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A sad day's night

Bouwmans, Maria

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CHAPTER 4

**Sleep quality predicts positive
and negative affect but not vice versa.
An electronic diary study in depressed
and healthy individuals.**

Mara E.J. Bouwmans, Elisabeth H. Bos,
H.J. Rogier Hoenders, Albertine J. Oldehinkel,
Peter de Jonge

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Abstract

The exact nature of the complex relationship between sleep and affect has remained unclear. This study investigated the temporal order of change in sleep and affect in participants with and without depression.

27 depressed patients and 27 pair-matched healthy controls assessed their sleep in the morning and their affect 3 times a day for 30 consecutive days in their natural environment. Daily sleep quality and average positive affect (PA) and negative affect (NA) were used to examine whether changes in sleep quality preceded or followed changes in PA and NA, and whether this was different for patients and healthy controls. Second, presumptive mediating factors were investigated. We hypothesized that fatigue mediated the effect of changes in sleep quality on subsequent PA/NA, and that rumination mediated the effect of changes in PA/NA on subsequent sleep quality.

Multilevel models showed that changes in sleep quality predicted changes in PA ($B=0.08, p<.001$) and NA ($B=-0.06, p<.001$), but not the other way around (PA: $B=0.03, p=.70$, NA: $B=-0.05, p=.60$). Fatigue was found to be a significant mediator of the relationship between sleep quality and PA (Indirect Effect= $0.03, p<.001$), and between sleep quality and NA (Indirect Effect= $-0.02, p=.01$). Rumination was not investigated because of non-significant associations between PA/NA and sleep quality. The associations were not different for patients and controls. The analyses were restricted to self-reported sleep quality, and conclusions about causality could not be drawn.

Improvements in sleep quality predicted improvements in affect the following day, partly mediated by fatigue. Treatment of sleep symptoms would benefit affect in clinical care and beyond.

Introduction

It is well known that sleep and affect are related¹⁻³. A disturbance of positive and negative affect is one of the core symptoms of a major depressive disorder (MDD)^{4,5}. The disturbance of sleep is also one of the symptoms of a diagnosis of MDD; approximately 70% of depressed patients report changes in sleep^{6,7}. The relationship between sleep and affect in depression is complex. Depression can be related to difficulty initiating or maintaining sleep (=insomnia), but sometimes also to sleeping too much (=hypersomnia), or both⁷. Similarly, interventions are targeted at increasing sleep time, but also at the opposite (i.e., sleep deprivation), even in patients who have insomnia. Sleep deprivation seems to have a positive effect on affect in some patients with depression, although the effect does not last long^{8,9}. In sum, although there is consensus in the literature that sleep and affect are associated with each other, the exact nature of the association remains unclear^{3,10-13}.

Along with sleep disturbances comes increased fatigue, which can be part of an MDD diagnosis as well (Diagnostic and Statistical Manual of Mental Disorders⁵). Decreased subjective sleep quality¹⁴ and decreased subjective sleep duration³ have been found to be highly correlated with same-time fatigue. Feelings of fatigue have been found to be associated with same-time positive and negative affect¹². Based on these findings it may be argued that fatigue mediates the temporal association between sleep and subsequent affect. However, in these previous studies there was no temporal separation between mediator and outcome, and no multilevel approach was used. The association in the opposite direction, from affect to subsequent sleep, may be mediated by rumination. In a recent review¹² it was shown that rumination had a significant impact on sleep quality. Next to that, rumination has been found to mediate the relationship between negative affect and sleep quality in healthy adults¹⁵. In the latter study there were two months between assessment of predictor versus mediator and outcome, and besides that there was again no temporal separation between mediator and outcome.

Sleep and affect can both change on a daily basis^{4,14}. These day-to-day changes can be captured by the use of multiple repeated assessments (i.e., daily diary study), and such a design enables the examination of the temporal order of these changes. This temporal order of change in sleep and affect has been investigated before in healthy adults and children^{3,10,16}, and in two of these studies a bidirectional effect was found between sleep and affect. In patients with depression, the one-way association between sleep quality and subsequent affect was investigated in only one study, in a design of 6 consecutive days⁴. Neither sleep duration nor sleep quality were associated with subsequent affect in this study. Thus, a depressive disorder might moderate the association between sleep and affect: the difference in results between the abovementioned studies may be explained by depression status. Possibly, depression weakens the temporal association between sleep and affect because of reduced emotional reactivity in depressed patients¹⁷. This notion needs more research, however, because neither of the abovementioned studies examined both healthy and depressed persons within one and the same study. Moreover, in the study by Peeters⁴ the relationship between sleep and affect was investigated only unidirectional, and only six time points were used for analyses. The examination of the bidirectional

