Insomnia disorder and endogenous neurophysiological dynamics

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Contents of Chapter 6

1. Summary ................................................................................................................................. 111
2. Hyperarousal .......................................................................................................................... 113
   2.1. Strong Oscillations in a Broad Beta range
   2.2. Interoceptive Hypersensitivity
   2.3. Shallow and Fragmented Sleep
3. Weaker inhibitory bias in cortical networks? ................................................................. 114
   3.1. Distribution of Spectral Power
   3.2. Stronger Long-Range Temporal Correlations in People with More Severe Insomnia Complaints
   3.3. Insomnia Disorder, Excitation/Inhibition Balance and Epilepsy
4. Deficient Attentional Filter ..................................................................................................... 121
   4.1. Deficits in Attentional Tasks
   4.2. Salience Network Malfunctioning?
5. Caveats and Recommendations for Future Insomnia Research ........................................... 123
6. Main points ................................................................................................................................ 125
7. References .................................................................................................................................. 126
Chapter 6

Discussion

This thesis investigated the endogenous neurophysiological dynamics of Insomnia Disorder and insomnia complaints during wakefulness and sleep, with the purpose of uncovering their underlying mechanisms. The present discussion first summarizes the results and the interpretations of the experiments described from chapter 2 to chapter 5. Subsequently, the functional implications of the findings are discussed more extensively, considering which neurophysiological and neuropsychological mechanisms are altered in Insomnia Disorder, with a particular emphasis on the construct of hyperarousal. The findings are moreover considered within the frameworks of (1) balanced excitatory and inhibitory signaling in the brain, and of (2) attentional filtering of information processing. Furthermore, parallels to other related pathological conditions, such as epilepsy and anxiety disorder, are proposed. Directions for future research are outlined contextually where issues remain unresolved. Finally, general caveats and recommendations for future neurophysiological research of Insomnia Disorder are discussed.

1. Summary

Chapter 2 addressed the overall strength of ongoing EEG oscillations across several frequencies and locations during wakefulness. Compared to controls, people suffering from Insomnia Disorder show stronger high-frequency oscillations in a broad beta-gamma frequency band over widespread cortical regions during the eyes closed condition. During the eyes open condition, they exhibit weaker low-frequency oscillations in a narrow upper-alpha frequency band over widespread cortical regions. Insomnia Disorder therefore entails strong beta oscillations not only during the sleep onset period and NREM sleep, as previously reported (Perlis et al., 2001a), but also during eyes closed wakefulness, suggesting a round-the-clock state of hyperarousal. The weaker upper-alpha band oscillations during eyes open could reflect suboptimal attentional filtering, resulting in poor suppression of irrelevant cognitive processes (Klimesch, 2012). Oscillations in the upper-alpha band may reflect the suppression of irrelevant and interfering cognitions—enabling selective access to sensory and semantic memory (Klimesch et al., 2006, 2007). Therefore, suboptimal expression of upper-alpha oscillations could be involved in both day-time difficulty to concentrate (Edinger et al., 2004) and bed-time intrusion of perceptions and cognitions—two core traits of Insomnia Disorder.

Chapter 3 addressed dynamical aspects of ongoing EEG oscillations during wakefulness, in particular their Long-Range Temporal Correlations (LRTC). The strength of LRTC in Insomnia Disorder and controls did not differ; however, within both groups, LRTC during eyes open increased with the severity of insomnia complaints. In Insomnia Disorder, the severity of insomnia complaints—ranging from moderate to severe—
correlated with LRTC in low frequencies. In controls, on the other hand, the severity of insomnia complaints—ranging from absent to mild—correlated with LRTC in high frequencies. Hence, the severity of subjective insomnia complaints increase with LRTC both in Insomnia Disorder and controls, but in different spectral ranges. Previous studies using EEG (Kantelhardt et al., 2015) or fMRI (Tagliazucchi et al., 2013) have shown LRTC to decrease with sleep. Therefore, if the interindividual differences in the strength of LRTC during daytime persist during the night, it would be conceivable that those with an insufficient decrease of LRTC experience low sleep quality. LRTC strengthen when increasing the excitation to inhibition ratio in simulated networks dominated by inhibition, and reach a maximum when excitation and inhibition are balanced (Poil et al., 2012). Further increasing the ratio beyond the balance point weakens LRTC. Several studies suggest that—while excitation and inhibition in cortical networks are approximately proportional over time—the exact excitation to inhibition ratio changes in time and across neurons (Bennett et al., 2013; Dehghani et al., 2016; Gao et al., 2016; Isaacson and Scanziani, 2011; Rudolph et al., 2007). Overall, cortical networks may be on average more skewed towards inhibition (Haider et al., 2013; Priesemann et al., 2014; Rudolph et al., 2007). Under this condition, a network showing stronger LRTC would be less biased towards inhibition. Our LRTC findings suggest that, on average, the balance between excitation and inhibition does not differ between people with Insomnia Disorder and controls. However, the associations between individual differences in insomnia complaints and LRTC within each group may still suggest an association of the subjectively experienced severity of sleep complaints with the balance between excitation and inhibition, but in brain processes specific to each population.

