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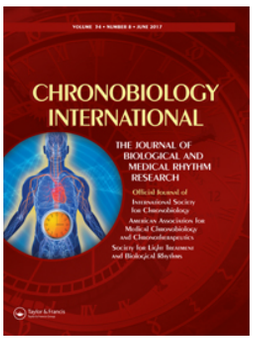

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Associations between chronotypes and psychological vulnerability factors of depression

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ABSTRACT

Chronotypes have been associated with psychopathology. The eveningness chronotype has been consistently linked with depressed states or depressive disorder, but the underlying mechanism remains unclear. Prior studies have shown associations between chronotype and personality traits that are linked to depression (e.g. neuroticism), but other psychological vulnerability factors have not been previously investigated in relation to chronotypes. The aim of this study was to examine the association between chronotypes, depression and psychological risk factors of depression (namely, cognitive reactivity and worry), in a large cohort of depressed patients and healthy individuals. We used data from the Netherlands Study of Depression and Anxiety (n = 1654), which includes 1227 clinically diagnosed individuals with a lifetime diagnosis of depression and 427 healthy controls. We assessed cognitive reactivity (Leiden Index of Depression Sensitivity-Revised) and trait worry (Penn State Worry Questionnaire). We controlled for sociodemographic factors as well as for insomnia and neuroticism. We found that the evening type is associated with higher cognitive reactivity scores, especially with increased rumination. Cognitive reactivity also mediated the relationship between chronotype and depression status, even when controlling for neuroticism and insomnia. Trait worry was not associated with chronotype. Our findings show that depressogenic cognitions are more prevalent in evening types and perhaps mediate the association between chronotype and depression. Further prospective research is needed to determine the timeline of the association. Nevertheless, results imply that targeting depressogenic cognitive processes, perhaps in combination with chronotherapeutic treatments, may be particularly useful in evening types.

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Evening types; rumination; worry; cognitive reactivity; neuroticism; personalized treatment

Introduction

Studies have shown a consistent association between eveningness and depressive symptoms (Kitamura et al., 2010; Levandovski et al., 2011; Merikanto et al., 2013; Selvi et al., 2010) or depressive disorder (Antypa et al., 2016; Drennan et al., 1991) with some variability in effect sizes, ranging from large to small. The mechanism underlying this association is largely unclear, however. Hypersomnia is more common in the evening chronotype (Vernet & Arnulf, 2009), but sleep does not seem to be the main factor explaining the link between eveningness and depression. In a large Japanese cohort study, eveningness was associated with an increased risk of depression, even after adjusting for sleep-related factors (Kitamura et al., 2010). Furthermore, eveningness and insomnia were recently found to be independent predictors of non-remission in depressed patients (Chan et al., 2014). A study designed to examine whether sleep problems (daytime sleepiness, insomnia and circadian misalignment) mediate the association between eveningness and negative emotionality found that eveningness was an independent risk factor (Simor et al., 2014). Similarly, eveningness and subjective sleep quality were independent risk factors for increased depressive symptomatology, and sleep quality failed to explain the link between eveningness and depressive symptoms (Muller et al., 2016a). Along the same lines, we previously found that the evening type was associated with clinically diagnosed major depression (and not dysthymia or anxiety disorders), after controlling for sociodemographic, somatic and sleep parameters

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(Antypa et al., 2016). Hence, a series of studies show that the association between eveningness and depression cannot be attributed to sleep disturbances.

In order to further understand the link between chronotypes and depression, it is necessary to investigate new pathways. For example, evening chronotypes may have an increased psychological vulnerability that renders them more susceptible to depression. The underlying rationale is that evening types may be more vulnerable to specific thinking patterns (e.g. worry or rumination) in the evening hours; this is a tentative hypothesis and has not been tested to date. Otherwise, evening types may carry personality traits that pose them at risk (e.g. neuroticism). Such associations have been scarcely investigated to date. With regard to personality, past research has shown inconsistent findings. Evening types scored higher on novelty seeking, neuroticism and harm avoidance (Adan et al., 2010; Caci et al., 2004; Hsu et al., 2012; Tonetti et al., 2009), but also opposite patterns have been observed, with morning type men showing increased neuroticism (Muro et al., 2009) and evening types showing lower harm avoidance (Adan et al., 2010). Although personality traits may be informative in terms of their relationship to chronotypes in a theoretical sense, targeting both traits (eveningness and neuroticism, for example) could be a challenge in treatment. Focusing on characteristics that are more malleable and that may be directly targeted during treatment – like negative thinking patterns – might be a better approach to disentangle the association between chronotypes and depression.

