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The person-specific interplay of melatonin, affect, and fatigue in the context of sleep and depression

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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 the person-specific level. Thereafter, we investigated how individual differences in the role of melatonin were related to sleep and depression severity.

PA and NA ($\beta = -0.47$), and PA and fatigue ($\beta = -0.44$) were related contemporaneously in the full sample. Substantial between-person 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 for dynamic person-specific 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 interplay of melatonin with affect and fatigue in depression.

1. Introduction

Major Depressive Disorder (MDD) is one of the most common and debilitating mental health disorders in the Western world (Center for Behavioral Health Statistics and Quality, 2015). 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 (Soehner, Kaplan, & Harvey, 2014). 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.

Previous studies have shown that associations among affect, fatigue and melatonin levels might play a role in the strong connection between depression and sleep. Until now, however, it has remained unclear how these associations are dynamically inter-related to each other. Perhaps that is because most of these studies have come from a nomothetic perspective, creating an average model for a sample and assuming that the model equally represents all individuals in that sample. For instance, this was done in previous studies on the sleep-related factors fatigue and melatonin (Arendt, Borbely, Franey, & Wright, 1984; Terlo et al., 1997). In both studies, administration of melatonin significantly increased average fatigue scores across the sample ($p < 0.05$). Looking into the results in detail, however, indicated that the group-level results did not reflect the individuals in the sample. For example, in the paper of Arendt et al. (1984), 17% of respondents had levels of fatigue that did not change at all after melatonin intake, and in another 17% of respondents, the opposite response

Abbreviations: MDD, Major Depressive Disorder; GIMME, Group Iterative Multiple Model Estimation; MOOVD, Mood and Movement in Daily Life; CIDI, Composite International Diagnostic Interview; MCTQ, Munich Chronotype Questionnaire; BDI, Beck Depression Inventory; HPA, hypothalamic-pituitary-adrenal; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MSSD, mean squared successive difference; RMSEA, Root Mean Square Error of Approximation; SRMR, Standardized Root Mean Square Residual; CFI, Comparative Fit Index; NNFI, Non-Normed Fit Index

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occurred (i.e., fatigue decreased following melatonin administration). Even studies that have focused on inter-individual (i.e., between-person) variation have resulted in knowledge gaps because they are based on individual variation around an average model. For example, in an earlier study by Bouwmans, Bos, Hoenders, Oldehinkel, and de Jonge (2016), a mean-level change in sleep quality was associated with a subsequent mean-level change in affect in a sample of depressed and healthy respondents. But, when estimating the individual-level linear fit between sleep quality and affect for this sample, individual lines differed significantly from each other, resulting in participants with positive or negative associations between sleep quality and affect, but also participants with no association at all. Thus, research coming from a nomothetic perspective and even research focusing on inter-individual variation does not reflect the *individuals* in a sample, who are heterogeneous due to large variability in both biological and contextual influences on depression and sleep. Eventually this is problematic for the treatment of depression, which is done at the individual, person-specific level. Studies of intra-individual variation (i.e., within-person), focused on person-specific associations instead of group-level averages, might fill this knowledge gap due to the emphasis on person-specific processes.

The knowledge gap is further due, in part, to a lack of intensive longitudinal data collected from multiple levels of analysis (e.g., behavioral reports of affect and biological measures of melatonin secretion). Traditional longitudinal data consisting of three to 10 repeated measurements are not well-suited to this investigation because sleep dynamics can change from night to night or even within a day (Totterdell, Reynolds, Parkinson, & Briner, 1994), making intensive longitudinal data consisting of many relatively rapidly-collected measurements over several days ideal. Another reason for this knowledge gap is heterogeneity in the associations among depression and sleep. Given variability in the etiology, presentation, and treatment outcomes of depression (Van Loo, de Jonge, Romeijn, Kessler, & Schoevers, 2012), it is unlikely that links between depression-related factors and sleep biology are homogenous, and that analytic approaches that rely on group averages (e.g., regressions) or deviations thereof (e.g., multilevel models) will accurately reflect the psychological processes at the person-specific level (Molenaar, 2004). Thus, intensive longitudinal data and person-specific analyses are – in tandem – uniquely situated to provide novel insight into the heterogeneous dynamics that underlie MDD and sleep.

