RUNNING HEAD: Mood swings development and its biological mechanisms

Mood variability during adolescent development and their relation to sleep and brain development

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Abstract

Background: Mood swings, or mood variability, are associated with negative mental health outcomes. Since adolescence is a time when mood disorder onset peaks, mood variability during this time is of significant interest. Understanding biological factors that might affect mood variability, such as sleep and structural brain development, could elucidate the mechanisms underlying mood disorders.

Methods: Data from the longitudinal Leiden Self-Concept study (N=171) over 5 timepoints was used to study the association between sleep, brain structure, and mood variability in healthy adolescents aged 11-21 at baseline in this pre-registered study. Sleep was measured both objectively, using actigraphy, as well as subjectively, using a daily diary self-report. Negative mood variability was defined as day-to-day negative mood swings over a period of 5 days after an MRI scan.

Results: It was found that negative mood variability peaked in mid-adolescence, and average negative mood showed a similar pattern. Sleep duration (subjective and objective) generally decreased throughout adolescence. Mood variability was not associated with sleep, but average negative mood was associated with higher self-reported lower energy. In addition, higher thickness in the dorsolateral prefrontal cortex (dlPFC) compared to same-age peers, suggesting a delayed thinning process, was associated with higher negative mood variability in early and mid-adolescence. Lastly, higher mood variability preceded higher levels of anxiety and depression, as well as current anxiety and depression.

Conclusions: Together, this study provides an insight into the development of mood variability and its association with brain structure.

Introduction

Mood variability, or emotional instability, refers to fluctuations in mood over time (1). Mood variability undergoes significant changes during adolescence (2) and has been associated with negative mental health outcomes, such as an increased risk of developing anxiety and depression (3–5). Since psychopathology has a peak onset during adolescence (6), it is highly important to study risk factors underlying mental disorders during development. The goal of this study was to provide a comprehensive analysis of the developmental pattern of mood variability in adolescence and to examine two biological mechanisms that may account for these developmental patterns: sleep changes (7) and structural brain development (8).

Mood variability has previously been studied for both positive (e.g., happiness, vigor) and negative (e.g., sadness, anger, tension) emotions (9). Mood variability is typically assessed using daily assessment of mood states, for example through self-report questionnaires, in which participants are asked to rate their mood across several days. This allows for the assessment of both general mood as well as daily fluctuations (10). Prior studies described several developmental patterns, although these are usually based on limited developmental time frames. First, one prior study described that female adolescents (10-14 years at the first time point) showed an increase in mood variability over a 4-year period (Larson et al., 2002), suggesting a rise in mood variability in adolescence. In contrast, a second longitudinal study in adolescents starting from the age of 13 years showed that mood variability for happiness, sadness and anger linearly decreased over a five-year period (12). Furthermore, it was found that in mid-adolescence emotion regulation strategies were used less compared to early and late adolescence (13). It is therefore thought that mood variability peaks in mid-adolescence, possibly associated with less efficient emotion regulation strategies, followed by a decrease into adulthood.

Prior studies have suggested an important link between mood states and sleep (14). During the developmental period of adolescence, melatonin release shifts to a later time, leading to a later bedtime, and thereby often causing sleep deprivation (15,16). Problems with sleep are often seen in people with mental disorders, and insomnia is even a diagnostic criterion for depression (17). Moreover, sleep problems have been identified to increase the risk for psychopathology onset later in life (18–20). Prior research showed that adolescents whose sleep was restricted to 6.5 hours per night reported worse emotion regulation compared to adolescents who slept almost 9 hours per night, but the relation with mood variability is still unclear (21). During development, total sleep duration decreases, which has been assessed using both subjective and objective measures (14,22,23). Most prior studies examining mood and sleep were cross-sectional and included adolescents of a narrow age-range, which limits the possibility to examine developmental changes. Longitudinal studies are therefore needed to study the effect of 'natural' sleep deprivation, which adolescents often experience, on mood variability (7). Due to the discrepancy between objective and subjective sleep measures, such as actigraphy underestimating sleep due to sleep motor activity, it is of importance that the association between both measures of sleep and mood variability are assessed (23).

In addition to sleep related changes, structural brain development may be related to changes in mood and maturation of emotion regulation strategies (24). During adolescence, cortical thickness of the prefrontal cortex and other cortical regions consistently reduces (25–27), and both delays and accelerations of this developmental process have been associated to mood disorders such as depression and anxiety (8,26,28,29). Brain regions that are of particular interest for the relation to mood variability because of their involvement in emotion regulation include the prefrontal cortex (PFC), more specifically the ventrolateral (vlPFC) and dorsolateral (dlPFC) regions, as well as the anterior cingulate cortex (ACC), ventral striatum (VS), amygdala, and orbitofrontal cortex (OFC) (30–33). Neuroscience models previously suggested that these regions do not develop simultaneously, as subcortical brain regions

such as the amygdala and ventral striatum are thought to develop in a faster fashion than cortical brain regions such as the dlPFC and vlPFC (34,35). It could be argued that this imbalance might lead to emotional instability.

