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Towards an Embodied Account of Sleep Loss

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By

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Abstract

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Sleep is fundamental to life. Multiple biological functions, from peripheral immune and cardiovascular systems, to central brain operations governing cognition and emotion, are perturbed by sleep when deficient and restored by sleep when sufficient. This evidence leads to the proposition that sleep is necessary for coordinating whole-organism adaptation, which requires the active co-regulation of both brain and body systems for optimal physiological stability during stress, termed allostasis. Although causal links within and between the brain and body are recognized as essential, a multi-system examination of these interactions under conditions of insufficient sleep has yet to be reported. Elucidating the interdependence of the multi-system impacts of sleep loss is not only necessary to build a deeper understanding of the function of sleep, but also to guide informed treatments for a number of chronic diseases characterized by both sleep disturbances and multi-system etiology, such as chronic pain and cardiovascular disease. This thesis combines functional magnetic resonance brain imaging with measurements of peripheral physiological function in order to test the overarching hypothesis that the dysfunction observed across multiple brain and body systems under conditions of sleep loss are intimately interrelated, rather than independent. Three specific aims emerge from this hypothesis and are addressed in this thesis: (1) The first aim sets forth the hypothesis that sleep loss impairs the function and architecture of brain networks with consequences for cognition, affect, and physiology. A comprehensive review of neuroimaging studies of sleep deprivation in humans demonstrates that sleep loss alters the architecture of human brain networks, and with it, the processes dependent on these networks. Many of the brain regions and networks most impacted by sleep deprivation are affective and viscerosensory brain regions involved in the master regulation of allostasis. (2) The second aim addresses the hypothesis that, in addition to the central brain, sleep loss impairs the functioning of peripheral adaptive systems and that central and peripheral dysfunction are interrelated, focusing on the immune system and pain. An experimental sleep deprivation study in humans demonstrates that sleep deprivation increases levels of circulating pro-inflammatory cytokines, and that this pro-inflammatory state contributes to increased pain perception assessed both objectively in the brain and subjectively through participant ratings. (3) The third aim tests the hypothesis that interrelated dysfunction in the brain and the body is evident in a different model system involved in allostasis, the cardiovascular system. A second sleep deprivation experiment establishes significant interdependence between sleep loss-increased blood pressure, disruption of

central brain viscerosensory networks, and worse mood state. Collectively, these results support an embodied framework of sleep loss wherein sleep loss contributes to disease through a disruption of the brain-body coordination required for allostasis. Considering the continual erosion of sleep across society, these findings hold important scientific, clinical and public health implications.

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I. General Introduction

Sleep and Allostasis

Sleep is ubiquitous across phylogeny. For this reason, sleep has been suggested to serve some universal function(s), common across species. Consistent with this possibility, numerous studies to date have demonstrated that sleep supports a wide variety of operations for both body and brain, and across species (Huber et al., 2004).

One potential framework that may underlie a universal function of sleep is that of energy allocation, predicated on organism homeostasis and regulation of allostatic load (Schmidt, 2014). First defined by Cannon, homeostasis is the continuous maintenance of vital physiological variables within operational ranges through the coordination of physiological and behavioral responses (Cannon, 1932).

Related, allostasis refers to the biological notion of "stability through change", in which an organism must adjust the operational ranges of vital physiological variables as required by new or changing demands (Sterling, 1988). Crucially, the adjustment of physiological parameters with changing demands comes at a cost. This cost of adaptation, termed allostatic load, is due to the multiple systems required to maintain biological optimality (McEwen and Stellar, 1993). This thesis offers the proposition that sleep is necessary for allostasis, and conversely, that sleep loss increases allostatic load leading to a state of homeostatic distress.

The thesis premise is based on the knowledge that allostasis requires the coordination of most all major physiological systems, such as the autonomic nervous system, neuroendocrine system, immune system, and central nervous system (McEwen, 2006). These systems form an interactive network with, in higher organisms, the brain serving as the master regulator (McEwen, 1998). This thesis contends that sleep loss results in disorganization of these adaptive systems, including the brain. This disorganization resulting from insufficient sleep is therefore proposed to lead to the development of allostatic overload (Sterling, 1988; McEwen, 1998; Jovanovic et al., 2012).

Under optimal conditions, allostasis reduces the cost of adaptation by anticipating environmental changes and allocating energy to physiological processes that best match the current demands on the organism (Sterling, 1988; Grillon and Morgan, 1999). Indeed, the 24-hour rhythms of sleep and wake are an example of this allostatic anticipation, in which certain biological processes are limited in time when their employment is maximally efficient (Schmidt, 2014). It is here that a unitary function of sleep is possible. While sleep involves a collection of heterogeneous processes, several outlined below, these processes are coordinated by the brain to match predictably cyclic environmental and physiological demands. A unitary function of sleep, therefore, may be to direct resources to biological investment and to simultaneously down-regulate processes required for wakefulness.

Such a universal theory of sleep necessarily includes an understanding of the brain and body changes that occur due to sleep's absence, either when reduced in amount, or completely prevented (i.e. sleep restriction or sleep deprivation). From the current thesis perspective of allostasis, sleep loss represents an *unanticipated* biological state. Humans appear to be the only species that deliberately deprive themselves of sleep for little or no evolutionary value. In select species, rare cases of sleep loss occur during specific and extreme demands on the organism that are of marked evolutionary gain, such as migration (e.g., white-crowned sparrow) or for protection of newborns (e.g. killer whales) (Grillon and Morgan, 1999; Siegel, 2009). Since humans did not face such extreme circumstantial pressures throughout the course of evolution, it is unlikely that humans have developed markedly effective mechanisms to adaptively cope with insufficient sleep.

This leads to the main proposal that this thesis seeks to address: namely, that any state of insufficient sleep, which will always be unanticipated (since sleep loss is not an innate circumstance of Homo sapiens), is expected to dysregulate energy utilization and distribution. The thesis model proposes that any such circumstance will result in inefficient allocation of resources and impaired homeostasis due to allostatic overload. That is, a lack of sleep in humans represents a biological stressor upon the operations of allostasis, for which humans are ill-prepared, resulting in increased allostatic load.

Supporting this possibility, sleep loss increases appetite, energy expenditure, increases levels of pro-inflammatory cytokines, decreases parasympathetic and increases sympathetic tone, increases blood pressure, increases cortisol levels, increases insulin and blood glucose, and disrupts brain function and structure in networks involved in memory, attention, reward, and emotion (McEwen, 2006). Additionally, disturbed sleep quality and quantity are common features of multiple pathophysiologies resulting from high allostatic load, including diabetes, hypertension, cardiovascular disease, chronic pain, depression, and anxiety disorders (McEwen and Wingfield, 2003; McEwen, 2006; Straus et al., 2017). This thesis aims to determine the effects of insufficient sleep across multiple physiological levels and *not in isolation* (e.g. just brain, or just body). The thesis aims to assess brain, body, and mental levels of descriptive analysis simultaneously, in concert. That is, an "embodied assessment" approach, rather than a compartmentalized organ or system assessment approach.

Sleep Deprivation and the Brain

To situate the thesis goal and experiments, it is first necessary to briefly offer an overview of the sleep loss-related impairments within the brain and within the body. With that context provided, the embodied model can be considered, wherein dysregulation is not only observed in isolated systems, but in the interactions of brain and body.

This overview begins with the most fundamental node in the allostatic network, which is the brain. As the central organ of adaptation, the brain has core efferent and afferent connections with peripheral systems, which demands the appreciation of the current embodied, not systems-segregated, view of sleep loss.

Brain Networks and Sleep Loss

Within the brain, sleep loss fundamentally alters functional network activity (reviewed in **Chapter 2**), the extent of which is associated with a broad array of cognitive and behavioral effects.

For example, the most reliable impact of sleep deprivation is impaired attention, which results from the instability of large-scale brain networks, especially of the default mode network (DMN) and ascending arousal systems (Doran et al., 2001; Drummond et al., 2005; Durmer and Dinges, 2005; Tomasi et al., 2009; Czisch et al., 2012). The DMN is a core network of the brain and includes midline frontoparietal regions that disengages during externally-driven, goal-directed task performance, and re-engages upon task termination (Greicius et al., 2003). Under sleep-rested conditions, ascending arousal input from the brainstem and thalamus supports reciprocal inhibition between task-related network activity, such as the Salience network, and DMN activity. Under sleep-deprived conditions, erratic brainstem arousal and thalamic input to the cortex results in an erosion of the functional separation between anti-correlated networks, such as between the DMN and Salience network (De Havas et al., 2012; Ben Simon et al., 2017). Consistent with this, the Salience network, including the frontoinsular cortex which also helps control switching between DMN activity and task-related activity (Sridharan et al., 2008), demonstrates reduced activity during the performance of attention tasks (Ma et al., 2015).

In addition to reduced functional segregation of the DMN with anti-correlated networks, activity within the DMN is significantly altered by sleep loss, particularly in the anterior cingulate cortex (ACC) and precuneus (Gujar et al., 2010). This evidence suggests that unstable control of the DMN may be a common phenotype underlying cognitive deficits. Thus, sleep loss impairs the intrinsic architecture of brain networks resulting in impaired performance required for goal-directed behavior (Durmer and Dinges, 2005).

Taken together, this evidence suggests that cognitive brain function associated with wakefulness is particularly sensitive to sleep loss due to impairment of functional network organization. These outcomes fit with the embodied framework of this thesis, wherein sleep deprivation impairs and alters the functional architecture of the human brain, and with it, the cognitive (and below, emotional) processes dependent on these networks. During sleep loss, brain-network restorative processes are deprived of energy resources because limited energy has been shuttled to sustain incongruous processes supporting the extension of wakefulness. This inefficient energy allocation causes impairments in the cognitive and behavioral functions of the brain.

The Affective Brain and Sleep Loss

In addition to cognition, the affective brain is similarly impaired by a lack of sleep (Goldstein and Walker, 2014). Many of the brain regions impacted by a lack of sleep receive viscerosensory input from brainstem and spinal cord pathways, including cortical (insula, cingulate, medial prefrontal) and subcortical (hypothalamus, striatum, amygdala) brain regions. Sleep loss-related dysfunction within affective brain networks, then, holds particular relevance for the brain's master regulation of whole-body allostasis.

Several regions of the affective brain, particularly the insula, cingulate, and hypothalamus are directly involved in sleep regulation, a fact fitting with the central role of the brain in coordinating sleep-related allostasis. Indeed, there is significant overlap between affective and interoceptive brain processes, suggesing important connections between impaired emotion processing and allostasis following sleep deprivation.

For example, a night of sleep deprivation in humans triggers changes in negative emotional processing, including increased irritability, emotional volatility, anxiety, and aggression (Horne, 1985; Dinges et al., 1997; Zohar et al., 2005; Anderson and Platten, 2011; Minkel et al., 2012). These changes in subjective emotional state are linked to altered emotional discrimination and emotion reactivity within the insula, cingulate, and amygdala, and through a loss of top-down regulatory control by prefrontal regions (Goldstein et al., 2013; Prather et al., 2013; Goldstein and Walker, 2014). Illustrating this, a night of sleep deprivation increases amygdala reactivity to aversive images, potentially due to reduced functional connectivity between the medial prefrontal cortex and amygdala (Yoo et al., 2007b; Motomura et al., 2013). In addition to emotional reactivity, anticipatory activity in the amygdala, anterior insula, and ACC is also amplified by sleep deprivation (Franzen et al., 2009; Goldstein et al., 2013).

Linking to the body, sleep loss-related amplifications in emotional anticipatory activity within core emotional regions is paralleled by heightened responses in the peripheral nervous system. This includes changes in the cardiovascular system, as well as autonomic nervous system (Franzen et al., 2009; Goldstein et al., 2013). Sleep loss, therefore, not only impairs the accurate assessment of emotional stimuli, but also an individual's own affective state. Indeed, the tracking of one's own affective state requires sensing the internal status of the body through interoceptive processing. This interoceptive processing in the brain requires the fidelity of these same affective brain regions, including the insula, medial prefrontal cortex, amygdala, and ACC (Craig, 2002). Thus, core regions of the affective brain form a cerebral viscerosensory network (Critchley and Harrison, 2013).

The affective brain regions underlying the viscerosensory network impaired by sleep loss have intimate afferent and efferent connections to bodily systems of adaptation, such as the autonomic, cardiovascular, endocrine, and immune systems (Pezzulo et al., 2015). Ascending lamina I spinothalamic tracts and vagus and glossopharyngeal nerves relay a wide variety of homeostatic information (mechanical, temperature, metabolic, immune, hormonal) to cerebral regions. These cerebral viscerosensory regions therefore form a fundamental representation of the current state of the body (Craig, 2002). Visceromotor regions, including the ACC, orbitofrontal cortex, and amygdala, then adjust bodily states through descending modulation of brainstem pre-autonomic nuclei (Shipley, 1982; Price et al., 2006), and through the generation of homeostatic emotions to modulate behavior (pain, hunger, thirst). This bidirectional communication between the visceral brain and the body is necessary for the regulation of not only the internal state of the body, but also for shaping behavior, cognition, and emotion required for adaptation (Craig, 2002; Critchley and Harrison, 2013).

Such findings support the hypothesis that sleep loss causes a state of central and peripheral body hypersensitivity due to impaired afferent-efferent communication between the affective brain and peripheral adaptive systems—that is, those within the body. Due to the privileged role of the brain as the central organ of allostasis and the afferent-efferent feedback between viscerosensory

networks and peripheral systems, the disruptive impacts of sleep deprivation on brain function may reverberate through peripheral adaptive networks.

Sleep Deprivation and the Body

Having established that sleep deprivation significantly disrupts the functional networks of the brain, including the viscerosensory network, this examination next turns to the issues of sleep loss and the peripheral systems of the body. Specifically, the following section focuses on the impairments in and interactions between two peripheral physiological systems and their relationships with central brain (dys)function, as examples of the central thesis premise.

This discussion begins with an examination of the effects of sleep deprivation on immune function and its connection to nociception and pain processing in the brain. Following this is a consideration of the autonomic nervous system, and its association with cardiovascular regulation and altered functional brain network activity under conditions of sleep loss. Two adaptive systems, the immune and autonomic nervous systems, are intimately related to both brain and body regulation, and therefore represent model systems for a test of the thesis model and hypothesis. Additionally, both the autonomic nervous system and immune system are known to be modulated by both the presence and absence of sleep (Irwin et al., 2006; Imeri and Opp, 2009; Tobaldini et al., 2017; Zoccoli and Amici, 2020). Furthermore, due to the importance of these systems in networks of allostasis, sleep loss-related disruption holds implications for physiological function and chronic disease, including chronic pain and cardiovascular disease (Smith et al., 2000; Jackowska and Steptoe, 2015).

The Immune System and Pain

Sleep and the immune system are intimately interconnected at both brain and body levels, having likely co-evolved (Preston et al., 2009; Besedovsky et al., 2019). Inflammatory factors act as sleep regulatory molecules, and sleep affects both the timing and pattern of immune activity (Imeri and Opp, 2009). Injection of pro-inflammatory cytokines in humans, including interleukin-6 (IL-6), increases the amount of slow-wave sleep (Opp, 2005).

Both acute and chronic sleep deprivation increase systemic inflammation, including increased levels of circulating pro-inflammatory cytokines such as IL-6, and impair host defense (Moldofsky et al., 1989; Everson, 1993; Redwine et al., 2000; Shearer et al., 2001; Hong et al., 2005; Irwin et al., 2006; Vgontzas et al., 2007), an effect that is reversed by slow-wave rich sleep (Dimitrov et al., 2004). Indeed, lengthened slow-wave sleep duration during infection confers a significant survival benefit (Toth et al., 1993). Furthermore, elevated levels of IL-6 and other pro-inflammatory cytokines have consistently been found in populations suffering from sleep disturbances, such as chronic pain, narcolepsy, sleep apnea, insomnia, and depression (Vgontzas et al., 1997; Yokoe et al., 2003; Prather et al., 2009a; Okun et al., 2013).

This evidence shows that sleep and immune function are bidirectionally related. Both sleep and sleep deprivation modify immune function in the body, and inflammatory signaling molecules are involved in the regulation of sleep under normal and pathological conditions, demonstrating the role of the immune system in allostasis.

Supportive of the embodied framework of this thesis in which sleep loss-related changes in the activity of allostatic systems contribute to disease, inflammation is a significant factor in the development of pain, a connection that may be potentiated by sleep loss. Pain is the prototypical homeostatic emotion (Craig, 2003), and therefore, is an optimal target for the current hypothesis that sleep deprivation alters stress-related brain-body coordination.

Pain is constructed by the brain from ascending interoceptive afferents conveying viscerosensory and viscerochemical changes in body state. These signals project to registration sites within the brainstem and to subcortical and cortical sensory and homeostatic regulatory centers in the affective brain. Pain is both a specific sensation and a felt emotion, one that drives homeostatic behaviors (Craig, 2002; Craig, 2003; Pollatos et al., 2012).

Because of their overlapping connections to the physiology of allostasis, sleep and pain are bidirectionally related. Pain is highly comorbid with sleep disturbances, both of quality and quantity, and especially of NREM sleep (Smith et al., 2000; Lavigne et al., 2004; Smith and Haythornthwaite, 2004; Ohayon, 2005; Onen et al., 2005). Sleep disruption is also known to causally increase pain sensitivity, assessed both subjectively and objectively.

For example, sleep loss increases nociceptive sensitivity in rodent models, linked in part to alterations in descending brain dopaminergic inhibition of nociceptive afferents (Hicks et al., 1978; Ukponmwan et al., 1984; Onen et al., 2000; Onen et al., 2001; Nascimento et al., 2007; Skinner et al., 2011; Sardi et al., 2018). In humans, sleep loss increases pain sensitivity (Lentz et al., 1999; Roehrs et al., 2006; Schuh-Hofer et al., 2013; Faraut et al., 2015), and recovery sleep following sleep loss reverses this hypersensitivity (Faraut et al., 2015).

Therefore, sleep is anti-nociceptive, whereas sleep deprivation is pro-nociceptive. However, the exact mechanisms underlying the pain-modulatory function of sleep and sleep loss remains largely unknown, including interactions with immune and brain function.

Inflammation appears to be a significant factor in the development of pain, leading to the hypothesis that increased inflammation due to sleep deprivation may promote a state of pain hypersensitivity. Supporting this hypothesis, the application of pro-inflammatory cytokines causally results in hyperalgesia and allodynia (Cunha et al., 1992; McMahon et al., 2005).

In chronic pain, a condition of high allostatic load and sleep disturbance (Smith et al., 2000), increased circulating levels of pro-inflammatory cytokines and decreased levels of anti-inflammatory cytokines are observed. Crucially, this pattern overlaps with that caused by sleep deprivation, suggesting that sleep loss-induced inflammation contributes to pain conditions.

While there are several sites at which sleep deprivation-enhanced inflammation influences pain (peripheral nociceptors (Ren and Dubner, 2010), sensory ganglia (Dublin and Hanani, 2007;

Miller et al., 2009), glial cells (Sandiego et al., 2015), sympathetic nervous system (Elenkov et al., 2000)), one pathway through which inflammation can alter pain sensitivity is the brain.

Cytokines are bidirectionally transported from brain-to-blood and blood-to-brain, a potential pathway through which peripheral inflammation can communicate with and alter the function of pain networks in the brain (Chen et al., 2000; Dantzer et al., 2008; Banks, 2015). Indeed, increases in peripheral pro-inflammatory cytokines alter corticostriatal function through reduced activity within the nucleus accumbens and connectivity with ACC (Harrison et al., 2009; Eisenberger et al., 2010), two important regions involved in the processing and modulation of pain (Craig, 2003; Critchley et al., 2004; Navratilova and Porreca, 2014). Interestingly, activity within the nucleus accumbens, involved in the descending regulation of pain signals, is known to be reduced by sleep loss in rodents. This connection leads to the current hypothesis that the increased inflammation due to sleep deprivation in humans increases pain in part through an impairment of striatal inhibition of ascending pain signals.

Supporting this hypothesis and linking to a role in the development of chronic pain, activation of brain cytokine signaling pathways within the thalamus and nucleus accumbens is observed in animal models of chronic pain (Apkarian et al., 2006). Furthermore, experimentally induced tonic pain by way of peripheral inflammation can be inhibited by activating dopaminergic neurons in the nucleus accumbens (Altier and Stewart, 1999). Conversely, upregulation of pro-inflammatory cytokines in the nucleus accumbens impairs opioid-based pain relief (Wu et al., 2014).

These findings linking changes induced by sleep deprivation in central pain processing in the brain and circulating peripheral inflammation, bolster the embodied framework of this thesis. The altered activity in the affective brain and the immune system, rather than being independent manifestations of sleep loss-increased allostatic load, are causally interrelated. Together, they represent a remodeling of physiological priorities resulting from increased allostatic load with increased pain as the subjective expression of this state.

Having established independent links between (1) sleep loss and pain, (2) sleep loss and inflammation, and (3) inflammation and pain, the current hypothesis is put forth. This hypothesis states that sleep deprivation-induced increases in circulating pro-inflammatory cytokines alter pain processing in the brain, resulting in an increased subjective pain experience. No study to date has examined this question in any species, a question addressed in **Chapter 3**.

The Autonomic Nervous System and Cardiovascular Function

In addition to the immune system, the autonomic nervous system (ANS) is another main governing system utilized in the control of allostasis, enacting commands by the affective brain (though several ANS processes can operate independently of the brain). Importantly, the ANS forms an interface between the brain and other peripheral adaptive systems. As a result, the ANS stands to play an especially instrumental role in manifesting sleep-dependent regulation, and under conditions of sleep loss, a vulnerable pathway through which homeostatic dysfunction can take place (Nance and Sanders, 2007; Valenza et al., 2019).

Sleep and wakefulness are characterized by different patterns of autonomic balance. During sleep, compared to wakefulness, parasympathetic (PNS) activity dominates and sympathetic (SNS) activity is reduced This pattern is required to reallocate energy away from SNS-dependent waking processes, such as motor activity and cardiovascular activation and to promote sleep homeostasis (Tobaldini et al., 2017; Zoccoli and Amici, 2020). On the other hand, sleep loss amplifies SNS activity and decreases PNS activity (Kato et al., 2000; Holmes et al., 2002; Zhong et al., 2005; Vaara et al., 2009; Franzen et al., 2011), though studies have found an increase in PNS activity (Lusardi et al., 1999). One reason for this discrepancy in the autonomic patterns observed in extended wakefulness is the instability of the ANS. Because sleep loss is a mixed state, representing both the absence of sleep and the presence of sustained wakefulness, these states compete for resources and this competition is reflected by unstable ANS activity. In other words, sleep deprivation-increased PNS activity (Lusardi et al., 1999) may reflect the current dominance of sleep-promoting homeostasis, while increased SNS activity (Kato et al., 2000; Holmes et al., 2002; Zhong et al., 2005; Vaara et al., 2009; Franzen et al., 2011) represents temporary resurgence of wake-related activity. Therefore, the pattern of ANS activity can be considered a proximate representation of the current state-priorities of the organism under unstable conditions of sleep loss.

The ANS adjusts physiological variables in response to the demands of sleep and sleep loss across several physiological systems, including the cardiovascular system (Critchley et al., 2001; Critchley, 2005; Amiya et al., 2014; Valenza et al., 2019). For example, during NREM sleep, heart rate and blood pressure are reduced, and heart rate variability increases with opposite patterns during rapid eye-movement (REM) sleep. These changes are an expression of continuous autonomic modulation of the cardiovascular system (Somers et al., 1993; Trinder et al., 2001).

The cardiovascular system, under moment-to-moment control by the ANS, is not only modulated by sleep, it is particularly affected by sleep loss. For example, short sleeping and poor sleep quality are associated with a greater incidence of hypertension and cardiovascular disease (Stokes 3rd et al., 1989; Gangwisch, 2014; Pepin et al., 2014; Jackowska and Steptoe, 2015). Additionally, experimental manipulations of sleep using partial or total sleep deprivation consistently increase blood pressure (Lusardi et al., 1999; Kato et al., 2000). Such evidence suggests that altered autonomic modulation of the cardiovascular system under conditions of sleep loss may link the increasing societal rates of sleep deficiency and cardiovascular disease, though the exact mechanisms remain largely unknown (Wolk et al., 2005).

One potential mechanism linking sleep loss, the ANS, and cardiovascular function is the brain. There are reciprocal (efferent and afferent) connections between the peripheral ANS and central brain (Yasui et al., 1991; Critchley et al., 2001; Valenza et al., 2019). Neural control of the autonomic modulation of the cardiovascular system involves a network of viscerosensory brain regions that map and also instigate cardiovascular changes through the ANS. This network includes the anterior insula, ACC, ventromedial prefrontal cortex, amygdala, and medial prefrontal cortex, demonstrating significant overlap with the affective brain (Pool and Ransohoff, 1949; Yasui et al., 1991; Oppenheimer et al., 1992; Dampney, 1994; Gianaros et al., 2008).

Evidence from both human and animal experiments demonstrates the role of this network in autonomic-dependent cardiovascular regulation. In animals, direct stimulation of these regions, including the amygdala (Dampney, 1994), cingulate (Pool and Ransohoff, 1949), insula (Yasui et

al., 1991; Oppenheimer et al., 1992), and medial prefrontal cortex (Pool and Ransohoff, 1949), produces changes in blood pressure. Similarly, in humans, both the activity in and connectivity between these same regions are required for the event-related reactivity of arterial blood pressure (Gianaros et al., 2008). Building on this evidence, it is predicted that sleep loss-related dysfunction within this viscerosensory brain network produces changes in cardiovascular function through its control of the ANS.

This final section of the introduction therefore establishes that: (1) sleep deprivation affects cardiovascular function, particularly by an increase in blood pressure, (2) sleep deprivation modifies sympathetic/parasympathetic balance, generally by an increase in sympathetic tone, (3) the ANS regulates cardiovascular function on a moment-to-moment basis, and (4) the ANS is under the control of the central nervous system including a network of viscerosensory brain regions.

However, the mechanistic pathway through which insufficient sleep alters cardiovascular functioning remains unclear. In **Chapter 4**, this unresolved hypothesis is addressed, namely that one pathway through which sleep deprivation instigates changes in cardiac and vascular functioning is through an altered relationship with central brain cardiovascular and autonomic control networks.

Dissertation Aims and Predictions

Causal relationships within and between the brain and the body are well-recognized as essential for allostasis. However, a multi-system examination of allostatic interactions under conditions of sleep deprivation, fitting the embodied model of the thesis, has yet to be investigated. This is relevant considering the increasing recognition of multi-system interactions in the etiology of many common first-world diseases (McEwen and Wingfield, 2003; Karatsoreos and McEwen, 2011), and separately, the increasing erosion of sleep time in developed nations (CDC, 2015).

Targeting these unresolved issues, this thesis seeks to test the **overarching hypothesis that homeostatic dysfunction is observed across multiple brain and body systems under conditions of sleep loss caused by allostatic overload, and furthermore, that these systems are intimately interrelated, rather than independent.** Three aims flow from this overarching hypothesis:

Aim 1: The first aim sets forth the hypothesis that sleep deprivation impairs brain function and network architecture, with cognitive, affective, and physiological consequences. Forming the basis for this discussion will be a review of neuroimaging studies of sleep deprivation in humans (subsequent **Chapter 2**).

