The effect of sleep deprivation on information processing and on the cortical system: Investigating functional connectivity and cognitive control

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May 2017
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2017

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Acknowledgments

First and foremost, I would like to thank Liisa Raud for the infinite amount of help and feedback she has provided during the course of the year. Without your supervision, this thesis would not exist. More importantly, you have provided a framework for high quality work and a professional attitude that has been very inspiring. I aim to produce my future work at the standard that you have set. I feel exceptionally grateful to have been able to learn from you.

I would also like to thank Nadine Farnes, Bjørn Erik Juel, Andre Sevenius Nilsen and Benjamin Thürer for helping me during the data collection, giving me feedback on my thesis and being truly motivated and exceptional scientists. I had the best time working with you. I would like to thank Johan Frederik Storm for giving me the opportunity to work in his research group and for supporting the whole project with curiosity and enthusiasm.

Furthermore, I would like to thank René Huster for his help and guidance given during this project. Your technical, methodological, and academic insights have been truly invaluable and you have really inspired the kind of scientist I would like to become. I would also like to thank Anna Maria Matziorinis for reading my draft and helping me when my English let me down.

A special thank you to all of the participants who joined the experiment! I am very grateful for your enthusiasm over the topic, your flexibility in the scheduling and for being interesting, amazing and kind people. I had the best time staying up all night with you!

Finally, I would like to thank Zoltan Madarassy for continuously supporting me and tolerating me when I was sleep-deprived.

Thank you!
Abstract

The effect of sleep deprivation on information processing and on the cortical system: investigating functional connectivity and cognitive control

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The current thesis aimed to investigate the consequences of sleep deprivation on functional connectivity and on the behavioral and electrophysiological correlates of cognitive control. In a counter-balanced within-subject design, twenty-four participants completed 24 hours of sleep deprivation and two control sessions. During each session, we collected EEG recordings in resting state and during a stop signal task. The resting state data was analyzed using a measure of phase synchronization, the phase lag index (PLI), as the marker of functional connectivity. We examined the phase synchronization of delta, theta and alpha frequency bands and demonstrated no significant effect of sleep deprivation. The stop signal task is a popular paradigm to study response inhibition and error monitoring as different aspects of cognitive control. The lack of sleep resulted in the significantly lower accuracy in the task indicating decreased performance. Moreover, we examined the mean amplitudes and latencies of event-related potentials (ERPs) associated with response inhibition and error monitoring such as N200, P300, error-related negativity (ERN) and error-related positivity (Pe). All four ERPs showed decreased amplitudes following sleep deprivation. Furthermore, we found prolonged latencies in the case of N200 and Pe related to sleep loss. In summary, the current study demonstrates that sleep deprivation has a complex impact on the cortical system. Nonetheless, several aspects require further investigation in order to establish an integrating hypothesis about mechanisms connected to sleep loss.

This study was an independent research project and the author of the thesis collected the data.
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Introduction

1.1 Sleep deprivation

Sleep influences our daily life very strongly, it provides a structure to daily activities and it contributes to our health and well-being (Alhola and Polo-Kantola, 2007). It also plays role in the normal functioning of several cognitive processes. However, our modern society does not prioritize getting sufficient amount of sleep every day. There is a an entire industry built around supplying exhausted people with caffeinated drinks and caffeine pills to help them cope with the effects of sleep deprivation on a daily basis. Due to the commercialization of sleep loss, it is important to investigate the role of sleep and sleep deprivation in normal physiological functioning.

Without environmental interference, sleep is regulated by two components: the homeostatic process and the circadian system (Goel, Rao, Durmer and Dinges, 2009). In general, homeostasis works towards reaching an ideal, balanced state. The homeostatic regulation of sleep induces increasing sleep pressure with time spent awake and this drive decreases with sleeping, whereas the circadian system provides an endogenous rhythm for the timing of wake-sleep cycles with a daily fluctuation of neuroendocrine and neurotransmitter levels from morning to evening. Under normal circumstances, the two systems work together in maintaining the structural integrity of sleep during the night and the awakened state during the day. In some cases such as sleep deprivation, the homeostatic process can overwrite the circadian control allowing the individual to fall asleep at any time of the day. If the context is appropriate for sleeping, the body and the cortical system go through several changes during the onset of sleep, such as a gradual decrease in muscle tonus, slow and sometimes asynchronous eye movements, perceptual disengagement, and unresponsiveness (Carskadon and Rechtschaffen, 2000).