association between sleep and affect in depressed patients and healthy controls with multiple repeated assessments could reveal whether depression status indeed moderates the association between sleep and subsequent affect, and whether it moderates the association between affect and subsequent sleep. The design with multiple repeated within-day assessments is the major strength of our study compared with earlier studies on this topic. This approach enabled to investigate how sleep and affect are temporally associated with each other within the day, and to study how the proposed mediators fatigue and rumination differentially contribute to these within-day associations. In contrast to previous studies on this topic, we were able to better separate the proposed mediators from the outcome measures in time. An additional benefit of a multiple repeated assessments design is the possibility to take heterogeneity among participants into account¹⁸. The first aim of the present study was to examine the temporal order of change in affect and sleep, with depression status as a potential moderator. In case of significant associations between sleep and affect, we investigated mediating factors of the significant association. We hypothesized that affect during the day predicts sleep quality the subsequent night, and that rumination in the evening mediates this association. Further, we hypothesized that sleep quality the previous night predicts affect during the day, and that fatigue in the morning mediates this association.

Methods

Design

Data from the Mood and Movement in Daily Life (MOOVD^{19,20}) were used in the present study. The MOOVD study was set up to investigate the dynamic relationship between physical activity, mood, and essential physiological processes, in patients with depression and healthy controls. A replicated single-subject time-series design was used, in which pair-matched depressed patients and healthy controls were monitored 3 times a day for 30 subsequent days within their natural environment. Participants filled out electronic diaries, wore an accelerometer, and sampled saliva at each assessment point, resulting in time series of up to 90 repeated measurements per individual.

Subjects and procedure

The MOOVD study was conducted from January 2012 until May 2014 in the Northern part of the Netherlands. In total, 27 patients with depression and 27 healthy controls completed the study. To obtain comparable groups and simplify pair-wise comparison, participants of both groups were pair-matched based on gender, age, smoking status and body mass index. Recruitment of the depressed patients occurred in the patient population of the University Center of Psychiatry (UCP), University Medical Center Groningen (UMCG), Center for Integrative Psychiatry (CIP, Lentis), and Dimence Deventer. Healthy controls were recruited from the general population by means of advertising in public places. Inclusion criteria for depressed patients were a Beck Depression Inventory (BDI²¹ score > 14 and

current or recent (< 2 months) presence of a DSM-IV major depressive disorder (MDD), and for the healthy controls a BDI score < 9 and the absence of MDD, assessed by means of the Composite International Diagnostic Interview (CIDI²²). Exclusion criteria for all participants were: episodes of psychotic or bipolar disorder (current or recent: < 2 years), assessed by means of the CIDI; visual or hearing impairments; pregnancy; somatic disorder or medication use that severely affects HPA axis or the autonomic nervous system. The Medical Ethical Committee of the University Medical Center Groningen approved the study protocol. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human research and with the Helsinki Declaration as revised in 1989.

Interested individuals received information about the study, a written consent form, BDI questionnaire, Munich Chronotype Questionnaire²³, and a health questionnaire. Eligibility was based on the health information and BDI. If eligible, the individual was invited for an appointment during which the CIDI was assessed. The second part of the appointment concerned clarification of the study protocol.

The first two days of the study served to get familiar with the protocol for the following 30 days. Participants were asked to assess themselves 3 times daily. Assessment times were fixed with intervals of 6 hours in between, and adjusted to the chronotype of the participant as estimated with the Munich Chronotype Questionnaire. This resulted in person-fit times of measurement to not interfere with their daily businesses. On average, the assessments took place during the late morning (\approx 10:00 AM), afternoon (\approx 4:00 PM), and evening (\approx 10:00 PM) for most participants. Measurements of the electronic diaries were facilitated by means of the PsyMate[®], an electronic device to assess daily behavior (PsyMate BV, Maastricht, The Netherlands). The diaries consisted of 60 questions about mood, sleep, activities and cognitions. The PsyMate[®] generated an alarm 30 minutes prior to the time filling out the questionnaires, with the message to refrain from food and drink intake (except for water), smoking, and brushing teeth until the measurement was completed. The alarm was generated again at the time the questionnaire had to be filled out. In case the alarm was missed, participants had a window of one hour to complete the diary questionnaire. After this hour the opportunity to enter the diary was lost and the measurement was treated as missing.

