A sad day's night

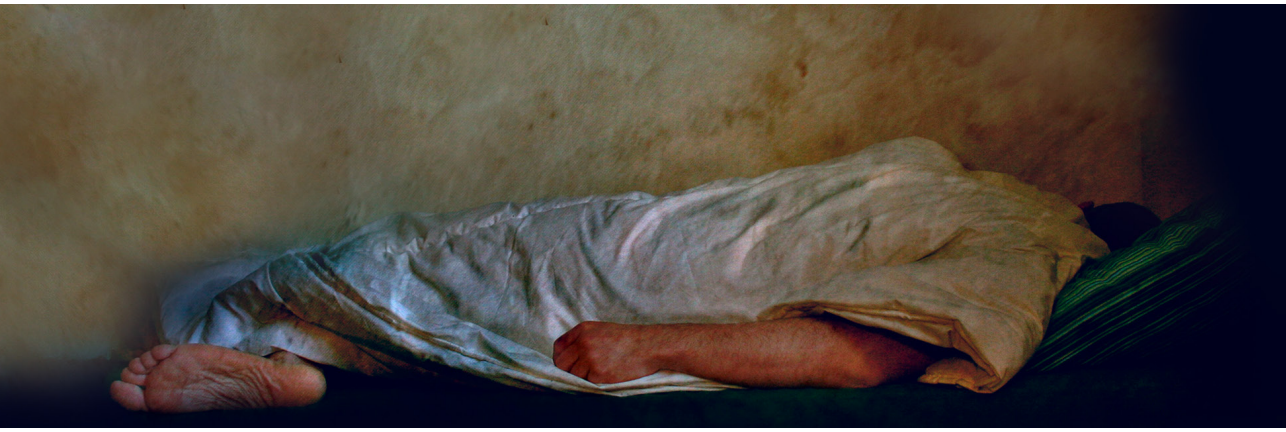
Bouwmans, Maria

CHAPTER 3

The dynamic interplay of melatonin, affect, and fatigue in the context of sleep and depression

Mara E.J. Bouwmans, Adriene M. Beltz, Elisabeth H. Bos, Albertine J. Oldehinkel, Peter de Jonge, Peter C.M. Molenaar

Submitted



Abstract

The aim of the present study was to reveal how positive affect (PA), negative affect (NA), fatigue, and melatonin are inter-related in individuals with and without MDD.

We used a unique dataset with up to 90 measurements of 14 depressed and 15 pair-matched non-depressed participants and the novel network analysis approach Group Iterative Multiple Model Estimation (GIMME) to reveal how affect, fatigue, and melatonin were related across time at the group- and individual level. Thereafter, we investigated how individual-level differences in the role of melatonin were related to sleep and depression severity.

PA and NA (β=-0.47), and PA and fatigue (β=-0.44) were related contemporaneously in the full sample. Substantial between-individual differences were found. In 83% of the study participants, melatonin was related to either affect or fatigue. Those who did not have associations with melatonin in their networks had relatively greater depression severity, worse sleep quality, and lower energy expenditure.

This study revealed the possibilities of network mapping (via GIMME) for dynamic individual psychological and biological data. The results underline not only the presence of large heterogeneity, but also show that despite this heterogeneity, meaningful generalizations can be made regarding the dynamics of melatonin with affect and fatigue in depression.

Introduction

Major Depressive Disorder (MDD) is one of the most common and debilitating mental health disorders in the Western world[1]. Depression has intricate ties with sleep, as up to 80% of patients who suffer from MDD also report sleep disturbances (insomnia, hypersomnia, or both) during a depressive episode[2]. Yet, little is known about the mechanisms underlying the link between MDD and sleep. In particular, it is unclear how depression-related factors, such as affect, and how sleep-related factors, such as fatigue and melatonin levels, are inter-related. This knowledge gap could be due to a lack of longitudinal data and analytic techniques necessary for unraveling these inter-relations.

Several theories suggest that disturbed sleep and depressed mood are both a physiological response to a disruption in circadian rhythms[3,4]. The circadian rhythm is colloquially referred to as the biological clock. Light helps to keep the biological clock in sync with humans' external 24-hour cycle of day and night[5,6]. Light sends signals to the pineal gland via the retina and the suprachiasmatic nucleus, and the pineal gland regulates the synthesis of melatonin[3,7]. The 24-hour cycle of melatonin synthesis is known to be responsible for the regulation of body temperature, metabolic activity, and sleep rhythm[8,9]. Changes in sleep rhythm are closely connected to disruption or changes of melatonin synthesis[10].

Mood-related processes are thought to be influenced by the circadian rhythm as well. A disrupted circadian rhythm has been suggested to change affect via a dysregulation of the neurotransmitter serotonin[11,12]. In the absence of light, serotonin is processed into melatonin within the pineal gland[7,13]. Exogenous administration of melatonin has been found to be effective in the treatment of mood disorders. Administration of slow-release melatonin decreased depression scores[14], and melatonin agonists showed a reduction in depression scores[15-17]. Less clear is the association between endogenous melatonin levels and affect[18].