In the present study, we explore the association between chronotypes and two psychological vulnerability markers of affective disorders: cognitive reactivity and pathological worry. Cognitive reactivity is the extent to which negative thoughts become activated when mood is low, and has been studied mainly in relation to depression. Cognitive reactivity predicts first onset of depression in healthy individuals (Kruijt et al., 2013) and relapse in remitted individuals (Segal et al., 1999; Scher et al., 2005; Elgersma et al., 2015). Cognitive reactivity is higher in remitted depressed than in never depressed individuals (Moulds et al., 2008; Van Der Does, 2002). Pathological worry, on the other hand, can be defined as negative thoughts or images that are uncontrollable, which often contain unsuccessful mental problem-solving on an issue with an uncertain outcome (Borkovec & Inz, 1990; Borkovec et al., 1983). Worry has been investigated in the context of a broader range of psychopathology, including generalized anxiety disorder (Borkovec & Inz, 1990; Reiss et al., 1986) and affective disorders (Drost et al., 2014; Starcevic, 1995). Higher levels of worry have been found in depressed patients compared to healthy controls, but patients with generalized anxiety disorder score even higher than depressed ones (Chelminski & Zimmerman, 2003). Although worry and cognitive reactivity may be similar in some aspects (such as repetitive negative thinking/perseverative cognition) they can often be differentiated with regard to time orientation; worry is more likely to be future-oriented whereas cognitive reactivity reflects how one cognitively responds to sad mood on the basis of prior "sad" experiences. They also differ with regard to thought content, worry being more related to threat/negative event anticipation whereas cognitive reactivity reflects more emotionally driven negative thoughts that surface when mood is low. We previously observed that worry was uniquely associated with generalized anxiety disorder and not with major depression when cognitive reactivity was taken into account (Drost et al., 2012).

The aim of the present study is to explore the role of cognitive reactivity and pathological worry in the association between eveningness and depression. We examined the contribution of cognitive reactivity and worry in clinically depressed and healthy groups, while taking into account pertinent characteristics, such as neuroticism and insomnia, each of which has been associated both with chronotype (Muller et al., 2016a; Randler, 2008) and depression (Kendler et al., 2006; Van Mill et al., 2010). We expect that both cognitive reactivity and pathological worry will be higher in evening types. We also expect that cognitive reactivity will have a stronger mediating role between chronotype and depression than worry, since cognitive reactivity is a more specific vulnerability marker of depression.

Materials and Methods

Participants

Participant data are included from the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008), which is a longitudinal cohort study that

follows the course of depressive and anxiety disorders. The study's rationale, recruitment and methods have been described elsewhere (Penninx et al., 2008), but in brief, it is comprised of a representative sample from three geographic regions in the Netherlands. Participants are recruited from primary care, mental health organizations and the community. Ethical committees of all participating institutes in the Netherlands approved the research protocol and all participants gave written informed consent.

NESDA started off with 2981 participants assessed at baseline and of those 2596 (87.1%) participated in the 2-year follow-up (this study includes only participants who participated at this follow-up). Nonresponders (dropouts since baseline) were more likely to be younger, with lower education and with a depressive disorder (Lamers et al., 2012). The chronotype measurement was only assessed at the 2-year follow-up, together with psychological constructs and all covariates. The lifetime status of psychopathology was determined using baseline and 2-year follow-up data since data from both assessments were required to classify lifetime psychopathology or healthy status.

