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CHAPTER 6

Chronotype in persons with depressive or anxiety disorders

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Abstract

Background
Being a morning or evening type, or 'chronotype' might be linked to psychopathology.

Aims
We examined the association between chronotype and depressive and anxiety disorders in a large cohort study, while taking into account relevant sociodemographic, somatic health, and sleep characteristics, as well as type and severity of disorder and the use of psychotropic medication.

Method
Data from the baseline and two-year assessment from the Netherlands Study of Depression and Anxiety (NESDA) were analyzed. Included were 414 controls without lifetime psychiatric disorders, 771 subjects with remitted and 639 subjects with current depressive and/or anxiety disorders. Psychiatric diagnoses were based on DSM-IV criteria. Chronotype was measured with the Munich Chronotype Questionnaire.

Results
Current depressive and/or anxiety disorders were significantly associated with an evening chronotype (β=.10, p<.001), also after adjustment for sociodemographic, somatic health and sleep factors (β =.12, p<.001). Chronotype was not significantly different in persons with remitted depressive and/or anxiety disorders as compared to controls.

Conclusions
Current depressive and anxiety disorders are associated with an evening chronotype indicative of a phase delay in circadian chronotype. Further research is needed to determine if a later chronotype is a vulnerability factor for or a consequence of psychopathology.

Introduction

The biological clock in the brain accurately times many rhythmically occurring biological processes in our body. It is a central pacemaker which is located in the anterior hypothalamus and is responsible for regulating these 'circadian rhythms', depending both on genetic factors, such as the clock-genes, and external synchronising zeitgebers, such as daylight and social rhythms (1). Daylight directly innervates the biological clock via the retinohypothalamic tract. The biological clock is also involved in sleep duration and the time of the evening at which we go to sleep (2), also called 'morning- or evening chronotype'. Morning-types function better during daytime, whereas evening-types function better in the evening or at night (3).

Chronotype has been associated with depressive symptoms. For instance, in a large rural population (n=4051), individuals with later chronotypes showed higher self-reported depressive symptom scores (4). In another sample without psychiatric disorders (n=200), evening-types also reported significantly more depressive symptoms (5). In addition, clinically depressed outpatients (n=39), when compared to age-matched controls, had a later chronotype (6). The underlying mechanism might be genetic, as mutations in clock (or circadian) genes (7) have been related to evening-type as well as to depressive disorders (8). It is also possible that subjects with a later chronotype are forced to adjust their rhythm to socially acceptable schedules, and develop depressive symptoms when unable to adjust to these rhythms (9). Furthermore, it is known that the biological clock is partially synchronized by light (10), and later chronotypes (11) spend fewer time outdoors. In seasonal affective disorder, it has been proposed that lower light levels contribute to depressive symptomatology (1). However, since chronotype is associated with various sociodemographic and somatic health factors, these could confound a link with psychiatric disorders.

Less research is available on the relationship of chronotype with anxiety. In 264 adolescents, being an evening-type was associated with more trait anxiety (12). In 6631 adolescents, eveningness was associated with being increasingly 'emotionally upset' (13). In adult fibromyalgia patients (n=1548), no differences were found between chronotypes and levels of anxiety, although late chronotypes suffered from more depressive symptoms (14).

In sum, there is some evidence for a link between late chronotype and depressive and anxiety symptoms. Insight into this potential link is important, since a different chronotype may provide us new clues about the role of a potentially differential phase delay in circadian chronotype among persons with depressive or anxiety disorders (15). This may also provide new keys to intervention opportunities since stimulation of the

biological clock, using bright light, has been shown to improve both mood and biological rhythmicity in elderly patients with a major depressive disorder (16).

However, whether chronotype is associated with depressive and anxiety disorders remains unclear, since most studies have focused on symptom checklists rather than diagnoses based on structured clinical interviews (5, 6, 14). Moreover, sociodemographic, somatic health and sleep factors that influence chronotype, have not consistently been taken into account when associating psychopathology with chronotype. In addition, a late chronotype could be a manifestation of sleep disturbances related to the depressive- or anxiety disorders itself or the use of antidepressants. Therefore, the main aim of this study is to examine the association between depressive and anxiety disorders and chronotype, while taking into account relevant sociodemographic, somatic health and sleep factors. In addition, it will be examined whether the chronotype association is dependent on disorder type, severity and psychotropic medication use.

