Insomnia disorder and endogenous neurophysiological dynamics
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Chapter 1

Introduction

1 Insomnia Complaints

Insomnia symptoms are the most common medical complaints, affecting up to a third of the general population. Insomnia symptoms constitute a dramatic and wide-ranging socioeconomic burden—tens of billions in the U.S. alone (Chilcott and Shapiro, 1996; Kessler et al., 2011)—not only due to health-care expenses, but also due to decreased work productivity and proneness to injuries. Insomnia symptoms include sleep problems as well their repercussions on wake-time functioning. Sleep-related symptoms concern non-restorative sleep, poor sleep quality or quantity despite adequate sleep opportunity, with problems at one or several parts of the sleep period: at the beginning (sleep initiation), middle (sleep maintenance) or terminal (early-morning awakening) part. Wake-time symptoms include the following: fatigue, inability to concentrate, memory impairments, altered mood, irritability, tension, headaches, reduced energy and motivation, daytime-sleepiness, worries about sleep, work/school dysfunctions and proneness for accidents (American Psychiatric Association, 2013; Edinger et al., 2004; Espie et al., 2012; Wilson et al., 2010).

On one hand, genetic, epigenetic and developmental factors may predispose one to insomnia, while on the other hand, adverse and stressful life events may precipitate insomnia symptoms (Morin et al., 2015; Spielman et al., 1987). Insomnia symptoms may also be precipitated by multiple somatic, psychiatric, neurological, and psychological conditions. Yet, it is not always possible to disentangle causal relationships between insomnia symptoms and other comorbid conditions. In fact, insomnia symptoms as a whole constitute the most central hub in the network of associations between all psychopathological symptoms (Borsboom et al., 2011). Interestingly, insomnia symptoms may persist even after the precipitating factors have remitted.

2 Insomnia Disorder

While acute insomnia symptoms tend to remit spontaneously over the short term (days or weeks) in most individuals, in some individuals they endure over the long term (months or years). In the latter case, when the symptoms become recurrent (i.e. at least 3 times a week) and persistent (i.e. more than 3 months), Insomnia Disorder can be diagnosed (American Psychiatric Association, 2013). Insomnia Disorder affects approximately 10% of the population (according to the DSM-IV definition), and has a staggering high persistence rate: 74% at 1 year, and 46% at 3 years of follow-up (Morin et al., 2009). Insomnia Disorder severely reduces the quality of life (Kyle et al., 2010), and carries an increased risk of severe, long-lasting health problems, including cardiovascular (Laugsand et al., 2011; Spiegelhalder et al., 2011) and mood (Baglioni et al., 2011) disorders. Given its high prevalence, persistence and impact on health, it is highly
important to study the pathophysiology of Insomnia Disorder.

3  Hyperarousal

Multiple theories of insomnia have been developed over the years (Espie, 2002; Perlis et al., 1997; Spielman et al., 1987) to explain how the disorder develops and is sustained over time. People who suffer from Insomnia Disorder mostly attribute their sleep troubles to cognitive and emotional factors such as intrusive negative thoughts and the inability to unwind a racing mind during bed-time (Lichstein and Rosenthal, 1980; Watts et al., 1994), as confirmed by recent British epidemiological data (https://www.sleepio.com/2012report/). Over the years, researchers gathered evidence that Insomnia Disorder entails a state of hyperarousal—which is a state of heightened cognitive, emotional, somatic and neurophysiological activation that interferes with the initiation and maintenance of sleep. (Bonnet and Arand, 1997; Riemann et al., 2010, 2015). Multiple neurobiological pathways could be involved in the etiology of hyperarousal, including wake and sleep promoting nuclei (Cano et al., 2008) and networks regulating emotion, reward and cortical excitability (Altena et al., 2010; Stoffers et al., 2014; Wassing et al., 2016). Hyperarousal can be investigated at multiple levels of the neurobiological organization, from the cellular up to the level of large-scale brain dynamics (Bonnet, 2010; Bonnet and Arand, 2010b; Morin et al., 2015; Riemann et al., 2010). Despite the large body of work conducted up to date, the current understanding of hyperarousal at the level of large-scale neurophysiological dynamics is still preliminary. Furthermore, while many studies have focused on neurophysiological activity evoked by a specialized task, the study of the endogenous, spontaneous activity is emerging as a promising new field (Michel and Murray, 2012; Stam, 2005). Thus, investigating the large-scale endogenous neurophysiological dynamics is a key step to understand the pathophysiology of Insomnia Disorder.