Measurements

Positive and negative affect were used as operationalized by Byslma^{24,25}, who used some items from the PANAS and some additional items used successfully in previous experience sampling studies. The positive affect (PA) scale consisted of the mean score on seven items (talkative, enthusiastic, confident, cheerful, energetic, satisfied, and happy), and so did the negative affect (NA) scale (tense, anxious, distracted, restless, irritated, depressed, and guilty). All items were rated on a Likert scale ranging from 1 'not' up to 7 'very', therefore high scores on PA and NA represented high levels of either positive or negative affect. According to²⁵, the PA and NA scale had high internal consistency based on person-level reliability estimates (all > .90). In the current study, the mean person-level Cronbach's alpha for PA was .85, and the mean Cronbach's alpha for NA was .64. The mean Cronbach's alpha for PA was .87 for the depressed and .83 for the non-depressed participants. The mean Cronbach's

alpha for NA was .75 for the depressed and .53 for the non-depressed participants. Average daily PA and NA were calculated from the 3-daily scores on both scales.

Three items of the Pittsburgh Sleep Diary (PghSD²⁶) were used to measure subjective sleep experiences: (1) 'Did you sleep well?', (2) 'How long did you sleep?', (3) 'Awakened by alarm clock/radio, someone whom I asked to wake me, noises, or just woke?'. For the present study we used the item about sleep quality 'Did you sleep well?', rated on a Likert scale ranging from 1 'not' to 7 'very', because recent studies indicate that subjective sleep quality reflects sleep experience better than subjective sleep duration¹¹. Subjective sleep quality is usually assessed by means of a questionnaire such as the Pittsburgh Sleep Quality Index²⁷, which has been validated against polysomnographic data, sleep log data, and clinical interviews¹⁴, and fits a cross-sectional study design. The use of one item to assess daily subjective sleep quality is not uncommon in the sleep field of prospective diary studies. For example, validity of the item "How was your sleep quality last night?" was examined¹⁴, and showed to have sufficient internal consistency ($\alpha=.89$) and sufficient criterion validity compared to the commonly used PSQI. Besides, perceived sleep quality was assessed with a 5-point Likert scale in the Consensus Sleep Diary²⁸. The sleep items in the present study were completed every time participants indicated they had slept since the last measurement, but we used only the morning ratings in this study, which reflect the quality of sleep during the past night.

Fatigue was measured 3-daily with the item 'I feel tired', rated on a scale ranging from 1 'not' to 7 'very'. In the present study we only used the morning assessment of fatigue, to take into account the order of events (t1 = sleep last night, t2 = fatigue in the morning, t3 = mean affect during daytime). A single-item measurement of fatigue has been used before and showed to be a valid measurement to monitor daily fatigue²⁹. Rumination was measured 3-daily with the item 'I brood a lot', rated on a scale ranging from 1 'not' to 7 'very'. For this study we only used the evening assessment, to take into account the order of events (t1 = mean affect during daytime, t2 = rumination in the evening, t3 = sleep the subsequent night).

Statistical analyses

The temporal relationship between sleep and affect

The temporal relationship between sleep and affect was investigated by means of multilevel analyses. We specified four autoregressive multilevel models by means of the Stata XT MIXED command in Stata 13 (StataCorp LP, College Station, TX). We first tested whether changes in sleep quality (deviations from the individual's mean sleep quality) assessed in the morning could predict changes in either PA or NA during the day, while controlling for lagged values of sleep quality (i.e., sleep quality the night before). Next, we tested whether changes in either PA or NA during the day (deviations from the individual's mean PA/NA levels) could predict changes in sleep quality the subsequent night. This time, the lagged value of PA/NA was incorporated in the model. An interaction term was included in every model to test if the relationship differed between depressed and non-depressed individuals.

A trend in the variables can lead to spurious associations between variables³⁰. Therefore, trends were removed from all variables before the analyses by means of ordinary least squares regression. In order to distinguish effects within participants from effects

between participants, the recommended approach of ‘person-mean centering of the predictor variables’ was used by calculating the daily deviation from the participants’ mean values^{31,32}. These person-mean centered variables, or within-person deviations, were used as predictor. We also allowed the coefficient of the predictors to vary among individuals (random slope), to take possible heterogeneity into account. Likelihood-ratio tests were used to estimate the significance of the random slopes. In search for factors that could account for some of the heterogeneity, we examined whether gender, chronotype (0=early, 1=late), and psychotropic medication (0=no, 1=yes) moderated the associations of interest by including interaction terms to the models in case of significant random slopes. Further, a random intercept was included in all models. The 95% range of the effect in the population was estimated per model, based on this random variation around the slope³¹. Different error-covariance structures were tested, and the best-fitting model was chosen based on the Akaike and Bayesian Information Criteria. *P*-values < 0.05 were considered significant.

