time point. NREM delta power density (DPD) did not change significantly over ages 9–11 years, and its level did not differ in boys and girls. DPD declined by 25% between ages 12 and 14 years. This decline was parallel in the two sexes, but levels were lower in girls, suggesting that their DPD decline began earlier. Mixed effect analyses demonstrated that DPD was strongly related to age with Tanner stage, height, weight and body mass index controlled but that none of these measures of physical and sexual development was related to DPD with age controlled. NREM delta is the sleep EEG component homeostatically related to prior waking duration and the intensity of waking brain activity. We hypothesize that the DPD decline is caused by age-programmed synaptic pruning that decreases waking brain metabolic rate. This reduced rate would decrease the “substrate” for delta homeostasis. Whether or not this interpretation proves correct, these longitudinal data demonstrate that the delta decline in adolescence reflects brain processes that are not predicted by physical growth or sexual maturation.

Keywords

sleep; adolescence; electroencephalograph; non-rapid eye movement

Across adolescence, the sleep EEG shows a massive decline in amplitude over a wide range of frequencies (17,21). The decline is most pronounced in non-rapid eye movement (NREM) delta (<4 Hz), a frequency range that behaves homeostatically (3,10). Cross-sectional data demonstrate that delta declines by about 50% between ages 10 and 20 years. First demonstrated with visual scoring of *stage 4* EEG epochs (10,13,33), this maturational change was further documented with computer measurement (7,14,17,21). The homeostatic behavior of NREM delta is manifested by an increase in delta power with increasing waking duration and a systematic decline in delta power across sleep. The decline across sleep has been interpreted as evidence that changes produced by waking brain activity are being reversed or consumed (10), preparing the brain for renewed waking activity.

In 1982, one of us (11) proposed that the delta decline during adolescence is a component of a widespread brain reorganization driven by the synaptic elimination discovered by Huttenlocher (20). Other manifestations of this reorganization include reductions in brain metabolic rate, decreased plasticity (as evidenced by diminished lesion recovery), and the emergence of adult cognitive capacity. This model also proposed that maturational brain changes during adolescence might sometimes be faulty. Such errors could give rise to abnormal circuits that cause mental illness, notably schizophrenia. Thus this model provided an early neuroscience-based explanation for the age of onset of this illness. The possibility that abnormalities in adolescent brain maturation cause mental disorders is now the subject of intensive research (for a review, see Ref. 26).

A second prominent brain-related development during adolescence is the attainment of reproductive capability, which is driven by reactivation of gonadotropin-releasing hormone (GnRH) secretion (reviewed in Ref. 9). GnRH is active in fetal development and in the first postnatal months when it may act to sexualize the brain. GnRH secretion becomes dormant shortly after birth until it is reactivated in puberty.

Because these two fundamental manifestations of human brain maturation—the decline in delta sleep and the emergence of sexual maturation—occur over the same age range, it has been suspected that they are causally related. This possibility was investigated by Carskadon and coworkers (5). In an early longitudinal study, they reported that the decline in visually scored delta was significantly correlated with increasing pubertal maturation (Tanner stage). They stated that this relation was independent of age but did not specify how they eliminated age effects. Their more recent work again shows the strong correlation between decreasing NREM delta and increasing Tanner stage (21,22) and now acknowledges the importance of controlling for age, preferably with a longitudinal design.

Here, we report the first longitudinal results of an ongoing study investigating the relation between the delta decline, pubertal maturation, physical growth, sleep schedule, and age. This study also tests the hypothesis that the delta decline is related to age with pubertal stage, sleep schedule, or physical growth [height, weight, and body mass index (BMI)] each statistically controlled.

