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A NEUROIMAGING PERSPECTIVE ON THE EMOTIONAL SLEEPY BRAIN

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Sleep has been shown to be important for a number of emotional functions. Brain correlates to the effect of sleep deprivation on emotion have been studied in the last decades and increased amygdala reactivity has been proposed as one possible mechanism. However, existing literature shows inconsistent consequences of sleep loss, both in terms of behavioral outcomes and measures of brain activity. Age is one factor that could modulate effects of sleep deprivation on emotional functions, since both sleep patterns and emotional reactivity change with aging. Beyond changes in amygdala reactivity, changes in the brain's intrinsic connectivity or immune factors could be possible mechanisms through which insufficient sleep affects specific emotional functions as well as fatigue and sleepiness.

The aim of this thesis was to investigate mechanisms underlying effects of insufficient sleep on emotional functions, including emotional contagion, empathy, emotional regulation, and mood, as well as sleepiness and fatigue. The thesis consists of five studies using different brain imaging methods and investigating both younger and older adults.

Studies I and III show that one night of restricted sleep was sufficient to cause changes in emotional behavior, i.e. a negativity bias, negative mood, and a decreased ability to regulate emotions (in young). However, increased amygdala reactivity was not shown to be increased after sleep restriction. Study II shows that empathic behavior was affected in older but not in young subjects after sleep restriction. Study IV shows that sleep restriction was associated with increased global signal variability in the brain, as a potential marker of wake-state instability and sleepiness. However, no significant effects on the brain's default mode network were found. Study V shows that patients with severe seasonal allergy had increased fatigue, sleepiness and disturbed sleep, and signs of peripheral inflammation. However, the study does not implicate increased translocator protein binding, as measured with positron emission tomography, and indicating possible microglia cell activation, as involved in these non-specific symptoms.

In conclusion, this thesis shows that restricted sleep is associated with a negativity bias and a decreased ability to regulate emotions, at least in young. Increased global signal variability in the brain's gray matter could be one possible correlate to the behavioral effects of sleep restriction. However, other brain mechanisms underlying emotional dysfunction related to poor sleep need further investigation, using reliable methods in large samples.

LIST OF SCIENTIFIC PAPERS

I. **Tamm, S.**, Schwarz, J., Thuné, H., Kecklund, G., Petrovic, P., Åkerstedt, T., Fischer, H., Lekander, M., Nilsonne, G. Effects of partial sleep deprivation on emotional contagion in humans: a combined fMRI and EMG study in young and older individuals (*manuscript*)

II. **Tamm S.**, Nilsonne G., Schwarz J., Lamm C., Kecklund G., Petrovic P., Fischer H., Åkerstedt T., Lekander M. The effect of sleep restriction on empathy for pain: An fMRI study in younger and older adults. *Sci Rep. 2017 Sep 25;7(1):12236.*

III. **Tamm, S.**, Nilsonne, G., Schwarz, J., Golkar, A., Kecklund, G., Petrovic, P., Fischer, H., Åkerstedt, T., Lekander, M. Sleep restriction caused impaired emotional regulation without detectable brain activation changes - a functional magnetic resonance imaging study. *Royal Society Open Science (accepted).*

IV. Nilsonne G., **Tamm S.**, Schwarz J., Almeida R., Fischer H., Kecklund G., Lekander M., Fransson P., Åkerstedt T. Intrinsic brain connectivity after partial sleep deprivation in young and older adults: results from the Stockholm Sleepy Brain study. *Sci Rep. 2017 Aug 25;7(1):9422.*

V. **Tamm S.**, Cervenka S., Forsberg A., Estelius J., Grunewald J., Gyllfors P.,.Karshikoff B., Kosek E., Lampa J., Lensmar C., Strand V., Åkerstedt T., Halldin C., Ingvar M., Olgart Höglund C., Lekander M. Evidence of fatigue, disordered sleep and peripheral inflammation, but not increased brain TSPO expression, in seasonal allergy: A [(11)C]PBR28 PET study. *Brain Behav Immun. 2018 Feb;68:146-157.*

CONTENTS

LIST OF ABBREVIATIONS

EEG	Electroencephalography
EOG	Electrooculography
EMG	Electromyography
BOLD	Blood oxygen level-dependent
DMN	Default Mode Network
fMRI	Functional magnetic resonance imaging
MRI	Magnetic resonance imaging
TSPO	Translocator protein
PANAS	Positive And Negative Affect Schedule
KSS	Karolinska Sleepiness Scale
REM	Rapid eye movement
NREM	Non-rapid eye movement
SWS	Slow wave sleep
IL	Interleukin
TNF	Tumor necrosis factor

1 PREFACE

During the work with this thesis I have had several opportunities to experience sleep deprivation. During the first years of the project, we were scanning participants late in the evening. In 2016, I started my clinical foundation program and as a junior doctor spent nights in the emergency department every now and then. In 2017 my son was born, changing my perspective on the meaning of a *full* night's sleep. As many people report, such nights without sufficient sleep do not pass unnoticed. I am sure that my patience and emotional control are certainly not always the same after a period without sleep, but is this effect really something that could be objectively measured and quantified? And what is actually happening in my brain and body that causes these sometimes inconvenient reactions? Would the effect be different if I was now a senior physician? In this thesis, I tried to further understand the question why we need to sleep to function well, specifically in the domain of emotion.

In the following sections, I aim to briefly present the main ideas behind the project, followed by a literature review setting the stage for the included studies, introduction of the methodologies and results. In the second part of the thesis, I aim to discuss some methodological and ethical considerations, as well as general theoretical ideas, conclusions and points related to further research questions and implications. My intention is to discuss not only scientific matters, but also to share personal perspectives and reflections when relevant– which necessarily also might have implications for how the research should be judged. This distinction should be clear from the text. However, to further avoid uncertainties about whether a sentence represents a personal reflection or not, I have restricted the use of first-person pronouns to statements that should be read as my personal view.

2 THEORETICAL INTRODUCTION

Many processes in the nervous system can be described in a hierarchical manner, where basic circuits are regulated by higher, more complex networks (Fuster, 2001; Mesulam, 1998). Information processing in the brain can occur through both so called top-down and bottom-up processes. Top-down processes are guided by higher-level mental processes, such as expectations and predictions about the world (Friston, 2010), whereas bottom-up processes originate with information from basic functions, such as sensory organs, that is integrated into the nervous system (Rauss & Pourtois, 2013). Three emotional processes that are of a certain importance to this thesis, and which can be described in a hierarchical manner (see (de Vignemont & Singer, 2006)), are *emotional contagion, empathy* and *emotional regulation*. Emotional *mimicry* occurs early in life (Field, Woodson, Greenberg, & Cohen, 1982; Meltzoff & Marshall, 2018), with babies smiling in response to a smile, initially likely without awareness of the social importance of this action. This phenomenon is closely related to emotional contagion (Hatfield, Cacioppo, & Rapson, 1994), by some referred to as primitive empathy (de Vignemont & Singer, 2006; Meltzoff & Decety, 2003), which involves the *sharing* of emotional experience, but still without knowledge that the own emotion is evoked by the emotion of the other person. Singer and Vignemont proposed that empathy, beyond sharing of the emotion, requires the knowledge that the other person's affective state is the source of the own affective state (Singer and Vignemont 2006), which in the hierarchical model places empathy above emotional contagion and mimicry. Top-down processes that aim to change emotional responses, such as both emotional contagion and empathy, can be viewed as regulatory functions in the hierarchy (de Vignemont & Singer, 2006). One example of such regulation is cognitive reappraisal (J. Gross, 1998), where a cognitive strategy is used to reinterpret the emotional response in a less emotional way, to reduce it.

As noted above, this thesis aims to understand the role of sleep for emotional recovery. However, to understand the role of sleep for any emotional function, it is also necessary to understand the importance of sleep for general recovery. The evolutionary basis for sleep is still not fully understood, but the role of sleep for emotional functioning likely evolved at a later evolutionary stage, compared to the roles for functions such as plasticity and metabolism (James M. Krueger, Frank, Wisor, & Roy, 2015). Effects of insufficient sleep on plasticity or metabolism at a cellular level, or at the level of large-scale brain networks, could indirectly or directly affect emotional processes anywhere in the brain. Along the emotional hierarchy

described above, we expected sleep to have stronger effects on complex top-down processes which to a large extent involve the prefrontal cortex, previously been shown to be affected by sleep deprivation (Krause et al., 2017), and weaker effects on more basic bottom-up functions. However, in the context of general effects of sleep on the brain, it appears important to study effects not only related to a specific function across all brain regions. Intrinsic connectivity, i.e. the brain's connectivity at rest, provides sets of metrics allowing the study of such general effects on the brain. If sleep restriction changes the brain's intrinsic connectivity, it could be questioned whether any specific brain functions could be studied in relation to sleep, without trying to take this into account.

The brain does not work in isolation, but interacts with the rest of the organism. The peripheral nervous system continuously exchanges information with the central nervous system, with the brain acting as a master control organ, but information can be carried to the brain also through other pathways, for example the endocrine and immune systems. Through such pathways, the periphery can influence the brain in order to launch adaptive behavioral changes, for example in terms of emotion, motivation, pain, fatigue and sleep. Factors such as inflammatory cytokines also play a part in physiological processes such as long-term potentiation (Prieto & Cotman, 2017) and regulation of sleep-wake patterns (Jewett & Krueger, 2012). The immune system is thus linked to sleep, and shown to react to changes in sleep (Imeri & Opp, 2009; J. M. Krueger & Opp, 2016). Another way through which insufficient sleep could affect the brain, specifically in terms of emotion, fatigue and sleepiness, is therefore through processes related to the immune system. Sleep disturbance has previously been associated with peripheral changes in the immune system (Irwin, Carrillo, & Olmstead, 2010; Irwin, Olmstead, & Carroll, 2016; Mullington, Simpson, Meier-Ewert, & Haack, 2010). Notably, acute sleep deprivation causes a behavioral pattern with depressed mood, increased fatigue and tension and lower vigor and positive affect (J. Schwarz et al., 2018). This pattern of behavioral changes closely resembles the so called *sickness response* (see example. Hart, 1988) seen in inflammatory conditions such as acute infection, after vaccination and in patients with chronic disease (R Dantzer, 2001; Harrison et al., 2009). In models of inflammation, e.g. after injection with lipopolysaccharide, the brain is influenced by pro-inflammatory cytokines signaling to the brain and causing a sickness response (R Dantzer, 2001; Robert Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Some effects of insufficient sleep on the brain could depend on a similar route, with the peripheral immune system, potentially controlled by the hypothalamic–pituitary–adrenal axis,

reacting to sleep loss and signaling to the brain through cytokines. In addition, some animal work indicate that sleep deprivation can cause increased microglia activation, i.e. low-grade inflammatory changes, in parts of the brain (Wisor, Schmidt, & Clegern, 2011; Zhu et al., 2012). Thus, effects of disturbed sleep can involve immune activation, both in the periphery and in the brain. Therefore, the present thesis also investigates immune parameters in relation to sleep, fatigue and emotional functioning. Some but not all of these data have been included in papers I-V.

Both emotional functions (Mather, 2012; Ziaei & Fischer, 2016) and sleep (Ancoli-Israel, 2005; Duffy, Zitting, & Chinoy, 2015; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004) as well as the immune system (Cao & Zheng, 2018) change during the life-course. However, most research in these fields is performed in young healthy participants. To increase generalizability, participants of different ages need to be included when possible. Therefore, differences between adult age groups were investigated in relation to sleep and emotional function in this thesis.

In conclusion, in order to understand effects of insufficient sleep on any function, including emotion, there are many other aspects of the brain and the body that need to be considered. This thesis therefore aimed to investigate the relation between insufficient sleep and emotional functioning, with a broad brain-body perspective. Study 1-3 aimed to investigate how sleep restriction affects specific emotional processes (emotional contagion, empathy and emotional regulation) and study 4 aimed to understand general effects of sleep restriction on resting state brain activity and connectivity. In study 5 the aim was to investigate the relation between sleep, fatigue and central as well as peripheral immune activation in a patient sample, where sleep problems and symptoms related to emotional dysfunction are common. After this brief introduction of the theoretical framework, a background literature review of research in areas related to this thesis will follow, further clarifying some of the concepts that were just touched upon in the introduction.

3 LITERATURE OVERVIEW

3.1 SLEEP

Sleep can be defined as a state of immobility with reduced responsiveness, different to coma by the rapid reversibility (Siegel, 2005) and operationally measured using electroencephalography (EEG) and electrooculography (EOG). Extensive sleep deprivation leads to death in rodents and flies (Rechtschaffen, 1998). In healthy humans, death caused by sleep deprivation has not been shown, but the importance of sleep for a number of functions, including brain plasticity and connectivity, metabolism and energy consumption (James M. Krueger et al., 2015), cognition and memory (Lim & Dinges, 2010), immune function (Hurtado-Alvarado et al., 2013) and emotion (Beattie, Kyle, Espie, & Biello, 2015), has repeatedly been demonstrated. In epidemiological studies, long-term poor sleep is associated with somatic (Anothaisintawee, Reutrakul, Van Cauter, & Thakkinstian, 2015; Kohansieh & Makaryus, 2015; Zhao et al., 2013) and psychiatric morbidity (Bernert & Nadorff, 2015; Rumble, White, & Benca, 2015) further underlining the importance of sleep for adequate functioning. However, the associations are likely bidirectional in many cases, indicating a need for more experimental studies in this field. As already mentioned in the introduction, it is debated which of all sleep functions that carry the primary evolutionary advantage. Presumably, sleep developed because of functions such as plasticity, connectivity and metabolism, with other functions, including emotions, taking advantage of its existence (James M. Krueger et al., 2015).