Mediation of the relationship between sleep and affect

In the case a significant association was observed between predictor and outcome, we tested whether this association was mediated by either fatigue or rumination, depending on the model. For the estimation of the mediation effects, the ‘lower level mediation with random indirect effects’ approach, as suggested by Bauer, Preacher, and Gil³³ was used. This approach allows estimation of the average effect of the mediator and the heterogeneity in the strength of this effect across individuals. With this ‘lower level mediation with random effects’ approach, the average indirect effect and variance of the indirect effect, as well as the average total effect were estimated. This variance of the indirect effect quantifies heterogeneity in the strength of the effect at the level of the individual.

Results

Group-level characteristics of depressed patients and healthy controls

In total 62 participants started the diary study period. Four of these participants dropped out before the end of the study was reached. Four other participants completed the study period but did not have enough valid measurements ($T \geq 60$) with regard to accelerometer data or diary observations. These participants were therefore removed from the final sample, resulting in 54 participants who completed the study period and had sufficient valid measurements. According to responses on the Munich Chronotype Questionnaire, sleep quality at baseline was higher in controls than in depressive participants on both free and working days. Sleep quality was somewhat lower on working days than on free days in both groups. Around 80% of the non-depressed participants was employed or student, in contrast to 52% of the depressive participants. Further demographic characteristics of the sample are presented in Table 1.

Table 1. Demographic and clinical characteristics

	Healthy Controls (N = 27)	Depressed patients (N = 27)	Group-comparison <i>Statistical Test</i>
Mean (SD)			
Age, years	34.0 (9.0)	34.7 (9.9)	$F=0.87, p=.80, \eta^2=.001$
Female, n	20	20	$\chi^2=0, p=1.00, \phi=0$
Smoking, n	6	7	$\chi^2=0, p=1.00, \phi=.04$
BMI, kg/m ²	22.5 (2.6)	24.2 (5.9)	$F=14.14, p=.17, \eta^2=.04$
Partner, n	17	15	$\chi^2=0.22, p=.64, \phi=-.11$
Level of education, n			$\chi^2=0.02, p=.88, \text{Cramer's } V=.06$
Low	6	6	
Middle	7	8	
High	13	11	
Missing	1	2	
Employment, n			$\chi^2=11.58, p=.17, \text{Cramer's } V=.47$
Employed	14	8	
Student	8	6	
Unemployed	3	8	
Other	2	4	
Missing	0	1	
Sleep Quality baseline MCTQ, 0 'low' – 10 'high'			
Free days	7.5 (1.0)	5.0 (1.8)	$F=6.06, p<.001, \eta^2=.45$
Working days	7.2 (1.1)	4.4 (1.8)	$F=5.52, p<.001, \eta^2=.46$
CIDI sleep symptoms at baseline			
Insomnia, n	0	14	$\chi^2=16.30, p<.001, \phi=.59$
Hypersomnia, n	0	16	$\chi^2=19.98, p<.001, \phi=.65$
BDI score			
Baseline	2.3 (2.7)	31.3 (10.0)	$F=41.12, p<.001, \eta^2=.80$
Follow-up	2.6 (3.6)	24.1 (14.7)	$F=32.14, p<.001, \eta^2=.52$
Psychotropic medication, n	1	17	$\chi^2=13.42, p<.001, \phi=.54$
Benzodiazepines, n	0	3	
Hypnotics, n	0	0	
Antipsychotics, n	0	5	
Sleep Quality during study, 1 – 7	5.3 (1.2)	4.4 (1.5)	$F=2.53, p<.001, \eta^2=.25$
Positive Affect during study, 1 – 7	4.6 (1.1)	3.4 (1.3)	$F=1.39, p<.001, \eta^2=.28$
Negative Affect during study, 1 – 7	1.5 (0.6)	3.1 (1.2)	$F=11.66, p<.001, \eta^2=.52$

Note. SD = Standard Deviation of the mean; N = number of participants; effect sizes: η^2 was calculated for t-tests, ϕ for 2x2 Chi-Square tests, Cramer's V for >2x2 Chi-Square tests; BMI = Body Mass Index; education level 'low' = primary school/ education, vocational education, preparatory secondary vocational education; 'middle' = senior general secondary school, pre-university education; 'high' = higher professional education, scientific education; MCTQ = Munich Chronotype Questionnaire; CIDI = Composite International Diagnostic Interview;

BDI = Beck Depression Inventory.

On average 0.35 out of 30 affect measurements (1.2%) were missing (s.d.=0.81, range 3, for both PA and NA). On average 2 out of 30 sleep quality measurements (6.7%) were missing (s.d.=3.2, range 18).

The association between sleep quality and subsequent affect

Model 1a. Do changes in sleep quality predict changes in PA and is this relationship moderated by depression?