METHODS

Subjects

Subjects were normal children living in the Davis community. Two age cohorts were studied. Subjects in cohort C9 ($n = 31$, 16 girls) were initially 9 years old (± 3 mo), and subjects in cohort C12 ($n = 38$, 19 girls) were initially 12 years old (± 3 mo). Subjects were recruited by word-of-mouth and descriptions of the study in the Davis newspaper. This recruitment produced a subject sample that is primarily Caucasian (80%) with 7% Asian, 4% Hispanic, 2% African American, and 7% mixed race. We selected subjects who had no sleep complaints; who had normal medical, neurologic, and psychiatric histories on interview with parents; and who had no first-degree relatives with major psychiatric illness. No subject was taking medications that affect the central nervous system, and each was performing at grade level or better. Subjects were paid for their participation. All experimental procedures were approved by the UC Davis human subjects Institutional Review Board. Our experimental design plans for C9 and C12 to be followed for 4 years with 1 year of overlap at ages 12–13 years.

Sleep schedule

Subjects were recorded at home on their normal sleep schedules using Grass H2O ambulatory recorders. Subjects were required to maintain their normal weekday bed and wake-up times

and to avoid naps during the 5 days before EEG recording. We used activity monitors (wrist actigraphs, Mini Mitter A16) to monitor their compliance with the schedules. The sleep schedules used in the analyses described below are mean bed- and wake-up times calculated from actigraphy data on the 3 days before recording. On the first two nights of recording, subjects continued with their habitual weekday time in bed. On the next two nights, subjects kept their weekday bedtimes but were asked to extend their time in bed (goal = 12 h). The four-night sleep recording protocol was carried out at ~6-mo intervals. Data from the first four semiannual recordings (spanning 1.5 years) are included in this report. For simplicity, we refer to this period in cohort C9 as ages 9–11 years (actual means 9.3–10.9 years) and in cohort C12 ages 12–14 years (actual means 12.3–13.9 years).

Electrode application and recording

Electrodes for recording EEG and electro-oculogram (EOG) potentials were applied in the subjects' homes in the evening by teams of two trained UC Davis undergraduates. Parents removed the electrodes in the morning. Placement of monopolar EEG electrodes was according to the 10–20 system using the following leads: C3, C4, Cz, Fz, O1, O2, A1, A2. EOG electrodes were left and right outer canthi referred to forehead. Electrode impedance was below 5 kOhms at the start of the recording. The Grass H2O recorder uses the sum of 6 EEG electrodes as reference, and electrode pairs (e.g., C3-A2) are obtained by subtraction. All signals were digitized at 200 Hz and saved on the H2O recorders' miniature hard disks.

Analysis of sleep EEG

Data from the H2O hard disks were transferred to laboratory computers and analyzed with PASS PLUS (Delta Software) EEG analysis software. Using a computer display of the digitized data, two raters scored each 20-s epoch as waking, stage 1, NREM, REM, or movement using modified Rechtschaffen and Kales (27) criteria. Artifacts were marked independently of sleep stage. Discrepancies between the two raters were reconciled by a third experienced rater.

C3-A2 or C4-A1 was chosen for analysis based on which electrode pair had fewer artifacts. In ~10% of recordings, C3-A1 or C4-A2 was analyzed because both C3-A2 and C4-A1 were contaminated with artifacts. For all artifact-free epochs, fast Fourier transform computations were performed on 5.12-s Welch-tapered windows with 2.62-s overlap, yielding 8 windows per 20-s epoch. Total sleep time varied between subjects. We, therefore, used delta power per minute in the first 5 h of NREM sleep as the delta measure for each subject. For each semiannual recording period, the data point for each subject was the mean of *nights 1–3*. Although *night 3* was an extended night, the first 5 h of NREM occur during the habitual time in bed before sleep extension. Ambulatory EEG recording at the subject's home allows for EEG recording in a comfortable setting, but the lack of supervision leads to some data loss when the electrodes fall off. Thus we obtained an average of 2.36 rather than 3 usable nights of baseline EEG for each semiannual recording period. At least one baseline night was usable for every subject at each time point. We have previously shown high night to night reliability in within-subject NREM delta EEG activity (31a). The ambulatory recordings in adolescents in this study also showed strong night-to-night consistency. The average variation of each baseline night from the 3 night mean was less than 10% for both C9 (9.2%) and C12 (9.0%). There was no evidence of a first night effect.