The wake-sleep transition is also associated with stereotypical alterations in cortical activity. The cortical oscillations recorded with electroencephalography (EEG) reflect relative potential changes in the brain (Klimesch, Sauseng and Hanslmayr, 2007). The oscillations can be categorized into certain frequency bands. The resting state related synchronized alpha (8 – 13 Hz) activity transforms into low-voltage, mixed frequency oscillations as wakefulness transitioning into the first stage of sleep. Together with the next two sleep stages, this phase is called non-rapid eye movement (NREM) sleep. The deepest stage of NREM sleep is slow-wave
sleep, which is associated with high-voltage delta (0.5–4 Hz) activity (Carskadon and Rechtschaffen, 2000). The final stage of the sleep cycle is the rapid eye movement (REM) sleep, which is also called as paradoxical sleep since the EEG activity becomes similar to awake EEG signal (low-voltage, higher frequency) and the eyes start to move rapidly while the muscles remain completely atonic (Mallick and Singh, 2011). Normally, one sleep cycle takes approximately 90 – 110 minutes from the beginning of NREM sleep to the final REM stage. However, the length of the different stages and the overall length of the whole sleep cycle changes during the night (Carskadon and Rechtschaffen, 2000). Sleep deprivation leads to changes in these sleep patterns resulting in longer sleep duration and increased delta and theta (4 – 8 Hz) power in the frontal regions during the following recovery sleep (Cajochen, Foy and Dijk, 1999).

The cortical activity changes after sleep deprivation in the awake state as well. The current thesis aims to examine how total sleep deprivation affects cortical oscillations and cognitive functioning. Total sleep deprivation is defined as the complete lack of sleep for a certain period (Lanza et al., 2015). Thus, in this study we examined the EEG activity after 24 hours of total sleep deprivation during resting state and during a cognitive task. In the following paragraphs, we are going to discuss physiological changes induced by the lack of sleep from the molecular level to the complex neural pathways, describe the consequences of sleep loss on functional connectivity, and summarize how cognitive functions are affected by sleep deprivation. Furthermore, we will discuss the effects of sleep loss on response inhibition and performance monitoring in detail since these two cognitive processes comprise the main focus of the conducted experiment.

1.1.1 Physiology of Sleep deprivation

Sleep contributes greatly to the efficient preservation of energy and the normal functioning of metabolic processes. Thus, sleep deprivation leads to several systematic physiological changes. The sympathetic nervous system will increase its activity with time spent awake, resulting in higher noradrenalin and adrenalin secretion leading to increased heart rate and blood pressure (Meerlo, Sgoifo and Suchecki, 2008; Liu, Zhou, Liu and Zhao, 2015). Some studies also reported higher cortisol levels after partial or total sleep deprivation, which can be interpreted as the nervous system perceiving sleep deprivation as a stressor and activating its neuroendocrine in response (Meerlo, Sgoifo and Suchecki, 2008). Sleep disturbances can affect glucose metabolism and hormonal regulation of appetite towards
seeking higher caloric consumption (Knutson et al., 2007). Moreover, 24 hours of sleep deprivation can decrease energy expenditure on the subsequent day (Benedict et al., 2011). These effects on the metabolic system suggest that chronic sleep restriction might contribute to the growing problem of obesity and diabetes in western society (Knutson et al., 2007).

Sleep deprivation also influences functioning of the cortical system. The previously mentioned hormonal changes display their effects on the brain in various manners. A recent study showed increased adenosine levels after total sleep deprivation in healthy adults (Elmenhorst, et al., 2017). Adenosine has been connected to the down-regulation of vigilance-promoting neurons in several regions, such as the brainstem and basal forebrain, which have been shown to return to baseline levels upon recovery of sleep (Elmenhorst, et al., 2017).

Accumulating evidence indicates that neural excitatory-inhibitory processes are also affected by sleep loss. Studies using selective REM sleep deprivation reported elevated noradrenalin activity in the brain, reduced intracellular calcium ion level, and increased Na – K ATPase activity (an enzyme that balances the transmembrane potential of neurons and determines excitability), all of which lead to increased neuronal excitability (Mallick and Singh, 2011). Interestingly, in rodents, REM sleep restriction resulted in decreased membrane excitability in the pyramidal neurons of the hippocampus and inhibited long-term potentiation (LTP) which might explain the impaired performance in hippocampal-related learning tasks (McDermott et al., 2003). On the contrary, total sleep deprivation in rats was associated with increased intrinsic excitability in the pyramidal neurons of the prefrontal cortex caused by the reduction of firing inhibition, which is mediated by calcium ion influx (Yan, et al., 2011).