Aim 2: The second aim seeks to test the hypothesis that, in addition to the central brain, sleep deprivation causes dysfunction in peripheral adaptive systems as a reaction to and result of increased allostatic load. The experiment addressing this hypothesis will test the prediction that the sleep loss-increased levels of circulating pro-inflammatory cytokines contribute to increased nociceptive pain state, assessed both objectively (within pain networks of the brain), and

subjectively (participant ratings) (**Chapter 3**). That is, an assessment of body, brain and mental state.

Aim 3: The third aim tests the hypothesis of sleep loss-related impairments in central brain, peripheral body and mental states in a different model system—that of the cardiovascular system. Addressing this will be an experiment testing the hypothesis that sleep loss confers an increased risk of cardiovascular dysfunction, including increased blood pressure, through disruption of central brain viscerosensory network control of the ANS and increased mood instability (**Chapter 4**).

II. The Sleep Deprived Human Brain

Introduction

Without sleep, our cognitive and emotional abilities become markedly disrupted. What are the neural changes underlying these abnormalities? What do these alterations tell us about the pervasive link between sleep disruption and numerous neurological and psychiatric disorders?

There are at least three motivating reasons to build an accurate account of how sleep deprivation (SD) affects the human brain. First, from a neurobiological perspective, it is important to characterize which networks in the human brain are vulnerable or resilient to the effects of insufficient sleep and to understand how such SD-induced changes (such as regional or network increases or decreases in activity or changes in functional connectivity) explain the maladaptive changes in behavior that are associated with SD. Of importance, SD does not simply represent the absence of sleep and the functions attributed to it. Rather, the sleep-deprived state is a composite of numerous detrimental factors, including extended wakefulness, as well as the absence of sleep. It is therefore insufficient only to develop an understanding of the functional benefits of sleep and then to reverse-infer an understanding of the neural and behavioral changes that would be expected following a lack thereof. Second, it is necessary to determine how comorbid sleep disruption — present in all major neurological and psychiatric conditions, including schizophrenia, Alzheimer disease, anxiety disorders and addiction disorders (Benca, 1996; Wulff et al., 2010)— contributes to or results from these disorders and may thus be a target for disease treatment and/or prevention. Third, from a societal standpoint, such scientific evidence informs debates regarding sleep recommendations for both public and professional health policies in light of the acknowledged sleep-loss epidemic that now pervades industrialized nations (CDC, 2015).

This Review seeks to move closer to these goals. We provide a focused overview of the impact of SD on the human brain across five functional domains: attention; working memory; positive, reward-related affect; negative affect; and hippocampus-dependent memory. Drawing on neuroimaging studies, we explore the neural signatures underlying phenotypic changes in cognition and affect following experimental SD. Moreover, we present examples of how these findings afford mechanistic insights into clinical disorders associated with disturbed sleep. The Review is necessarily focused on acute (24–48-hour) SD unless otherwise specified, as most neuroimaging studies to date are restricted to these time frames. Nevertheless, the issue of acute versus chronic sleep loss is discussed in more detail in **Box 1**.

Attention and Working Memory

Attention

One cognitive ability that is especially susceptible to sleep loss is attention, which serves ongoing goal-directed behavior (Durmer and Dinges, 2005). Performance on attentional tasks deteriorates in a dose-dependent manner with the amount of accrued time awake, owing to

Box 1: Acute versus chronic sleep deprivation and inter-individual variability

A well-characterized feature of both acute sleep deprivation (SD) and chronic partial sleep restriction is a dose-dependent effect on task performance, especially in the domain of attention. The greater the amount and/or the longer duration of SD, the worse the accumulating attention deficit (Belenky et al., 2003; Fox and Raichle, 2007). Thus, attentional impairment may be strongly coupled with extended wakefulness and with sleep pressure. These objectively measured impairments in performance are distinct from increases in subjective ratings of sleepiness following SD, which depend on the form of SD applied; for example, sleepiness increases as acute SD continues but does not always increase as chronic sleep restriction continues (Van Dongen et al., 2003). Thus, the physiological response to sleep loss may depend to some degree on the form of SD.

Regardless, the brain processes that mediate these cumulative deficits remain largely uncharacterized. For example, is there a brain region or set of brain regions involved in, or associated with, the tracking of sleep pressure (Porkka-Heiskanen et al., 1997; Kaufmann et al., 2016), or are there processes that track sleep pressure locally in a use-dependent manner within individual neuronal ensembles (Van Dongen et al., 2011)? Sleep pressure-related molecules, such as adenosine, and the hypothalamic system governing the switch mechanism between sleep and wake (Saper et al., 2010) are logical candidates for the chemical signaling and network mediation of this prototypical dose-dependent attentional impairment with sleep loss. In humans, neuroimaging analysis has revealed that association cortices, especially in the frontoparietal attention network, are particularly sensitive to sleep pressure, whereas subcortical thalamic and basal ganglia brain regions seem to be more affected by circadian processes (Muto et al., 2016).

A second behavioral feature of SD that is poorly defined at the whole-brain level is a phenotypic difference in vulnerability to SD-associated cognitive impairments (Van Dongen et al., 2004; Habukawa et al., 2007; Preston et al., 2009; Mollicone et al., 2010; Rattenborg et al., 2016). Approximately one third of participants show minimal impairments in sustained attention under SD conditions, and this seems to be a reliable, stable trait. By contrast, one third of participants manifest a severely vulnerable phenotype, showing marked attentional impairments. Moreover, it seems that differential vulnerability to the effects of acute sleep loss on attention is, in part, heritable (Sämann et al., 2010; Kuna et al., 2012). Adding further complexity, the extent of an individual's cognitive impairment also depends on which cognitive domain is tested (Frey et al., 2004). Thus, although performance impairments following SD within any given cognitive domain are highly reliable within the same individual, the degree of impairment is not necessarily reliable across cognitive domains within the same individual. The underlying brain correlates that differentiate these stable intra-individual and inter-individual differences are unclear, but the functional integrity of the frontoparietal attention network and genetic influences on sleep and circadian regulation are probably key factors (Cui et al., 2015).

increasing sleep pressure (Borbély, 1982; Belenky et al., 2003; Van Dongen et al., 2003). The prototypic impairments on such tasks are known as ‘lapses’ or ‘microsleeps’, which involve response failures that reflect errors of omission (Belenky et al., 2003; Van Dongen et al., 2003; Durmer and Dinges, 2005). More specifically, attentional maintenance becomes highly variable and erratic (with attention being sustained, lost, reestablished, then lost again), resulting in unstable task performance (Durmer and Dinges, 2005). Although the focus of this Review is sleep loss, it should be noted that daytime circadian alerting signals interact with SD, resulting in exponentially scaling attentional impairment with extended wakefulness (for reviews, see (Borbély, 1982; Goel et al., 2013)). Nevertheless, the cumulative amount of extended time spent awake predicts lapses

in attention with acute SD and with chronic partial sleep restriction (the latter occurring across many nights; (Van Dongen et al., 2003)) (**Box 1**). Why some individuals are more or less vulnerable to these attentional impairments following SD than others is less well understood.

An increasingly clear picture is emerging of how brain function related to attentional tasks is altered by acute SD. Reductions in functional MRI (fMRI) signal in the dorsolateral prefrontal cortex (DLPFC) and intraparietal sulcus while performing attentional tasks are a robust and reliable consequence of SD (Drummond et al., 1999; Thomas et al., 2000; Chee et al., 2008; Tomasi et al., 2009; Chee and Tan, 2010; Chee et al., 2010; Chee et al., 2011; Czisch et al., 2012) (**Fig. 1**). Indeed, sleep loss not only decreases task-related activity in these frontal and parietal regions but also diminishes activity in, and connectivity with, the extrastriate visual cortex during visuospatial attention tasks (Chee and Tan, 2010; Chee et al., 2010; Chee et al., 2011). The behavioral consequences of these neural changes are reflected in deficiencies in attending to one specific stimulus while ignoring distractors (Chee and Tan, 2010; Chee et al., 2010; Kong et al., 2012) or deficits in top-down allocation of attentional resources, such as orienting to a location where a target is expected to appear (Mander et al., 2008; Chee et al., 2011). Beyond attentional focus at any particular moment, sleep loss impairs the capacity to sustain attention over time (Durmer and Dinges, 2005). Here again, reductions in activity in the DLPFC and intraparietal sulcus contribute to attentional performance failure (Drummond et al., 1999; Thomas et al., 2000; Chee et al., 2008; Chee and Tan, 2010; Czisch et al., 2012; Muto et al., 2016).

In addition, thalamic activity during sustained attention is altered with SD, suggesting that the thalamus could be an interacting node in this SD-affected network. However, the profile of activity change within the thalamus is not uniform. Some studies demonstrated greater activity under conditions of sleep loss (Portas et al., 1998; Chee and Choo, 2004; Habeck et al., 2004; Choo et al., 2005; Tomasi et al., 2009; Chee and Tan, 2010), whereas others have reported intermittent periods of diminished thalamic activity (Chee et al., 2008; Chee and Tan, 2010). These discrepancies may be understood in the context of performance and of the cortical arousal that thalamic activity provides. When thalamic activity is elevated under conditions of sleep loss, attentional performance is frequently maintained but, when substantial reductions in thalamic activity are observed, lapses in attention are common (Thomas et al., 2000; Durmer and Dinges, 2005; Chee et al., 2008; Chee and Tan, 2010). The thalamus therefore represents a pivotal gating hub through which alterations in brainstem ascending arousal signals affect cortical attentional networks under SD conditions. Extant data therefore support a model in which the instability in ascending arousal-promoting input contributes both to the emergence of canonical attentional lapses during SD and the erratic, unpredictable expression of these lapses over time (Doran et al., 2001; Durmer and Dinges, 2005) (**Fig. 1**). Notably, the observed reductions in thalamic activity are not present during attentional lapses in well-rested conditions (Chee et al., 2008), suggesting that increased homeostatic sleep pressure may have a unique role in lapses following SD.

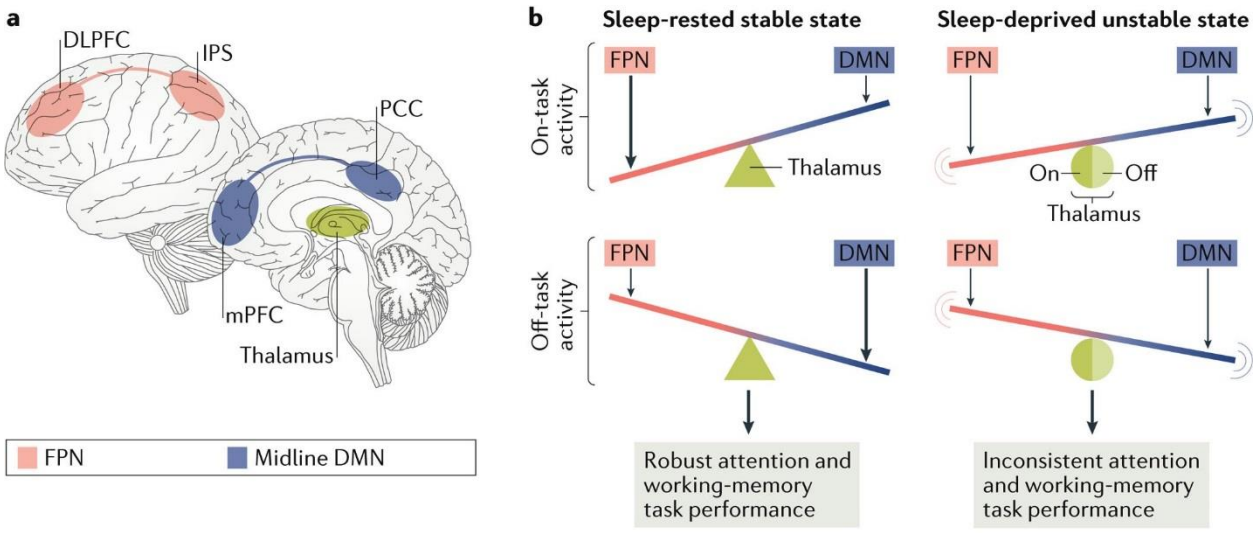


Figure 1: Sleep loss, attention and working memory. a | Brain regions and networks associated with attention and working memory (frontoparietal network (FPN); red), arousal (thalamus; green) and the default mode network (DMN; blue) are affected by sleep deprivation. The DMN is a collection of brain areas, including midline frontoparietal regions, that often disengage when an individual performs an externally driven, goal-directed task and then re-engage when an individual stops performing that task. Suppression of the DMN is necessary to mobilize appropriate on-task brain networks to achieve successful goal-directed behavior (Greicius et al., 2003), unless that task requires access to internally stored relevant information such as autobiographical memories or previously learned predictive cues (Mander et al., 2008; Spreng and Grady, 2010; Spreng et al., 2010). Brain regions across multiple brain networks, including the dorsolateral prefrontal cortex (DLPFC), intraparietal sulcus (IPS), thalamus, medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC), are differentially altered by sleep loss. **b** | In the sleep-rested state, there is reciprocal inhibition between task-related FPN activity and DMN activity, supported by sustained ascending arousal input from the thalamus. This leads to consistent attentional and working-memory performance. In the sleep-deprived state, there is unstable reciprocal inhibition between task-related FPN activity and DMN activity, and erratic ascending arousal activity influencing thalamic activity. As a result, there is reduced task-related FPN activity and intermittent intrusions of DMN activity during task engagement. The behavioral consequence is variable and/or impaired attention and working-memory performance, worsening with lowered thalamic activity and improving with higher thalamic activity.

More recently, instability of the default mode network (DMN) has been implicated in attentional impairments with SD. Several reports describe an inability to fully disengage midline anterior and posterior cortical regions of the DMN during both selective and sustained attentional task performance under SD conditions (Drummond et al., 2005; Tomasi et al., 2009; Czisch et al., 2012) (**Box 2**; **Fig. 1**). Moreover, increased DMN activity during on-task performance for both sustained and selective attention tests was predictive of slower and less accurate performance by the participants (Drummond et al., 2005; Tomasi et al., 2009).

Box 2: The unrested resting brain: sleep loss and resting-state activity

In addition to inducing differences in task-related brain activity, sleep deprivation (SD) also affects resting-state brain connectivity. Resting-state networks are typically derived from the connectivity profile of spontaneous fluctuations in functional MRI (fMRI) signal and are thought to reflect the brain's intrinsic functional architecture that emerges without external task demands (Raichle, 2010). Across these networks, SD is associated with reduced connectivity within the default mode network (DMN), the dorsal attention network, and the auditory, visual and motor networks (Yeo et al., 2015). In fact, measures of abnormal change in whole-brain connectivity enable classification of an individual as either being rested or sleep deprived with more than 60% accuracy (Lavie et al., 1979; Kaufmann et al., 2016).

Of the many different discrete resting-state networks, the DMN has demonstrated alterations under SD in two specific ways. First, connectivity between individual nodes of the DMN is decreased following one night of total SD (Yeo et al., 2015), especially between midline anterior and posterior nodes of the DMN (Wang et al., 2015). Thus, SD degrades network integrity within the DMN, functionally uncoupling individual nodes. The second consequence of SD is the failure of the DMN to remain functionally distinct from other normally dissociable networks. Under normal rested conditions, the DMN is functionally decoupled from the brain's attentional networks — when the latter is engaged, the former is disengaged, and vice versa (Mellman et al., 2002; Fox et al., 2005; Rupp et al., 2012; Huelsmann et al., 2019). Both total SD and partial sleep restriction (Chuah et al., 2009; Diekelmann and Born, 2010; De Havas et al., 2012; Kuna et al., 2012; Basner et al., 2013; Blumberg et al., 2020) impair this adaptive decoupling, and this impairment is further associated with participants' cognitive vulnerability to SD (Yeo et al., 2015).

The resting profiles of individual regions, specifically the amygdala and the thalamus, have also been examined following SD (Shao et al., 2013). Similar to task-related connectivity changes (see **Fig. 3**), decreases in resting-state connectivity of the amygdala with regulatory and executive regions of the dorsolateral prefrontal cortex and anterior cingulate cortex have been demonstrated after 36 hours of SD. Conversely, resting-state connectivity of the amygdala with the posterior cingulate cortex and the precuneus increases after SD, possibly reflecting the role of these posterior midline cortical regions in regulating the balance between internally and externally directed cognition (Leech and Sharp, 2014). Resting-state connectivity between the thalamus and cortical regions is also generally decreased following sleep loss, especially thalamic connectivity with anterior and posterior cingulate regions of the DMN (Yeo et al., 2015) and with attentional and executive regions of the superior and medial prefrontal cortex (Shao et al., 2013). As reductions in thalamocortical connectivity have also been demonstrated during sleep onset (Tagliazucchi et al., 2013), it remains possible that resting-state measures in sleep-deprived individuals capture mixed states of sleep and wake, comprising rapid transitions into sleep (known as microsleeps), while some degree of wake-like behavioural responding is nevertheless maintained (Vyazovskiy et al., 2011). This concern is emphasized by reports that have demonstrated reduced functional coupling between midline anterior and posterior nodes of the DMN under conditions of SD and once individuals have entered non-rapid eye movement sleep (McEwen and Wingfield, 2003; Horovitz et al., 2009; Jovanovic et al., 2012). Overall, the limited evidence to date suggests that SD triggers reductions in the brain's intrinsic connectivity profile, ultimately leading to a breakdown of network integrity and a loss of adaptive functional segregation. These alterations may precede or exacerbate changes in task-related responses observed after sleep loss, and might predict the magnitude of cognitive and emotional impairments elicited by SD. A combination of task-related and resting-state fMRI studies of SD seems to be a fruitful avenue for future work, although accurate assessment of sleep or wake states inside the MRI scanner is warranted to assure the absence of microsleeps.

Why the sleep-deprived brain suffers this unstable ‘flip-flop’ gating between on-task

functional activity and off-task DMN activity remains unclear. One candidate is abnormal activity of the right frontoinsular cortex, which controls the switch between DMN activity and task-related activity (Sridharan et al., 2008). Consistent with this thesis, the salience-detection network, which includes the frontoinsular cortex, demonstrates reduced activity during the performance of attention tasks following sleep loss (Ma et al., 2015). Together with changes in the frontoparietal attention network described above, these insula-based alterations may explain SD-induced impairments in attention to novel, salient targets (Gumenyuk et al., 2011) and in the tracking of salient moving targets (Gazes et al., 2012). Nevertheless, trial-by-trial analyses of fMRI signal during salience-detection and attention tasks will be required to test this hypothesis.

Working Memory

Working memory — the neural basis of which overlaps anatomically with the attention system — is also impaired by SD (Turner et al., 2007; Drummond et al., 2012). Deficits in both working-memory and attention tasks have been found to correlate with reductions in DLPFC and posterior parietal activity (Chee and Choo, 2004; Habeck et al., 2004; Choo et al., 2005; Chee and Chuah, 2007; Lythe et al., 2012). As during attention tasks, fluctuations in thalamic activity (Chee and Choo, 2004; Habeck et al., 2004; Choo et al., 2005) and inappropriate perseverance of DMN activity are observed during working-memory task performance under SD conditions (Chee and Choo, 2004; Choo et al., 2005; Chee and Chuah, 2007). In addition, the degree of aberrant, on-task DMN activity predicts the severity of working-memory impairment in sleep-deprived individuals (Chee and Choo, 2004; Choo et al., 2005; Chee and Chuah, 2007) (**Fig. 1**). Inappropriate gating of on-task relative to off-task network control may therefore provide one common mechanism underlying deficits in both attention and working memory caused by SD.

Also mirroring changes observed during attention tasks, alterations in thalamic activity and connectivity predict impairments in working-memory performance under SD conditions, most likely owing to the key role of the thalamus in cortical arousal. For example, increased connectivity between the hippocampus, the thalamus and the DMN predicts higher subjective sleepiness and is associated with worse working-memory performance under sleep-loss conditions (Lei et al., 2015; Chengyang et al., 2017). By contrast, increased connectivity between the thalamus and the precuneus under SD conditions predicts greater recovery of working-memory performance, relative to the sleep-rested state. This finding is consistent with the hypothesis that, in the context of SD, the brain exhibits compensatory neural activity that can enable partial recovery of the performance of certain behaviors (Yoo et al., 2007a; Chengyang et al., 2017).

Beyond reductions in activity in frontoparietal areas, extrastriate (visual) cortical regions also demonstrate reduced signal during visual working-memory task performance under conditions of sleep loss (Habeck et al., 2004; Choo et al., 2005; Chee and Chuah, 2007). Recent evidence suggests a causal contribution of this regional decrease in task-related activation to performance deficits, as transcranial magnetic stimulation (TMS) targeted to the extrastriate cortex of sleep-deprived individuals improved visual working-memory performance, restoring it back to baseline levels (Luber et al., 2008; Luber et al., 2013). Remarkably, repeated TMS application every 6 hours for 18 hours to extrastriate regions maintained working-memory performance for up to 3 days without sleep (Luber et al., 2013). However, TMS stimulation intervention in the context

of SD is not always consistent, and thus the reproducibility of such effects remains unclear (Luber et al., 2007). Should a robust method for intervention emerge, it may have real-world relevance — for example, for professions in which attentive focus is crucial and SD is common (aviation or the military).

Reward and Incentive Processing

Reward Processing in the Sleep-Deprived Brain

The mesolimbic reward system is a network of interconnected brain regions, including the midbrain ventral tegmental area, striatum and regions of the PFC. The ventral tegmental area provides dopaminergic innervation to the striatum, which is connected to, and regulated by, areas of the PFC, particularly by the medial PFC (mPFC) and inferior orbitofrontal cortex (OFC) regions, guiding motivated actions and learning. This system has repeatedly been demonstrated to show sensitivity to SD, leading to alterations in motivated behaviors, such as risk taking, sensation seeking and impulsivity (**Fig. 2**).

In rats, SD disrupts dopaminergic function by modifying dopamine receptor sensitivity and availability in basal ganglia regions (Tufik, 1981; Volkow et al., 2012). Humans deprived of sleep for one night show increases in ventral striatum activity in a mixed monetary gamble task during the anticipation and receipt of monetary rewards (Venkatraman et al., 2007; Mullin et al., 2013). Activity in affect-related regions in the frontal cortex that are associated with valuation and viscerosensory functions, including the insula and mPFC, is also substantially increased following SD (Venkatraman et al., 2007; Mullin et al., 2013).

Together, these findings suggest that subcortical reward-related regions of the brain, together with related cortical regions coding salience and valuation, seem to become hypersensitized by the state of acute SD. However, the degree to which fMRI signal amplitude tracks reward magnitude in these subcortical and cortical regions does not seem to differ between rested and deprived conditions (Libedinsky et al., 2011). Rather, SD triggers a generalized increase in reward sensitivity that impairs reward discrimination accuracy, such that the brain becomes less capable of accurately coding incremental increases in reward value, from low to high.

Consistent with this thesis, fMRI signal in the mPFC, OFC and anterior insula cortex in sleep-deprived individuals does not accurately discriminate between trials involving monetary reward and punishment values and trials involving no monetary reward or punishment (Venkatraman et al., 2007; Mullin et al., 2013). This inaccurate representation of reward value within frontal regions is similarly observed during the outcome phase of incentive decision trials (Venkatraman et al., 2007; Mullin et al., 2013), suggesting a further failure to update accruing reward history and probability. Inaccurate coding of reward and/or punishment valence in the PFC following sleep loss may therefore prevent the ability to update changing incentive value (weights) of reinforcing stimuli over time (Venkatraman et al., 2007; Mullin et al., 2013) (**Fig. 2**). This would further contribute to non-optimal reward-dependent decision making and actions. Fitting this profile, sleep-deprived individuals performing the Iowa Gambling Task make more-risky decisions and assign greater weights to more-recent rewards (Killgore et al., 2006; Olson et al.,

2016). This pattern indicates a failure to appropriately integrate rewards and their accumulating value over time following SD, reflecting temporally shorter-sighted updating of rewards.

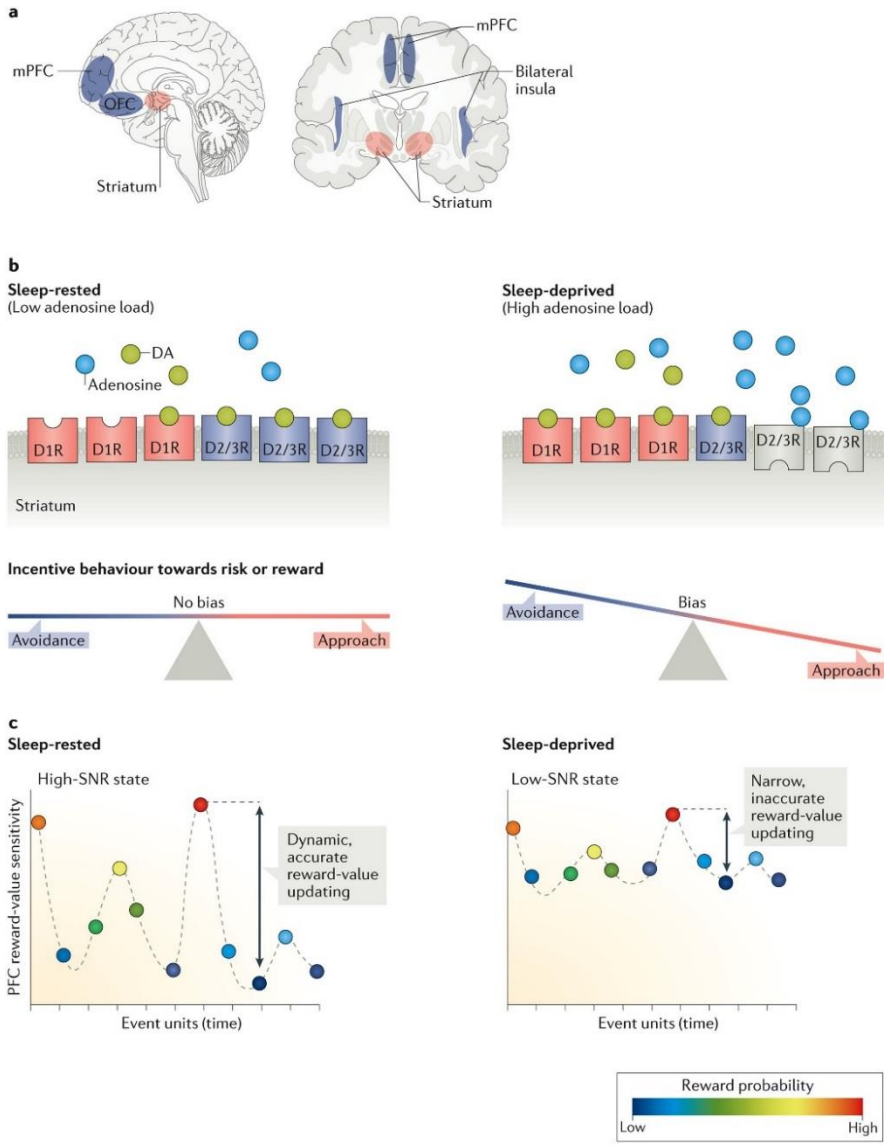


Figure 2: Sleep loss and incentive processing. a | Reward-relevant brain regions that are affected by sleep deprivation (SD) include cortical regions (blue) such as the medial prefrontal cortex (mPFC), insula and orbitofrontal cortex (OFC), and the subcortical region of the striatum (red). **b** | Increased adenosine load (blue circles) associated with SD triggers downregulation of dopamine (DA) D2 and D3 receptors (D2/3Rs), resulting in decreased receptor membrane expression within the striatum (internalized receptors; grey). Consequently, there is a greater ratio of D1R to D2/3R availability, and the relative increase in striatal D1R activation by DA (green circles) under SD conditions is proposed to increase risk-related and reward-related approach behaviours, shown in the see-saw imbalance. **c** | SD further disrupts incentive processing within PFC regions and thus is proposed to result in a lower signal-to-noise ratio (SNR) under SD conditions (represented by a narrow dynamic range of PFC sensitivity). This consequentially impairs the ability to accurately map and update changing value or reward probability (coloured dots) over time — such as that involved in reinforcement learning, ultimately contributing to non-optimal incentive-based decision making.