Delta power density (DPD) was calculated as power in 0.3–3 Hz divided by minutes of artifact-free NREM. Although it also behaves homeostatically (4), 0.3–1 Hz EEG is generated by different mechanisms than the 1- to 4-Hz frequencies (31) and may have a different functional significance. We, therefore, present data on power density for 0.3–3, 0.3–1, and 1–4 Hz. This experiment addresses hypotheses derived from cross-sectional studies that defined delta as 0.3–3 Hz EEG. We present the results for this band, although it includes two different “kinds”

of EEG slow waves, to rule out the possibility that any differences between our longitudinal and previous cross-sectional data were not caused by the use of different frequency bands.

Other measures

Sexual maturation was assessed by Tanner stage ratings, according to published criteria (19). These ratings classify sexual maturation into stages based on breast development and pubic hair growth in girls and genital development and pubic hair growth in boys. The same board-certified internist performed all Tanner ratings via direct observations of subjects in her examining room. These examinations were performed within 1 mo of the sleep recordings. We measured height and weight on our laboratory scale during the recording week. BMI was computed according to the formula $BMI = 10,000 \cdot \text{weight (kg)} / \text{height (cm)}^2$. During the recording week, subjects completed a Child Depression Inventory (24), and parents completed the Child Behavior Checklist (1). A sleepiness questionnaire was completed by the subjects and their parents and teachers based on observations of apparent sleepiness during the 2 wk preceding the EEG recordings. Observations on the relations of sleepiness, depression, and behavior ratings to sleep measures will be presented in a future report.

Statistical analyses

An ANOVA evaluating effects of cohort, sex, and recording session on delta power density showed significant interactions between cohort and the other terms; therefore, the two cohorts were analyzed separately. The recording and sex effects were evaluated with ANOVA using recording as a repeated measure and sex as a grouping factor. Mixed effect analyses (29,32) were used to describe the relationships between DPD and the predictor variables age, height, weight, BMI, and Tanner stage. Mixed-effect analyses were also used to determine whether sleep schedule (bedtime, wake-up time, and time in bed) influenced the relationship of DPD to age. This statistical method is well suited for longitudinal data because it can determine the separate effects of multiple time-linked variables. Our a priori hypothesis, based on our 1982 model (11), was that the decline in delta power would be independent of Tanner stage, height, weight and BMI when age was controlled and that the DPD decline would retain its strong relation to age when measures of sexual maturation and physical growth were controlled.

RESULTS

DPD: repeated-measures ANOVA

Figure 1 shows that DPD did not change between ages 9 and 11 years in cohort C9 but decreased between ages 12 and 14 years in cohort C12. In C12, DPD declined significantly ($F_{3,108} = 40.3$, $P < 0.0001$) across the four recordings and was significantly lower ($F_{1,36} = 13.1$, $P = 0.0009$) in girls than boys in all four recordings. The lack of interaction ($F_{3,108} = 0.08$, $P = 0.96$) between the recording and sex effects indicates that the rate of DPD decline did not differ in boys and girls across ages 12 and 14 years. In C9, there was no significant effect of recording session ($F_{3,87} = 0.32$, $P = 0.81$) or sex ($F_{1,29} = 0.0$, $P = 0.97$) on DPD nor was there a recording by sex interaction ($F_{1,29} = 2.05$, $P = 0.11$).

DPD: mixed-effect analysis

Mixed-effect analysis estimated that in cohort C12, average DPD at age 12 years was $122,200 \mu V^2 \text{ s/min}$ and declined by $18,900 \mu V^2 \text{ s/min}$ (15% of age 12 value) per year ($F_{1,113} = 119.4$, $P < 0.0001$). Including the factor “sex” in the analysis showed that the intercept (value at age 12 years) differed significantly ($F_{1,36} = 8.44$, $P = 0.0062$) between boys ($137,500 \mu V^2 \text{ s/min}$) and girls ($106,500 \mu V^2 \text{ s/min}$). This corroborates the significant sex difference in DPD found with ANOVA. Mixed-effect analyses also confirmed the ANOVA finding that boys and girls did not differ in the “rate” of DPD decline across ages 12–14 years ($F_{1,112} = 0.17$, $P = 0.68$).