Fatigue, often present during MDD, is known to influence affect[19], and has been thoughto be associated with melatonin secretion too[13,20,21]. Earlier studies show contradicting results: in one earlier study manipulated suppression of melatonin by light did not influence fatigue scores[20], but in another study the administration of melatonin was associated with a significant increase in evening fatigue[21]. Up to know it is still unknown whether natural fluctuations in melatonin influence experienced fatigue, and vice versa.

The abovementioned paragraph show that several uncertainties have remained about the associations among melatonin, affect, and fatigue in the context of MDD, and the role of sleep therein. Although it is thought that abnormalities in circadian rhythmicity are reflected by changes in affect[11,14,16-18] and fatigue[13,20,21], it remains unclear how endogenous melatonin is related to these changes. Furthermore, it is not clear if and how depression and sleep are related to these associations among melatonin, affect, and fatigue.

The daily fluctuations in affect[22], melatonin[23], and fatigue[24,25], and individual differences therein, make it complex to investigate their associations over time. The recently developed approach Group Iterative Multiple Model Estimation (GIMME[26]), can

accurately model complex relations such as these. GIMME maps the covariation among variables, revealing a network that shows how variables are related across time at the group- and individual level. Although GIMME was developed to model connectivity among brain regions of interest[26], it has also been applied to behavioral data from clinical populations to reveal, for example, the inter-relations among facets of internalizing and externalizing behavior reported in the daily diaries of individuals with personality pathology[27]. The current use of GIMME to uncover the associations among dynamic psychological (e.g., affect) and biological (e.g., melatonin) variables is a novel method that fills a substantive gap in the literature concerning the mechanisms underlying MDD and sleep disturbances. Thus, the current study used a unique data set, consisting of up to 90 measurements from each of nearly 30 participants, and a novel network analysis approach to unravel how affect, fatigue, and melatonin are related in individuals with and without MDD.

The first aim of the present study was to identify the role of melatonin in moment-to-moment changes of affect and fatigue in depressed patients and healthy controls. Based on earlier literature we expected that fatigue, affect, and melatonin would be associated with one another at multiple time scales. However, due to the many uncertainties in the literature, we did not have hypotheses about the directions and signs of these associations. Second, we investigated how individual-level differences in the role of melatonin were related to sleep and depression severity. Again, we expected associations based on earlier literature, but were unsure about the signs of these associations.

Methods

Participants

We used a subsample of data from the Mood and Movement in Daily Life (MOOVD) study, a study that was created to investigate dynamics between physical activity, mood, and physiological processes in patients with and without MDD. Participants monitored themselves for 30 consecutive days, 3 times a day, by completing electronic diary questions, wearing an accelerometer 24/7, and providing saliva samples at every assessment point. This resulted in a maximum of 90 measurements per participant.

Participants were included from January 2012 until May 2014 in the Northern part of the Netherlands, resulting in a total of 54 participants that completed the study. The subsample consisted of the 15 first depressed and 15 pair-matched non-depressed participants that completed the study. Depressed and non-depressed participants were pair-matched based on gender, age, smoking status, and body mass index to enable pair-wise comparison and in order to create comparable groups. Depressed patients were recruited in the patient population. The non-depressed participants were recruited from the general population with advertisements in public places and on social media.

Depressed participants were included if they reported a score > 14 on the Beck Depression Inventory (BDI[28]), and if a current or recent (<2 months) episode of DSM-IV major depressive disorder (MDD) was classified, assessed with the Composite International

Diagnostic Interview (CIDI[29]). Non-depressed participants were included with BDI scores < 9 and if MDD assessed with the CIDI could not be classified. Depressed and non-depressed participants were excluded from participation in the case of: current or recent (<2 years) episodes of psychotic or bipolar disorder according to CIDI assessment; visual or hearing impairments; pregnancy; and somatic disorders or medication use influencing the HPA-axes or the autonomic nervous system. Informed consent of the participants was obtained after the nature of the procedures had been fully explained. The research protocol was approved by the Medical Ethical Committee of the UMCG. 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 of 1975, as revised in 2008.

When interested in participating, individuals were supplied with information about the study, a written consent form, the BDI questionnaire, the Munich Chronotype Questionnaire (MCTQ[15]), and a health questionnaire. If BDI criteria were met, individuals were invited for an appointment to assess the CIDI. If individuals appeared eligible for participation, the second part of the appointment was used to clarify the study procedure.