Several studies investigated the cortical excitability changes after sleep deprivation on a larger neural scale. Studies using transcranial magnetic stimulation (TMS) are able to examine the response of neural groups on the surface of the cortex to a short lasting magnetic field that generates electric current. By stimulating the motor cortex with paired-pulse TMS, the intracortical inhibition can be measured which reflects GABA-related neural inhibition in the cortical system (Lanza et al., 2015). Cumulating evidence suggests that sleep deprivation promotes reduction in intracortical inhibition (Scalise et al., 2006, Kreuzer et al., 2011). A similar study with selective REM and non-REM sleep deprivation has also reported decreased intracortical inhibition in case of REM sleep deprivation and no effect in non-REM sleep deprivation (Placidi et al., 2013). A different approach for TMS application is the assessment of TMS-evoked potentials (TEP) with EEG. One study reported increased amplitude of the first
TEP component (around 0-20 ms) after 24 hours total sleep deprivation (Huber et al., 2013). The authors interpreted the results as the sign of increased cortical excitability.

The paragraph above indicates that the molecular mechanisms of sleep deprivation are fairly complicated and a significant amount of research is required to describe how the different brain regions are affected and whether neural excitability increases or decreases. It appears that lack of sleep interacts with the cortical excitability processes. A recent study proposed that REM sleep is responsible for both pruning and strengthening certain groups of newly formed synapses (Li et al., 2017). The study found that new synapses in the pyramidal neurons of the motor cortex in mice are pruned during the REM phase after motor learning. Furthermore, a small number of newly formed connections were strengthened. The process utilizes dendritic calcium ion spikes although the exact interaction remains unclear.

The claims about the role of sleep in synaptic pruning are not entirely new. The sleep homeostasis hypothesis (Tononi and Cirelli, 2006) suggests that slow-wave sleep reduces the number of synaptic connections to reach a more ideal signal to noise ratio of information flow in the cortex. It has been demonstrated that delta activity increases during sleep in certain regions that are associated with visual learning using a visual perceptual learning task (Tononi and Cirelli, 2006). According to the sleep homeostasis hypothesis theory, the argument for the particular role of slow-wave sleep in memory consolidation and synaptic pruning is supported (for review: Tononi and Cirelli, 2014). However, the concrete molecular processes are not described in detail yet. A potential explanation to integrate the role of non-REM and REM sleep might be that during non-REM sleep, certain synapses are tagged to be strengthened later in REM sleep; though, there has been no evidence linking this process directly (Tononi and Cirelli, 2014). It can be concluded that sleep loss has several consequences on the cellular level of the cortical system including changes in the level of neurotransmitters (e.g. adenosine, noradrenalin, GABA) and the potential modification of neural connections and excitability.

1.1.2 Sleep deprivation and connectivity

The functional connectivity of the brain can be examined with several methods, however, the two main directions are functional magnetic resonance imaging (fMRI) and EEG connectivity studies.

In fMRI studies, the blood oxygenation level dependent (BOLD) signal is used to describe neural activity. The majority of the fMRI studies can be categorized into resting state
related and task related paradigms. During wakeful resting without any task, the so-called Default Mode Network (DMN) becomes activated which corresponds to the posterior cingulate cortex, retrosplenial cortex, inferior parietal lobule, medial prefrontal cortex, segments of the hippocampal formation, and the lateral temporal cortex (Buckner, Andrews-Hanna and Schacter, 2008; Sämann et al., 2010). After one night of sleep deprivation, the DMN displays decreased functional connectivity within the functionally integrated regions and reduced separation for the functionally segregated networks (Sämann et al., 2010, Yeo, Tandi and Chee, 2015). Yeo and colleagues (2015) have also tested the individual differences in vulnerability to sleep loss and found that highly resilient participants had more strongly separated networks in the well-rested state.

In task-related paradigms, similar findings have been reported. A recent study (Ben Simon et al., 2017) reported supporting evidence for diminishing functional segregation after sleep deprivation. Furthermore, it showed increased connectivity for the limbic regions, which was supported by stronger amygdala activity in an emotional-distraction task. The hyperactivity of amygdala after sleep deprivation has been demonstrated in previous studies as well (Yoo et al., 2007; Gujar et al., 2011). In these studies, enhanced limbic activation correlated with increased emotional reactivity and decreased frontal connectivity, which suggests the loss of top-down control after sleep deprivation.