Measures

Chronotype

Chronotype was assessed with the Munich Chronotype Questionnaire (MCTQ, Roenneberg et al., 2003). The MCTQ is a self-report questionnaire, containing 29 questions about times of waking up and falling asleep on work days and on free days. The chronotype has been defined as the mid-point in time between falling asleep and waking up on *free days* (Mid Sleep on Free Days (MSF)). Observing sleep–wake patterns on free days is most likely to reflect one's natural circadian rhythm, without the interference of work schedules (Roenneberg et al., 2007, 2003). A higher score on the MSF indicates a later chronotype (evening type) and a lower score indicates an earlier chronotype (morning type). For the late types, sleep duration during workdays is often decreased due to work demands and compensated for during the free days, therefore a "sleep debt" is accumulated; this leads to a much higher MSF. An improved measure, namely the "mid-sleep on free days corrected for the sleep-debt accumulated during the work week" (MSFsc), has been developed and recommended for use as primary outcome (Roenneberg et al., 2003). This is calculated by subtracting from the MSF half of the difference between sleep duration on free days and average total sleep duration (see supplement of Roenneberg et al. (2012) for the algorithm); the MSFsc was used for our analyses. No imputation of missing values was used for calculating the MSFsc. The correlation between MSF and MSFsc was $r = .95$ ($p < 0.001$) in our sample. We also conducted descriptive analyses using categories ("early", "intermediate" or "late" chronotypes), which was based on quintiles of the MSFsc in our sample, with early chronotype being the 1st quintile (<3.13), intermediate chronotype consisted of the 2nd, 3rd and 4th quintiles, and the late chronotype was the 5th quintile (>4.67).

Depression

Major depressive disorder (MDD) was determined using the Composite International Diagnostic Interview (CIDI; version 2.1), a standardized diagnostic psychiatric interview which uses *DSM-IV* criteria to assess diagnosis (Wittchen, 1994). The CIDI was administered both at baseline and 2-year follow-up. Participants were categorized as follows: lifetime MDD (including currently depressed), remitted MDD (no current disorder in past 6 months at the 2-year measurement), and healthy controls (no past or current diagnosis of depressive or anxiety disorder). We focused only on MDD and not dysthymia because in our previous report from the same sample we only found an association between chronotype and MDD and not between chronotype and dysthymia (Antypa et al., 2016).

Psychological constructs

Depressive cognitions were measured using the Leiden Index of Depression Sensitivity (LEIDS-R), which measures cognitive reactivity to sad mood (Solis et al., 2017; Van Der Does, 2002) and consists of 34 items. Participants have to imagine that they feel "somewhat sad" and report to what extent the items apply to them (in a Likert scale which varies from 0 (not at all) to 4 (very strongly)). The LEIDS-R has six subscales which measure: (a) hopelessness/suicidality (HOP) (e.g. "when I feel sad, I feel more hopeless about everything"), (b) acceptance/coping (ACC) (e.g. "When I feel sad, I am more helpful"), (c) aggression (Spielberger CD) (e.g. "when I feel

down, I lose my temper more easily"), (d) control/perfectionism (CTR) (e.g. "when I feel somewhat depressed, I think I can permit myself fewer mistakes"), (e) risk aversion (RAV) (e.g. "when I feel down, I take fewer risks"), and (f) rumination (RUM) (e.g. "when I feel sad, I spend more time thinking about the possible causes of my moods"). The total score is the sum of all the items. The scale has been validated and has good psychometric properties (Solis et al., 2017; Van Der Does, 2002).

Trait worry was assessed with the Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990), which consists of 16 items that assess pathological worry and its characteristics and is assessed using a 5-point Likert scale: 1 ("not at all typical of me") to 5 ("very typical of me"). In NESDA, an abbreviated version of the PSWQ has been administered, containing the 11 positively worded items from the questionnaire (e.g. "I am always worrying about something"). Norms for the cut-off scores in NESDA are as follows: very low <17, low 18–23, average 24–31, high 32–39 and very high >39 (Van Der Heiden et al., 2009).

Covariates

Sociodemographic factors (measured at the 2-year follow-up) examined included age, gender, education (in years), working status, having a partner and having children living in the household. Factors such as smoking and alcohol intake have been previously associated with chronotypes (Adan et al., 2012; Urban et al., 2011) and were also considered. Smoking was based on self-report (currently smoking: yes/no). For alcohol consumption we used the Alcohol Use Disorder Identification Test (AUDIT), which consists of 10 questions measuring frequency, quantity of drinking and symptoms of dependency (Saunders et al., 1993). Average sleep duration was also assessed, since it has been linked to depressive disorders in NESDA (Van Mill et al., 2010); average sleep duration in hours per night was calculated from the MCTQ. Insomnia was measured with the Women's Health Initiative Insomnia Rating Scale (Levine et al., 2003) which contains five questions assessing sleep (trouble falling asleep, waking up during the night, early-morning awakenings, trouble getting back to sleep after waking up, and sleep quality) during the past 4 weeks. Higher scores indicate severe insomnia. Neuroticism was measured with the NEO-Five Factor Inventory (NEO-FFI) (Costa & Mccrae, 1992), and refers to aspects such as anxiety, anger, hostility, depression, self-consciousness, impulsiveness and vulnerability.

