Chapter 1.

Introduction
Chapter 1.

Opening statement
Sleep is generally regarded as an enigmatic state of unconsciousness, from which we awaken with fresh and renewed physical energy and mental clarity. It is indeed this fascinating product of sleep that portrays an active and complex role of sleep on our daytime functioning. In a definition, sleep is a period of physical and behavioral quiescence during which we cycle through various levels of consciousness and arousability. The functional neuronal processes that sleep facilitates may therefore also be perturbed by interruptive arousals. Importantly, one of the key characteristics of insomnia disorder (ID) is high number of arousals, especially during REM sleep (Riemann et al. 2012). Recently, rapid eye movement (REM) sleep has been implicated in the regulation of emotional distress (Gujar et al. 2011, Van Der Helm et al. 2011, Rosales-Lagarde et al. 2012, Spoormaker et al. 2012). This thesis aims to evaluate the hypothesis that insomnia disorder involves an insufficiency to resolve emotional distress due to processes underlying its characteristic restless REM sleep.

In this first chapter, I will review the neurophysiological and neurobiological characteristics of sleep with a focus on those that play a role in overnight memory processes and regulation of emotional distress. Based on this literature, I will propose a rationale for the regulation of emotional distress associated with memories through sleep dependent reorganization of neuronal memory circuits. Importantly, I will implicate this rationale in the aetiology of insomnia disorder and provide an outline of this thesis that evaluates the evidence for hampered regulation of emotional distress in insomnia disorder.

Sleep and its characteristics
The circadian rhythm and its interaction with sleep propensity
The mammalian sleep-wake cycle is governed in part by a central circadian rhythm engendered in the hypothalamic suprachiasmatic nuclei in interaction with neural circuits in the brainstem and basal forebrain (Klein et al. 1991, Saper et al. 2005, Mccarley 2007). Importantly, as low as at the level of eubacteria, circadian rhythms regulate gene-expression patterns and metabolism (Huang et al. 2011); the
circadian rhythm is a fundamental biological process that is evolutionary consolidated in most living organisms. The 24-hour rhythmicity of the suprachiasmatic nuclei is entrained by Zeitgebers, one of which is the input from specialized light-sensitive melanopsin-containing cells in the retina (Cassone et al. 1986). The suprachiasmatic nuclei convey this 24-hour rhythmicity to its afferent connections with the hypothalamic subparaventricular zone and the dorsomedial nucleus of the hypothalamus (DMH), governing body temperature, feeding behavior, corticosteroid release, and sleep-wake cycles.

The reversible transition between wakefulness and sleep is governed for a large part by modulation of the ascending activating projections of the reticular activating system (RAS) in the brainstem by neurons in the hypothalamus including the inhibitory GABAergic ventrolateral-preoptic nucleus (VLPO), the excitatory histaminergic tuberomammillary nucleus (TMN), and the excitatory orexinergic lateral hypothalamus (LH; Saper et al. 2005, Mccarley 2007). The ascending RAS includes the cholinergic pedunculopontine nucleus (PPT), the noradrenergic locus coerules (LC) and the serotonergic Raphe Nucleus (RN), and is responsible for central arousal by increasing excitability of the cortex via thalamo-cortical and ventral projections (Saper et al. 2005). Inhibition of the LH and the ascending RAS by the VLPO results therefore in globally decreased cortical excitability and supports the transition to slow-wave sleep. On the other hand, the LH and TMN operate in concert to promote wakefulness by activation of the excitatory cholinergic basal forebrain system and the ascending RAS nuclei, the latter inhibiting the VLPO. Taken together, the neurobiological mechanism of the circadian control over sleep has been ascribed to the influence the SCN has over the DMH, since the DMH on its turn disinhibits the VLPO and activates the LH, resulting in a wakefulness-drive (Chou et al. 2003).