Sleep can be classified into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. NREM can be further divided into stages 1-4 (3 and 4 referred to as slow wave sleep) (Rechtschaffen & Kales, 1968). In the current sleep scoring manual NREM is divided in N1, N2 and N3 (formerly stage 3 and 4) (Iber, Ancoli-Israel, Chesson, & Quan, 2007). Slow wave sleep (SWS) occurs more in the beginning of the night and is considered to be of a certain importance for recovery as well as cognition (Walker, 2009), while REM sleep occurs repeatedly during sleep, but in greater amounts towards the end, and has been proposed to be related to emotional and memory functions (Walker & van der Helm, 2009). Slow wave sleep increases linearly with time awake (Borbély, Daan, Wirz-Justice, & Deboer, 2016) and time awake causes increased sleepiness and decreased functional ability (Dijk 2010).

3.2 SLEEPINESS AND FATIGUE

An obvious consequence of sleep restriction is sleepiness. Sleepiness can be defined as a physiological drive for sleep and a behavioral measure of falling asleep at a certain time (Akerstedt & Gillberg, 1990; Dement & Carskadon, 1982). It increases with time awake (Van Dongen, Maislin, Mullington, & Dinges, 2003) and can be measured using self-reports (Akerstedt & Gillberg, 1990) or as latency to stage 1 sleep (Carskadon & Dement, 1982). Sleepiness is thus a reliable marker of insufficient sleep and impaired waking function (Torbjörn Åkerstedt, Anund, Axelsson, & Kecklund, 2014). However, sleepiness as a state is not well defined in terms of functional brain activation.

Oxford Dictionaries define fatigue as extreme tiredness resulting from mental or physical exertion or illness ("Oxford Dictionaries," 2019). It is a commonly reported symptom in both somatic and psychiatric disorders (Cathébras, Robbins, Kirmayer, & Hayton, 1992). Fatigue is argued to be a multidimensional construct (Karshikoff, Sundelin, & Lasselin, 2017), and some measurements of fatigue actually include a dimension of sleepiness (Åhsberg, 2000). Fatigue and sleepiness are indeed interrelated, and in daily speech sometimes also used interchangeably. However, previous work indicate that the two concepts can be separated (Hossain et al., 2005; Karshikoff et al., 2017). While sleepiness is primarily a consequence of sleep loss, fatigue usually occurs as a consequence of exhaustion (Hossain et al., 2005). Fatigue is also more often associated with depressed mood and negative emotion (Hossain et al., 2005).

3.3 SLEEP, EMOTION AND COGNITION

An important motivation to study the relationship between sleep and emotional functions is the association between sleep disturbance and psychiatric disorders (Baglioni & Riemann, 2012; Rumble et al., 2015). Insomnia has been suggested as a precursor of depression (Baglioni & Riemann, 2012), and counterintuitively acute sleep deprivation leads to a reduction of depressive symptoms in depressive patients (Boland et al., 2017). However, to understand mechanisms behind these effects, experimental studies are needed.

Many aspects of sleep and cognition, especially memory, have been studied in more depth, compared to emotion. Vigilance, i.e. to sustain attention is highly dependent on sleep and

therefore the psychomotor vigilance task is considered a sensitive measure of sleep loss (Van Dongen & Dinges, 2005). Higher cognitive functions, such as working memory, have by some been proposed to be less sensitive to sleep deprivation (Lo et al., 2012). However, previously shown effects of sleep deprivation on the prefrontal cortex would suggest the opposite (Krause et al., 2017). In laboratory settings, sleep can be studied through different types of manipulation, such as total sleep deprivation, partial sleep deprivation, (interchangeably used with sleep restriction in this context) and sleep disruption or suppression of specific sleep stages. Total sleep deprivation has a stronger effect on sleepiness, compared to repeated sleep restriction, but 14 days of sleep restriction (6 hours) can affect cognitive performance similarly to what is seen after 2 nights of total sleep deprivation (Van Dongen et al., 2003). Importantly, not only the length but also the balance between different sleep stages differ in between total sleep deprivation and partial sleep deprivation.

Despite emotion being studied less compared to cognition, the importance of sleep for adequate emotional functioning has consistently been shown (Beattie et al., 2015; Deliens, Gilson, & Peigneux, 2014), at least for some functions. Emotional memory, i.e. memories with an emotional content, has been studied more thoroughly, compared to other aspects of emotion and it is well-established that sleep is needed both before coding of a new emotional memory, during the consolidation and for the retrieval (Beattie et al., 2015). Recently, the "sleep to remember, sleep to forget" theory (Walker & van der Helm, 2009) claimed that REM sleep is of a certain importance for consolidation of emotional memories, i.e. that REM sleep is needed for preserving the core memory, while washing out the emotional connotation. However, this theory is still questioned and studies specifically suppressing REM have not been able to confirm the core features of the theory (Beattie et al., 2015).

It has been suggested that perception of emotional stimuli is affected by sleep deprivation (Cote, Mondloch, Sergeeva, Taylor, & Semplonius, 2014; Franzen, Buysse, Dahl, Thompson, & Siegle, 2009; Tempesta et al., 2010). In some studies, facial emotional expressions were not recognized to the same extent after sleep deprivation, compared to normal sleep (Cote et al., 2014; Goldstein-Piekarski, Greer, Saletin, & Walker, 2015), an aspect that might be particularly important for social interaction. Notably, this finding was later not replicated in a larger sample (Holding et al., 2017). One study suggested that sleep-deprived subjects rated

lower emotional intensity of both happy and angry faces, i.e. a blunting of emotional responses (van der Helm, Gujar, & Walker, 2010). Other studies rather suggest that the effect of sleep deprivation can be described as a negativity bias, i.e. a shift towards negative emotion (Gobin, Banks, Fins, & Tartar, 2015; Pilcher, Callan, & Posey, 2015; Tempesta et al., 2010; Tempesta, Socci, De Gennaro, & Ferrara, 2018). This shift is nonetheless seen primarily for positive, neutral and ambiguous stimuli that are perceived as more negative after sleep deprivation, compared to after normal sleep (Pilcher et al., 2015; Tempesta et al., 2010). Also, expression of emotion is affected by sleep deprivation, so that the speech is perceived as less emotional (McGlinchey et al., 2011) and the appearance as sadder (Sundelin et al., 2013).

Recent imaging studies have investigated emotional functioning in relation to sleep deprivation (Ninad Gujar, Yoo, Hu, & Walker, 2011; Yuki Motomura et al., 2013; Yoo, Gujar, Hu, Jolesz, & Walker, 2007). In one early study, amygdala reactivity to increasingly negative stimuli increased after 36 hours of sleep deprivation, with decreased connectivity between prefrontal cortex and amygdala as the suggested mechanism (Yoo et al., 2007). The findings have partly been replicated using similar stimuli (van der Helm et al., 2011) and face stimuli (Yuki Motomura et al., 2013). However, not all studies report congruent findings (Beattie et al., 2015) and the evidence for decreased functional connectivity from the prefrontal cortex is so far limited. Therefore, it needs to be clarified whether the differences between studies depend on complexity in the relationship, or simply lack of statistical power. A few studies also investigated brain circuits underlying positive emotions showing increased reactivity in reward-related networks following sleep deprivation (Ninad Gujar et al., 2011; Mullin et al., 2013).

Three aspects of emotion that are of a certain importance to this thesis are emotional contagion, empathy and emotional regulation. As pointed out in the introduction, these social emotional functions can be viewed in a hierarchical manner, and the effect of sleep deprivation could vary across levels. Below, these emotions will be presented in greater detail. The evidence of effect of sleep manipulations in relation to these emotions will be presented in relation to each emotional function.

3.4 EMOTIONAL CONTAGION

As early as in 1907 Lipps proposed that observation of emotional expressions leads to mimicry and a convergence of subjective emotional states (Lipps, 1907). A number of electromyography (EMG) studies demonstrated that viewing facial expressions cause similar expressions on the observer's own face (Dimberg, Thunberg, & Elmehed, 2000; Tamietto et al., 2009), including our previous work (G. Nilsonne et al., 2017). It has also indeed been shown that observation of emotional expressions not only give rise to motor and autonomic mimicry but also corresponding emotional responses (Hatfield et al., 1994). Automatic mimicry (synchronization of expressions, vocalizations, postures and movements with those of another person) can be viewed as a part of *emotional contagion*, defined as the tendency to take on the sensory, motor, physiological and affective states of others (Hatfield et al., 1994).

According to Preston and de Waal's perception-action model, emotional contagion is the most basic form of empathy (Preston & de Waal, 2002). The perception-action model also states that perceiving a target's state automatically activates the corresponding representations of that state in the observer, leading to somatic and autonomic responses. The mechanisms behind emotional mimicry and contagion are proposed to be synchronization of autonomic arousal (reviewed in (Prochazkova & Kret, 2017)) as well as through a mirroring neural system in the brain (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Lacoboni, 2009; Likowski et al., 2012; Nummenmaa, Hirvonen, Parkkola, & Hietanen, 2008). Synchronization of autonomic arousal is proposed to rely on neural pathways that are also involved in emotional responses and autonomic nervous system activation, and of a specific interest to this theses is the amygdala (Prochazkova & Kret, 2017). The mirroring (neuron) system in this case is a brain network connecting areas including the inferior parietal lobe, the inferior frontal gyrus and the superior temporal sulcus (Dinstein, Hasson, Rubin, & Heeger, 2007; Lacoboni, 2009).

Emotional faces are important social cues and the ability to identify and to respond adequately to emotional faces is necessary for social interaction. However, it has been shown that the ability to identify and classify emotional faces is contextually dependent (Mobbs et al., 2006). It has also been suggested that responses to emotional faces are changed in psychiatric disorders, including depression (Bourke, Douglas, & Porter, 2010). As discussed above, the perception of emotional faces have been studied in relation to sleep with

inconsistent behavioral results (Cote et al., 2014; Holding et al., 2017). Amygdala reactivity in response to emotional faces has also in one study been shown to increase after sleep deprivation (Y Motomura et al., 2014). However, to my knowledge, no experimental study specifically investigated sleep and emotional contagion. Neither has facial mimicry been studied specifically in relation to sleep, but one study showed slower facial EMG-responses to positive and negative stimuli, including happy and angry faces after sleep deprivation (J. F. A. Schwarz et al., 2013). Based on the notion that both perception of emotional faces and facial EMG-responses could be affected by sleep deprivation, it could be expected that emotional contagion is affected by sleep restriction.

3.5 EMPATHY

Empathy is a basic social mechanism, needed for interaction and a main motivator for prosocial behavior (de Waal, 2008). The construct has various definitions (Bernhardt & Singer, 2012; de Waal, 2012; Preston & de Waal, 2002). A crucial part of empathy is the ability to be affected by another's emotional state (de Waal, 2008) and for a full-blown empathic response, perspective taking, i.e. the ability to distinguish the own emotional state from the state of the individual giving rise to the initial emotion is needed, according to Lamm et al. (C Lamm, Decety, & Singer, 2011). Consequently, Singer and Vignemont define empathy as following: “There is empathy if: (i) one is in an affective state; (ii) this state is isomorphic to another person's affective state; (iii) this state is elicited by the observation or imagination of another person's affective state; (iv) one knows that the other person is the source of one's own affective state” (de Vignemont & Singer, 2006). This is slightly different from the definition by Hoffman, adapted by Preston and de Waal that defines empathy as “any process where the attended perception of the object’s state generates a state in the subject that is more applicable to the object’s state or situation than to the subject’s own prior state or situation” (Hoffman, 2000; Preston & de Waal, 2002), which, as mentioned above would include concepts like emotional contagion.

In the last decades, empathy, specifically for pain, has been studied using modern brain imaging techniques (C Lamm, Batson, & Decety, 2007; C Lamm et al., 2011; Morrison, Lloyd, di Pellegrino, & Roberts, 2004; Singer et al., 2004). Seeing someone else in pain consistently activates brain regions involved in the experience of first-hand pain, i.e. anterior insula and anterior cingulate cortex (C Lamm et al., 2011), and it is thought that this shared

representation in the brain corresponds to the shared emotional experience. Different experimental paradigms have been used to study empathy, including watching a person present experiencing pain (Singer et al., 2004), or watching pictures (Schott, 2015) or movie clips (C Lamm et al., 2007) of someone in a painful situation. Activity in empathy for pain-related areas in anterior insula and anterior cingulate cortex have been claimed to be predicted by degree of self-rated trait empathy (Singer et al., 2004), but this early finding has mostly not been replicated (C Lamm et al., 2011).

One behavioral study examined emotional empathy and experimental sleep (Guadagni, Burles, Ferrara, & Iaria, 2014), suggesting decreased empathy after sleep deprivation. Another study suggested that better self-rated sleep quality is related to increased blood oxygen level-dependent (BOLD) signal within the left insula during an empathy task (Guadagni, Burles, Ferrara, & Iaria, 2018), also highlighting the role of sleep for empathy. However, no brain imaging study examined empathy for pain after sleep deprivation and in a recent review (Beattie et al., 2015), studies on sleep and social emotions, specifically empathy, including diverse measures of emotional functioning and brain imaging, were asked for.

3.6 EMOTIONAL REGULATION

The ability to regulate emotions is necessary for adequate functioning. It can be defined as "the processes by which we influence which emotions we have, when we have them, and how we experience and express them" (J J Gross, 1998). There are several strategies, both conscious and unconscious, for regulating emotions and the strategies take place during different points in time in the processing of emotional information (J J Gross, 2002). For example both avoiding an emotional situation as well as changing the physiological response to the emotional situation or stimulus could be seen as emotional regulation strategies. Once the emotional situation/stimulus is perceived, it is also possible to change the emotional response. An effective way of doing this is through cognitive reappraisal, "construing a potentially emotion-eliciting situation in non-emotional terms" (J J Gross, 2002). The strategy to reappraise emotions is used not only as a common emotional regulation strategy in daily life, but also for example in psychotherapy (Bowins, 2013).