Statistical analyses

Data were analyzed using IBM SPSS Statistics 23.0 (SPSS Inc., Chicago, IL). Sociodemographic and clinical characteristics were compared between chronotype (MSFsc) categories using chi-square tests for categorical variables and analysis of variance for continuous variables. We performed analysis of covariance (ANCOVA) to examine the differences between chronotype groups on cognitive reactivity and worry and a multivariate ANCOVA for the cognitive reactivity subscales. For mediation analyses we used Hayes' PROCESS tool in SPSS (using model 4), with MSFsc (continuous) as predictor, cognitive reactivity/worry as mediators and MDD lifetime/healthy status as outcomes. The main outcome was the indirect effect and its bootstrapped confidence interval which was taken as indication of significance (the Sobel test is also reported, but the bootstrap confidence intervals (for 5000 samples of the indirect effect are considered a better approach to inference of mediation) (Hayes & Scharkow, 2013).

Results

Participant flow

Of the 2596 individuals participating in the 2-year follow-up, 269 did not fill out the MCTQ. Participants who did not fill out the scale were younger, more likely to be male, had fewer years of education, and were more likely to suffer from a current depressive and/or anxiety disorder. Of the remaining 2327 participants, 1885 participants had data on MSF (without any sort of imputation). Of those, 231 participants were excluded because they had only anxiety disorders (no MDD). This yielded a final sample size of 1654 for analysis, with 427 healthy controls (no depressive or anxiety disorders) and 1227 with a lifetime MDD (365 had a current diagnosis during the past 6 months and 862 were remitted with no MDD diagnosis during the past 6 months).

Table 1. Participant characteristics, stratified by chronotype categories.

	"Early" types	"Intermediate" types	"Late" types	
	N = 331	*N* = 992	*N* = 331	
	N (%)	*N* (%)	*N* (%)	
	M (SD)	M (SD)	M (SD)	*p* Value
Sociodemographic characteristics				
Age	46.2 (11.3)[a]	43.0 (12.5)[b]	38.1 (12.8)[c]	**<0.001**
Gender (female)	221 (66.8%)[a,b]	673 (67.8%)[b]	203 (61.3%)[a]	.09
Education (years)	11.8 (3.4)[a]	13.1 (3.2)[b]	13.1 (3.1)[b]	**<0.001**
Partner	239 (89.2%)[a]	598 (80.8%)[b]	144/197 (73.1%)[c]	**<0.001**
Missing	*63*	*252*	*134*	
Children	148 /268 (55.2%)[a]	355 /740 (48.0%)[b]	62 /197 (31.5%)[c]	**<0.001**
Missing	*63*	*252*	*134*	
Employment	248 /326 (76.1%)[a]	721 /972 (74.2%)[a]	217 /325 (66.8%)[b]	**0.01**
Missing	*5*	*20*	*6*	
Clinical characteristics				
Smoking–current	78/227 (34.4%)[a]	267/685 (39.0%)[a]	148/270 (54.8%)[b]	**<0.001**
Missing	*104*	*307*	*61*	
Alcohol	3.7 (4.3)[a]	4.6 (4.2)[b]	6.6 (5.9)[c]	**<0.001**
Average sleep duration	7.6 (1.0)[a]	7.8 (1.0)[a]	7.8 (1.1)[a]	0.08
Missing	*43*	*108*	*49*	
Insomnia	8.5 (5.0)[a]	6.8 (4.5)[b,A]	6.6 (4.3)[b,A]	**<0.001**
Neuroticism	33.8 (9.3)[a,b]	32.6 (8.8)[b]	34.7 (9.3)[a,A]	**0.001**
Depression				
Current (past 6 months)	78 (23.6%)[a,b]	191 (19.3%)[b]	96 (29.0%)[a]	**0.001**
Remitted[B]	157 (47.4%)[a]	542 (54.6%)[b]	163 (49.2%)[a,b]	
Healthy	96 (29.0%)[a]	259 (26.1%)[a,b]	72 (21.8%)[b]	

[A]One missing value; [B]remitted status indicates no MDD diagnosis in the past 6 months.
Post hoc analyses show significant differences between groups: same letter indicates no difference.
p Value is the result of an ANOVA or chi-square test.

