

# Sleep and depression

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## **Valorization addendum**

## **Introduction**

Major depression is one of the most prevalent psychiatric disorders. In the Netherlands, approximately 5% of the general population is affected by this disabling condition and around 19% develops a depressive episode at some point during their lifetime (Nuijen et al., 2017). These prevalence rates correspond with international estimates including a 12-month prevalence of 3-6% and a lifetime prevalence of 4-10% (Kessler et al., 2009). Depression is characterized by persistent sadness and anhedonia (American Psychiatric Association, 2013; World Health Organization, 2016) and thereby severely impacts the quality of life of those affected. The classification of depression as one of the primary causes of disability worldwide (Vos et al., 2012) coincides with a broader societal impact. In a given year, the 550.000 individuals diagnosed with depression in the Netherlands comprise around 1.6 billion of the total healthcare costs and an approximate 1.8 billion of expenses related to leave of absence (Nuijen et al., 2017). This poses an important challenge for mental health care and emphasizes the need to develop adequate treatment and prevention strategies.

Contemporary treatments for depression comprise both psychological- and pharmacological interventions. Psychological interventions, including cognitive-behavioral therapy (Cuijpers, Cristea, Karyotaki, Reijnders, & Huibers, 2016) and interpersonal psychotherapy (Cuijpers, Donker, Weissman, Ravitz, & Cristea, 2016), are successful strategies to alleviate depression. Pharmacological treatments are equally effective (Robinson, Berman, & Neimeyer, 1990). A recent meta-analysis of 522 published and unpublished randomized controlled trials demonstrated that all of the 21 included antidepressants were more efficacious relative to placebo (Cipriani et al., 2018). Despite a proven average efficacy, clinical studies report that not even half of the patients respond to the initial antidepressant prescribed. The sequential administration of multiple different antidepressants is therefore frequently needed to achieve remission, which is accomplished in around 67% of the patients (Rush et al., 2006). Together with the limited knowledge on the precise mechanisms of action of antidepressant drugs (Harmer, Duman, & Cowen, 2017), these findings emphasize the importance to gain insight into the pathophysiology of depression.

The identification of genetic risk factors is thought to particularly advance the neurobiological understanding of depression (Levinson, 2006). Heritability studies demonstrate that genetic factors account for 30-40% of the variance in depression vulnerability (Sullivan, Neale, & Kendler, 2000) whereas the remaining 60-70% is explained by environmental influences and gene-environment interactions. Despite this clear genetic

contribution, research aimed to uncover the genetic architecture of depression has been largely unsuccessful. Research failed to identify any replicable gene or gene-environment interaction that predisposes the risk for depression (Flint & Kendler, 2014).

The limited success of genetic studies presumably relates to the heterogeneity of depression. Hence, depression is a complex condition that is characterized by profound interindividual differences in etiological background and clinical expression (Hasler, 2010). This is illustrated by the diverse range of neurobiological mechanisms implicated in the pathophysiology of depression (Hasler, 2010) and the clusters of symptoms that define a depression diagnosis according to current criteria (American Psychiatric Association, 2013; World Health Organization, 2016). These observations indicate that depression does not necessarily comprise a homogenous disorder but rather reflects a final common pathway of different pathophysiological mechanisms (Charney et al., 2002). In order to elucidate more consistent risk factors for depression, it may therefore be more valuable to focus on more homogenous subgroups of depressed patients who share common etiology or phenotypic expression instead of investigating depression as a unitary construct.

Sleep impairment comprises an important pathway in the etiology of depression. Besides representing one of the core symptoms of clinical depression (American Psychiatric Association, 2013; World Health Organization, 2016), it has been well-established that inadequate sleep independently contributes to the development of depression. A recent meta-analysis demonstrated that insomnia confers a two-fold risk increase in non-depressed individuals, thereby classifying sleep as one of the primary risk factors for depression (Baglioni et al., 2011). These findings coincide with a large body of research demonstrating that inadequate sleep results in a diverse range of alterations that resemble characteristic features of clinical depression. Encouraged by this intimate relationship, the findings presented in the following sections illustrate how sleep could advance the current understanding of depression. In line with the work presented in this dissertation, a specific emphasis is placed on the identification of genetic risk factors, pathophysiological mechanisms and treatment strategies. This valorization addendum concludes with a brief description of how the included studies utilize this conceptual framework.

