Restless REM sleep in insomnia disorder and its detrimental effects on regulation of emotional distress

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Chapter 7.

Discussion

Aims of the thesis

In the introduction, I have reviewed the neurophysiological and neurobiological characteristics of overnight memory processing, and synthesized the rationale that the sleep-dependent reorganization of neural memory circuits effectively regulates the associated emotional distress. Not excluding a role for NREM sleep, this overnight reorganization may critically depend on the unique characteristics of REM sleep. Therefore, REM sleep fragmentation may be the primary malicious factor that prevents the flexible integration of new memories and adaptation of the associated emotional distress. This thesis aimed to evaluate the hypothesis that insomnia disorder involves an insufficiency to resolve emotional distress due to processes underlying its characteristic restless REM sleep.

This main hypothesis was first formulated in a structural equation model as described in ***chapter 2***. This model predicted that ID involves a maladaptive type of sleep that results in emotional distress to last overnight. We designed a repeated-measures experimental study, described in ***chapter 3***, to evaluate this impact of maladaptive sleep in ID on the overnight regulation of emotional distress. Furthermore, in ***chapter 4*** we studied the neurobiological implications of the resulting long-lasting emotional distress in ID, and devised an experimental neuroimaging study in ***chapter 5*** aiming to provide evidence for the role of restless REM sleep in maladaptive sleep in ID. Finally, recent advances in automated detection of sleep stages bear the promise to advance sleep analysis beyond what is possible with traditional manual analysis. In ***chapter 6*** we used a topic-modelling approach to identify the maladaptive sleep characteristics in ID as compared to normal sleepers.

Below I will first summarize the aim, approach, and main findings in each chapter, followed by a general discussion of the findings across chapters in relation to previous research.

Main findings

Hyperarousal: an accumulation of emotional distress due to restless REM sleep

In ***chapter 2*** we commenced to investigate whether the hypothesized chronic interference with overnight emotion regulation due to restless REM sleep would indeed result in a slower resolving of emotional distress and whether hyperarousal could in fact represents the resulting accumulation of this distress. Since large-scale polysomnographic recordings were not feasible in this large sample, a proxy questionnaire variable correlating with restless REM sleep was derived in N = 32 participants, who were polysomnographically assessed at the Department of Psychiatry and Psychotherapy, University Medical Center of Freiburg. The proxy variable was subsequently assessed in 1,199 participants of the Netherlands Sleep Registry (NSR), along with other questionnaires on the subjective duration of emotional distress, insomnia severity, and hyperarousal.

The findings support the hypothesis that restless REM sleep interferes with overnight resolution of emotional distress. In turn, the characteristic hyperarousal in ID could be seen as an accumulation of distress. First, we found that people rating high on the proxy variable of restless REM sleep were more likely to report long-lasting distress and hyperarousal. The structural equation model showed that the association between the two typical characteristics of insomnia, restless REM sleep and hyperarousal, is mediated by experiencing long-lasing emotional distress. The model provided indirect support for the idea that hyperarousal may be a result of accumulated long-lasting distress and that restless REM sleep plays a role in the insufficiency to resolve emotional distress overnight in insomnia disorder.

Support for a maladaptive type of sleep worsening next day's emotional reactivity

As compared to an equal period of wakefulness, sleep can have a beneficial effect on the regulation of emotional distress, if sleep can take place within a critical time window of about 6 hours (Nader *et al.* 2000, Agren *et al.* 2012). Outside this time window—or if sleep is perturbed within this time window—downregulation of emotional distress would not occur, i.e. the benefit of sleep is lost. As outlined in the introduction, emotion regulation is defined as the modification of any of the

components of an emotional response, which could pertain to e.g. subjective emotional appraisal, physical distress, and social implications. In the study described in ***chapter 3,*** we induced shame and embarrassment by exposing people with ID and normal sleepers to their own imperfect singing four times across three consecutive days, either in the morning or in the evening. This within-subject repeated measures paradigm allowed us to study the hypothesized beneficial effect of immediate sleep relative to immediate wakefulness, and how restless sleep in insomnia might interfere with this effect. After each exposure, the three components of the Experiential Shame Scale evaluated the subjective emotional, physical, and social consequences of the shame-inducing manipulation.