In addition to deficits in the activation of frontal reward circuits following SD, studies have revealed that responses of the striatum and amygdala to emotionally pleasurable or hedonic images (Gujar et al., 2011), as well as desirable food stimuli (Greer et al., 2013), are amplified with SD. Moreover, the same studies reported failures of discriminatory signaling of stimulus valence (for example, discriminating desirable from undesirable foods) in the anterior insula, mPFC and OFC, of sleep-deprived participants. Furthermore, sleep-deprived individuals were more likely to rate neutral pictures as positive (Gujar et al., 2011), or to express a greater desire for high-calorie foods (Greer et al., 2013). That is, participants fail to accurately disambiguate non-rewarding from rewarding stimuli when sleep deprived, shifting towards an over-generalized reward bias, even for normally less-rewarding stimuli.

Although current results of reward processing point to effects in the mPFC, OFC and insular cortex, together with the basal ganglia, other affective regions, such as the limbic regions of the medial temporal lobe and executive lateral regions of the PFC, should not be discounted. Equally important, not all human SD studies have reported amplified basal ganglia activity during reward-related decision making (Menz et al., 2012), an inconsistency returned to below.

Beyond monetary reward processing, another behavioral feature sensitive to a lack of sleep is impulsivity. Impulsivity is a multifactorial construct, and different types of impulsivity can manifest in behaviorally different ways. Nevertheless, impulse control is central to many incentive-based decision processes (Bechara et al., 2000; Franken et al., 2008). Changes in impulsivity may therefore contribute to alterations in reward decision making and risk taking that occur following SD.

In tasks that require either cued motor response execution or withholding, often referred to as a Go/No-Go task, participants with either partial sleep restriction (6 hours of sleep per night for 4 consecutive nights) or one night of total sleep deprivation showed considerably lower response inhibition and cognitive control, produced more frequent errors of inhibition, and exhibited slower learning of cue–incentive associations (Acheson et al., 2007; Ayalon et al., 2009; Cedernaes et al., 2014; Demos et al., 2016) (**Fig. 2**).

However, in delay-discounting tasks, which require participants to choose between small, immediate rewards relative to large, delayed rewards, SD does not seem to alter impulsivity — a lack of an effect that is similarly observed in probabilistic discounting tasks, in which participants choose between small but certain rewards and large but uncertain rewards (Acheson et al., 2007; Menz et al., 2012; Libedinsky et al., 2013; Demos et al., 2016). Similarly, total acute SD and partial sleep restriction (4 nights of 6 hours of sleep per night) do not affect delay discounting or probabilistic discounting (Acheson et al., 2007). However, measures of effort discounting (whereby rewards are discounted according to the effort required to attain them) are affected by SD. Under conditions of sleep loss, low-effort rewards elicit even greater reward-related brain activity than high-effort rewards, relative to sleep-rested conditions (Menz et al., 2012).

Similarly, inconsistent effects of SD have been reported using the Balloon Analogue Risk Task (BART) — a standard test of reward-seeking, risk-taking behavior that involves impulse control. Partial sleep restriction (1 night of 5 hours of sleep) results in a significant increase in the tendency to overinflate a computerized balloon to obtain more reward (Acheson et al., 2007; Rossa et al., 2014). By contrast, total SD for a single night resulted in no change in BART performance by male participants but a decrease in risky overinflation by female participants (Demos et al.,

2016) (for a review, see (Womack et al., 2013)). Studies that focus on this and other specific features of impulsivity, such as response withholding, while systematically keeping other factors constant (for example, reward magnitude, reward delay and sex) are necessary to develop a clearer understanding of sleep loss and risk-taking impulsivity.

Inconsistencies in the effects of SD on incentive processing are not limited to the domain of impulsivity. Some reports using incentive tasks that do not involve impulsivity (wherein participants simply expect or receive rewards and/or punishments without needing to resist impulsive responses) have also failed to show significant differences in mesolimbic brain activity and/ or behavior caused by SD (Libedinsky et al., 2011; Menz et al., 2012; Libedinsky et al., 2013). Instead, these studies only demonstrate effects on an individual-participant level (Libedinsky et al., 2011; Menz et al., 2012; Libedinsky et al., 2013). One possible explanation is that some studies employ mixed gambles, combining gains and losses in the same trial. This may limit the ability to identify differences in processing of gains or losses independently (Greer et al., 2016). A second possibility is that individual differences may interact with the effects of SD, thus obscuring group-level significance if not explicitly considered. A recent study (Greer et al., 2016) found that individuals expressing a variant of the dopamine transporter that was previously associated with differences in synaptic dopamine availability showed different striatal reward responses following sleep loss. Unlike the control group, only participants with trait-elevated synaptic dopamine exhibited greater striatal responses during reward anticipation following SD than when well rested. This suggests that phasic dopamine availability is increased in these individuals, thereby elevating SD-associated increases in the reward-responsivity of the nucleus accumbens. Thus, effects of sleep loss on reward processing seem to be sensitive to several interacting factors, including sex and trait genetics.

Sleep Deprivation and Dopamine Function

With these nuances taken into account, studies to date nevertheless indicate that SD significantly increases the tendency of reward sensitivity, risk taking and impulsivity, and disrupts reward-value updating and integration. One possible mechanism that might explain these increases in approach and consummatory behavior is altered dopamine signaling, which is associated with extended wakefulness perhaps more than with the absence of sleep itself. Several lines of evidence support this dopaminergic framework (**Fig. 2**).

First, dopamine is associated with arousal; innately higher levels of dopamine predict lower sleep propensity (Perogamvros and Schwartz, 2012). Second, rodent studies have established that wake-promoting stimulant drugs such as amphetamine seem to operate in part by blocking dopamine metabolism, thereby increasing dopamine transmission and thus arousal. Third, depleting catecholamines, including dopamine, reduces wake propensity, lowering vigilance and inducing sleep (McCann et al., 1993) (although interestingly the antihypertensive and antipsychotic reserpine, which reduces catecholamine function, has nominal effects on sleepiness; (Curb et al., 1988).

Changes in dopamine receptors may also contribute to alterations in reward-driven behavior following SD. Positron emission tomography (PET) ligand studies have reported that one night of total SD downregulates the availability of dopamine D2 and D3 receptors (D2/3Rs) in

both the dorsal striatum (which includes the caudate and putamen) and ventral striatum (Volkow et al., 2012) (**Fig. 2**), consistent with earlier PET studies showing general hypometabolism in the basal ganglia following SD (Wu et al., 1992). PET-assessed downregulation of D2/3Rs in the ventral striatum predicted fMRI-measured decreases in thalamic activity during an attentional task (Tomasi et al., 2015), as did the degree of generalized hypometabolism in the basal ganglia after SD (Wu et al., 1992; Wu et al., 2006). Besides the relevance of this change for objective attention and working-memory performance, the degree of D2/3R downregulation similarly predicts subjective sleepiness under SD conditions (Volkow et al., 2012). This result suggests that sleep pressure might be indexed by the levels of different dopamine receptors; consistent with this, adenosine accumulates with increasing time awake, activating A2A receptors and thereby driving D2R internalization (Elmenhorst et al., 2007; Volkow et al., 2012). Moreover, agonists of the A2A receptor and D2R demonstrate allosteric interaction such that A2A receptor agonists decrease the affinity of D2Rs for their agonists, including dopamine (Bonaventura et al., 2015). Thus, adenosine accumulation, which is associated with increased time spent awake, may decrease D2/3R activity by at least two possible mechanisms: by increasing D2/3R internalization and by reducing binding of dopamine to D2Rs (**Fig. 2**).

That SD is associated with a downregulation of D2/3Rs may initially seem to contradict the SD-associated increases in neural and behavioral reward sensitivity described above. However, one tenable (and experimentally testable) hypothesis that may reconcile this paradox involves D1Rs. Specifically, decreases in D2/3Rs could result in an imbalance of dopamine receptor availability, leading to the remaining D1Rs becoming disproportionately stimulated by the same amount of presynaptically released dopamine (**Fig. 2**). Outside the context of SD, in rodents, this imbalance causes greater approach behavior to food rewards (Richard and Berridge, 2011) and increases the addictive potential of cocaine (Park et al., 2013) (behavioral consequences that, notably, have both been independently associated with SD; (Brondel et al., 2010; Berro et al., 2014). Furthermore, the increase in striatal fMRI signal elicited by reward incentives under SD conditions seems to principally reflect D1R action (Knutson and Gibbs, 2007). Thus, SD-associated decreases in D2/3R availability may, by indirectly increasing dopamine binding to the remaining D1Rs, increase approach-driven and reward-driven behavior and fMRI-indexed striatal activity (**Fig. 2**). The neural and behavioral consequences of sleep loss on incentive processes also offer mechanistic and therapeutic insights into the conditions of obesity, addiction and substance use (**Box 3**).

Box 3: Clinical insights concerning sleep loss and emotion

Positive emotion

The interaction between sleep deprivation (SD) and dopaminergic reward functioning is relevant for clinical conditions involving sleep disruption and dysfunction of reward or dopamine signaling. In alcohol addiction, ~60% of alcohol-addicted individuals seeking treatment complain of insomnia symptoms in the 6 months leading up to intervention, and more than half of these individuals report using alcohol under the (erroneous) assumption that it helps to regulate sleep (Brower et al., 2001). In addition, alcohol-addicted individuals who report insomnia are more likely to relapse than those without sleep problems (Brower et al., 2001). Thus, sleep loss seems to be an important factor in the development and/or maintenance of addiction disorders associated with changes in mesolimbic dopamine function and a vulnerability factor predisposing individuals to fail in efforts of abstinence. Of concern, sleep disruption in childhood predicts subsequent substance use in later adolescence stages (Wong et al., 2004).

There is now also considerable epidemiological evidence linking sleep disruption and obesity (Van Cauter et al., 2007). Experimental work has characterized the associated causal mechanisms, including changes in the appetite-regulating hormones leptin and ghrelin, and in the central brain mechanisms that regulate appetite and food choice selection (Markwald et al., 2013). Decreased activity in decision-regulating regions of the frontal cortex following SD, combined with enhanced subcortical mesolimbic sensitivity, leads to increased desire for, and selection of, high-calorie food items (Greer et al., 2013). Indeed, compared with a sleep-rested state, experimental sleep restriction increases calorie consumption and promotes weight gain (Markwald et al., 2013).

Notably, the alterations in brain function that have been associated with obesity overlap with those observed in drug addiction (Mellman et al., 1997; Michaelides et al., 2012; Gao et al., 2015); for example, a reduction of dopamine D2 and D3 receptors is observed in both. Such findings warrant a deeper consideration of insufficient sleep as a possible predisposing factor underlying obesity and drug addiction. If true, targeted sleep restoration may aid by re-engaging neural mechanisms that govern adaptive food choices and craving, respectively.

Box 3 continued: Clinical insights concerning sleep loss and emotion

Negative emotion

A recent model has proposed that sleep loss prevents the normal overnight lowering and thus restoration of central adrenergic signaling that normally occurs during rapid eye movement (REM) sleep, leading to heightened noradrenergic tone and thereby an over-generalized responsivity within select affective salience networks (Goldstein and Walker, 2014). The translational ramifications of this model are well exemplified in post-traumatic stress disorder (PTSD), which is associated with sleep disruption and fragmentation, decreases in total and REM sleep duration (Germain, 2013), and nocturnal hyperarousal (Breslau et al., 2004). In parallel, people with PTSD show marked alterations in noradrenergic activity (Bosch et al., 2013; Germain, 2013; Nunn and Samson, 2018), including the lack of normal overnight reduction in noradrenaline levels (Mellman et al., 1995). The REM-sleep model may help to understand these co-occurring features. Specifically, decreases in night-time, total and REM sleep quantity, and increases in high-frequency electroencephalogram (EEG)-assessed activity (associated with hyperarousal) during REM sleep, are proposed to contribute to daytime hyperadrenergic tone in PTSD. Moreover, persistent hyperadrenergic activity during wakefulness could reduce subsequent night-time sleep quantity and quality, producing a vicious cycle. Crucially, this cycle could lead to over-generalized emotional sensitivity within the affective salience network of the brain that is innervated by noradrenaline, including the amygdala, and the viscerosensory regions of the insula and anterior cingulate cortex, as already reported in a meta-analysis of functional MRI studies in PTSD (Etkin and Wager, 2007; Vandewalle et al., 2009; Shao et al., 2014). This same model could explain how nocturnal use of prazosin — an α1-adrenergic receptor antagonist commonly prescribed for PTSD — can, in some cohorts, restore the duration and quality of total and REM sleep, and decrease PTSD symptoms (Raskind et al., 2003; Raskind et al., 2007; Taylor et al., 2008; Calohan et al., 2010). Our framework may also account for the excessive emotion reactivity and impaired emotional discrimination observed in PTSD (Jovanovic et al., 2009), and the maladaptive generalization of fear responses to commonly non-threatening stimuli (Jovanovic et al., 2009). Interestingly, PTSD-like symptomatology was experimentally induced by selective deprivation of REM sleep in healthy individuals; this manipulation resulted in increased autonomic sensitivity to previously extinguished conditioned stimuli (that is, heightened sensitivity) and impaired autonomic discrimination of conditioned from safety signals (decreased emotional specificity) (Spoormaker et al., 2012; Menz et al., 2013). Conversely, the amount and EEG quality of REM sleep predicts participants' ability to accurately discriminate between threat and safety signals (indicating improved emotional specificity) (Karatsoreos and McEwen, 2011; Marshall et al., 2014).

Aversive Stimulus Processing

Sleep loss reliably triggers changes in negative (aversive) emotional processing, including irritability, emotional volatility, anxiety and aggression (Horne, 1985; Dinges et al., 1997; Zohar et al., 2005; Anderson and Platten, 2011; Minkel et al., 2012), as well as suicidal ideation, suicide attempts and suicide completion (Bernert and Joiner, 2007; Kamphuis et al., 2012; Stubbs et al., 2016). These findings suggest that SD alters specific process domains, including basic affective reactivity, as well as emotional discrimination and emotional expression, which are more complex.

Aversive Stimulus Response

Early neuroimaging studies focused on the effects of SD on responsivity to rudimentary aversive stimuli; for example, one night of SD was shown to result in a 60% increase in amygdala reactivity to negative images, such as weapons, venomous snakes and spiders, and mutilations (Yoo et al., 2007b) (**Fig. 3**). This signature of amygdala hyper-reactivity has since been replicated following sleep restriction (4 hours of sleep per night for 5 nights) (Motomura et al., 2013) and in individuals with poor sleep quality, as assessed at their homes (Prather et al., 2013). Notably, amygdala hyper-reactivity has been reported during rapid, subconscious viewing of faces expressing fear after sleep restriction (Motomura et al., 2013), indicating that this amplified limbic reactivity can occur subliminally, independent of conscious, deliberative cognition (Motomura et al., 2013).

One possible mechanism underlying such amygdala hypersensitivity involves a loss of regulatory control, resulting in contextually inappropriate amygdala reactivity (Goldstein and Walker, 2014). Decreases in functional connectivity between top-down control regions of the mPFC and the amygdala have been reported following a night of total SD or 5 nights of partial sleep restriction (4 hours sleep per night), as well as in participants reporting less than 6 hours of habitual sleep (Yoo et al., 2007b; Chuah et al., 2010; Killgore, 2013; Motomura et al., 2013; Prather et al., 2013) (**Fig. 3**).

SD further alters the brain anticipation of cued emotional experiences. For example, one night of SD elevates cue-evoked activity in the amygdala, anterior insula and anterior cingulate cortex in anticipation of impending emotional picture slides, similar to those described above (Goldstein et al., 2013), and also increases anticipatory responses of the peripheral autonomic nervous system (Franzen et al., 2009).

Interestingly, inter-individual differences in trait anxiety levels predict the size of these SD-induced increases in anticipatory brain activity, with highly trait-anxious individuals expressing the largest increases in pre-emptive anterior insula activity (Goldstein et al., 2013). The latter result is of clinical relevance to anxiety disorders (which have been associated with apprehensive worry about future events) for at least three reasons: first, highly trait-anxious individuals are already those at greatest risk for developing an anxiety disorder; second, excessive anticipatory insula activity is a characteristic of most anxiety disorders (Simmons et al., 2006; Etkin and Wager, 2007; Simmons et al., 2011); and third, sleep disruption is a recognized symptom of anxiety disorders (Harvey, 2011).

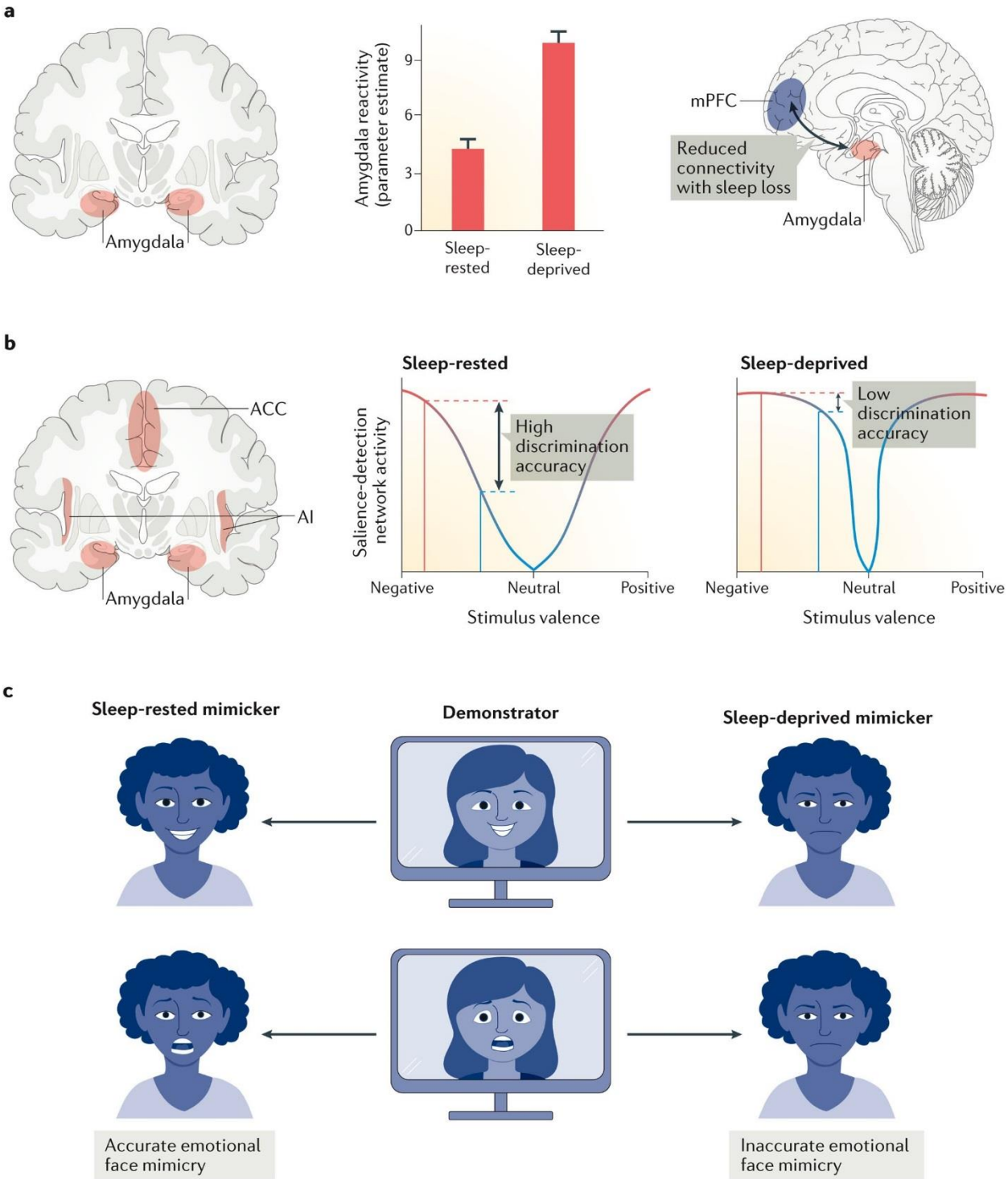

a
Amygdala
Amygdala reactivity (parameter estimate)
9
6
3
0
Sleep-rested
Sleep-deprived
mPFC
Reduced connectivity with sleep loss
Amygdala
b
ACC
AI
Amygdala
Sleep-rested
Salience-detection network activity
High discrimination accuracy
Negative
Neutral
Positive
Stimulus valence
Sleep-deprived
Low discrimination accuracy
Negative
Neutral
Positive
Stimulus valence
c
Sleep-rested mimicker
Demonstrator
Sleep-deprived mimicker
Accurate emotional face mimicry
Inaccurate emotional face mimicry

Figure 3: Sleep loss and aversive processing. a | Sleep deprivation (SD) amplifies amygdala reactivity (red) in response to negative emotional stimuli and decreases associated amygdala–medial prefrontal cortex (mPFC) connectivity (blue). **b** | SD alters sensitivity of the salience-detection network (the amygdala, anterior cingulate cortex (ACC) and anterior insula (AI)) to varying levels of emotional stimuli that range in valence strength (*x* axis in the two graphs) from negative (red) to neutral (blue) to positive (red). Under sleep-rested conditions (left graph), there is a wide and dynamic range of salience-detection sensitivity, resulting in the ability to accurately discriminate between degrees of emotional salience (tall vertical difference arrow; discerning emotional (red vertical line) from neutral stimuli (blue vertical line)). By contrast, SD (right graph) is proposed to trigger a narrowing and thus more nonspecific detection sensitivity range, impairing the ability to accurately discriminate between degrees of emotional salience (short vertical difference arrow). This loss of 'net neutrality' results in over-generalized emotional sensitivity, wherein an otherwise largely neutral stimulus (blue vertical line) is inappropriately registered as 'emotional' by the salience-detection network; further observed in biased emotional ratings of neutral stimuli. **c** | A downstream behavioral consequence of these central brain changes, in combination with disrupted peripheral autonomic nervous system feedback of visceral body information, could lead to inaccurate and even absent outward expression of emotions. This is supported by experimental evidence demonstrating that individuals deprived of sleep fail to register emotional faces shown to them on a screen and consequently are unable to accurately mimic the emotional face expressions of these target faces themselves.

Emotion Discrimination and Expression

An additional phenotype of the sleep-deprived human brain emerges when participants are challenged with the more complex task of disambiguating between varied emotional signals. In sleep-rested participants, regions of the amygdala, insula and cingulate that are associated with salience detection can discriminate between stimuli of different emotional strengths. By contrast, in sleep-deprived participants, these regions demonstrate a saturated and flattened response to emotional stimuli. Sleep-deprived individuals therefore express a generalized excess of emotional sensitivity, with impairment in emotional discriminatory specificity (Goldstein and Walker, 2014) (**Fig. 3**). For example, sleep-deprived individuals are less accurate at rating facial expressions within the moderate range of emotional strength (Van Der Helm et al., 2010) and rate neutral images as more emotionally negative (Daniela et al., 2010). SD further impairs the accurate discrimination of threatening (antisocial) from affiliative (pro-social) facial signals (Goldstein-Piekarski et al., 2015), again promoting an overall bias towards increased (inaccurate) perception of negative threat.

Recent work has begun to uncover the neural basis of these impairments in emotional discrimination (**Fig. 3**). Consistent with the failure to accurately code positive, reward incentive signals (described above), one night of SD impairs the discrimination of faces expressing negative emotions by viscerosensory regions of the anterior insula and anterior cingulate cortices, and to a degree, the subcortical amygdala (Goldstein-Piekarski et al., 2015). Similarly, sleep loss results in generalized, nonspecific increases in amygdala activity (as measured by fMRI or electroencephalography) in response to aversive and neutral emotional pictures (Alfarra et al., 2015; Simon et al., 2015).

These findings have led to the proposal that SD causes a state of central and peripheral emotional hypersensitivity that prevents emotional reactivity from being appropriately graded

(Goldstein and Walker, 2014). As a result, SD impairs the afferent–efferent communication between the brain and body, which is crucial for the 'embodied' mapping of, and disambiguation between, different emotions. The consequence is a behavioral phenotype of indiscriminate emotional generalization, or blunting, consistent with poor signal-to-noise balance during emotional processing (Goldstein and Walker, 2014) (**Fig. 3**).

Such blunting may disrupt not only the internal mapping of an individual's own affective state but also the ability to simulate the feelings of others. Supporting this hypothesis, sleep-deprived individuals and habitually poor sleepers demonstrate impaired empathetic sensitivity, which involves sensing the emotional state of individuals in picture slides (Guadagni et al., 2014; Guadagni et al., 2017). Sensing the internal homeostatic status of the body, and thereby tracking one's own affective state, requires interoceptive processing within a network that includes the insula, mPFC and amygdala (Craig, 2002). Sleep loss degrades the sensitivity of this network, leading to a shift of the homeostatic set point used to register, and differentiate between different levels of, emotional salience (Goldstein-Piekarski et al., 2015). In an emotional face discrimination task, sleep-deprived individuals showed overgeneralized activity in viscerosensory brain regions and impaired autonomic cardiac discrimination (indexed using moment-by-moment changes in heart rate; (Goldstein-Piekarski et al., 2015)). Compared with when they were rested, individuals who were sleep deprived also showed a weaker correlation between the activity of the central and peripheral autonomic (cardiac) systems. Thus, SD compromises the faithful discrimination of emotional signals within higher-order emotional brain regions by inducing network hypersensitivity and, in tandem, disrupts the 'embodied' reciprocity between viscerosensory central and peripheral autonomic processing of complex social signals. As a result, there can be a loss of sensitivity in detecting, and accuracy in recognizing, emotions.

It is possible, although currently untested, that this same disruption within and between central and peripheral autonomic nervous system networks explains why sleep-deprived adults (Minkel et al., 2012) and infants deprived of a day-time nap (Berger et al., 2012) show incongruent or even absent outward expression of emotions (**Fig. 3**). Individuals restricted to 4 hours of sleep for a single night also demonstrate a slowing of reactive facial expressions in response to emotional stimuli (Schwarz et al., 2013). Emotional vocalizations following short-term sleep restriction have similarly been reported to be blunted (McGlinchey et al., 2011).

Thus, multiple modes of emotional expression are diminished by insufficient sleep; a feature pertinent considering that emotional expressions are all influenced in some manner by the autonomic nervous system, specifically the vagal system (Porges, 2001). This same explanatory model of central–peripheral autonomic decoupling may offer further mechanistic insights into the recognized associations between reduced sleep and decreased interpersonal functioning (Killgore et al., 2008), increased antisocial interactions (Sadeh et al., 1995), a lower understanding of relationship concerns (leading to greater interpersonal conflict; (Gordon and Chen, 2014)) and, in children and adolescents, increased peer-related problems, such as hyperactivity and inattention, conduct problems, and peer disagreement (Hödlmoser et al., 2010; Baum et al., 2014).