The two-process model of sleep regulation states that the timing and intensity of sleep is regulated by the interaction between this circadian rhythm and a homeostatic process that increases sleep propensity with time spend awake and declines during sleep (Borbely 1982, Borbely et al. 2016). Functionally, this homeostatic process is reflected by the brain’s slow-wave activity during non-rapid eye movement (NREM) sleep, since slow-wave activity increases after sleep deprivation (Dijk et al. 1993) and in proportion to the amount of synaptic
potentiation during wakefulness (Tononi and Cirelli 2003, 2006). While the neural mechanisms for the homeostatic sleep drive remain unclear, adenosine-receptors are found throughout the cortex and its ligand (adenosine) is a metabolite of the “energy-molecule” adenosine triphosphate (ATP). With extended wakefulness and enduring neural activity, metabolic adenosine rises (Porkka-Heiskanen et al. 2000), and the cortical adenosine-receptors start to saturate. In combination with the finding that administration of adenosine induces sleep in rats by disinhibiting the VLPO (Chamberlin et al. 2003), it seems that the homeostatic process of sleep regulation at least involves adenosine-pathways (Benington and Heller 1995).

**Recording and evaluating sleep**

Neurophysiologically, the characterization of sleep is performed with the technique polysomnography (PSG), with *poly* indicating the use of simultaneous electrographic recordings of neuronal activity (electroencephalography; EEG), eye-movements (electrooculography; EOG), the heart (electrocardiography; ECG), muscle-tone (electromyography; EMG), and respiration. Together, these signals allow for a qualitative categorization of the subject’s physiological state into wakefulness, NREM sleep, and REM sleep (Rechtschaffen and Kales 1968, Iber et al. 2007, Berry et al. 2012). NREM sleep is further divided into three sub-states reflecting the depth of unconsciousness: stage N1, N2, and N3 sleep. Such a classification is made for each 30-second segment of the PSG recording, ultimately showing the cyclic nature of the sleep-stages across time.

**General sleep physiology**

*Macro-structure*

Although both between-subject and night-to-night variability is high, a full night’s sleep usually has four to five sleep cycles, the first often lasting a bit longer than the subsequent cycles of about 90 minutes. Each cycle is a successive transition from light to deep sleep (stages N1, N2 and N3) denoted as the descending phase, followed by a stable deep sleep phase consisting of mainly stage N3 sleep, succeeded by an ascending phase from stage N3, via stage N2 to the onset of the REM sleep period which concludes the cycle (Feinberg and Floyd 1979, Terzano et al. 2000). From wakefulness to sleep onset, the EEG changes such that *alpha* wave
activity (8-12 Hz) diminishes to intermittent activity and the EEG signal generally becomes of low amplitude (Tanaka et al. 1997). At sleep onset, the EOG signal shows slow and rolling eye movements and the EMG signal shows low muscle tone. Further into the sleep-cycle, the onset of stage N2 sleep is marked by the occurrence of sleep spindles, which are short (1-3 seconds) bursts of activity in the sigma frequency range (11-16 Hz), and K-complexes, characterized by their sharp deflections, large in amplitude exceeding 100 µV. Eye movements and muscle tone are virtually absent. While stage N2 sleep remains stable, slow-wave activity (<4 Hz) starts to rise, and when slow-waves become dominant it marks the onset of stage N3 sleep. Finally, sleep can transition to REM sleep, and portraits stereotypical saw tooth-like oscillations in the alpha and theta (4-8 Hz) frequency range.

**REM sleep micro-structure**

Throughout sleep, but mostly in and around REM sleep periods, the cortex can portrait sudden deviant neuronal activity shown in the EEG signal as alpha, beta (12-30 Hz) and gamma (>30 Hz) activity, which resembles wake EEG, but does not always result in a full awakening (Bonnet et al. 1992). Although such arousals are regarded to be detrimental for sleep, it must be noted that they are an endogenous neurophysiological feature and also occur in healthy sleepers. From an evolutionary perspective, arousals are possibly related to enable fast transitions to wakefulness in case of a harmful or demanding external situation (Halasz et al. 2004). Arousals can be induced by exogenous stimuli or a stimulus with a physiological origin e.g. a movement or apnoea, however can also occur spontaneously in absence of such a stimulus; a central arousal.

