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Is moderate depression associated with sleep stage architecture in adolescence? Testing the stage type associations using network and transition probability approaches

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Abstract

Background Depression even at the subclinical level is often accompanied by sleep disturbances, but little is known about the dynamics of the sleep stages in relation to depressive symptoms. We examined whether the amount, associations, and transition probabilities of various sleep stages were associated with depressive symptoms in a community sample of adolescents.

Methods The participants (N =172, 59% girls, mean age 16.9 years) underwent overnight polysomnography and provided data on depressive symptoms (Beck Depression Inventory II). The association between depression status and total duration of each stage type was analyzed using ANOVA and survival analyses. The associations between the number of different sleep stage types were analyzed using graphical Gaussian models, mixed graphical models, and relative importance networks. A Markov chain algorithm was used to estimate the transition probabilities between each state and these probabilities were further compared between depression status groups.

Results The associations between N1 and N3 were significantly stronger in both directions of the association (*p*-values for interactions .012 and .006) in those with more depressive symptoms. Similarly, a stronger association was observed from N1 to wake stage in those with more depressive symptoms (*p*-value for interaction .002). In those with more depressive symptoms, it was more likely to transition from N2 to N3 and from REM to N2 compared to others.

Conclusions These findings indicate that changes in sleep architecture are not limited to clinical depression and that the transitional dynamics of sleep stages are an important marker of subclinical depression.

Key words: Adolescence, epidemiology, centrality, survival

Introduction

Depression is the most common form of psychiatric pathology and affects approximately 350 million people (WHO, 2014) and is one the most common reasons for disability-adjusted life years worldwide (DALYs & Collaborators, 2018). Depression leads to several unfavorable medical and social consequences and decreases quality of life and adaptive ability (Kendler, Hettema, Butera, Gardner, & Prescott, 2003; Mathers & Loncar, 2006). Depressive symptoms include depressed mood, loss of pleasure, and loss of interest in most daily activities (DSM-5). Depression is also associated with sleep disturbances (Gebara, Kasckow, et al., 2018; Staner, 2010). Disturbed sleep is one of the diagnostic criteria for depression in multiple screening instruments. Compared with those without depression, individuals with depression have abnormal sleep characteristics on objective and subjective assessments, including delayed sleep onset, decreased sleep efficiency, more frequent arousals, and increased or decreased total sleeping time (Wiebe, Cassoff, & Gruber, 2012). Furthermore, there is evidence that insomnia-specific interventions, such as cognitive behavioral therapy for insomnia, may also lead to improvements in depression (Gebara, Siripong, et al., 2018).

Sleep disturbances in depressed patients have been studied using polysomnography (PSG). Researchers have already for some time focused on changes in sleep architecture as a potential neurophysiological substrate of depression (Kupfer, 1976). A large body of evidence suggests that adults with depression show clear reductions in slow wave sleep (SWS) and increased daytime dysfunction (Armitage, 2007; Baglioni et al., 2013; Wiebe et al., 2012). Young adults with clinical depression also have lower levels of slow wave activity (SWA) compared with healthy controls, particularly in the beginning of the night (Cheng, Goldschmied, Deldin, Hoffmann, &

Armitage, 2015). There is also evidence that children and adolescents with internalizing disorders (Holm et al., 2009) and depressed adolescents (Rao et al., 2002) have significant reductions in SWS.

Another finding related to clinical depression is altered rapid eye movement (REM) sleep. Adolescents and adults with internalizing disorders, including depression, show decreased REM latency (the time between sleep onset and first REM period), increased REM length and density(Riemann, Berger, & Voderholzer, 2001), and more recently, higher REM sleep discontinuity (Pesonen et al., 2018). A higher number of REM arousals is associated with insomnia, depression, and anxiety(Baglioni et al., 2016) and is suggested to hinder overnight resolution of emotional distress (Wassing et al., 2016) in adults. REM sleep instability may promote chronic hyperarousal and dysfunction in emotional neural networks, increasing the risk for internalizing disorders.