Participant characteristics

Table 1 shows sociodemographic characteristics of the sample stratified by chronotype groups (see Materials and Methods section for category cut-offs of the MSFsc). Late types were more likely to be younger, unemployed, current smokers and used more alcohol than the other chronotype groups. Early types had fewer years of education and were more likely to have a partner and children than the other chronotypes. With regard to clinical characteristics, late types reported lower insomnia than early types. No differences were found between early and late types on average sleep duration and neuroticism. There were significant differences between chronotype groups on the proportion of depression status, with late types being more likely to be currently depressed compared to intermediate types (but not to early types, as seen in post hoc comparisons). Similarly, late types were less likely to be classified as healthy compared to early types (but not compared to intermediate types, as seen in post hoc tests).

Chronotype and psychological vulnerability constructs

Early, intermediate and late types' (according to MSFsc quantiles) psychological vulnerability scores are presented in Table 2. ANCOVA with age and sex as covariates showed significant differences among chronotype groups on the cognitive reactivity total score and also on most of its subscales (Multivariate ANCOVA with all subscales). Simple contrasts showed that late types scored significantly higher than the other two groups on the total score and all reactivity subscales apart from control/perfectionism (on the latter subscale differences reached a trend, $p = 0.07$). The differences were moderate to small (effect size varying from $d = .39$ (RUM) to $d = .16$ (HOP)) when

Table 2. Mean (±SD) scores of the psychological constructs stratified by early, intermediate and late chronotypes in the whole sample.

	Early types	Intermediate types	Late types	
	N = 331	*N* = 992	*N* = 331	
	M (SD)	M (SD)	M (SD)	*p* Value
Cognitive reactivity	28.7 (20.2)	29.0 (18.3)	34.5 (19.5)	<0.001
Hopelessness/ suicidality	4.1 (4.6)	3.7 (3.9)	4.8 (4.4)	<0.001
Acceptance	1.2 (1.8)	1.2 (1.9)	1.6 (2.4)	<0.001
Aggression	4.0 (4.2)	3.7 (3.7)	5.0 (4.3)	<0.001
Control/ perfectionism	4.9 (3.9)	5.1 (3.9)	5.5 (3.6)	0.15
Risk aversion	7.4 (5.1)	7.4 (4.8)	8.3 (4.7)	0.002
Rumination	7.5 (5.4)	7.9 (5.0)	9.6 (5.3)	<0.001
Worry	29.0 (12.4)	27.1 (11.5)	29.9 (12.2)	<0.001

The table shows means and standard deviations in the whole sample; *p* value is the result of (M)ANCOVAs with age and gender as covariates.

comparing the early types versus the late types. ANCOVA showed significant differences in worry between chronotype groups but contrasts showed that those were significant only between intermediate types and late types (see Table 2).

Adding other sociodemographic and clinical factors that could influence these associations (education, partner, children, employment, smoking, alcohol, insomnia and neuroticism) as covariates in the model yielded similar results, namely, the cognitive reactivity total score, and the rumination and acceptance/coping subscales remained significantly higher for late types compared to other chronotypes. Other subscale differences between chronotype groups (n = 813 due to missing values in the covariates) were no longer significant. The results reported for worry remained the same as in previous analyses.

Statistical mediation analyses

Mediation analyses were run with cognitive reactivity total score (Model 1), cognitive reactivity subscales (Model 2) and worry (Model 3) as mediators of the relationship between chronotype (MSFsc, continuous) and lifetime depression (coded 0,1). These models were first run with age and gender as covariates. We found that chronotype significantly predicted cognitive reactivity and all its subscales but not worry. In turn, cognitive reactivity total score, hopelessness/suicidality, risk aversion, rumination and worry predicted lifetime depression (see Table 3 for the results). The "direct" effect of chronotype on lifetime depression controlling with cognitive reactivity total or its subscales as mediators was not significant. There was a significant indirect effect of chronotype on lifetime depression through cognitive reactivity total score, indicating full mediation. From its subscales hopelessness/suicidality, risk aversion and rumination showed significant indirect effects, with rumination showing the largest effect. For worry we found a significant "direct effect" of chronotype on depression status, but no significant indirect effect (no mediation).