Cognitive reappraisal has been studied repeatedly using fMRI (Buhle et al., 2014; Kalisch, 2009; Ochsner, Silvers, & Buhle, 2012). In the experiments participants are usually instructed to reappraise negative emotional stimuli (such as pictures of natural disasters or car accidents) in a non-emotional way (Kalisch, 2009) and this condition is compared to a passive viewing condition, or another type of emotional regulation such as distraction (Kanske, Heissler, Schonfelder, Bongers, & Wessa, 2011). Reappraising can be done through, for example, imagining that a negative stimulus represent fiction (e.g. a movie scene) or through convincing yourself that the accident is happening to someone that you do not know. However, details in the experimental tasks (such as timing, instructions, stimuli) vary substantially across studies and probably explain some of the observed differences. Two recent meta-analyses have been performed to summarize the findings (Buhle et al., 2014; Kalisch, 2009). Kalisch (Kalisch, 2009) found consistent activity in lateral superior, middle and inferior frontal gyri, the lateral orbital gyri and parts of the medial superior frontal gyrus (including pre-supplemental motor area and the anterior cingulate cortex), for 13 studies contrasting reappraise conditions to passive viewing condition, mostly using stimuli from the International Affective Picture System (Lang, Bradley, & Cuthbert, 1997). Amygdala activity was consistently decreased in the reappraise compared to passive viewing condition. The second meta-analysis (Buhle et al., 2014), including data from 48 studies with a wider range of stimulus types, concluded consistent activity in cognitive control regions in dorsomedial prefrontal cortex, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and in the posterior parietal lobe, but not in the orbitofrontal cortex. However, there is a substantial overlap between ventrolateral prefrontal cortex and lateral orbitofrontal cortex, and some differences between the two meta-analyses can possibly be attributed to differences in terminology rather than actual brain differences. Amygdala was in the second meta-analyses also modulated across studies, showing less activity to negative stimuli after reappraising, compared to passive viewing (Buhle et al., 2014). In an influential study by Wager et al. (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008) it was shown that the cognitive reappraisal success was specifically related to the activity in lateral orbitofrontal cortex/ventrolateral prefrontal cortex (bilaterally) during the reappraisal condition.

Cognitive reappraisal has been studied in relation to habitual sleep quality, but the findings are contradictory so far. In one study, poorer self-rated sleep quality was shown to predict lower ability to reappraise emotions (Mauss, Troy, & LeBourgeois, 2013), while another study found no relation between subjective sleep quality and success in emotional regulation

through cognitive reappraisal (Minkel et al., 2012). One EEG study also investigated cognitive reappraisal after 24 hours of sleep deprivation and found reduction in the centroparietal late positive potential compared to after a normal night sleep condition (Zhang, Lau, & Hsiao, 2018). These studies indicate a role of sleep for cognitive reappraisal, but highlight the need for studies using experimental sleep manipulations and other types of brain imaging (e.g. fMRI) measures.

3.7 THE AGING BRAIN AND EMOTION

Aging is associated with changes in brain functions as well as behavior. Cognitive aspects of aging have been studied extensively and an age-related decline in memory capacity seems to be established (C. Grady, 2012). Emotional functions have been less studied in older individuals, but during the last decade this research topic has also gained a lot of attention (Mather, 2012; Williams et al., 2006). Even though older individuals tend to have increased morbidity, decreased social interaction and increased personal loss (in terms of friends and partners dying), well-being tends to increase with higher age (Mather, 2012).

From research regarding cognition some general aspects of brain responses are known, that might also have implications for studies of emotion in aging. When performing a cognitive task, older individuals recruit larger prefrontal brain areas compared to young, when performing at the same level (R Cabeza et al., 1997; Cappell, Gmeindl, & Reuter-Lorenz, 2010; C. L. Grady, 1996). This over-recruitment has been interpreted as neural correlates of cognitive decline or compensation for decreased function (Roberto Cabeza, Anderson, Locantore, & McIntosh, 2002; Reuter-Lorenz & Park, 2010). The latter view is supported by the fact that at higher cognitive load, older individuals perform worse compared to younger (Cappell et al., 2010). The increase in prefrontal activity, combined with decreased activity in posterior brain areas (occipital and temporal) in older individuals is sometimes referred to as *the posterior-anterior shift in aging* (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008), reflecting a general change in brain function with aging. It has also been proposed that older individuals' more widespread brain activity reflect a dedifferentiation, i.e. that some brain areas become less specific for a function with aging (Cheryl L Grady, 2008).

Functional MRI is a widely used technique to study brain function in aging. It has been proposed that the BOLD response differs between younger and older individuals (including amplitude reduction and time lag for the response), primarily due to cerebrovascular changes (D'Esposito, Deouell, & Gazzaley, 2003), which might question whether all observed differences are due to true effects in brain function or rather methodological shortcomings. Yet, the described cerebrovascular changes are not sufficient to explain all the differences observed (C. Grady, 2012).

Compared to cognition, emotional processes are less affected by age (Kensinger, 2009). Older individuals focus more on wellbeing and a general positivity effect exists in older compared to younger people (Reed & Carstensen, 2012; Williams et al., 2006). Older individuals show a positivity bias for memory (James J. Gross et al., 1997; Mather & Carstensen, 2005), increased positive emotion recognition and decreased negative emotion recognition (Williams et al., 2006) and are less distracted by negative, but not positive stimuli (Lamonica, Keefe, Harvey, Gold, & Goldberg, 2010). Consistent across studies is a decrease in amygdala activity in response to negative stimuli, accompanied with decreased amygdala-frontal connectivity (St Jacques, Bessette-Symons, & Cabeza, 2009). This pattern is referred to as *the fronto-amygdalar age-related differences in emotion* (St Jacques et al., 2009), and is suggested to reflect increased spontaneous emotional regulation. This is supported by decreased ratings of valence to negative stimuli by older people (Gunning-Dixon et al., 2003; Tessitore et al., 2005). However, *the aging-brain model*, proposed by Cacioppo (see Todorov, Fiske, & Prentice, 2011), rather suggests a decrease in amygdala activity due to amygdala atrophy as the underlying mechanism.

Emotional contagion and mimicry, empathy and cognitive reappraisal have partly been studied in the context of aging. One study suggested that older and younger subjects have a similar amount of emotional mimicry measured with EMG (Bailey, Brady, Ebner, & Ruffman, 2018). Two imaging study compared empathy between younger and older adults (Chen, Chen, Decety, & Cheng, 2014; Riva et al., 2018), showing that older individuals had smaller responses in anterior mid-cingulate cortex and anterior insula compared to younger. None of these studies showed any significant effects on empathic behavior. However, the Chen study reported that older individuals scored less on trait empathy (Chen et al., 2014). Across three studies of cognitive reappraisal in aging, younger participants have been shown

to be more efficient in emotional regulation, but with different areas in the prefrontal and temporal cortices as proposed brain correlates (Allard & Kensinger, 2014; Opitz, Rauch, Terry, & Urry, 2012; Winecoff, Labar, Madden, Cabeza, & Huettel, 2011).

3.8 AGING AND SLEEP

With aging, sleep patterns change. Insomnia is common among older people, with a reported prevalence ranging between 10% and 60% in different parts of the world (Gulia & Kumar, 2018), but also among older adults without sleep complains, some changes in sleep architecture exist (Edwards et al., 2010; Vitiello, 2012). Aging is accompanied by increased over all morbidity and some of the changes observed in sleep patterns can be related to these comorbidities (Ancoli-Israel, 2005). However, some changes remain consistent even when this is accounted for and aging is associated with decreased total sleep time, sleep efficiency and slow wave sleep and increased wake after sleep onset (Ohayon et al., 2004). Another clear change with respect to sleep and aging is the shift to earlier circadian rhythm (Duffy et al., 2015).

Of special importance for this thesis is the interaction between aging and sleep restriction. After sleep restriction, older adults react with smaller increase in sleepiness compared to young (Dijk, Groeger, Stanley, & Deacon, 2010). Cognitive functions, such as memory, executive functions and reaction times are less affected by sleep restriction in older compared to younger adults (Scullin & Bliwise, 2015) and it has been argued that the crucial role that sleep plays in cognition for younger adults is not the same for older (Scullin & Bliwise, 2015). Less is known about the sensitivity to sleep deprivation for emotional functions, but we have in a recent publication shown that the effect of sleep restriction on mood is stronger in young compared to older adults (J. Schwarz et al., 2018).

3.9 SLEEP AND RESTING STATE CONNECTIVITY

Because sleep is a global phenomenon, it is important to understand overall effects of sleep restriction on the brain. In relation to emotional functioning, it is also of a certain importance to study brain correlates to sleepiness and fatigue. One way to understand general effects of sleep restriction on the brain is to study *intrinsic connectivity*, i.e. the brain's connectivity during rest, either in the whole brain or in specific regions or networks. Resting state brain

imaging is a method where the participants' brains are studied at rest, typically without any specific instruction beyond whether to keep eyes open or closed, and to let the mind wander. Studies of resting state activity, i.e. spontaneous activity fluctuations measured at rest, have found that certain brain networks can be identified that have a high intra-network correlation (Auer, 2008; Fox & Raichle, 2007; Fransson, 2005) and a number of networks are considered *resting state brain networks*. The most important network for this thesis is the Default Mode Network (DMN), a network that is most correlated when participants do not engage in any specific task and the intra-network correlation of which decreases with engagement in a task (Raichle, 2015).

Resting state brain connectivity and particularly the DMN has been studied in relation to sleep and sleep deprivation in a number of publications (e.g. De Havas, Parimal, Soon, & Chee, 2012; Lei et al., 2015; Sämann et al., 2010; Shao et al., 2014). The most consistent findings are that sleep deprivation is associated with reduced connectivity within the default mode network and reduced anticorrelation to the task-positive network (De Havas et al., 2012; Sämann et al., 2010; Yeo, Tandi, & Chee, 2015), but findings also include increased regional homogeneity following sleep deprivation (Gao et al., 2015) and changes in connectivity between the amygdala and cortical areas (Lei et al., 2015; Shao et al., 2014). One previous study showed increased global signal variability after sleep deprivation, but without providing inferential statistics on this measure (Yeo et al., 2015).

Some studies have also investigated resting state networks in the sleeping brain. It has for example been shown that contributions of the posterior cingulate cortex/retrosplenial cortex, parahippocampal gyrus, and medial prefrontal cortex to the DMN decrease with increasing sleep depth (Sämann et al., 2011). It has also been suggested that changes in functional magnetic resonance imaging (fMRI) functional connectivity data can be used to perform automatic sleep staging through a machine learning algorithm (Tagliazucchi et al., 2012). Interestingly, a similar method have been used to decode wakefulness in a large set of resting state scans from non-sleep deprived subjects, showing that about 50% of participants fell asleep with 10 minutes of resting state scans (Tagliazucchi et al., 2014). This might further suggest that some of the effects reported after sleep deprivation, actually partly represent participants sleeping.

The actual falling asleep process has also been studied using brain imaging. Some work suggest that falling asleep begins with local slow waves, structured macroscopically in networks that resemble the resting-state networks and when sleep depth increases these local slow waves merge into a global undifferentiated, broadly synchronized network (Deco, Hagmann, Hudetz, & Tononi, 2014). In summary, a growing body of evidence suggests that sleep and sleep deprivation are related to resting state brain networks. However, earlier studies have not connected changes in resting state activity to subjective feelings of sleepiness.

3.10 INFLAMMATION AND SICKNESS BEHAVIOR

There are several routes by which the brain communicates with the rest of the body, of which the peripheral nervous system is the most obvious. Of relevance for this thesis, also the immune system communicates with the brain through neural and humoral routes. Everyone who has experienced a cold recognizes the symptoms of fatigue, loss of interest in their physical and social environments, and even depressed mood, pain and impaired cognition. This set of behavioral changes are referred to as *sickness behavior* (Robert Dantzer et al., 2008; Hart, 1988) and is caused by pro-inflammatory cytokines signaling from the periphery to the brain, causing a secondary low-grade inflammatory state in the brain (Robert Dantzer et al., 2008). Inflammation is suggested to be involved in a number of psychiatric conditions, such as depression and schizophrenia (Savitz & Harrison, 2018). Notably, chronic inflammation is also associated with an increased risk of depression (Miller & Raison, 2016). In the recent years, much research has focused on the role inflammation plays in the course of these disorders. One way to study inflammatory activity in the brain is to target microglia, immune cells of the brain, using positron emission tomography (PET). Activated microglia has indeed been found in response to injection of lipopolysaccharide, a model for sickness (Sandiego et al., 2015) as well as after brain injury and stroke (Folkersma et al., 2011; Tóth et al., 2016).

3.11 SLEEP AND INFLAMMATION

As noted in the introduction, sleep is closely related to the immune system (Imeri & Opp, 2009). Recent findings have highlighted a role for sleep in oxidative stress (Villafuerte et al., 2015). Wakefulness results in an oxidative burden which sleep provides a protective mechanism against, whereas sleep deprivation is suggested to lead to a pro-inflammatory

state (Irwin, 2015; Irwin et al., 2010; Redwine, Hauger, Gillin, & Irwin, 2000). Sleep is reciprocally related to the immune system, making central inflammatory changes important to understand. In fact, some parts of the immune system (cytokines such as IL-1 or Tumor Necrosis Factor-alpha) directly regulate sleep in the brain (Jewett & Krueger, 2012). This suggests that sleep quantity and/or quality could be related to increased inflammatory activity also in the brain, and that neuroinflammation explains part of the negative consequences of insufficient sleep.

3.12 SLEEP AND DEPRESSIVE SYMPTOMS IN CHRONIC INFLAMMATION

As noted above, chronic inflammation is associated with depressive symptoms (Thompson, Sardana, & Craig, 2013). One group of patients that show a seasonal variation of systemic inflammation and depressive symptoms are patients with severe seasonal allergy (Hurwitz & Morgenstern, 1999; Kurt, Aktas, Gulbas, Erginel, & Arslan, 2010; Trikojat et al., 2017). These patients often suffer from a number of non-specific symptoms, such as fatigue (Benninger & Benninger, 2009; Marshall, O'Hara, & Steinberg, 2002), increased risk of depression (Hurwitz & Morgenstern, 1999; Sanna et al., 2014), disturbed sleep (Jernelöv et al., 2009; Mullol, Maurer, & Bousquet, 2008) and sleepiness (Thompson et al., 2013). To some extent these symptoms are similar to the sickness behavior discussed above. It has also been shown by us (Karshikoff in prep) and others (Hurwitz & Morgenstern, 1999; Trikojat et al., 2017) that depressive symptoms and anxiety in subjects with allergy aggravate during pollen season. The same holds true for sleep problems (Bender & Leung, 2005; Ferguson, 2004; Santos, Pratt, Hanks, McCann, & Craig, 2006). Because of this predictable variation in sleep, inflammatory markers and symptoms of depression and anxiety, the study of patients with seasonal allergy can serve as a quasi-experimental model to study brain changes related to sleep, emotion and inflammation.