Taken together, there is some evidence that mood variability is developing throughout adolescence (2,11) and heightened levels of mood variability possibly have a negative effect on mental health (36,37), but this question has not yet been examined using longitudinal measures across the whole range of adolescence. In addition, the contributions of two potential mechanisms, sleep (14) and neural development (8), on the development of mood variability remain unknown. Therefore, the present study had three aims: 1) to study the development of mood variability throughout adolescence in a longitudinal sample, 2) to study the relation between sleep, brain structure and mood variability, 3) to examine if mood variability during adolescence can predict anxiety and depressive symptoms.

We examined these questions in a pre-registered (https://osf.io/xmbg4/) comprehensive longitudinal study including three waves of neural development and daily variability in mood and sleep in adolescents between 11-24 years of age. We hypothesized that (a) mood variability develops in an inverted U-shape, (b) sleep decreases throughout development, (c) lower sleep length is associated with higher mood variability, (d) brain development of regions involved in emotion regulation is associated with mood variability, and (e) higher mood variability precedes symptoms of anxiety and depression.

Methods and materials

Participants

In this study, data from adolescents from the Leiden Self-Concept Study was used (38,39). The Leiden Self-Concept Study is a longitudinal study with 5 time points. Participants were aged 11–21 years at the first time point. They were followed for three consecutive years with lab visits, and two additional years with online questionnaires. Healthy adolescents (N=171) took part in the study (Table 1, Supplementary Table S1). Exclusion criteria included the following: being left-handed, not having normal or corrected-to-normal vision, neurological or psychiatric diagnoses, and usage of psychotropic medication. Participants and parents of participants younger than 18 years signed informed consent. The study (NL54510.058.16) was approved by the Medical Ethics Committee of the Leiden University Medical Centre (LUMC).

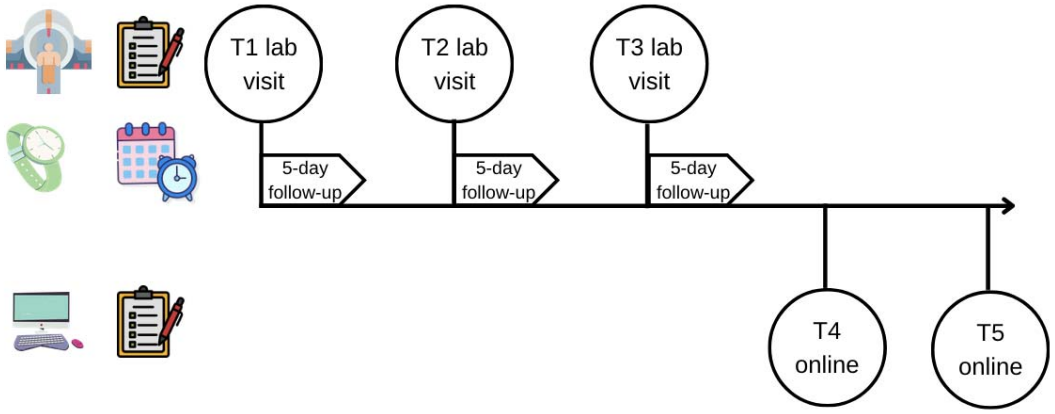

Figure 1. Timeline of the Leiden Self-Concept Study. At the first three time points, participants visited the lab to undergo an MRI and fill out questionnaires. In the 5 days after the lab visit, participants reported their daily mood and sleep in a diary, and sleep was measured using a wristband that detected motion. Participants were given the option to

participate in two follow-up visits that only entailed filling out questionnaire measures at home.

Measures

Mood variability

The Profiles of Mood States (POMS) questionnaire was used to assess daily mood (40). In this questionnaire participants were asked to rate 32 adjectives on a 5-point Likert scale to which degree the adjective described their current mood. The POMS questionnaire consists of 5 subscales: anger, depression, fatigue, tension, and vigor. Mood variability was calculated per subscale as the absolute difference between successive days (12). These scores per day were summed and then divided by the number of consecutive days the participants rated their mood. Total mood variability was defined as the sum of the mood instability on the subscales. Only participants with ratings on 3 or more consecutive days were included. Higher scores indicate a higher mood variability. In addition, the total average mood was calculated by summing the averaged subscales and subtracting the average of the vigor subscale. Missing items were imputed using predictive mean matching from the 'mice' package in R (41).