When adding neuroticism and insomnia (total scores) as covariates in these models, we found that the indirect effect of cognitive reactivity total remained significant (effect = 0.08, SE = 0.02, CI: 0.045, 0.125), as well as the indirect effects for the following subscales: risk aversion (effect = 0.02, SE = 0.01, CI: 0.003, 0.046) and rumination (effect = 0.09, SE = 0.02, CI: 0.045, 0.141). Normal theory test (Sobel test) showed that the risk aversion scale failed to reach significance (z = 1.68, p = 0.09), whereas the rumination subscale was significant (z = 3.53, p = 0.0004). Effects of the two subscales were independent from each other (effect = – 0.07, SE: 0.03, CI: –0.125, –0.020). Neuroticism and insomnia were significant predictors of lifetime depression in these mediation models. We did not run this extra covariate analyses for worry, since the first mediation model was not significant.

Since cognitive reactivity has been repeatedly used in the past to distinguish never depressed and recovered depressed individuals, we repeated the analyses (with age, gender, neuroticism and insomnia as covariates) while excluding the currently depressed (depression past 6 months (n = 1277)). The outcome was: recovered depressed status (n = 855) versus healthy (n = 425). The indirect effect of chronotype on the outcome was significant with cognitive reactivity total score as a mediator (effect = 0.08, SE = 0.02, CI: 0.045, 0.131). When examining cognitive reactivity subscales as potential mediators, the same pattern as in the whole sample was found, namely that rumination was the stronger mediator (effect = 0.08, SE = 0.03, CI: 0.037, 0.138).

Post hoc analyses

For examining the direction of the mediation, which could be vice versa, namely eveningness leading to higher rumination levels via a depressed status, we performed a subsequent mediation

Table 3. Summary of statistical mediation model (using PROCESS) between chronotype (IV) and lifetime depression/healthy status (DV).

		Effect of IV on M (a)		Effect of M on DV (b)		Direct effect (c′) of IV on DV			
Model	(M)	Effect (SE)	*p*	Effect (SE)	*p*	Effect (SE)	*p*	Indirect effect (SE) of IV on DV (a × b)	95% CI (a × b)
1	Cognitive reactivity total	1.99 (0.49)	<0.001	0.09 (0.005)	<0.001	0.05 (0.07)	0.51	***0.17 (0.05)***	***0.087 to 0.269***
2	Hopelessness/suicidality	0.24 (0.10)	0.02	0.16 (0.04)	0.001	0.02 (0.7)	0.78	***0.04 (0.02)***	***0.002 to 0.093***
	Acceptance	0.20 (0.05)	<0.001	0.03 (0.05)	0.48	0.02 (0.7)	0.78	0.007 (0.01)	−0.014 to 0.035
	Aggression	0.29 (0.10)	0.003	−0.2 (0.03)	0.59	0.02 (0.7)	0.78	−0.005 (0.01)	−0.029 to 0.017
	Control/perfectionism	0.20 (0.10)	0.04	−0.02 (0.03)	0.57	0.02 (0.7)	0.78	−0.003 (0.007)	−0.023 to 0.007
	Risk aversion	0.30 (0.12)	0.01	0.11 (0.03)	0.001	0.02 (0.7)	0.78	***0.03 (0.02)***	***0.007 to 0.073***
	Rumination	0.75 (0.13)	<0.001	0.17 (0.03)	<0.001	0.02 (0.7)	0.78	***0.13 (0.03)***	***0.073 to 0.193***
3	Worry	0.30 (0.30)	0.31	0.14 (0.008)	<0.001	0.17 (0.07)	0.02	0.04 (0.04)	−0.040 to 0.123

IV: independent variable, M: mediator, DV: dependent variable
Model with age and gender as covariates. Numbers in bold show significant indirect effects.

model in the whole sample. In this model, eveningness predicts rumination (b = .68, p < 0.001), eveningness predicts depression (b = .11, p < 0.05), depression predicts rumination (b = 5.4, p < 0.001), but there is no indication of mediation since in the final model (c′) both predictor and mediator are significant and the Sobel test (1.8, SE: 0.3, p = 0.07) is not. These analyses were run using the Baron and Kenny (1986) method to test mediation, because "PROCESS" does not allow a dichotomous mediator. Therefore, we assume that the direction of the relationship as we tested it is valid, even if not causal due to the concurrent time point assessment.