4 AIMS

4.1 OVERALL AIM

The overall aim of the present thesis was to investigate mechanisms underlying effects of insufficient sleep on emotional functions, sleepiness and fatigue. In study I-IV, effects of acute experimental sleep restriction on emotional contagion, empathy for pain, emotional regulation and resting state brain activity were investigated using fMRI. In study V, low-grade inflammation in the brain was investigated as a possible mechanism behind non-specific symptoms such as depressive symptoms and fatigue in a chronic disease where sleep problems are common.

Based on the assumption that the three emotional functions (emotional contagion, empathy and emotional regulation) would be impaired by sleep restriction, we specified a number of hypotheses for each emotional function, that would involve the most important brain structure and behavioral response, in relation to previous literature. For study IV, we specified a number of hypotheses that built on previous reports of resting state activity after manipulated sleep and investigated all these hypotheses in relation to sleepiness. For study V we specified hypotheses that would be in line with immune-to-brain signaling and inflammatory activity (i.e. microglia activation) in the brain as a mechanism behind non-specific symptoms in allergy.

4.2 SPECIFIC AIMS AND HYPOTHESES

4.2.1 Study 1

To investigate the effect of sleep restriction on emotional contagion. Main hypotheses were that

1) Sleep restriction will cause decreased ratings of happiness and increased ratings of angriness in response to emotional faces, in line with a negativity bias.

2) Sleep restriction will cause decreased activity in *m. corrugator* and in *m. zygomaticus* during exposure to both happy and angry faces, in line with a less sensitive facial feedback system.

3) Angry and happy faces will cause greater BOLD responses in the amygdala and fusiform gyrus than neutral faces, confirming validity of the task. Sleep restriction will interact with this increase to cause greater increases to angry faces, in line with previous findings (Y Motomura et al., 2014; Yoo et al., 2007), whereas the direction of the interaction effect is not specified for happy faces, because of limited previous evidence.

4.2.2 Study 2

To study the effect of sleep restriction on empathy for pain. Specific hypotheses were that

1) Sleep restriction will cause decreased ratings of unpleasantness in response to pictures of pain in others, in line with decreased empathic responding.

2) Pictures of pain will cause greater BOLD responses in the anterior insula and anterior/middle cingulate cortex than control stimuli, confirming validity of the task. Sleep restriction will interact with this increase to cause less increase to pain stimuli, likewise in line with less empathy after sleep restriction.

4.2.3 Study 3

To investigate the effect of sleep restriction on emotional regulation through cognitive reappraisal. Specific hypotheses were that

1) Sleep restriction will lead to decreased self-rated success in emotional regulation in response to negative stimuli, in line with (Mauss et al., 2013; Zhang et al., 2018).

2) Sleep restriction will lead to decreased activation of dorsolateral prefrontal cortex and lateral orbitofrontal cortex, increased amygdala activation, and decreased connectivity between of dorsolateral prefrontal cortex/lateral orbitofrontal cortex and amygdala, in line with an amygdalar-prefrontal disconnect (Krause et al., 2017; Yoo et al., 2007).

4.2.4 Study 4

To investigate the effects of sleep restriction on intrinsic brain connectivity. A number of previous studies have investigated resting state activity and the hypotheses aimed at replicating and extending earlier findings, specific previous studies given in brackets for each hypothesis. Main hypotheses were that sleep restriction will cause

1) decreased connectivity within the default mode, salience, frontoparietal attention, and executive control networks (De Havas et al., 2012; Sämann et al., 2010),

2) decreased anticorrelation between default mode network and the task-positive network during resting state (De Havas et al., 2012; Sämann et al., 2010),

3) changes in thalamocortical connectivity (Shao et al., 2013),

4) changes in connectivity from amygdala, specifically decreased connectivity between amygdala and prefrontal cortex (Lei et al., 2015; Shao et al., 2014),

5) changes in regional homogeneity (Dai et al., 2012; Gao et al., 2015) and

6) increased global signal variability (Yeo et al., 2015).

All the above-mentioned measures were hypothesized to correlate to self-rated sleepiness.

4.2.5 Study 5

To investigate if seasonal allergy is reflected in immune cell activation in the brain, as a possible mechanism behind fatigue and other non-specific symptoms. Specific hypotheses were that

1) Allergic subjects will display increased binding of the TSPO ligand [^{11}C]PBR28 in the grey matter across the brain during pollen season compared to outside pollen season and compared to healthy subjects, similar to what has been shown in experimental models of inflammation (Sandiego et al., 2015).

2) The degree of [^{11}C]PBR28 binding will be related to increased fatigue as well as worse subjective and objective sleep quality in subjects with allergy, indicating low-grade inflammation as the mechanism.

3) Both allergy specific (IL-5) and pro-inflammatory cytokines (TNF-α, IL-6 and IL-8) will be higher in allergic subjects during pollen season, reflecting a proinflammatory state.

4) The degree of peripheral immune activation, i.e. levels of circulating cytokines, will be associated with the extent of [^{11}C]PBR28 grey matter binding in the brain, as indicating immune-to-brain-signaling.

5 METHODS AND MATERIALS

5.1 OVERVIEW OF THE DATA COLLECTIONS

5.1.1 The Sleepy Brain Study

Studies I-IV are based on the Stockholm Sleepy Brain study I. This was an experimental study with younger (20-30 years) and older (65-75 years) healthy participants, investigated with MRI after normal sleep and sleep restriction in a crossover design, see fig 1.

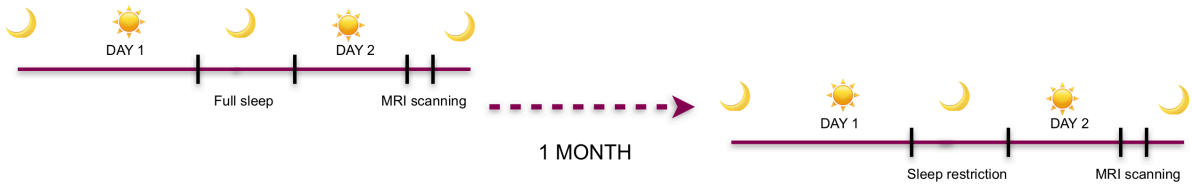

Figure 1. Overview of the Sleepy Brain study

The participants were healthy, without contraindications for MRI scanning and with low self-reported sleep problems and depressive symptoms (see (Gustav Nilsonne et al., 2017) for detailed inclusion criteria). Participants were screened for inclusion using an online form, and before scanning. 278 young and 226 older participants were screened for inclusion and 47 younger and 39 older participants were included in at least one analysis, see fig 2.

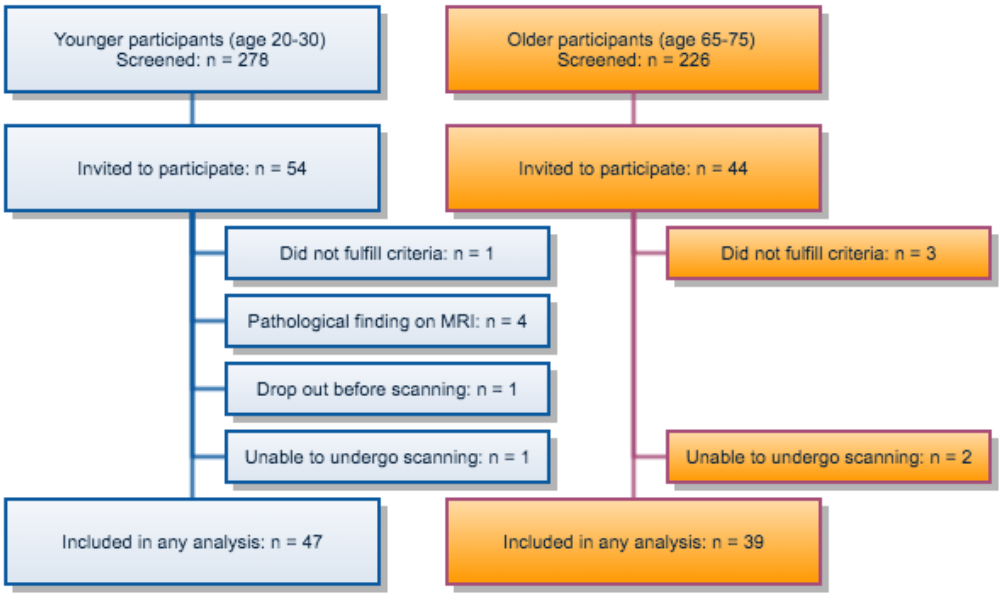

Figure 2. Inclusion flowchart, the Sleepy Brain study

Demographical data and sleep measures for the Sleepy Brain study are presented in table 1. Because of data loss, motion artifacts and technical problems, described in detail in each study, the number of participants differs slightly between study I-IV.

Table 1. Demographic data, Sleepy Brain study. Continuous values are reported as means with standard deviations, unless otherwise indicated. Categorical data are reported with percentages.

	Young	**Older**
Number of subjects	47	39
Demographics		
Age (median, interquartile range)	23.0 (21.5–25.0)	68.0 (67.0–71.0)
Sex (females)	24 (51.1%)	20 (51.3%)
Body Mass Index	22.9 (±3.1)	24.7 (±3.4)
Education		
Elementary school	1 (2.1%)	3 (7.7%)
High school	10 (21.3%)	17 (43.6%)
University degree	6 (12.8%)	18 (46.2%)

University student	30 (63.8%)	1 (2.6%)
Interpersonal reactivity index		
Empathic concern	3.9 (±0.6)	3.9 (±0.4)
Fantasy	3.4 (±0.7)	2.9 (±0.6)
Perspective taking	3.6 (±0.6)	3.8 (±0.4)
Personal distress	2.6 (±0.6)	2.4 (±0.7)
Hospital Anxiety and Depression Scale		
Depression	1.1 (±1.4)	1.2 (±1.0)
Anxiety	2.8 (±2.4)	1.4 (±1.4)
Sleep		
Insomnia severity index	3.6 (±2.1)	2.3 (±1.7)
Karolinska Sleepiness Scale, full sleep	5.9 (±1.8)	4.5 (±1.8)
Karolinska Sleepiness Scale, sleep restriction	7.7 (±1.4)	5.8 (±1.7)
Total sleep time (min), full sleep	429.1 (±77.4)	388.9 (±68.3)
Total sleep time (min), sleep restriction	185.3 (±36.7)	158.9 (±31.9)
REM sleep (min), full sleep	86.8 (±29.9)	74.9 (±35.6)
REM sleep (min), sleep restriction	28.2 (±15.8)	25.7 (±18.7)
Slow wave sleep (min), full sleep	98.0 (±32.0)	41.1 (±33.1)
Slow wave sleep (min), sleep restriction	70.5 (±16.5)	27.2 (±24.4)

During the sleep intervention night, participants were instructed to go to bed 3 hours before their habitual wake up time and then to wake up as usual, and their sleep was recorded using polysomnography, the gold standard method for sleep recording (Rechtschaffen & Kales, 1968), during both the experimental and control nights. For analyses of the effect of the sleep intervention we only included participants with a total sleep time >4 hours in the full sleep

condition, <4 hours in the sleep deprivation condition, and a difference between the two conditions >2 hours.

During the scanning session, participants performed 3 emotional tasks in the scanner, as well as 2 resting state scans, anatomical scans and diffusion tensor imaging (DTI), see fig 3a. The emotional tasks are presented in fig 3 and were chosen to investigate emotional contagion (3b), empathy (3c) and emotional regulation (3d).

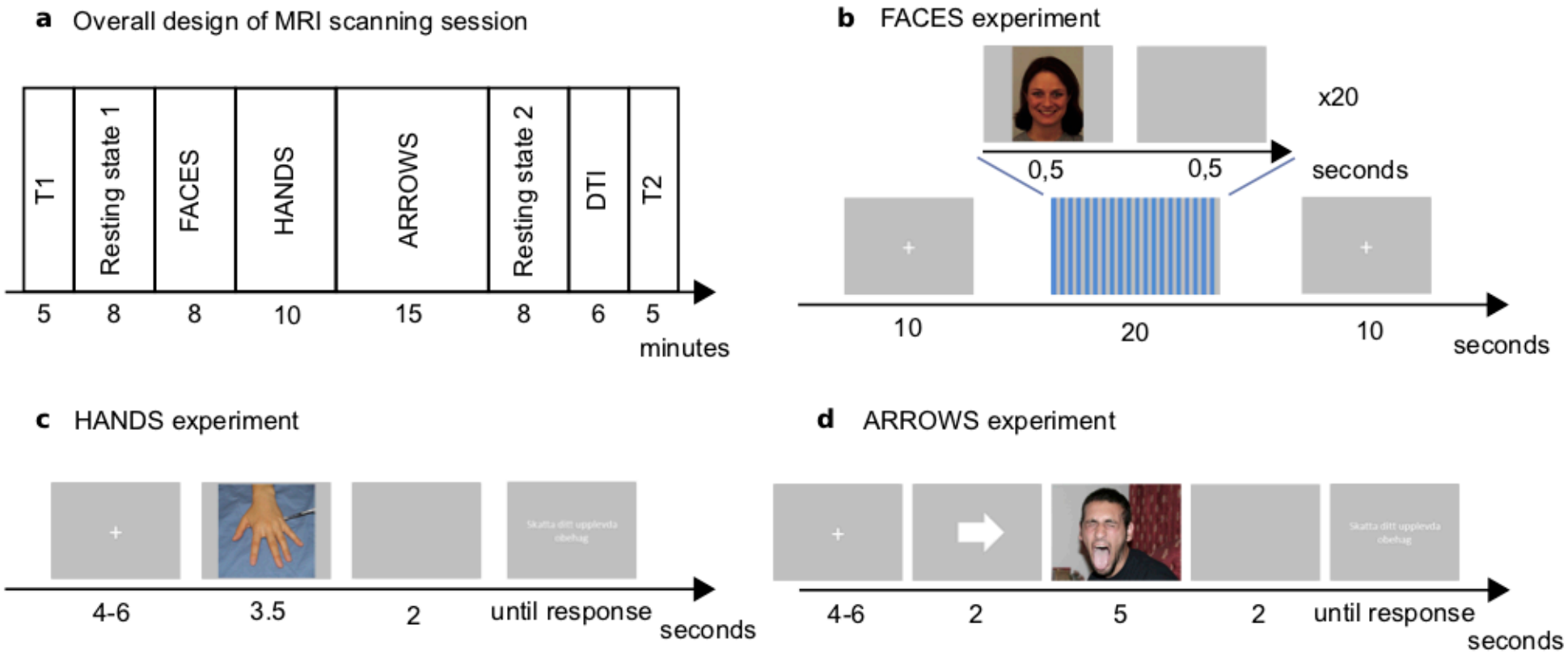

Figure 3, A. Overview of experiments during the scanning session. B. Experimental task for study I. C. Experimental task for study II. D. Experimental task for study III. The figure is previously published in (Gustav Nilsonne et al., 2017)

5.1.2 The RAALLPET study

Study V was based on a data collection referred to as *RAALLPET* (Rheumatoid Arthritis and Allergy Positron Emission Tomography), where 13 healthy participants and 18 subjects with allergy were studied in and out of pollen season, with PET as well as several other outcome measures[1], see fig 4.