Procedure

The first two days following the appointment were used to familiarize participants with the procedure for the following month. Participants complied to assess themselves 3 times a day for 30 consecutive days. Times of assessment were fixed every 6 hours, and were based on the participants' chronotypes as assessed with the MCTQ. Assessments took place around 10:00 AM, 4:00 PM, and 10:00 PM for most of the participants. The PsyMate®, an electronic device, was used for diary assessments. The diary questions were about affect, sleep, activities, and cognitions. Thirty minutes prior to every assessment the PsyMate® produced a warning sound and message to stop food and drink intake (besides water), smoking, and brushing teeth until the assessment was completed. This was generated to prevent interference with the saliva collection. The warning sound was produced again at the fixed time point, when participants had to complete the assessment. Completion of the assessment could be delayed with a maximum of 1hr in case of unexpected circumstances (e.g. appointment or work meeting). The assessment started with the message to start saliva collection by keeping a synthetic swab (Salivette®) in the mouth for at least 3 minutes while completing the assessment. During the clarification of the study procedure participants were instructed not to chew the Salivette®, and to store the Salivette® in their refrigerator immediately after, or in any case within 4 hours after saliva collection. The assessment contained several check-up questions to control whether participants complied with the 30-min restrictions of food- and drink intake, smoking, and brushing their teeth. Participants were provided with a logbook to note abnormalities and/or protocol violations every day. Salivettes® were collected weekly by researchers and centrifuged the same day at the special chemistry lab (Laboratory Medicine, UMCG) before they were stored at -80°C until they were assayed.

Measures

Melatonin

The Salivettes® of the first 15 depressed and 15 pair-matched non-depressed participants were assayed in the chemistry lab of Laboraty Medicine (UMCG). All samples of one participant were assayed in the same batch with liquid chromatography-tandem mass spectrometry (LC-MS/MS), by means of online-solid phase extraction in combination with isotope dilation. LC-MS/MS is known to be analytically compatible and to perform well[30]. The quantification limit for melatonin was 5.0 pmol/L. Mean intra- and inter-assay coefficients of variation were below 9.0%.

Diary data

Positive affect (PA), negative affect (NA) as operationalized by Bylsma[31] and fatigue were assessed 3 times a day. The positive and negative affect scale both consisted of the mean score on 7 items (PA: talkative, enthusiastic, confident, cheerful, energetic, satisfied, and happy; NA: tense, anxious, distracted, restless, irritated, depressed, and guilty). All items were scored on a Likert scale from 1 'not' up to 7 'very'. The PA and NA scales have high internal consistency based on person-level reliability estimates in an earlier study (both > .90 in[31]). The mean Cronbach's alpha coefficient was .86 for PA, and .67 for NA. Fatigue was assessed with one item during every assessment, and also scored on a Likert scale from 1 'not' up to 7 'very'. A single-item measurement of fatigue has been used before and showed to be a valid measurement to monitor daily fatigue[32].

Predictors of individual-level differences in the role of melatonin

Baseline and diary data of depression severity and perceived sleep were used to assess if and how individual-level differences in the role of melatonin in the network models (described below) could be explained by differences in depression- and sleep-related variables. Subjective sleep quality was assessed at baseline with the item 'I grade my night's rest' from 1 'bad' up to 10 'excellent' by means of the MCTQ. Subjective sleep quality and duration were monitored at every assessment during the diary study as well, with the item 'Did you sleep well?' with response categories ranging from 1 'not well' to 7 'very well', and the item 'How long did you sleep?' with response categories '<30 minutes'; '1/2-1 hour'; '1-2 hours'; '2-4 hours'; '4-6 hours'; '6-7 hours'; '7-8 hours'; '8-9 hours'; '9-10 hours'; '10-11 hours'; '11-12 hours'; '> 12 hours'. We used the mean squared successive difference (MSSD) as a measure of moment-to-moment stability, and calculated the average MSSD over the 90 sleep duration measurements for each participant. High MSSD scores represent instability, and low MSSD scores represent stability. Time spent outside was measured at baseline with the MCTQ item 'On average how much time do you spent outside every day (by daylight, not under a roof)?' answered in amount of hours and minutes. Weekly exercise at baseline was assessed as 'If you add all exercise during the week, on average how many time do you spend on exercise every week?' answered in amount of minutes. Daily exercise during the diary study was assessed with an accelerometer. Caffeine intake was assessed with a question at baseline: 'Do you drink coffee or other caffeine-containing drinks and if yes, how many cups/cans per day?'. Depression score was measured at baseline by means of the BDI. We examined medication use by asking if

participants used medication, and if yes, what type of medication and what dosage.

Data Analysis Plan

The average amount of missing melatonin data was 5.4% for the depressed participants and 8.2% for the controls. Depressed participants had on average 7.1% missing diary data and controls 7.2% missing diary data. We imputed missing data per participant by means of the multiple imputation approach Amelia II, available as R package[33]. With Amelia II it is possible to take the dynamic structure of a dataset into account. Fifty imputations were estimated for every dataset, and we used the average as the final value that was imputed in the original dataset. One depressed participant had to be excluded from analyses because of highly collinear variables. The final sample thus consisted of 14 depressed and 15 non-depressed participants.