Chapter 4 addressed the EEG response to one’s own heart-beat as a possible marker of interoceptive sensitivity. The Heart-beat Evoked Potential (HEP) during eyes closed showed a stronger late (± 500 ms) frontal component in Insomnia Disorder than in controls. Future studies may address whether the interoceptive hypersensitivity may involve insufficient attentional filtering and regulation of the brain’s salience network (Menon and Uddin, 2010). Indeed, people with insomnia have increased coactivation of the salience network with the insula, a structure of key importance to interoception (Chen et al., 2014). The finding of interoceptive hypersensitivity supports the notion that hyperarousal in Insomnia Disorder persists during wakefulness.

Chapter 5 addressed the macrostructure of EEG dynamics during sleep. We observed a steeper decline of the survival functions of sleep bouts, specifically for stage non-REM 2 (N2), in Insomnia Disorder. Stage N2 was more likely to be followed by N1 and wakefulness in Insomnia Disorder as compared to controls. Furthermore, in Insomnia Disorder light-sleep N1 was more frequent, whereas deep sleep N3 was less frequent. The findings point to a specific vulnerability of stage N2 in Insomnia Disorder, with shorter bouts that tend to be interrupted by lighter sleep or wakefulness. This specific sleep structure may be indicative of the night-time hyperarousal in Insomnia Disorder. Indeed, shallower and fragmented sleep
can result from the activation of wake-promoting structures simultaneously with sleep promoting structures (cf. Riemann et al., 2015).

2. **Hyperarousal**

Hyperarousal of the central nervous system is proposed to play a key role in the pathophysiology of Insomnia Disorder (Bonnet and Arand, 2010a; Riemann et al., 2010). Our findings on the endogenous EEG dynamics during wakefulness and sleep corroborate the construct of neurophysiological hyperarousal. Indeed, Insomnia Disorder is characterized by stronger oscillations in the beta-gamma band and increased interoceptive sensitivity during wakefulness; and by shallower and more fragmented sleep. Overall, the results converge to suggest that neurophysiological hyperarousal is characteristic of Insomnia Disorder across wakefulness and sleep.

2.1. **Strong Oscillations in a Broad Beta range**

In chapter 2 we observed that, during eyes-closed wakefulness, the power of high-frequency oscillations relative to the background spectral power was stronger in Insomnia Disorder as compared to controls. As a novelty of the study, we showed that such alteration is spatially and spectrally widespread, thereby suggesting a rather global alteration of high-frequency spontaneous neurophysiological oscillations, in a broad beta range that reached the gamma range. Strong high-frequency oscillations, in the beta and gamma range, constitute a classical signature of neurophysiological hyperarousal (Freedman, 1986), which is typically observed around sleep onset and in NREM sleep in Insomnia Disorder (Perlis et al., 2001b). Strong beta oscillations in Insomnia Disorder have also been observed in wakefulness epochs during bed-time prior sleep onset (Corsi-Cabrera et al., 2012; Freedman, 1986; Wolynczyk-Gmaj and Szelenberger, 2011), and in resting-state wakefulness (Freedman, 1986), though the finding was not replicated by others (Buckelew et al., 2009; Cervena et al., 2014; Hauri, 1981). One study failed to find strong beta oscillations in insomnia throughout different vigilance states, which was interpreted as lack of hyperarousal in the selected sample (Wu et al., 2013). The study also showed moderately strong correlations of spectral power in the beta range during wake and sleep, which suggested that the strength of beta oscillations could represent a trait with individual differences represented in both sleep and wakefulness. Furthermore, sleep quality modulates the overnight decline of power in high frequencies: people with Insomnia Disorder show a smaller overnight decline in EEG beta and gamma power as compared to controls (Corsi-Cabrera et al., 2016). Of note, individual differences in subjective sleep quality correlated with the strength of their overnight decline in EEG beta and gamma power. Strong beta oscillations might be a stable trait of people with Insomnia Disorder, since these have been observed during sleep as early as adolescence (Fernandez-Mendoza et al., 2016).
In conclusions, the relatively stronger beta oscillations that we observed during evening wakefulness with eyes closed support the idea that insomnia is a 24 hour disorder characterized by round-the-clock hyperarousal.

2.2. **Interoceptive Hypersensitivity**

Besides the abnormalities in spontaneous oscillations, we observed neurophysiological signatures of heightened sensitivity to interoceptive signals in Insomnia Disorder. As detailed in chapter 4, people with Insomnia Disorder displayed a larger neurophysiological response to the heart-beat, in a late frontal Heart-beat Evoked Potential component during eyes closed wakefulness. Such finding is consistent with a state of hyperarousal, inasmuch interoceptive hypersensitivity may hamper the disengagement from bodily signals that normally accompanies the process of falling asleep (Ogilvie, 2001). In order to further confirm this hypothesis, the analysis of the HEP should be extended to the sleep onset period.

A larger cortical response to the heart-beat extends previous finding of altered autonomic balance in Insomnia Disorder, with increased sympathetic activity and reduced parasympathetic activity (Bonnet and Arand, 1998, 2010a), thus linking hyperarousal of the central and peripheral branch of the nervous system. It remains to be addressed how the peripheral and central components of hyperarousal influence and reinforce each other.