Less understood are the cellular and molecular mechanisms underlying the emotional brain and body dysfunction that is caused by a lack of sleep. One proposed mechanism has centered on the heightened noradrenergic tone from the locus coeruleus (Siegel and Rogawski, 1988; Mallick and Singh, 2011; Goldstein and Walker, 2014); according to this hypothesis, sleep loss prevents

the normal overnight reduction in noradrenergic tone that usually occurs during rapid eye movement (REM) sleep (Siegel and Rogawski, 1988; Kametani and Kawamura, 1990; Marrosu et al., 1995). The resulting hypernoradrenergic tone may thus lead to heightened and over-generalized responsivity within the affective salience network that is innervated by noradrenaline: the amygdala and the viscerosensory cortical regions (Goldstein and Walker, 2014). Consequently, there may be a loss of specificity in affective signaling within this network, possibly helping to explain the SD-associated inaccuracy in emotional discrimination. This REM sleep model (Goldstein and Walker, 2014) offers several testable predictions regarding the reliable co-occurrence of sleep disruption (including REM sleep disruption) in clinical anxiety disorders (**Box 3**). However, noradrenaline alone is unlikely to be the sole neurochemical factor underlying the affective dysregulation caused by SD. Integrating changes in other sleep-dependent neurochemicals, such as dopamine, may provide a more accurate explanatory model.

Hippocampal Memory Processing

Many studies have characterized the beneficial impact of sleep on the post-learning, offline consolidation of hippocampus-dependent memories (for a review, see (Abel et al., 2013)). By contrast, few studies have explored the adverse effects of SD on this process (Abel et al., 2013); instead, the majority of such neuroimaging investigations have examined the impact of sleep loss on initial hippocampus-dependent memory encoding, on which we focus here.

In rodents, SD substantially decreases the ability to induce hippocampal long-term potentiation (LTP; an electrophysiological measure of neuroplasticity) and, if LTP is induced, the enhancement subsequently decays more rapidly (McDermott et al., 2003). Further, sleep loss reduces hippocampal synthesis of proteins associated with neuroplasticity and impairs hippocampal neurogenesis (Fernandes et al., 2015).

The extracellular build-up of the metabolic product adenosine during extended wake affects plasticity. High levels of adenosine disrupt intracellular cAMP signaling in rodents and decreases hippocampal AMPA and NMDA receptor signaling; all of which are necessary for stable LTP (Abel et al., 2013). Given that adenosine is cleared from the brain during sleep, these effects on plasticity may result from two mutually non-exclusive reasons: abnormally extended wake or a loss of sleep.

Building on these findings, early human neuroimaging and behavioral studies established that one night of SD impairs learning and encoding-related activity within the medial temporal lobe (Drummond et al., 2000), specifically the hippocampus (Yoo et al., 2007a) (**Fig. 4**). Moreover, selective deprivation of non-rapid eye movement (NREM) slow-wave sleep using auditory stimulation, which preserves total sleep time, also lowers encoding-related activity in the hippocampus and associated learning (Van Der Werf et al., 2009). Conversely, enhancing the power of NREM slow-wave activity, using transcranial stimulation, increases hippocampal learning ability after sleep (Antonenko et al., 2013), further supporting a causal role for slow-wave sleep in hippocampal memory encoding.

In addition, SD alters learning-related hippocampal connectivity. Functional coupling between the hippocampus and perceptual regions of the occipital (visual) cortex and nearby

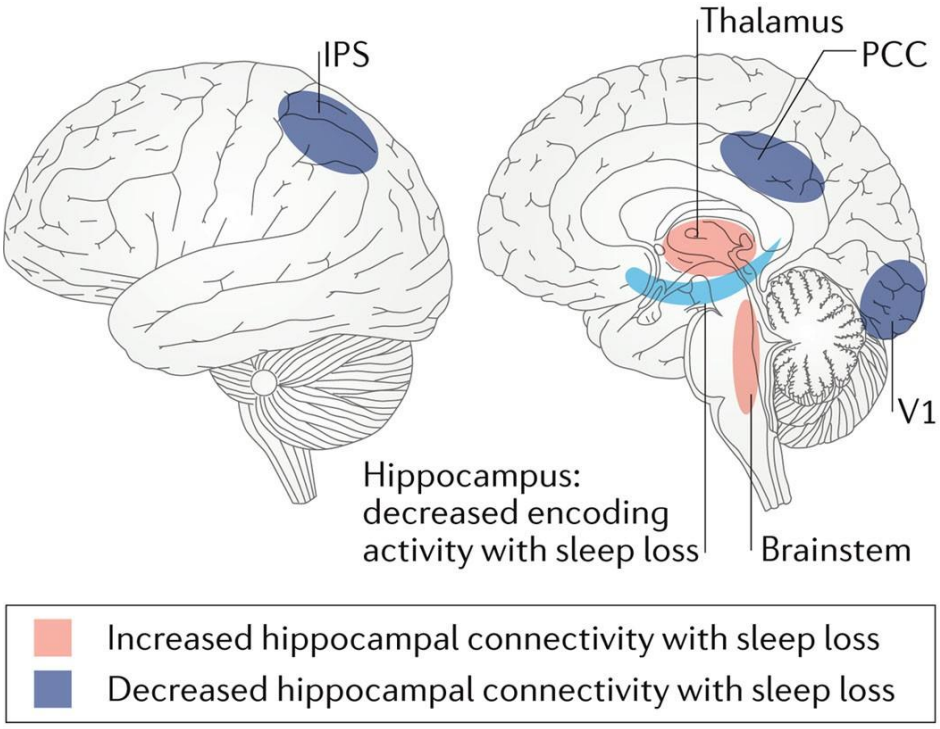


Figure 4: Sleep loss and hippocampal memory encoding. Sleep deprivation (SD) decreases encoding-related activity within the hippocampus (light blue), compared with normal sleep-rested conditions. Moreover, in sleep-deprived individuals, hippocampal connectivity with encoding-relevant cortical regions of the intraparietal sulcus (IPS), posterior cingulate cortex (PCC) and primary visual cortex (V1) (purple regions) during encoding is lower than in sleep-rested individuals. By contrast, hippocampal encoding-related connectivity with subcortical arousal regions of the thalamus and brainstem (red) after SD is increased.

regions in the medial temporal lobe during visual episodic-memory encoding is decreased under SD conditions (Yoo et al., 2007a) (**Fig. 4**). By contrast, SD is also associated with increases in hippocampal connectivity with subcortical arousal regions, including the brainstem and the thalamus (Yoo et al., 2007a) (**Fig. 4**). The latter observation has been interpreted as reflecting a compensatory effort to mobilize basic arousal networks, albeit insufficient to rescue behavioral performance (Yoo et al., 2007a).

A recent report has demonstrated that the structural morphology of the human hippocampus, and specifically the volume of the CA3–dentate gyrus subfield region, predicts the degree of vulnerability to the impact of SD on memory encoding (Saletin et al., 2016). Moreover, this same measure also predicted the amplitude of NREM slow-wave oscillations during recovery sleep and, by way of this mediating influence, determined how well memory-encoding ability was restored when assessed again after recovery sleep. Thus, human hippocampal subfield anatomy may represent a novel trait-like factor and potential biomarker of susceptibility of memory processing to, and recovery from, the disrupting effects of SD.

The hippocampus does not operate in isolation during memory encoding, however, but acts in a broad network of anatomically and functionally connected cortical regions. Some of these are proposed to participate in encoding memory representations themselves (for example, sensory perceptual regions), whereas others are involved in operations that support the act of encoding,

such as the DLPFC and posterior parietal regions, which are required for directed attention (Chee and Chuah, 2007). Consistent with this, human neuroimaging studies have revealed that SD is associated with larger-network impairments that co-occur or are functionally linked with deficits in hippocampus-dependent encoding of new memories. For example, SD for 24 hours decreases activity in regions of the DLPFC and posterior parietal cortex required for goal-directed attention during a visual episodic-memory encoding task (Chuah et al., 2009). Reductions in the activity of the scene-selective fusiform cortex following SD are less clear to interpret and may reflect impairment in the functional role of the visual cortex in processing visual scenes and/or the failure of the top-down control of attention by frontoparietal networks (Poh and Chee, 2017). Nevertheless, the size of the alterations in activity of all three of these cortical regions (frontal, parietal and occipital) predict the degree of memory impairment under SD conditions and the severity of attentional task lapses.

As with working-memory and selective attention tasks, significant differences in DMN activity within cortical regions have been reported during episodic-memory encoding following SD (Gujar et al., 2010). Indeed, the size of reductions and increases in the activity of the anterior cingulate and precuneus (which are both nodes of the DMN), respectively, discriminated sleep-deprived from sleep-rested participants with 93% sensitivity and 92% specificity (Gujar et al., 2010). Unstable control of the DMN might therefore be a common neural phenotype underlying deficits in various cognitive tasks (including attention, working memory and episodic memory) in the sleep-deprived human brain (**Box 2**).

Only one study to date has examined the underlying neurochemical basis of memory-encoding deficits associated with SD. Administration of an acetylcholinesterase inhibitor, which prolongs the central synaptic effects of acetylcholine, partially restored activity in frontoparietal and fusiform regions in sleep-deprived participants towards levels observed under sleep-rested conditions (Chuah et al., 2009) (**Fig. 4**). Interestingly, the greatest benefit of this acetylcholinesterase inhibitor treatment was observed in those individuals who, with SD, demonstrated the largest decreases in brain activity during a semantic judgement task and the worst performance in word recognition. That is, those most susceptible to sleep loss on these tasks were those who recovered most function after being treated with the drug.

Given that acetylcholinesterase inhibitors enhance attentional processes that support episodic memory (Pepeu et al., 2013) and directly affect sensory processing (Sato et al., 1987), some part of this benefit might be mediated by cholinergic influences on arousal. An alternative or additional plausible hypothesis is that the actions of the inhibitor facilitate hippocampal plasticity mechanisms that consequentially increase hippocampal engagement of sensory and attentional networks in the cortex. Accordingly, acetylcholinesterase inhibitors enhance activation of the visual and parietal cortices in sleep-deprived individuals during a visual short-term-memory task and, compared with placebo, improve task performance (Chuah and Chee, 2008).

At a translational level, impaired hippocampus-dependent memory encoding following sleep loss is relevant to several disorders and conditions that involve deficiencies in both sleep and memory encoding. Two such examples are ageing and dementia. Older, cognitively normal adults show marked impairments in NREM sleep, and these deficits are magnified in size in Alzheimer disease (Mander et al., 2016). Disruptions of NREM sleep and associated reductions in slow-wave activity and sleep spindles in older adults and, even more dramatically, in patients with Alzheimer

disease predict reductions in encoding-related activity in the hippocampus on the following day, which, in turn, predict the degree of learning impairment (Van Der Werf et al., 2009; Mander et al., 2012). Sleep disruption therefore may contribute to cognitive decline, and especially impairments in hippocampus-dependent memory processing, with ageing. This evidence raises the possibility that sleep restoration may be a novel therapeutic intervention, as well as a midlife preventative measure against age-related decline in hippocampus-dependent memory (for a more detailed discussion, see (Mander et al., 2016)).

Conclusions

Several insights emerge from this Review. First, SD triggers a complex set of bidirectional changes in brain activity and connectivity — depending on the specific functional operation and anatomical regions in question. Equally important, however, are moment-to-moment fluctuations in brain activity that occur during performance across the timescale of minutes, reflecting a neural phenotype of regional and network instability. This is especially apparent in the domains of attention and working memory. Second, the heterogeneous array of brain changes (averaged and moment-to-moment) results in an equally diverse set of disruptions in human behavior across nearly all domains of cognition and affect. Nested within this statement is another related subtlety: not all changes in brain function that are associated with sleep loss are maladaptive and thus represent deficiencies. Instead, some aspects of these neural alterations seem to correlate with preserved task performance, indicating that they may be compensatory and thus adaptive. That the human brain can compensate for SD to a certain degree seems tenable, given that individuals use compensatory effort and behavioral strategies (for example, talking or standing) when attempting to stay awake when sleep deprived. However, the extent and duration of compensatory brain function, which networks and associated operations they are in, and which behaviors are maintained as a consequence, remain poorly characterized. For example, do the effects of SD depend on interactions among hierarchies of functional brain networks, such that deficits or compensation in a fundamental, base-level network (for example, the attention network) dictates respective impairment (or compensation) in higher-level, dependent operations (such as intentional memory encoding or conscious emotional processing)?

Equally important, this Review reveals our current inadequacies of knowledge regarding the sleep-deprived human brain. For example, we have remarkably little understanding of the whole-brain consequences of long-term, chronic sleep loss, as most studies have focused on acute, total SD (**Box 1**). Such knowledge would be crucial considering that chronic partial sleep restriction, from weeks to years, is representative of (and thus relevant to) the sleep deficiency observed in the developed world. We also lack any comprehensive understanding of whether and how human brain networks may recover from acute and chronic sleep restriction. Are the underlying neural mechanisms that support recovery from these different forms of sleep loss the same, partially overlapping, or entirely separable? Relatedly, does neural recovery occur across the same time period or over a different temporal duration following different forms and doses of sleep loss? What types of recovery sleep stages and/or aspects of sleep physiology transact functional brain restoration following sleep loss? These questions are important from a societal and public-health perspective, both in professional circumstances in which the privation of sleep is rife (for example, in the military, in aviation and in medicine) and in subtler forms (for example,

the public trend of short sleep durations during the week followed by longer sleep durations at weekends).

Another key unresolved issue extends beyond the phenotypic between-participant differences in vulnerability to the neural and behavioral effects of SD within a cognitive domain (such as attention) (**Box 1**) and centers on emerging evidence suggesting within-participant, between-domain differences in vulnerability: an individual who is resilient to the effects of SD in one functional domain (such as attention) may conversely be vulnerable to that same dose of sleep loss in other functional domains (such as memory or emotion processing) (Frey et al., 2004). This suggests that different brain networks in the same individual may be differentially susceptible to sleep loss. These hypothetical within-subject differences in neural network vulnerability and resilience to SD have not yet been experimentally tested.

Finally, the basic scientific findings regarding sleep loss have not yet been routinely applied in the clinic, despite the examples that we describe in **Box 3**. Sleep abnormalities are robustly observed in every major disorder of the brain, both neurological and psychiatric. Sleep disruption merits recognition as a key relevant factor in these disorders at all levels, from diagnosis and underlying etiology, to therapy and prevention. More collaborative work between basic and clinical scientists in the field will be necessary to accomplish this goal. Notably, the answers to all these questions have perhaps never been more pressing considering the professional, societal and clinical implications that continue to scale in lockstep with the precipitous decline in sleep duration throughout industrialized nations.

III. The Pain of Sleep Loss: A Brain Characterization in Humans

Introduction

Sleep loss amplifies the experience of pain. Causal manipulations in animals demonstrate that sleep deprivation enhances nociceptive behavior (Lautenbacher et al., 2006). Experiments in humans establish that total (Schuh-Hofer et al., 2013), partial (Faraut et al., 2015), and selective sleep deprivation (Lentz et al., 1999; Roehrs et al., 2006) increase pain, including a lowering of pain thresholds (Schrimpf et al., 2015).

Recent reports implicate circulating inflammation as a potential factor modulating the impact of sleep loss on increased pain sensation. Increases in circulating proinflammatory cytokines, including interleukin-6 (IL-6), are associated with enhanced pain sensitivity following sleep deprivation (Mullington et al., 2010). Consistent with a participatory role in pain enhancement, injection of exogenous IL-6 in rodents causally results in hyperalgesia and allodynia (De Jongh et al., 2003). Linking to sleep, experimentally increasing IL-6 causes increases in non-rapid eye movement (NREM) sleep (Mullington et al., 2000; Hogan et al., 2003), suggesting a homeostatic interaction between NREM sleep physiology and inflammatory cytokine activity.

Despite robust links between sleep and pain, the central brain mechanisms underlying the impact of sleep loss on pain perception remain unknown, in any species. Moreover, whether such alterations in pain processing within the brain are significantly linked with changes in peripheral body inflammation, suggesting an embodied explanatory framework, is similarly uninvestigated. This brain-body link is of special relevance considering that proinflammatory cytokines can alter processing within the brain (Dantzer and Kelley, 2007). Finally, it is unknown whether more subtle, night-to-night variability in sleep quality in addition to quantity predicts consequential day-to-day changes in pain, impressing ecological relevance.

Although no reports have explored the brain basis of sleep loss-induced hyperalgesia, neuroimaging studies in non-sleep deprived individuals have established a pattern of functional magnetic resonance imaging (fMRI) activity in regions responsive to pain (Brown et al., 2011; Wager et al., 2013); for review, see (Tracey and Mantyh, 2007; Woo et al., 2017). These include primary and secondary somatosensory cortices that map noxious stimuli (Apkarian et al., 2005; Atlas et al., 2014). Activity within somatosensory cortex scales as a function of pain intensity, including at pain threshold (Coghill et al., 1999; Timmermann et al., 2001; Apkarian et al., 2005; Atlas et al., 2014).

Corticolimbic regions of the cingulate and insula are consistently activated by pain and are involved in the second-order mapping of internal state changes associated with pain (Craig, 2002). Subcortical regions, including spinal-afferent-receiving regions of the thalamus, as well as nucleus accumbens (NAcc), also show robust pain reactivity (Navratilova and Porreca, 2014). The NAcc in particular plays a role in encoding affective value and saliency, including that of pain (Redgrave et al., 2008; Schultz, 2013; Navratilova and Porreca, 2014), allowing the modulation of ongoing pain through descending brain and spinal cord pathways (Navratilova and Porreca, 2014).

This pain-reactive network provides a set of candidate-hypothesized ROIs to account for increased pain caused by sleep deprivation. Specifically, activity within regions related to the magnitude of experienced pain, including somatosensory cortex and thalamus should scale with the degree of enhanced pain following sleep loss. In contrast, higher-order evaluative regions of the insula, cingulate, and NAcc that play a role in the gating, integration, and relief from classification of pain signals, would conversely fail to appropriately modulate pain following sleep loss, evidenced by a reduction in activity.

Beyond changes in functional brain network activity associated with acute sleep deprivation, an additionally unanswered question centers on whether more subtle changes in sleep from one night to the next, within an individual, lead to ensuing daily fluctuations in pain sensitivity. This not only represents an extended test of the central sleep-pain hypothesis, complementing experimental acute sleep deprivation manipulations, but further determines whether such findings hold public health relevance. Previous survey studies have established that sleep disruption and pain are significantly linked (Afolalu et al., 2018). However, these studies use cross-sectional analyses at a single time point, and in clinical populations (e.g., chronic pain and/or insomnia) (Tang et al., 2012). It therefore remains unknown whether micro-longitudinal studies that examine changes in night-to-night sleep and day-to-day pain within an individual are significantly and predictively interrelated. Moreover, which features of sleep (e.g., duration, quality, efficiency) are the deterministic factors underlying the sleep-pain relationship remains similarly unknown (Edwards et al., 2008).

Building on this evidence, this chapter tests a set of interrelated hypotheses: (1) Acute sleep deprivation increases pain-related activity within the human primary somatosensory cortex and subcortical thalamus yet disrupts pain processing in regions of second-order limbic cortex and pain relief-associated regions of the NAcc. (2) These central brain changes are significantly related to increases in concomitant peripheral body inflammation following sleep loss, specifically circulating pro-nociceptive IL-6. (3) Outside of the laboratory, an additional experiment is performed to test whether ecologically typical nightly changes in sleep within individuals in a sample of the general population results in a similar lowering of pain thresholds, leading to daily increases in experienced pain.

Materials and Methods

Experimental Design

To test the experimental hypotheses, two related studies were performed: (1) an in-laboratory study and (2) an online study. The in-laboratory study involved 25 healthy adult participants enrolled in a counterbalanced, repeated-measures design involving two conditions: one night of sleep and one night of sleep deprivation (**Fig. 1A**). In each condition, participants performed a standardized thermal pain sensitivity assessment. Thermal pain thresholds were assessed outside of the fMRI scanner, with additional pain-experiential questions asked during the task inside the scanner (both described below).

In the sleep-deprived session, participants arrived at the laboratory at 10:00 P.M. and were continuously monitored throughout the enforced waking period. Activities during the sleep deprivation period were limited to use of the internet, Email, short walks, reading, movies of low emotionality, and playing board games, thereby providing a standardized regimen of waking activity without undue stress. Participants were also required to fast after 12 AM in both conditions in preparation for the drawing of serum. In the sleep-rested session, participants came to the laboratory at 8:00 P.M. and were prepared for an ~8 h in-bed polysomnographic night of sleep recording in the laboratory (11:00 P.M. to 7:30 A.M. ±30 min; details below). The following morning at ~8:30 A.M. (±60 min) in both conditions, participants had their blood drawn and underwent quantitative sensory testing outside of the MRI scanner to determine their pain threshold (described in detail below). Thereafter, participants performed a thermal pain sensitivity task in the fMRI scanner. These two sessions were separated by at least 7 d, with the order of the sleep-rested and deprived sessions counterbalanced across subjects.

In the online phase of the study, a separate cohort of 236 users of Amazon Mechanical Turk (MTurk) was assessed across 2 nights and 2 subsequent days, sleeping as they chose (**Fig. 1B**, described below). This allowed for a test of how natural night-to-night variability in sleep quality, efficiency, and duration was associated with consequential day-to-day changes in pain.

Studies were approved by the local human ethics committee, with all participants providing written informed consent.

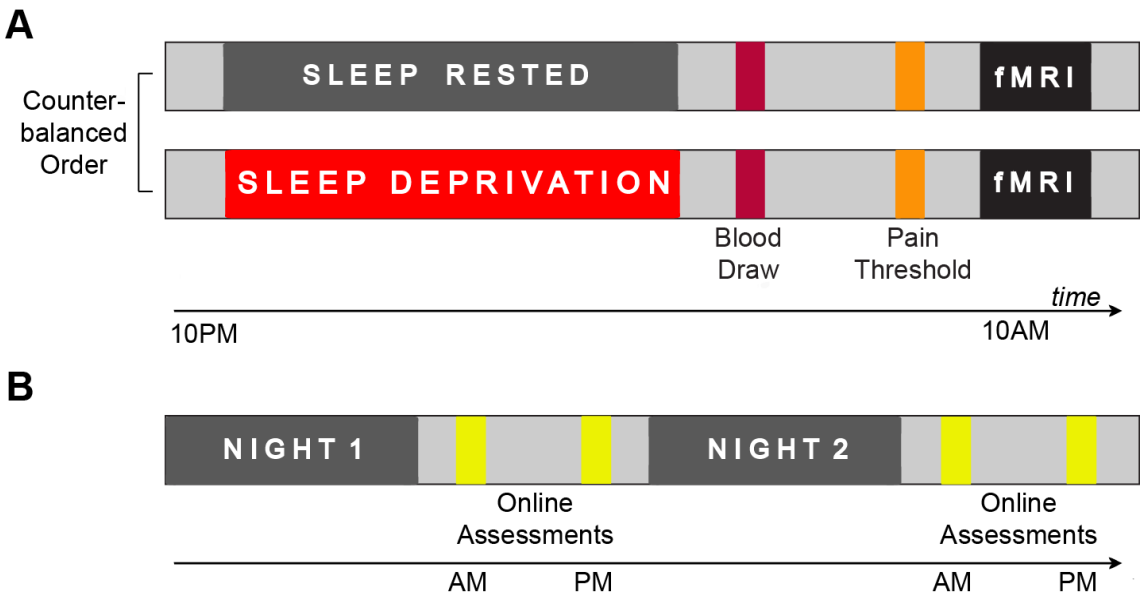


Figure 1. Experimental design. ***A***, Design of the in-laboratory repeated-measures counterbalanced study involving one night of sleep deprivation and one night of sleep, followed by a blood draw and an fMRI scanning session involving a pain-evoking task. ***B***, Design of the online study involving daily sleep diaries for two consecutive nights tracking habitual variations in sleep time, followed later by daily pain assessment.

Participants: In-laboratory Study

Twenty-five healthy adults, age 18–30 years (mean ± SD: 20.8 ± 1.95 years, 48% female) completed a repeated-measures crossover design (described above). Participants abstained from caffeine and alcohol for the 72 h before and during the entire course of the study and kept a normal sleep-wake rhythm (7–9 h of sleep per night with sleep onset before 1:00 A.M. in the morning and rise time no later than 9:00 A.M.) for the 3 nights before the study participation, as verified by sleep logs and actigraphy.

Exclusion criteria, assessed using a prescreening semi-structured interview, were as follows: a history of sleep disorders, chronic pain or pain disorder, current pain or injuries, neurologic disorders, autoimmune disorders, open and closed head injury, Axis I psychiatric disorders according to the DSM-IV-TR criteria (encompassing mental disorders, including depression, anxiety disorders, bipolar disorder, attention deficit disorder, and schizophrenia), history of drug abuse, and current use of antidepressant, psychostimulant, or hypnotic medication. Subjects who reported drinking 3 or more caffeine-containing beverages a day, such as caffeinated coffee, tea, or soft drinks, were excluded.

Finally, before their first session, participants underwent quantitative sensory testing to measure baseline thermal sensitivity. Two temperature levels were established for each participant to be used in subsequent fMRI pain tasks in both conditions: first, a lower temperature described as “warm, but not painful”; and, second, a higher temperature consistently described as “painfully hot” (corresponding to a 7/10 on a visual analog pain scale). These individualized temperatures were estimated using established psychophysical methods (described below). Crucially, by matching temperatures across experimental conditions, further comparisons of brain pain reactivity controlled for objective stimulus temperature. This importantly means that observed neural changes caused by sleep deprivation could not be due to subjective differences in pain experience elicited by objectively different stimulus temperatures.

To assess the degree of difference between the structured sleep schedule of the experiment and each participant's unrestricted sleep schedule, participants completed the Pittsburgh Sleep Quality Index upon study entry. This instrument contains questions relating to the bed time, rise time, and duration of sleep episodes across the past month (Buysse et al., 1989). Additionally, to better characterize recent sleep status, participants further completed sleep logs 3 days before each experimental session.

Participants conformed to the structured sleep schedule during the month before the experiment, including across the 3 d before the experimental session. Specifically, in the month leading up to the study, participants reported average bed times before 1:00 A.M. (mean: 12:07 A.M., SD ± 44 min), rise times before 9:00 A.M. (mean: 8:25 A.M., SD ± 41 min), and sleep duration lengths between 7 and 9 h (mean: 7.63 h, SD ± 0.65 h). Similarly, for the 2 d before the start of the structured sleep schedule, participants reported sleep-log mean bed times of 12:16 A.M. (SD ± 40 min), mean rise times of 8:05 A.M. (SD ± 43 min), and mean sleep durations of 7.71 h (SD ± 0.62 h). While it is important to note the inherent limitations of self-report measures, these

findings support the likelihood that participants entered the study in a rested state, and that their normative schedules were congruent with the study requirements.