Sleep measures

Objective and subjective measures of sleep were included. Actigraphy watches were used to measure sleep duration and sleep efficiency objectively and using daily diaries subjective sleep duration and energy levels were assessed on the same days (Supplementary Methods).

Anxiety and depressive symptoms

The Revised Child Anxiety and Depression Scale (RCADS) was used to assess the participants' feelings of anxiety and depression. Participants rated 47 questions on a Likert scale of 0–3. The answers were summed to create two subscales: total anxiety (sum of the

anxiety subscales) and total depression (42). Up to two missing items were allowed per subscale. Missing items were replaced by prorating the other items within the subscale.

MRI acquisition

MRI scans for the three waves were acquired on a Philips Ingenia 3.0 Tesla MR scanner. A standard whole-head coil was used. First, functional scans were obtained, followed by a high-resolution 3D T1-FFE scan (TR=9.72 ms, TE=4.6 ms, flip angle=8°, 140 slices, voxel size=0.875x0.875x0.875 mm, FOV=224×178.5×168 mm). Participants watched a film while they were in the MRI.

MRI processing

The MRI data was processed in the longitudinal stream in FreeSurfer 6.0 (https://surfer.nmr.mgh.harvard.edu/) (43,44). Parcellation of the cortex was based on the Desikan-Killiany atlas and Fischl atlas for subcortical regions (45,46). Regions of interest were selected based on prior literature on emotion regulation. Cortical thickness and surface area of the following regions were included: dlPFC, vlPFC, ACC, and OFC, as well as volume of the following regions: ventral striatum and amygdala. The average of the left and right hemisphere was used.

The regions-of-interest were constructed by combining the following regions (8,47–49): dlPFC: superior frontal, rostral middle frontal cortex and caudle middle frontal, vlPFC: pars opercularis, pars triangularis and pars orbitalis, ACC: rostral ACC and caudal ACC, OFC: lateral orbitofrontal cortex and middle orbitofrontal cortex and ventral striatum: caudate, putamen and nucleus accumbens. This resulted in a total of 6 ROIs, which consisted of 4 cortical thickness, 4 cortical surface area, and 2 subcortical volume measures. The quality of the T1 images was assessed using Qoala-T (50). Parts of these data were previously published (51,52).

Statistical analyses

Generalized additive mixed models (GAMMS) were used to study the development of mood variability and its association with sleep and brain structure. Generalized additive mixed models (GAMMs) are semi-parametric models that use penalized smoothing splines (53) (Supplementary Methods).

First, an exploratory analysis was performed on the subscales (tension, anger, depression, fatigue, and vigor) to test for developmental patterns. Based on these findings, we created separate models for negative mood variability and average negative mood score, based on the first four subscales (see Supplementary Material). The main analyses (analyses 1 to 4 described below) were therefore done using these negative mood measures, as well as the general mood variability and average mood.

Data from the first three timepoints were used in the first four analyses, to study:

1) the development of mood variability (by testing the effect of age by sex on mood variability).

$$Mood\ variability_{ij} = \beta_0 + s1\left(Age_{ij}\right)Sex_i + u_i + error_{ij}$$

2) the development of sleep (by testing the effect of age by sex on sleep (separately for sleep duration, sleep efficiency, subjective sleep duration, energy level)).

$$Sleep_{ij} = \beta_0 + s1\left(Age_{ij}\right)Sex_i + u_i + error_{ij}$$

3) the association between mood variability and sleep (separately for each sleep measure, scaled by age) over time corrected for age and sex:

$$Mood\ variability_{ij} = \beta_0 + s1\left(zSleep_{ij}\right) + s2\left(Age_{ij}\right)Sex_i + s3(zAverage\ Mood_{ij}) + u_i + error_{ij}$$

4) the association between mood variability and brain structure (scaled by age) over time corrected for age and sex.

$$Mood\ variability_{ij} = \beta_0 + s1\left(zROI_{ij}\right) + s2\left(Age_{ij}\right)Sex_i + s3\left(zAverageMood_{ij}\right) + u_i + error_{ij}$$

The same analyses were repeated for average mood. In each analysis, i = subject, j = time point and ui = random effect per subject. The analyses for mood variability and average mood were FDR corrected per question to correct for multiple testing. For analysis 4 it was corrected per brain measure (volume, surface area and thickness).

A thin plate spline was used to fit the data. Model fit, to choose the best *k*, was assessed using the BIC. *k* represents the basis dimensions, the maximum degrees of freedom for a smoothing spline. The 'mgcv' package in R was used for the analyses (54). Participants were added as a random effect and restricted maximum likelihood (REML) was used for smoothness selection. The interaction effect of age and sex was included to test whether the development of mood variability differed between sexes. In analyses 3 and 4, sleep and brain structure were transformed into z-scores by scaling them to age. Participants with a large ROI or longer sleep duration at a certain age compared to their same-age peers had a higher z-score.