Finally, for exploratory purposes and to understand the associations further, we examined chronotype as predictor of cognitive reactivity subscales and total score in each of the diagnostic groups (healthy, remitted depressed and currently depressed) separately. Results showed that in healthy controls, chronotype (MSFsc) was related to the total score (β = .15, p = 0.002), to the rumination subscale (β = .16, p = 0.001), to the acceptance subscale (β = .15, p = 0.002) and to the aggression subscale (β = .13, p = 0.007). In remitted depressed patients, chronotype was related to the rumination subscale (β = .12, p = 0.001) and to the aggression subscale (β = 0.09, p = 0.01). In the currently depressed group (past 6 months), chronotype was only associated with the acceptance subscale (β = .13, p = 0.01).

Discussion

The present study shows that late (evening) types score higher on a specific psychological factor of depression vulnerability, namely cognitive reactivity. Cognitive reactivity and its rumination subscale were related to eveningness and were significant mediators of the relationship between chronotype and depression, even after correcting for related factors such as insomnia and neuroticism (known to be associated with depression (Kendler et al., 2006; Van Mill et al., 2010)). This statistical mediation remained significant when examining recovered depressed individuals versus controls (as outcome), indicating that eveningness is not a result of current depressive symptomatology, but most likely a risk factor for increased depressive cognitions, and consequently depression. Worry was not related to chronotype and was not a significant mediator of the link between chronotype and depression. Worry levels were within the average range according to norms (Van Der Heiden et al., 2009). Cognitive reactivity levels, especially for the late type, were similar to those reported by recovered depressed patients (Antypa et al., 2010).

This is the first study that has examined a depression-specific cognitive vulnerability factor in relation to chronotypes. Cognitive reactivity has been established as a vulnerability factor of depression in prior studies. In a prospective analysis of the NESDA sample, we found that higher cognitive reactivity predicted the onset of depression in a healthy group (Kruijt et al., 2013). Furthermore, higher cognitive reactivity measured with the LEIDS-R was also found to be a predictor of relapse in a longitudinal study, with the rumination subscale being the best predictor (Figueroa et al., 2015). We have shown previously that rumination reactivity is a unique cognitive construct related to MDD (and not to dysthymia or anxiety disorders) (Drost et al., 2012). Rumination measured with other

scales (Nolen-Hoeksema, 2000) is a known predictor of depression, as well as a maintaining factor (Nolen-Hoeksema et al., 2008). With regard to the other subscales of cognitive reactivity, we observed that risk aversion was higher in evening types. Prior research has associated evening types with higher harm avoidance traits (Hsu et al., 2012), although conflicting findings have been reported on this trait (Adan et al., 2010). Overall, our findings showing higher cognitive vulnerability in late types are in line with recent research showing that depressed individuals who are evening types report more cognitive symptoms (both upon admission and dismissal), whereas no differences are found on somatic and affective symptoms between morning- and evening- type patients (Muller et al., 2016b).

With regard to the lack of an association between worry and chronotypes, results are not entirely surprising considering that worry and rumination share some similar qualities (such as negative repetitive thinking) but they are different also on a number of issues. These issues are time orientation (worry is future-oriented, rumination is present–past oriented) and thought content (worry is more related to threat anticipation whereas rumination reflects more deeper meaning and emotion analysis) (see Nolen-Hoeksema et al. (2008) for a thorough distinction). We also previously observed that worry was uniquely associated with generalized anxiety disorder and not with MDD when cognitive reactivity is taken into account (Drost et al., 2012). This adds to the current understanding of the role of chronotype in depressive and anxiety disorders. In particular, it seems that the association with the late type is specific to MDD (and not anxiety) (Antypa et al., 2016) and to rumination (and not worry) as potential underlying mechanisms.