Several theories suggest that disturbed sleep and depressed mood are both a physiological response to a disruption in circadian rhythms (Kripke, Mullaney, Atkinson, & Wolf, 1978; Pandi-Perumal et al., 2009). 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 (Saper, Scammell, & Lu, 2005; Welsh, Takahashi, & Kay, 2010). Light sends signals to the pineal gland via the retina and the suprachiasmatic nucleus, and the pineal gland regulates the synthesis of melatonin (Pandi-Perumal et al., 2009; Tosini, Baba, Hwang, & Iuvone, 2012). The 24-hour cycle of melatonin synthesis is known to be responsible for the regulation of body temperature, metabolic activity, and sleep rhythm (Peuhkuri, Sihvola, & Korpela, 2012; Tan et al., 2003). Changes in sleep rhythm are closely connected to disruption or changes of melatonin synthesis (Cajochen, Krauchi, & Wirz-Justice, 2003) at group-level.

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 (Lewy, Emens, Jackman, & Yuhas, 2006; McClung, 2007). In the absence of light, serotonin is processed into melatonin within the pineal gland (Lanfumey, Mongeau, & Hamon, 2013; Tosini et al., 2012). Exogenous administration of melatonin has been found to be effective in the treatment of mood disorders. Administration of slow-release melatonin decreased depression scores (Kayumov, Brown, Jindal, Buttoo, & Shapiro, 2001), and melatonin agonists showed a reduction in depression scores (Millan, 2006; Quera-Salva et al., 2005; Roenneberg et al., 2007). Less clear is the association between endogenous melatonin levels and affect (Boyce & Barriball, 2010).

Fatigue, often present during MDD, is known to influence affect (Bouwmans et al., 2016), and has been thought to be associated with melatonin secretion too (Arendt et al., 1984; Lanfumey et al., 2013; Ruger, Gordijn, Beersma, De Vries, & Daan, 2005). Earlier nomothetic studies show contradicting results: in one earlier study manipulated suppression of melatonin by light did not influence fatigue scores (Ruger et al., 2005), but in another study the administration of melatonin was associated with a significant increase in evening fatigue (Arendt et al., 1984). Up to now it is still unknown whether natural fluctuations in melatonin influence experienced fatigue, and vice versa.

The abovementioned paragraph shows 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 the previous studies suggest that abnormalities in circadian rhythmicity are reflected by changes in affect (Boyce & Barriball, 2010; Kayumov et al., 2001; McClung, 2007; Millan, 2006; Quera-Salva et al., 2005) and fatigue (Arendt et al., 1984; Lanfumey et al., 2013; Ruger et al., 2005), it remains unclear how endogenous melatonin is related to these changes on the person-specific level. Furthermore, it is not clear if and how depression and sleep are related to these person-specific associations among melatonin, affect, and fatigue.

The daily fluctuations in affect (Peeters, Berkhof, Delespaul, Rottenberg, & Nicolson, 2006), melatonin (Bouwmans et al., 2015), and fatigue (Adam, Hawkley, Kudielka, & Cacioppo, 2006; Dahlgren, Kecklund, Theorell, & Akerstedt, 2009), and individual differences therein, make it complex to investigate their associations over time. The recently developed approach Group Iterative Multiple Model Estimation (GIMME; (Gates & Molenaar, 2012)), can accurately model complex relations such as these, as established in large-scale simulations in which GIMME outperformed over 30 other network mapping approaches (e.g., in Smith et al., 2011). GIMME maps the covariation among variables, revealing a network that shows how variables are related across time (at the same and future measurement occasions) at the group- and the person-specific level. Although GIMME was developed to model connectivity among brain regions of interest (Gates & Molenaar, 2012), 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 (Beltz, Wright, Sprague, & Molenaar, 2016). The current use of GIMME to uncover the associations among dynamic psychological (e.g., affect) and biological (e.g., melatonin) variables fills a substantive gap in the literature concerning the person-specific temporal mechanisms underlying MDD and sleep disturbances. It does this not by delineating average predictors (or mediators or moderators) of sleep disturbance that are assumed to apply to all people, but rather by considering the temporal interplay among all variables and the ways in which they are both similar across people and unique to individuals. 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 person-specific 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 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.