Rather than a mere loss of benefit, our findings revealed a maladaptive type of restless sleep in people suffering from insomnia that even inverses the sleep-dependent adaptive processes and worsens next-days outcomes. Adaptation to shame, especially the physical and emotional components of it, benefitted from immediate sleep in normal sleepers. In contrast, immediate sleep adversely affected this adaptation in people suffering from insomnia, especially for the physical component of experienced shame. The findings suggest that the disturbed sleep in ID interferes in particular with overnight adaptive processes involved in somatic reactivity, rather than with adaptive processes involved in higher order emotional and social cognitive appraisal.

Abiding recruitment of the ACC with memories of emotional distress from the distant past in insomnia disorder

The studies discussed above suggest a chronic deficiency to regulate emotional distress in connection with maladaptive sleep in insomnia. ***Chapter 4*** describes the first imaging study of this thesis. This study aimed to identify the brain circuits affected by the insufficient long-term adaptation to emotional experiences in ID. Specifically, we hypothesized that adaptation, supported by good sleep, would result in a lack of overlap in brain responses to novel emotional experiences and relived experiences from the distant past. Consequently, we hypothesized that interference with this adaptation due to chronic poor sleep would result in insufficient discrimination between novel and past emotions indicated by overlap in brain responses.

The findings from this study indicate that ID involves a deficiency to reorganize the neuronal circuits involved in emotional distress. In both normal sleepers and ID we observed a limbic response in the anterior cingulate cortex (ACC) while experiencing novel emotional distress. In normal sleepers, this response was no longer present when reliving emotional distress from the distant past. In ID however, we observed an abiding limbic response in the ACC while experiencing relived emotional distress from the distant past. Conjunction analysis confirmed that this response overlapped with the response to novel emotional distress. A possible deficiency to reorganize emotional memory circuits in ID thus seems detectable with fMRI in the ACC in particular, and identifies it as an area of interest for studies on neuronal correlates of insomnia vulnerability.

Experimental support for the role of REM fragmentation in the insufficiency to regulate emotional distress in insomnia disorder

Combined, the previous chapters provide indirect support for the main hypothesis that insomnia disorder involves an insufficiency to resolve emotional distress due to processes underlying its characteristic restless REM sleep including cortical arousals. An animal model on the role of sleep in resolving emotional distress proposes an interplay of memory trace reactivation and synaptic plasticity during the time window that starts when slow waves subside and the sleep spindle-rich 'transition to REM sleep' period emerges, and lasts until the end of REM sleep. The study described in ***chapter 5*** applied the experimental manipulation of odor-induced targeted memory reactivation during sleep to evaluate the hypothesis that overnight neuronal network reorganization within the limbic circuitry is best facilitated by REM sleep and the preceding period of transition to REM sleep, but *only* if these sleep episodes are relatively consolidated, free from interruptions.

The overnight adaptation of the amygdala response to emotional stimuli was proportional to the total duration of REM episodes. Moreover, this effect was enhanced by longer preceding transition to REM episodes. Overnight amygdala adaptation could also be enhanced by targeted memory reactivation (TMR) during REM episodes, aiming to elicit replay of the neuronal activity previously elicited by emotional stimuli. The TMR effect was specific to REM episodes and to the odor that was previously conditioned to the emotional stimulus. No effects on overnight

adaptation of the amygdala response were found when this odor was presented during other sleep episodes, nor with other odors that were conditioned to corresponding neutral experiences. Importantly however, the odor conditioned to the emotional stimulus could also have negative effects: it also boosted the adverse effect of REM episode interruption density on overnight amygdala adaptation. Our study replicated the previously reported restless REM sleep in ID. Given the key role of the amygdala in emotion processing, our findings provide the most direct support for the hypothesis that insomnia disorder involves a crucial insufficiency in overnight regulation of emotional distress.