2.3. **Shallow and Fragmented Sleep**

Evidence consistent with hyperarousal was also found in the macrostructure of sleep dynamics of Insomnia Disorder, as mentioned in chapter 5. Classic PSG indexes indicated an overall shallower sleep: light sleep N1 was more frequent, and deep sleep N3 was less frequent. The dynamics of NREM sleep, and in particular of sleep stage N2, were characterized by shorter bouts and more frequent transitions to more vigilant stages (either lighter sleep or wakefulness). Stage-N2 sleep was fragmented. A similar shallow and fragmented sleep was reported as a result of simultaneous activation of wake and promoting circuits of the brain (Cano et al., 2008; Riemann et al., 2015; Saper et al., 2005). Future studies should investigate the EEG microstructure during N2 sleep, to observe possible irregularities in the recurrence of spindles, k-complexes and cyclic alternating patterns. Investigating the dynamics of EEG microstructural components could aid our understanding of the neurophysiological mechanisms underlying N2 sleep fragmentation in Insomnia Disorder.

3. **Weaker inhibitory bias in cortical networks?**

The hyperarousal model of insomnia posits that heightened neurophysiological activity hampers the sleep of people with Insomnia Disorder. Heightened neurophysiological activity may result from increased activation of arousal mechanisms (Bonnet and Arand, 2010b), as well as from reduced activation of ‘de-
arousal’ mechanisms (Espie, 2002). Conceivably, Insomnia Disorder may result from increased excitatory and/or reduced inhibitory signaling in cortical networks (Bastien, 2011), even during wakefulness. Under normal physiological conditions, inhibitory and excitatory signaling are almost in proportion: they exhibit wide coordinated fluctuations, while maintaining an overall slight bias towards inhibition (Hahn et al., 2017; Haider et al., 2013; Priesemann et al., 2014; Rudolph et al., 2007). This baseline net inhibitory bias may therefore be reduced in Insomnia Disorder.

Molecular, cellular and network mechanisms act jointly to shape the amount of excitatory and inhibitory signaling, while maintaining their ratio approximately constant across spatial and temporal scales. The two main regulatory neurotransmitters of the balance between excitation and inhibition in the central nervous system are glutamate and GABA. The glutamatergic system promotes arousal and inhibits sleep; vice versa the GABAergic system promotes sleep and inhibits arousal (Saper and Fuller, 2017). Even though the proportion of glutamatergic neurons is 4 to 5 times larger than that of GABAergic neurons, the latter form stronger synapses and fire more frequently than the former (Isaacson and Scanziani, 2011; Peyrache et al., 2012). Together, glutamatergic and GABAergic systems constitute the majority of neuronal signals mediated by receptors and require most of glucose metabolic expenses in cortical grey matter (Chowdhury et al., 2007). Cortical arousal is also modulated by diffuse projections from monoaminergic, cholinergic and peptidergic neurons in the brainstem (Saper and Fuller, 2017).

The balance between excitation and inhibition in cortical networks is favored structurally by two prototypical connectivity patterns. Feedforward and feedback inhibitory circuits ensure that incoming and local excitatory neurons also recruit inhibitory interneurons (Isaacson and Scanziani, 2011) with a time lag of few milliseconds. This lag is crucial for gating activity transients (Kremkow et al., 2010).

Balanced excitation and inhibition has been observed during both spontaneous- and stimulus induced- neuronal activity, as measured by intracellular recordings of postsynaptic potentials in neighboring excitatory neurons (Atallah and Scanziani, 2009; Okun and Lampl, 2008). Furthermore, excitation and inhibition in a cortical network vary widely over time, but they remain approximately balanced through all stages of the wake-sleep cycle (Dehghani et al., 2016).

Still, excitation and inhibition are not in a perfect static balance throughout the brain. Despite the overall proportionality of excitation and inhibition, their ratio varies dynamically over time and spatially across neurons (Isaacson and Scanziani, 2011; Rudolph et al., 2007). Although the ratio of excitation and inhibition (E/I) in a cortical network is instantaneously determined by incoming synaptic inputs, it displays highly rich dynamics across multiple temporal scales. Temporary deviations from a perfect balance happen at short-time scales—within a single oscillation cycle (Gao et al., 2016)—and on longer-time scales—at least up to the scale of ten seconds (Dehghani et al., 2016). Furthermore, the strength and amount of excitatory and inhibitory connections are shaped on even longer-time scales by synaptic plasticity (Hennequin et al., 2017; Turrigiano and Nelson, 2004).
The ratio of excitation and inhibition influences how neural activity propagates across a neural network. Subtle change in the E/I facilitates or suppresses the propagation of neural firing rates (Vogels and Abbott, 2009). With a bias towards excitation, the network loses the capacity to give specific responses to inputs—due to excessive background noise; with a bias towards inhibition, the network loses sensitivity to inputs—due to suppression of propagating activity (Shew et al., 2009). Extreme non-physiological modulations of the E/I strongly affect the propagation of neural activity. Selective pharmacological suppression of inhibitory or excitatory activity can lead to a hyper-excitable or silent state, respectively resembling epileptiform or comatose activity (Dudek and Sutula, 2007). Consistently, a pathological imbalance towards inhibition is observed during general anesthesia (Gao et al., 2016); and an imbalance towards excitation promotes epileptic seizures (DiNuzzo et al., 2014; Scharfman, 2007). Thus, modulating the E/I provides a gating mechanism that is crucial for information processing, action selection, and it sets the dynamical state of the network between two extremes.