The thalamus, formed by grey-matter areas on either side of the third ventricle in the dorsal diencephalon, functions as a major gateway for sensory and motor information between the periphery and the neocortex (Sherman and Guillery 2001). Recent studies in rats and humans indicate that thalamo-cortical neurotransmission is still responsive during sleep, especially to low-level sensory information (Sela et al. 2016, Makov et al. 2017). The same cholinergic and noradrenergic neural circuits responsible for the maintenance of wakefulness in the brainstem and hypothalamus are also involved in arousals during sleep (Foote et al.
Chapter 1.

1980, Aston-Jones and Bloom 1981), generating short bursts of ascending activity towards the cortex via the thalamus (Moruzzi and Magoun 1949) and activate thalamo-cortical pathways (Steriade 2000) resulting in a transient activated cortical state. Cortical arousals are more prominent during REM sleep as opposed to NREM sleep. Importantly, REM sleep is governed by a precise balance between activating cholinergic neurotransmission on the one hand, and inhibited noradrenergic, serotonergic, and orexinergic neurotransmission on the other hand (reviewed by Riemann et al. 2012). An increased incidence of arousals in REM sleep, as seen in insomnia disorder, could be hypothesized to involve slight disturbances in the balance of excitation and inhibition (E/I balance) in the brain.

**Cognitive neuroscience of memory consolidation**

The regulation of emotional distress has to be investigated in the context of memory formation, recall, and reconsolidation. Not surprisingly, the emotional salience of the original event or stimulus plays a critical role in the each of these processes. From an evolutionary perspective, the stress response to a hazardous experience promotes adaptive behavior on the long term (Mcewen 1998), preventing the organism from harm and increasing the chances of proliferation. Emotionally salient experiences induce release of stress-hormones such as adrenaline and glucocorticoids and prompt parallel activation of noradrenergic systems in the brain stem, including the locus coeruleus which in turn releases noradrenalin into the basolateral nucleus of the amygdala (Roozendaal et al. 2009). This stress-induced amygdala response enhances the initial formation of the memory of that experience. After the initial formation of the brain’s memory representation undergoes widespread reorganization across many orders of time scales. In the following sections I will discuss how emotional circuits are critically involved in the formation and re-consolidation of memory circuits and vice versa, that the reorganization of neural memory circuits effectively regulates emotional distress.

**Memory formation**

The taxonomy of memory systems broadly divides memory into two arms: the explicit declarative “knowing what” and the implicit non-declarative “knowing
how” (Milner et al. 1998). The non-declarative arm is also referred to as procedural memory and constitutes primed, sensitized, and conditioned responses, habitual behavior, and skills. These are memory systems that are trained through repetition, intended to serve appropriate behavior in given situations, while minimizing cognitive load through relatively fast habituated neural responses. Declarative memory, on the other hand, is the memory about semantic facts and meanings, and episodic events.

Memory formation involves the incorporation of novel synaptic connections and modulation of the synaptic connections between neurons by molecular core processes called long-term plasticity (Davis and Squire 1984, Bliss and Collingridge 1993, Kandel 2001, Kemp and Manahan-Vaughan 2007). Importantly, the very neuronal systems that are active during the encoding of the events are also involved in the formation of the long-term memory of these events (Fonseca et al. 2006), famously postulated by the Canadian psychologist Donald O. Hebb (Hebb 1949). It depends therefore on the type of memory, which brain regions are involved with the formation of that memory. Generally, declarative memory relies heavily on the diencephalon and the medial temporal lobe which includes the hippocampal formation, whereas non-declarative memory is more dependent on the basal ganglia (Poldrack and Packard 2003) and cerebellum (Squire and Zola 1996). However, these systems do not operate in isolation and are intricately connected (Poldrack and Packard 2003).

Memory reactivation, reconsolidation and the role of sleep
Once the long-term memory has formed it is normally highly resistant against interference (Kandel 2001). However, with later memory recall, the neural memory trace not only becomes active, but also renders the neural memory trace susceptible to transformations (Nader et al. 2000). This susceptibility allows for a secondary memory process that further stabilizes and integrates the memory in relation to pre-existing memories (Sara 2000, Dudai 2004, Alberini 2005), or alternatively weakens the memory by interference with new information (Walker et al. 2003).