4  Scope of the Thesis

If we had a better understanding of the pathophysiology of Insomnia Disorder and insomnia complaints, we could expose the fundamental mechanism that underlie the disorder, and thus highlight potential therapeutic targets. Current pharmacological treatments of Insomnia Disorder are devoted to alleviate symptoms and not the underlying causes of the disorder. Insomnia Disorder often endures years, if not decades, suggesting it is underpinned by neurophysiological alterations that settle the nervous system to a novel equilibrium. We argue that a better understanding of the endogenous neurophysiology of medication-free people suffering from Insomnia Disorder is needed to evaluate the efficacy of hypnotics, and help developing new treatments in general. By studying the neurophysiological basis of Insomnia Disorder we aim to highlight which neurophysiological processes are altered and contribute to the maintenance of the disorder.
5 Outline of the Thesis

In the current thesis we focus on the underlying mechanisms of Insomnia Disorder, specifically on the endogenous (i.e. not experimentally manipulated) neurophysiological dynamics at the macroscopic level, assessed through different vigilance states. For this purpose, we recruited a relatively large cohort of participants that spanned from early to late adulthood, were free from sleep medications, and belonged to either a group suffering from Insomnia Disorder, or to a group of age and sex–matched controls. Endogenous neurophysiological dynamics were investigated by means of high-density electroencephalography (HD-EEG), obtained during resting-state evening wakefulness and during nighttime sleep. Specifically, we evaluated wake neurophysiological dynamics—related to ongoing oscillations and to the response to cardiac activity—and the macrostructure of sleep dynamics—related to the transition between sleep stages. We then considered how the endogenous neurophysiological dynamics were altered in Insomnia Disorder and how these modified with the severity of insomnia complaints, to uncover potential signatures of hyperarousal.

6 EEG Dynamics During Wakefulness

We begin by considering the endogenous neurophysiological dynamics occurring during quiet wakefulness. Even in absence of any explicit task, the brain at rest generates highly complex dynamics. The structure of these dynamics carries a wealth of information about the brain's functional organization, which can reveal—through sophisticated analysis techniques—the dysregulations occurring in Insomnia Disorder and with individual differences in insomnia complaints. A large part of these endogenous brain dynamics is generated by the ongoing intrinsic oscillatory brain activity, and a tiny part is evoked by the ever-present heartbeat. First, we investigated the intrinsic, ongoing brain oscillations during evening resting-state wakefulness: specifically the strength of oscillations (through power spectral analysis) and the temporal autocorrelation of oscillations (through the analysis of long-range temporal correlations).

6.1 Power Spectral Analysis of EEG Oscillations

Multiple studies have analyzed how the spectral composition of sleep EEG is altered in Insomnia Disorder. A common finding is elevated amplitude of high-frequency oscillations—a long-standing signature of hyperarousal (Freedman, 1986; Perlis et al., 2001a). However, few studies have considered the spectral composition of the wake EEG, and the majority of these studies looked at wake epochs during night-time bed recordings. The findings have been relatively inconsistent, plausibly due to small sample sizes, different inclusion criteria and heterogeneity of conditions and settings. Furthermore, these studies usually analyzed few channels and frequency bands, which granted them poor spatial and spectral resolution. To overcome these limitations, we undertook a study of adequate sample size, with stringent inclusion criteria, in a standardized setting for data acquisition. In chapter 2 we will consider the amplitude of the ongoing brain
oscillations during wakefulness, with a fine-grained spatiotemporal resolution. For multiple electrodes we estimated the spectral composition of the EEG-signals at multiple frequency bins, and explored possible group differences related to Insomnia Disorder, using a powerful and rigorous framework to correct for multiple comparisons. We will discuss plausible neuropsychological processes that are functionally involved in the observed neurophysiological alterations, and the implications for the construct of hyperarousal.

6.2 Long-Range Temporal Correlations in EEG oscillations

The spectral composition of the brain's ongoing oscillations revealed important characteristics of the brain functional organization in Insomnia Disorder. However, the amplitude of these ongoing brain oscillations varies over time in a highly structured manner—oscillations wax and wane—hence the mean amplitude does not capture these complex temporal dynamics. Brain oscillations display a temporal organization that is sustained across multiple scales, such that even small changes in the activity in the past can shape future activity over the long run. This scale-invariant temporal organization of brain oscillations can be characterized by their Long-Range Temporal Correlations (LRTC)—autocorrelations that decay over time according to a power-law (Hardstone et al., 2012).