Inclusion criteria for all participants were to be healthy with no chronic disease (except allergy, well-controlled hypothyroidism or hypertension), to have no regular medication (except for allergy, hypothyroidism or hypertension), no chronic pain or migraine and no mental illness, BMI < 29, fluent in Swedish, right-handed and 20–70 years of age. Exclusion criteria were being pregnant, reporting use of estrogen containing hormonal contraceptives or having a current infection, based on symptoms and CRP ≥ 10. Allergy patients were excluded if having a pet allergy and regular contact with animals, or if they recently had a cortisone injection. Demographical data are presented in table 2.

[1] In parallel, patients with rheumatoid arthritis and matched healthy controls were investigated in a similar design, results presented elsewhere.

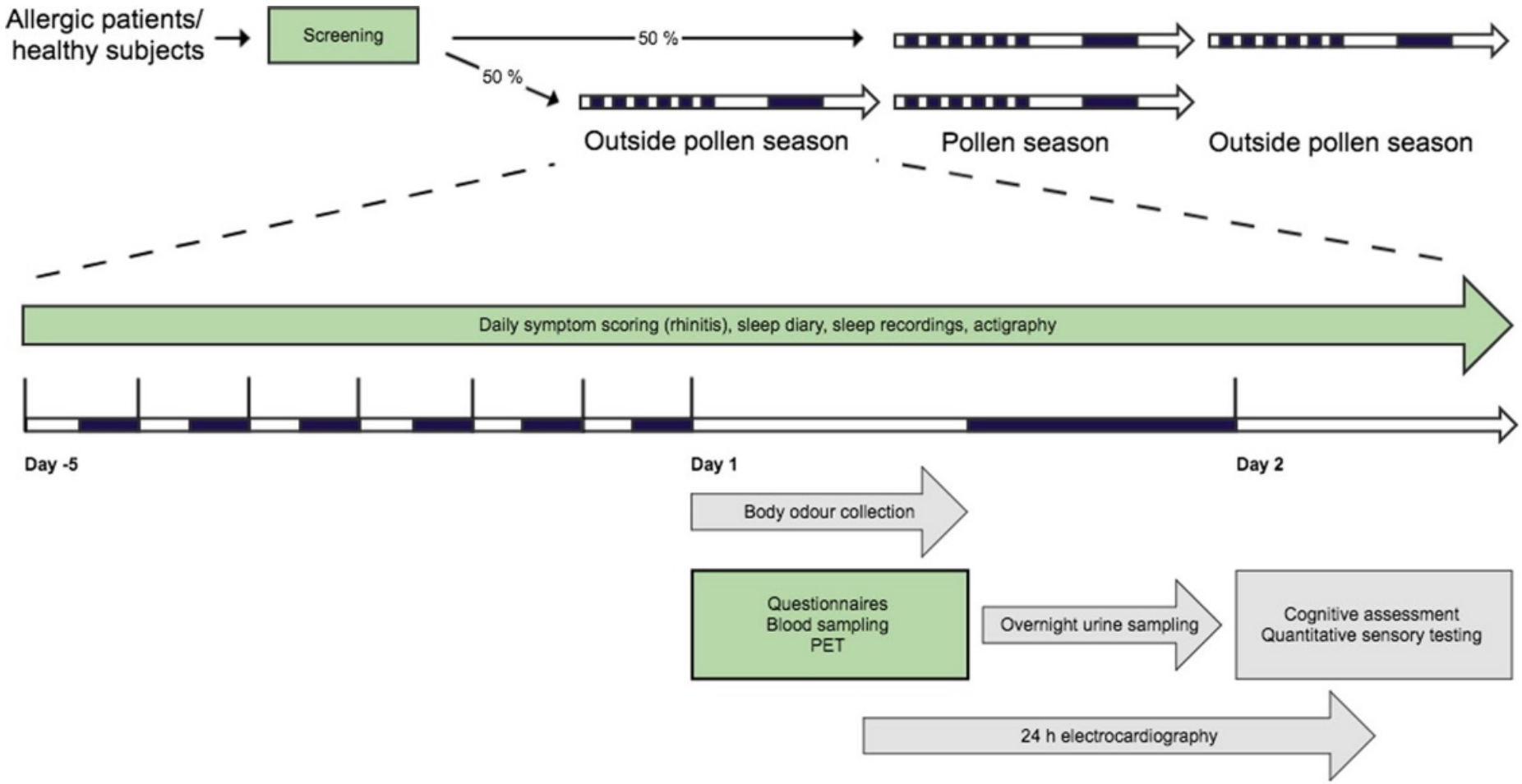

Figure 4. Overview of the RAALLPET study. Previously published in (Tamm et al., 2018)

Table 2. Demographic variables, RAALPET study. Continuous values are reported as means with standard deviations, unless otherwise indicated). Categorical data are reported with percentages.

	Allergy	**Control**
Number of subjects	18	13
Genotype		
Low affinity binders	2 (11.1%)	0 (0.0%)
Mixed affinity binders	9 (50.0%)	5 (38.5%)
High affinity binders	7 (38.9%)	8 (61.5%)
Demographics		
Age (median, interquartile range)	34.0 (30.2 - 44.2)	34.0 (27.0 - 46.0)
Sex (females)	8 (44.4%)	5 (38.5%)
BMI (mean, SD)	25.3 (±4.4)	22.4 (±3.0)
Education		
College graduate	1 (5.6%)	0 (0.0%)
Elementary/High School	0 (0.0%)	1 (10.0%)
Other	1 (5.6%)	0 (0.0%)
Some college	5 (27.8%)	1 (10.0%)
Some university	2 (11.1%)	5 (50.0%)
University graduate	9 (50.0%)	3 (30.0%)

PET imaging with the radioligand PBR-28 was used to measure microglial activation and indicating low grade inflammatory activity in the brain (Venneti, Lopresti, & Wiley, 2013). The PBR-28 is a translocator protein (TSPO) ligand, used as a marker of activated microglia that in some studies (Dimber et al., 2016; Folkersma et al., 2011; Setiawan et al., 2015; Tóth et al., 2016) has indeed successfully been used to capture inflammatory activity within the brain.

Sleep was monitored using self-reports, actigraphs (Actiwatch, Philips Respironics) and a single electrode EEG (MyZeo, Zeo Inc., Boston MA, USA). This EEG method does not give as detailed information as a full polysomnography recording, but could be administered by the participants themselves in their homes. The single electrode EEG has also been validated against polysomnography showing > 90 % agreement for sleep/wakefulness (Shambroom, Fábregas, & Johnstone, 2012). Furthermore, in our own data the agreement with other sleep measures (i.e. actigraphy and sleep diaries) was high, see fig 5.

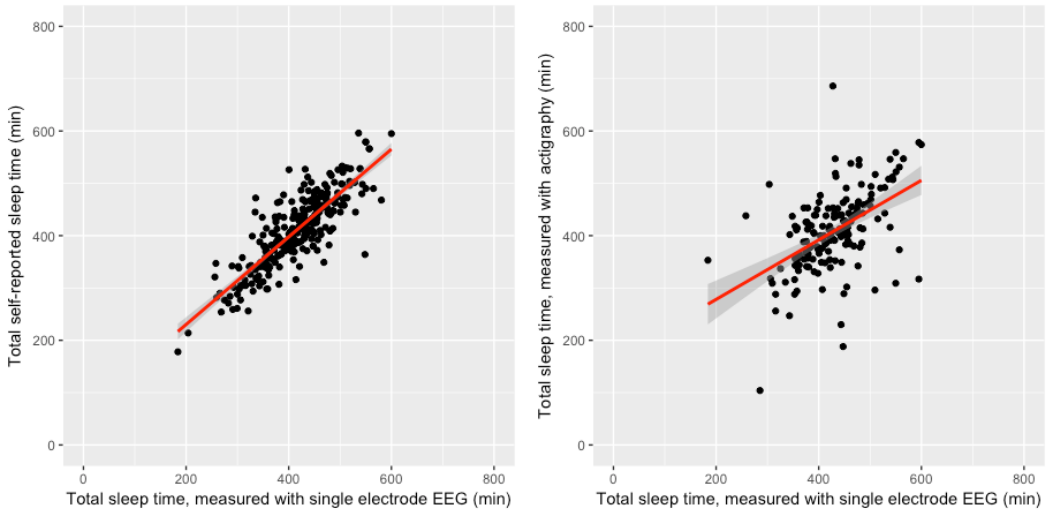

Figure 5. Single electrode EEG recordings in relation to sleep diaries and actigraphy in the RAALLPET study.

5.2 OVERVIEW OF STUDIES I-V

An overview of participants, imaging methods and outcomes for the specific studies is presented in table 3.

Table 3. Overview of studies I-V

Study	**Study I**	**Study II**	**Study III**	**Study IV**	**Study V**
Title	Effects of partial sleep deprivation on emotional contagion in humans: a combined fMRI and EMG study in young and older individuals	The effect of sleep restriction on empathy for pain: An fMRI study in younger and older adults	Sleep restriction caused impaired emotional regulation without detectable brain activation changes - a functional magnetic resonance imaging study	Intrinsic brain connectivity after partial sleep deprivation in young and older adults: results from the Stockholm Sleepy Brain study	Evidence of fatigue, disordered sleep and peripheral inflammation, but not increased brain TSPO expression, in seasonal allergy: A [11C]PBR28 PET study
Participants (for main analysis)	36 young (age 20—30) and 33 older (age 65-75)	38 young (age 20—30) and 33 older (age 65-75)	38 young (age 20—30) and 23 older (age 65-75)	30 young (age 20—30) and 23 older (age 65-75)	15 (18) patients with allergy and 13 healthy controls
Main research question	Does sleep restriction affect emotional contagion?	Does sleep restriction affect empathy for pain?	Does sleep restriction affect emotional regulation through cognitive reappraisal?	Does sleep restriction affect intrinsic connectivity?	Is immune cell activation in the brain a possible mechanism behind non-specific symptoms in seasonal allergy?
Imaging method	Task-fMRI	Task-fMRI	Task-fMRI	Resting state fMRI	PET with the TSPO ligand [^{11}C]PBR28
Exposure(s)	Experimental sleep restriction (3 hours)	Experimental sleep restriction (3 hours)	Experimental sleep restriction (3 hours)	Experimental sleep restriction (3 hours)	Seasonal allergy Pollen season

Design	Experimental Cross-over Intra-individual	Experimental Cross-over Intra-individual	Experimental Cross-over Intra-individual	Experimental Cross-over Intra-individual	Observational Between group (allergic patients vs healthy) Intra-individual (out of/inside pollen season)
Task during scanning	Viewing of angry, happy and neutral faces (blocks)	Pictures of needles stinging or Q-tips poking hands (event-related)	Negative or neutral pictures with the instruction to maintain, upregulate or downregulate the emotional response (event-related)	Resting state, eyes open	None
Main behavioral outcome(s)	Ratings of happiness and angriness Facial EMG responses	Ratings of vicarious unpleasantness	Ratings of success in emotional regulation	Rated sleepiness	Rated fatigue and sleepiness
Main brain imaging outcome(s)	BOLD responses in amygdala and fusiform gyrus	BOLD responses in anterior insula and anterior midcingulate cortex	BOLD responses in amygdala, lateral orbitofrontal cortex and dorsolateral prefrontal cortex	Connectivity in the default mode network Global signal variability	[11C]PBR28 binding in the total grey matter in the brain

6 MAIN RESULTS[2]

Study I

Mirroring faces

of anger and happiness

shorter sleep less fun

Study II

Pain in others hurts

after sleep restriction too

yet, aging matters

Study III

After shorter sleep

cognitive top-down control

does not work so well

Study IV

Connectivity

in the sleep restricted brain

increased variance

Study V

Poor sleep and fatigue

microglia on or off

in birch allergy

[2] For details, see appendix I-V.