The lack of prefrontal control has also been presented in the cognitive domain by a study investigating cognitive functions with a paradigm measuring response inhibition (Chuah et al., 2006). The task related activation was reduced in ventral and anterior prefrontal cortex after 24 hours sleep deprivation. Moreover, in the case of successful stopping (or inhibition) of the motor response, the activation of the right ventrolateral prefrontal cortex and right insula was also affected depending on the individual differences in vulnerability to the effects of sleep deprivation. The same interaction was true for the error-related activation in the anterior cingulate cortex.

Besides fMRI, functional connectivity changes can be investigated during resting state with EEG as well. In general, it has been proposed that the synchronisation of cortical oscillatory activity may be an important marker of functional integration between different brain regions (Stam, Nolte and Daffertshofer, 2007). One study used a graph theory approach on resting state data to describe functional connectivity after sleep deprivation (Verweij et al., 2014). They reported a significant alteration of oscillatory activity on the electrodes over the prefrontal region. Regarding the alpha frequency band (8 – 13 Hz), the marker of local
connectivity was decreased while in the theta frequency band (4 – 8 Hz), the marker of global connectivity was increased. The authors emphasized that the findings might reflect the disconnection of the frontal region, which are congruent with the results of the resting state studies with fMRI.

Studies on cortical oscillations have also provided novel insight in task related paradigms. An interesting hypothesis was proposed about the role of theta activity in a recent paper (Bernardi et al., 2015). The hypothesis suggests that theta waves might represent an inactive state (‘OFF state’) for neural groups, or in other words, a form of local sleep. In the experiment, executive functions (psychomotor vigilance test and go/no-go test) and visuomotor performance were assessed after 24 hours of total sleep deprivation. The authors reported a positive spatial and temporal correlation between the occurrence of theta waves around the task-relevant area and impaired performance in the task. Additionally, the global theta power showed significant increase after sleep deprivation.

Numerous experiments have provided convincing evidence for the disintegrating effect of sleep deprivation on cortical connectivity measured with both fMRI and EEG methods. The different cortical networks seem to work less efficiently introducing errors and compromising top-down control. Moreover, the frontal lobe and prefrontal cortex appears to be especially sensitive to sleep loss.

1.1.3 Cognitive disorganization

In the following paragraphs, we are going to review the literature on cognitive impairments caused by sleep deprivation. This topic inspired countless articles and several extensive reviews (e.g. Alhola and Polo-Kantola, 2007; Goel, Rao, Durmer and Dinges, 2009; Kerkhof and Van Dongen, 2010; Whitney and Hinson, 2010). There is a consensus about the detrimental effects of sleep deprivation on cognitive functioning; however, the extent of this effect is still very much in question. Notably, it is important to recognize how lower level cognitive mechanisms, such as attention, can influence the performance of higher functions. There are three competing hypotheses in the literature explaining the detrimental effects of sleep deprivation on cognition (Lim and Dinges, 2010). The Controlled Attention Hypothesis puts the emphasis on the role of top-down control and predicts that less interesting and engaging tasks are more drastically affected by sleep loss due to the difficulties in staying focused on the activity. Thus, this interpretation signifies the role of attention and explains the dysfunctions of higher cognition with inattentiveness. The Neuropsychological Hypothesis argues that sleep
deprivation inherently changes the normal functioning of the prefrontal cortex. Therefore, the extent of the cognitive impairments are based on the involvement of the PFC in a certain action. One advantage of this explanation can be found in neuroimaging evidence (e.g., fMRI studies) that supports its claim. However, merely focusing on one region of the cortical system might be an oversimplification of the mechanisms. Finally, according to the Vigilance Hypothesis the underlying variable is the level of arousal or vigilance that influences the dynamics of information processing. All three hypotheses account for some the experimental results. However, their explanatory power remains mainly on the behavioral level and does not address neurophysiological findings. Thus, it is beneficial to further investigate how cognitive impairments manifest into neural activity.

Simple attention and vigilance is often measured by reaction time tasks such as the Psychomotor Vigilance Test (PVT). Studies reported slower reaction times and greater variability in response speed after prolonged wakefulness (Kerkhof and Van Dongen, 2010). According to a recent meta-analysis (Lim and Dinges, 2010), sleep deprivation has the strongest impact on reaction times, which was reflected by the highest effect sizes in studies measuring the performance in simple attentional tasks.