Changes in mood and anxiety state were assessed at 9:00 A.M. on the experimental mornings, in both rested and deprived conditions, using the Positive and Negative Affective Scale (Watson et al., 1988) and the State-Trait Anxiety Inventory (Spielberger, 1983), respectively. As alterations in mood and anxiety commonly co-occur with sleep disruption (Harvey, 2011), these measures provide an important test of whether changes in pain experience were not due to heightened anxiety and/or reduced mood.

Thermal Sensitivity Assessments

Quantitative sensory testing was performed within the scanner room, with the participant supine, by the same investigator in each session. Testing was performed on the left leg, and thermal stimuli were delivered using a 3 × 3 cm contact thermode consisting of Peltier elements (TSA-II Neurosensory Analyzer, Medoc Advanced Medical System). In all following tests, cutoff temperature was set at 50°C.

Warm detection thresholds were measured using the ascending method of limits (Gracely and Naliboff, 1996). A series of 6 ascending stimuli, starting at a baseline temperature of 32°C and increasing at a rate of 1°C/s, were delivered until the participant terminated the stimuli with a button press when warmth was detected, at which point the temperature returned to baseline at a rate of 2°C/s. The warm detection threshold measured before the first experimental session was used to determine the nonpainful warm stimulus later used in the fMRI task. Specifically, 2°C was added to each participant's baseline warm detection threshold, and this new temperature was presented to subjects to confirm that it was perceived as “warm, but not painful.”

To determine the high temperature, painful stimulus for use in the fMRI task, baseline suprathreshold sensitivity, a temperature corresponding to a 7/10 (with 10 being unbearable pain) on a visual analog pain scale, was obtained for participants before their first session. A standard staircase psychophysics method was used in which the temperature is changed on a trial-by-trial basis according to the participant's rating (Gracely and Naliboff, 1996). In this method, a series of 8 temperatures was successively applied to accurately estimate a consistently painful temperature. Starting at the baseline temperature of 32°C, stimuli were increased at a rate of 4°C/s until the target temperature was reached and held for 10 s. The first suprathreshold test stimulus was set at 45°C for all participants and adjusted based on subsequent individual responses. Following a ramp-down at a rate of 4°C/s, participants were asked to rate the intensity of the previous temperature on a visual analog pain scale. Unless the stimulus was rated as the target of 7 of 10, the subsequent trial temperature was adjusted by 1°C to bring it closer to the target. Once a temperature was identified as having the target intensity, stimuli were held constant for subsequent trials until it was rated as a 7/10 for 3 trials in a row, or the end of the stimuli set was reached, in which case, the last 3 temperatures were averaged and used as the individualized painful temperature in the fMRI task.

Thermal pain thresholds were measured in each experimental condition (sleep-rested, sleep-deprived) using the ascending method of limits. Here, participants are instructed to terminate

the increasing temperature with a button press once the stimulus was perceived to be unpleasant, at which point the temperature returned to baseline at a rate of 4°C/s. The mean of these 6 temperatures was then used for subsequent analyses. In each of the two experimental sessions, pain thresholds were assessed 30 min before scanning.

FMRI Acquisition

BOLD contrast functional images were acquired with echo-planar T2*-weighted (EPI) imaging using a Siemens 3 tesla MRI scanner with a 12-channel head coil. Each image volume consisted of 37 descending 3.5 mm slices (96 × 96 matrix; TR = 2000 ms; TE = 22 ms; size 3.5 × 3.5 × 3.0 mm, flip angle = 50°, 0.5 mm slice spacing). A high-resolution T1-weighted structural scan was acquired at the end of the sleep-rested session (256 × 256 matrix; TR = 1900; TE = 2.52; flip angle = 9°; FOV 256 mm; 1 × 1 × 1 mm voxels).

FMRI Thermal Pain Sensitivity Task

Each scanning session for the thermal pain sensitivity task consisted of a pseudo-randomly ordered sequence of two stimulus intensity phases: painful hot and nonpainful warm. Twelve painful and 12 nonpainful warm stimulus "trials" (24, total) were presented across three scanning blocks in each of the sleep-rested and sleep-deprived conditions. Each block was separated by at least 60 s, with each of the three blocks lasting ~5 min.

For each of the 24 experimental trials per session, participants were presented with a visual cue signaling impending thermal stimulation lasting 6 s, after which the cue was removed from the screen and replaced with a fixation cross, followed by painful/nonpainful stimulation. The stimulation period consisted of a ramp-up period in which heat increased at a rate of 4°C/s and was held at the target temperature for 12 s. Consistent with prior fMRI studies of neural pain assessments (Becerra et al., 1999; Brown et al., 2011; Zunhammer et al., 2015), only the 12 s period of peak temperature stimulation was used in modeling of brain activity during painful/nonpainful trials. The heat returned to baseline (32°C) at a rate of 8°C/s, after which an 8 s period of relief from stimulation occurred. Finally, after each stimulation trial, subjects rated both the intensity and unpleasantness of the previous temperature on an 11 point scale. All trial durations were jittered according to a uniform distribution, producing intertrial interval variability that is optimal for mixed block/event-related designs (Petersen and Dubis, 2012).

Cytokine IL-6 Assessment

Blood was drawn under fasting conditions at 8:30 AM (one hour before scanning) in both the sleep-rested and sleep-deprived session. After centrifugation of clotted blood, serum was stored at −80 °C until assaying in batches. IL-6 was measured in serum with a high sensitivity ELISA (Quantikine HS, R&D Systems, Minneapolis, MN) with coefficient of variation of 3.4% ± 2.4%. The assay standard range is 0.2 – 10 pg/ml with an assay sensitivity of 0.11 pg/ml. Four participants were excluded from analyses due to either deviant IL-6 readings (± 2 s.d., 2 participants), or missing data in one of the conditions (2 participants). Values were log-transformed to conform to normality of their distribution.

Online Mechanical Turk Study

The online phase of the study was conducted through MTurk. We sought to assess a cohort of at least 50 participants who reported experiencing some current pain, thereby allowing a determination of whether night-to-night changes in sleep predicted subsequent day-to-day changes in their pain experience. All participants were queried at 4 time points across 2 nights and days. In the mornings, participants reported on the prior nights' sleep, and in the evenings, reported on the days' pain.

A total of 236 (mean ± SD age, 36.61 ± 10.8 years; 50% female) participants were surveyed. Only participants who reported pain on one or both assessment days, an IP address in the United States, and a prior online MTurk approval rating of ≥95% were included in subsequent analyses. Based on these factors, a subset of 60 participants (mean ± SD age, 38.4 ± 10.4 years, 42% female) of candidates surveyed were eligible for participation (**Fig. 1B**).

Across the experimental phase, participants quantified a number of factors related to sleep and pain within specified time windows of the mornings and evenings. In morning assessments, participants filled out the Karolinska Sleep Diary, which included bed time, sleep latency, wake-up time, sleep duration, and subjective sleep quality on a 5 point scale (Åkerstedt et al., 1994). Sleep efficiency was calculated from these daily diaries, based on percentage of time asleep out of total sleep duration (i.e., total sleep time minus sleep latency and total wake time after sleep onset). To characterize changes in affect, participants reported current mood and anxiety, using the Positive and Negative Affective Scale and State-Trait Anxiety Inventory questionnaires, respectively.

To assess the influence of nightly sleep on subsequent next-day pain, participants quantified their physical pain experience that day (input between 6:00 P.M., day's end) and rated the average magnitude of that pain on a 100 point scale (0 representing No Pain and 100 representing Worst Pain Imaginable).

Similar to the in-laboratory experiment, the online study used a within-subject, repeated-measures design. This minimized differences beyond the variable of sleep that could otherwise influence the outcome measure of pain (e.g., sex, age, health status). We deliberately did not provide instructions to subjects to curtail or elongate their sleep to maintain ecologically naturalistic sleep changes. To maximize the representativeness of the online sample, participants were deliberately not excluded based on age or health status, including the presence of chronic pain or pain disorders. Data points for either sleep or pain metrics that were ±2 SD of the group mean were considered outliers and excluded from analyses.

Statistical Analyses

FMRI Preprocessing

Preprocessing and data analysis were performed using the Statistical Parametric Mapping (SPM12, RRID:SCR_007037) software implemented in MATLAB R2015b (MATLAB,

RRID:SCR_001622). Functional images were motion corrected and slice time corrected. Structural images were then coregistered to the mean functional image and normalized to a standard template. Functional images were spatially normalized to the MNI template using those parameters and smoothed using a 6 mm FWHM Gaussian kernel. For all preprocessing steps, we used the default parameters in SPM12. For each subject, trial-related activity was assessed by convolving a vector of trial onsets with a canonical hemodynamic response function. The six movement-related covariates (three rigid-body translations and three rotations determined from the realignment preprocessing step) were used as regressors in the design matrix for modeling movement-related artifact in the time series. To further address the influence of motion on BOLD data, framewise displacement of head motion was calculated based on the motion parameters estimated during preprocessing using the ArtRepair toolbox (ArtRepair for robust fMRI, RRID:SCR_005990). TRs with framewise displacement values >0.8 were interpolated with the nearest artifact-free TRs surrounding the time point affected by motion. Autocorrelation in the data was accommodated for using a first-order autoregressive (AR1) model, estimated by pooling over suprathresholds (Friston et al., 2002).

To control for physiological noise, 5 principal components of CSF and white matter (WM) signal were added as regressors to the design matrix, implemented through the CompCor pipeline (Behzadi et al., 2007). Extraction of CSF/WM signal was derived from probabilistic maps segmented from T1-weighted structural images of each participant, using the segment function within SPM12. CSF/WM masks were then thresholded at a probability of 0.99 for WM and 0.95 for CSF, converted to functional-scan resolution, and eroded to eliminate isolated voxels and minimize partial volume effects.

FMRI Analyses

A general linear model (GLM) was specified for each participant, using the task-related and nuisance regressors outlined above, to investigate the neural effects of interest (Friston et al., 1994). Contrasts were created at the first (individual) level with two events: painful and nonpainful heat. Specifically, the 12 s period during which the stimulus was at its peak temperature, excluding temperature ramp-up and ramp-down periods, was used to construct these contrasts. The experimental hypotheses were tested at the second (group) level using a priori ROIs centered on previously reported coordinates. Averaged activity from the current study was extracted from these ROIs and further analyses with correction for multiple statistical tests were performed on these values. The approach prevents analysis circularity arising from nonindependence of the selected regions and the results and is in accord with standardized fMRI methods (Poldrack, 2007; Poldrack and Mumford, 2009).

A set of cortical and subcortical ROIs were defined on the basis of three convergent criteria. First, regions were selected from previously reported fMRI patterns associated with objective pain intensity. These regions were derived from machine-learning analysis of fMRI brain activity during thermal pain stimulation, and thus, represent a set of candidate neural regions whose activity reliably relates to objective noxious stimulus intensity (Wager et al., 2013). Within this network, only those regions in which increased activity was independently and significantly (q < 0.05 false discovery rate [FDR]) related to the painful stimuli were considered in the current ROI analysis.

Second, regions contributing to subjective pain experience, but not directly related to objective stimulus intensity, were considered. These regions were derived from prior findings of fMRI brain activity associated with subjective thermal pain experience (Woo et al., 2017). This was important in the context of the current experiment because prior studies of sleep loss have shown changes in subjective estimates of pain in response to the same objective noxious stimulus intensity (Tiede et al., 2010; Campbell et al., 2011). Here again, only those regions in which activity independently and significantly ($q < 0.05$) contributed to subjective pain were included as candidate ROIs.

Third, affective processes participate in painful experiences (Price, 2000; Wiech and Tracey, 2009), and this may contribute to the hyperalgesic effect of sleep deprivation. We therefore additionally required that a priori pain-related ROIs were known to be sleep loss-sensitive in prior studies of basic affective and emotional neural processing (Venkatraman et al., 2007; Yoo et al., 2007b; Gujar et al., 2011; Goldstein et al., 2013; Greer et al., 2013; Goldstein-Piekarski et al., 2015).

From these three criteria, a set of 15 candidate ROIs emerge, reflecting the Venn diagram overlap of these previously published empirical studies: areas that are conjointly involved in objective noxious stimulus processing, subjective pain sensation, and sensitive to the effects of sleep deprivation in affective tasks. Sphere sizes of the ROIs used in the current study were selected to approximate the cluster sizes (mm^3) reported in the original studies from which coordinates were taken (**Table 1**).

Pain, Brain, and Immune Analysis

To characterize the impact of sleep deprivation on the pain-related ROIs, average contrast estimates (Pain vs No Pain) were extracted from each ROI volume independently and condition differences were calculated using two-tailed paired *t* tests. All statistical tests were performed within MATLAB. Consistent with imaging recommendations to correct for multiple statistical comparisons across the 15 ROIs, the Benjamini–Hochberg procedure for controlling FDR was applied, with $q = 0.05$ (Benjamini and Hochberg, 1995). This procedure addresses the problem of simultaneously performing multiple significance tests by using an adaptive stepwise procedure to control the expected ratio of erroneous rejections to the number of total rejections. *p* values that survived the FDR criterion after correction were considered statistically significant.

To test the relationships between sleep loss-related changes in ROI brain activity, inflammation, and subjective pain reports, percentage change in circulating IL-6, pain thresholds, and suprathreshold pain (intensity and unpleasantness) was calculated for each subject, and Pearson correlated to changes in pain ROIs. The same FDR approach described above was used to correct for multiple tests.

Mechanical Turk Analysis

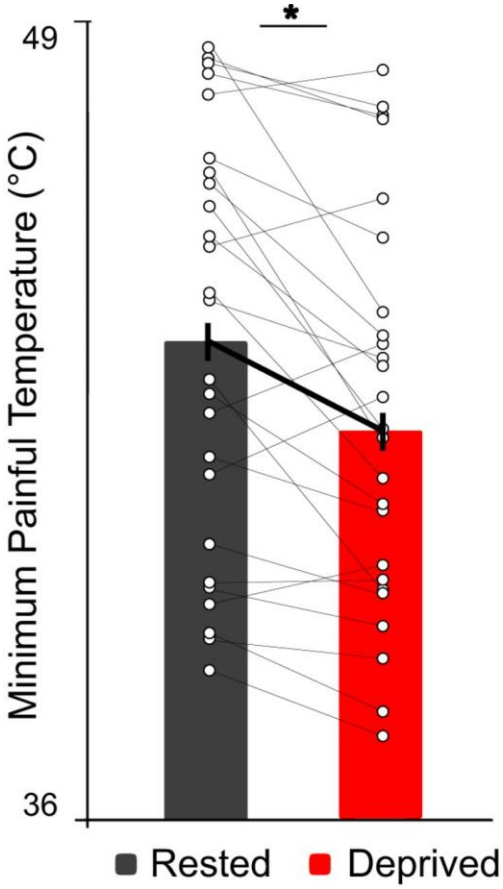
Day-to-day (day 2 to day 1) changes in reported pain and night-to-night (night 2 to night 1) changes in sleep were calculated for each participant. Testing the hypothesis that natural

fluctuations in three measures of sleep predicted subsequent next-day pain, participants were categorically separated on the basis of whether they experienced an increase or decrease from one night to the next in each of the three sleep measures (>0%/<0% change). Of the 60 participants, 55% improved their sleep quality from one night to the next. Forty-percent of subjects improved their sleep quantity/duration, and 52% improved their sleep efficiency relative to the first assessed night. Daily changes in reported pain were compared between categorical groups, defined on the basis of each of the three measured sleep factors, using two-tailed paired *t* tests ($\alpha = 0.05$).

Results

Sleep Deprivation and Pain Sensitivity

Consistent with the hypothesis, the standardized thermal pain threshold assessment (performed outside of the MRI scanner) demonstrated a significant impact of sleep deprivation on pain processing. Specifically, sleep loss expanded the temperature range for classifying a stimulus as painful through a lowering of pain threshold, such that sleep-deprived participants registered pain at a significantly lower temperature than when sleep-rested ($t_{(24)} = 4.36$, $p = 0.0002$; **Fig. 2**).



Inside of the scanner, there were no significant main effects of sleep deprivation on ratings of intensity and unpleasantness of suprathreshold noxious blocks (intensity: $t_{(24)} = 0.67$, $p = 0.51$; unpleasantness: $t_{(24)} = 0.94$, $p = 0.36$). This was similarly true for ratings of nonpainful stimulus blocks (warmth) (both: $t_{(24)} < 0.98$, $p > 0.33$). Such a result importantly demonstrates that sleep loss did not significantly alter sensation of unambiguous non-noxious thermal stimuli.

Therefore, sleep deprivation expressly resulted in a shift, specifically a lowering, in the decision threshold to classify a stimulus as painful (assessed outside of the scanner), as shown by the significant decrease in pain thresholds, whereas the extremes of pain sensitivity used in the canonical scanning paradigm remained similar in each condition. The latter meant that any differences in brain activity between the sleep-rested and sleep deprivation conditions assessed during fMRI scanning could not simply be accounted for by one condition having an imbalance in subjective experience ratings.

Figure 2. Thermal pain threshold. Following sleep deprivation, there was an increase in pain sensitivity demonstrated by a significant lowering of pain thresholds, relative to sleep-rested. Sleep-deprived mean ± SD = 42.47 ± 3.22°C; Sleep-rested mean ± SD = 43.89 ± 3.49°C. *$p < 0.0002$.

Sleep Deprivation and Neural Pain Processing

Analyses of fMRI data revealed bidirectional changes in brain activity in participants under conditions of sleep loss within recognized a priori pain regions, relative to when sleep-rested. Specifically, sleep deprivation significantly increased pain reactivity within right primary somatosensory cortex ($t_{(24)}$ = 3.20, p = 0.004; FDR-corrected for multiple ROI tests at q = 0.05; **Fig. 3**) (Benjamini and Hochberg, 1995). This finding is consistent both with the role of somatosensory cortex in the registration and representation of noxious painful stimuli (including heat), and the contralateral crossing of sensory signals because the stimulation was to the left side of the body (Coghill et al., 1999; Craig, 2002; Apkarian et al., 2005; Atlas et al., 2014).

In contrast to the somatosensory cortex, significant decreases in activity were observed within subcortical a priori ROIs of the thalamus as well as the NAcc following sleep deprivation, relative to the rested condition (thalamus: $t_{(24)} = -3.13$, p = 0.005; NAcc: $t_{(24)} = -3.11$, p = 0.005; FDR-corrected). Such NAcc disengagement is congruent with the prediction of a shift in decision threshold regarding what constitutes a painful stimulus because this striatal region is associated with pain valuation and relief (Altier and Stewart, 1999; Baliki et al., 2010; Navratilova and Porreca, 2014; Lee et al., 2015; Woo et al., 2015; Sardi et al., 2018). Appropriate cortical estimation of pain within the human brain is not limited to representations within primary somatosensory strip but involves further higher-order cortical evaluation within interoceptive integration regions of the insula and cingulate (Craig, 2003; Critchley et al., 2004). A priori ROI regions of the right middle insula and left anterior insula demonstrated significant decreases in activity during pain under conditions of sleep deprivation (right middle insula: $t_{(24)} = -4.06$, p = 0.0005; left anterior insula: $t_{(24)} = -3.11$, p = 0.005; FDR-corrected). The latter left hemisphere association is relevant considering that the left anterior insula receives parasympathetic afferent information, and lesions of this insula region increase pain sensitivity, indicative of a loss of anodyne homeostatic signaling under sleep deprivation conditions (Craig, 2005; Starr et al., 2009).

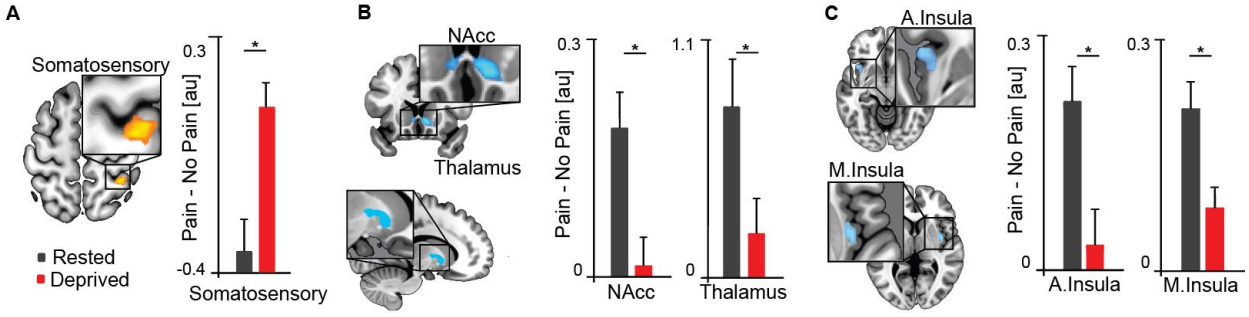


Figure 3. Changes in pain-related brain activity. Data are mean ± SD. ***A–C***, Brain maps (left) displaying pain-related ROIs that were significantly altered by sleep deprivation, relative to sleep-rested (all FDR-corrected). Bar plots represent brain activity (Pain > No Pain) contrast estimates. Somatosensory: sleep-deprived mean = 0.09 ± 0.34; sleep-rested mean = −0.34 ± 0.46. NAcc: sleep-deprived mean = 0.02 ± 0.18; sleep-rested mean = 0.19 ± 0.21. Thalamus: sleep-deprived mean = −0.21 ± 0.81; sleep-rested mean = 0.79 ± 1.06. Anterior insula: sleep-deprived mean = 0.12 ± 0.82; sleep-rested mean = 0.79 ± 0.8. Middle insula: sleep-deprived mean = 0.08 ± 0.12; sleep-rested mean = 0.21 ± 0.17. Error bars indicate SEM. *p < 0.005. Nucleus Accumbens (NAcc); Anterior and middle insula (A. Insula and M. Insula, respectively). Threshold for display set to p < 0.005 (whole-brain, uncorrected).

Sleep Deprivation > Sleep Rested						
Region (L/R)	Radius(mm)	X	Y	Z	P	R
Somatosensory (R)	**8**	**36**	**-45**	**59**	**0.004**	**0.55**
Dorsal ACC (R)	8	16	-7	39	0.02	0.04
Superior Parietal (R)	5	26	-42	66	0.51	-0.04

Sleep Rested > Sleep Deprived						
Region (L/R)	Radius(mm)	X	Y	Z	P	R
Middle Insula (R)	**8**	**32**	**4**	**11**	**0.0005**	-0.02
Thalamus (L)	**4**	**-10**	**6**	**10**	**0.005**	**-0.54**
Anterior Insula (L)	**8**	**-27**	**25**	**0**	**0.005**	0.24
Nucleus Accumbens	**6**	**±9**	**2**	**-7**	**0.005**	0.23
Operculum (R)	5	57	1	5	0.04	-0.36
Substantia Nigra (R)	4	10	-8	12	0.09	-0.31
Caudate	4	±18	-2	24	0.38	-0.32
IFG (R)	4	64	24	-6	0.47	-0.47
Middle Cingulate / SMA	10	6	-6	48	0.48	0.01
Precuneus (R)	4	4	-54	48	0.60	0.32
ACC (R)	6	12	28	28	0.63	0.36
DLPFC (R)	8	33	35	42	0.90	0.10

Table 1. Regions of interest analysis. Brain ROI analysis showing center (MNI coordinates) and radius (millimeters) of extracted spheres. Bolded rows are significant, following FDR correction, for paired comparison (sleep rested </> sleep deprived) of pain-related brain activity. Column R shows Pearson correlations between pain-related brain changes (sleep deprived – sleep rested) and changes in thermal pain threshold (sleep rested – sleep deprived), and bolded rows are significant following FDR correction. ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; SMA, supplementary motor area; DLPFC, dorsolateral prefrontal cortex.

No other regions within the a priori cortical pain network demonstrated significance that exceeded FDR correction for multiple ROIs, including the cingulate cortex. Several were significant below this threshold and reported for completeness in **Table 1**, but not discussed further.

Having identified condition differences (sleep-rested < > sleep-deprived) in pain-related brain activity, we next sought to determine whether the extent of change in activity within these pain-related regions predicted interindividual differences in the change in pain threshold caused by sleep deprivation.

Across participants, the extent of amplified somatosensory pain reactivity positively and significantly predicted the lowering of pain thresholds (i.e., the expansion of pain sensation) caused by sleep deprivation ($r_{(23)}$ = 0.55, p = 0.004; FDR-corrected; **Fig. 4A**). In addition, the degree of decrease in thalamic activity associated with sleep deprivation significantly and negatively predicted the lowering of pain thresholds across individuals ($r_{(23)}$ = −0.54, p = 0.005; FDR-corrected; **Fig. 4B**). That is, the extent of increased somatosensory pain reactivity, and the associated decrease in thalamic reactivity, following sleep deprivation, both predicted greater pain-sensitivity increases across individuals following sleep loss. No other such associations (positive or negative) were identified within other a priori ROIs (all p > 0.05; **Table 1**).

Therefore, the somatosensory cortex and left thalamus both showed a main effect of sleep deprivation; furthermore, their respective extent of change in pain reactivity predicted the magnitude of expanded sensitivity to pain caused by sleep deprivation, measured using the threshold assessment.

Mood and anxiety are known to be impacted by sleep deprivation (Harvey, 2011) and, independent of sleep, are recognized to influence pain (Wiech and Tracey, 2009). To test the specificity of the pain-amplifying effect of sleep deprivation, relationships between self-reported changes in mood and anxiety following sleep deprivation were examined in relation to the change in pain.

Levels of both positive and negative mood, reported immediately before scanning, were numerically, but not significantly, different between sleep-deprived and sleep-rested conditions (positive mood: sleep-deprived mean = 17.4 ± 4.8 SD; sleep-rested mean = 20.12 ± 7.4; p = 0.14; negative mood: sleep-deprived mean = 15.2 ± 1.9 SD; sleep-rested mean = 16.64 ± 4.8; p = 0.19).

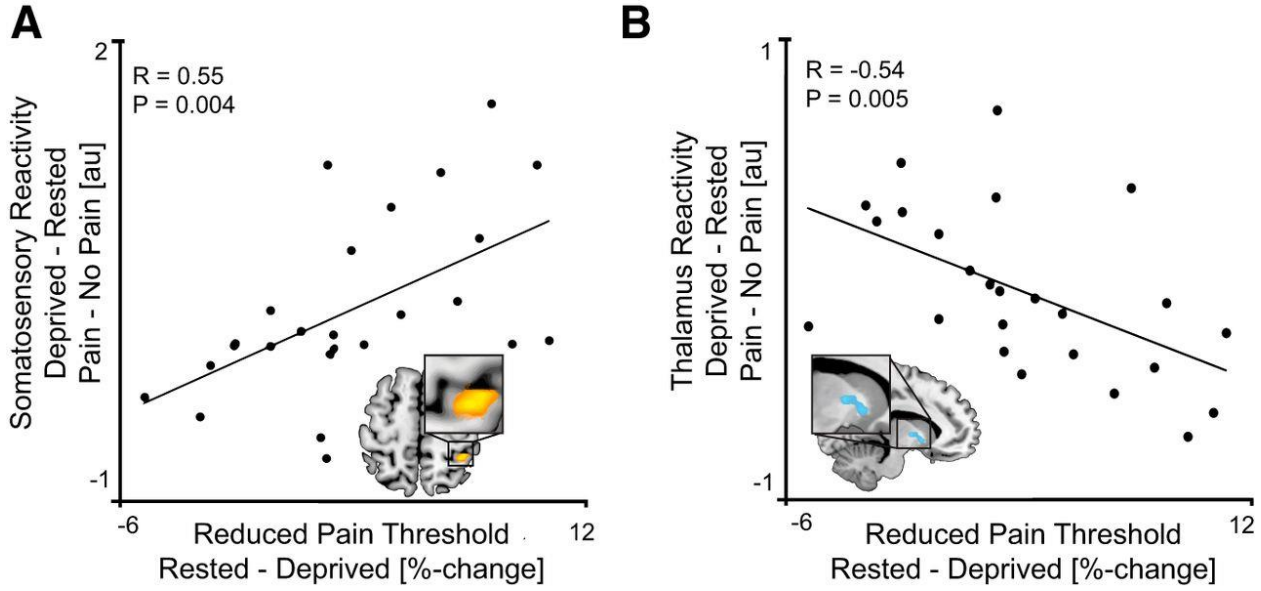


Figure 4. Pain reactivity and subjective pain sensitivity. Scatterplot represents significant positive correlation between sleep loss-related increases in (***A***) somatosensory and (***B***) thalamic pain reactivity (Pain > No Pain), and the sleep loss-related increases in subjective pain sensitivity (change in pain threshold). Threshold for display set to p < 0.005 (whole-brain, uncorrected).