Balanced excitation and inhibition confer many advantageous properties to a neural network. When inhibitory and excitatory mechanisms are balanced, network activity can be sustained: it does not fade away nor it propagates explosively across the network (Vogels et al., 2005). An approximate balance of excitation and inhibition in cortical and simulated networks yields spontaneous cascades of activity that do not have a prevalent spatial or temporal scale, such that spatial and temporal correlations take a power-law form (Poil et al., 2012; Shew et al., 2009). Balanced excitation and inhibition enables a rich dynamical repertoire (Shew et al., 2009), and maximal information and transmission capacity (Beggs, 2008; Shew et al., 2011). However, awake cortical networks may actually be somewhat biased towards inhibition—as observed in spontaneous and sensory-evoked activity (Haider et al., 2013; Priesemann et al., 2014; Rudolph et al., 2007)—while retaining the possibility of transiently getting closer to a balanced state (Hahn et al., 2017).

In sum, cortical networks may operate in a state slightly biased towards inhibition (E/I < 1), which at once prevents runaway activity and retains the computational and transmission benefits of approaching a balanced state. Therefore, maintaining the E/I of cortical networks within a functional range is of the utmost importance for the whole organism. Sleep is hypothesized to homeostatically maintain the E/I of cortical networks within a functional range (Meisel et al., 2015; Pearlmutter and Houghton, 2009). Poor sleep quality reported by people with Insomnia Disorder could therefore involve a different functional range of the E/I. Since the hyperarousal model posits that Insomnia Disorder is a 24 hours disorder, we hypothesized that in Insomnia Disorder the E/I may be higher than in controls even during wakefulness—specifically, while the ratio may still be lower than 1, the net balance may be less biased towards inhibition in Insomnia Disorder. In chapter 2 and chapter 3 we obtained EEG indexes during spontaneous wakefulness that provide indirect evidence of the excitation to inhibition ratio over large-scale cortical networks on the time-scale of minutes.
3.1. Distribution of Spectral Power

In chapter 2, we observed that the ratio between the EEG power of the lower (1.5–16 Hz) over that of the upper (16–40 Hz) part of the spectrum (LO/HI RATIO), was reduced in Insomnia Disorder as compared to controls, both during eyes open and eyes closed wakefulness. In agreement with spectral changes related to different vigilance states, this finding suggests that in Insomnia Disorder the E/I is less biased towards inhibition. When vigilance drops during drowsiness and sleep onset, the power in the range of low frequencies increases and the power in the range of high frequencies decreases (De Gennaro et al., 2001). During deeper states of pharmacological sedation, these two spectral changes can be exploited to track anesthetic depth, using the median frequency, spectral edge frequency and related spectral indexes (Tonner and Bein, 2006). Compelling support for weaker inhibition in Insomnia Disorder comes from a study on patients undergoing surgery to treat an unrelated hepatic condition, cholelithiasis (Erden et al., 2016). In this study, sevoflurane levels were continuously adjusted during surgery according to the bispectral index, a common proprietary measure derived from the EEG. People with chronic insomnia needed a larger amount of anesthetic agent as compared to controls, in order to maintain an appropriate state of anesthesia during surgery.

Thus, according to the distribution of the spectral content among spontaneous neurophysiological oscillations, the E/I in Insomnia Disorder appears to be higher than that of controls, yielding a balance where the net inhibitory bias is weaker. However, when looking at the evidence obtained from the temporal organization of these spontaneous neurophysiological oscillations, the picture gets more complicated.

3.2. Stronger Long-Range Temporal Correlations in People with More Severe Insomnia Complaints

In chapter 3, we investigated the autocorrelation structure of fluctuations in the power of EEG oscillations during wakefulness; specifically Long-Range Temporal Correlations (LRTC). Simulations of neuronal networks operating near a critical transition between order and disorder (Bak et al., 1987) have revealed that LRTC increase with the E/I as long as the neuronal network is not dominated by excitation (Poil et al., 2012)—a condition that holds across multiple species and vigilances states (Priesemann et al., 2013, 2014). This provided the conceptual framework to test our hypothesis that insomnia involves a net weak inhibitory bias. We hypothesized that the E/I—while remaining <1—would be larger in Insomnia Disorder as compared to controls, and that this ratio would positively correlate with insomnia severity. Results however showed a similar strength of LRTC between Insomnia Disorder and controls. This finding may suggest that the E/I is does not differ between the two groups, an interpretation which is at odds from the interpretations drawn in chapter 2.

To conciliate the seemingly discordant findings, obtained from group comparisons on different properties of spontaneous EEG oscillations, we should consider how LRTC relates to individual differences in insomnia complaints. In spite of the absence of group differences, within each group, more severe
insomnia complaints occurred in people with stronger LRTC. The relationship held specifically in low frequency oscillations among people with Insomnia Disorder, and specifically in high frequency oscillations among controls. Since a distinct spectral range is involved in each group, subjective insomnia complaints may therefore involve distinct dynamical processes in people with Insomnia Disorder and controls.