A topic model approach for automated sleep-scoring reveals light sleep related features during deep sleep

The studies described in ***chapters 2, 4,*** and ***5*** depended on laborious visual scoring of sleep states and identification of cortical arousals within polysomnography recordings. Automated sleep-scoring algorithms bear the promise to facilitate future research on cortical arousals. A set of original studies developed and validated an integral topic-modelling approach to describe a polysomnographic recording as a mixture of vigilance states, each with its own probability at any time-point of the night (Koch *et al.* 2014, Christensen *et al.* 2016). We applied this topic-modelling approach in a sample of 55 participants with ID and 64 normal sleepers to evaluate group differences in the main outcome measures of this model: the probability dominance and co-occurrence distribution of vigilance states related to wakefulness, light and deep NREM sleep, and REM sleep, as well as the transition-probabilities reflecting sleep-state (in)stabilities.

The findings presented in ***chapter 6*** indicate that people with ID show a higher dominance of a light sleep-related vigilance-state. They moreover show more co-occurrence of a light sleep-related vigilance-state even when they are in deep sleep. In addition, as compared to normal sleepers, people with ID were found to have a two-fold increase in the likelihood to transition from a deep sleep to a light sleep vigilance state, and from a vigilance state related to NREM stage-2 sleep to wakefulness. The findings indicate that sleep in insomnia disorder is characterized by increased light sleep EEG signatures, even during deep sleep, indicating that hyperarousal never rests in ID.

General discussion

Altogether, the findings in this thesis support the notion that a *maladaptive type of sleep*, characterized by REM sleep fragmentation, could contribute to *long-lasting emotional distress* by hampering overnight processing of emotional memories. The maladaptive sleep could even *worsen* emotional reactivity overnight. Chronic maladaptive sleep may result in accumulation of distress, i.e. in a state that we usually refer to as *hyperarousal*. Below, I will discuss these three main conclusions in relation to previous research, and I will elaborate on some unexpected findings.

Restless REM sleep signifies maladaptive sleep

The most consistent findings in ID may be restless REM sleep (Feige *et al.* 2008, Riemann *et al.* 2012) and chronic hyperarousal (Bonnet and Arand 2010, Riemann *et al.* 2010). Interestingly, these characteristics have not previously been unified in one mechanistic model. The findings in ***chapter 2*** suggest a maladaptive role of restless REM sleep in emotion regulation, resulting in a state of accumulated chronic distress referred to as hyperarousal. The role of restless REM sleep in long-lasting emotional distress may signify a selective insufficiency of overnight resolution of emotional distress in insomnia, which suggests that restless REM sleep is key in maladaptive sleep. Indeed, in ***chapter 3*** we show that people with ID experience a worsening of physically perceived shame from one exposure to the next if the first exposure is immediately followed by sleep. The finding indicates that maladaptive sleep could actually worsen next day outcomes, rather than merely impeding the benefits of sleep. Furthermore, in line with previous research (Merica *et al.* 1998, Perlis *et al.* 2001, Feige *et al.* 2008, Riemann *et al.* 2012), ***chapter 4*** once more replicates that increased REM fragmentation may be the most significant difference between ID and normal sleepers. The findings also suggest insufficient long-term adaptation to emotional distress from the distant past in people suffering from insomnia. Finally, in ***chapter 5***, we experimentally manipulated overnight memory reactivation processes in people representing a range of differences in restlessness of REM sleep: from well consolidated to highly fragmented. We show that the amygdala response to re-exposure of an emotional stimulus adapts with memory reactivations in stable REM sleep, but remains the same or even increases with reactivations in fragmented REM sleep. In conclusion,

while several studies have shown that sleep aids to the resolution of emotional distress (Sterpenich *et al.* 2007, Pace-Schott *et al.* 2011, Van Der Helm *et al.* 2011, Talamini *et al.* 2013), we now add a boundary condition: this process depends on stable REM sleep. Our findings indicate that REM sleep fragmentation may best signify the underlying malicious factor that impedes or even worsens next day outcomes with respect to emotional distress. What could this malicious factor be?

Specifically during stable REM sleep, noradrenergic locus coeruleus activity subsides (Vanderheyden *et al.* 2014), permitting long-term depotentiation (Kemp and Manahan-Vaughan 2004). In addition, REM sleep is characterized by theta-rhythm and cholinergic activity. Hippocampal theta-rhythm activity supports long-term potentiation (Winson 1978, Mizumori *et al.* 1990, Rashidy-Pour *et al.* 1996) and acetylcholine is an important modulator of cortical associative memory function (Hasselmo and Bower 1993). This unique neuromodulatory milieu in REM sleep may simultaneously serve to depotentiate the limbic synaptic connection strengths and to integrate the memory trace from hippocampal circuits into neocortical circuits (Poe *et al.* 2010). However, as in PTSD animal models (Poe 2017), abundant arousals during sleep in ID suggests that locus coeruleus activity continues into sleep, and may result in a net synaptic potentiation, rather than depotentiation, within the limbic circuitry.