Importantly, however, these sleep loss-related differences in both positive and negative mood did not significantly correlate with the change in pain thresholds (positive mood: $r_{(23)} = -0.04$, $p = 0.85$; negative mood: $r_{(23)} = -0.18$, $p = 0.39$). There were similar numeric but nonsignificant differences in state anxiety following sleep deprivation. However, like mood, these sleep loss-associated changes in self-reported anxiety were also not correlated with changes in pain thresholds measured at the same time (anxiety: sleep-deprived mean = 35.5 ± 10.2 SD; sleep-rested mean = 32 ± 9.3 SD; $p = 0.18$; $r_{(23)} = -0.27$, $p = 0.19$).

Together, this suggests that the observed associations between sleep and pain were not parsimoniously accounted for by co-occurring changes in affect in the current study.

Peripheral Body Inflammation and Neural Pain Processing

Confirming the second hypothesis, central brain alterations in pain reactivity co-occurred with changes in the peripheral body following sleep loss. Specifically, an increase in circulating serum concentrations of the nociceptive-sensitive cytokine, IL-6, was observed in participants when sleep-deprived, relative to when they were sleep-rested ($p < 0.03$) (**Fig. 5A**).

Beyond the co-occurrence of this proinflammatory state, we further examined whether these brain- and body-related changes in response to sleep deprivation were inter-related, focusing on those brain regions showing main effects. The extent of reduced pain responsivity within the (normally analgesic) NAcc significantly correlated with the increase in peripheral IL-6 ($p = 0.005$, FDR corrected for multiple ROIs), such that the greater the disengagement of the NAcc across individuals, the larger the increase in circulating IL-6 (**Fig. 5B**). This was similarly true of the insula, wherein the degree of reduction in pain-related processing was negatively correlated with the relative upregulation of IL-6 across individuals ($p = 0.007$, FDR corrected for multiple ROIs) (**Fig. 5C**).

Importantly, these brain-body immune associations were unique to pain stimulation, and not observed for brain activity from these same regions during warm, non-noxious stimulation (all $p > 0.4$). This selectivity suggests that inflammatory body changes following sleep loss are

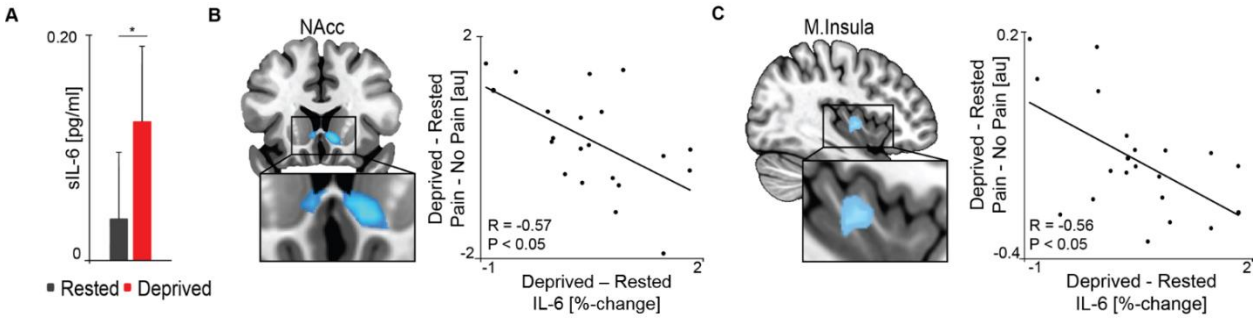


Figure 5. Change in interleukin-6 (IL-6). (A) Significant increase in serum IL-6 following sleep deprivation, relative to the sleep rested condition. Error bars represent SEM. *P<0.03 (B & C) Associations between sleep-loss related decreases in pain reactivity (Pain > No Pain) in nucleus accumbens (NAcc; B) and middle insula (M. Insula; C) ROIs and corresponding sleep-loss related increase (%) in peripheral circulating IL-6.

selectively associated with pain-specific activity within the brain, rather than reflecting a more diffuse, non-noxious brain-body interaction.

While sleep-loss-related changes in IL-6 correlated significantly with corresponding changes in brain activity, IL-6 was not itself significantly associated with inter-individual differences in subjective pain threshold ($p > 0.6$), nor with any changes in emotional state ($p > 0.33$). However, that the sleep-loss increase in IL-6 was pain-associated was evinced by the association with the NAcc, since this NAcc activity was expressly related to pain processing (i.e. painful heat > nonpainful warmth). In the context of sleep deprivation, pro-inflammatory changes in the body therefore relate to objective changes in pain-related brain activity, rather than the shift in subjective pain sensitivity.

Ecological Night-to-night Changes in Sleep and Subsequent Day-to-day Changes in Pain

While the in-laboratory experiment establishes that acute total sleep deprivation leads to altered neural pain processing and an associated expansion of sensitivity to pain, it intimates, but does not itself address, whether ecologically relevant night-to-night variation in sleep, within an individual, similarly results in consequential day-to-day changes in experienced pain during the subsequent day. This was the goal of the online experiment.

Supporting the experimental hypothesis, and the directional predictions from the in-laboratory acute sleep deprivation experiment, participants who had a decrease in sleep efficiency from one night to the next experienced a corresponding increase in pain from one day to the next ($t_{(58)} = 2.4$, $p = 0.018$; **Fig. 6**; each bar represents a different group of subjects).

A similar relationship was observed for night-to-night changes in subjective sleep quality, such that reduction in the quality of sleep was associated with increased consequential daily pain ($t_{(58)} = 2.1$, $p = 0.04$; **Fig. 6**). Interestingly, however, nightly changes in total amount of sleep did not similarly predict daily changes in pain ($t_{(58)} = 0.39$, $p = 0.7$).

Although the current study was not designed to prove a causal order of changes in sleep and changes in pain, the data suggest that altered sleep statistically forecasts next-day pain. To further examine whether this was true, we used partial correlation analysis to examine the relative strength of the association between nightly sleep quality and next-day pain while controlling for effects of pain on the previous day. If sleep quality still predicted next-day pain, even when controlling for prior pain status, it would lend support to the idea that it is the change in sleep that is robustly predicting subsequent changes in pain. Additionally, we extend this test and performed a second partial correlation analysis of pain and next-day sleep quality while controlling for prior sleep status. This affords an additional exploration that speaks to causal precedence; were pain to be associated with subsequent sleep quality independent of the effects of prior sleep, it would suggest that pain changes precede sleep changes, not vice versa.

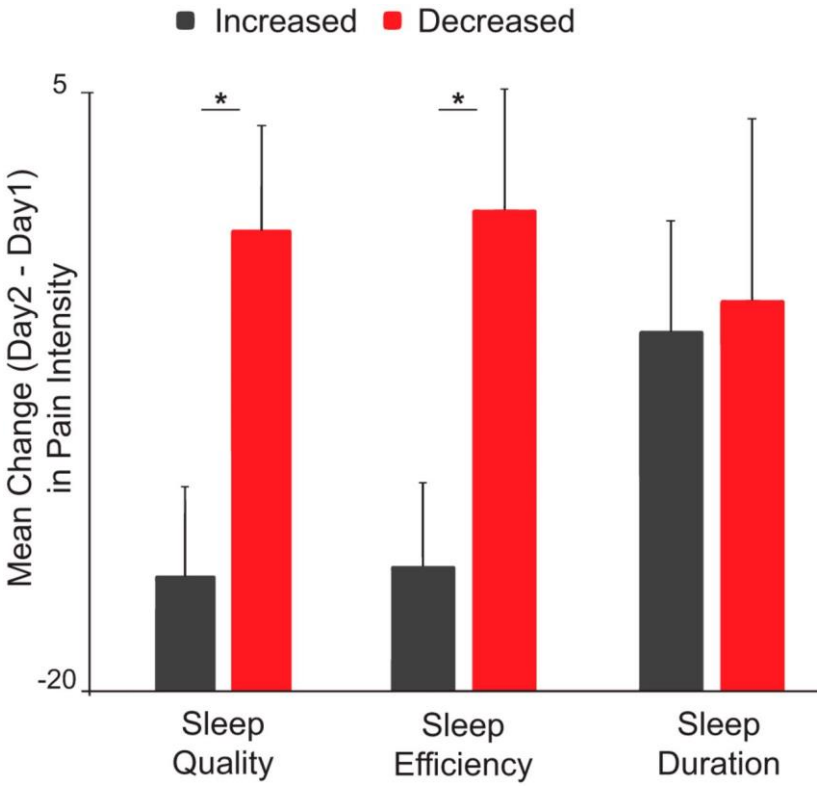


Figure 6. Online study results. Data are mean ± SD. Bar graph represents participants experiencing a decrease (red bar) or increase (black) in measures of sleep efficiency (SE) (Night 2 to Night 1 mean decreased SE = −3.8 ± 5.6%; Night 2 to Night 1 mean increased SE = 10.1 ± 11.1%), quality (SQ) (Night 2 to Night 1 mean decreased SQ = −0.48 ± 0.75; Night 2 to Night 1 mean increased SQ = 1.7 ± 0.81), and duration (Night 2 to Night 1 mean decreased duration = −54.375 ± 45.7 min; Night 2 to Night 1 mean increased duration = 90.7 ± 48.9 min). Error bars indicate SEM. Each point represents a single-subject's change in reported pain from day 1 to day 2. Night-to-night decreases in sleep efficiency and quality, but not duration, resulted in corresponding higher pain from one day to the next, relative to those with night-to-night increases in these sleep measures. *$p < 0.05$.

When controlling for the effects of pain intensity on day 1, a significant relationship between sleep quality and pain on the following day (day 2) still remained ($r = -0.26$, $p = 0.04$). This suggests that the evening sleep quality is a stronger predictor of subsequent next-day pain than prior pain predicting subsequent sleep. In addition, when controlling for prior sleep quality (night 1), the partial correlation between pain and sleep quality on the following night (night 2) was nonsignificant ($r = -0.04$, $p = 0.72$). These results therefore affirm that it is sleep quality that predicts next-day pain, even when factoring in the influence of prior pain status.

Importantly, self-reported changes in mood and anxiety were not associated with day-to-day fluctuations in experienced pain (positive mood: $r_{(58)} = -0.14$, $p = 0.29$; negative mood: $r_{(58)} = -0.21$, $p = 0.11$; anxiety: $r_{(58)} = 0.07$, $p = 0.59$). As with the in-laboratory study, this would indicate that the observed associations between sleep and pain do not appear to be robustly explained by parallel changes in these emotional constructs.

Thus, ecological night-to-night variability in sleep efficiency and subjective quality within an individual, but not quantity, predicted consequential day-to-day reductions in corresponding pain. This online counterpart to the in-laboratory experiment corroborates the pain-enhancing effect of inadequate sleep but further establishes that even modest changes in sleep quality are sufficient to affect pain and can be observed within individuals across nights, beyond cross-sectional examinations.

Discussion

Together, these findings help establish the following: (1) that acute sleep deprivation expands the temperature range for classifying a stimulus as painful, specifically through a lowering of pain thresholds; (2) that the underlying neural correlates of such sleep loss-induced hyperalgesia involved increasing pain reactivity within primary somatosensory cortex, yet a blunting of pain reactivity in higher-order valuation analgesic-relief, and decision-making regions of the striatum and insula cortex; and (3) that the same effect can be observed following more ecologically relevant changes in sleep, such that modest night-to-night changes in sleep quality within an individual (increases and decreases) determine consequential day-to-day changes in experienced pain (decreases and increases, respectively).

Sleep and Neural Pain Processing

Current models view pain as a homeostatic emotion. Pain is constructed from ascending interoceptive afferents conveying viscerosensory and viscerochemical changes in body state. These signals project to registration sites within brainstem, and on to subcortical and cortical sensory, homeostatic regulatory, and valuation centers. Pain is therefore a specific sensation and a felt emotion, one that drives homeostatic behavior (Craig, 2002; Craig, 2003; Critchley and Harrison, 2013).

Fitting this distributed model of pain processing, our findings describe a bidirectional set of neural changes within the recognized network of the brain that processes pain following sleep deprivation. Specifically, sleep loss triggered an increase in pain reactivity within sensory-discriminative regions of somatosensory cortex. Notably, heightened somatosensory cortex reactivity was lateralized to the opposite side of the cortex, relative to the application of the noxious stimulus on the body. This is fitting with the contralateral organization of primary somatosensation and indicates an intensification of first-order cortical pain registration resulting from sleep deprivation (Craig, 2002).

Beyond this main condition effect, the magnitude of increased activity in somatosensory cortex following sleep deprivation predicted the relative decrease in thermal pain threshold in the sleep-deprived state, the greater the increase in somatosensory cortex noxious reactivity, the greater the shift (lowering) of pain sensitivity across individuals. That the somatosensory cortex explained individual differences in pain thresholds aligns well with the role of somatosensory cortex in the initial magnitude registration of pain (Coghill et al., 1999; Apkarian et al., 2005; Atlas et al., 2014). Therefore, one component of the exacerbation of pain caused by a lack of sleep involves amplified primary pain processing in rudimentary areas of human sensory cortex, the activity of which scales with sleep loss-induced expansion of pain sensation.

A converse decrease in pain reactivity was observed in subcortical NAcc, thalamus, and insula cortex. A recognized function of the insula involves the integration of afferent signals from somatosensory cortex into second-order representation of affective body state, available for conscious perception (Craig, 2002; Craig, 2003; Critchley and Harrison, 2013). Indeed, the broad connectivity of the insula with regions, including the prefrontal and orbitofrontal cortices, thalamus, ACC, and NAcc, suggests that the insula is well situated to be a key regulator of sensed pain (Craig, 2002; Craig, 2003).

Related, the NAcc is linked with pain valuation, decision-making, and analgesia-related pain-regulation in a number of studies (Navratilova and Porreca, 2014; Woo et al., 2015; Woo et al., 2017). This includes NAcc-associated relief from ongoing pain, the analgesic influence of which is transacted through descending pain efferent pathways (Altier and Stewart, 1999; Baliki et al., 2010; Lee et al., 2015; Woo et al., 2015; Woo et al., 2017; Sardi et al., 2018). In addition, the NAcc has reciprocal connections to pain-integrating and pain-modulating cortical regions, including ventromedial prefrontal cortex, ACC, insula, and somatosensory cortex (Borsook et al., 2010).

The thalamus is consistently activated in acute pain experiments and plays a role in the gating of contralateral ascending sensory information as it reaches the cortex (Craig, 2003). However, the function of the thalamus in pain processing is not limited to classical sensory gating. First, decreases in thalamic gray matter structure and functional activity are a characteristic of multiple chronic pain conditions with different etiologies (Pridmore et al., 2003; Apkarian et al., 2004; Gustin et al., 2011). Indeed, the reduction of thalamic function due to lesions predicts the severity of central pain conditions, including reduced pain thresholds (Vartiainen et al., 2016), the proposed mechanism of which is the loss, or disinhibition, of normal thalamocortical pain signaling (Craig et al., 1996; Craig, 2000; Vartiainen et al., 2016).

Building on this functional circuitry, increased somatosensory, yet reduced insula, thalamus, and NAcc, pain reactivity challenges any rudimentary model in which sleep loss triggers hyperalgesia through unidirectional increases in neural pain representations. Instead, the impact of insufficient sleep on pain involves both an amplification of primary cortical pain registration, potentially due to thalamic disinhibition, and a shift in affective valuation and decision-making involving insula and NAcc. We propose that these changes can parsimoniously account for the observed shift in the decision threshold for categorizing a potentially noxious stimulus as painful through misrepresentation of pain signals within insula and NAcc. This misrepresentation of the salience of thermal stimuli may consequentially lead to an inaccurate amplification (gain increase) of pain registration within somatosensory cortex. Indeed, this exact pattern has been reported in patients with lesions to the insula cortex, who demonstrate simultaneously higher pain sensitivity, elevated somatosensory cortex activity, and an absence of pain-modulatory activity in the insula (Starr et al., 2009).

Peripheral Body Inflammation and Neural Pain Processing

Accompanying these central brain changes, sleep deprivation significantly increased circulating levels of the pro-inflammatory cytokine, IL-6. Raised levels of IL-6 have consistently

been reported in populations suffering from sleep disturbance (Irwin et al., 2006; Prather et al., 2009b; Prather et al., 2009a), and when jointly assessed, increased pain sensitivity as well (Haack et al., 2007). Moreover, animal models have demonstrated that administration of IL-6 causally produces pain, and, moreover, the administration of anti-inflammatory drugs targeting IL-6 aid in reducing pain (McMahon et al., 2005).

Importantly, IL-6 receptors are expressed in the cerebral cortex, brainstem, hippocampus, thalamus, and hypothalamus (Aniszewska et al., 2015). IL-6 is also bidirectionally transported from brain-to-blood and blood-to-brain; a potential pathway through which peripheral inflammation can communicate with and alter brain function (including pain processing), and conversely, centrally-produced IL-6 can alter peripheral inflammation (Chen et al., 2000; Banks, 2015).

From these reports, our findings suggest an interacting, inter-related change in body and brain states linked to pain sensitivity caused by sleep loss, leading to an "embodied" explanatory framework of the associated pain hypersensitivity. Supporting this interpretation, sleep-deprivation increases in peripheral IL-6 were not only co-occurring with central brain changes in pain reactivity, but were significantly coupled. Specifically, the relative increase in IL-6 following sleep loss correlated negatively with the proportional decrease in NAcc activity, which is otherwise linked to pain relief.

That peripheral cytokines impacted striatal brain processing of pain under conditions of sleep loss aligns with evidence that these circulating inflammatory signals modify dopamine-related activity within the NAcc (Felger and Miller, 2012). Cytokine increases robustly alter processing in corticostriatal reward pathways during affective experiences (Harrison et al., 2009; Felger and Miller, 2012). This is similarly true for changes in dopamine metabolism and binding within the brain (Harrison et al., 2009; Felger and Miller, 2012). The pro-nociceptive effect of sleep disruption may therefore involve increases in peripheral inflammatory cytokines that, consequentially, influence pain-modulating striatal pathways.

Sleep-loss increases in IL-6 negatively correlated with the proportional decrease in right middle insula cortex; a region involved in the integration and modulation of interoceptive input, pain included (Craig, 2002; Craig, 2003; Critchley et al., 2004). Not only is the insula sensitive to registering peripheral inflammation (Harrison et al., 2009; Slavich et al., 2010), but linking with the above changes in NAcc, the ventral striatum receives cortical inputs from insula (Chikama et al., 1997). Furthermore, this striatal signaling is related to pain modulation within the insula, as increasing dopamine in the insula cortex increases pain thresholds (Burkey et al., 1999). Animal models of pain (including inflammatory-induced pain) demonstrate that endogenous dopamine, and its metabolites, are reduced in the insula during hyperalgesia. Therefore, impairments of insula-striatal processing and higher-order representation of noxious signals offer one recognized pathway through which brain-body amplifications in pain sensitivity are engendered in the sleep-deprived state, in part through pro-inflammatory IL-6 signaling.

Whether sleep-loss increases in peripheral inflammation alter pain-related brain activity, or vice versa, cannot be resolved by the current study design. It should be noted, however, that this a non-mutually exclusive proposition. Circulating IL-6, produced by activated monocytes, affects

the brain in two parallel pathways: 1) an impact on pain-related neural processing by slow diffusion to brain targets from circumventricular organs, and 2) activation of primary afferent neurons in the body, which increases activity in viscerosensory-mapping regions of the brain (Dantzer and Kelley, 2007). Nevertheless, NAcc and insula are typically associated with the representation, rather than instigation, of peripheral inflammation (Harrison et al., 2009; Felger and Miller, 2012).

Therefore, a parsimonious hypothesis is that peripheral inflammation initiated by sleep deprivation modifies central, viscerosensory brain responses to pain by means of ascending neural afferent signaling, leading to increased pain. This leads to the testable, directional prediction that blocking the peripheral inflammatory cytokine response associated with sleep loss should, in turn, lessen the changes in pain-related brain activity reported, above.

Ecological Variations in Sleep and Pain

Further testing our hypothesis, the second study demonstrated that subtle, ecological changes in sleep in the general population predict consequential day-to-day changes in self-reported pain intensity. Interestingly, it was night-to-night changes in sleep quality, rather than sleep quantity, that were deterministic of changes in pain sensitivity.

Insufficient sleep, self-reported, has been shown to correlate, cross-sectionally, with self-reported pain in a sample of the general population (Smith and Haythornthwaite, 2004; Afolalu et al., 2018) and clinical cohorts (Tang et al., 2012). Our findings add to this link by establishing that, beyond cross-sectional associations, changes in the quality of night-to-night sleep within an individual in a micro-longitudinal assay, more so than the quantity, predict consequential day-to-day changes in pain intensity (Edwards et al., 2008). That even modest reductions in sleep quantity/quality impact next-day pain is increasingly relevant given the continued erosion of sleep time in developed nations (National Sleep Foundation Sleep in America Poll, 2013; http://sleepfoundation.org/sleep-polls-data/sleep-in-america-poll/2013-exercise-and-sleep). This is additionally pertinent when considered alongside the escalating prevalence and economic health burden of pain in these same countries (Goldberg and McGee, 2011). Indeed, findings from a recent national poll (National Sleep Foundation Sleep in America Poll, 2015; https://sleepfoundation.org/sleep-polls-data/sleep-in-america-poll/2015-sleep-and-pain) demonstrate that 64% of those suffering chronic pain, and 54% of those with acute pain, report co-occurring poor sleep quality.

Our findings perhaps offer encouragement, in that they suggest that even modest improvements in sleep quality have the potential to reduce subjectively significant pain. That is, sleep can be seen as a modifiable risk factor and intervention target for pain, and the magnitude of sleep improvement necessary to result in measurable reductions in pain is modest, and thus pragmatically realistic.

Given that pain is among the costliest health burdens in both direct healthcare spending and indirect lost productivity (Phillips, 2009), improving sleep may additionally confer broader economic savings. This concern (and therapeutic opportunity) is exemplified by the inpatient hospital setting, where sleep quality is consistently poor and pain is frequently co-occurring.

Placing sleep quality closer to the center of inpatient treatment approaches may reduce patient suffering, and potentially, the dosage of narcotic and non-narcotic analgesics (Walker, 2018).

Study Considerations

Potential limitations of the current studies should be noted. First, the in-laboratory experiment was performed with healthy young adults. Because pain becomes more frequent in middle and late life, it remains to be determined whether these findings translate across the lifespan. Second, only noxious heat was examined in the laboratory study. It therefore remains unclear whether different brain changes would be observed using different stimulus modalities, such as noxious mechanical, electrical, or chemical stimuli. This seems less likely, however, considering that previous studies show a commonality of pain-enhancing effects of sleep loss across such modalities (Lautenbacher et al., 2006). Third, as brain activity was only collected during the suprathreshold pain sensitivity task, inferences regarding the mechanisms of reduced thresholds rely on significant correlations with subsequent suprathreshold neural pain reactivity. Fourth, only IL-6 was examined as a marker of inflammation. There are multiple interacting peripheral markers of inflammation related to pain, including other cytokines and prostaglandins, many of which may be similarly pain and sleep sensitive. Finally, while *post hoc* analyses established that changes in nightly sleep statistically forecast next-day pain changes, even when accounting for prior pain status, they do not prove this fact causally (as this experiment was not designed to directly address causal ordering). Nevertheless, a meta-analysis of longitudinal and micro-longitudinal studies in both clinical and nonclinical populations has established that two-thirds of relevant studies demonstrate stronger evidence supporting a causal influence of prior sleep on subsequent experienced pain, rather than the opposite direction (Finan et al., 2013).

IV. Head, Heart, Mind and Sleep: Sleep Loss Impacts the Interconnected Brain-Body-Mood Regulation of Cardiovascular Function

Introduction

Poor sleep is associated with hypertension, which is a primary risk factor for cardiovascular disease (Stokes 3rd et al., 1989; Gangwisch, 2014). Epidemiological studies indicate that both habitual short sleep duration and poor-quality sleep are associated with a greater incidence of hypertension, even when controlling for numerous other risk factors (Gangwisch, 2014; Pepin et al., 2014).

Prospective longitudinal studies have demonstrated that short sleep duration and worse quality sleep predict a higher future risk of hypertension (Gangwisch, 2014; Jackowska and Steptoe, 2015). Manipulations using partial or total sleep deprivation causally and consistently increase blood pressure (Lusardi et al., 1999; Kato et al., 2000). Such evidence supports a possible link between the coinciding increase in sleep deficiency and increasing rates of cardiovascular disease in numerous first world nations (Wolk et al., 2005).

However, the mechanistic pathway(s) through which insufficient sleep increases blood pressure and thus cardiovascular disease risk remains unclear. This is especially true regarding a possible interaction between impaired central brain and peripheral body systems that are known to control vascular blood pressure. Indeed, the brain plays a causal role in the regulation of peripheral physiology, including that of blood pressure and heart rate (Critchley et al., 2001). Core to this control are a discrete set of viscerosensory brain regions that map and also instigate changes in vascular function.

Defining this cortical and subcortical network have been animal models demonstrating that direct stimulation of the amygdala (Dampney, 1994), the cingulate (Pool and Ransohoff, 1949), the insula (Yasui et al., 1991; Oppenheimer et al., 1992) and medial prefrontal cortex (MPFC) (Pool and Ransohoff, 1949) all elicit changes in blood pressure. In humans, activity within, and connectivity between, the amygdala, cingulate, and insular cortices aids in the regulation of arterial blood pressure, as well as event-related reactivity of vascular blood pressure (Gianaros et al., 2008).

Of this collection of regions, the insular cortex and MPFC are of particular importance in the regulation of vascular state. Both regions are involved in the central brain regulation of autonomic state, including the mapping of current autonomic balance and modulating autonomic outflow (Yasui et al., 1991; Critchley et al., 2001; Valenza et al., 2019). Activity in the insula and MPFC have further been linked with increased vasoconstriction in subjects with a history of coronary artery disease (Shah et al., 2019), and ischemic injury to the insula induces endothelial dysfunction and inflammation (Balint et al., 2019). Similarly, lesioning of the MPFC increases plasma levels of adrenocorticotropic hormone and corticosterone (Diorio et al., 1993), both important stress-response factors which can impact cardiovascular function (Burford et al., 2017). The insula and MPFC are unique in the regulation of cardiovascular function through direct

connections to brainstem areas (Frysztak and Neafsey, 1994; An et al., 1998). Finally, the brain, including the insula and MPFC, can further impact vascular function through its influence on immune function as vascular endothelial cells are sensitive to inflammatory processes (Vecchiarelli et al., 2016; Chen et al., 2020).