It also confirmed that DPD in cohort C9 did not change significantly across ages 9–11 years ($F_{1,92} = 0.34$, $P = 0.56$). In C9, there was a sex-by-age interaction of borderline significance ($F_{1,91} = 4.85$, $P = 0.03$). However, separate analysis of C9 boys and girls showed that neither the slightly increasing DPD trend in the boys ($F_{1,44} = 1.63$, $P = 0.21$) nor the slightly decreasing DPD trend in the girls ($F_{1,47} = 3.28$, $P = 0.076$) was statistically significant.

DPD relationship to age, sexual maturation, and physical growth

Table 1 shows the average Tanner stage ratings at each semiannual recording for boys and girls in the C9 and C12 cohorts. Figure 2, A–D, shows the temporal relation of the DPD decline to increasing sexual maturation (Fig. 2A), height (2B), weight (2C), and body mass index (2D), for boys and girls combined. Mixed-effect analyses (Table 2) for cohort C9 showed that none of the predictor variables was significantly related to DPD in this age group. In cohort C12, DPD showed a significant negative relationship to age, sexual maturation, height, weight, and BMI. Table 3 shows that each of the four measures of physical and sexual maturation was strongly related to age. In C12, when all five predictor variables were included in the mixed-effect analysis, only age maintained a significant relationship to delta, and this effect was quite powerful ($F_{1,84} = 21.2$, $P < 0.0001$). Covariation may act to cancel out the effects of multiple predictor variables. Therefore, we separately analyzed the effect on DPD of each predictor paired with age (Table 4). In each analysis, the effect of age on DPD was significant, but the effect of the other variable was not. For example, Table 4 shows that, with Tanner stage controlled, DPD was significantly related to age ($F_{1,87} = 66.5$, $P < 0.0001$), but with age controlled, DPD was not significantly related to Tanner stage ($F_{1,87} = 0.60$, $P < 0.44$). Separate analysis of the data for boys and girls produced the same results. In both the boys and girls, DPD was significantly related to age when the contribution of each of the other predictor variables was removed, but Tanner stage, height, weight, and BMI were each unrelated to DPD when the age effect was removed.

DPD relationship to sleep schedule

It is well established that sleep schedules change across adolescence. We, therefore, tested whether there was a relationship between these changes in sleep schedule and the DPD decline. In cohort C9, bedtime and wake-up time both became later across ages 9–11, but DPD did not decrease over this age range. It is, therefore, not surprising that DPD was not related to the C9 sleep schedule changes (see Tables 2 and 3). In cohort C12, both bedtime ($F_{1,113} = 7.88$, $P = 0.0059$) and time in bed ($F_{1,113} = 6.69$, $P = 0.011$) were significantly related to DPD. Wake-up time ($F_{1,113} = 0.01$, $P = 0.93$) was unrelated to DPD. Bedtimes become later ($F_{1,113} = 16.73$, $P < 0.0001$) and time in bed diminishes ($F_{1,113} = 4.87$, $P = 0.029$) between ages 12 and 14. With age controlled, neither bedtime ($F_{1,112} = 0.00$, $P = 0.95$) nor time in bed ($F_{1,112} = 1.59$, $P = 0.21$) was significantly related to DPD. In contrast, the decline in DPD with age remained highly robust with bedtime or time in bed controlled ($F_{1,112} = 103.5$, $P < 0.0001$; $F_{1,112} = 109.5$, $P < 0.0001$, respectively).