7 SUMMARY OF FINDINGS

Study I investigated the effect of sleep restriction on emotional contagion. The hypothesis that sleep restriction would cause decreased ratings of happiness and increased ratings of angriness was partly confirmed, such that sleep restriction caused decreased ratings of happiness without increased ratings of angriness to emotional faces. The hypothesis that sleep restriction would cause decreased activity in *m. corrugator* and in *m. zygomaticus* during exposure to both happy and angry faces could not be confirmed. EMG responses did show an effect of happy faces on muscular activity in the zygomatic muscle, but no effect of sleep restriction. The third main hypothesis concerned BOLD responses in amygdala and fusiform gyrus. We hypothesized that the main effect of emotional faces vs neutral faces would be an increase in activity in amygdala and fusiform gyrus, which could be confirmed for angry faces in fusiform gyrus, but not in amygdala. The main effect of happy vs neutral faces was not significant in fusiform gyrus or amygdala. Sleep restriction was further hypothesized to increase the responses to angry faces, and to change (without specified direction) the response to happy faces in the same areas. Contrary to this hypothesis, sleep restriction was associated with a decreased response in fusiform gyrus and amygdala (n.s.) for angry faces, and no effects were seen on responses to happy faces. Sleep restriction was also associated with a decrease in positive affect, rated on The Positive and Negative Affect Schedule (PANAS). Other findings were that older participants reported higher ratings of angriness, compared to younger, but no age differences were seen on EMG responses. For emotional vs neutral faces, no age differences were seen on fMRI responses. However, in response to all types of faces compared to a baseline, older participants showed less amygdala activity, compared to young. In summary, the results were in line with a negativity bias after sleep restriction, but did not support the idea of increased amygdala reactivity as the mechanism. Thus *shorter sleep less fun.*

Study II investigated the effect of sleep restriction on empathy for pain. The hypothesis that sleep restriction would cause decreased ratings of unpleasantness could not be confirmed. However, sleep restriction and aging interacted so that sleep restriction was associated with decreased vicarious unpleasantness in young and increased unpleasantness in older (main effect only significant in older). The hypothesis that pictures of pain stimuli would cause greater BOLD responses in the anterior insula and anterior/middle cingulate cortex than control stimuli was confirmed, indicating a main effect of the empathy for pain task. However, the hypothesis that sleep restriction would interact with this increase

to cause less increase to pictures of pain could not be confirmed. Older age was associated with increased activity in angular gyrus in response to pain in others. Furthermore, clusters in bilateral middle insula showed a pattern with less activity in younger and more activity in older after sleep restriction. The results from study II suggest that empathy is relatively stable to acute sleep restriction in young. *Yet, aging matters* and caution needs to be taken when generalizing effects of sleep restriction across different age groups.

Study III investigated the effect of sleep restriction on emotional regulation through cognitive reappraisal. The hypothesis that sleep restriction would lead to decreased self-rated success in emotional regulation in response to negative stimuli was confirmed for younger participants. However, the hypothesis that sleep restriction would lead to decreased activation of dorsolateral prefrontal cortex and lateral orbitofrontal cortex, increased amygdala activation, and decreased connectivity between of dorsolateral prefrontal cortex/lateral orbitofrontal cortex and amygdala could not be confirmed. Watching negative pictures was associated with increased activity in amygdala in all participants. In young participants, emotional regulation was associated with increased activity in dorsolateral prefrontal cortex and lateral orbitofrontal cortex, confirming a main effect of the paradigm. Older participants were not able to perform the task to the same extent as young. However, no effect of sleep restriction was seen on older participants. The results suggest that emotional regulation is affected by sleep restriction, at least in young, thus *cognitive top-down control does not work so well.* However, the results do not support the idea of a prefrontal-amygdala disconnect as the mechanism.

Study IV investigated the effect of sleep restriction on resting state activity in the brain. Only one of the hypotheses specified could be confirmed, showing increased global signal variability after sleep restriction. The hypothesis that sleep restriction would cause decreased functional connectivity between the nodes of the default mode network could not be confirmed, but the pattern of results were in the expected direction. Neither other investigated networks (salience, frontoparietal attention, and executive control networks), nor regional homogeneity were significantly altered by sleep restriction. Sleep restriction caused an increase in self-rated sleepiness. However, sleepiness was not significantly correlated to any objective measure of brain activity or connectivity. In summary, the results indicate that there are general effects on the brain activity and connectivity after restricted sleep, potentially

reflecting the brain state of sleepiness. We speculate that the increased global signal variability effect is due to wake-state instability, affecting neural activity as well as respiration, heart rate, and head movements. Thus, there is *increased variance in the sleep restricted brain.*

Study V investigated low-grade inflammation, as measured with the TSPO ligand [^{11}C]PBR28, as a mechanism behind nonspecific symptoms such as depression, fatigue and disturbed sleep in seasonal allergy. The hypothesis that allergic subjects would display increased binding of the TSPO ligand [^{11}C]PBR28 in the grey matter across the brain during pollen season compared to outside pollen season and compared to healthy subjects could not be confirmed. The hypothesis that the degree of [^{11}C]PBR28 binding would be related to increased fatigue as well as worse subjective and objective sleep quality in subjects with allergy could likewise not be confirmed. The hypothesis that both allergy specific (interleukin (IL)-5) and pro-inflammatory cytokines (tumor necrosis factor (TNF)-α, IL-6 and IL-8) would be higher in allergic subjects during pollen season was confirmed for IL-5 and TNF-alpha, but not IL-6 and IL-8, in line with a pro-inflammatory state. Opposed to the hypothesis, the degree of peripheral immune activation, i.e. levels of circulating cytokines, was not associated with the extent of [^{11}C]PBR28 grey matter binding in the brain. Other findings were that allergic subjects reported increased levels of fatigue and sleepiness, especially during pollen season, but also shorter total sleep time across pollen seasons, compared to healthy subjects. In summary, allergic subjects showed increased fatigue and sleepiness, reported lower sleep quality and had elevated levels of TNF-α and IL-5 compared to healthy subjects. Yet, these effects were not paralleled by changed TSPO levels in the brain. The results indicate a need for development and use of more specific markers to identify neural immune activation in humans to answer the research question if *microglia* is *on or off in birch allergy.*

8 METHODOLOGICAL AND ETHICAL LIMITATIONS, ADVANTAGES AND REFLECTIONS

8.1 BRAIN IMAGING METHODS

For all studies in the present thesis, functional brain imaging methods were used; task fMRI in study I-III, resting state fMRI in study IV and PET in study V. These methods all have in common that they allow researchers to study the brain in a living organism. However, all brain imaging techniques also have some shortcomings that need to be kept in mind. MRI techniques take advantage of the fact that oxygenated and non-oxygenated hemoglobin have different magnetic properties, resulting in the BOLD response (Arthurs & Boniface, 2002). The BOLD response is considered to be a measure of underlying brain activity (Ekstrom, 2010), and sometimes researchers, including myself at times, seem to forget that the indirect, statistically modeled, colorful blobs presented on the background of a structural brain image to represent a statistical contrast, are very far from inserting a probe in a single cell and actually record activity in the neuron. My impression is also that there is often a poor consistency between brain activity measured with fMRI and behavioral outcomes of interest such as ratings or psychophysiological measures, to some extent questioning the relevance of the measurements.

As pointed out before, this thesis aimed at studying both specific and general effects of sleep restriction on the brain. For this purpose, both task-fMRI methods as well as resting state fMRI, were used. Task-fMRI refers to methods were participants are presented with some sort of tasks with two or more conditions, that are compared with respect to the BOLD response. In resting state, on the other hand, the idea is to study spontaneous fluctuations in the brain activity/BOLD response, that arise without any specific task. An advantage of the latter is that confounding effects, such as participants misunderstanding the instructions (which likely could happen after sleep restriction) or interpreting the stimuli in a certain way, are less. However, when using resting state fMRI on the other hand, participants are instructed not to engage in any specific task. This could result in participants thinking of practically anything, a condition that is not very well controlled. Also, the absence of a specific task likely results in a higher risk of participants falling asleep.

A further problem with both task-fMRI and resting state fMRI is that although the spatial resolution is higher compared to for example PET or EEG, we still cannot say anything about specific neurons involved in a process. Also, the time resolution is limited, and processes that take place on a time scale faster than a few seconds, cannot really be disentangled. Another drawback is that the values are on an arbitrary scale and cannot be translated into a biologically relevant unit. Despite this, fMRI has been proven to be a very useful technique to understand brain mechanisms and for strong effects, such as comparing having eyes open versus eyes closed, a few repetitions in one subject are enough to yield significant and reproducible effects. However, for most effects of interest a large number of repetitions in a large number of subjects are needed to obtain reliable effects. Accordingly, it has been brought to notice that a large proportion of fMRI studies have low statistical power, median power estimated to be between 8 and 31 % (Button et al., 2013). In studies I-IV, approximately 86 participants (less in some studies and for some outcomes), with a repeated measures design, were studied, which compared to many brain imaging studies constitutes a considerable sample. However, since the effects of interest were probably small, specifically when studying interactions with sleep and age, power is still a critical issue. In study V, the number of included subjects was in total 31 (28 with PET measures), considered a small sample size. Initially, a larger sample was planned for, but during the data collection a planned interim analysis was performed, showing no signs of an effect, and after this it was decided to close the data collection for ethical reasons.

8.2 EMOTIONAL TASKS

In study I-III, three different emotional tasks to study emotional contagion, empathy and emotional regulation, were used. The tasks were performed during fMRI, with pictures presented to the participants through goggles. The limited ecological validity in these paradigms is an obvious disadvantage, only partially compensated by the fact that they are much more controlled and standardized, compared to dynamic social interactions with present people. When scanning participants in fMRI, certain limitations necessarily arise in how similar such tasks can be compared to behavior in real life, since participants need to lie down and not move, are surrounded by noise and presented with stimuli through a pair of goggles or on a screen. The specific tasks used were chosen to minimize the risk of confounding by sleep deprived subjects misunderstanding the instructions or not engaging in complex tasks. However, to strive towards more realistic paradigms should always be the goal, and in future studies of sleep restriction and emotion, increased ecological validity

should be aimed for, without compromising the quality of the data. New techniques, such as virtual or augmented reality, could possibly be one way to do this. Another problem with using task-fMRI is, as mentioned, that general effects on the brain that would affect both the control condition (e.g. responses to neutral faces) and the emotional condition (e.g. emotional faces), might not be found. This problem can to some extent be handled through analyzing effects of stimuli against an implicit baseline, which was done through study I-III. However, the implicit baseline could of course also be affected by overall changes related to for example fatigue, sleepiness and wake-state instability.

8.3 METHODS TO STUDY EMPATHY

As mentioned in the introduction, empathy is a complex concept with a number of definitions (de Vignemont & Singer, 2006; Hoffman, 2000; Preston & de Waal, 2002). The definition that is commonly used in cognitive neuroscience is the definition by Vignemont and Singer, i.e. "there is empathy if: (i) one is in an affective state; (ii) this state is isomorphic to another person's affective state; (iii) this state is elicited by the observation or imagination of another person's affective state; (iv) one knows that the other person is the source of one's own affective state" (de Vignemont & Singer, 2006). In accordance, empathy, and especially empathy for pain, have been studied using different types of experimental paradigms. In the pioneering study by Singer and colleagues (Singer et al., 2004), participants were watching their romantic partner receiving electric shocks. The activity in anterior insula and cingulate cortex overlapped with the activity seen when the participants themselves were receiving the electric shocks and this was interpreted as a sharing of emotion. In the same study, self-reported empathy, using the subscale Empathic Concern from the Interpersonal Reactivity Index and the Balanced Emotional Empathy Scale, was correlated to activity in anterior cingulate cortex and left insula. However, the statistical approach to this correlation has later been questioned (Vul, Harris, Winkielman, & Pashler, 2009). Later studies have used movies and pictures of individuals experiencing pain, with similar brain activation patterns as shown in the original paper (C Lamm et al., 2011). Notably, the brain activation pattern and empathic behavior (i.e. ratings) seems to be affected by the type of instruction given to the participants (Claus Lamm, Batson, & Decety, 2007), contextual factors (Hein & Singer, 2008) and experimental manipulations with drugs (Rütgen et al., 2015), suggesting that the task can be sensitive to manipulations, possibly including sleep manipulations. In study II, pictures of needles stinging hands compared to Q-tips poking hands, were used. These stimuli have been shown to activate similar brain areas as paradigms using a present person in the

room, and are therefore often used to study empathy. However, it should be noted that there was no correlation between ratings of vicarious unpleasantness, or self-rated empathy and brain imaging outcomes in this study. This might of course represent lack of power to demonstrate such an effect, but also raises the question if brain measures (e.g. fMRI) can be used to *quantify* empathic responses. It can also be questioned whether the unpleasantness reported by participants while watching pictures of needles stinging a hand represent empathy. I am not convinced that the participants had *knowledge that the other person is the source of one's own affective state,* and were not just afraid of themselves being stung with a needle.

8.4 THE TYPE OF SLEEP MANIPULATION

In study I-IV, sleep restricted to 3 hours was used as a sleep manipulation. The rationale behind this was to mimic the type of sleep restriction that is common in daily life, as well as to avoid that participants would fall asleep in the scanner. Previous studies of sleep and emotion has commonly used total sleep deprivation, with potentially stronger consequences on brain and behavior. Some previous work has also indicated that specifically REM-sleep is important for emotional recovery (van der Helm et al., 2011). Allowing participants to sleep for 3 hours, might have been sufficient to get enough of this sleep stage. There was however a robust increase in ratings on the Karolinska Sleepiness Scale, indicating that the sleep manipulation had a strong effect at least in this respect. In fig 6, rated unpleasantness in study II is shown in relation to total sleep time, REM and slow wave sleep, indicating that the amount of REM, but not SWS is related to self-reported unpleasantness. Thus, these data indicate an important role of REM for emotional processing, but further studies of REM-suppression are needed.