Both animal and human studies have shown evidence of spontaneous memory reactivation of neuronal circuits involved in declarative memory during NREM sleep (for reviews see Stickgold 1998, Peigneux et al. 2001, Walker and Stickgold
Specifically, thalamo-cortical sleep spindles and cortical slow waves have been implicated in overnight memory consolidation. Sleep spindles occur predominantly during the depolarizing phase of slow-waves, and these brain oscillations couple with hippocampal sharp-wave ripple activity (Eschenko et al. 2008). Reactivation of hippocampus-dependent memories is thought to occur during the synchronized occurrence of these oscillations. Indeed, hippocampal activity during slow-wave sleep in humans predicts next day improvement of spatial memories (Peigneux et al. 2004).

Both NREM and REM sleep have a complex and multifaceted role in memory formation. The precise role of sleep on memory consolidation moreover depends on the emotional salience of the memory (Wagner et al. 2001, Walker and Stickgold 2006). A model has been proposed based on the observation that NREM and REM sleep occur in cycles, where early sleep cycles are relatively rich in NREM sleep, and late sleep cycles are relatively rich in REM sleep. The model proposes that after an initial role for NREM sleep in the reactivation and consolidation of the memory, REM sleep may promote further memory transformation during late sleep (Gais et al. 2000). The sleep dependent reorganization of memories is evidenced by the physical translocation of the activated neural circuits upon recall after sleep. Relative to the brain activity elicited during motor skill learning before sleep, a retest after sleep showed activity in other parts of the primary motor cortex, cerebellum, and hippocampus (Walker et al. 2005). Taken together, the findings suggest that after the initial memory reactivation during NREM sleep, REM sleep could further support memory re-consolidation. These two sleep periods seem to function in synergy to integrate this new information in existing mnemonic schemas (Lewis et al. 2018).

**Sleep dependent memory reorganization and emotions**

Sleep dependent memory consolidation is a selective process, that is to say, it is a process that prefers to consolidate certain memories over others (Stickgold and Walker 2013). This selection is proposed to be based on “tags” that identify the memories important for remembering, and to forget the memories without such a tag. These tags seem to pertain to emotionally salient, rewarding, novel or explicitly
important memories, and act to induce long-term potentiation (Ballarini et al. 2009). But, while it would be important to preferably consolidate emotional memories over non-emotional ones, we would certainly not like to reinstate the same distressed state with each recollection to our past. Clearly, over time, the distress related to our past emotional experiences has to adapt. In addition, over time, the emotional memory transforms from a detailed episodic memory to a more semantic and symbolic form. Next, I will discuss the principles of such emotion regulation and the main hypothesis of this thesis on the role of overnight reorganization of emotional memory circuits on regulation of emotional distress.

Psychological perspective on emotion regulation
The most widely accepted theory on emotion regulation is the process model of emotion regulation, postulated by Gross (1998b). In that model, emotion regulation is defined as the modification of any of the components of an emotional response—feelings, behaviours, or physiological activations—with the objective to modulate the incidence, intensity, and duration of emotional states (see also Gross 1998a, 2001).

First, antecedent-focused emotion regulation concerns a set of behaviours that aim to avoid, divert, or manipulate potential emotional situations. Before an emotional event has even occurred, one could anticipate a potential emotional event and avoid such situations altogether or modify the situation to divert away from the potential emotional event. Moreover, once an emotional event has occurred, one could regulate the incidence of an emotional response by directing their attention away from the emotional event (attentional deployment), or by cognitive effort that re-evaluates the meaning and impact of an emotional event (reappraisal). Secondly, response-focused emotion regulation comes into play once an emotional response is initiated. This regulation concerns a suppressive mechanism that actively inhibits the experiential, behavioral, or physiological expression of emotional distress.
Neuroscientific perspective on emotion regulation