The moment-to-moment interplay among melatonin, affect, and fatigue

The moment-to-moment interplay among melatonin, PA, NA, and fatigue was estimated by means of GIMME[26], which is implemented in MATLAB® (Mathworks, r2014a) and LISREL[34]. GIMME was used to specify unified structural equation models, which explain the covariation among variables using lagged (at the next measurement occasion) and contemporaneous (at the same measurement occasion) directed relations, at the group- and the individual level in an iterative approach[35]. First, connections among melatonin, PA, NA, and fatigue at the level of the group were freed if they significantly improved model fit based on Lagrange Multiplier equivalents[36] for at least 75% of the sample. Second, the estimated group model was optimized by dropping connections that were no longer significant for > 75% of the group because of other freed connections. Third, models were estimated at the level of the individual, starting by freeing the connections that were significant in the group model. Then again, connections that significantly improved model fit based on Lagrange Multiplier equivalents were freed for each individual. Fourth, freed connections that were no longer significant were dropped from the individual's model, and a confirmatory model was fit. Fit indices were checked after optimal model identification. Minimal requirements were RMSEA ≤ .05, SRMR ≤ .05, CFI ≥ .95, and NNFI ≥ .95 (RMSEA = Root Mean Square Error of Approximation; SRMR = Standardized Root Mean Square Residual; CFI = Comparative Fit Index; NNFI = Non-Normed Fit Index). Two out of four requirements should be met[37]. Sleep could not be included in the GIMME model estimation. The reason is that the measurement of sleep did not align with the measurement of the other study variables, as sleep only occurred once – not thrice – a day. We therefore decided to incorporate the sleep measures in the group-level comparison in order to test possible associations with sleep.

Predictors of individual-level differences in the role of melatonin

Independent t-tests or Chi-square tests were performed with IBM SPSS Statistics 22 (IBM, SPSS Inc., Chicago, IL) to compare participants that showed associations of melatonin with PA, NA, or fatigue in their final models with participants that did not show associations of melatonin with the other variables in their final models, to find out whether interindividual differences in the role of melatonin might be related to depression status, sleep duration

and sleep quality at baseline and during the diary study, time spent outside measured at baseline, weekly exercise at baseline and daily exercise during the diary study, amount of daily caffeine at baseline, depression score at baseline, and medication use at baseline. The significance level was $p<.05$.

Results

Descriptive statistics

In total 15 healthy controls and 14 pair-matched depressed patients were included in the analyses. Participants were on average 36 years old (SD = 9), and 76% of the sample was female, reflecting the gender difference in depression. The groups did not show differences in baseline characteristics except for BDI scores, medication use, and sleep quality. BDI scores differed significantly between healthy controls (BDI = 2.2, SD = 3.1) and depressed patients (BDI = 30.4, SD = 10.0). Only 20% of non-depressed participants reported baseline medication use, in contrast to 64.3% of the depressed participants. The depressed participants reported significantly lower sleep quality but not sleep duration ($p<.01$). More details and the means and standard deviations for depressed patients and controls can be found in Table 1.

The moment-to-moment interplay among melatonin, affect, and fatigue

The final model (containing group- and individual-level relations) showed good fit for all individuals, with average fit indices of RMSEA = 0.02, SRMR = 0.06, CFI = 0.99, and NNFI = 1.00. At the group level, significant contemporaneous associations were found between PA and NA (β = -0.47) and between PA and fatigue (β = -0.44). This means that an increase in PA was associated with a decrease in NA and fatigue at the same measurement occasion. This group-level model with corresponding average β's is visualized in Figure 1.

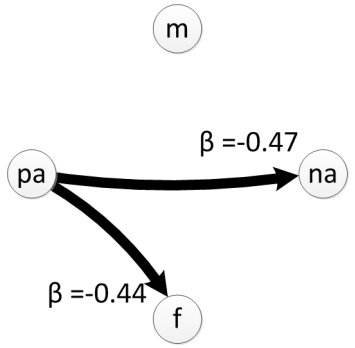


Figure 1. *Dynamic interplay at the level of the group*
No lagged group-level relations were found, therefore only contemporaneous associations estimated for all participants are shown; m=melatonin; pa=positive affect; na=negative affect; f=fatigue; beta coefficients represent the mean value of the association averaged over all 29 participants.