In addition to analyzing differences in various individual sleep stages using conventional sleep parameters, some recent studies have focused on the overall dynamics of sleep stage architecture. For instance, Wei and others (Wei et al., 2017) used Markov chain analyses to demonstrate that sleep stage dynamics derived from whole-night PSG characterizes insomnia better and independently of any conventional sleep parameter. Yetton and coworkers (Yetton, McDevitt, Cellini, Shelton, & Mednick, 2018) further developed the analytic method by examining the static (e.g. minutes in stage, sleep efficiency) and dynamic measures of sleep architecture (e.g. transition probabilities and stage duration distributions) using a large dataset of 3202 nights from a non-clinical population. They observed that age, gender, time of day, and sleep time were associated with dynamic sleep architecture. Older

participants and men had shorter bouts (more fragmentation) of Stage N2 and N3 (SWS) and transitioned less frequently to these stages.

In the current study, we examined whether sleep dynamics and architecture (defined as the cyclical pattern of sleep as it shifts between the different sleep stages, including non-rapid eye movement (NREM, stages N1, N2 and N3) and rapid eye movement sleep), the amount of various sleep stages (specifically SWS and REM), as well as interrelations between different sleep stages are associated with depressive symptoms at a subclinical level in an adolescent population. We focused on investigating the associations and transition probabilities between the four sleep stages and studying the potential differences in those probabilities according to the level of depressive symptoms in adolescents. We hypothesized to find more disrupted sleep, ie. more sleep stage transitions in depressed vs. non-depressed individuals. However, in the absence of prior research with this methodological approach, the questions related to the specific dynamics of these transitions (from which to which stage) remain explorative.

Methods

Sample

Participants were derived from a community‐based cohort including 1049 healthy singletons born between March and November 1998 in Helsinki, Finland (Strandberg, Jarvenpaa, Vanhanen, & McKeigue, 2001). In years 2014–15, all the cohort members who participated in the previous follow-up at age 12 (Pesonen et al., 2014), and who lived within the 30 km radius from Helsinki (N = 279, 77.1% of the participants of the previous follow-up) were invited to a late adolescence follow-up (Kuula, Pesonen, Heinonen, et al., 2018; Merikanto et al., 2018). Of them, 197 (70.6%) participated,

and the analytic sample of the current study comprised 173 (mean age 16.9 years, SD = 0.3; 59% girls) adolescents who had complete records of an overnight sleep EEG measurement and depressive symptoms.

There were no reported diagnoses of schizophrenia or psychotic symptoms. The participants included in this study (n = 173) were more often girls than those in the original cohort (n = 873) (p-value for difference .004). There were no differences when compared with the original cohorts'(Strandberg et al., 2001) age, mother's body mass index, mother's age at time of birth, gestational age, maternal alcohol consumption, length at birth, or birthweight (all p-values were not significant).

The Ethics Committees of the City of Helsinki Health Department and Children's Hospital in Helsinki University Central Hospital approved the study protocols. Informed written child and parent consents were obtained in early adolescence and only adolescent consent in late adolescence.

Polysomnography

Participants underwent overnight ambulatory PSG arranged according to the participants' schedules. Each participant completed a PSG measurement in their own homes, and in their own beds and they were asked to abstain from any stimulants, such as caffeine products after 4 p.m. in the measurement night. According to study protocol, actigraphy measurements were initiated a week before the scheduled PSG night in order to investigate potential differences between the measurement night and other nights (see (Kuula, Pesonen, Merikanto, et al., 2018) for detailed description of the actigraphy measurements). All received monetary compensation (€50) for their effort. The measurements were performed throughout the entire school year excluding the summer holiday. Ninety percent of all PSG recordings were completed on school

nights. All recordings were performed using SOMNOscreen plus (SOMNOmedics GmbH, Randersacker, Germany). A trained research nurse attached gold cup electrodes at six electroencephalogram (EEG) locations (frontal [F] hemispheres, F3, F4; central [C] hemispheres, C3, C4; occipital [O] hemispheres, O1, O2) and at two locations for the mastoids (A1, A2). Overall frontal and central measurements were calculated as the means from both hemispheres. The electro-oculogram (EOG) and the electromyogram (EMG) were performed using disposable adhesive electrodes (Ambu Neuroline 715, Ambu A/S, Ballerup, Denmark), with two locations for the EOG and three locations for the EMG. In addition, an online reference Cz and a ground electrode in the middle of forehead were used. The sampling rate was 256 Hz (the hardware filters for SOMNOscreen plus are 0.2–35 Hz).