In a broad neuroscientific definition, emotions are engendered by reciprocal neuronal dynamics between somatic responses and subsystems of the central nervous system, accompanied by endocrine and muscular changes (Panksepp 2000). Damasio (1996) postulated the well-known somatic marker theory in which he states that these somatic affective signals can be expressed as emotions, prompt a set of behavioral response tendencies, and modulate the selection of a behavioral response. The somatic marker signals are conveyed by the spino-thalamo-cortical pathway to the ventroposterior medial and the ventromedial nucleus of the thalamus (Craig 2002, Craig 2003). The posterior dorsal insula and the anterior cingulate cortex receive this integrated homeostatic information, and have been identified as key regions in interoception and emotional motivations respectively (Craig 2002, Craig 2003). The anterior cingulate cortex has further been divided in the dorsal region that serves cognitive appraisal and expression of emotions and a ventral region for emotion regulation through its strong connectivity with the limbic regions (Vogt et al. 1992, Devinsky et al. 1995, Bush et al. 2000, Etkin et al. 2011). The anterior insula engenders the basis for explicit awareness of the emotional affect and also has reciprocal connections with the anterior cingulate cortex, orbitofrontal cortex, hypothalamus (endocrine response), and limbic system including the amygdala (Craig 1995, Morris 2002, Craig 2003).

Emotion regulation is also part of the somatic marker hypothesis (Damasio 1996), stating that voluntary reappraisal recruits distributed brain networks such as the executive and salience network. These networks contain key regions for expression and regulation of emotions such as the medial and lateral prefrontal cortex, dorsal anterior cingulate cortex, lateral orbitofrontal cortex, and the inferior frontal gyrus (Levesque et al. 2003, Ochsner et al. 2004, Phan et al. 2005, Urry et al. 2006). In addition, Phan et al. (2005) showed that voluntary reappraisal decreases activity in the extended amygdala, and nucleus accumbens: brain regions known for the assembly and generation of a physiological and behavioral emotional response.

Finally, Damasio (1996) postulated that the ventromedial prefrontal cortex establishes the memory linkage between current experiences and behavioral response tendencies. Indeed, in an extensive review on emotion-research, the
ventral medial prefrontal cortex and the ventral rostral anterior cingulate gyrus were identified to regulate the limbic system with respect to the generation of emotional responses (Etkin et al. 2011). Furthermore, Nieuwenhuis and Takashima (2011) proposed that the ventral medial prefrontal cortex initially serves to integrate limbic activity in response to emotional events, and that, over time, the integrated memory representation of these events could be used to inhibit the limbic response to similar novel experiences. Finally, as an additional benefit of this reorganization of emotional circuits, the association between the memory representation and the limbic system decays over time, effectively “forgetting” the emotional response and leaving a semantic representation of the emotional event. As proposed above, it seems therefore that emotional circuits are not only critically involved in the formation and re-consolidation of memory circuits, but also vice versa, that the reorganization of neuronal memory circuits effectively regulates emotional distress.

The role of sleep in emotion regulation

The overnight reorganization of emotional memory circuits has been shown to depend on REM sleep, and this reorganization facilitates inhibition of the amygdala by the medial prefrontal cortex (Takashima et al. 2006, Nieuwenhuis and Takashima 2011, Van Der Helm et al. 2011). As stated before, not only REM sleep but also NREM sleep has a complex and multifaceted role in emotional memory reorganization. Vanderheyden et al. (2014) proposed that it may be necessary for the target memory trace to be spontaneously reactivated first during the NREM sleep period that precedes REM sleep as a prerequisite before REM sleep can exert its role on the functional reorganization of the memory circuit. 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). Interestingly, functional coupling between the hippocampus and medial prefrontal cortex is especially high during spindle generation in slow-wave sleep in rats (Siapas and Wilson 1998). It seems therefore that spontaneous reactivation of memories during NREM sleep could serve to promote the
integration of limbic activity in the medial prefrontal cortex as proposed by Nieuwenhuis and Takashima (2011).