In chapter 3 we will consider the LRTC of band-filtered oscillations during restful wakefulness. Previous modeling work related the strength of LRTC to the critical balance between excitatory and inhibitory processes (Poil et al., 2012). Specifically, in the physiological domain where excitation does not dominate over inhibition, (Priesemann et al., 2013, 2014) stronger LRTC can index a stronger excitation to inhibition ratio (Poil et al., 2012). Sleep is hypothesized to regulate these scale-invariant dynamics (Pearlmutter and Houghton, 2009), by enabling the brain to maintain the balance between excitatory and inhibitory signaling. Sleep therefore prevents the formation of self-reinforcing excitatory loops that could yield an imbalance towards excitation. A net imbalance towards excitation would favor large cascades of activity and ultimately seizures (Meisel et al., 2013, 2015). Seizures are likely due to a large increase of the ratio between excitation and inhibition (DiNuzzo et al., 2014; Scharfman, 2007) and can arise after prolonged total sleep deprivation in susceptible individuals (Ellingson et al., 1984; Friis and Lund, 1974; Gunderson et al., 1973; Rodin et al., 1962). Consistently, in healthy individuals sleep deprivation yields a net increase of cortical excitability (Huber et al., 2013). Insomnia Disorder involves only a moderate amount of sleep loss, therefore it could involve a subtle alteration of the ratio between excitation and inhibition, preserving the overall inhibitory bias of the physiological balance between excitation and inhibition. In line with the notion of hyperarousal, we hypothesized that Insomnia Disorder and the severity of sleep complaints would yield a reduction of the net inhibitory bias, and thereby also increase LRTC.
6.3 Heart-beat Evoked Potentials

We then considered the spontaneous wake neurophysiological dynamics that are not intrinsically generated in the brain, in particular those evoked by cardiac activity. While previous studies have shown heightened sensitivity to exogenous sensory information in Insomnia Disorder, it remains to be addressed whether insomnia also entails heightened sensitivity to endogenous sensory information—as observed in depression and anxiety disorder. In chapter 4 we will consider the neurophysiological response to the heart-beat, as a marker of interoceptive sensitivity. We reasoned that interoceptive hyper-sensitivity may be one possible phenotype of hyperarousal, interfering with the process of sleep initiation. We therefore hypothesized that Insomnia Disorder would entail a larger neurophysiological response evoked by the heartbeat.

7 Macrostructure of Sleep EEG: Dynamics of Stage Transitions

Finally, we will consider the macrostructure of sleep dynamics. Previous studies on the macrostructure of sleep considered the standard polysomnographic measures derived from the amount of each sleep stage (absolute or relative to the amount a person slept), revealing higher intrusion of wakefulness after sleep onset, reduced slow-wave sleep and reduced Rapid Eye Movement (REM) sleep (Baglioni et al., 2014). However, previous studies typically did not consider the dynamics in the sleep macrostructure. Sleep stages are usually structured into a 90 - 120 minute sleep cycle, going from light to deep non-REM sleep, to REM sleep. Therefore, some sleep stages are more likely to be followed by others. Furthermore, each sleep stage may last from a few to tens of epochs, such that longer epochs are exponentially rarer than shorter ones. In chapter 5 we will consider the stability of each sleep stage and the transitions between sleep stages. Specifically, we investigated the survival rate of each sleep stage, and the likelihood of transition between each sleep stages. We hypothesized that the macrostructure of sleep dynamics in Insomnia Disorder would show signatures of hyperarousal, and thus be characterized by shorter bouts of sleep and by a higher probability of deeper stages to revert to lighter stages of sleep.

8 Discussion

In Chapter 6 we will summarize the findings of the previous chapters, and put them in perspective within the growing literature on the neurophysiology of Insomnia Disorder. The alterations in spontaneous neurophysiological dynamics that we uncovered in the thesis will be discussed with respect to the current understanding of hyperarousal. We will connect the neurophysiological findings to the neuropsychological processes that are involved in Insomnia Disorder and with individual differences in the severity of insomnia complaints. Finally, we will discuss the caveats for future research and give recommendations.
References


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