Several control analyses were conducted. The analyses for mood variability were corrected for average mood (2,10). In addition, for analyses 2 and 3, the analyses were repeated with an additional covariate to correct for whether the participant was on holiday or at school/work. The analyses with objective sleep measurements were also repeated separately for weekend and weekdays.

To study the prediction of anxiety and depressive symptoms based on the development of mood variability, a linear regression was used to predict average symptoms at follow-up

based on the average level of mood variability (55,56). The analysis was corrected for the baseline level of anxiety and depressive symptoms by adding the mean level of anxiety or depressive symptoms at the first three waves as a covariate.

Results

Data from 171 participants over 5 time points were included, leading to a total of 661 observations (Table 1, Supplementary Table S1).

Table 1. Overview participants over 5 time points. Mean (SD) are being displayed.

	Time point 1 (N=161)	**Time point 2 (N=168)**	**Time point 3 (N=175)**	**Time point 4 (N=117)**	**Time point 5 (N=40)**
Sex N (%)					
Male	71 (44.1%)	78 (46.4%)	81 (46.3%)	55 (47.0%)	67 (47.9%)
Female	83 (51.6%)	81 (48.2%)	88 (50.3%)	62 (53.0%)	73 (52.1%)
Age	15.3 (2.92)	16.0 (3.21)	17.5 (3.46)	18.9 (3.39)	20.0 (3.72)
Education N (%)					
Primary school	30 (19.1%)	24 (14.3%)	7 (4.0%)		
High school	85 (52.8%)	87 (51.8%)	80 (45.7%)		
Higher education	39 (24.2%)	48 (28.6%)	83 (47.4%)		
Country of birth N (%)					
Netherlands	147 (91.3%)	152 (90.5%)	161 (92.0%)		
Turkey	0 (0%)	0 (0%)	1 (0.6%)		
Netherlands Antilles	1 (0.6%)	1 (0.6%)	1 (0.6%)		
Other	6 (3.7%)	6 (3.6%)	7 (4.0%)		
Mood variability (negative)	8.41 (5.72)	8.93 (6.29)	9.39 (6.02)		
Average mood (negative)	10.8 (10.7)	12.2 (11.3)	13.5 (10.7)		
Mood variability	11.7 (6.26)	12.2 (7.16)	12.5 (6.54)		
Average mood	3.09 (12.3)	4.08 (12.7)	6.04 (12.7)		
Subjective sleep duration	9.26 (1.08)	9.16 (0.94)	9.02 (0.97)		
Sleep Energy	2.89 (0.54)	2.83 (0.53)	2.70 (0.58)		
Objective sleep duration	7.73 (0.86)	7.58 (1.22)	7.35 (1.03)		
Sleep Efficiency (%)	93.0 (5.63)	91.8 (8.13)	92.1 (7.61)		
Total anxiety	19.5 (11.8)	15.6 (9.99)	23.1 (14.4)	26.6 (13.8)	28.4 (17.2)
Total depressive symptoms	5.72 (3.74)	5.65 (3.95)	7.10 (4.53)	7.49 (4.65)	9.63 (5.96)

Development of mood

The development of mood based on all 5 subscales of the POMS has been reported in the supplementary materials. The development of mood was further examined using only the four negative subscales of the POMS (tension, depression, anger, and fatigue), as it was found that the positive subscale (vigor) was not associated with age-related changes.

First, we tested for sex differences in average mood and mood variability. This analysis showed that females had higher negative mood variability and negative average mood than males (p=0.02, p=0.02), therefore in all subsequent analyses the age by sex interaction was examined. The best-fit model of the age by sex interaction on negative mood variability and negative average mood can be observed in Figure 2 (BIC: 2028.89, p<0.001, k=4; BIC: 2512.30, p=0.002). Negative mood variability showed a peak during mid-adolescence for females, showing a rapid increase and a modest decrease across adolescence (BIC: 1066.82, p=0.02, k=4; Figure 2 and Supplementary Figure S6). For males, negative mood variability increased throughout adolescence (BIC: 705.65, p=0.03, k=4). Individual trajectories of mood variability are displayed in Supplemental Figure S7. Negative average mood increased during early adolescence, also showed a peak during mid-adolescence and a decline during late adolescence for females but did not show an association with age in males (BIC: 1319.27, p<0.001, k=4; BIC: 1018.82, p=0.66, k=4).