Furthermore, next to the formation of new or potentiated synaptic connections, in order to fully reorganize emotional neuronal circuits, also existing connections would have to be depotentiated. Especially this depotentiation has been attributed to the lack of noradrenergic neurotransmission from the locus coeruleus during REM sleep (Vanderheyden et al. 2014). Noradrenalin supports the consolidation of memories by promoting long-term potentiation and preventing long-term depression (Izumi et al. 1992, Thomas et al. 1996, Izumi and Zorumski 1999). During REM sleep however, the neurons in the locus coeruleus decrease their firing rate, thus providing downstream projection areas a milieu that permits long-term depotentiation (Kemp and Manahan-Vaughan 2004). At the same time, REM sleep is characterized by theta-rhythm activity throughout the cortex and in the hippocampus and is important for long-term potentiation (Winson 1978, Mizumori et al. 1990, Hasselmo and Bower 1993, Rashidy-Pour et al. 1996). Taken together, the unique combination of the absence of noradrenalin, high acetylcholine, and theta-rhythms during REM sleep could allow for bidirectional neuronal plasticity, and may simultaneously serve to incorporate the semantic aspects of the memory into neocortical circuits (Poe et al. 2010) and prepare the medial prefrontal cortex to pose functional inhibition on the amygdala (Takashima et al. 2006, Nieuwenhuis and Takashima 2011, Van Der Helm et al. 2011). Taken together, it is conceivable that the mechanisms outlined above are critically involved in the overnight regulation of emotional distress, and if perturbed could have severe repercussions including increased risk for disorders of emotional memory (Kindt 2018) such as major depression disorder and post-traumatic stress disorder.

Causes, characteristics and consequences of insomnia disorder

Definition of insomnia disorder
The DSM-5 classifies Insomnia Disorder (ID) as a mental disorder with a predominant dissatisfaction with sleep initiation, maintenance, and or early-morning awakenings, accompanied by significant distress or impairment in
daytime functioning including fatigue, altered mood and motivation, and attention and memory problems (American Psychiatric Association 2013). In addition, to diagnose ID, the sleep problems occur despite adequate opportunity for sleep, at least 3 nights a week for at least 3 consecutive months, and cannot uniquely be explained by other sleep-wake disorders, e.g. a breathing-related sleep disorder, the use of substances, or coexisting mental disorders or medical conditions.

**Causes of insomnia disorder**

**Genetics**

Heritability of ID has been established with genetic factors explaining about 38% in males and 59% in females (Lind et al. 2015). This indicates that genetic factors that influence insomnia complaints should be identifiable. However, genetically informed cohorts seldom include a phenotype that discriminates people with ID well. Recently, we managed to cross-validate a phenotype of the UK biobank against the broadly phenotyped ID cases and controls participating in the Netherlands Sleep Registry (Benjamins et al. 2017). After demonstrating the validity of the UK biobank question and determining an optimal cut-off for its answer options, 7 genes in 3 loci were found to be implicated with ID (Hammerschlag et al. 2017). These findings are important, since ID is widely regarded as a learned and completely reversible disorder. However, interventions targeting the maladaptive “learned” behaviours and cognitions are effective in only two-thirds of cases, and when effective, ameliorate complaints only by about 30% (Harvey and Tang 2003, Morin et al. 2009). These findings support the likelihood of biological predispositions for ID from the bottom-up.

**Hyperarousal theory**

Historically, ID has been investigated predominantly from a psychological top-down perspective. First based on electrophysiological techniques and later extended with neuroimaging, a hyperarousal model of insomnia was developed (Perlis et al. 1997, Bonnet and Arand 2010, Riemann et al. 2010). The hyperarousal theory links the psychological perspective on the development of insomnia to underlying biological brain mechanisms. It describes the trajectory of the aetiology of insomnia based on predispositions, and precipitating and perpetuating factors. Importantly, 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.

Indeed, next to the genetic predisposition described above, stress-sensitivity and the tendency to worry and ruminate are some cognitive examples of insomnia predispositions. Increased high frequency EEG activity in pre-sleep resting-state recordings has been regarded as a neurophysiological marker of those cognitions (Colombo et al. 2016). Another predisposition, for instance, is increased sensitivity of interoceptive processing. Subjects suffering from ID were found to portrait increased sensory responses to their own heart-beat (Wei et al. 2016) indicating that abnormalities in the salience network involved in interoceptive awareness may be a key insomnia predisposition.