0.3- to 1-Hz and 1- to 4-Hz power density

The results for age, sex, and pubertal status found for 0.3–1 Hz and 1–4 Hz were similar to those presented above for 0.3–3 Hz power density. No significant sex or age effects were found in the C9 cohort. For the C12 cohort, both 0.3–1 and 1–4 Hz power density showed strong age effects ($F_{3,108} = 33.3$, $P < 0.0001$ and $F_{3,108} = 43.4$, $P < 0.0001$, respectively) and sex effects ($F_{1,36} = 15.8$, $P = 0.0003$ and $F_{1,36} = 8.2$, $P = 0.0069$) with no significant age by sex interaction. Mixed-effect analysis showed that in the C12 cohort, the decline in power density for both 0.3–1 and 1–4 Hz was significantly related to age with Tanner stage controlled ($F_{1,87} = 46.7$, $P < 0.0001$ and $F_{1,87} = 80.3$, $P < 0.0001$, respectively) but not related to Tanner stage with age controlled ($F_{1,87} = 0.08$, $P = 0.78$ and $F_{1,87} = 1.51$, $P = 0.22$, respectively).

DISCUSSION

It may be useful to begin this discussion by describing how synaptic pruning during adolescence could reduce delta wave power. EEG waves recorded at the scalp are produced by synchronous oscillations in membrane potential of large populations of cortical neurons. These synchronous changes are produced by complex interactions between the cortex and thalamus (30). Synaptic pruning during adolescence could decrease cortical connectivity and decrease the size of the neuronal populations capable of oscillating in unison. This would reduce the amplitude of delta EEG waves, reducing DPD.

DPD is now accepted as a marker of a homeostatic process by which sleep reverses the effects of waking brain activity. In our view, the decline of DPD during adolescence reflects the declining need for homeostatic recovery due to declining intensity of waking brain activity. Our 1974 homeostatic model of NREM delta proposed that delta EEG reflects a homeostatic process during which the brain reverses the effects of plastic neuronal activities during waking (10). In this model, the amount of homeostatic reversal is proportional to the intensity of waking brain activity, as well as to waking duration. [The more widely known two-process model (3) did not include the intensity component and does not offer an explanation for the DPD decline during adolescence.] Our 1974 homeostatic model hypothesized that more intense waking neuronal activity causes higher metabolic rates. These higher rates produce a larger “substrate” for homeostatic reversal, resulting in higher delta levels. At the time the 1974 model was proposed, cross-sectional studies had shown that waking whole brain metabolic rate declines over adolescence by 20–30% (23), an amount equal to the average difference between Alzheimer disease and normal elderly (16). Later cross-sectional measurements of “cortical” metabolic rate with PET demonstrated a 50% decline across adolescence (6). The ontogenetic curves for cortical metabolic rate, synaptic density, and delta wave amplitude are parallel over the first three decades of human life, supporting the possibility that they are biologically related (15).

Age of onset of the DPD decline

The longitudinal data here show that DPD does not decline significantly between ages 9 and 11. This contradicts our own previous cross-sectional data that suggested an earlier onset (15). We have now reexamined our published scattergram for delta-integrated amplitude vs. age (14). With the advantage of the longitudinal observations here, we observe that the data points in our previous scattergram could be fit with a flat line across ages 5 to 12 years followed by a linear decline beginning around age 12 years. It would be valuable to confirm this inference with empirical data from a longitudinal cohort followed from age 5 to 10 years.

The longitudinal data here also reveal a sex difference that was not apparent in previous cross-sectional data. Comparing C9 and C12 data suggests that girls, on average, begin adolescent brain maturation at least 1 year earlier than boys. However, the C12 data show that, once begun, this maturational process proceeds at the same rate in both sexes. Interestingly, longitudinal MRI measures of frontal lobe cortical grey matter thickness also indicate an earlier onset of adolescent brain maturation in girls (18).

The DPD decline is age dependent rather than Tanner stage dependent

Our data show that the DPD decline is strongly related to both age and stage of sexual maturation (Tanner). Two recent cross-sectional studies have also demonstrated that DPD and Tanner stage are strongly correlated (21,22). This finding is virtually inevitable because sexually more mature subjects are also, on average, older. In discussing their results, the authors of these studies acknowledged the need for longitudinal investigation to distinguish the role of age in the apparent Tanner stage-DPD relationship. The mixed-effect analyses here

accomplish this separation. They demonstrate that the DPD decline is strongly related to age with the contribution of Tanner stage removed. However, when the effects of age are removed, there is no relation between Tanner stage and DPD.