Table 1. *Demographic and clinical characteristics*

Mean (SD)	Total (N=29)	Controls (N=15)	Depressed (N=14)
Baseline measures			
Age, years	35.8 (9.4)	35.1 (8.4)	36.5 (10.6)
Female, n	22 (75.9%)	11 (73.3%)	11 (78.6%)
Smoker, n	5 (17.2%)	3 (20.0%)	2 (14.3%)
BMI, kg/m^2	22.9 (3.8)	22.5 (2.7)	23.5 (4.7)
Sleep Quality Working Days, 1-7	6.07 (1.77)	7.27 (0.80)	4.79 (1.63)***
Sleep Quality Free Days, 1-7	6.43 (1.71)	7.47 (0.99)	5.23 (1.59)***
Sleep Duration Working Days, min	451 (79)	453 (57)	450 (99)
Sleep Duration Free Days, min	481 (92)	488 (78)	473 (109)
Time Outside Working Days, min	84 (50)	86 (53)	82 (47)
Time Outside Free Days, min	146 (165)	167 (224)	125 (74)
Weekly Exercise, min	109 (102)	116 (108)	102 (100)
Daily Caffeine Intake	2.43 (2.48)	2.97 (2.57)	1.81 (2.32)
BDI score baseline	15.8 (16.0)	2.2 (3.1)	30.4 (10.0)***
BDI score follow-up	13.0 (14.5)	3.6 (4.3)	23.1 (15.0)***
Medication use, n	12 (41.4%)	3 (20.0%)	9 (64.3%)*
Diary measures			
Sleep Quality, 1-7	4.91 (0.96)	5.36 (0.83)	4.44 (0.88)**
Sleep Duration, 1-12	5.83 (0.83)	5.85 (0.58)	5.81 (1.06)
Sleep Stability MSSD	1.69 (2.18)	1.15 (1.08)	2.27 (2.88)
Energy Expenditure, kcal	248 (84)	256 (83)	240 (88)

Note. SD = Standard Deviation of the mean; N = number of participants; BMI = Body Mass Index; BDI = Beck Depression Inventory; MSSD = Mean Squared Successive Difference; if not otherwise specified, mean and standard deviation (in parentheses) are given; *** p<.05; ** p<.01; * p<.001.

For each individual, 12 possible associations existed between melatonin and affect or fatigue. Because of substantial interindividual differences in the presence, strength and direction of each of these associations, the associations were not found significant at the level of the group. Still, melatonin was associated with affect or fatigue in 83% of individual models, summarized in Figure 2. Momentary increases in melatonin were significantly associated with a same-time decrease in PA in 3 participants, a same-time decrease in NA in 5 participants, and a same-time increase in fatigue in 5 participants. Next to these contemporaneous associations we found that an increase in melatonin predicted a decrease in PA in 6 participants at the next moment (i.e., measurement occasion), a next-moment decrease in NA in 3 participants, and a next-moment decrease in fatigue in 5 participants.

Momentary changes in PA, NA, and fatigue, were associated with same-time changes in melatonin in respectively 3, 4, and 5 participants. Again, lagged associations were found next to the contemporaneous ones. Changes in PA predicted next-moment changes in melatonin in 6 participants, and changes in NA predicted next-moment changes in melatonin in 1 participant. Changes in fatigue predicted changes in melatonin in 4 participants.

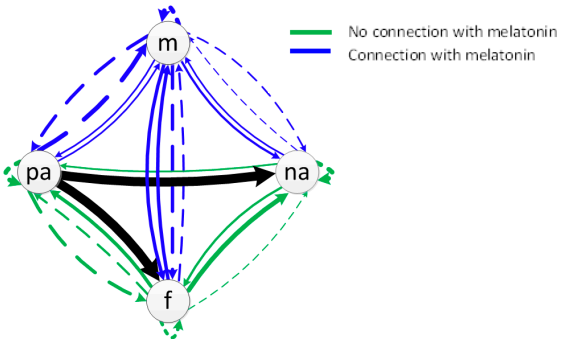


Figure 2. *Dynamic interplay among melatonin, affect, and fatigue - a summary of individual models*
Thick black lines represent group-level connections; solid lines represent contemporaneous connections; dashed lines represent lagged connections; thickness of the coloured lines represents the number of individuals with a specific connection.

Predictors of individual-level differences in the role of melatonin

For illustrative purposes, Figure 3 shows a random selection of the final models and estimated β-coefficients of 4 participants per melatonin group. We compared characteristics of the participants without melatonin associations in their final models (n = 5) to participants with melatonin associations in their final models (n = 24). 41.7% of participants in the "melatonin group" was depressed, in contrast to 80% of participants in the "non-melatonin group" (p=.12). We found that participants without melatonin associations reported higher BDI scores at baseline and follow-up compared to participants with melatonin associations. Further investigation showed that the depressed patients in the group without melatonin assocations showed worse BDI scores than the other depressed patients at both baseline (mean 38.5, SD = 12.7 versus mean 27.1, SD = 7.0) and follow-up (mean 40.8, SD = 8.0 versus mean 16.0, SD = 10.4). Sleep quality at both working and free days as measured at baseline was significantly lower for participants without melatonin associations. The match variables age, gender, smoking status, and BMI did not differ between melatonin groups. Medication use, sleep duration, time spent outside, weekly amount of exercise and daily amount of caffeine did not differ between groups either. We found that the average reported sleep quality during the diary study was lower in participants without melatonin associations. Sleep duration and stability during the diary study did not differ between the groups. Last, energy expenditure during the diary study was significantly lower in the participant group with no melatonin associations in their final models. Details of the results are shown in Table 2.