Overall, within the populations of Insomnia Disorder and controls, sleep complaints may be worse in individuals where the E/I is less biased towards inhibition. This interpretation is in agreement with the hypothesis that sleep allows the brain to regulate its critical balance between excitation and inhibition, thereby recovering from the net build-up of excitability during wakefulness (Pearlmutter and Houghton, 2009). The hypothesis also states that sleep prevents the formation of self-reinforcing excitatory loops to reduce the risks associated with excitation dominating over inhibition: uncontrolled propagation of large cascades of activity and runaway oscillations that could spread in the form of seizures. Accordingly, sustained wakefulness yields progressively larger cascades of neuronal activity—indicative of a bias toward excitation—whereas sleep recovers previous power-law distribution of neuronal activity—indicative of a balance between excitation and inhibition (Meisel et al., 2013). Prolonged sleep deprivation can promote epileptiform activity (paroxysms) among susceptible non-epileptic, non-alcoholic people and, rarely, it can even promote seizures in predisposed subjects without a previous history of seizures—particularly if in combination with seizure-provoking procedures or with stress and fatigue (Ellingson et al., 1984; Friis and Lund, 1974; Gunderson et al., 1973; Rodin et al., 1962). The wealth of sleep deprivation studies that have been performed without reporting any adverse event however show that sleep deprivation is unlikely to trigger paroxysmal activity. Rodin et al. (1962) suggested that this could involve the decreasing cerebral excitability with further progressing sleep loss. Conceivably, mechanisms other than the proportion of excitatory and inhibitory signaling—such as intrinsic membrane excitability or the time-constants of excitation and inhibition—help to minimize the risk of seizures following sleep loss in healthy subjects.

3.3. Insomnia Disorder, Excitation/Inhibition Balance and Epilepsy

In people with epilepsy, sleep loss and altered sleep-wake patterns are a well-known trigger of seizures (Matos et al., 2013; Samonsen et al., 2016). The study of the electrocorticogram in people with intractable epilepsy revealed that cortical excitability fluctuates over the sleep cycle, increasing with time awake and decreasing during sleep (Meisel et al., 2015). The authors concluded that sleep has the homeostatic role to rebalance cortical excitability, thereby influencing the initiation and spread of seizures. In this account, altered sleep-wake patterns, excitability and seizure proneness are tightly linked together. Yet, the relationship between insomnia and epilepsy remains largely unknown (Manni and Terzaghi, 2010). While insomnia involves a certain amount of sleep loss, it’s important to stress that insomnia is not equal to sleep deprivation. We now turn to consider the relationship between Insomnia Disorder and epilepsy.
Studies assessing the incidence of epilepsy in Insomnia Disorder are scarce or lacking, possibly due to the lower prevalence of epilepsy in the general population as compared to that of insomnia. However, a recent study found that 12 out of 24 patients diagnosed with primary idiopathic insomnia showed abnormal EEG patterns with irritative activity during sleep, displaying sharp-wave paroxysms and phase inversion spikes, with a predominantly left frontal and fronto-central origin (Lechuga et al., 2011). Furthermore, the sub-group of patients with EEG abnormalities displayed a worse insomnia phenotype, as measured by PSG parameters: less total sleep time, worse sleep efficiency, increased sleep-onset latency, longer and more frequent awakenings. This study suggests that idiopathic insomnia and epilepsy might have a close connection, which is still largely under-investigated and deserves more attention. On the other hand, Insomnia Disorder is the most common sleep/wake disorder among people with epilepsy (Grigg-Damberger and Ralls, 2014); in one study 55% of epilepsy patients had severe insomnia complaints (Vendrame et al., 2013).

People with epilepsy share similar PSG architecture to those with Insomnia Disorder: reduced total sleep time and sleep efficiency, reduced amount of REM sleep and fragmented sleep, as marked by a large number of awakenings, arousals and stage shifts (Manni et al., 1990; Montplaisir et al., 1987; Touchon et al., 1991). Particularly, patients with medically refractory epilepsy, as compared to those with well-controlled seizures, had less total sleep time, worse sleep efficiency, increased wake after sleep onset, and greater number of arousals (Zanzmera et al., 2012). Although nocturnal seizures often induce arousals and sleep fragmentation (Chokroverty and Nobili, 2017), sleep in epilepsy can be fragmented even in absence of seizures or anti-epileptic-drugs, suggesting that in certain forms of epilepsy sleep is inherently unstable (Foldvary-Schaefer and Grigg-Damberger, 2009; Manni et al., 1990). Furthermore, both people with epilepsy and Insomnia Disorder tend to overestimate the time required to fall asleep and to underestimate the total time spent asleep (Ng and Bianchi, 2014). This phenomenon, called sleep state misperception, appears in both groups by a similar amount.

Importantly, treating sleep disorders can improve seizure control; conversely, treating epilepsy can ameliorate sleep disorders co-occurring with epilepsy (Malow and Vaughn, 2002; Vaughn and Ali, 2012; Vendrame et al., 2011). For instance, sedating anti-epileptic drug gabapentin ameliorates both seizures and sleep in epilepsy patients with insomnia (Lo et al., 2010; Placidi et al., 2000).