Three experienced researchers scored the PSG data manually using the DOMINO program (v2.7; SOMNOmedics GmbH, Randersacker, Germany) in 30-s epochs and categorized into N1, N2, N3, and REM according to AASM guidelines (The AASM Manual for the Scoring of Sleep and Associated Events). The relative amount of each stage was calculated based on total sleep time.

Depressive symptoms

Depressive symptoms were measured using the 21-item Beck's Depression Inventory II (BDI-II) (Beck, Steer, & Garbin, 1988) on the same night as the PSG measurement. In the BDI-II each item is rated on a 4-point scale (0–3) in terms of symptom intensity during the last 2 weeks, yielding a total score ranging from 0 to 63. In this study, internal consistency (Cronbach's α) was 0.92. To create a binary variable of depression risk and to correct for a potential gender and cultural bias, we

used ≥ 90th percentile score of BDI-II defined separately for boys and girls as a cutoff for moderate depression (Whisman & Richardson, 2015).

Statistical analyses

Statistical analyses were conducted in the following order:
First, we calculated the total number of each 30-s epoch for each participant and tested the association between depression status and total duration of each epoch type using ANOVA. Shapiro-Wilk -test results suggested that all sleep stage variables (W - range from .51 to .98, all p-values <0.001) were normally distributed except N1 (p-value = 0.10). No sign of homoscedasticity in the association between sleep stages and moderate depression status (p-value range from 1.00 to 0.10) based on Breusch-Pagan test were found.

Second, we calculated the number and mean duration of each epoch type before each transition and tested the potential differences between depression status groups using ANOVA. We also investigated overall sleep versus wake bouts as consecutive epochs scored as stages N1, N2, N3, or REM and wake bouts as consecutive epochs scored as being at wake stage. We analyzed bout lengths of all individual sleep stages (staying in the same stage before the next, any other stage). For all five bout categories and being asleep versus wakefulness, survival analysis was used to estimate the probability for each observed duration in both depression status groups. We repeated the bout duration distributions survival analyses using the recurrent event multilevel (mixed effects) survival analyses, taking into account the fact that multiple bouts were observed from each participant for both depression status groups. These analyses were performed to compare group-level sleep bout duration distributions with similar survival-analytical techniques as in previous studies on sleep–wake transition patterns (Lim et al., 2011).

Third, we analyzed the independent associations (regularized partial correlations) between different epoch types in both depression status groups separately using a graphical Gaussian model (GGM) with the graphical least absolute shrinkage and selection operator (gLasso) algorithm. The gLasso eliminates spurious associations (edges) attributable to the influence of other nodes in the network and shrinks trivially small associations to zero (removes "false positive" edges) (Witten, Friedman, & Simon, 2011). In the final network, edges represent conditional independence relationships between nodes controlling for the effects of all other nodes (Epskamp, Borsboom, & Fried, 2017). We set the value of the hyper-parameter gamma (γ) to 0.2 to minimize the probability of false-positive edges (Epskamp et al., 2017). The centrality of the individual stages within networks was calculated using the node strength centrality (number of connections weighted by the absolute strength of the connections). GGM illustrates the associations between various sleep bouts and whether these associations were different between depression status groups.

Fourth, we repeated the network analyses using relative importance regressions to detect the potential directions and direction differences between depression status groups. Fifth, we estimated using a Markov algorithm the transition probabilities between each state and these probabilities were further compared between depression status groups. A Markov algorithm defines a discrete sequence of states, this time sleep bouts, and thus models the probability of shifting from a specific bout to any other bouts to model the most probable sequence of various sleep bouts. Thus, we wanted specifically analyze differences in sequential sleep bout dynamics between those with minor depression and others.