Long-lasting emotional distress: abiding involvement of the ACC in the fronto-amygdala circuitry

The hyperarousal theory links the psychological perspective on insomnia with underlying neurobiological and neurophysiological mechanisms (Perlis *et al.* 1997, Bonnet and Arand 2010, Riemann *et al.* 2010). With regards to the physiological manifestation of distress, the findings in ***chapter 3*** show that disruptions in overnight regulation of emotional distress particularly affected the physical component of shame in ID, not the components representing higher-order emotional appraisal or social implications of shame. Furthermore, ***chapter 4*** implicates the dorsal ACC in the aetiology of ID which may represent a neurobiological substrate of the link between long-lasting emotional distress and hyperarousal, as shown in ***chapter 2***. Dorsal ACC activation correlates with sympathetic nervous system activity (Wager *et al.* 2009a, Wager *et al.* 2009b) and is

involved in the expression of emotions through its connections with the amygdala and other limbic areas (Etkin *et al.* 2011). Therefore, other limbic regions could be affected by REM sleep fragmentation as well. Indeed, the findings of a region-of-interest analysis in ***chapter 5*** show hampered overnight adaptation of amygdala reactivity due to REM sleep fragmentation. In conclusion, the abiding activation in the dorsal ACC signified stronger expression of distress while reliving emotional events from the distant past in ID. On the shorter time scale of a single night, REM sleep fragmentation impeded overnight adaptation of amygdala reactivity to a novel emotional experience.

Interestingly, the ACC is one of the few areas activated during REM sleep (Renouard *et al.* 2015, Luppi *et al.* 2017) in a neuromodulatory milieu that is optimal for reorganization of neuronal networks, i.e. high acetylcholine and absent noradrenalin (Poe *et al.* 2010). Anatomically, the ACC is a hub capable of communication with both the amygdala and prefrontal cortices, which may be crucial for the overnight reorganization of emotional memory circuits that facilitates inhibition of the amygdala by the medial prefrontal cortex (Takashima *et al.* 2006, Nieuwenhuis and Takashima 2011, Van Der Helm *et al.* 2011). It could be that the activation of specifically the ACC during REM sleep is involved in the integration of limbic activity by the medial prefrontal cortex and depotentiation of the ACC-amygdala subnetwork, during reactivation of an emotional memory trace (Nieuwenhuis and Takashima 2011).

Worsening next day outcomes and augmentation of the characteristic hyperarousal in ID

The findings in ***chapter 3*** show that the restless sleep in ID is associated with inverse overnight emotion regulation: re-exposure to a self-conscious emotional stimulus is experienced as more rather than less distressing. The mediation model approach of ***chapter 2*** suggests that distress may accumulate into chronic hyperarousal. Importantly, the association of abiding long-lasting distress with hyperarousal was also observed in a sensitivity analysis excluding all cases with mood disorders. It is therefore unlikely that this association was observed through negative mood as a common factor. Hyperarousal can be seen as a chronic form of the emotional state that all people show during short-lived stress, anxiety, or in

response to emotional events—a first indication that ID could be regarded as a disorder of emotional distress. The key problem in such disorders is the persistence and generalization of anxiety. Similarly, the anxious state that is elicited by sleep-initiation problems in acute insomnia can generalize if the restless sleep persists, and perpetuates insomnia to a chronic form (Perlis *et al.* 1997). In this respect, ID can be regarded as a disorder of emotional distress. Futhermore, both genetically and phenotypically, insomnia is most markedly associated with anxiety disorders (Hammerschlag *et al.* 2017). Lastly, in a PTSD population, Insana *et al.* (2012) showed that early-life traumatic events explained restless REM sleep in adulthood, which in turn related to the severity of current PTSD symptomology. Altogether, these findings converge to the conclusion that, at least in part, ID can be regarded as a disorder of emotional distress, and that restless REM sleep may be the most salient marker of the underlying maladaptive processes that precipitate and perpetuate the disorder.