Although the peripheral autonomic nervous system is a known regulatory pathway for vascular and endothelial function control (Amiya et al., 2014), how the autonomic nervous system interacts with these central brain viscerosensory networks under conditions of sleep loss, resulting in a shift towards hypertension, remains uninvestigated.

Building on this collective evidence, and addressing this unresolved question, here, we sought to test the hypothesis that one pathway through which insufficient sleep instigates a shift from normotensive towards a hypertensive increase in blood pressure is through an altered relationship with central functioning of brain vascular control networks and the peripheral body cardiovascular system. Specifically, we tested the prediction that elevations in blood pressure caused by a night of sleep deprivation are significantly associated with changes in the functional connectivity state of the above-described a priori vascular control networks of the human brain, indicative of a brain-body mechanistic inter-relationship.

In short (and see Methods for details), 66 healthy adult participants who were otherwise normotensive, were enrolled in a counterbalanced, repeated-measures design involving two conditions: one night of sleep (Sleep Rested) and one night of sleep loss (Sleep Deprivation). In each condition, participants had their cardiovascular state, including blood pressure and heart rate, assessed at circadian-matched morning timepoints, and received a resting-state functional magnetic resonance imaging (fMRI) scan following sleep or sleep deprivation—the latter being a recognized method for mapping the state of network connectivity of the human brain (Van Den Heuvel and Pol, 2010).

Methods and Materials

Sixty-six healthy adults aged 18-24 years (mean ± SD: 20.7 ± 1.7, 52% female) completed a repeated-measures cross-over design (described below). Participants abstained from caffeine and alcohol for 72 hours before and during the entire course of the study and kept a normal sleep-wake rhythm (7-9 hours of sleep per night) with sleep onset before 1:00 A.M. and rise no later than 9:00 A.M. for the three nights before the study participation, as verified by sleep logs and actigraphy.

Exclusion criteria, assessed using a prescreening semi-structured interview, were as follows: a history of previously-diagnosed sleep disorders, neurological disorders, closed head injury, Axis 1 psychiatric disorders according to the DSM-IV-TR criteria (encompassing mental disorders, including depression, anxiety disorders, bipolar disorder, attention deficit disorder, and schizophrenia), history of drug abuse and current use of antidepressant or hypnotic medication, nicotine use, consumption of more than five alcoholic drinks per week, crossing of time zones in the 3 months before the study, and general contraindications to MRI. Participants also had blood pressures within normotensive ranges, confirmed with a blood pressure reading of less than 120/80 mmHg at the time of consenting (Whelton et al., 2018). Participants who reported sleeping <7

hours per night or consuming three or more daily caffeine-containing drinks were also excluded from entering the study. The Pittsburg Sleep Quality Index (Buysse et al., 1989) was employed to determine the quality of recent sleep history, and participants considered poor sleepers (global score > 5) were excluded. The study was approved by the UC Berkeley Committee for the Protection of Human Subjects, with all participants providing written consent.

Experimental Design

To test the experimental hypotheses, participants entered a repeated-measures study design, including two sessions—one following a normal night of sleep and one after 24 hours of total sleep deprivation. The two sessions were separated by at least 7 days (mean ± SD: 9.8 ± 3.8), with the order of the sleep rested and deprived conditions counterbalanced across subjects.

In the sleep deprived session, participants arrived at the laboratory at 10:00 P.M. and were continuously monitored throughout the enforced waking period. Activities during the sleep deprivation condition were limited to use of the internet, email, short walks, reading, movies of low emotionality, and playing board games, thereby providing a standardized regimen of waking activity without undue stress. Participants also avoided exercise during the experimental sessions. In the sleep rested session, participants came to the laboratory at 8:00 P.M. and were prepared for an 8-hour night of sleep (~11:00 P.M. to 7:30 A.M. ± 30 min). In both conditions, mood and anxiety were assessed in the morning at the time of the cardiovascular assessment using the Positive and Negative Affective Scale and State-Trait Anxiety Inventory questionnaires, respectively (Spielberger, 1983; Watson et al., 1988). The following morning, participants' cardiovascular state was measured followed by fMRI scanning.

Cardiovascular Assessments

In each condition, cardiovascular state was assessed to determine blood pressure, heart rate, and heart rate variability. These assessments were performed approximately 1 hour after awakening, and at circadian-matched times in the sleep rested and sleep deprivation conditions for each participant.

Blood pressure measurement was performed with Omron BP742 blood pressure monitor (Omron Healthcare Europe BV, Hoofddorp, The Netherlands), fitted to the participant's nondominant arm over the brachial artery. Participants were instructed to remain motionless with open eyes while sitting with feet flat on the floor during the recording with rested cuffed arm at heart height, consistent with standard blood pressure recording guidelines (Muntner et al., 2019). Two consecutive measurements were taken and the mean of these two measurements was used for analyses.

Immediately following blood pressure assessment, participants were fitted with electrodes for bipolar electrocardiography (ECG), and cardiac activity was recorded for five minutes. Electrodes were applied in a lead II format with the reference electrode placed below the right

clavicle parallel to the right shoulder and a second electrode placed on the torso at the fourth intercostal space on the left side parallel to the left hip. Similar to the blood pressure recording, participants sat motionless with open eyes while sitting with feet flat on the floor. All data were screened for measurement artifacts and beat-to-beat intervals extracted using ARTiiFACT software (Kaufmann et al., 2011), and all flagged interbeat intervals were visually checked. If confirmed as artifactual, they were deleted and substituted by means of cubic spline interpolation of neighboring intervals. The time-domain measure pNN50 was calculated for each participant, which is the percentage of differences between adjacent interbeat intervals (NN) that are greater than 50ms and represent a recommended measure of vagally-mediated heart rate variability (Electrophysiology, 1996).

FMRI Acquisition

During fMRI resting-state scanning, participants were instructed to stay awake and keep their eyes open on a fixation cross. The resting-state scan lasted for 7:20 min and was performed at the same time of day in both conditions (~9:00 A.M.). Functional brain images were acquired with echo-planar T2*-weighted (EPI) imaging using a Siemens 3-Tesla MRI scanner with a 12-channel head coil. Each image volume consisted of 37 descending 3.5 mm slices (96 X 96 matrix; TR = 2000 ms; TE = 28 ms; size: 3.5 X 3.5 X 3 mm; flip angle = 78°, 0.5 mm slice spacing). A high-resolution T1-weighted structural scan was acquired at the end of the sleep-rested session (256 X 256 matrix; TR = 1900; TE = 2.52; flip angle = 9°; FOV 2.56 mm; 1 X 1 X 1 mm voxels).

FMRI Preprocessing

Preprocessing was performed using fMRIPrep 1.2.5 (RRID:SCR_016216). The T1-weighted image was corrected for intensity non-uniformity using N4BiasFieldCorrection and used as a reference throughout the analysis. Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template was performed through nonlinear registration with antsRegistration using brain-extracted version of both T1-weighted volume and template (ANTs 2.2.0 RRID:SCR_004757). Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1-weighted image using fast (FSL 5.0.10, RRID:SCR_002823).

For fMRI data, the mean BOLD image was co-registered to the T1-weighted reference using flirt. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using mcflirt. BOLD runs were slice-time corrected using 3dTshift from AFNI (RRID: SCR_005927), and the BOLD time-series (including slice-timing correction when applied) were resampled to MNI152NLin2009cAsym standard space. Known time-series factors requiring covariate accommodation were calculated based on the preprocessed BOLD: framewise displacement (FD), DVARS and three region-wise global signals. The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (CompCor, (Behzadi et

al., 2007)). Finally, regression was used to estimate and remove the whole-brain global signal time series, and functional images were smoothed using a 6 mm FWHM Gaussian kernel.

Statistical and FMRI analyses

Connectivity analyses were performed using the CONN toolbox version 19b (www.nitrc.org/projects/conn, RRID:SCR_009550). First, denoising was performed by regressing the six motion parameters, FD, and physiological noise components. The resulting BOLD time series was band-pass filtered (0.008 – 0.09 Hz), followed by region of interest (ROI) analysis, specifically ROI-to-ROI connectivity analysis.

Based on the experimental hypotheses, analyses focused on an a priori set of brain ROIs known to be involved central brain cardiovascular control (Pool and Ransohoff, 1949; Yasui et al., 1991; Oppenheimer et al., 1992; Dampney, 1994; Critchley et al., 2001; Gianaros et al., 2008; Valenza et al., 2019). These ROIs were drawn from anatomical atlases (Harvard-Oxford Cortical and Subcortical Atlas) included in the CONN toolbox, and were extracted using an ICA approach. For each ROI, the connectivity to all other ROIs was calculated for each subject in each condition separately, generating a symmetric correlation matrix wherein each element is the correlation between two ROIs in each condition and each participant.

In addition to ROI-to-ROI connectivity analyses, control analyses for specificity examined connectivity within and between additional prototypical brain networks of the Default-Mode Network (DMN), Dorsal Attention Network (DAN), Ventral Salience Network (VSN), and Somatomotor Network (SMN) (Yeo et al., 2011). Within-network connectivity was calculated for each network by extracting the mean resting-state BOLD time-series from each voxel within a region of a network and calculating the mean Pearson correlation with all other regions of the network. Between-network connectivity was similarly calculated for each network by extracting the mean resting-state BOLD time-series from every voxel within a network, and then calculating the correlation with the mean time-series of all other networks.

The resulting correlation coefficients from these fMRI analyses across participants in each condition were then statistically compared (two-tailed paired t-test) to determine the effect of sleep loss on brain connectivity. Consistent with imaging recommendations to correct for multiple statistical comparisons among the eight ROIs and four networks, the Benjamini-Hochberg procedure for controlling FDR was applied, with $q = 0.05$ (Benjamini and Hochberg, 1995). This procedure addresses the problem of simultaneously performing multiple significance tests by using an adaptive stepwise procedure to control the expected ratio of erroneous rejections to the number of total rejections. Only connectivity changes that survived the FDR criterion after correction were considered statistically significant and used in analyses. Pearson correlations were employed to test the relationships between sleep loss-related changes in brain connectivity and sleep loss-related changes in cardiovascular state. All statistical analyses were performed in Python using the Pingouin package (Vallat, 2018).

Results

Sleep Loss and Cardiovascular Function

We first tested the hypothesis that sleep deprivation significantly alters key vascular, cardiac and autonomic metrics linked with cardiovascular disease (Stokes 3rd et al., 1989; Benetos et al., 1999): systolic and diastolic blood pressure, heart rate, and heart rate variability.

Supportive of the hypothesis and prior findings (Stokes 3rd et al., 1989; Gangwisch, 2014; Pepin et al., 2014; Jackowska and Steptoe, 2015), sleep deprivation significantly increased peripheral systolic blood pressure, relative to the same individuals under sleep rested conditions (**Fig. 1A**; Systolic: sleep-rested mean = 107.6 mmHg ± 11.8 SD, sleep-deprived mean = 112.1 mmHg ± 12.8 SD, p = 0.003). This was similarly true of diastolic blood pressure, which also increased significantly following sleep loss (**Fig. 1A**; Diastolic: sleep-rested mean = 71.1 mmHg ± 7.3 SD, sleep-deprived mean = 73.7 mmHg ± 7.9 SD, p = 0.03). Therefore, sleep loss resulted in an increase in peripheral vascular pressure, reflecting a shift away from a normotensive state (Stokes 3rd et al., 1989).

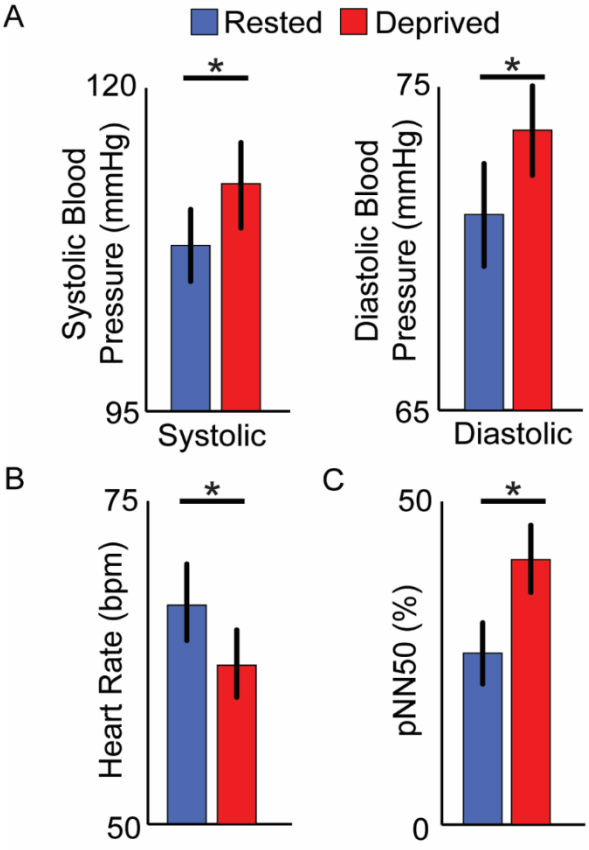


Figure 1. Cardiovascular outcomes. A, Following sleep deprivation, there was an increase in both systolic and diastolic blood pressure, relative to the sleep rested condition. B, Sleep deprivation resulted in a reduction in heart rate, relative to the sleep-rested condition. C, Sleep deprivation resulted in an increase in heart rate variability (pNN50), relative to the sleep-rested condition. Error bars indicate SEM. *p<0.05.

Of mechanistic relevance, these changes in blood pressure occurred in the absence of an increase in the rate of heart contraction. More specifically, there was an overall reduction of resting heart rate under conditions of sleep loss, relative to the sleep rested condition (**Fig 1B**; sleep-rested mean = 67.5 bpm ± 11.6 SD, sleep-deprived mean = 62.9 bpm ± 10.2 SD, p < 0.001), a finding that is consistent with previous reports regarding sleep loss (Kato et al., 2000; Holmes et al., 2002; Zhong et al., 2005; Vaara et al., 2009; Franzen et al., 2011), but see (Lusardi et al., 1999).

Corresponding to the decrease in heart rate, there was an increase in heart rate variability under conditions of sleep deprivation, relative to the sleep-rested condition (**Fig 1C**; pNN50: sleep-rested mean = 27.5% ± 20.5% SD, sleep-deprived mean = 42.0% ± 19.1%, p < 0.0001). Since the pNN50 reflects beat-to-beat variability related to the vagal modulation of the heart

(Electrophysiology, 1996), this observed increase in heart rate variability under conditions of sleep loss is consistent with an increased parasympathetic input to the heart linked to the state of extended wakefulness (Holmes et al., 2002; Vaara et al., 2009).

Further advancing a dissociation between increased peripheral vascular blood pressure in the absence of accelerated contracting heart rate, there was no significant association between the differential change in blood pressure and change in heart rate between the conditions ([sleep-rested] – [sleep deprivation]) for either systolic or diastolic measures (**Fig 2A,B**; Systolic: r = 0.06, p = 0.61; Diastolic: r = 0.03, p = 0.84). That is, the sleep loss-related changes in blood pressure showed no significant inter-relationship with sleep loss-related changes in heart rate across participants.

Of further relevance to this cardiac-vascular dissociation, a similar lack of association was observed between the sleep loss-changes in heart rate variability and sleep loss-changes in blood pressure (**Fig 2C,D**; Systolic: r = -0.09, p = 0.48; Diastolic: r = -0.05, p = 0.69). In contrast, there

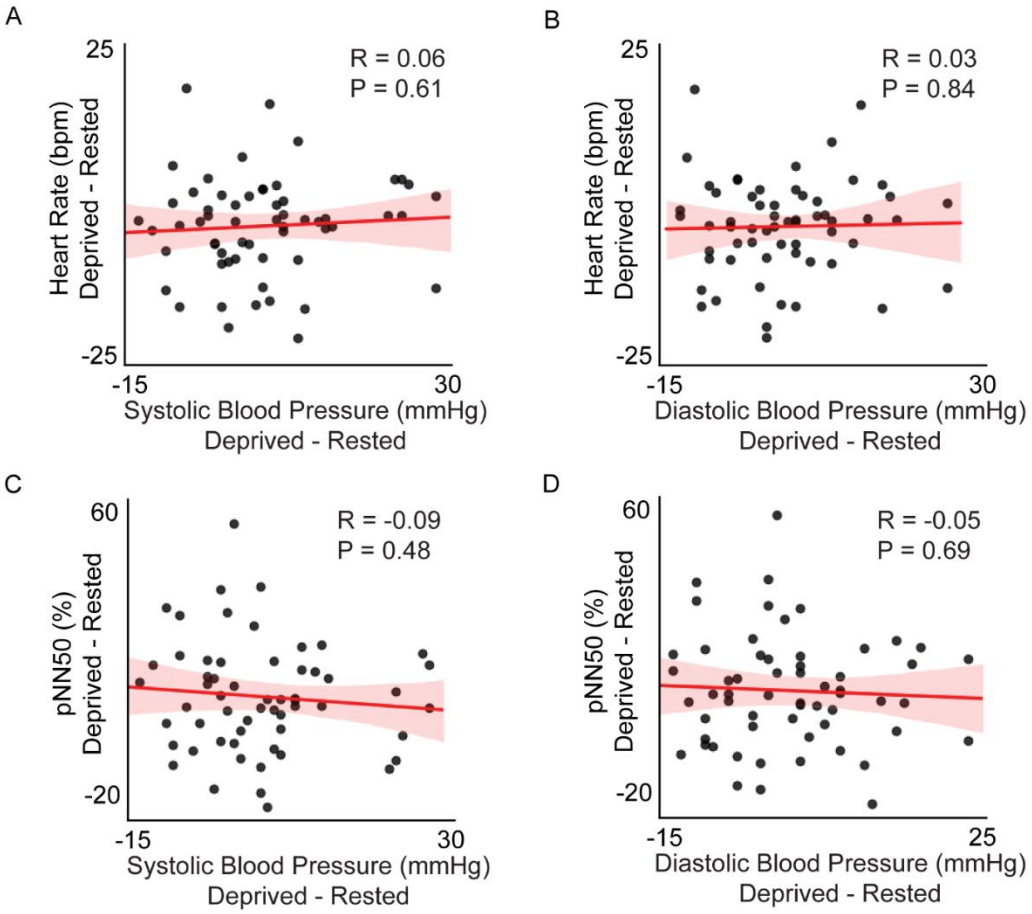


Figure 2. Associations between cardiovascular outcomes. Scatterplots represent non-significant correlations between sleep-loss changes (deprived – rested) in cardiovascular outcomes, including (A) heart rate and systolic blood pressure, (B) heart rate and diastolic blood pressure, (C) heart rate variability (pNN50) and systolic blood pressure, and (D) heart rate variability (pNN50) and diastolic blood pressure.

was a significant association between the sleep loss-related reduction in heart rate and the corresponding sleep loss-associated increase in heart rate variability ($r = -0.48$, $p < 0.0001$).

In summary, this first set of results indicate a dissociable effect of sleep loss on peripheral cardiovascular function, one in which sleep loss increases peripheral systolic and diastolic blood pressure, yet this vascular pressure change does not co-occur with an increase in heart rate or a decrease in heart rate variability. Such a dissociation suggests separable mechanisms regarding the influence of sleep loss in the heart (vagal parasympathetic), relative to an independent influence on vasculature control (see Discussion, and (Kato et al., 2000; Holmes et al., 2002; Zhong et al., 2005; Vaara et al., 2009; Franzen et al., 2011).

Sleep Loss and Viscerosensory Resting Brain Connectivity

Next, to test the impact of sleep loss on central brain networks linked to cardiovascular control, we assessed functional connectivity within the a priori region of interest (ROI) network known to be associated with cardiovascular control in humans and non-human primates, including the amygdala, anterior cingulate, insula, and ventromedial and medial prefrontal cortices (Pool and Ransohoff, 1949; Yasui et al., 1991; Oppenheimer et al., 1992; Dampney, 1994; Critchley et al., 2001; Gianaros et al., 2008).

Within this network, twelve connections were found to be significantly altered following FDR-correction for multiple tests under conditions of sleep deprivation, relative to the sleep rested state ($q = 0.05$) (Benjamini and Hochberg, 1995). These included connectivity pathways between the insula and anterior cingulate, the insula and MPFC, the anterior cingulate and the MPFC, the anterior cingulate and the amygdala, the ventromedial frontal and MPFC, and MPFC and amygdala (**Fig 3A,B, Table 1**).

Of these twelve, there was a significant reduction in connectivity between the ventromedial frontal and MPFC following sleep deprivation, relative to a night of normal sleep ($t(65) = 3.2$, $p = 0.008$, FDR-corrected, **Fig. 3B**). This reduction is of relevance for the observed reduction in heart rate and increase in heart rate variability considering both regions, when otherwise active and engaged, are associated with sympathetic nervous system drive to the heart rate (Valenza et al., 2019).

The remaining eleven ROI pairs demonstrated a significant increase in their connectivity (**Fig. 3A**, **Table 1**), with the connectivity changes all jointly sharing at least one of two nodes: the insula and MPFC. First, the insula had significantly increased connectivity with the anterior cingulate cortex ($p = 0.01$, FDR-corrected)**.** Second, there were widespread increases in connectivity between the insula and the MPFC ($p < 0.0008$, FDR-corrected). The second of these shared nodes, the MPFC, demonstrated increased connectivity to both the anterior cingulate in the right hemisphere ($p < 0.0001$, FDR-corrected), and amygdala in both hemispheres ($p < 0.02$, FDR-corrected). Details of these connectivity changes and their significance are described in **Table 1.**

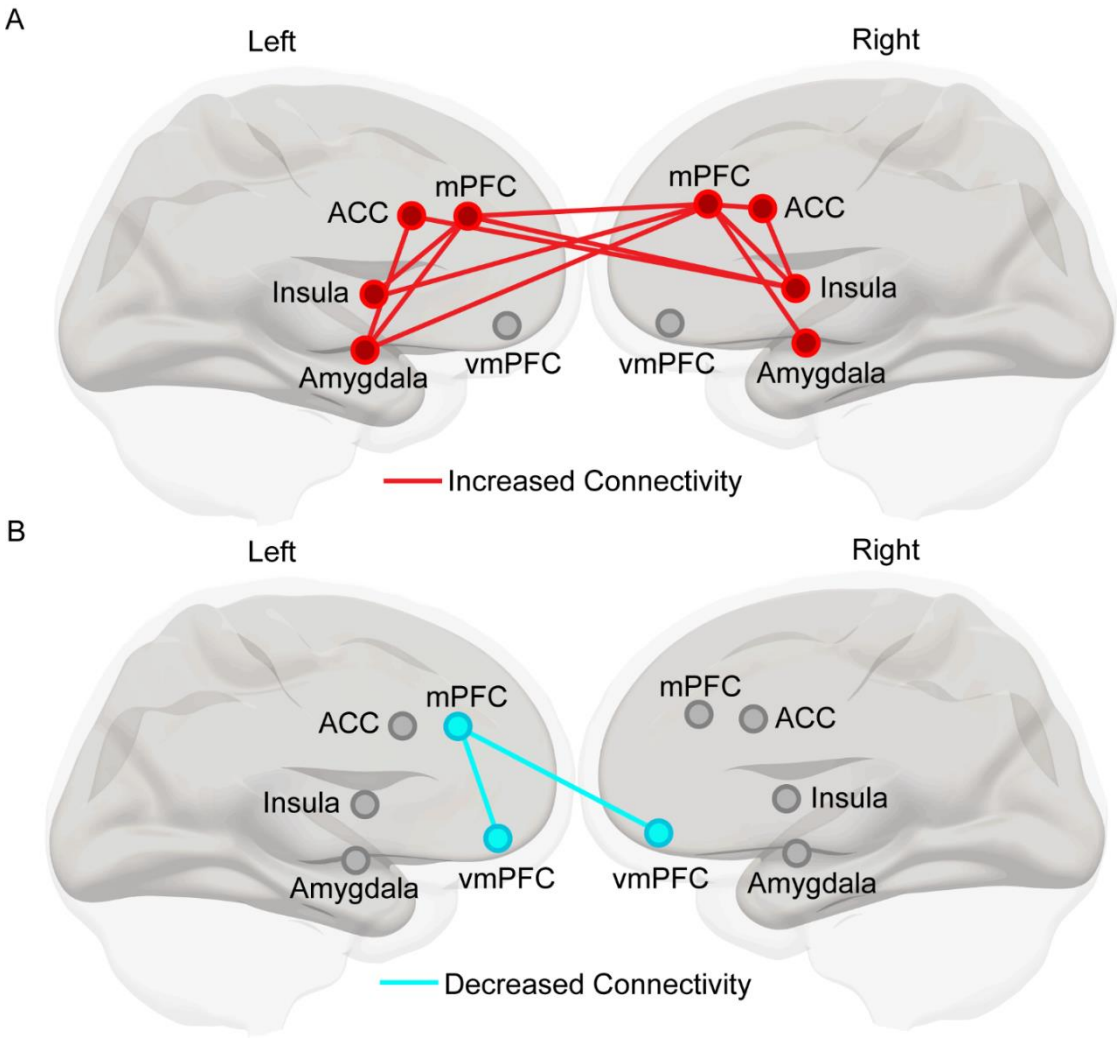


Figure 3. Changes in brain connectivity in regions of interest. Connections shown are significant following FDR-correction (q = 0.05). A, Connections that are significantly increased in the sleep deprived condition relative to the sleep-rested condition. B, Connections that are significantly decreased in the sleep-deprived condition relative to the sleep rested condition.

Source	Brain Region	Condition Effects (P-value)
Deprived > Rested		
Insula (R)	ACC (L/R)	0.01
	MPFC (R)	<0.001
	MPFC (L)	<0.001
Insula (L)	MPFC (R)	<0.001
	MPFC (L)	<0.001
MPFC (R)	ACC (L/R)	<0.001
	MPFC (L)	0.01
	Amygdala (R)	<0.005
	Amygdala (L)	<0.001
MPFC (L)	Amygdala (L)	0.02
ACC (L/R)	Amygdala (L)	0.01
Rested > Deprived		
MPFC (L)	vmPFC (L/R)	0.002

Table 1. Resting Brain Connectivity. Significant condition effects (sleep rested < > sleep deprived) on brain connectivity, with all condition effects shown significant following FDR-correction. ACC, anterior cingulate cortex; MPFC, medial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; HR, heart rate; HRV, heart rate variability (pNN50).

Sleep Loss, Cardiovascular Function and Viscerosensory Resting Brain Connectivity

We next tested whether these two sets of identified changes—alterations in central brain connectivity and alterations in peripheral body blood pressure were significantly interrelated.