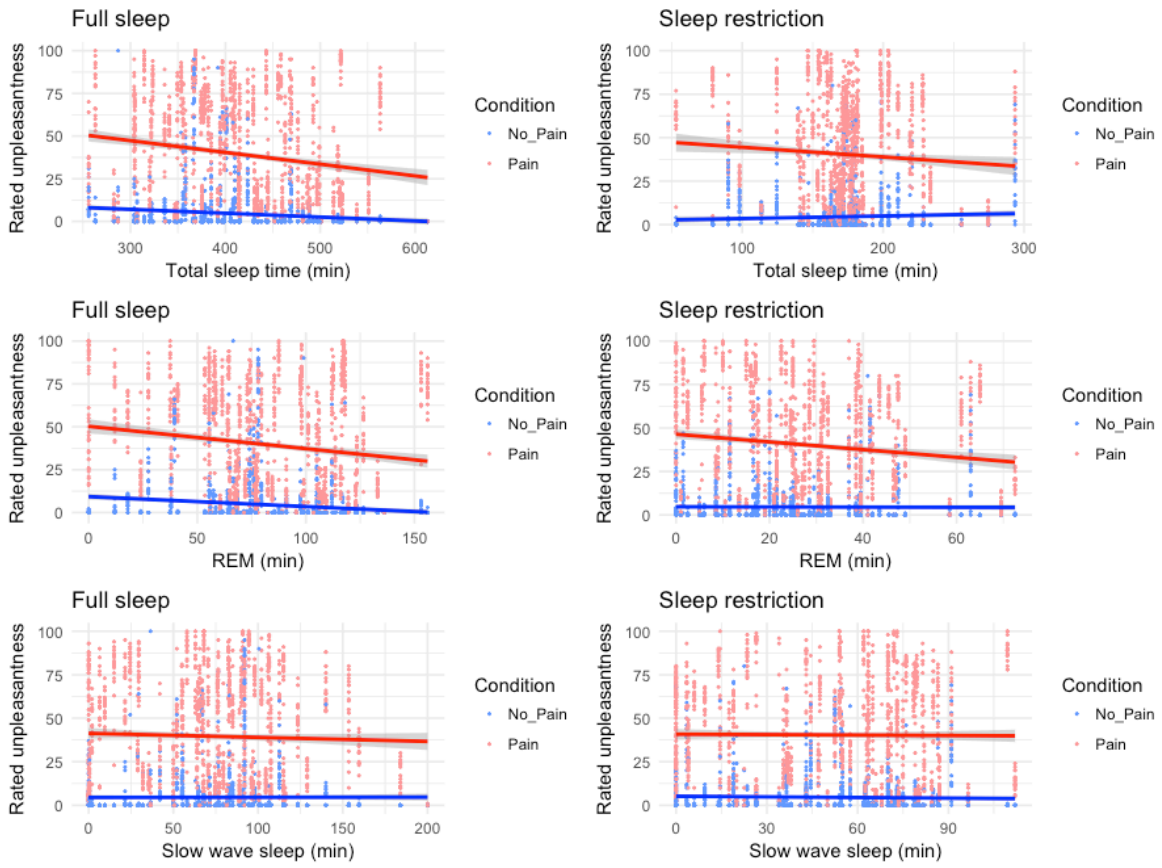

Figure 6. Rated vicarious unpleasantness (from study II) in relation to total sleep time, REM-sleep and slow wave sleep

Another aspect of the sleep manipulation in studies I-IV is that many of the subjects slept rather short during the normal sleep condition, potentially being slightly sleep deprived in the control condition. If this is true, the consequences of sleep restriction were underestimated and the noise in the data increased. However again, the strong effect on Karolinska Sleepiness Scale indicate that the sleep manipulation induced significant sleepiness. It should also be noted that since the participants could not be blinded to the sleep condition, there was an obvious risk for biases related to expectations etc., that in studies with other types of manipulations could be reduced through a placebo condition.

A further point that needs to be addressed is the difference between acute and long term sleep restriction. Some data indicate that long-term sleep disturbance is associated with poor emotional regulation (Klumpp et al., 2017) and decreased activity in the left insula in an empathy task (Guadagni et al., 2018). In epidemiologic studies sleep problems are linked to depression, and it is likely that sleep problems can indeed cause depression (Baglioni & Riemann, 2012). Studies of sleepiness and cognition have compared the use of long-term

sleep restriction and acute total sleep deprivation (Van Dongen et al., 2003), indicating that chronic sleep restriction have strong effects on cognition, with less strong effects on sleepiness, whereas acute total sleep deprivation affects both cognition and sleepiness. In line with these differences, it is possible that the effect of sleep restriction on emotional function also depends on the time perspective, i.e. the studied duration of sleep restriction. Further studies need to address this question.

8.5 REFLECTIONS ON REPRODUCIBLE RESEARCH

During a doctoral course, I encountered the following statement: "What is the general idea of a good study? To gain knowledge. And how do you know that you gained knowledge? Because you performed a good study." The statement is circular, and to me represents a fundamental problem in research. Most researchers that I have met are in theory very good at criticizing their own, as well as others' work, when asked to. Most researchers are also, in theory, aware of the impact of chance on statistical inference. Why is this theoretical knowledge not always translated into research practice? The Open Science Collaboration estimated that 36% of studies in psychology can be replicated (Open Science Collaboration, 2015) and the reproducibility crisis in research has been acknowledged in recent years. However, when reading research articles (including my own), I have the impression that we are still all over-confident in our own results, in the sense that we believe that they would hold in a replication attempt. Whether this is true, or whether it represents an academic writing tradition, is not always clear to me. In any case, we know that the individual studies could represent a dot in a future meta-analysis, that will at least be a more accurate effect-estimate than our own study on its own. We should also expect some of our own results to fail in later replication attempts (Lakens, Hilgard, & Staaks, 2016). Therefore we cannot actually know that we gained knowledge, even if the study is good. The findings can still be the result of randomness.

Another point that seems to be caused by the mismatch between theoretical and practical knowledge, is the sometimes excessive fear of committing type 1 errors (i.e. false positive findings), resulting in an increase in type 2 errors (i.e. false negatives), or sometimes decisions not to explore already collected data. To look at multiple outcomes in small samples carries the increased risk that the findings might not represent a true effect, but could still be very useful. Especially if findings later can be replicated using more data.

I have had the privilege to work in an environment where issues related to open science and reproducibility are frequently discussed, but I nevertheless believe we could do much better in translating this knowledge in to actual research practice. One way to deal with the issues discussed above is to publish the data and code for analysis openly available, which we have so far only been partly able to. However, publishing data might, if not adequately handled, violate the integrity of participants. Another way is to publish hypotheses as well as an analysis plan before acquiring data, which in our case (studies I-IV) appeared to be much more difficult than thought. Publishing detailed hypothesis lists might decrease the risk of *p*-hacking, but on the other hand might require researchers to foresee sometimes unpredictable aspects of the data. Some ideas also need to mature during the work with complex studies and the development of knowledge in an area.

8.6 ETHICAL CONSIDERATIONS

As a general ethical consideration, I find it unethical to perform low quality research. The time and effort invested by researchers and participants should not be in vain. However, it is likely impossible to perform perfect studies. Through the work with this thesis a number of decisions were taken, that in retrospect were not optimal. Despite this, all people involved have gained knowledge that can be applied in future work. This concerns both methodological aspects such as the method of sleep deprivation, neuroscientific concepts such as problematization of empathy as a construct and of course the research questions that we have addressed. It is estimated that a substantial proportion of the studies that are performed that never get published (Jones et al., 2013; Open Science Collaboration, 2015). This most likely contributes to the publication bias, since results confirming the hypotheses are more often published compared to studies not supporting the hypothesis (Fanelli, 2012). Several of the studies in this thesis did not support the specific hypotheses stated. Nevertheless, the data and analyses were not discarded, instead they are published, or will be, openly for other researchers to use. Publishing data is, as noted above, one way to deal with many types of research biases, but also results in risk of violating the personal integrity if not adequately anonymized. In a future scenario, with technology we cannot predict, any data might be misused in a way that is very hard to foresee. Certain sensitive information was collected from the participants, including e.g. self-rated psychiatric symptoms and genotypes related to brain function. To ensure confidentiality, participants were identified with a code and the codes were stored in a secure system. The openly published data is also anonymized.

In studies I-IV, volunteers were exposed to acute sleep restriction. One night of sleep restriction is not expected to have any long-term adverse health effects, but it does affect participants during the experiment. Considering the potential knowledge gain, we judged that the discomfort for the participants could be tolerated. However, even one night of restricted sleep could be a potential risk in traffic, why this risk was reduced through offering the participants to travel by taxi to and from the experiment. Blood sampling was also performed and some subjects experienced some discomfort because of this. The participants were compensated with 2500 SEK for their time as well as the potential suffering. This compensation mitigated to some degree the intrusion into the participants' time, but also carried the risk that participants would volunteer for monetary gain, despite reasons not to.

Some general ethical issues necessarily arise when scanning healthy individuals with imaging techniques. The most important issue relates to possible pathological findings on MRI. Subjects with indisputable severe findings should and have been referred to follow-up in health care, but whether all non-specific findings with unclear clinical significance should be reported could be discussed. Magnetic field exposure due to MRI scanning is per se not associated with any known health risks in healthy individuals, but might be dangerous for people with for example implants. Therefore, participants were extensively screened with respect to MRI safety.

Study V includes PET as an imaging method. This method includes injecting participants with a radioactive ligand. Radiation is obviously dangerous in a dose-dependent manner, but in the study the routines at the PET center and the Radiation Safety Committee were followed, with respect to dosages and the use of a radioligand with relatively short half-life (i.e. fast radioactive decay), which reduces the radiation the subjects are exposed to. In the project of which this study is a part, a lot of other data was collected, to enable pooling of data across studies. This is done to maximize the use of PET data, to avoid unnecessary later examinations.

9 GENERAL DISCUSSION

9.1 DOES SLEEP RESTRICTION AFFECT EMOTIONAL BEHAVIOR?

The main aim of this thesis was to investigate mechanisms underlying effects of insufficient sleep on emotional functions. An important question to answer is therefore which emotional functions that are affected by sleep restriction. In study I, ratings of happiness, but not angriness, were decreased after sleep restriction, in line with a negativity bias. Further, it was also shown that positive, but not negative, affect, i.e. ratings on PANAS, was lower after sleep restriction compared to normal sleep. No effect of sleep restriction was seen on facial EMG responses, indicating that emotional mimicry is not affected by shortened sleep. In study II, no main effect of sleep restriction on ratings of vicarious unpleasantness was seen, indicating that empathy for pain might be stable to one night of sleep restriction (at least for young). In study III, self-rated success in cognitive reappraisal was lower after sleep restriction, compared to normal sleep, indicating that emotional regulation depends on adequate sleep the previous night. Altogether, these findings suggest that sleep restriction causes less positive emotion, and additionally a decreased perceived ability to regulate the emotions. There was no clear indication that more complex functions (e.g. emotional regulation) were more affected than basic emotional functions (e.g. perception of emotional faces). However, the effects of sleep restriction were not primarily related to social emotional functions, but to more general aspects of emotion, such as positive and negative affect, perception of emotional stimuli and emotional regulation. Possibly, this suggest that the effects of sleep restriction on behavior are caused by a shift towards depressed mood, increased sleepiness and fatigue and negative thoughts, rather than inability to engage in specific social emotional tasks, such as empathizing with someone.

9.2 WHAT EFFECTS DOES SLEEP RESTRICTION HAVE ON MEASURES OF BRAIN FUNCTION?

My motivation when starting working with the projects presented in this thesis was to understand the effects of sleep restriction on emotional functions using objective measures of brain function. I believed that this could primarily be done through investigating the effects of sleep restriction on three emotional tasks. Through the process it appeared that the effects of sleep restriction that could be captured in terms of brain activity in specific emotional tasks in the scanner were not very strong. In study I, sleep restriction was associated with decreased

activity in fusiform gyrus for angry vs neutral faces, whereas no measurable significant effects of sleep restriction on brain activity or connectivity were seen in any of the other emotional tasks. A number of previous studies have shown effects of sleep restriction on behavioral outcomes related to emotion (e.g. Beattie et al., 2015; Cote et al., 2014; J. F. A. Schwarz et al., 2013; Sundelin et al., 2013; Tempesta et al., 2010, 2018), but only a few studies have indeed found possible brain correlates to these effects (e.g. N. Gujar, Yoo, Hu, & Walker, 2011; Y Motomura et al., 2014; Yuki Motomura et al., 2013; Mullin et al., 2013; Yoo et al., 2007). Notably, none of the previously reported findings related to increased amygdala reactivity could be replicated in the present thesis. However, it should be noted that the tasks where sleep restriction primarily affected behavior (i.e. study I and III) are indeed tasks that are previously shown to involve amygdala. One possible explanation to the absence of measurable brain changes is of course lack of power, but the discrepancy between behavioral and brain imaging findings presumably also indicate a need for a broadened perspective on how to probe for brain changes related to the behavioral consequences of shortened sleep. Keeping in mind the reproducibility problem in the field, the earlier proposed mechanism, i.e. increased amygdala reactivity caused by decreased connectivity from prefrontal cortex (Yoo et al., 2007), need further confirmation before taken for granted.

In order to understand general effects of sleep restriction on the brain, resting state connectivity was investigated in study IV. In this study, it was shown that sleep restriction was associated with an increased global signal variability, potentially representing an increased propensity to drift in and out of sleep (wake-state instability), that could affect the ability to for example control emotions. It needs to be further studied whether this measure represent a biologically relevant change, or artifacts related to motion or physiological variables such as breathing and hear rate. However, if sleep restriction affects variability in the brain activity and causes decreased connectivity inside core networks, this could possibly affect emotional behavior as well.

9.3 VARIABILITY IN BRAIN AND BEHAVIOR AFTER SLEEP RESTRICTION

Global signal variability was shown to increase after sleep restriction in study IV. For behaviors such as reaction times, that are more extensively studied after sleep deprivation, the impaired performance also seems to be caused by an increase in variability in responses, e.g. lapses (Krause et al., 2017). Fig 7 shows variability in ratings of vicarious unpleasantness

from study II, indicating that for the no pain condition, there was a non-significant increase in variability after sleep restriction. In line with previous work reporting that the negativity bias seen after sleep deprivation (Tempesta et al., 2010) is primarily related to neutral or ambiguous stimuli being perceived as more negative, this was shown specifically for neutral stimuli. In study IV, we speculate that the increased global signal variability might reflect a wake-state instability. Such instability in the brain's ability to stay awake, but also to perform a specific task, could possibly result in increased variability for different types of responses, including emotional.