Unexpected findings

In ***chapter 6***, we evaluated a data-driven topic modelling approach for automated sleep-scoring. The topic modelling approach utilizes symbolization of EEG power-spectral patterns to predict the probability for six vigilance states in each 30 second EEG-segment. The model is trained to predict sleep macro-architecture, and not to identify sleep micro-architecture, such as arousals. Even though the topic model would not be sensitive to arousals, we expected a stronger co-occurrence of wakefulness-related or light sleep-related topics during the REM-like vigilance states in people suffering from ID. However, we found that the EEG of people with ID express more N1-related vigilance signatures in deep sleep, not in REM sleep. Next to the first explanation that the model was not trained to be sensitive to sleep micro-architecture, a second possible explanation is that we evaluated differences in vigilance state features between normal sleepers and ID only in *stable* epochs: epochs that were part of at least three consecutive epochs with the same dominant vigilance state. Importantly, REM arousals are themselves a feature of instable sleep, and thus leaving these epochs out of the analysis may have been another reason for the lack of differences in REM sleep related features between normal sleepers and

ID. Altogether, we deemed the topic model a valuable approach for automated sleep-scoring, however insensitive for detailed analysis on sleep-microarchitecture.

A second set of findings that requires closer examination and discussion is that ***chapter 5*** showed that restless REM sleep impedes the overnight adaptation of the amygdala in response to re-exposure of an emotional stimulus, whereas ***chapter 4*** implicated the dorsal ACC in long-lasting emotional distress. Rather than a site for long-term storage of emotional memory, the amygdala is part of a memory modulating system that serves to bind emotional states to contexts, e.g. the context of a novel emotional experience or of recalling an autobiographical memory (Cahill and Mcgaugh 1998). The dorsal ACC, on the other hand, may engender a more long-term association between emotional memories and contexts. Indeed, our studies suggest a role for the dorsal ACC in abiding emotional distress from the distant past in ID, whereas the lack of adaptation of the amygdala due to restless REM sleep pertained to the effect of one night's sleep and novel emotional stimuli. Nonetheless, both the dorsal ACC and the amygdala seem to be affected by the insufficiency of restless REM sleep to reorganize neuronal emotional memory circuits.

Future directions

First, throughout the thesis I consider cortical arousals to index continued noradrenergic activity, and indeed the noradrenergic neural circuits responsible for the maintenance of wakefulness are also involved in arousals during sleep (Foote *et al.* 1980, Aston-Jones and Bloom 1981). However, arousals can be induced by exogenous or endogenous stimuli, e.g. a sound, movement, or apnoea, or can occur spontaneously in absence of such a stimulus. There may be important differences between the various different arousal types with respect to their interruptive effects on overnight memory processing. Our unpublished data indicate that especially the central arousals are enhanced in ID, rather than movement-related arousals or micro arousals (lasting <3 seconds). Future studies should confirm the specificity of the association between central arousals and noradrenergic activity, and evaluate important differences of the various arousal types on overnight memory reorganization.

Secondly, as described in the introduction, REM and NREM sleep have a complex and multifaceted role in emotional memory reorganization, yet these interactions are often neglected in memory research. Indeed, in ***chapter 5*** we report that REM sleep and the preceding transition to REM sleep episodes interact to affect the overnight adaptation of amygdala reactivity. Vanderheyden *et al.* (2014) proposed that it may be necessary for the target memory trace to be spontaneously reactivated first during NREM sleep as a prerequisite before REM sleep can exert its role on the functional reorganization of the memory circuit. We did not find direct evidence for this hypothesis, but our study may have lacked sensitivity to do so. Furthermore, spontaneous reactivation has previously been shown to depend mostly on thalamocortical spindles and hippocampal sharp-wave ripples during NREM sleep (for reviews see Stickgold 1998, Peigneux *et al.* 2001, Walker and Stickgold 2006, Born and Wilhelm 2012). Future studies could aim to specifically modulate sleep spindles during the transition to REM sleep period in order to evaluate its supporting role in emotional memory processing.