Table 2. *Between-participant comparisons based on presence or absence of melatonin connections*

	No connection with melatonin (*n*=5)	Connections with melatonin (*n*=24)	Group comparison		
Baseline measures			t	*p*	η^2
Age, years	35.8 (10.5)	35.8 (9.4)	0.01	.99	<0.01
BMI, kg/m^2	22.7 (3.6)	23.0 (3.9)	-0.16	.88	<0.01
Sleep quality Working Days, 1-7	4.0 (1.9)	6.5 (1.4)	-3.36	.002	0.29
Sleep quality Free Days, 1-7	4.8 (1.9)	6.8 (1.5)	-2.59	.016	0.20
Sleep duration Working Days, min	464 (74)	449 (81)	0.38	.70	0.01
Sleep duration Free Days, min	491 (112)	479 (89)	0.26	.78	<0.01
Time Outside Working Days, min	80 (74)	85 (45)	-0.20	.84	<0.01
Time Outside Free Days, min	92 (77)	158 (178)	-0.80	.43	0.02
Weekly Exercise, min	78 (110)	114 (102)	-0.66	.52	0.02
Daily Caffeine Intake	1 (1.4)	2.7 (2.6)	-1.26	.22	0.06
BDI score baseline	30.8 (20.4)	12.7 (13.4)	2.51	.018	0.19
BDI score follow-up	32.8 (19.1)	8.9 (9.5)	2.73	.047	0.22
			χ^2	*p*	Cramer's V
CIDI depression baseline	80.0	41.7	2.44	.12	0.29
Female, %	80.0	75.0	0.06	.81	0.44
Smoker, %	40.0	12.5	2.19	.14	0.28
Medication use, %	13.8	27.6	2.04	.15	-0.36
Diary measures			t	*p*	η^2
Sleep Quality, 1-7	4.0 (1.0)	5.1 (0.8)	-2.66	.013	0.21
Sleep Duration, 1-12	5.9 (1.3)	5.8 (0.7)	0.08	.94	<0.01
Sleep Stability MSSD	2.8 (2.5)	1.5 (2.1)	1.21	.24	0.05
Energy Expenditure, kcal	176 (18)	263 (85)	-4.55	<0.001	0.43

Note. n = number of participants; BDI = Beck Depression Inventory; if not otherwise specified, mean and standard deviation (in parentheses) are given.

Figure 3. *Individual final models - a random selection*
Beta coefficients are given; ID1 to ID4 represent participants without melatonin associations, ID5 to ID8 represent participants with melatonin associations; gender (F = female, M = male), age, and depression status (MDD = Major Depressive Disorder; HC = Healthy Control) are given below ID number; black lines represent group-level connections; solid lines represent contemporaneous connections; dashed lines represent lagged connections.

Participants without melatonin associations were mostly depressed patients (4 out of 5). We checked baseline characteristics of the participants in this subgroup to see whether they were characterized by salient features, and this revealed that the healthy control in this group was a frequent cannabis user, reporting cannabis use at least twice a week (i.e., over 100 times a year), next to the daily consumption of on average 17 cigarettes. No other characteristic aspects could be found.

Discussion

The application of GIMME to the diaries of participants with and without depression and sleep disturbances revealed dynamic associations between endogenous melatonin levels, affect, and fatigue. At the level of the group (i.e., for >75% of the sample), PA was associated with NA and with fatigue, while there were no associations with melatonin. However, melatonin was found to be differentially associated with affect or fatigue in 83% of individual-level models. These results underline the importance of GIMME, as it detected heterogeneity in melatonin relations as well as affective patterns common to all participants.

The finding that endogenous melatonin secretion was associated with changes in affect and fatigue, such that changes in melatonin secretion, a proxy for dynamics in circadian rhythmicity, were associated with changes in affect and fatigue is novel. We also found associations the other way around, such that changes in affect and fatigue predicted changes in melatonin levels. This set of findings might point towards the presence of a feedback loop between psychological and physiological phenomena for some people, and not a one-way association in which melatonin fluctuations are responsible for subsequent changes in affect and fatigue. Another explanation is that an external unmeasured factor was responsible for the associations. Either way, this opens new avenues for research.

The individual final models of five participants did not show associations between endogenous melatonin levels and other variables. Some provocative characteristics were found between the "non-melatonin group" and the "melatonin group" in spite of the small group size of the "non-melatonin group" (N=5). The majority of these participants were suffering from MDD (n = 4), and the healthy control was a frequent cannabis user. It was recently shown that chronic marijuana use is associated with a more robust synchrony of the circadian rhythm with the 24-hour cycle compared to non-users[38]. This synchronizing effect of marijuana might have overruled the effect of melatonin, and therefore be responsible for a disconnection between melatonin secretion and its psychophysiological effect.

The depressed patients in the subgroup without melatonin associations reported the highest depression scores of all participants at baseline and at follow-up, suggesting that the depression was most severe in this subgroup. Arguably, particularly severe depression is associated with circadian rhythm disturbances, although the direction of this association remains unclear. The depression and affect or fatigue levels that accompany depression

could be caused by circadian rhythm disruptions, the disruptions could be an effect of the severe depression and corresponding alterations in affect or fatigue, or a feedback loop might exist between the two processes.