The results of all multilevel models are summarized in Table 2. The default covariance-structure “independent” provided the best model fit in all multilevel models. The multilevel model for PA showed that changes in sleep quality predicted changes in PA ($B=0.08$, 95% CI 0.06 to 0.11, $p<.001$); an improvement in sleep quality predicted a subsequent improvement of PA. A significant autoregressive effect of PA was found as well ($B=0.14$, 95% CI 0.09 to 0.19, $p<.001$). This means that an improvement in PA predicted a higher score on PA the next day. The relationship was not significantly moderated by depression ($B=0.04$, 95% CI -0.09 to 0.01, $p=.14$), and the moderation term was therefore removed from the model. Significant random slopes were found for both sleep quality and lagged PA, indicating that the magnitude of the associations differed significantly between individuals. Gender, chronotype, and psychotropic medication did not significantly moderate the association between sleep quality and PA (B for interaction with gender = 0.004, s.e. = 0.03, $p = .91$; B for interaction with chronotype = -0.01, s.e. = 0.03, $p = .63$; B for interaction with psychotropic medication = -0.04, s.e. = 0.03, $p = .16$). The standard deviation around the sleep quality slope was 0.25, corresponding with a variance of 0.06. On the basis of this variance it was estimated that 95% of the population has coefficients between -0.41 and 0.57 for the effect of sleep quality on PA.

Model 1b. Do changes in sleep quality predict changes in NA and is this relationship moderated by depression?

Changes in sleep quality predicted changes in NA ($B=-0.06$, 95% CI -0.08 to -0.03, $p<.001$). An improvement in sleep quality predicted a decrease in NA, and here an autoregressive effect of NA was observed as well ($B=0.26$, 95% CI 0.21 to 0.31, $p<.001$). This indicates that an increase in NA predicted more negative affect the subsequent day. Again, the relationship was not significantly moderated by depression ($B=-0.03$, 95% CI -0.08 to 0.02, $p=.29$). Significant random slopes were estimated for both sleep quality and lagged NA. Again, gender, chronotype, and psychotropic medication did not significantly moderate the association between sleep quality and NA (B for interaction with gender = 0.05, s.e. = 0.03, $p = .07$; B for interaction with chronotype = -0.04, s.e. = 0.03, $p = .10$; B for interaction with psychotropic medication = -0.004, s.e. = 0.03, $p = .86$). The standard deviation around the sleep quality slope was 0.25, corresponding with a variance of 0.06. On the basis of this variance, 95% of the population has estimated coefficients between -0.55 and 0.43 for the effect of sleep quality on NA.

In summary, a change in sleep quality was significantly associated with subsequent changes in affect in both depressed and non-depressed participants. Figure 1 shows the demeaned and detrended associations between sleep quality and PA and NA for every participant.

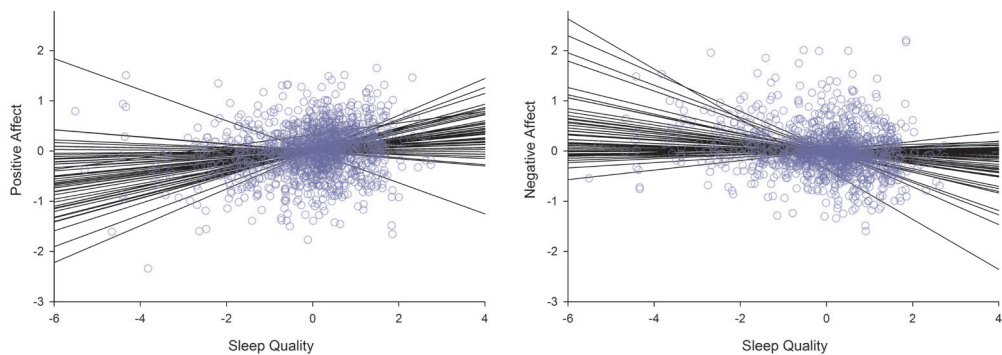


Figure 1. Demeaned and detrended associations between sleep quality and PA and NA

Sleep Quality, Positive Affect, and Negative Affect values were demeaned and detrended; dots represent all values of PA or NA give the value of Sleep Quality; the line represents the linear fit between sleep quality and subsequent PA or NA for each participant.

The association between affect and subsequent sleep quality

Model 2a. Do changes in PA predict changes in sleep quality and is this relationship moderated by depression?

We did not find a dynamic effect of PA on sleep quality; changes in PA did not predict changes in sleep quality ($B=0.03$, 95% CI -0.12 to 0.18 , $p=.70$). The autoregressive effect of sleep quality was not significant ($B=-0.03$, 95% CI -0.10 to 0.03 , $p=.29$), and again the relationship was not significantly moderated by depression ($B=-0.17$, 95% CI -0.42 to 0.09 , $p=.21$). Once again we found significant random slopes for both PA and lagged sleep quality, indicating substantial heterogeneity between individuals. The association between NA and sleep quality was not significantly moderated by gender (B for interaction = -0.11 , $s.e. = 0.13$, $p = .38$), chronotype (B for interaction = -0.08 , $s.e. = 0.13$, $p = .54$), or psychotropic medication (B for interaction = -0.25 , $s.e. = 0.17$, $p = .14$). The standard deviation around the PA slope was 0.59 , corresponding with a variance of 0.35 . This gives an estimation of coefficients between -1.13 and 1.19 for the effect of PA on sleep quality in 95% of the population.