The power density relationship to age and the independence of power density and pubertal development that we found for 0.3–3 Hz (our traditional “delta” band) were also present at equally high significance levels in 0.3–1 Hz and 1–4 Hz power density. Thus, although 0.3–1 Hz is produced by different neurophysiological mechanisms from those that give rise to the higher delta frequencies, it shares the same developmental patterns. This finding is consistent with the fact that 0.3–1 Hz manifests the same homeostatic relations to prior waking duration shown by 1–4 Hz (4), although 0.3–1 Hz has a different within-night dynamic pattern (2).

It may seem surprising that age is the prepotent factor in the DPD decline. However, many maturational events in the development of the nervous system proceed on a programmed schedule. Repeated age-dependent proliferation and subsequent pruning of neurons and neural elements in fetal development are well established. What is surprising here is that the maturational processes producing the DPD decline in humans occur so late and over such an extended period. However, if the DPD decline reflects synaptic pruning, its functional significance seems apparent. Synaptic pruning during adolescence could sacrifice plasticity or relative neural equipotentiality for efficiency of information processing (11).

The absence of a significant relation between Tanner stage and DPD does not disprove the possibility that sex hormone regulatory mechanisms play a role in the DPD decline. Tanner stages are relatively crude estimates of pubertal maturation based on observed body changes. These changes are the physical outcome of a complex series of brain and endocrine events initiated by the reactivation of GnRH in puberty. To the best of our knowledge, this critical distinction between observable secondary sex characteristics and the brain stimuli that initiate their development has not been made in previous discussions of the relationship between Tanner stage and delta power.

GnRH is secreted by a small group of neurons in the basal forebrain and hypothalamus during late fetal development and for a few months after birth. These neurons then become dormant until reactivated in puberty. It has recently been discovered that the secretion of KISS peptides and their attachment to G protein-coupled receptor 54 play a vital role in the pubertal reactivation of GnRH (8,25,28). It remains possible that the delta decline is linked to sexual maturation but that the linkage is to the stimuli initiating the brain's release of GnRH rather than the downstream changes in Tanner stage.

Sleep schedule, height, weight, and BMI

Previous studies have shown that bedtime becomes later and time in bed decreases across adolescence (34). That pattern was observed in our subjects between ages 12 and 14 and could be considered a potential confound. However, mixed-effect analyses showed that neither bedtime nor time in bed was related to DPD with age controlled. In contrast, the strong relationship between age and DPD persisted when sleep schedule was controlled, demonstrating that the powerful age-dependent maturational decline outweighed any effects of decreased time in bed. The absence of any relationship between DPD and height, weight, or BMI when age is controlled supports the view that the changes in delta EEG during adolescence reflect brain rather than bodily maturation.

The ontogenetic decline in DPD from its childhood peak does not stop after adolescence. Delta EEG continues a slower, but still substantial, decline over adulthood. It has been traditional to consider the adolescent decline as maturational and the adult decline as a degenerative (i.e., aging) change. We have proposed that the same underlying biological process produces both

changes (12). Thus we have noted that the ontogenetic delta curve exhibits no apparent inflection point or increase in variability in the third or fourth decade, changes that might signify that an aging process has replaced normal development. Others disagree with our view (21), and the question remains to be decided. If future research shows that the same process produces both declines, it would cast one of the major sleep changes of adulthood in a new and intriguing biological perspective.

Whatever the mechanism producing the delta decline, our data here show that this robust physiological change can be measured longitudinally during the second decade of life. Such studies can be done inexpensively and noninvasively with ambulatory (home) EEG recorders under naturalistic conditions. Maturational changes in EEG provide an important complement to MRI measures of cortical thickness, and it is possible that sleep EEG changes will prove a relatively direct indicator of synaptic pruning. Longitudinal sleep EEG measurement could also provide a new arena for clinical studies of subjects at high risk for schizophrenia and other neurodevelopmental disorders.

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Fig. 1.