Some considerations regarding the analyses should be mentioned. Although sleep is known to be associated with affect[39], fatigue[40], and melatonin secretion[10], we did not include sleep in the GIMME model estimation. Future studies should measure participants for a longer time period and with a time interval of one day instead of 6 hours in order to incorporate daily fluctuations of sleep within the models. The disadvantage of a larger time interval between measurements is that within-day melatonin fluctuations cannot be detected anymore. A second limitation is the fact that GIMME only included 1 lag. Arguably, this could have resulted in loss of information. However, a posteriori model validation showed that a lag of 1 is generally sufficient when the measurement occasions are relatively infrequent, as in hours versus seconds[41]. Besides, the half-life of melatonin is estimated to be around 30 minutes[42], and we argued that recently synthesized melatonin will not have an impact on affect or fatigue ≥2 lags after secretion. A third difficulty with regard to the present study is that the contemporaneous associations estimated by means of GIMME are pointed in a direction. The directed contemporaneous relations may not be intuitive, because the measurement of the parameters between which a direction was estimated occurred at the same point in time. Statistically the direction can be interpreted as a difference in explained variance between the parameters. The advanced GIMME-MS was recently developed to verify the direction of these contemporaneous relationships. The utilization of GIMME-MS to verify these associations is a key area of future work in this perspective. This point and how to interpret GIMME in clinical data was further elaborated on in a recent publication of Beltz et al.[43].

Our study holds some implications for future research. We found that participants in whom melatonin was not associated with affect or fatigue showed some remarkable characteristics such as severe depression scores. It would be of particular interest to figure out what mechanisms might be responsible for these characteristics. We believe this group is definitely interesting to give some further attention because this may explain why melatonin fluctuations are not associated with affect or fatigue and what implications this has for depression course in these participants. This study was among the first in which the potential GIMME analyses for repeated psychophysiological diary data were shown, opening up new area for research. Moreover, the present study holds some content-related implications about the dynamics of melatonin with behavioral data. Significant heterogeneity existed in the contributions of melatonin to depression-related sleep, and it was the marriage of the unique time-series data and GIMME's combined sample- and person-centered approach that revealed this important finding.

References

1. Center for Behavioral Health Statistics and Quality. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health 2015; HHS Publication No. SMA 15-4927, NSDUH Series H-50.
2. Soehner AM, Kaplan KA and Harvey AG. Prevalence and clinical correlates of co-occurring insomnia and hypersomnia symptoms in depression. J Affect Disord 2014; 167: 93-97.
3. Pandi-Perumal SR, Moscovitch A, Srinivasan V, et al. Bidirectional communication between sleep and circadian rhythms and its implications for depression: Lessons from agomelatine. Prog Neurobiol 2009; 88: 264-271.
4. Kripke DF, Mullaney DJ, Atkinson M, et al. Circadian-Rhythm Disorders in Manic-Depressives. Biol Psychiatry 1978; 13: 335-351.
5. Saper CB, Scammell TE and Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005; 437: 1257-1263.
6. Welsh DK, Takahashi JS and Kay SA. Suprachiasmatic Nucleus: Cell Autonomy and Network Properties. Annu Rev Physiol 2010; 72: 551-577.
7. Tosini G, Baba K, Hwang CK, et al. Melatonin: An underappreciated player in retinal physiology and pathophysiology. Exp Eye Res 2012; 103: 82-89.
8. Peuhkuri K, Sihvola N and Korpela R. Dietary factors and fluctuating levels of melatonin. Food & Nutrition Research 2012; 56.
9. Tan DX, Manchester LC, Hardeland R, et al. Melatonin: a hormone, a tissue factor, an autocoid, a paracoid, and an antioxidant vitamin. J Pineal Res 2003; 34: 75-78.
10. Cajochen C, Krauchi K and Wirz-Justice A. Role of melatonin in the regulation of human circadian rhythms and sleep. J Neuroendocrinol 2003; 15: 432-437.
11. McClung CA. Circadian genes, rhythms and the biology of mood disorders. Pharmacol Ther 2007; 114: 222-232.
12. Lewy A, Emens J, Jackman A, et al. Circadian uses of melatonin in humans. Chronobiol Int 2006; 23: 403-412.
13. Lanfumey L, Mongeau R and Hamon M. Biological rhythms and melatonin in mood disorders and their treatments. Pharmacol Ther 2013; 138: 176-184.
14. Kayumov L, Brown G, Jindal R, et al. A randomized, double-blind, placebo-controlled crossover study of the effect of exogenous melatonin on delayed sleep phase syndrome. Psychosom Med 2001; 63: 40-48.
15. Roenneberg T, Kuehnle T, Juda M, et al. Epidemiology of the human circadian clock. Sleep Medicine Reviews 2007; 11: 429-438.
16. Millan MJ. Multi-target strategies for the improved treatment of depressive states: Conceptual foundations and neuronal substrates, drug discovery and therapeutic application. Pharmacol Ther 2006; 110: 135-370.
17. Quera-Salva MA, Vanier B, Chapotot F, et al. Effect of agomelatine on the sleep EEG in patients with major depressive disorder (MMD). European Neuropsychopharmacology 2005; 15: S435-S436.
18. Boyce P and Barriball E. Circadian rhythms and depression. Aust Fam Physician 2010; 39: 307-310.
19. Bouwmans MEJ, Bos EH, Hoenders HJR, et al. Sleep quality predicts positive and negative affect but not vice versa. An electronic diary study in depressed and healthy individuals. J Affect Disord.
20. Ruger M, Gordijn MCM, Beersma DGM, et al. Weak relationships between suppression of melatonin and suppression of sleepiness/fatigue in response to light exposure. J Sleep Res 2005; 14: 221-227.
21. Arendt J, Borbely AA, Franey C, et al. The Effects of Chronic, Small Doses of Melatonin Given in the Late Afternoon on Fatigue in Man - a Preliminary-Study. Neurosci Lett 1984; 45: 317-321.