Model 2b. Do changes in NA predict changes in sleep quality and is this relationship moderated by depression?

Similar to Model 2a, changes in NA did not predict changes in sleep quality ($B=-0.05$, 95% CI -0.25 to 0.14 , $p=.60$). Again, the autoregressive effect of sleep quality was not significant ($B=-0.03$, 95% CI -0.09 to 0.03 , $p=.27$), and depression did not significantly moderate the associations ($B=0.28$, 95% CI -0.02 to 0.58 , $p=.07$). A significant random slope was found for the lag of sleep quality but not for NA. The 95% population range for the effect of NA on sleep quality was therefore not estimated.

To conclude, changes in affect were not significantly associated with subsequent changes in sleep quality. The nonsignificant association between affect and sleep quality precluded further investigation of rumination as a mediator of this relationship.

Table 2. Results of the multilevel models

	Model 1a PA _t	Model 1b NA _t	Model 2a Sleep Quality _t	Model 2b Sleep Quality _t
Fixed Effects				
Intercept	4.04 (0.01)	2.28 (0.01)	4.77 (0.03)	4.77 (0.03)
Sleep Quality _t	0.08 (0.01)***	-0.06 (0.01)***		
Sleep Quality _{t-1}	-	-	-0.04 (0.03)	-0.03 (0.03)
PA _{t-1}	0.14 (0.03)***	-	0.03 (0.08)	-
NA _{t-1}	-	0.26 (0.01)***	-	-0.05 (0.10)
Random Effects				
Intercept	1.11 (0.01)	1.10 (0.01)	1.10 (0.02)	1.10 (0.02)
Slope				
Sleep Quality	0.06 (0.01)***	0.06 (0.01)***	-	-
Sleep Quality _{t-1}	-	-	0.16 (0.02)***	0.16 (0.02)***
PA _{t-1}	0.13 (0.02)***	-	0.35 (0.07)***	-
NA _{t-1}	-	0.17 (0.02)***	-	n.s. (omitted)
Residual	0.45 (0.01)	0.39 (0.01)	1.11 (0.03)	1.12 (0.04)
N/observations	54/1451	54/1451	54/1377	54/1377

Note. *** $p < 0.01$. N.s. = non-significant; N = number of participants. Fixed Effects are estimated coefficients (B). Between parentheses: standard error of the observed coefficient (SE). Random Effects are standard deviations. Depression x Predictor interaction was not significant and therefore removed from the final models.

Lower level mediation

Model 3a. Mediation of the temporal relationship between sleep quality and PA by fatigue.

Results of the lower level mediation analyses are summarized in Table 3. A significant mediation effect of fatigue in the association between sleep quality and PA was observed. The indirect effect ($B=0.03$, 95% CI 0.02 to 0.05, $p<.001$) explained one third of the total effect of sleep quality on PA ($B=0.09$, 95% CI 0.07 to 0.12, $p<.001$; note that this total effect differs slightly from the effect estimated in model 1a; this is due to small differences in model specification). Variance of the indirect effect in the population equaled 0.0001. This small amount of variance means that the mediation effect was not substantially different between individuals. To conclude, the relationship between sleep quality and PA was partially mediated by fatigue. An increase in sleep quality resulted in a subsequent decrease in fatigue, and a decrease in fatigue resulted in an increase of PA the following day (see Figure 2a).

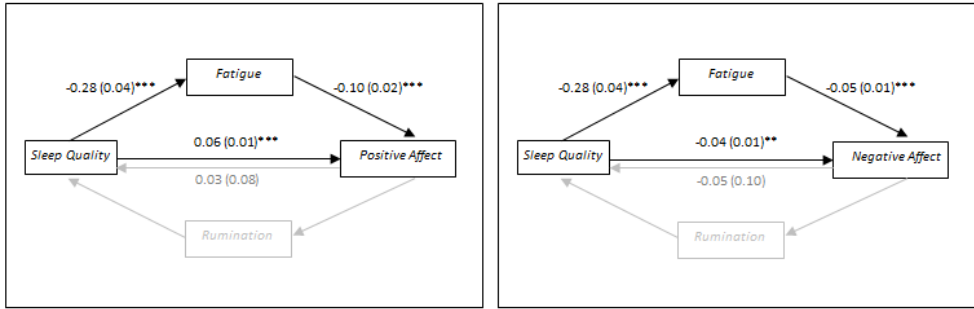
Model 3b. Mediation of the temporal relationship between sleep quality and NA by fatigue.