We used the R package "qgraph" (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012) to plot and illustrate the final networks and the transition

(probability) matrixes. Solid lines represent positive and dashed lines negative associations (a thicker edge denotes a larger association between two stages). When illustrating transition probabilities, the solid lines represent similar and dashed significantly different transition probabilities between the depression status groups. Data analyses were performed with R (3.5.1) and a complete list of packages used are reported in the Supplement.

Results

Initial and sleep bout analyses

The sample consisted of 12% mild (≥14 points) and 7% moderate (≥20 points) depression scores. Of the participants, 21 were classified as having moderate depression. Table 1 presents descriptive characteristics of the participants according to depression status. Those with moderate depression smoked more often ($p < .001$) and reported lower physical activity ($p = 0.049$) than others. Most of the frequencies time asleep were spent in the N2 and N3 stages among all participants (Figure 1). There were only small differences in the total times in each stage between depression status groups; none of the differences were statistically significant (p-value range from .28 to .87). There were no significant differences in the total duration of any sleep stage before the next stage between those with moderate depression compared to those without depression. Figure 2 shows the estimated bout survival functions for sleep, wakefulness, and individual sleep stages in those with moderate depression and others with associated 95% confidence intervals. All sleep bout survival curves took convex shapes. The wake bout survival curve took a concave shape. The group differences were all non-significant (p-value range from .21 to .95). Mixed survival analyses also revealed that none of the between-group differences were significant. The largest differences between the groups were in the N2 and N3 stages. Regarding

actigraphy measurements of sleep duration or quality, the PSG night did not differ from other nights significantly (data not shown).

Sleep stage network analyses

GGM analyses suggested some differences in the network structure of the associations of the number of times spent in each sleep stage between those with moderate depression and those without (Figure 3). The associations between N1 and N3 were significantly stronger in both directions of the association (interaction *p*-values .012 and .006) in those with moderate depression. Similarly, a stronger association was found from N1 to wake stage in those with moderate depression (*p*-value for interaction .002). These associations can also be detected in Figure 4, which presents the relative importance networks in those with moderate depression and others. N1 was the most central in the network among those with moderate depression, whereas N2 had this position among others (Supplement Figure 1).

Markov chain (transition probabilities) analyses within sleep stages

The transition probabilities between individual sleep stages in all participants are reported in Supplement Figure 2. Most transitions are measured naturally within all stages and also within non-rapid eye movement (NREM) stages (within N1, N2 and N3). The sleep stage transition probabilities in participants with moderate depression and those without depression are presented in Figure 5 (significantly different transitions are marked with dashed lines). In participants with moderate depression, it was more probable to transit from N2 to N3 and from REM to N2 compared to those without depression (all tests presented in Supplement Figure 3).

DISCUSSION

Depressive symptoms and sleep characteristics are closely associated (Pesonen et al., 2018; Riemann et al., 2001). However, as most studies have focused on quantitative mean indicators of different sleep stages in relation to depression status, there is a lack of understanding on whether the dynamic organization of sleep stages (i.e., the transition probability between the stages) is driven by depressive symptoms at subclinical level. We report a series of findings that advance the knowledge of the potential association of moderate levels of depressive symptoms and sleep stage dynamics. The dynamic flow of sleep stage transitions is of interest in trying to understand how exactly the sleep is organized in a temporal mode in normal versus depressed individuals.