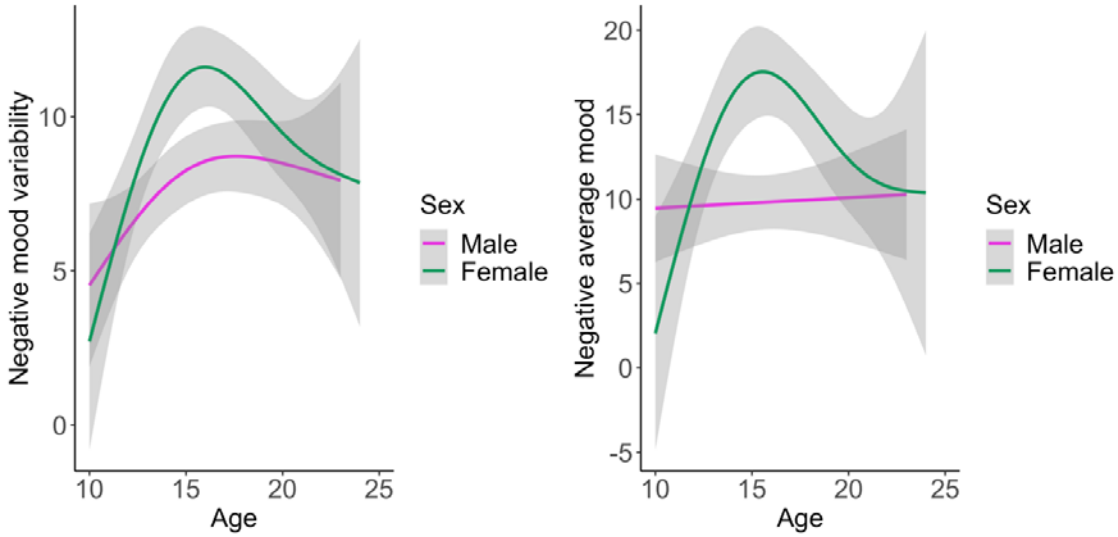

Figure 2. Best-fit model of negative average mood and negative mood variability development by sex. Left: average negative mood based in four POMS subscales (depression, anger, tension, and fatigue), Right: negative mood variability, showing fluctuations in mood across 5 days.

Development of sleep

Next, the development of sleep: objective sleep duration, objective sleep efficiency, subjective sleep duration and subjective energy level, was investigated. The best-fit model for the age by sex interaction effects are displayed in Table 2, Figure 3, and Supplementary Figure S8.

There was a significant age by sex interaction for objective and subjective sleep duration. Objective and subjective sleep duration decreased for both males and females, but in males there was a subsequent flattening in late adolescence. Objective sleep efficiency did not show an age by sex interaction. However, subjective energy level decreased throughout adolescence, for both males and females.

Table 2. Best-fit model of sleep development.

Sleep measure	Age * sex interaction (p_{FDR})	BIC (k)	Association with negative	BIC (k)	Association with negative	BIC (k)

			average mood (p_{FDR})		**mood variability (p_{FDR})**	
Sleep duration (objective)	<0.001	1967.91 (3)	0.50	1122.98 (3)	0.91	898.89 (3)
Sleep efficiency	0.134	1269.87 (3)	0.17	1121.57 (3)	0.94	862.20 (3)
Sleep duration (subjective)	<0.001	877.30 (3)	0.68	2292.06 (3)	0.94	1761.15 (3)
Energy level	0.003	692.04 (3)	<0.001	2420.67 (3)	0.94	1844.75 (3)