Fatigue also significantly mediated the association between sleep quality and NA. The indirect effect via fatigue ($B=-0.02$, 95% CI -0.03 to -0.01, $p=.001$) explained 33% of the total effect ($B=-0.06$, 95% CI -0.09 to -0.03, $p<0.001$) of sleep quality on NA. We could hardly detect interindividual differences in the indirect effect. The variance of the indirect effect equaled 0.00003. To conclude, an increase in sleep quality predicted a decrease in NA, and this relationship was partly mediated by fatigue (see Figure 2b).

Table 3. Results of the lower level mediation models

	Model 1a PA_t	Model 1b NA_t
Fixed Effects		
a	-0.28 (0.04)***	-0.28 (0.04)***
b	-0.10 (0.02)***	0.05 (0.01)***
c'	0.06 (0.01)***	-0.04 (0.01)**
Indirect Effect	0.03 (0.01)***	-0.02 (0.01)**
Total Effect	0.09 (0.01)***	-0.06 (0.01)***
N/observations	54/1451	54/1451

Note. *** $p < 0.001$, ** $p < 0.01$. Effects are estimated coefficients (B). Between parentheses: standard error of the estimated coefficient (SE). a = effect of sleep quality on fatigue; b = effect of fatigue on positive affect; c' = effect of sleep quality on positive affect; N = number of participants. Random effects are not shown, but estimated for all fixed effects.



2a. Lower level mediation between sleep quality and positive affect by fatigue

2b. Lower level mediation between sleep quality and negative affect by fatigue

Figure 2. Results of the lower level mediation models

Discussion

This study is the first to examine the temporal order of change in sleep quality and affect in depressed patients and healthy controls. We found that changes in sleep quality predicted changes in PA and NA but not vice versa. The dynamic association between sleep quality and PA and between sleep quality and NA was significantly mediated by fatigue. We did not find systematic differences between depressed patients and controls, but significant heterogeneity was observed among participants within both groups.

The present results support our hypothesis that changes in sleep quality predict changes in positive and negative affect. A change in sleep quality was positively associated with a subsequent change in PA, and negatively associated with a subsequent change in NA. This is in line with earlier findings¹⁶ in a sample of healthy students, in children with MDD¹⁰, and in healthy adults³. This association was not found in a sample of depressed and non-depressed participants who assessed their sleep and affect for one consecutive week⁴. Possibly, an assessment period of one week (i.e., 6 consecutive measurements) was too short to find significant associations between variables, as in the current study we did find an association between sleep and affect using 30 consecutive measurements. In accordance with the abovementioned study⁴, no differences were found between participants with or without depression in the present study. Although depressed patients did report lower levels of sleep quality and positive affect and higher negative affect than controls in the present study, the associations between these variables were not moderated by depression status. This is also in line with findings from another study in which the association between retrospectively assessed sleep at baseline and ambulatory assessments of positive and negative affect of 3 consecutive days was similar for depressed and healthy participants³⁴. Altogether, these findings suggest that the effect of sleep quality on PA and NA is similar for depressed and non-depressed people.

We found that fatigue was a significant mediator of the relationship between sleep quality and our affect measures, congruent with earlier studies which showed that sleep quality was associated with increased fatigue^{12,14}. It was previously shown that how tired a person feels when waking up is among the most important factors associated with judging one's sleep quality in insomnia patients and healthy persons³⁵. This overlap between fatigue and sleep quality could explain (part of) the variance in the estimated association between sleep quality, fatigue, and subsequent affect. Contrary to this earlier review¹², and to earlier ambulatory assessment studies^{10,16}, we did not observe a dynamic relationship between PA or NA and subsequent sleep quality, and therefore did not test the assumed mediation of the association between affect and sleep quality by rumination¹⁵.