The physiology underlying the temporal regulation of the ultradian rhythm of REM/NREM alternation is not fully understood, but there is some evidence pointing to mechanisms that can be disturbed in depression. While the switch between the two brain states occurs rapidly within seconds, the recurrence of the NREM/REM cycle follows a usually a much slower ultradian rhythm, ranging from few minutes on a in rodents to hours in humans (Weber et al., 2018). The cyclicity of NREM and REM sleep depends on the signaling of GABAergic neurons in ventral periaqueductal gray (vPAG) (Weber et al., 2018), modulated via projections from medial prefrontal cortex (mPFC) (Chang, Chen, Qiu, & Lu, 2014). Depression alters the activity of mPFC (Drevets, Price, & Furey, 2008), and consequently, vPAG, which is suggested to underlie REM sleep abnormalities in depressed people (Chang et al., 2014). Additionally regulating NREM/REM pattern is the antagonist interaction of cholinergic and aminergic brainstem cells (O'Malley & Datta, 2013), which is destabilized in depression (Palagini, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013).

First, we observed some differences in the association between various sleep stages when analyzed as a sleep stage network using a GGM. This method has been previously used in network analytics, such as in mental health research. In psycho(pathological) networks, the focus is on individual symptoms or psychological states and how such symptoms or states influence each other. Symptom networks have been inferred and analyzed for several psychopathological domains, including depression (Borsboom, 2017; Boschloo, Schoevers, van Borkulo, Borsboom, & Oldehinkel, 2016; Boschloo, van Borkulo, Borsboom, & Schoevers, 2016; Fried et al., 2017; van Borkulo et al., 2015). We applied this concept to analyze the dynamics of sleep stages and our results suggest that stage N1 seems to be an influential node stage, as it associates with the amount of other stages most strongly in individuals with moderate depression. As N1 is closest to wake and follows the short arousals that are not scored as true wake, this might indicate that homeostatic sleep regulation is impaired, both in terms of the sleep-wake switch and in terms of reaching deeper sleep from N1.

Second, we used Markov chain analyses to examine the transition probabilities by focusing more directly on the differences in sequential structure of the sleep stages between those with moderate depression and others. We found that transitions from REM to N2 and also from N2 to N3 were more probable in those with moderate depression compared to those without depression, which suggests more instability in sleep stages among those with moderate depression. However, we did not find differences in survival probabilities in any of the sleep stage bouts.

Our results are consistent with the previous study of Wei (2017) on sleep stage transitions in insomnia, suggesting that SWS (and especially N2) may be the central stages that warrant further attention in future studies. Studies on sleep-disordered breathing have also previously reported instability of stage N2 and REM sleep (Bianchi, Cash, Mietus, Peng, & Thomas, 2010). Thus, it is possible that the

microstructure and phasic components of stage N2 (spindles and K-complexes) may be particularly useful in examining the brain mechanisms related to moderate depression and other mental disorders.

There were no statistically significant differences in the survival functions of sleep stages between the depression status groups. The largest differences between the groups were for N2 and N3. We calculated the survival function probabilities using both means of each sleep bout and also using the recurrent event (mixed effects) survival analyses, which produced similar results. Previous studies have used various parametrizations of sleep bout survival probabilities and thus we repeated our analyses using the semiparametric coxph -function (flexsurv -package). The only difference was that the survival function in the N3 bout was shorter in those with moderate depression compared to others (estimate -0.11, p = 0024).

Strengths and limitations

The sleep measures in this study were based on state-of-the-art PSG in the participants' own homes, which increases measurement comfort and improves sleep quality. However, PSG measurements covered only one night for each participant, and repeated measurements would have provided more information and enabled more detailed analyses (Wei et al., 2017). However, actigraphy measurement comparisons between the PSG night and measurements covering a week before the PSG night suggested no differences regarding sleep duration or quality. Thus, the PSG measurement can be considered to represent a typical night's sleep. Although the specific timing of the PSG measurement in relation to the circadian phase of the participants may influence sleep staging, we were not able to define the circadian phase with sufficient specificity. Again, knowing that the measurements were conducted according to the participants' usual sleep schedules, measured with

actigraphy for one week, lowers the probability of bias. As a similar methodological limitation, although BDI-II is a widely used and reliable instrument for measuring depressive symptoms, clinical interviews may have provided more reliable cutoff points for moderate depression. Using community-based samples with no clinical population also means that our cutoff point may have included mild cases in the case group. Related to that there was an unavoidable imbalance of group sizes derived from the sample and the depressed group is of modest size compared to the rest of the sample and that may problematic as unequal sample size makes it more important that homogeneity of variance assumption would be met although we did not found this to be exceptionally problematic in group differences in the transition probabilities. Furthermore, our participants were all young and sleep stage architecture is known to be dependent on age (Tarokh, Van Reen, LeBourgeois, Seifer, & Carskadon, 2011; Yetton et al., 2018).