Values are expressed as means $\pm$ SE. 0.3–3 Hz non-rapid eye movement (NREM) EEG power density in the C9 and C12 cohorts. Delta power density did not change between ages 9 and 11 and did not differ between girls and boys. Delta power density decreased between ages 12 and 14 and was lower in girls than in boys.

Fig. 2.

The progression of means $\pm$ SE. 0.3–3 Hz NREM EEG power density in the first four recording periods in C9 and C12 is compared with progression of sexual maturation (A), height (B), weight (C), and body mass index (D). Note that the y-axes are broken; the actual rates of change of these variables are smaller than the apparent slopes of these lines.

Table 1

Tanner stage ratings at each semiannual recording

	Recording 1	Recording 2	Recording 3	Recording 4
Cohort C9	1.3±0.1	1.3±0.1	1.4±0.1	1.7±0.1
Girls	1.4±0.1	1.4±0.1	1.6±0.2	1.9±0.2
Boys	1.1±0.1	1.2±0.1	1.3±0.1	1.3±0.1
Cohort C12	2.5±0.2	3.0±0.2	3.3±0.2	3.5±0.1
Girls	3.0±0.2	3.2±0.2	3.3±0.2	3.4±0.2
Boys	2.2±0.2	2.9±0.2	3.4±0.2	3.6±0.1

Values are presented as means ± SE.

Table 2

Results of mixed-effect analyses showing that delta power density was strongly related to age, sexual maturation, physical growth, and sleep schedule in cohort C12 but not cohort C9

Predictor variable	C9 cohort		C12 cohort	
	$F_{1,92}$	P	$F_{1,113}$	P
Age	0.34	0.56	119.4	<0.0001
Tanner stage *	0.65	0.42	20.7	<0.0001
Height	0.33	0.57	74.7	<0.0001
Weight	0.33	0.56	66.2	<0.0001
Body mass index	0.04	0.84	18.3	<0.0001
Bedtime	0.44	0.51	7.88	0.0059
Wake-up time	0.05	0.83	0.01	0.93
Time in bed	0.83	0.36	6.69	0.011

* Because of missing data, degrees of freedom for Tanner stage are $F_{1,87}$ for C9 and $F_{1,88}$ for C12.

Table 3

Results of mixed effect analyses showing that sexual maturation, physical growth, and sleep schedule were strongly related to age in both the C9 and C12 cohorts

Outcome variable	C9 cohort		C12 cohort	
	$F_{1,92}$	P	$F_{1,113}$	P
Tanner stage [*]	18.5	<0.0001	67.0	<0.0001
Height	657.6	<0.0001	401.3	<0.0001
Weight	279.5	<0.0001	247.1	<0.0001
Body mass index	32.0	<0.0001	60.8	<0.0001
Bedtime	10.3	0.0019	16.7	<0.0001
Wake-up time	10.7	0.0015	1.56	0.21
Time in bed	0.28	0.60	4.87	0.029

* Because of missing data, degrees of freedom for Tanner stage are $F_{1,87}$ for C9 and $F_{1,88}$ for C12.

Table 4

Results of mixed effect analyses distinguishing the effects of age and other predictor variables on delta power density in cohort C12

Variable	Age		2nd Predictor Variable	
	$F_{1,112}$	P	$F_{1,112}$	P
Tanner stage*	66.5	<0.0001	0.6	0.44
Height	31.02	<0.0001	0.32	0.57
Weight	44.4	<0.0001	1.1	0.29
Body mass index	86.8	<0.0001	0.29	0.59
Bedtime	103.5	<0.0001	0.00	0.95
Wake-up time	121.1	<0.0001	1.61	0.21
Time in bed	109.5	<0.0001	1.59	0.21

* Because of missing data, degrees of freedom for age and Tanner stage are $F_{1,87}$ and $F_{1,87}$ when evaluating Tanner and age effects on delta power density. These analyses show that delta power density is strongly related to age when a second predictor variable (sexual maturation, physical growth, or sleep schedule) is controlled but that delta power density is not related to physical growth, sexual maturation, or sleep schedule with age controlled.