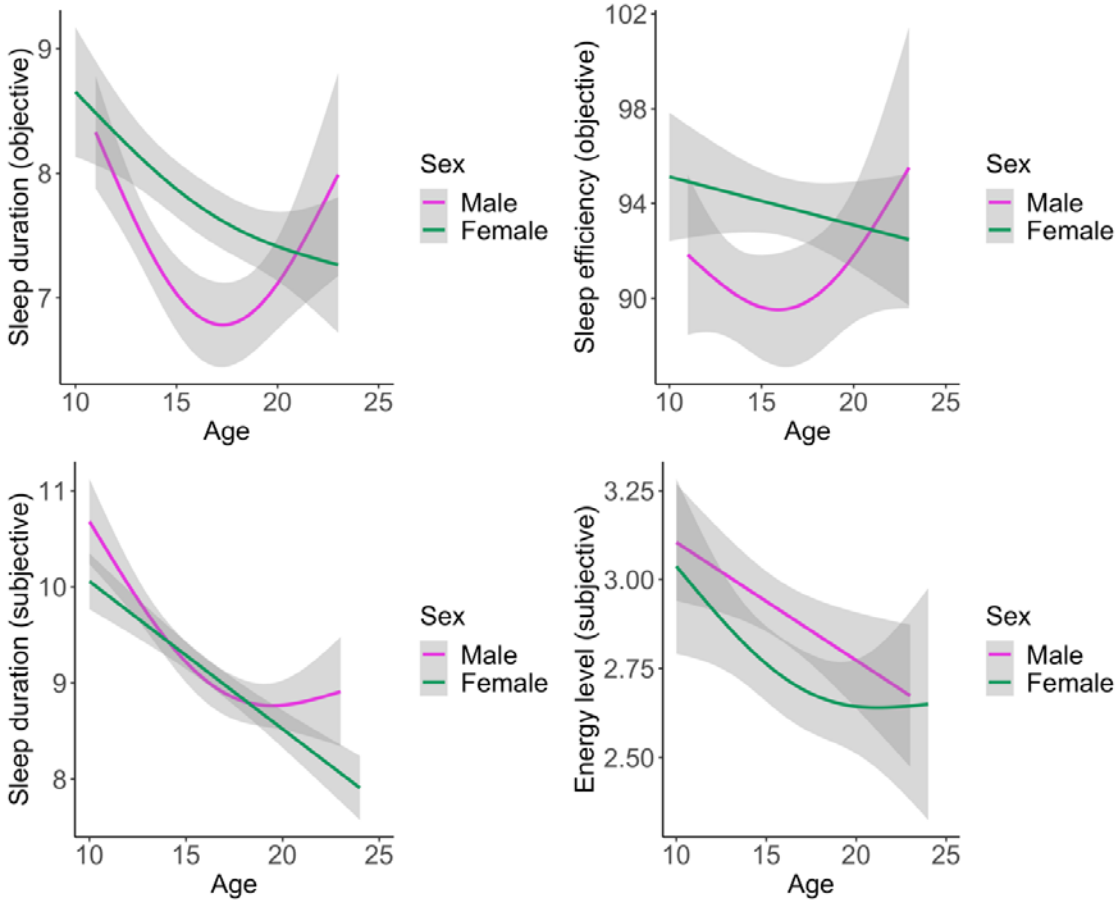

Figure 3. Best-fit model of sleep development by sex. Upper left: objective sleep duration, upper right: objective sleep efficiency, lower left: subjective sleep duration, lower right: energy level.

Association between sleep and mood throughout adolescence

To study the association between sleep measures and mood, sleep measures were scaled to age. Sleep duration and sleep efficiency were not associated with negative mood variability or average mood. The best-fit models showed that energy level and negative mood variability (BIC: 2483.68, p_{FDR}<0.001, *k*=3) showed an association, however, this association did not survive correction for average negative mood (Table 2). A second association was also observed between energy level and average negative mood (BIC: 2149.39, p_{FDR}=0.009, *k*=3). People with lower level of energy compared to their age-matched peers showed higher negative mood throughout development (Figure 4).

Subsequent control analyses confirmed that no effect of holidays was found, and the results did not change when the analyses were repeated separately for weekends and weekdays.

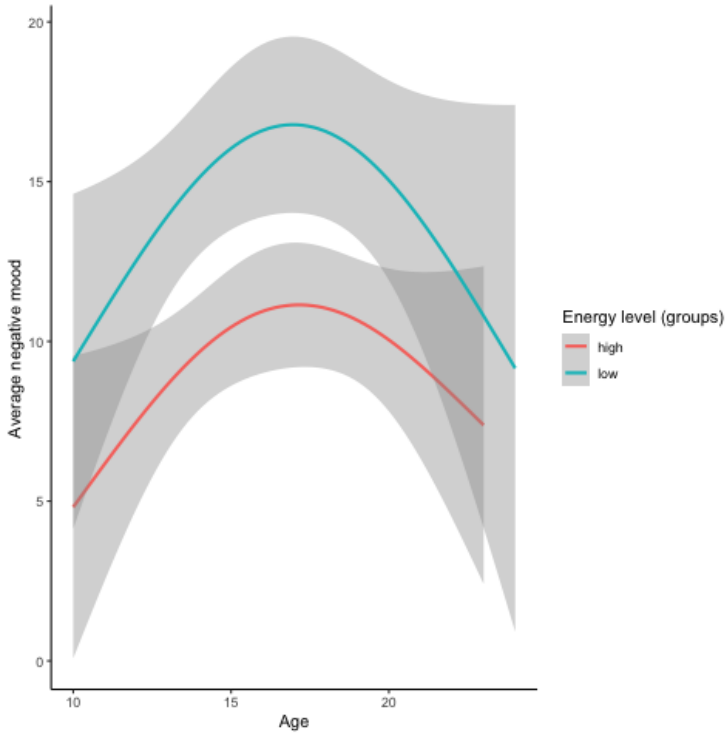

Figure 4. Mood variability development in groups with high or low levels of energy (subjective measure of sleep). Subjects are divided into groups only to visualise the effect.

Association between brain structure and mood throughout adolescence

Next, the association between brain structure and mood was examined. Consistent with prior studies (51,52), cortical thickness for all regions decreased during adolescent development (for example: dlPFC in Figure 5A).