## **The relevance of sleep in depression research**

### **Genetic risk factors**

Despite a clear heritability of depression (Sullivan et al., 2000), recent meta-analyses of genome-wide association data including up to 9.000 patients failed to identify replicable genetic variants related to major depressive disorder (Ripke et al., 2013; Wray et al., 2012). This limited success corresponds with the assumption that the genetic architecture of depression comprises the combined influence of multiple loci of small effect (Flint & Kendler, 2014). It is important to recognize that the effect of a single genetic variant represents an average across all etiological backgrounds and clinical representations which might conceal more consistent effects in homogenous subsets of depressed patients. It has therefore been suggested that substantial advances could be made by exploring the genetic architecture of depression in individuals that share common etiology and/or phenotypic expression (Wray et al., 2012).

Stratification by sleep-related symptomatology could provide valuable subgroups for more homogenous genetic analyses. Comorbid insomnia is common in depressed patients with approximately 40% fulfilling the criteria for clinical diagnosis (Stewart et al., 2006). Besides this frequent comorbidity, it has been well-established that insomnia independently contributes to the etiology of depression (Baglioni et al., 2011). In the light of these findings, depression with or without comorbid insomnia could represent subsets of patients with more similar etiology and clinical representation. The value of stratification by insomnia is more directly supported by genome-wide association studies of insomnia reporting a significant genetic overlap of insomnia with depressive symptoms, neuroticism and major depressive disorder (Hammerschlag et al., 2017). Differentiating the genetic makeup of depression with comorbid insomnia could therefore potentially reveal specific genetic variants involved in sleep-related depression. Investigating genetic risks factors in depressed patients free of sleep complaints could conversely help to identify variants related to different pathophysiological processes.

### **Pathophysiological mechanisms**

Depression is characterized by a diverse range of pathophysiological mechanisms. The most robust and clinically relevant evidence has been found for neurobiological theories describing a role for psychosocial stress, stress hormones, immune function, neurotransmitters (serotonin, norepinephrine, dopamine, glutamate, and gamma - aminobutyric acid), neuro

circuitry, neurotrophic factors and circadian rhythms (Hasler, 2010). Although the origin of these neurobiological abnormalities remains largely unknown, recent evidence suggests that impaired sleep could be an important factor contributing to most of these alterations.

Research at the intersection of sleep and the pathophysiology of depression demonstrates that impaired sleep induces various neurobiological alterations that resemble those associated with depression and/or depression susceptibility. Besides a general deterioration of mood (Palmer & Alfano, 2017), inadequate sleep is found to negatively impact neuroendocrine stress adaptation systems (Meerlo, Sgoifo, & Suchecki, 2008; van Dalen & Markus, 2018), neuro circuitry of emotion regulation (Yoo, Gujar, Hu, Jolesz, & Walker, 2007), immune function (Besedovsky, Lange, & Born, 2012) and the availability of neurotrophic factors (Schmitt, Holsboer-Trachsler, & Eckert, 2016). Together with the independent contribution of sleep impairment to the development of depression (Baglioni et al., 2011), these findings indicate that inadequate sleep may have a prominent role in the pathophysiology of depression.