Little is known about the potential interactions between Insomnia Disorder and epilepsy and about potential common neural correlates. Although the etiology of Insomnia Disorder and epilepsy are different, in both conditions a higher E/I may entail worse insomnia symptoms and more proneness to seizures. The findings of chapter 3 suggest that individuals with more severe insomnia complaints could have higher cortical excitability.

Globally increased cortical excitability appears to be a stable trait of Insomnia Disorder—since absolute motor evoked potentials, induced by single and paired TMS pulses, were higher in Insomnia
Disorder and remained high even after successful therapy (van der Werf et al., 2010). Interestingly, the relative responses to paired pulses at long inter-pulse intervals were reduced in Insomnia Disorder, such that the large TMS response could not be facilitated further, resembling a ceiling effect. Paired-pulse TMS studies in juvenile myoclonic epilepsy revealed reduced intracortical inhibition. These epileptic patients also showed a greater increase in cortical excitability, as compared to normal subjects, following a night of sleep deprivation (Manganotti et al., 2006). Repetitive low frequency (1 Hz) TMS pulses is a technique used to treat disorders of hyper-excitability. Repetitive low-frequency TMS was applied over daily sessions throughout 10 days in a cohort of insomnia with EEG abnormalities (Sánchez-escandón et al., 2014), and also in a cohort of patients with focal epilepsy (Sánchez-Escandón et al., 2016). In both cohorts, the treatment resulted in large improvements in most PSG parameters related to insomnia. Specifically, the treatment increased total sleep time by 90 minutes in the first cohort and by 120 minutes in the second cohort; it enhanced sleep efficiency by 20% in the first cohort and by 24% in the second cohort; it reduced sleep-onset latency by 30 min in the first cohort and by 45 min in the second cohort. In addition, the sleep epileptiform abnormalities decreased in both cohorts. Repetitive TMS seems a very promising treatment for insomnia, for it has proven more efficacious than medication or psychotherapy treatments in improving subjective severity of insomnia and neuroendocrinological indexes of adrenal and thyroid functioning, as well as in reducing relapse and 3-month recurrence rates (Jiang et al., 2013).

GABA is the main inhibitory substance in the brain, promoting sleep by inhibiting arousal systems (Mendelson and Martin, 1992). GABAergic deficiency is thought to underlie both Insomnia Disorder and epilepsy (Mohler, 2006). Global expression of GABA, as measured by Magnetic Resonance Spectroscopy (MRS), was found to be reduced in Insomnia Disorder (Winkelman et al., 2008). Regional expression of GABA was also found to be reduced in the rostral anterior cingulate cortex as well as in the occipital cortex (Plante et al., 2012a); although an increase in the occipital cortex has also been observed (Morgan et al., 2012). Contradictory results may arise from methodological differences, different sample profiles and time of measurement across the two studies (Plante et al., 2012b). Further evidence that insomnia severity involves weaker net inhibition comes from a MRS study in a cohort of people exposed to trauma, with- or without- posttraumatic stress disorder. People with more severe insomnia complaints had significantly higher glutamate and lower GABA levels in parieto-occipital cortex, and a tendency to have lower GABA in the anterior cingulate. Interestingly, the relationship between parieto-occipital GABA and Post-Traumatic Stress Disorder was mediated by insomnia severity (Meyerhoff et al., 2014).

MRS observations in people with epilepsy determined that there is an increase in the concentration of Glutamate near the epileptic focus, and an increase of the GABA concentration in cortical areas away from the epileptic focus (Petroff et al., 2002; Petroff and Spencer, 2005). Cortical GABA concentration is associated with the quantity of epileptic seizures (Petroff et al., 1996) and increasing GABA cortical concentration via GABAergic drugs allows for a dose-dependent benefit in preventing seizures (Petroff et
The observed alterations in neurotransmitters concentration act jointly to promote seizures, since enhanced excitatory and reduced inhibitory signalling would increase excitability and facilitate the spread of epileptic activity across the brain (DiNuzzo et al., 2014).

In sum, Insomnia Disorder and epilepsy share some of the PSG characteristics, misperception of sleep, and an E/I that is less biased towards inhibition—resulting in enhanced excitability, as revealed by TMS and MRS studies. Furthermore, in people with epilepsy, treating insomnia symptoms benefitted epileptic symptoms and vice versa. Future studies should elucidate whether a higher E/I worsen insomnia complaints and proneness to seizures in both conditions.

4. Deficient Attentional Filter

Insomnia Disorder seems to involve a deficiency of the attentional filter, according to the observations of ongoing EEG oscillations (chapter 2) and of the heartbeat evoked potential (chapter 4). In chapter 2 we observed low amplitude of the upper-alpha oscillations during eyes open wakefulness. Long-standing theoretical and empirical work links alpha oscillations, particularly in their upper frequency-range, to the suppression of irrelevant and interfering cognitions (for reviews, see Klimesch, 2012; Klimesch et al., 2007). Accordingly, the observed low amplitude of upper-alpha oscillations during resting-state in Insomnia Disorder could reflect suboptimal attentional filtering, suggesting that upper-alpha oscillations may be crucially involved in blocking intrusive cognitions during bed-time.