The next step in the puzzle is to investigate what possible neural correlations correspond to deteriorating performance. Event-related potentials (ERP) are often used in cognitive tasks in order to examine the evoked cortical response to a stimulus. In a visual attention task the decreased reaction times and the increased number of response omissions was demonstrated after 24 hours of total sleep deprivation (Jackson et al., 2008). The early ERP components such as N100 and P100 were not affected by the lack of sleep. Contradicting results were reported in a study using the cued spatial-attention task in which the amplitude of the early component (N100) was reduced and the later P200 component was increased after sleep deprivation (Trujillo, Kornguth and Schnyer, 2009). Another study has revealed reduction in the amplitude of the P100 during PVT (Hoedlmoser et al., 2011). In other words, great variability regarding the effect of sleep deprivation has been shown in the early stages of cognitive processing.

The above-discussed studies were more consistent with later ERP components such as the P300. Several studies have reported decreased amplitude of the P300 (e.g., Jackson et al., 2008, Trujillo, Kornguth and Schnyer, 2009). Reduced ERP amplitudes can be considered as potential markers for declining processing. Results reported in a face recognition task where the sleep-deprived participants were less capable in discriminating between familiar and
unfamiliar faces resulting in the attenuation of N200 and P600 components (Mograss et al., 2009). It appears that the temporal course of information processing is substantially affected by sleep deprivation, resulting in slower, less efficient performance.

1.1.4 Cognitive control after sleep deprivation

Cognitive control is defined as the ability to allocate attentional capacity, monitor behavior, and to initiate actions based on our goals and available information (Huster et al., 2013). It also involves the ability to stop ongoing behavior and adapt our response according to the changing environment. Response inhibition and performance monitoring are fundamental for normal functioning in our society. Several mental disorders have been associated with the impairment of cognitive control such as attention deficit and hyperactivity disorder, obsessive-compulsive disorder, depression and schizophrenia (Verbruggen and Logan, 2009; Taylor, Stern and Gehring, 2007).

Popular paradigms to examine response inhibition and performance monitoring are the go/no-go task and the stop signal task (Verbruggen and Logan, 2009, Huster et al., 2013). In these tasks, when go signals are presented the participants have to respond to them, usually with button pushing. When a no-go or stop signal occurs following several go signal, the participants need to inhibit the motor response. While the go/no-go task varies the order of go and no-go stimuli, the stop signal task presents the stop signals right after a go signal, which results in the inhibition of an already initiated response (Enriquez-Geppert, et al., 2010). Successful inhibition correlates with activity in the bilateral anterior insular cortex, and the pre-supplementary motor area (Swick, Ashley and Turken, 2011). Moreover, the anterior cingulate cortex, the midcingulate cortex, and the inferior frontal gyrus have been also proposed to participate in attentional and error-monitoring processes (Huster et al., 2011).

Response inhibition and performance monitoring task are associated with eliciting specific electrophysiological markers as well. The fronto-medial N200 ERP component has been suggested to indicate conflict detection during the inhibitory process, whereas the P300 may be connected to evaluative and updating mechanisms (Huster et al., 2013). Regarding performance monitoring, the error-related negativity (ERN) and error positivity (Pe) have been discussed as the evaluation of the committed error (Huster et al., 2011). ERN is likely to relate to general error detection, while Pe diminishes when the subject is unaware of the error (Taylor, Stern and Gehring, 2007).
Sleep deprivation studies have mainly focused on the go/no-go task. On the behavioural level, sleep loss decreases the ability to withhold responses (Drummond, Paulus and Tapert, 2006). The ERP components are also affected by sleep deprivation. After 43 hours of wakefulness, the N100 did not change. In contrast, both N200 and P300 showed decreased amplitudes, and the P300 had prolonged latency in the no-go condition (Qi et al., 2010). Similar results have been reported by another recent study (Jin et al., 2015), in which the participants completed 36 hours of sleep deprivation and go/no-go task was recorded after 12, 24 and 36 hours. After 24 hours, the latency of the N200 was prolonged and the amplitude of the P300 was reduced. This effect has become more pronounced as time duration increases.

Error detection has been shown to be sensitive to sleep deprivation. In a study using go/no-go task with changing rules, the error related skin conductance markers diminished after 48 hours of sleep deprivation and the participants had difficulties adapting their behaviour to the changing conditions (Whitney et al., 2015). Another study reported that the ERN was attenuated after sleep loss, but the Pe was not affected (Renn and Cote, 2013). This result completely contradicts an earlier study that showed significant reduction of the Pe after 20 hours of extended wakefulness, but no effect on the ERN (Murphy, Richard, Masaki and Segalowitz, 2006). The variability of the results indicate that experimental features such as the length of sleep restriction, the number of participants, the different versions of the tasks, or the subsequent data analysis might introduce random errors. Therefore, further investigation needs to be undertaken to characterize the effect of sleep deprivation on different aspects of cognitive control.