The neurobiological connection between sleep and depression is further illustrated by the shared neurotransmitter systems involved in both sleep- and mood regulation. Evidence from these different research disciplines suggest that the neurotransmitter abnormalities associated with depression are very-well positioned to promote sleep alterations. This predominantly relates to the serotonergic system which is one of the most extensively studied neurotransmitters in depression (Hasler, 2010) and known to have a prominent role in sleep-wake regulation (Ursin, 2002). Experimental reductions in serotonin synthesis have for instance been found to cause a deterioration of mood in depression vulnerable individuals (Neumeister et al., 2002; Neumeister et al., 2004) and induce severe sleep impairment (Jouvet, 1972; Koella, Feldstein, & Czeisler, 1968). The neurobiological overlap between sleep and depression is further illustrated by the observation that the profound REM sleep disinhibition observed in clinical depression can be reversed by antidepressant treatment (Palagini, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013). Taken together, these findings suggest that sleep and depression share common neurobiological underpinnings. This emphasizes the relevance to study these factors in concert and could provide valuable opportunities to improve contemporary treatment.

### **Treatment strategies**

Comorbid insomnia is common in clinical depression (Stewart et al., 2006). The independent contribution of insomnia to the etiology of depression (Baglioni et al., 2011) illustrates that sleep impairment may negatively influence the clinical course of depression. This is more directly supported by clinical evidence demonstrating that insomnia is associated with an increased risk for depression, elevated depression severity, prolonged duration of a depressive episode and higher relapse rates (Franzen & Buysse, 2008; Riemann, 2009). These findings illustrate the importance to target sleep-related symptomatology in the treatment for depression and suggest that sleep-related interventions could be a promising treatment strategy for depression.

Several studies investigated whether the treatment of insomnia in depressed patients may concurrently alleviate affective symptomatology. Although not consistently observed, several studies have shown that adjunctive sleep medication may improve depression outcomes following antidepressant treatment (for review see: (Riemann, 2009)). Moreover, accumulating evidence suggests that the singular treatment of insomnia (cognitive behavioral therapy for insomnia; CBT-I) alleviates depression with a comparable efficacy as antidepressants and psychotherapy (for review see: (Cunningham & Shapiro, 2018)). The improvement in depressive symptomatology following CBT-I is mediated by a reduction in insomnia symptoms, directly supporting the relevance of targeting sleep-related symptomatology in the treatment for depression.

The role of sleep impairment in the treatment for depression may have important implications for the prescription of antidepressants and could provide valuable opportunities for the development of more innovative pharmacological agents. In general, most antidepressants suppress REM sleep and thereby reduce the REM sleep disinhibition that characterizes clinical depression (Palagini et al., 2013). Based on the antidepressant properties of selective REM sleep deprivation (Vogel, McAbee, Barker, & Thurmond, 1977), it has been suggested that this inhibition of REM sleep contributes to the clinical efficacy of antidepressants (Vogel, Buffenstein, Minter, & Hennessey, 1990). However, the few effective antidepressants that do not suppress REM sleep challenge this hypothesis (Palagini et al., 2013). In contrast to a relative consistent influence on REM sleep regulation, contemporary antidepressants vary considerably on the effects on symptoms of insomnia. These differences are mainly observed during the first weeks of treatment and most agents improve sleep after three to four weeks of treatment analogous to their therapeutic efficacy (Wilson & Argyropoulos, 2005). Taken together, these findings support a role for sleep in the

pharmacological treatment for depression and suggest that dysfunctional sleep, either insomnia or REM sleep abnormalities, could be an important target for the development of antidepressants.

## **Conclusion**

Sleep and depression are closely related. This intimate relationship provides valuable opportunities to advance current understanding of depression by facilitating the discovery of genetic risk factors, pathophysiological mechanisms and more efficacious treatment strategies. The present thesis aimed to utilize this conceptual framework by investigating sleep-related influences of a functional polymorphism presumed to modulate the risk for depression (serotonin transporter gene-linked polymorphic region; 5-HTTLPR). The systematic reviews and studies included in this dissertation illustrate how this genetic variation may modulate the risk for insomnia, sleep-related affective symptomatology, sleep-promoting effects of pharmacological interventions, sleep-related neuroendocrine stress sensitivity and REM sleep architecture. Taken together, the presented findings illustrate how sleep may contribute to depression research that either aims to uncover genetic risk factors, pathophysiological mechanisms or pharmacological interventions.

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