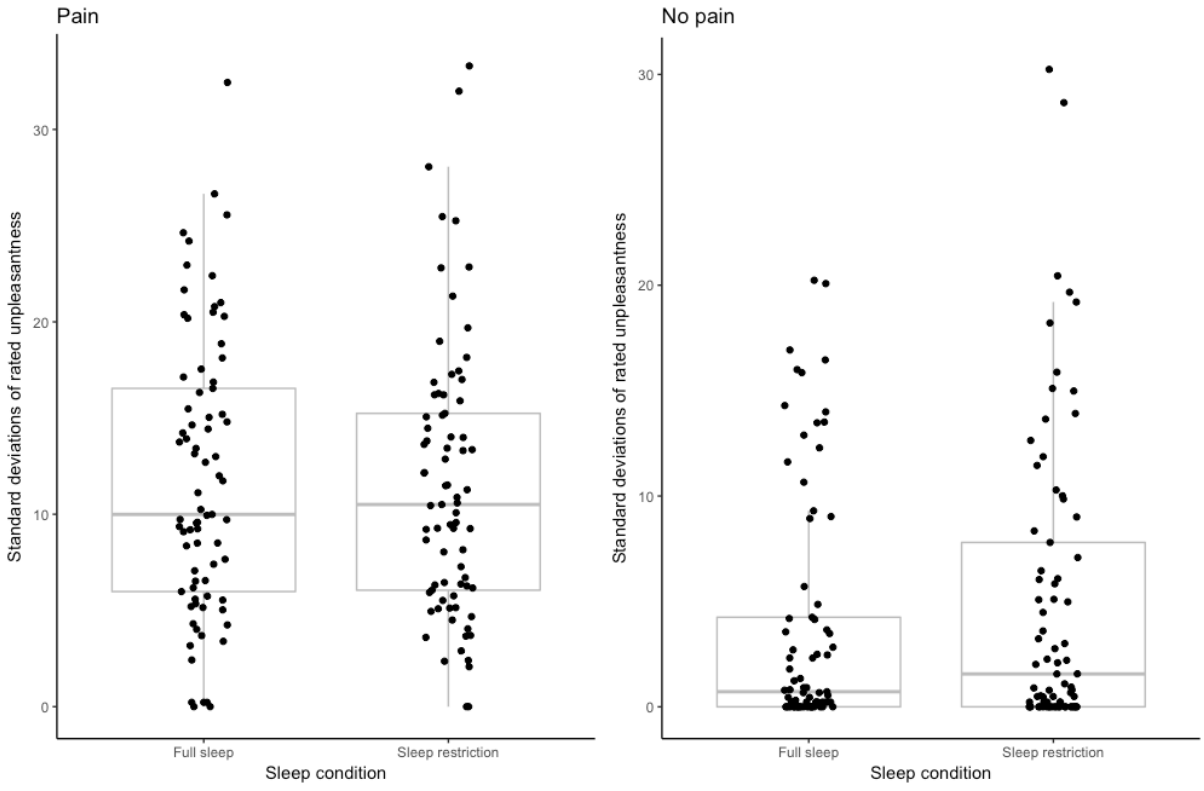

Figure 7. Variability in responses for rated unpleasantness in study II.

9.4 EMOTIONAL CONTAGION, EMPATHY AND EMOTIONAL REGULATION IN AGING

In study I-IV both younger and older participants were investigated. Understanding effects of aging on emotional functions was not the primary goal of this work. However, in all studies of emotional functions, there were significant differences in both behavior and brain imaging responses between younger and older participants, which for future research highlights the importance of including participants of different age groups, to increase generalizability. In study I, older participants reported increased angriness in response to emotional faces

compared to younger, which is surprising in the context of the previously reported positivity effect in older (Reed & Carstensen, 2012; Reed, Chan, & Mikels, 2014). In response to all types of faces, compared to a baseline, older participants showed less amygdala activity, in line with both the previously discussed *fronto-amygdalar age-related differences in emotion* (St Jacques et al., 2009) and *the aging-brain model* (Todorov et al., 2011). In study II, older participants showed increased activity in angular gyrus in response to pain in others, compared to younger. This was accompanied by non-significantly increased vicarious unpleasantness. Older participants also showed increased activity in the fusiform gyrus in response to both pictures of pain and no pain. In study III, older participants showed less brain activity in emotional networks in response to negative stimuli, as well as in control regions during cognitive reappraisal. Older participants also reported higher unpleasantness in response to negative pictures, and lower success in the emotional regulation task, compared to younger. Based on observations during the data collection, we suspected that many of the older participants did not follow the instructions given in the task, and the results should be interpreted in the light of this. However, altogether the results from studies I-III indicate that younger and older differ in their emotional functions across the emotional hierarchy described in the introduction. As discussed in the background, it has been suggested by some that decreased amygdala activity in older represent spontaneous emotional regulation (St Jacques et al., 2009). However, in study III, there was no indication of older participants being more effective in emotional regulation, compared to younger participants. Based on this observation, the other proposed explanation, that changes in emotion perception in older might primarily be related to amygdala atrophy (Todorov et al., 2011), is more likely.

9.5 DOES AGING AFFECT THE RESPONSE TO SLEEP RESTRICTION?

As already discussed, previous literature of sleep and emotion show some inconsistency. This was one rationale behind including both older and younger subjects in the present thesis, since age can be one possible factor modulating the effect of sleep restriction on emotion. In study I, no differences in how younger and older participants responded to the sleep manipulation was seen. In study II, sleep and aging interacted for both ratings of vicarious unpleasantness and brain activity in middle insula. After sleep restriction, older but not younger participants reported increased vicarious unpleasantness, compared to the full sleep condition. In parallel, activity in middle insula in response to pain in others compared to an implicit baseline was higher after sleep restriction in older, but lower in younger. In study III, sleep restriction did not have any significant effects on ratings of success in emotional

regulation in older participants, as in contrast to young. In summary, these findings indicate that aging might modulate the effect of sleep restriction on emotion, similarly to what has been shown for sleepiness (Dijk et al., 2010) and cognition (Scullin & Bliwise, 2015).

9.6 WHAT ELSE CAUSES THE INCONSISTENCY IN THE EFFECTS OF SLEEP DEPRIVATION ON EMOTION?

Beyond aging, many other possible factors could modify the effect of sleep deprivation on emotion. For example, people with a certain psychiatric vulnerability could be more affected by acute sleep deprivation. Preliminary data from our colleagues (Floros et al, unpublished) indicate that subjects with attention deficit hyperactivity disorder traits are more easily affected in their performance on an emotional stroop task after sleep restriction. For practical reasons, most experimental studies of sleep deprivation are not performed in population based representative samples, potentially explaining some of the differences between studies.

In all the three emotional paradigms, participants were asked to perform a certain task. A personal experience is that participants, also in the sleep restriction condition, want to perform their best. Whether this is because of their wish not to disappoint the researchers, or to prove their competence or something else is unclear. However, these types of compensatory tendency, that likely depend on underlying personality traits, might also affect the effects of sleep deprivation at the moment of investigation.

Possibly, the systems also need to be further strained to show a distinct effect of restricted sleep. I think many readers recognize the feeling you have at the end of day, when you are tired, hungry and have been arguing with your colleagues, resulting in screaming at your family. The decreased ability to regulate emotions in such a setting can possibly be caused by depletion of backup resources. Resourses that in the beginning of the day could compensate for some of the effects of sleep loss.

9.7 SLEEPINESS, DEPRESSION AND FATIGUE – THE ROLE OF SLEEP AND INFLAMMATION

As discussed above, insufficient sleep appears to cause a shift towards negative mood and fatigue. Increased fatigue, disturbed sleep and negative mood are also commonly reported

symptoms in both psychiatric conditions, such as depression (Rumble et al., 2015), and chronic inflammatory disorders such as pollen allergy (Thompson et al., 2013; Trikojat et al., 2017). These connections were partly probed in study V. This study investigated inflammatory changes in the brain as a possible mechanism behind – and correlate to – this set of non-specific symptoms in allergic patients. Allergic subjects displayed increased fatigue and sleepiness during pollen season, as well as persistent sleep disturbances. Data from the same sample show that patients with allergy also reported increased symptoms of depression and anxiety during pollen season (Karshikoff in prep). Analyses of plasma revealed an increase of allergy-specific and non-specific inflammatory markers in allergic patients, especially during pollen season. These non-specific symptoms, and signs of immune changes, were however not paralleled by changed TSPO levels in the brain. Notably, it has been questioned whether the ligand used, PBR-28, can differentiate between pro-inflammatory vs anti-inflammatory microglial phenotypes (Liddelow et al., 2017; Tronel et al., 2017) and detect inflammatory changes related to psychiatric symptoms (Collste et al., 2017; Forsberg et al., 2017; Notter et al., 2017).

Because changes in sleep may be associated with changes in peripheral inflammatory markers (Irwin, 2015; Redwine et al., 2000) and because a growing body of evidence suggest inflammation to play a role in psychiatric conditions such as depression (Kiecolt-Glaser, Derry, & Fagundes, 2015; Miller & Raison, 2016), there is a strong need to develop methods to study inflammatory changes in the brain. These methods should be used to understand mechanisms underlying non-specific symptoms in chronic diseases, but also in studies investigating the effect of disturbed or restricted sleep on emotional functions and fatigue.

10 CONCLUSIONS

The aim of this thesis was to investigate mechanisms underlying effects of insufficient sleep on emotional functions, including emotional contagion, empathy, emotional regulation, mood, sleepiness and fatigue.

Study I-III showed that one night of restricted sleep was sufficient to cause changes in emotional behavior, i.e. a negativity bias, negative mood and decreased ability to regulate emotions. Social emotional functions, i.e. empathy and emotional mimicry, were less affected. Notably, increased amygdala reactivity, suggested as a potential mechanism behind emotional problems after sleep deprivation, was not shown after sleep restriction. Study IV showed that sleep restriction was associated with increased global signal variability in the brain, as a potential marker of wake-state instability and sleepiness. Study V showed that patients with severe seasonal allergy had increased fatigue, sleepiness and disturbed sleep, and signs of peripheral inflammation. However, the study did not implicate increased TSPO binding, as measured with PET, as involved in these non-specific symptoms.

Adult aging was investigated as a potential modulator of the effect of sleep restriction. Study II suggested that sleep restriction might affect older more than young for empathy. Study III on the other hand, suggested that younger, but not older adults, are affected by sleep restriction for emotional regulation. The results highlight a need for including people of varying age in studies of sleep and emotion.

Thus, this thesis corroborates earlier findings, showing that sleep is needed for emotional functioning. However, brain mechanisms underlying emotional dysfunction related to poor sleep need further investigation, using reliable methods in large samples.

11 FUTURE DIRECTIONS AND IMPLICATIONS FOR MENTAL HEALTH

In this thesis, the idea was to have a broad brain-body perspective to understand the effects of sleep loss on emotional functions. This was one of the reasons to include study V, which takes another approach to understanding relations between factors of importance for fatigue, sleepiness, emotional functioning and health. TSPO binding could not be confirmed as a mechanism behind this set of non-specific symptoms. However, beyond changes in global signal variability, changes in the immune system can still be a possible mechanism through which shortened sleep can act on the brain. To further investigate inflammation as a potential mediator of the effect of sleep restriction on emotion, inflammatory markers (circulating cytokines) from the Sleepy Brain study (study I-IV) will be analyzed. Future sleep deprivation studies should also include markers of inflammatory changes in the brain.

Except for study V, this thesis describes studies of healthy participants. Sleep problems are as mentioned very common in the general population. However, most psychiatric disorders have a component of disturbed sleep (Rumble et al., 2015). Moreover, several psychiatric disorders including bipolar disorder, psychosis and ADHD, may worsen with less sleep. In the future, studies using similar methods therefore need to be performed in psychiatric patients. This is especially true for patients with affective disorders, where both emotional dysfunction and sleep disturbance is common. Further questions that need to be answered in the context of sleep and emotion in psychiatric patients are if and how acute total sleep deprivation can cause a reduction of depressive symptoms and suicidality in depression (Boland et al., 2017) and how long term sleep problems seem to cause depression (Baglioni & Riemann, 2012).

12 A LOOK BACK

To get a PhD is of course more than writing a book. I think of these years as similar to getting a driver's license, for doing research instead of driving a car. (Unlike with the driver's license, I hope I will pass on the first attempt.) When being admitted to the doctoral education, we specified a number of learning goals to achieve. To summarize what I have learnt since beginning my PhD journey is beyond the scope of this, or any other, book, but such a summary would include things like writing and reading research articles, plan and perform data collections as well as data analysis of behavioral and imaging data. Apart from

the studies presented in the thesis, I have also had the opportunity to collaborate on a number of different projects that have also helped me develop towards an independent researcher and contributed to fulfilling several learning outcomes. For example, one project investigated how the sleep itself is affected by sleep deprivation, using polysomnography recordings from the Sleepy Brain study (T. Åkerstedt et al., 2017), and one study examined the effect of total sleep deprivation on mood in older and younger subjects (J. Schwarz et al., 2018). One project that was initiated during the work with my master thesis investigated the effect of the benzodiazepine Oxazepam on emotional mimicry and empathy (G. Nilsonne et al., 2017)) and emotional regulation (Nilsonne et al. in prep), with emotional tasks that were later developed and partly used in study I-III in the present thesis. In relation to the same project we also validated a psychometric scale for psychopathy (Sörman et al., 2016). During one discussion on how to use the structural images acquired in the Sleepy Brain study we decided to put together a meta-analysis of studies investigating the association between hippocampus volume and leukocyte telomere length (G. Nilsonne, Tamm, Månsson, Åkerstedt, & Lekander, 2015). Another discussion during a journal club related to disease avoidance theory evolved into a paper that – in fact – investigated politicians' sexiness in relation to voting behavior (G. Nilsonne, Renberg, Tamm, & Lekander, 2016). Beyond helping me to develop as a researcher, these projects (together with the ones included in the thesis) reminded me of how fun it is to come up with a research question, find suitable data to answer the question and actually, at least sometimes, be able to understand something more about the complex creatures called humans.

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