Negative mood variability showed an association with dlPFC thickness (BIC: 1792.19, p_{FDR}=0.04, *k*=3). Those participants with higher dlPFC thickness compared to same-age peers showed higher levels of negative mood variability in early and mid-adolescence (Figure 5B). Negative average mood was not associated with brain structure. None of the other brain regions showed associations with negative mood variability or average mood.

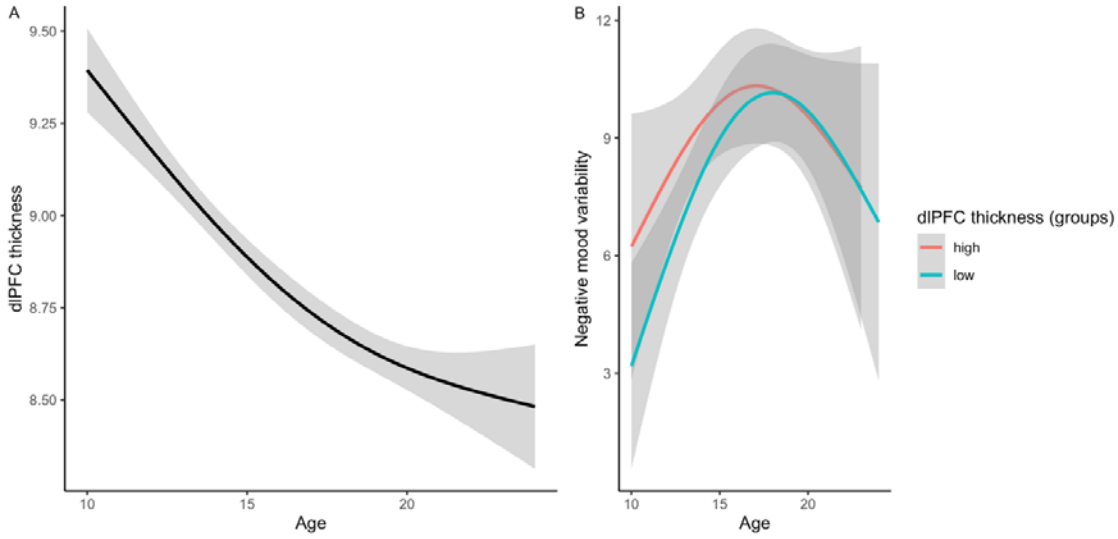

Figure 5. Development of dlPFC thickness (A) and mood variability development in groups with high or low dlPFC (B). Subjects are divided into groups only to visualise the effect.

Association between mood variability and future anxiety and depressive symptomatology

The final aim was to investigate the association between mood variability and mental health, specifically whether mood variability preceded anxiety and depressive symptoms. It was found that mean mood variability at wave 1 to 3 preceded higher anxiety and depressive symptoms at wave 4 and 5 (depression: B=0.22, p=0.004; anxiety: B=1.02, p<0.001).

Finally, we tested whether this effect remained after correcting for average anxiety and depressive symptoms over wave 1 to 3, but it did not survive this correction (depression: B=-0.04, p=0.61; anxiety: B=0.31, p=0.14).

Discussion

The present study used a longitudinal design to examine the development of day-to-day mood variability during adolescent development. As predicted, negative mood variability peaked in mid-adolescence but only for females, whereas males showed linear increases in negative mood variability with age and lower levels of mood variability overall, consistent with prior research (2,11). Objective and subjective sleep duration dropped in mid-adolescence and males but not females showed a subsequent flattening in sleep duration. Sleep duration was not associated with mood variability, but subjective energy levels were negatively associated with average mood (see also (14)). Lastly, consistent with prior research dorsolateral prefrontal cortex thickness declined with age ((28)), and negative mood variability showed an association with the development of thickness in the dorsolateral prefrontal cortex.

Our first aim was to provide a longitudinal assessment of mood variability in adolescence. Due to the developmental patterns of mood, we specifically focused on negative mood (9). The timing of the peak seen in mood variability was slightly later compared to previous research where a decrease was seen after age 13-years (2). Additionally, this peak overlapped with the peak in average negative mood seen in females, showing that females not only showed larger mood swings but also an on average more negative mood in mid-adolescence. The development of mood variability was especially of interest because of its association with depression and anxiety, and onset of these psychiatric disorders peaks during adolescence (57). Larger mood variability preceded anxiety and depressive symptoms over the following two years, suggesting that mood variability may be a susceptibility marker for internalizing disorders, which are higher in females than males (58). However, while mood swings are associated with future negative mood, this is mostly explained by its association with current negative mood.