Methods

Sample
Data were analyzed from the baseline and two-year assessment of the Netherlands Study of Depression and Anxiety (NESDA), an on-going longitudinal cohort study investigating the course of depressive and anxiety disorders (n=2981). A detailed description of the study's rationales, methods and recruitment strategy is described elsewhere (17). The research protocol was approved by the ethical committees of participating universities and all respondents provided written informed consent. Since chronotype was measured at the two-year assessment, our sample was restricted to subjects who participated in both the baseline measurement and the two-year follow-up. Of the 2981 subjects measured at baseline, 2596 (87.1%) participated in the 2-year interview. Non-response was higher in those with younger age, lower education or depressive disorder (18). Of the 2596 individuals participating in the 2-year interview, 2322 filled out the written questionnaire regarding chronotype (our main outcome measure). Subsequently, 498 individuals had to be excluded because of missing data on chronotype measures. Our final sample size consisted of 1824 individuals. Excluded individuals (N=1157) did not differ in gender but were significantly younger (38.2 versus 42.7 years, p< .001), less educated (11.9 versus 12.9 years, p< .001) and less often suffered from a current depressive and or anxiety disorder (21.4% versus 35.0%) compared to included individuals.

Measurements

Since chronotype was assessed at the 2-year follow-up assessment, we also used information for determinants collected at the 2-year follow-up assessment.

Chronotype

Chronotype was measured with the Munich Chronotype Questionnaire (MCTQ, (19)) at the two-year measurement. The MCTQ is a self-report questionnaire, which contains 29 questions about activities, going to bed and waking up, asked separately for working days and non-working ('free') days. Chronotype was defined as the mid-point in time between falling asleep and waking up on free days (Mid Sleep on Free Days or MSF), as it is hypothesized that chronotype is measured most accurately on days when subjects' natural chronotype is not disturbed by alarm clocks or working schedules (3,1920). A higher score on the MSF implicates that this point lies farther away from twelve o'clock at night (24:00 hours). The MCTQ has been validated against the widely used Morning-Eveningness Questionnaire (MEQ), with high correlations between them (21). For our analyses, chronotype was both used as a continuous measure, and as a categorical measure ('early', 'intermediate' or 'late' chronotype). Since no clearly defined cut-off scores are mentioned in the literature and various ways of categorizing exist (14, 22), we based this categorization on quintiles of our MSF-scores. 'Early chronotype' was defined as the quintile with the lowest score, 'intermediate chronotype' consisted of the second through fourth quintile, and 'late chronotype' was defined as the quintile with the highest MSF-score.

Predictor variables:

Psychopathology

Presence of depressive and anxiety disorders was determined using the Composite International Diagnostic Interview (CIDI, version 2.1), combining data from the baseline and two-year measurement. The CIDI is a standardized diagnostic psychiatric interview which uses DSM-IV criteria to establish diagnoses (23). Included disorders were depressive disorder (DEP, including major depressive disorder and dysthymia) and anxiety disorders (ANX, including social phobia, generalized anxiety disorder, panic disorder and agoraphobia). Subjects were categorized as follows: no lifetime disorder (never a diagnosis of depressive or anxiety disorder), remitted disorder (past depressive and/or anxiety disorder, no current disorder in past six months) or current depressive and/ or anxiety disorder (6-month diagnosis).