Initial neurofeedback studies provided some support for a role of low-amplitude upper-alpha oscillations in insomnia symptoms. Neurofeedback studies in Insomnia Disorder targeted a frequency range between 12-15 Hz, slightly higher than the band where Insomnia Disorder displayed weaker oscillations (11-12.7 Hz)—as determined in chapter 2. Whereas suboptimally controlled studies suggested improvement of objective and subjective sleep quality (Cortoos et al., 2014; Hauri, 1981; Hauri et al., 1982; Hoedlmoser et al., 2008; Schabus et al., 2014), a recent better controlled study showed that effects are no better than placebo (Schabus et al., 2017).

However, the sharply narrow-band alterations observed in chapter 2 suggest that neurofeedback for insomnia should target a rather precise frequency range—that of upper-alpha oscillations. Recently, neurofeedback therapy successfully enhanced upper-alpha oscillations during training and task-related activity, with subsequent improvements in working memory, concentration and impulsivity in children with attention deficit hyperactivity disorder (Escolano et al., 2014). In another neurofeedback study with healthy subjects, the more people benefitted from the training—as seen by the increase in the relative amplitude of the upper-alpha band during training—the larger they improved their working-memory performance (Nan et al., 2012). Working-memory and concentration capacity are cognitive domains particularly disturbed in Insomnia Disorder (Edinger et al., 2004; Fortier-Brochu et al., 2012). Hence, future neurofeedback studies should seek to enhance upper-alpha oscillations in Insomnia Disorder. Yet, people
with Insomnia Disorder may need more neurofeedback sessions than healthy controls, since low resting state alpha power—as observed in Insomnia Disorder in chapter 2—correlates with subsequent impaired learning capacity across individuals (Wan et al., 2014). It remains to be evaluated whether neurofeedback could enhance upper-alpha oscillations among individuals with Insomnia Disorder, and if so, whether it would ameliorate insomnia complaints, particularly intrusive cognitions during bedtime and working memory deficits.

4.1. Deficits in Attentional Tasks

A systematic review of the cognitive deficits in insomnia suggests subtle impairments in attention tasks with a high cognitive load, and in working memory (Shekleton et al., 2010). A meta-analysis of cognitive impairments in Insomnia Disorder concluded as well that individuals with Insomnia Disorder have a mild to moderate impairment in working memory (manipulation and retention), episodic memory and problem solving (Fortier-Brochu et al., 2012). The authors of the meta-analysis also stated that people with Insomnia Disorder tend to have a mild to moderate impairment in complex tasks probing attention—although the meta-analysis support did not reach the .05 significance threshold. These tasks included the digit symbol substitution test, the complex reaction time test and other tasks involving response inhibition and selective responses. Interestingly, other basic facets of attention remain unaltered: divided attention, sustained attention, vigilance and alertness. Furthermore, other perceptual, psychomotor, verbal, mnemonic, executive processes and general cognitive functioning remain intact in Insomnia Disorder. It remains to be evaluated by means of dedicated psychomotor tasks whether the relatively consistent deficiencies in working memory and problem solving specifically involve attentional impairment or other information processing requirements of these cognitive domains.

4.2. Salience Network Malfunctioning?

In chapter 4 we observed an enhanced EEG response to the heart-beat. Specifically, as compared to controls, people with Insomnia Disorder showed a larger amplitude of the later part of the Heart-beat Evoked Potential (HEP) during eyes open wakefulness at frontal electrodes. This later part of the HEP at frontal electrodes was moreover larger during eyes closed as compared to eyes open wakefulness. Since eyes closed can be conceived as promoting interoception, and eyes closed exteroception (Marx et al., 2003), the increased amplitude of the later part of the HEP during eyes closed in people with Insomnia Disorder suggests enhanced interoceptive processing, in line with previous questionnaire studies (Hammad et al., 2001; Jansson and Linton, 2007). Interoceptive hypersensitivity has also been reported in people suffering from anxiety disorders (Domschke et al., 2010; Paulus and Stein, 2010), where it has been suggested to result from a deficient attentional filter, underpinned by alterations in the anterior insula and anterior cingulate (Damsa et al., 2009; Menon and Uddin, 2010). These two regions together form the salience
network, which is involved in switching between executive network and default-mode network activation. Salience network is involved in evaluating the emotional or motivational salience of stimuli, thus integrating features from the external environment according to internal drives (Menon and Uddin, 2010; Seeley et al., 2007).