One reason why we did not find a significant temporal relationship between PA/NA and subsequent sleep quality in this study may be individual heterogeneity. We found significant random slopes indicating substantial differences between individuals in the examined temporal relationships. This heterogeneity could not be explained by gender, chronotype, or psychotropic medication, however it could be possible that other unmeasured factors were responsible for the individual differences. The estimated confidence intervals of the random slopes showed the presence of negative as well as positive regression coefficients at the individual level. A combination of negative and positive coefficients could result in an average group effect of about zero, because opposing regression coefficients at the level of the individual cancel each other out. A possible explanation for this heterogeneity is that, in contrast to earlier studies that did find significant associations between affect and subsequent sleep^{10,16}, our affect measures had a pleasure and an activation dimension³⁶. In the present study, an individual could report high PA because of being energetic (=high activation, high pleasure), or because of feeling relaxed (=low activation, high pleasure). Arguably, an increase in energy influences sleep quality negatively because the individual may become restless due to feeling energetic. High arousal could be the underlying mechanism that is responsible for this relationship. Contrary, an increase in feelings of relaxation may influence subsequent sleep quality positively because it relaxes the body due to low activation and high pleasure. In this case, low arousal has the opposite impact on sleep behavior. The same argument holds for NA. An individual might report high NA because of anxiety (=high activation, low pleasure), or because of depression (=low activation, low pleasure). Low activation items were not incorporated in the affect measurements of the previous studies^{10,16}, which may explain the discrepancy in results compared with our study.

Some methodological limitations should be kept in mind. The mean Cronbach's alpha of the NA scale was low (.64 for the group and .53 for the non-depressed participants). The influence of each item was checked for each individual separately in order to investigate whether there was one item that lowered Cronbach's alpha in the majority of participants. Different items were responsible for a low alpha in different participants. No items were removed from the NA scale because of these interindividual differences. Quality of sleep was assessed with a single self-report item. It could be argued that one item is not sufficient to measure sleep quality reliably. Nevertheless, recent studies showed the validity of using this item to assess subjective sleep quality^{14,28}. We believe that this measure is at least as valuable as more complex and objective sleep assessment methods such as actigraphy

registration, because patients report experienced sleep quality in a similar 'self-report' manner in contact with their therapist. This makes our findings connect closely to the reported experiences in clinical practice. The same could be argued about fatigue and rumination. A single-item assessment of fatigue was used in an earlier study and shown to be a valid measurement to assess daily fatigue¹⁴. We could not find studies that used a single-item assessment of rumination. The use of a more extensive measurement tool to assess rumination would obviously be better. However, this was not an option in the present study because questionnaires in diary studies should be as short as possible to keep participants motivated. An additional limitation is the partial overlap between morning fatigue, evening rumination and the daily affect measurements. One-third of the daily affect measurement was confounded with fatigue and rumination, but two-thirds was not. Besides, fatigue may be confounded with the sleep measure: both were assessed at the same time point, and fatigue is known to be an important factor in judging sleep quality³⁵. This could have explained (part of) the variance in the observed associations. Another limitation of the observational design that was used in this study is that we could not draw conclusions about causality between sleep quality and affect. Future intervention studies would be helpful in our understanding of causality between sleep and affect. Still, this is the first study in which one of the most important criteria of causality, i.e. the temporal order of change between sleep and affect was established in depressed and non-depressed participants. The ambulatory assessment design with its many repeated assessments of both sleep and affect within individuals made this possible.

Sleep disturbance is among the core symptoms of the diagnosis of major depressive disorder. In clinical practice, sleep is often part of the treatment and relapse prevention plan, as impaired sleep is an important risk factor for relapse or recurrence. Still, interventions with a focus on sleep are often not mentioned in treatment protocols for depression³⁷⁻³⁹. A positive change in self-reported sleep quality might be the start of a virtuous spiral or self-reinforcing cycle in patients: the improved sleep quality might improve mood, which then could have a positive impact on the overall functioning of the patient, which in turn may improve mood, and so forth. Our results point towards the importance of a tailored sleep-oriented treatment in MDD, taking individual differences into account to provide the best-fitting treatment. Heterogeneity between patients in within-person associations might be uncovered by the use of daily sleep and mood diaries. This personalized approach may be a helpful tool because it might give insight into the association between sleep and affect for each individual patient. A behavior-oriented approach to sleeping problems (e.g., sleep hygiene advice such as: always go to bed at same time, sleep in a dark, cool, silent room, avoid alcohol, caffeine, and heavy meals before sleeping, practice exercise during day, don't nap after 4pm, do relaxation before sleeping⁴⁰) or Cognitive Behavioral Therapy for Insomnia (CBT-I) instead of prescribing medication may be adopted by the general practitioner as well. This approach could be adapted to individual needs based on severity of sleep disturbances assessed with sleep diaries, actigraphy information, or an insomnia/hypersomnia questionnaire. Treatment of sleep disturbances may not only decrease the sleep disturbances (without the risk of side effects or dependence) but could also improve mood and thus prevent (non-)depressed patients from ending up in a negative vicious cycle in which poor sleep

quality increases negative mood and so forth.

To conclude, our study showed that changes in sleep quality predicted subsequent changes in affect, partly via fatigue, underlining the need for more attention to sleep problems in the treatment of depression. Heterogeneity in the strength and sign of the observed associations suggests substantial interindividual differences, which calls for a personalized approach.

4

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