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Other psychiatric clinical characteristics

In addition to just the presence of psychiatric disorders, specific clinical characteristics such as severity of symptoms and use of psychotropic medication may further be differentially linked to chronotype . For instance, the severity of depressive symptoms was found to be related to chronotype (24). Therefore, we decided to explore the impact of type and severity of symptoms and treatment variables on chronotype. Type of disorder was categorized as the presence of anxiety disorder only, depressive disorder only or the presence of comorbid anxiety and depressive disorder. Severity of depressive symptoms was measured at the 2-year assessment with the Inventory of Depressive Symptoms (IDS), a 30-item self-report questionnaire (25). Because of possible (partial) overlap with our main outcome variable (chronotype), we excluded the four sleep-related items from the IDS, resulting in a maximum score of 58. Severity of anxiety symptoms was measured with the Beck Anxiety Inventory (BAI, (26). Antidepressant and benzodiazepine use in the past month was classified according to the World Health Association's ATC classification (23). Antidepressants were categorized as selective serotonin reuptake inhibitors (SSRIs, ATC code NO6AB), tricyclic antidepressants (TCAs, ATC code NO6AA) and other antidepressants (ATC codes N06AF and N06AX). For benzodiazepines ATC codes NO5BA, NO5CF, NO5CD and NO3AE were used if indicated use was frequent (≥50% of the days during past month).

Covariates

Sociodemographics

Sociodemographics of interest (which are associated with both chronotype and with psychiatric disorders) included age (in years), gender (male/ female), education (in years), currently working (yes versus no, with 'currently working' being defined as a paid job with a minimum of eight hours per week), having a partner (yes versus no) and children living in the household (yes versus no).

Somatic health factors

Somatic health factors such as body mass index, smoking, alcohol intake and chronic diseases have been found to be associated with psychopathology as well as with chronotype (27, 28) and were therefore considered in our analyses. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Currently smoking was based on self-report (yes versus no). Number of alcoholic drinks per week was calculated using the Alcohol Use Disorder Identification Test (AUDIT) (29). A total count of the following self-reported chronic diseases for which persons received

treatment was used: chronic non-specific lung disease, heart condition, diabetes, stroke, arthritis, cancer, hypertension, intestinal disorders and thyroid gland disease.

Sleep

Sleep disturbances are associated with both current depressive and anxiety disorders (30) and could influence chronotype. Therefore, insomnia and sleep duration were taken into account in our analyses, which both have been linked to depressive and anxiety disorders in the current study before (31). Insomnia was measured with the Women's Health Initiative Insomnia Rating Scale (IRS, (32)). This scale consists of 5 questions concerning sleep in the past 4 weeks. It concerns trouble falling asleep, waking up during the night, early morning awakenings, trouble getting back to sleep after waking up and sleep quality. Answers are on a 4-point scale, resulting in a maximum score of 20. We also dichotomized scores at a cut-off point of 9 (9 or higher), which has been shown to indicate clinically significant insomnia (32). Sleep duration was calculated using information from the MCTQ (3). In our analyses, we used sleep duration both as a continuous measurement and categorical (short sleep duration ≤6 hours, normal sleep duration 7-9 hours and longs sleep duration ≥10 hours), as we did in an earlier publication (3,30).

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Statistical analyses

Data were analyzed using SPSS 20.0 (SPSS Inc, Chicago, Illinois). Correlations between the continuous MSF score and continuous sleep variables were calculated using Pearson's Correlation Coefficient. Baseline characteristics were compared according to chronotype categories (early, intermediate and late) using independent t-tests for continuous variables and chi-square statistics for dichotomous and categorical variables. Linear regression analyses were performed with MSF (continuous score) as the outcome variable and psychopathology (categories) as main predictor variable. First, we adjusted for sociodemographics (age, gender, education, currently working, having a partner and presence of children in the household). Secondly, we also adjusted for somatic health factors (BMI, chronic diseases, smoking, alcoholic drinks per week). Finally, we additionally adjusted for sleep variables (insomnia score and sleep duration).

Subsequently, in order to explore whether psychiatric characteristics do further discriminate associations with chronotype, we performed additional analyses in the subset of subjects with a current depressive or anxiety disorder (n=639). We ran separate linear regression analyses associating one of the following variables (type of psychiatric disorder, IDS, BAI, use of antidepressants or use of benzodiazepines) with MSF while adjusting for age and gender.