The findings of a decrease in sleep duration (objective as well as subjective) fit well with prior research showing that there are sex differences in sleep development, and that overall, a decrease in sleep duration is observed (14,22). For males, a larger dip was observed for objective sleep duration, followed by a flattening of the duration in older adolescents. Contrary to our predictions, neither objective nor subjective sleep duration were related to mood variability. Notably, developmental patterns associated with sex were inverted for males and females, with females showing a larger peak in mood variability and males showing a larger drop in objective sleep duration. These sex differences are currently not well understood, but some of these effects may be related to social experiences and expectations. For example, males show higher levels of online gaming than females during adolescence (52), possibly resulting in less objective sleeping time in mid-adolescence. In addition, it might be speculated that males might not report their sleep as accurately as females, which is reflected in the discrepancy between the subjective and objective sleep duration.

Despite the absence of a relation between mood variability and sleep, lower subjective energy levels were associated with lower average mood. Even though energy levels decreased during adolescence, the relationship between average mood and energy levels did not change during development, suggesting that decreasing energy levels during adolescence co-occur with generally increasing negative mood. This potentially points to a causal relationship, therefore, increasing sleep duration by for example adjusting school times could be beneficial for mood. These questions should be studies in future research using sleep intervention designs, as the current study, despite being longitudinal, is correlational and cannot draw causal conclusions.

One alternative explanation should be considered; subjective sleep has often been more strongly associated with depressed and anxious mood than objective sleep, which might be due to low mood being associated with the misperception of sleep, meaning that when people experience low mood, they often perceive their sleep as worse (59,60). However, it

could also be that the association is explained by physical activities or other circumstances that could affect energy level, but not sleep duration.

Brain structure and mood variability

One of the mechanisms underlying the increased levels of mood variability in mid-adolescence might be emotion regulation (13). Even though we did not measure emotion regulation strategies directly, we examined whether mood variability was associated with structural brain development of regions involved in emotion regulation (62). A thicker dlPFC was associated with higher levels of negative mood variability in early and mid-adolescence, and a similar pattern was observed for mood variability and vlPFC thickness at trend level. Since adolescence is a time of cortical thinning, this could be interpreted as higher mood variability being associated with a delayed cortical maturation process. While this is the first study to show an association with mood variability, an earlier study, consistent with the current findings, showed that the development of dlPFC and vlPFC thickness was associated with the use of emotion regulation strategies, with greater cortical thinning associated with higher levels of cognitive reappraisal later in life (61). Taken together, dlPFC thickness might be a biological marker that explains why some adolescents are more affected by mood swings than others.

Interestingly, no association between mood variability and limbic regions, the amygdala and ventral striatum, was found. This is however in line with work on the association between emotion regulation and subcortical development, also not reporting a direct association (63). One possible explanation could be that subcortical regions do not show large intra-individual brain volume differences during adolescence and therefore no relation with developmental processes of mood variability (47,64). Differences between surface area and thickness might explain why only an association between mood variability and thickness was found. For example, thickness is more susceptible to environmental influences whereas surface area is more strongly impacted by genetic factors (65). In future research, examining the

maturational coupling or functional activity or connectivity might provide more insight into the role of the subcortical regions in mood variability (66,67).

A few limitations of the current study should be noted. First, the subjective sleep data was subject to recall bias, and the objective data to the adolescents wearing the actigraphy watch correctly. However, the strength of assessing both subjective as well as objective reports of sleep was that the relation of these two aspects of sleep to mood variability could be compared (59). It should be noted that we measured day-to-day variability of mood, whereas within-day variability might show a different pattern and different associations with biological mechanisms. Thus, we might not have picked up on the relation between mood variability and for example sleep because of the sampling rate of mood variability (68,69). Future studies could examine a higher temporal resolution to measure mood variability by applying a method such as ecological momentary assessment (EMA) (70). Finally, the relation to pubertal hormone timing and development was not assessed. Since there were sex differences in the developmental trajectory of mood variability, and mood variability increased throughout puberty in females, hormone levels might play a role. Moreover, hormones have previously been related to brain development, and pubertal timing can affect the risk for developing psychopathology in adolescence (64,71).

In conclusion, this study confirmed the hypothesis of increased levels of mood variability in adolescence with a peak in mid-adolescence, especially in females (2,11), and that higher levels of mood variability are associated with future symptoms of anxiety and depression (36). We found moderate evidence for a relation between average mood and subjective sleep energy levels, and small evidence for a relation between mood variability and structural brain development. Together, these findings suggest that mood variability, sleep duration changes, and neural development are co-occurring in adolescence. Yet, the study also highlighted sex differences which may be associated with different societal expectations and experiences. This study provides initial and important insight into the normative

developmental patterns and biological aspects associated with risk factors for future depressive and anxiety symptoms.

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Disclosures

The authors declare no conflicts of interests

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