22. Peeters F, Berkhof J, Delespaul P, et al. Diurnal mood variation in major depressive disorder. Emotion 2006; 6: 383-391.
23. Bouwmans MEJ, Bos EH, Booij SH, et al. Intra- and inter-individual variability of longitudinal daytime melatonin secretion patterns in depressed and non-depressed individuals. Chronobiol Int 2015; 32: 441-446.
24. Dahlgren A, Kecklund G, Theorell T, et al. Day-to-day variation in saliva cortisol-Relation with sleep, stress and self-rated health. Biol Psychol 2009; 82: 149-155.
25. Adam EK, Hawkley LC, Kudielka BM, et al. Day-to-day dynamics of experience-cortisol associations in a population-based sample of older adults. Proc Natl Acad Sci U S A 2006; 103: 17058-17063.
26. Gates KM and Molenaar PCM. Group search algorithm recovers effective connectivity maps for individuals in homogeneous and heterogeneous samples. Neuroimage 2012; 63: 310-319.
27. Beltz AM, Wright AGC, Sprague BN, et al. Bridging the Nomothetic and Idiographic Approaches to the Analysis of Clinical Data. Assessment 2016. DOI: 10.1177/1073191116648209.
28. Beck AT, Erbaugh J, Ward CH, et al. An Inventory for Measuring Depression. Arch Gen Psychiatry 1961; 4: 561-571.
29. WHO. The Composite International Diagnostic Interview (CIDI). Geneva: Geneva, 1997.
30. de Jong WHA, de Vries EGE and Kema IP. Current status and future developments of LC-MS/MS in clinical chemistry for quantification of biogenic amines. Clin Biochem 2011; 44: 95-103.
31. Bylsma LM, Taylor-Clift A and Rottenberg J. Emotional Reactivity to Daily Events in Major and Minor Depression. J Abnorm Psychol 2011; 120: 155-167.
32. Van Hooff MLM, Geurts SAE, Kompier MAJ, et al. "How fatigued do you currently feel?" convergent and discriminant validity of a single-item fatigue measure. J Occup Health 2007; 49: 224-234.
33. Honaker J, King G and Blackwell M. Amelia II: A Program for Missing Data. Journal of Statistical Software 2011; 45: 1-47.
34. Jöreskog, K.G., & Sörbom, D. LISREL VIII: A guide to the program and applications. Mooresville: Mooresville, 1992.
35. Gates KM, Molenaar PCM, Hillary FG, et al. Automatic search for fMRI connectivity mapping: An alternative to Granger causality testing using formal equivalences among SEM path modeling, VAR, and unified SEM. Neuroimage 2010; 50: 1118-1125.
36. Sorbom D. Model Modification. Psychometrika 1989; 54: 371-384.
37. Brown TA. Confirmatory factor analysis for applied research. New York: New York, 2006.
38. Whitehurst LN, Fogler K, Hall K, et al. The effects of chronic marijuana use on circadian entrainment. Chronobiol Int 2015; 32: 561-567.
39. Sonnentag S, Binnewies C and Mojza EJ. "Did you have a nice evening?" A day-level study on recovery experiences, sleep, and affect. J Appl Psychol 2008; 93: 674-684.
40. Fung CHL, Nguyen M, Moineddin R, et al. Reliability and validity of the Daily Cognitive-Communication and Sleep Profile: a new instrument for monitoring sleep, wakefulness and daytime function. International Journal of Methods in Psychiatric Research 2014; 23: 217-228.
41. Beltz AM and Molenaar PCM. A posteriori model validation for the temporal order of directed functional connectivity maps. Frontiers in Neuroscience 2015; 9: 304.
42. Ito Y, Iida T, Yamamura Y, et al. Relationships between Salivary Melatonin Levels, Quality of Sleep, and Stress in Young Japanese Females. International journal of tryptophan research : IJTR 2013; 6: 75-85.
43. Beltz AM and Molenaar PCM. Dealing with Multiple Solutions in Structural Vector Autoregressive Models. Multivariate Behavioral Research 2016. DOI: 10.1080/00273171.2016.1151333.