Table 1: Baseline characteristics, according to chronotype (n=1824)

	Early Chronotype (n=378)	Intermediate Chronotype (n=1096)	Late chronotype (n=350)	p-value[**]
Chronotype				
Chronotype (MSF), range (hours)	0.38-3.25	3.26-5.00	5.01-11.25	
Chronotype (MSF) (mean±SD)	2.7±0.5	4.0±0.5	5.8±0.8	<.001
Psychopathology				
Psychopathology status, %				
– no lifetime DEP or ANX	24.9	22.2	22.0	
– remitted DEP or ANX	40.7	45.2	34.9	.003
– current DEP or ANX	34.4	32.7	43.1	
Other psychiatric clinical characteristics				
Depression severity (mean IDS[*]score ±SD)	13.0±10.8	11.4±10.0	13.0±10.4	.006
Anxiety severity (mean BAI score ±SD)	8.7±9.2	7.4±7.7	8.8±8.4	.004
Use of antidepressants, %:				
– no	81.7	79.9	78.3	
– SSRI	11.1	13.1	14.0	.89
– TCA	2.1	2.5	2.3	
– Other antidepressants	5.0	4.5	5.4	
Frequent use of benzodiazepines, %	4.2	2.7	2.6	.30
Demographics				
Age (mean years ±SD)	46.7±11.4	43.3±12.4	36.8±12.6	<.001
Female gender, %	68.3	66.1	61.1	.11
Education (mean years ±SD)	11.9±3.4	13.1±3.2	13.3±3.0	<.001
Currently working, %	71.2	71.3	68.6	.62
Partner, %	73.3	61.5	40.9	<.001
Presence of children in the household, %	37.0	35.9	18.0	<.001
Somatic health factors				
BMI (mean ± SD)	26.1±4.4	25.5±4.6	24.7±4.8	<.001
Nr. of chronic diseases (mean ± SD)	1.0±1.1	0.7±1.0	0.6±0.9	<.001
Currently smoking, %	22.0	27.3	43.6	<.001
Alcoholic drinks/week (mean±SD)	1.5±2.6	1.7±2.6	2.0±3.0	.04
Sleep				
Presence of insomnia, %	51.3	33.2	25.4	<.001
Insomnia score (mean ± SD)	8.6±4.8	6.8±4.4	6.2±4.2	<.001
Sleep duration (mean hours ±SD)	7.4±1.7	7.9±1.4	8.6±1.4	<.001

*   Abbreviations: IDS=Inventory of depressive symptoms, BAI= Beck Anxiety Index, DEP=depressive disorder, ANX=anxiety disorder, NA= Not applicable, BMI=body mass index, MSF=Mid Sleep duration on free days

** p-values based on t-tests (continuous variables) and chi-square tests (dichotomous indicators).

Results

Mean age of the study sample was 42.7 years (SD=12.6), 65.6% was female. The mean MSF was 4.2 (SD=1.11) reflecting that the mid-sleep point during free days is around 4.12 AM. MSF and sleep duration were moderately positively correlated (correlation coefficient= .26, p<.001). We also found a significant, negative correlation between MSF and insomnia score (correlation coefficient =-.15, p<.001). This implies that MSF and sleep variables are only moderately related, and can be considered as separate concepts. Table 1 shows baseline characteristics of the study sample (n=1824), according to chronotype. Subjects with a late chronotype had the highest rate of current depressive and current anxiety disorders. Severity of depressive/ anxious symptoms was lowest in subjects with an intermediate chronotype. No differences across chronotype groups were found for use of antidepressants or use of benzodiazepines. Subjects with a late chronotype were younger, more educated, less often had a partner, less often had children present in the household, had a lower BMI, less chronic diseases, more often smoked and had a higher number of alcoholic drinks per week as compared to subjects with intermediate/early chronotypes. Subjects with a late chronotype also reported lowest rates of insomnia scores and the longest sleep duration.