Finally, anxious hyperarousal and mood disorders impede sound sleep, and insomnia is a limiting factor for the therapeutic effects of cognitive behavioral therapy for depression (Thase *et al.* 1997). Indeed, for the prevention of new-onset or recurrent affective disorders, insomnia may be the major risk factor that can be targeted best (Manber *et al.* 2008, Baglioni *et al.* 2011). Our findings uncover a maladaptive type of sleep characterized by REM sleep fragmentation that impedes emotion regulation in ID. Importantly, REM sleep fragmentation as is also observed in major depressive disorder (Duncan *et al.* 1979), post-traumatic stress disorder (Mellman *et al.* 2002, Germain 2013), and in people that have been exposed to childhood adversity (Insana *et al.* 2012). It seems that the two separate research lines on the mechanisms of affective disorders and ID have converged to the model that both can be regarded as *disorders of emotional memory*. A collaborative strategy between these research lines could propel the insights required for better treatments. Sleep-dependent memory consolidation renders the memory highly resistant against interference (Kandel 2001, Stickgold and Walker 2005). These stable memories enable us to anticipate and predict the outcome of similar experiences (Schultz and Dickinson 2000). However, this mechanism is a core problem in disorders of emotional memory: contextual cues, even neutral cues,

can signal the anticipation of the emotional distress as predicted by the aversive memory. A true paradigm shift in the practice of psychotherapy would involve targeted memory reconsolidation-based therapy with the aim to modify the aversive memory in a way that neutralizes the anticipated emotional distress (Kindt 2018). Sevenster *et al.* (2013) uncovered that aversive memory traces become labile and undergo reconsolidation after the participant experiences a prediction-error: a discrepancy between the predicted outcome and actual experience. Furthermore, a single administration of an amnegic agent (propranolol) during this time, neutralized the anticipated emotional distress response, but only after a night of sleep (Kindt and Soeter 2018). The studies presented in this thesis now add that sleep in this time window should be free from interruptions in REM sleep, or otherwise could potentially lead to worse outcomes. Furthermore, as highlighted above, the interactions between REM and NREM sleep states should be considered. Our findings can be incorporated into studies on novel interventions that target overnight neutralization of hyperarousal or the emotional impact of distressing memories. Patients suffering from significant emotional distress and co-occurring sleep disturbances might benefit especially from combined efforts of targeted interventions to prevent the occurrence of fragmented REM sleep while aiming to neutralize the emotional impact of distressing memories.

References

Agren T, Engman J, Frick A, Bjorkstrand J, Larsson EM, Furmark T and Fredrikson M (2012). Disruption of reconsolidation erases a fear memory trace in the human amygdala. *Science* 337(6101): 1550-1552.

Aston-Jones G and Bloom FE (1981). Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J Neurosci* 1(8): 876-886.

Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, Lombardo C and Riemann D (2011). Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord* 135(1-3): 10-19.

Bonnet MH and Arand DL (2010). Hyperarousal and insomnia: State of the science. *Sleep Med Rev* 14(1): 9-15.

Born J and Wilhelm I (2012). System consolidation of memory during sleep. *Psychol Res* 76(2): 192-203.

Cahill L and Mcgaugh JL (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci* 21(7): 294-299.

Christensen JaE, Jennum P, Koch H, Frandsen R, Zoetmulder M, Arvastson L, Christensen SR and Sorensen HBD (2016). Sleep stability and transitions in patients with idiopathic rem sleep behavior disorder and patients with parkinson's disease. *Clin Neurophysiol* 127(1): 537-543.

Duncan WC, Jr., Pettigrew KD and Gillin JC (1979). Rem architecture changes in bipolar and unipolar depression. *Am J Psychiatry* 136(11): 1424-1427.

Etkin A, Egner T and Kalisch R (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci* 15(2): 85-93.

Feige B, Al-Shajlawi A, Nissen C, Voderholzer U, Hornyak M, Spiegelhalder K, Kloepfer C, Perlis M and Riemann D (2008). Does rem sleep contribute to subjective wake time in primary insomnia? A comparison of polysomnographic and subjective sleep in 100 patients. *J Sleep Res* 17(2): 180-190.

Foote SL, Aston-Jones G and Bloom FE (1980). Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. *Proc Natl Acad Sci U S A* 77(5): 3033-3037.