Characteristics and consequences of ID

The salience network plays a central role in emotional brain circuits by linking and integrating the emotional somatic markers with activity in the limbic system and brain regions necessary for adequate regulation of emotional distress. Abnormalities in the salience network may therefore have negative implications for the regulation of emotional distress. Riemann et al. (2010) further proposed that acute stress affects sleep onset and night-time awakenings including perturbations in the RAS and VLPO. It is conceivable that pre-sleep RAS perturbations could linger on during sleep as would be reflected in arousals and awakenings from sleep. Indeed, disrupted sleep continuity is a key characteristic of insomnia (Baglioni et al. 2014). Given the proposed role of REM sleep in the adaptive reorganization of emotional memories, these perturbations could negatively impact overnight regulation of emotional distress, and perpetuate insomnia towards a chronic maladaptive phase.

There is a gap in our knowledge on the role of regulation of emotional distress and its possible failure related to restless REM sleep in the aetiology of insomnia. We have commenced to address this gap in a set of observational and experimental studies. The studies evaluated whether insomnia disorder might involve an
insufficiency to resolve emotional distress due to the processes underlying fragmentation of REM sleep.

**Outline of the thesis**

The hyperarousal model of ID proposes that maladaptive regulation of acute emotional distress can lead to chronic forms of conditioned arousal that perpetuates insomnia. Especially the failing resolution of emotional distress seems crucial in the understanding of the aetiology of ID. Given the role of REM sleep in overnight regulation of emotional distress, the characteristic restless REM sleep in ID seems a logical primary candidate involved in the failing resolution of emotional distress. In chapter 2, we aim to formally evaluate this hypothesis using a structural equation model on a large-scale dataset.

If the supportive role of sleep to regulate emotional distress overnight is hampered by sleep perturbations in ID, we should be able to identify differences in the next day emotional response to emotional stimuli between healthy volunteers and those with ID. In chapter 3, we report on a repeated-measures experimental study in which we induced shame and embarrassment by confronting people with ID and normal sleepers with their own imperfect singing, and evaluate the case-control differences in the sleep-related change in emotional distress.

As outlined above, normal sleep aids reorganization of neuronal networks and thereby effectively enables the regulation of emotional distress associated with past experiences. However, chronically perturbed sleep in ID could impede such neuronal network reorganization. If reorganization fails, the brain response to remembering past emotional experiences would continue to resemble its original response to the novel experience. In chapter 4, we report on a functional MRI study which tests the hypothesis of insufficient reorganization of emotional networks to past experiences.

The overnight reorganization of emotional neuronal circuits is dependent on rapid eye movement (REM) sleep in concert with spontaneous reactivation of the neuronal memory trace during NREM sleep. Furthermore, it was outlined that sleep fragmentation may reflect an underlying malicious factor that interferes with this overnight regulation of emotional distress. In chapter 5, I report on our study
that experimentally induced odor-mediated targeted memory reactivations to evaluate the impact of sleep fragmentation during NREM and REM sleep on the overnight change in brain responses to emotional stimuli.

Finally, in accordance with the hyperarousal theory, ID is characterized by a reduction in sleep continuity, reduced amount of slow-wave sleep and REM sleep (Baglioni et al. 2014). However, there is a consensus that PSG is not required for the routine evaluation of insomnia and that PSG-abnormalities are no defining characteristic of ID (Standards of Practice Committee of the American Sleep Disorders Association 1995). The use of discrete classification of sleep stages in wide and constant epochs may be too crude to capture the transient and dynamic neurophysiological sleep disturbances in ID. In chapter 6, we will use a data-driven modelling approach, that describes each 30-second PSG epoch as a combination of multiple vigilance states, to reveal insomnia-related sleep changes that are not detectable by current manual PSG scoring methods.

References

Introduction


Chapter 1.