Table 2 (model 1) shows multivariable regression analyses associating depressive/anxiety disorder status with chronotype after adjusting for sociodemographics. As compared to healthy controls, persons with current DEP and/or ANX had a significantly later MSF (β=.10, p<.001). Although associations with remitted disorders pointed out in the same direction, these were not significantly different from healthy controls (β=.03, p=.27). Independent of psychopathology status, a higher age, female gender, lower education, having a partner, and having children in the household were significantly associated with an earlier MSF in multivariable analyses. In previous studies (19) it has been found that chronotype is dependent on working status with subjects building up 'sleep debt' during work weeks. However, in our study, we found no association between working status and chronotype.

In model 2, which further adjusted for somatic health factors, associations between current DEP and/or ANX with MSF remained significant (β=.08, p=.006). Of the somatic health factors, currently smoking and a higher intake of alcoholic drinks per week were independently associated with a later MSF. Also in the sleep variable adjusted model 3, associations between current DEP and/ or ANX and MSF remained significant (β=.12, p<.001). The insomnia score (continuous, β=-.09, p<.001) and a short sleep duration (β= .09, p<.001) were significantly associated with earlier MSF. A long sleep duration was associated with a higher MSF (β=.14, p<.001).

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Table 2: Results of associations between chronotype (MSF) and demographics, somatic health factors and sleep n=1824)[a]

Chronotype	Model 1		Model 2		Model 3	
	β	p	β	p	β	p
Psychopathology						
Psychopathology status	REF.	REF.	REF.	REF.	REF.	REF.
– no lifetime DEP or ANX	.03	.27	.01	.67	.04	.15
– remitted DEP or ANX	.10	<.001	.08	.006	.12	<.001
– current DEP and/or ANX						
Demographics						
Age (years)	-.26	<.001	-.26	<.001	-.21	<.001
Female gender	-.10	<.001	-.07	.002	-07	.001
Education (years)	.11	<.001	.13	<.001	.13	<.001
Currently working	-.01	.65	-.02	.44	-.02	.48
Partner	-.16	<.001	-.15	<.001	-.15	<.001
Presence of children in household	-.10	<.001	-.09	<.001	-.09	<.001
Somatic health factors						
BMI			.03	.28	.03	.27
Nr. of chronic diseases			-03	.27	-.011	.65
Currently smoking			.17	<.001	.16	<.001
Nr. of alcoholic drinks per week			.07	.003	.08	.001
Sleep						
Insomnia Rating Scale					-.09	<.001
Sleep duration					-.09	<.001
– short sleep duration					REF.	REF.
– normal sleep duration					.13	<.001
– long sleep duration						

[a] Based on multivariable linear regression analyses.

Model 1: adjusted for psychopathology and demographics

Model 2: Model 1+ somatic health factors

Model 3: Model 2+ sleep factors

Abbreviations: DEP=depressive disorder, ANX=anxiety disorder, BMI=body mass index

When we analysed the subsample of currently anxious or depressed individuals (N=639, Table 3), we found no significant associations between type of disorder, symptom severity (IDS/ BAI), use of antidepressants or use of benzodiazepines and MSF. This indicates that associations appear rather consistent for depressive and anxiety disorders and that severity and medication use did not further differentiate the associations found between current anxiety or depressive disorders and later chronotype.

Table 3: Results of associations between chronotype (MSF) and clinical characteristics in currently depressed and/or anxious patients (n=639)[a]

Chronotype	β	p
Type of disorder		
– ANX, no DEP	REF.	REF.
– DEP, no ANX	.07	.08
– DEP+ANX	-.05	.21
Severity of psychiatric symptoms		
IDS	.05	.18
BAI	-.01	.73
Antidepressants		
– No medication	REF.	REF.
– SSRI	.07	.10
– Other AD	-.01	.73
– TCA	0.06	.12
Benzodiazepines		
– No benzodiazepine	REF.	REF.
– Benzodiazepine	-.02	.64

[a] Based on linear regression analyses, adjusted for age and gender one analysis per row

Discussion

This large-scale study found that persons with current depressive and/or anxiety disorders have a later chronotype than healthy controls, this might be indicative of a phase delay. Although pointing in the same direction, associations were not significantly present for persons with remitted disorders. We also found that later chronotype was associated with a wide range of sociodemographic (younger age, male gender, higher education, no partner, children in the household), health (smoking and alcohol use), and sleep characteristics (long sleep duration, absence of insomnia). However, the association between the presence of depressive and anxiety disorders with chronotype was independent of these variables.