Germain A (2013). Sleep disturbances as the hallmark of ptsd: Where are we now? *Am J Psychiatry* 170(4): 372-382.

Hammerschlag AR, Stringer S, De Leeuw CA, Sniekers S, Taskesen E, Watanabe K, Blanken TF, Dekker K, Te Lindert BHW, Wassing R, Jonsdottir I, Thorleifsson G, Stefansson H, Gislason T, Berger K, Schormair B, Wellmann J, Winkelmann J, Stefansson K, Oexle K, Van Someren EJW and Posthuma D (2017). Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. *Nat Genet* 49(11): 1584-1592.

Hasselmo ME and Bower JM (1993). Acetylcholine and memory. *Trends Neurosci* 16(6): 218-222.

Insana SP, Kolko DJ and Germain A (2012). Early-life trauma is associated with rapid eye movement sleep fragmentation among military veterans. *Biol Psychol* 89(3): 570-579.

Kandel ER (2001). The molecular biology of memory storage: A dialogue between genes and synapses. *Science* 294(5544): 1030-1038.

Kemp A and Manahan-Vaughan D (2004). Hippocampal long-term depression and long-term potentiation encode different aspects of novelty acquisition. *Proc Natl Acad Sci U S A* 101(21): 8192-8197.

Kindt M (2018). The surprising subtleties of changing fear memory: A challenge for translational science. *Philos Trans R Soc Lond B Biol Sci* 373(1742): 20170033.

Kindt M and Soeter M (2018). Pharmacologically induced amnesia for learned fear is time and sleep dependent. *Nat Commun* 9(1): 1316.

Koch H, Christensen JA, Frandsen R, Zoetmulder M, Arvastson L, Christensen SR, Jennum P and Sorensen HB (2014). Automatic sleep classification using a data-driven topic model reveals latent sleep states. *J Neurosci Methods* 235: 130-137.

Luppi PH, Billwiller F and Fort P (2017). Selective activation of a few limbic structures during paradoxical (rem) sleep by the claustrum and the supramammillary nucleus: Evidence and function. *Curr Opin Neurobiol* 44: 59-64.

Manber R, Edinger JD, Gress JL, San Pedro-Salcedo MG, Kuo TF and Kalista T (2008). Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. *Sleep* 31(4): 489-495.

Mellman TA, Bustamante V, Fins AI, Pigeon WR and Nolan B (2002). Rem sleep and the early development of posttraumatic stress disorder. *Am J Psychiatry* 159(10): 1696-1701.

Merica H, Blois R and Gaillard JM (1998). Spectral characteristics of sleep eeg in chronic insomnia. *Eur J Neurosci* 10(5): 1826-1834.

Mizumori SJ, Barnes CA and Mcnaughton BL (1990). Behavioral correlates of theta-on and theta-off cells recorded from hippocampal formation of mature young and aged rats. *Exp Brain Res* 80(2): 365-373.

Nader K, Schafe GE and Le Doux JE (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* 406(6797): 722-726.

Nieuwenhuis IL and Takashima A (2011). The role of the ventromedial prefrontal cortex in memory consolidation. *Behav Brain Res* 218(2): 325-334.

Pace-Schott EF, Shepherd E, Spencer RM, Marcello M, Tucker M, Propper RE and Stickgold R (2011). Napping promotes inter-session habituation to emotional stimuli. *Neurobiol Learn Mem* 95(1): 24-36.

Peigneux P, Laureys S, Delbeuck X and Maquet P (2001). Sleeping brain, learning brain. The role of sleep for memory systems. *Neuroreport* 12(18): A111-124.

Perlis ML, Giles DE, Mendelson WB, Bootzin RR and Wyatt JK (1997). Psychophysiological insomnia: The behavioural model and a neurocognitive perspective. *J Sleep Res* 6(3): 179-188.

Perlis ML, Smith MT, Andrews PJ, Orff H and Giles DE (2001). Beta/gamma eeg activity in patients with primary and secondary insomnia and good sleeper controls. *Sleep* 24(1): 110-117.

Poe GR (2017). Sleep is for forgetting. *J Neurosci* 37(3): 464-473.