Conclusions

Our results suggest that there are some differences in the dynamic sleep structure between those with moderate depression and others. These differences have previously been observed in those with diagnosed insomnia disorder or severe clinical depression. Although the results obtained in our study should be replicated, they suggest that differences in these transitions may be detected already in earlier and sub-clinical stages of depression or depressive symptoms. The network model of sleep stages offers new insights to the temporal organization of sleep in humans in relation to mood. While animal models provide strong candidate mechanisms for the physiological regulation of the rapid REM/NREM alterations (Weber et al., 2018), there is need for translational research to advance the clinical implications in humans.

Disclosure Statement

Declaration of Interests: We declare that we have no conflicts of interest.
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Contributor statement: KR designed the original GLAKU study. ME and A-KP designed the original hypothesis and ME performed all the analyses in close collaboration with JL and A-KP. ME wrote the first draft of the manuscript. All the authors interpreted the results, revised the text, and approved the final draft of the report.

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The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Elovainio takes final responsibility for the decision to submit for publication.

Table 1. Sample characteristics (n= 173)

	Depression status		*p*-value
	No depression n=152	With moderate depression n=21	
Age, mean (SD)	16.92 (0.30)	16.79 (0.26)	.08
BMI, mean (SD)	22.11 (3.01)	22.77 (4.47)	.38
Gender, male n (%)	59 (38.8)	8 (38.1)	1.00
Parental education (%)			.24
Secondary or less	12 (7.9)	4 (19.0)	
Vocational	31 (20.4)	3 (14.3)	
University degree	109 (71.7)	14 (66.7)	
Birthweight(g), mean (SD)	3571.35 (441.00)	3574.05 (337.79)	.97
Sleep duration, mean (SD)	27520.98 (4449.39)	26896.05 (5775.02)	.57
Sleep latency (sec), mean, SD	1013. 3 (1301.4)	750. 5 (997.2)	.39
Sleep efficiency (%), mean (SD)	92.6 (7.5)	92.8 (7.7)	.94
Smoking (%)			<.001
No	135 (90.0)	13 (61.9)	
Yes	13 (8.7)	5 (23.8)	
Menstrual cycle (days), mean (SD)	17.4 (17.2)	18.3 (14.0)	.87
Alcohol consumption (audit sum), mean (SD)	2.30 (2.41)	2.19 (2.09)	.84
Physical activity n(%)			.049
Never or less than once a month	5 (3.4)	3 (14)	
1 to 4 times a month	20 (13.4)	5 (23.8)	
2 to 5 times a week	89 (59.7)	11 (52.4)	
Every day	35 (23.5)	2 (9.5)	
Sleep stages			
N1, mean (SD)	94.2 (47.9)	85.2 (48.9)	.42
N2, mean (SD)	358.9 (124.9)	335.2 (126.3)	.42
N3, mean (SD)	226.4 (78.0)	255.0 (76.6)	.16
REM, mean (SD)	180.8 (73.7)	176.0 (83.4)	.79
Wake, mean (SD)	40.6 (81.5)	42.0 (41.5)	.94

FIGURE LEGENDS

Figure 1. Means and SDs of the various sleep stages in those with moderate depression and others.

Figure 2. Survival curves of all sleep bouts in those with moderate depression and others.

Figure 3. Gaussian graphical network of various sleep stages in those with moderate depression and others.

Figure 4. Relative importance network of sleep stages in those with moderate depression and others.

Figure 5. Sleep stage transition probabilities (Markov chains) in those with moderate depression and others (statistically significantly different transitions in dashed lines).

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