Our findings are in line with the recent literature, showing depressive symptoms to be associated with a later chronotype (4,5). We extend these findings to depressive disorders in a large sample, and we had the opportunity to adjust for a large set of confounders. In addition, our study extends the finding of a later chronotype to anxiety disorders. The fact that a later chronotype is associated with current depressive and/or anxiety disorders, can be explained in various ways: 1) it may represent a vulnerability factor as well as 2) a consequence of depressive and anxiety disorders, or 3) chronotype and psychopathology may partly have a shared underlying mechanism. It may be that behavioral factors, such as exposure to bright light by spending time outdoors, are

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responsible for the association between chronotype and psychopathology. Bright light is one the best known 'Zeitgebers' of the biological clock (9), and a lack of bright light might affect both circadian rhythmicity and mood. In depressed patients with seasonal affective disorder, phototherapy in the morning has been associated with a shift from eveningness towards morningness (33).

It could also be the other way around: depression and anxiety might lead to a severe disturbance in sleep rhythm, which in turn leads to eveningness. Depressed patients who are 'morning types', showed less sleep disturbances and a more adequate sleep (33, 34). However, in our study, we found that the association between psychopathology and a later chronotype is not explained for by sleep duration and insomnia, suggesting that disrupted sleep may not be the explaining mechanism linking chronotype to psychopathology. Finally, according to the 'social Zeitgeber theory', also life events can trigger a disruption in social and biological rhythms, affecting both circadian rhythmicity and mood in vulnerable subjects (24).

A later chronotype can also exist as a condition on its own, the so-called delayed sleep phase syndrome, with subjects being abnormally delayed in their circadian clock. Subjects do not feel sleepy until late at night. Biological measures regarding the biological clock such as plasma melatonin and core body temperature have also been found 'out of phase' in this condition (35, 36). It has been reported that depression is the most frequent comorbidity of this disorder (9, 37). Part of the patients suffering from both conditions, do not respond to antidepressants, but do respond to bright light or melatonin, suggesting that these disorders share an underlying dysregulation of the biological clock. Being 'out of phase' could also lead to depression or anxiety due to the fact that subjects are unable to adjust to work or social rhythms (9).

Another explanation might be that underlying genetic factors, such as clock genes, causing both mood symptoms and differences in chronotype are responsible for the found association. This has been reported before: circadian clock-related polymorphisms have been associated both with seasonal affective disorder and diurnal preference (38). This hypothesis has been studied extensively with a specific genetic mutation: the CLOCK T3111 C mutation, which has been linked to a later chronotype (7). However, whether this mutation is also linked to depressive disorder remains to be elucidated, since prior studies have not been consistent (39). Consequently, whether shared genetic vulnerability is underlying the link between psychopathology and chronotype deserves further research. On the other hand, the fact that the association between psychopathology and chronotype in subjects with remitted disorders was slightly less strong, suggest that this genetic vulnerability hypothesis may not be the only explaining mechanism either.

Strengths of our study include the large sample with DSM-IV based diagnoses of both depressive and anxiety disorders, and with the opportunity to adjust for a large set of potential confounders. However, our study had some limitations. First, we had a large proportion of subjects who did not fill out the questionnaire on chronotype and had to be excluded from our analyses. Second, we used self-reports for chronotype as well as other sleep measures. It could be that subjects with a depressive or anxiety disorder may not accurately estimate the time of falling asleep and waking up, due to their underlying psychopathological condition. Third, because of our cross-sectional nature, it is impossible to provide strong indications about the causality of the chronotype-association with depressive and anxiety disorders.

Despite these limitations, our study strongly suggests that current depressive and anxiety disorders are accompanied by a later chronotype indicative of a phase delay in circadian chronotype. These findings suggests that it is relevant to determine whether subjects with a later chronotype may benefit more from treatments aimed at synchronizing the biological clock, such as bright light therapy or activity, and to what extent this would reduce depression and anxiety symptomatology.

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