First, greater sleep loss-related increases in insula connectivity were significantly associated with a greater rise in systolic blood pressure, especially between the insula and the MPFC ($r(60) = 0.25$; $p = 0.05$; **Fig. 4A**). Second, sleep loss-related decreases in MPFC connectivity with the amygdala was significantly related to sleep loss-increases in peripheral diastolic blood pressure ($r(61) = -0.29$, $p = 0.02$; **Fig. 4B**). Therefore, sleep loss changes in peripheral systolic and diastolic blood pressure were associated with signature alterations in central

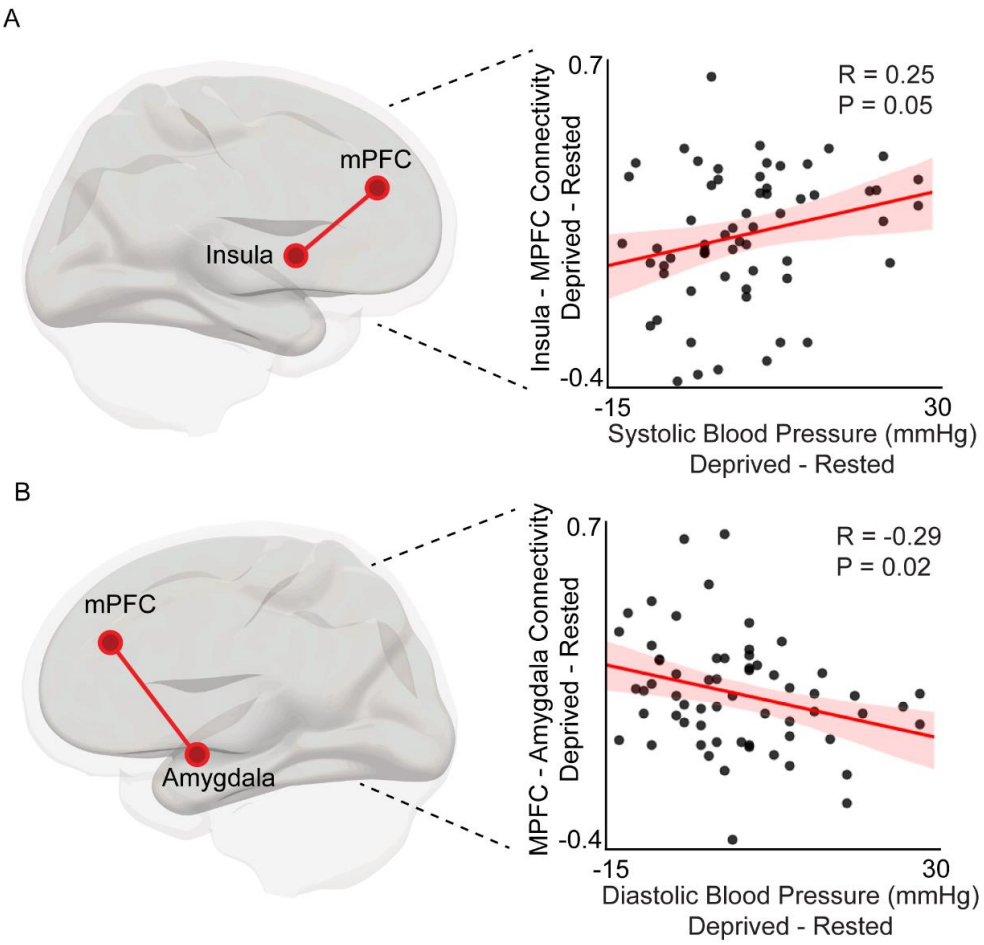


Figure 4. Brain connectivity and cardiovascular changes. A, Scatterplot represents significant positive correlation between sleep-loss related increases in insula and MPFC connectivity and sleep-loss related increases in systolic blood pressure. B, Scatterplot represents significant negative correlation between sleep-loss increases in MPFC and amygdala connectivity and sleep-loss related increases in diastolic blood pressure.

brain connectivity, with a clustering around changes in insular and medial prefrontal connectivity of the a priori viscerosensory network, respectively.

Unlike the association between central brain and peripheral body blood pressure, no associations between sleep loss-related changes in heart rate or heart rate variability and sleep loss-related changes in functional connectivity were observed across any of the network regions (all $p > 0.05$). Therefore, the association between changes in brain connectivity and the peripheral cardiovascular state was significant for changes in blood pressure, and not for the changes in cardiac activity or variability.

To better understand the specificity of central brain changes and cardiovascular changes, a set of post-hoc analyses examined associations between sleep loss-related alterations in four non-a-priori, though well-recognized, larger-scale resting-state brain networks: the Default-Mode Network (DMN), Dorsal Attention Network (DAN), Ventral Salience Network (VSN), and Somatomotor Network (SMN) (Yeo et al., 2011).

Neither differences in connectivity within or between these large-scale resting state networks showed significant associations with the sleep loss-related increases in blood pressure, the decrease in heart rate, or the increase in heart rate variability (all $p > 0.05$). Therefore, local changes within the specific a priori cardiovascular control network (Pool and Ransohoff, 1949; Yasui et al., 1991; Oppenheimer et al., 1992; Dampney, 1994; Critchley et al., 2001; Gianaros et al., 2008), rather than global changes in larger-scale brain networks (Yeo et al., 2011), best accounted for sleep loss-related changes in peripheral blood pressure (i.e., vascular) activity.

Emotion Interactions with Brain Connectivity and Cardiovascular Function

Independent of sleep, mood and anxiety have well-recognized relationships with peripheral autonomic activity, including changes in cardiac and vascular activity (Räikkönen et al., 1999). Mood states and anxiety have also been related to changes in activity and functional connectivity of some nodes of the cardiovascular control network, specially the insular and MPFC nodes that are central to emotional brain processes (Fornito et al., 2008; Bijsterbosch et al., 2014; Namkung et al., 2017). Furthermore, both positive and negative mood states are deleteriously impacted by sleep loss (Harvey, 2011).

As expected (Harvey, 2011; Simon et al., 2020), sleep deprivation was associated with a worsening of mood: a reduction in positive mood ($t(65) = 6.8$, $p < 0.0001$) and an increase in negative mood ($t(65) = -5.2$, $p < 0.0001$), relative to the sleep rested condition. Sleep loss also resulted in an increase in state anxiety, relative to the sleep rested state ($t(65) = -4.3$, $p < 0.0001$).

Sleep loss-increases in negative mood state were associated with sleep loss-increases in blood pressure, such that the greater the negative mood increase, the greater the increase in diastolic blood pressure, though this was not significant following FDR correction ($r(59) = 0.32$, $p = 0.18$; FDR-corrected). Moreover, sleep loss changes in heart rate and heart rate variability were not associated with changes in any of the affective measures, (all $p > 0.24$, FDR-corrected), once again demonstrating specificity to changes in vascular control, rather than heart contractility rate. The association between negative mood and systolic blood pressure was not significant ($r(60) = 0.12$, $p = 0.51$, FDR-corrected).

Sleep loss-related reduction in positive mood was instead significantly associated with the sleep loss change in connectivity between the left MPFC and ventromedial frontal cortex ($r(65) = 0.32$, $p = 0.01$**;** and trend levels with changes in left insula cortex and right MPFC connectivity ($r(65) = -0.24$, $p = 0.06$). Connectivity changes in the MPFC and insula regions also demonstrated significant associations with sleep loss-related changes in systolic and diastolic blood pressure, fitting with the roles of these areas in both affective and cardiovascular regulation (Yasui et al., 1991; Critchley et al., 2001; Fornito et al., 2008; Namkung et al., 2017; Valenza et al., 2019). No associations were evident for changes in negative mood (all $p > 0.26$).

Counter to our experimental hypothesis, however, sleep loss changes in anxiety were not significantly associated with changes in a priori brain vascular control networks (**Table 2**).

Therefore, a dissociable influence of mood was observed, with sleep loss amplifications in negative mood state selectively associated with the amplifications in peripheral body blood pressure, and the loss of positive mood state was expressly associated with impairments in viscerosensory brain connectivity. Such findings lend further support to an embodied framework of sleep loss in which changes in brain, body, and mental state are mutually related in their association with the sleep loss-induced shift towards hypertension.

Source	Brain Region	Brain Correlation with Affect (R-value)		
Deprived > Rested		**Positive Mood**	**Negative Mood**	**Anxiety**
Insula (R)	ACC (L/R)	-0.03	-0.09	0.07
	MPFC (R)	-0.20	-0.05	0.18
	MPFC (L)	-0.15	-0.05	0.08
Insula (L)	MPFC (R)	-0.24	-0.001	0.13
	MPFC (L)	-0.16	0.07	0.13
MPFC (R)	ACC (L/R)	-0.05	0.11	0.001
	MPFC (L)	-0.05	0.10	-0.13
	Amygdala (R)	-0.003	-0.14	-0.02
	Amygdala (L)	-0.03	-0.13	-0.13
MPFC (L)	Amygdala (L)	0.05	-0.04	-0.10
ACC (L/R)	Amygdala (L)	-0.02	-0.03	0.04
Rested > Deprived				
MPFC (L)	vmPFC (L/R)	0.32*	0.06	-0.18

Table 2. Connectivity Associations with Affect. Columns show the Pearson correlation between sleep-loss related changes in brain connectivity and changes in affective state, including mood (positive and negative) and anxiety. * significant following FDR-correction. ACC, anterior cingulate cortex; MPFC, medial prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

Discussion

Taken together, the current study demonstrates that (1) experimental sleep loss significantly and selectively increases peripheral blood pressure, independent of any increase in heart rate, (2) sleep loss simultaneously compromises functional brain connectivity within regions that help regulate vascular tone—the viscerosensory network, (3) the sleep loss-related changes in viscerosensory functional brain connectivity and in peripheral vascular tone were significantly inter-dependent, with the changes in brain nodes explaining the vascular shift towards hypertension, and (4) sleep loss-related reductions in positive state and amplification in negative state each showed a significant additive interactions with the selective impairments in brain network activity and peripheral hypertension caused by sleep loss, consistent with mental-state influence.

Sleep Loss and Cardiovascular State

Chronic sleep disturbances, including sleep disorders such as insomnia and sleep apnea, are recognized risk factors for hypertension and cardiovascular disease (Stokes 3rd et al., 1989; Gangwisch, 2014; Pepin et al., 2014; Jackowska and Steptoe, 2015). Moreover, experimental sleep loss causally increases blood pressure (Lusardi et al., 1999; Kato et al., 2000). However, the underlying mechanism(s) by which poor sleep increases blood pressure are poorly understood.

While blood pressure and heart rate can change in parallel in response to varied demands (both increased, or both decreased), each are regulated through separable mechanisms, including at the level of the autonomic nervous and endocrine systems. Indeed, uncoordinated or directionally opposite changes in cardiac and vascular function occur under conditions of excess allostatic load (McEwen, 1998, 2006), a sign of impaired homeostasis.

Our findings comport well to a model of impaired homeostasis caused by a lack of sleep (McEwen, 2006). Specifically, there was a significant increase in both systolic and diastolic blood pressure, yet no concomitant (rather, a deceleration) of heart rate contractility. Indeed, the sleep loss-related changes in blood pressure and heart rate showed no evidence of being significantly correlated with one another, further fitting a state of allostatic distress (McEwen, 1998; Karatsoreos and McEwen, 2011).

The heart is known to receive both sympathetic and parasympathetic input, yet most vessels (arteries and veins) only receive sympathetic innervation (Gordan et al., 2015). Based on the dissociation observed, one parsimonious mechanism is that increases in blood pressure caused by sleep deprivation are triggered by an increase in sympathetic tone, while the decrease in heart rate reflects a separable shift in cardiac-mediated autonomic balance towards the influence of parasympathetic input (Paton et al., 2005). That is, an autonomic dissociation caused by sleep loss, wherein increased sympathetic output dominates in peripheral vessels, yet the opposite is true in the heart. This possibility is also supported by the sleep loss-related increase in heart rate variability—a measure reflecting vagal (parasympathetic) modulation of the heart (Electrophysiology, 1996). Indeed, the high sleep pressure resulting from sleep deprivation increases parasympathetic cardiac drive slowing heart rate (Holmes et al., 2002; Vaara et al., 2009).

Combining these prior reports with findings from the current study, one candidate, though speculative, explanation for the observed dissociable impact of sleep loss on vascular and cardiac function involves three independent mechanistic pathways, with each, or their combination, accounting for our findings. The first is a reduction in sympathetic and increased parasympathetic drive in the heart, evidenced by the increase in heart rate variability, resulting in a lowering of contraction rate. The second is endothelial dysfunction resulting from secretion of inflammatory mediators or increased sympathetic input to the endothelium, thereby increasing blood pressure. The third, and non-mutually exclusive pathway, involves changes in the activation of adrenergic receptors in the vasculature. Since α-adrenergic receptors are largely expressed in vascular smooth muscle, increased sympathetic activation due to sleep loss will thus elicit vasoconstriction (Gordan

et al., 2015). Nevertheless, these possibilities do not discount non-autonomic mechanisms that may further contribute or modulate peripheral systems, including central brain regulation.

Sleep Loss and Resting Brain Connectivity

Peripheral functions of the body, including the regulation of the autonomic nervous system, are causally influenced by a select set of regions in the brain involved in viscerosensory and cardio-modulatory processes (Critchley et al., 2001; Critchley, 2005; Valenza et al., 2019). The second component of our experimental hypothesis sought to determine whether changes in connectivity within specific brain networks that regulate cardiovascular state occurred under conditions of sleep deprivation, and whether any such changes in these brain networks were interrelated or unrelated to the observed peripheral body changes in cardiovascular function.

First, at a main effects level, sleep loss resulted in a collection of connectivity changes within our a priori set of brain regions, the majority of which showed increases in their nodal connectivity. These connectivity changes all jointly shared at least one of two nodes: the insula and MPFC. The insular cortex is not only sensitive to sleep status (Sämann et al., 2010; Greer et al., 2013), but independent of sleep, is of central importance in the coordination of homeostatic processes through the registration and control of bodily states, including cardiovascular state (Yasui et al., 1991; Oppenheimer et al., 1992; Critchley et al., 2001; Gianaros et al., 2008). The MPFC, as with the insula, is also sensitive to sleep quality and quantity (Greer et al., 2013; Goldstein-Piekarski et al., 2015; Jiang et al., 2019; Simon et al., 2020), and separate from sleep, is known to orchestrate adaptive cardiovascular-challenge responses, including changes in blood pressure (Gianaros et al., 2008).

These findings therefore corroborate but also extend previous reports, indicating that sleep loss-related changes in insula and MPFC connectivity may reflect impairment of central brain networks involved in the fundamental coordination of basic cardiovascular physiology, potentially a reflection of a broader whole-body allostatic overload caused by sleep deprivation (McEwen, 1998, 2006). Fitting this proposition, both of these brain regions are highly interconnected with several cortical regions as well as subcortical and brainstem nuclei that can dictate peripheral autonomic activity through the registration and modulation of visceral states (Yasui et al., 1991; Oppenheimer et al., 1992; Critchley et al., 2001; Gianaros et al., 2008; Valenza et al., 2019).

In contrast to the dominant increases in connectivity caused by sleep loss, one pathway showed a decrease in connectivity under conditions of sleep loss: the link between the MPFC and ventromedial frontal cortex. Both regions have been previously associated with sympathetic nervous system drive and are part of the central autonomic network of the brain (Valenza et al., 2019). Lesioning of the MPFC is associated with increased hypothalamic-pituitary-adrenal axis stress responses (Diorio et al., 1993), which is of central importance for the integration of central brain and peripheral body states and vascular function (Burford et al., 2017). Furthermore, reduced activation in the MPFC has been associated with increased stress-induced vasoconstriction (Shah et al., 2019). Thus, the MPFC shows a bidirectional pattern of connectivity changes following sleep loss, wherein decreases in connectivity with the ventromedial frontal cortex may contribute to the withdrawal of cardiac sympathetic input (accounting for the withdrawal of cardiac

sympathetic input to the heart), while increases in connectivity with the insula, anterior cingulate, and amygdala contribute to the converse sleep loss-increase in blood pressure; a concept we address in more detail in the following section.

Sleep Loss, Cardiovascular State and Resting Brain Activity

Adding to the findings of sleep loss-related changes in peripheral cardiovascular state and central viscerosensory brain-network connectivity, we further demonstrate that changes in each of these domains are significantly associated with one another in several specific ways, fitting a potential brain-body interrelationship (Critchley et al., 2001; Valenza et al., 2019).

First, the increase in systolic blood pressure was associated with increased connectivity between two regions involved in the regulation of vascular tone: the insula and MPFC. Both the insula and MPFC are involved in the representation and generation of visceral states, including cardiovascular reactions (Gianaros and Sheu, 2009). Thus, these two regions, along with a network of corticolimbic and brainstem systems, play instrumental roles in tuning cardiovascular and autonomic adjustments in response to contextual physiological and behavioral demands (Critchley, 2005; Gianaros et al., 2008; Gianaros and Sheu, 2009). Indeed, the insula and MPFC are multi-synaptically connected to pre-autonomic nuclei which innervate both the heart and vasculature (Augustine, 1996; Öngür and Price, 2000). There is also evidence that increased resting activity in the insula and MPFC predicts greater evoked blood pressure reactions, which has been interpreted as signaling increased sympathetic-mediated blood pressure reactivity (Gianaros and Sheu, 2009).

A different part of the cardiovascular control network was observed to be associated with the sleep loss-increase in diastolic blood pressure. Here, the magnitude of sleep loss-increase in diastolic blood pressure was significantly associated with the degree of decreased connectivity between the MPFC and amygdala. The amygdala is broadly instrumental in coordinating behavioral and physiological adjustments through connections to cortical, hypothalamic, and brainstem nuclei involved in stress processing and autonomic-cardiovascular control (Gianaros and Sheu, 2009). Additionally, the amygdala can impact blood pressure through influence over the baroreflex, which serves to maintain blood pressure homeostasis through autonomic balance which regulates heart rate, cardiac output, and vascular resistance (Dampney, 1994). Thus, the reduction in amygdala connectivity to other regions involved in cardiovascular control (MPFC) could represent a degree of disorganization of central brain homeostatic functions. Indeed, suppressed baroreflex function has been associated with preclinical atherosclerosis (Gianaros et al., 2002) and cardiovascular disease risk (De Ferrari et al., 2007). Interestingly, the amygdala has been reported to contain both α- and β-adrenergic receptors (Rainbow et al., 1984; Unnerstall et al., 1984), and is intimately involved in the renin-angiotensin regulation of blood pressure in a dose-dependent manner (Heshmatian et al., 2007).

The vascular system is subject to several forms of regulation, including behavioral, autonomic, and endocrine (Oparil et al., 2003). The complexity of these multiple interacting pathways suggest that altered blood pressure control is due to a failure of a central control system, namely the brain (Jennings and Zanstra, 2009). Notably, in the current data, the sleep loss-decrease

in heart rate was not associated with the increase in blood pressure. Furthermore, blood pressure-related changes in functional connectivity in the brain were similarly not associated with heart rate. Taken together, it is likely that multiple, perhaps counteractive, processes underlie the conflicting vascular and cardiac responses to sleep loss, fitting with a loss of central brain regulation.

Sleep Loss, Mood States, Brain, and Body

The final component of the study examined inter-relationships with changes in mood state and anxiety. Independent lines of research have demonstrated that sleep loss detrimentally impacts affective states, including mood (Harvey, 2011). Moreover, mood states are known to causally alter cardiovascular function, including peripheral blood pressure (Räikkönen et al., 1999). In addition, the regulation of positive and negative mood states is further controlled by overlapping brain regions to those that are known to form the basis of central brain cardiovascular control, notably the insula and MPFC (Fornito et al., 2008; Namkung et al., 2017).

Fitting with prior findings (Harvey et al., 2011; Simon et al., 2020), sleep loss significantly worsened mood state through a reduction in positive mood and an increase in negative mood. We extend these findings, establishing that sleep loss-related increases in negative mood are further related to physiological changes within the body, here the shift towards hypertension.

Indicating potential mood-type specificity, we further show that this affective link to visceral function was specific to peripheral-body vascular tone and was significant for the increase in negative mood, and not the decrease in positive mood. Instead, the link to visceral function and the sleep loss reduction in positive mood was specific to the changes in functional brain connectivity, notably the viscerosensory network regions of the insula and MPFC.

These latter findings may therefore suggest a dissociable influence of affective mental state on vascular regulation under conditions of sleep loss: negative mood state linked to peripheral body vascular function, yet the loss of positive mood state linked to central brain visceral regulation. That there is significant overlapping functionality of the MPFC and insula in both emotional and viscerosensory brain regulation (Fornito et al., 2008; Bijsterbosch et al., 2014; Namkung et al., 2017) further suggests a convergence of regulatory function in these brain regions underpinning an embodied framework of sleep loss, one in which sleep deprivation impacts affective and cardiovascular function through impairment of core regulatory centers in the brain.

More generally, our results indicate the presence of a coupled relationship between vascular responses to sleep loss, brain function and mental-state changes in affect. Such findings impress the previously proposed conception of sleep loss triggering broad homeostatic biological distress caused by allostatic overlap (McEwen, 2006). Pragmatically, these findings highlight the target of sleep as a risk factor, and modifiable intervention target, determining cardiovascular disease risk, here through regulation of central brain and mental-state mechanisms that control cardiovascular function with the goal of maintaining vascular tone within a normotensive range.

Study Considerations

Our findings must be appreciated within the context of several key limitations. First, the design of the study means that the direction of causality between brain and body in the noted associations cannot be determined. Towards this end, studies that manipulate one of the two (e.g., using transcranial direct current stimulation to modulate specific functional connectivity circuits in the desired direction, thereby blocking an increase in peripheral body blood pressure) will be necessary. Second, this experiment was performed on healthy young adults by design so as to investigate any shifts from a healthy to an unhealthy cardiovascular profile. However, it remains to be determined whether these findings would translate to those with pre-existing hypertension or other forms of cardiovascular disease. Related, it remains unknown how our findings would be altered under conditions of a specific cardiovascular challenge, since the brain and body changes measured in the current study were obtained under passive resting conditions. That said, several of the brain changes we observed, including the insula, MPFC and amygdala have all been previously shown to be implicated in cardiovascular-challenge-induced modulation of blood pressure and heart rate (Gianaros et al., 2008). Finally, whether similar changes in brain, body and brain-body interrelationships would be observed under conditions of partial sleep restriction—across a single night, or chronically, fitting a common profile of sleep insufficiency in society—remains to be determined.

V. General Conclusions

Taken together, the results presented in this thesis support the overarching hypothesis that sleep contributes to allostatic load by disturbing the whole-organism coordination of adaptive systems, including both the brain and the body. **Chapter 2** demonstrated the first premise of this hypothesis. As the central organ and master regulator of allostasis (McEwen, 1998), sleep deprivation produces marked disturbances in the activity and connectivity of the brain, resulting in significant changes in the cognitive and emotional functions governed by these brain networks. However, as the main organ of adaptation, the brain does not only serve cognitive and emotional function and their associated behaviors. According to the embodied framework of this thesis, the brain is situated in the body, in constant contact with the internal environment, as required for allostasis. Therefore, it was predicted that changes in brain function resulting from sleep loss would not only be paralleled in the body; sleep loss-related dysfunction in the brain and the body were expected to be significantly interrelated. **Chapter 3** and **chapter 4** supported this hypothesis, each demonstrating interrelationships between changes in brain function and the activity of two model peripheral body systems of adaptation, the immune and cardiovascular systems. Two general conclusions emerge from these chapters.

First, the experiment presented in **chapter 3** demonstrated the pro-nociceptive effects of sleep deprivation. As the prototypical example of a homeostatic emotion (Craig, 2002), that is, an emotion generated by homeostatic afferents in the body that motivates behavior, pain is a distributed process. It requires the bidirectional communication of the brain and the body, including the immune system. It was therefore predicted that sleep deprivation would result in increased pain perception through both central brain and peripheral immune dysfunction, and that this distributed dysfunction would be significantly related. Indeed, it was found that sleep loss amplified the registration of nociceptive signals within the first-order registration site of the somatosensory cortex. Perhaps more significant, sleep loss impaired activity within integrative brain regions of the insular cortex and NAcc. These regions, particularly the dopaminergic NAcc, are involved in pain valuation and regulation through descending efferent pathways. However, the crucial evidence supporting the main hypothesis comes from the body. It was found that sleep loss-increased levels of the pro-inflammatory and pro-nociceptive cytokine, IL-6, accompanied changes in pain processing in the brain. Rather than simply co-occurring, the sleep loss-increased levels of IL-6 were significantly associated with the decrease in NAcc activity during pain. Therefore, this evidence suggests that the increase in circulating inflammatory signals interferes with dopamine-related analgesic activity within the NAcc, resulting in a brain-body amplification of pain sensitivity. Collectively, this experiment supports the embodied framework of sleep loss and suggests that sleep loss-increased pain is a direct consequence of the changes within and communication between allostatic systems in the brain and body.

Second, the experiment presented in **chapter 4** aimed to extend this embodied framework to another major system of adaptation, the cardiovascular system. It was predicted that sleep loss would result in increased blood pressure and that this change in peripheral vascular tone would be interrelated with connectivity changes in viscerosensory and autonomic control networks of the brain. Sleep loss did result in increased blood pressure and simultaneous broad changes in the connectivity pattern of cardiovascular control brain networks. Furthermore, and fitting with the overarching hypothesis of this thesis, these changes in peripheral vascular tone and central brain networks were significantly associated. However, it was expected that altered autonomic balance

would mediate this relationship between increased blood pressure and compromised brain connectivity, as these cardiovascular control networks are known to modulate cardiovascular state partially through the regulation of the ANS (Critchley et al., 2001; Critchley, 2005; Amiya et al., 2014; Valenza et al., 2019). Interestingly though, a vascular-cardiac dissociation was discovered in which peripheral blood pressure increased while heart rate decreased and heart rate variability increased. As a measure of vagal modulation to the heart, heart rate variability represents the current autonomic outflow of the viscerosensory brain to the heart. The experimental findings therefore suggest dissociable mechanisms of influence on cardiovascular state following sleep deprivation. Increased vagal influence on the heart results in slowed heart rate and increased heart rate variability, while a separate mechanism causes an increase in blood pressure. Notably, only the change in blood pressure was associated with changes in viscerosensory brain network connectivity, suggesting a non-autonomic mechanism relating altered brain connectivity to increased vascular blood pressure. As all systems of adaptation in the body, including the cardiovascular system, are subject to multiple forms of, perhaps even counteractive, regulation, the dissociable effects of sleep loss on cardiac and vascular function fit with a loss of central brain coordination of allostasis. Finally, this experiment also showed an influence of affective mental state on vascular regulation following sleep loss. Increases in negative mood were linked to increased blood pressure, while decreases in positive mood were linked to changes in brain connectivity. The embodied framework of this thesis holds that there is significant overlap between emotional and viscerosensory brain function. Fitting with this, these findings demonstrate a convergence of affective and vascular dysfunction through sleep loss-impairment of the viscerosensory brain.

In summary, this thesis challenges the notion that sleep loss simply impairs the biological functioning of isolated systems. The dysfunction observed across the brain and the body caused by sleep loss are intimately interrelated, and this is explained by the function of sleep. Sleep serves allostasis by coordinating adjustments in the activity of adaptive systems, such as the immune and cardiovascular systems, under the central control of the brain. The absence of sleep, then, represents a challenge to the very process of allostasis itself, resulting in a high cost of adaptation, or allostatic load. Considering that many chronic diseases are characterized by both sleep disturbances and high allostatic load, the evidence presented in this thesis demonstrates that sleep loss contributes to disease by increasing the physiological cost of adaptation.

VI. References

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