Insomnia, although predictive of depression in our models, was not related to eveningness (Table 1); in fact, eveningness has been associated previously with hypersomnia (Vernet & Arnulf, 2009). Neuroticism has been previously associated with eveningness (Randler, 2008; Tonetti et al., 2009), but not consistently so. Other studies, consistent with the present study, do not show differences on this trait between early and late chronotypes (Gray & Watson, 2002; Hogben et al., 2007; Jackson & Gerard, 1996). Other research on personality styles has shown that optimism and happiness are higher among morning types, whereas pessimism is associated with eveningness (Antúnez et al., 2015; Levy, 1985); this is in line with our observation of increased depressive cognitions (cognitive reactivity) also in healthy late types. With regard to this aspect, we observed from our post hoc analyses that late healthy types are more likely to have higher cognitive reactivity levels on a range of subscales including rumination and the total score, whereas fewer associations were found in the remitted group and even less in the currently depressed group. This is not contrary to expectation, since the questionnaire (the LEIDS-R) is addressed to participants who are not in the middle of a depressive episode, since they have to imagine themselves to be "somewhat sad" and how they would react cognitively to this mild sad mood. We have previously shown that the scale is able to capture vulnerability to depression in healthy participants and to predict prospectively the onset of depression (Kruijt et al., 2013).

The present study has several strengths. Our large sample is comprised of participants with current and/or past clinically diagnosed depression as well as a healthy group, and participants are recruited from different areas (community, general practitioners and mental health organizations). MDD diagnosis was based on clinical interviews and the various additional assessments in the study allowed us to control for and take into account a number of factors (sociodemographic and clinical factors) in our analyses.

A limitation of the present report is its cross-sectional nature, precluding any inferences on causality from the mediation models. Future studies should apply a prospective design in order to assess the issue of timeline. Also, although the mediation models do not provide effect size estimates, we can observe that coefficients were not very large and differences in cognitive reactivity between chronotype categories (Table 2) range from moderate to low effect sizes. Since this is the first study examining cognitive reactivity and rumination in relation to chronotype and depression, the size of such effects remains to be further determined. Finally, it should be noted that we used the MCTQ as a measure of chronotype assessment, whereas most prior studies examining

the association between chronotype and depression (Chan et al., 2014; Chelminski et al., 1999; Kitamura et al., 2010; Merikanto et al., 2013; Muller et al., 2016a) have used the Morningness–Eveningness Questionnaire (Horne & Ostberg, 1976). The MCTQ correlates with the MEQ (r = – 0.73) (Zavada et al., 2005) and while the MCTQ reflects actual sleep patterns during work days and free days, the MEQ represents a more global preference for sleep patterns as well as for performing mental and physical activities either in early or late hours (Adan et al., 2012).

Clinical considerations

Eveningness has been found to be a predictor of non-remission (odds ratio = 3.36), independent of insomnia severity, in patients with MDD, with such patients reporting higher depressive symptomatology and suicidality (Chan et al., 2014). Similarly, eveningness has been found to be associated with impairments in remitted bipolar disorder, where evening types were more associated with a worse outcome in several functional aspects (such as sleep–wake problems, dietary habits and interpersonal relationships) and they also reported higher sleep-related dysfunctional cognitions (Ng et al., 2016). Such studies indicate the clinical relevance of targeting eveningness during treatment.

Evening types have a particular sleep rhythm (i.e. late bed time, late awake time and social jetlag) and it could be assumed that shifting the clock time could have beneficial results in mood-related aspects in this group. Jankowski (2015) recently examined this hypothesis in a longitudinal design and found that the natural shift toward an earlier chronotype in terms of earlier bedtime, longer sleep duration, and decrease in sleep-onset latency and social jetlag was not accompanied by an improvement in mood or life satisfaction. On the other hand, another study showed that a shift to morningness was associated with lower depression and increased positive affect and sleep quality, after a behavioral treatment for insomnia or an information intervention (changes applied to both groups, n = 29) (Hasler et al., 2016). The latter study, either through active treatment or psychoeducation, managed to improve both sleep- and mood-related aspects together with a shift to morningness. Assuming that evening types are more vulnerable to depressogenic cognitions (as shown in our study), a combination of cognitive/behavioral treatments and chronotherapeutics may be preferred as compared to phase-shift treatments alone. Eveningness is a promising target during treatment (Chan et al., 2014; Ng et al., 2016), but also a potential "alarm" in young vulnerable populations, that should be taken into account during early monitoring and prevention.

Declaration of interest

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of this article.

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