Poe GR, Walsh CM and Bjorness TE (2010). Cognitive neuroscience of sleep. In: *Prog brain res*(eds.), Elsevier. 185**:** 1-19.

Rashidy-Pour A, Motamedi F, Semnanian S, Zarrindast MR, Fatollahi Y and Behzadi G (1996). Effects of reversible inactivation of the medial septal area on long-term potentiation and recurrent inhibition of hippocampal population spikes in rats. *Brain Res* 734(1-2): 43-48.

Renouard L, Billwiller F, Ogawa K, Clement O, Camargo N, Abdelkarim M, Gay N, Scote-Blachon C, Toure R, Libourel PA, Ravassard P, Salvert D, Peyron C, Claustrat B, Leger L, Salin P, Malleret G, Fort P and Luppi PH (2015). The supramammillary nucleus and the claustrum activate the cortex during rem sleep. *Sci Adv* 1(3): e1400177.

Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M and Nissen C (2010). The hyperarousal model of insomnia: A review of the concept and its evidence. *Sleep Med Rev* 14(1): 19-31.

Riemann D, Spiegelhalder K, Nissen C, Hirscher V, Baglioni C and Feige B (2012). Rem sleep instability--a new pathway for insomnia? *Pharmacopsychiatry* 45(5): 167-176.

Schultz W and Dickinson A (2000). Neuronal coding of prediction errors. *Annu Rev Neurosci* 23: 473-500.

Sevenster D, Beckers T and Kindt M (2013). Prediction error governs pharmacologically induced amnesia for learned fear. *Science* 339(6121): 830-833.

Sterpenich V, Albouy G, Boly M, Vandewalle G, Darsaud A, Balteau E, Dang-Vu TT, Desseilles M, D'argembeau A, Gais S, Rauchs G, Schabus M, Degueldre C, Luxen A, Collette F and Maquet P (2007). Sleep-related hippocampo-cortical interplay during emotional memory recollection. *PLoS Biol* 5(11): e282.Stickgold R (1998). Sleep: Off-line memory reprocessing. *Trends Cogn Sci* 2(12): 484-492.

Stickgold R and Walker MP (2005). Memory consolidation and reconsolidation: What is the role of sleep? *Trends Neurosci* 28(8): 408-415.

Takashima A, Petersson KM, Rutters F, Tendolkar I, Jensen O, Zwarts MJ, Mcnaughton BL and Fernandez G (2006). Declarative memory consolidation in humans: A prospective functional magnetic resonance imaging study. *Proc Natl Acad Sci U S A* 103(3): 756-761.

Talamini LM, Bringmann LF, De Boer M and Hofman WF (2013). Sleeping worries away or worrying away sleep? Physiological evidence on sleep-emotion interactions. *PLoS ONE* 8(5): e62480.

Thase ME, Buysse DJ, Frank E, Cherry CR, Cornes CL, Mallinger AG and Kupfer DJ (1997). Which depressed patients will respond to interpersonal psychotherapy? The role of abnormal eeg sleep profiles. *Am J Psychiatry* 154(4): 502-509.

Van Der Helm E, Yao J, Dutt S, Rao V, Saletin JM and Walker MP (2011). Rem sleep depotentiates amygdala activity to previous emotional experiences. *Curr Biol* 21(23): 2029-2032.

Vanderheyden WM, Poe GR and Liberzon I (2014). Trauma exposure and sleep: Using a rodent model to understand sleep function in ptsd. *Exp Brain Res* 232(5): 1575-1584.

Wager TD, Van Ast VA, Hughes BL, Davidson ML, Lindquist MA and Ochsner KN (2009a). Brain mediators of cardiovascular responses to social threat, part ii: Prefrontal-subcortical pathways and relationship with anxiety. *Neuroimage* 47(3): 836-851.

Wager TD, Waugh CE, Lindquist M, Noll DC, Fredrickson BL and Taylor SF (2009b). Brain mediators of cardiovascular responses to social threat: Part i: Reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. *Neuroimage* 47(3): 821-835.

Walker MP and Stickgold R (2006). Sleep, memory, and plasticity. *Annu Rev Psychol* 57: 139-166.

Winson J (1978). Loss of hippocampal theta rhythm results in spatial memory deficit in the rat. *Science* 201(4351): 160-163.