Enhanced intrinsic connectivity between nodes of the salient network has been found in insomniacs as compared to controls, while participants were at rest or trying to fall asleep in the scanner (Chen et al., 2014). Specifically, the ventral and dorsal anterior insula showed greater coactivation with bilateral anterior insula. The coactivation of the ventral anterior insula with the anterior insula moderately correlated with ratings of alertness and negative affect among insomniacs, thus constituting a plausible neural correlate of interoceptive dysregulations in Insomnia Disorder. Dedicated studies would be required to investigate whether interoceptive hypersensitivity in Insomnia Disorder involves altered salience network functioning. One approach to do so could be microstate analysis of EEG signals. Microstates are brief (60-120 ms) quasi-stable periods that display a characteristic voltage topography, rapidly forming, dissipating and reforming over time (Lehmann et al., 1987). Microstates cluster into four classes, highly consistent across time, individuals and even across vigilance states (Brodbeck et al., 2012; Khanna et al., 2015). Different classes of microstates were found to be linked to specific resting state networks obtained from fMRI (Britz et al., 2010), enabling researchers to perform simple and interpretable neuroimaging with EEG, in a comfortable environment suited for long sleep recordings (Michel and Murray, 2012). In particular, the crossmodal approach could link the microstate class C to insular-cingulate ‘salience’ network activation (Britz et al., 2010). It would be interesting to evaluate whether Insomnia Disorder involves a specific alteration in microstate class C.

5. **Caveats and Recommendations for Future Insomnia Research**

As compared to the severe subjective complaints about sleep and daytime functioning in people suffering from Insomnia Disorder, neurophysiological and neuropsychological alterations reported here and in the literature are relatively small in size. Neurophysiological features currently do not allow to discriminate accurately people with Insomnia Disorder from controls, despite the extensive search for biomarkers performed up to date. Quite likely, neurophysiological alterations of Insomnia Disorder show a large inter-individual variability. Insomnia Disorder inherently covers a large heterogeneity of night-time and daytime symptoms, of etiologies and of psychological profiles. Indeed, Insomnia Disorder is highly comorbid with other psychopathological conditions, such that insomnia complaints constitute the most central symptom in the network of associations between psychopathological symptoms (Borsboom et al., 2011). Due to the different inclusion criteria and the population samples used across studies, the positive findings in the literature are difficult to replicate and do not always get confirmed.
According to a long-standing hypothesis, Insomnia Disorder results from the internalization and somatization of psychological distress; moreover Insomnia Disorder self-sustains itself through a vicious cycle between maladaptive cognitive and behavioral factors, peculiar to the individual (Hauri et al., 1982). The neurophysiological substrate for the somatized distress and for this vicious cycle could therefore also vary on an individual basis, making it hard to observe a common mechanism across individuals. Future research of Insomnia Disorder should investigate the involvement of integrative regions with diffuse projections. A neural correlate of the integration of multiple somatic stressors is the insula (Domschke et al., 2010; Menon and Uddin, 2010). Interestingly, the insula is also the single cortical region most often involved in the generation of the slow waves of sleep (Murphy et al., 2009); thus the insula seems a particularly relevant region for Insomnia Disorder.

Given the high inter-individual variability in Insomnia Disorder, it is crucial to advance the research for sub-types and factors, respectively aimed at clustering persons with- and symptoms of- Insomnia Disorder. This would allow subsequent research to identify core neurophysiological alterations in relatively homogeneous subtypes of Insomnia Disorder, according to stringent inclusion and exclusion criteria.

Research on neurophysiological alterations in Insomnia Disorder will also benefit from careful data-processing. Some analysis techniques are crucial to enhance the signal to noise ratio, such as reducing noise from muscular, cardiac and ocular origins, or considering the power of a frequency band relative to the spectral background instead of the absolute power. Advanced analysis techniques of EEG dynamics may be combined with computational modelling to disentangle excitatory from inhibitory cortical signaling. Finally, adequate sample sizes and rigorous methods to correct for multiple comparisons are strongly recommended to further explore the neurophysiological alterations of Insomnia Disorder.
6. Main points

- People suffering from Insomnia Disorder show signs of round-the-clock hyperarousal, as indexed by relatively stronger beta oscillations, larger late frontal reactivity to the heart-beat, and a shallower and more fragmented sleep architecture with a particular vulnerability of stage N2, warranting further analysis of its microstructure.

- A shift of the spectral power distribution of wake EEG towards high frequencies suggested that Insomnia Disorder involves an increased excitation to inhibition ratio in cortical networks (E/I).

- Subsequent analyses showed that the interpretation of an increased E/I is an oversimplification. Estimates of this ratio based on Long-Range Temporal Correlation (LRTC) analyses showed no group differences between cases with Insomnia disorder and controls. Only within groups, individual with more severe sleep complaints showed stronger LRTC. Under physiological conditions where cortical networks are not dominated by excitatory signaling (E/I <1), stronger LRTC index a higher E/I, less biased towards inhibition. More severe insomnia complaints thus likely entail a net weaker inhibitory bias.

- Future studies should assess whether, in people with Insomnia Disorder and in people with epilepsy, a higher E/I worsen insomnia complaints and increase proneness to seizures.

- The wake EEG of people suffering from Insomnia Disorder shows signs of enhanced late processing of sensory input resulting from their own heart-beat, suggesting altered interoceptive processing.

- The wake EEG of people suffering from Insomnia Disorder shows a relatively weak amplitude of oscillations in the upper-alpha range. Although alpha has widely been implicated as supporting attention by inhibiting irrelevant information processing, it remains to be investigated whether there is indeed such a cognitive counterpart to the low amplitude in Insomnia Disorder.
7. References


for Salience Processing and Executive Control. J. Neurosci. 27.