The stop signal task has not yet been properly tested in a sleep-deprived condition. The only available paper used auditory stop signals and only focused on behavioral data, but half of the participants were not able to complete the task after sleep deprivation, and those who did complete the task, showed no significant differences in reaction times (Acheson, Richards and de Wit, 2007). Since the stop signal task commonly elicit the N200, the P300, the ERN, and Pe components, it provides a useful tool to examine how sleep deprivation can affect neurophysiological correlates of cognitive control (Gruendler, Ullsperger and Huster, 2011). Beside of the ERP components, we can also examine behavioral measures such as the stop signal reaction time (SSRT). An important advantage of stop signal task over go/no-go task is that by adjusting the time between the go and the following stop sign we can estimate the speed of motor inhibition in the form of SSRT (Verbruggen and Logan, 2009). Thus, stop signal task can provide novel insight into the effect of sleep deprivation on cognitive control.
1.2 Current experiment

1.2.1 Aims

Even though sleep deprivation has been investigated rigorously over the last decades, there are numerous gaps in our knowledge. Accumulating evidence indicates that lack of sleep induces neuroendocrine and neurotransmitter interactions which lead to changes in neural excitability. This molecular level alteration might influence the functioning of higher networks and different brain regions resulting in less effective information processing. The malfunctioning of the brain as a system can provide meaningful insight into the substantial elements of normal functioning. Thus, sleep deprivation can be used as a relatively cost-effective but powerful tool to model abnormal states of the cortical system. Moreover, several studies (for review: Alhola and Polo-Kantola, 2007) have concluded that only one night of proper sleep can reverse the detrimental effect of acute sleep loss on cognitive impairments and ensure recovery. Ethical implications for the researcher involve providing appropriate information for the potential participants about the possible short-term distress they may experience, as well as relating the relatively low risk of long-term consequences of sleep deprivation.

The main goal of this study is to contribute to the growing literature about the consequences of approximately 24 hours of total sleep deprivation on cortical connectivity and cognitive control. In order to examine these questions, we recorded resting state EEG and used the stop signal task after at least 24 hours of wakefulness and two control appointments. Functional connectivity changes in resting state were quantified by the phase synchronization of the delta, theta, and alpha frequency bands. Studies have reported increased theta, delta (Bernardi et al., 2015, Hoedlmoser et al., 2011) and alpha (Finelli et al., 2000) power after sleep deprivation. Thus, these three frequency bands seem to be affected by sleep loss. However, the changes of the tonic oscillatory activity raise the question, how the frequency-specific connectivity is influenced by sleep deprivation. To describe phase synchronization, we chose the phase lag index (PLI) which measures the distribution of phase differences between two sources, namely between the pairing of electrodes (Stam, Nolte and Daffertshofer, 2007). Thus, it can act as marker of consistent, non-zero phase-lag across the cortical surface, which may be interpreted as a sign of ongoing interactions between regions. This aspect of the experiment can provide novel insights since the number of studies using EEG connectivity measure on sleep-deprived state is very low.
To extend knowledge regarding how cognitive control, particularly response inhibition and error monitoring is affected by sleep deprivation, the stop signal task was used to collect behavioral data such as go and stop signal reaction times and performance accuracy. Secondly, the N200, P300, ERN, and Pe ERP components were also examined in order to describe the effect of sleep deprivation on the temporal and spatial EEG patterns of cognitive processing.

### 1.2.2 Hypotheses

Based on the available literature on sleep deprivation, the following hypotheses were proposed. First, we proposed that sleep deprivation has an impact on cortical connectivity, which can be quantified with PLI. Due to the results of the previously described article by Verweij and colleagues (2014), we predicted that the different frequency bands might be affected differently.

1. Hypothesis: Decreased overall PLI in the alpha band after sleep deprivation.
2. Hypothesis: Increased overall PLI in the delta and theta bands after sleep deprivation.

Furthermore, we proposed that the frontal cortex was affected by sleep deprivation more strongly than other regions.

3. Hypothesis: Decreased connectivity of within frontal regions in the alpha frequency band.
4. Hypothesis: Increased connectivity between frontal and posterior regions in the theta frequency band.

Second, we expected an increase in reaction times during stop signal task based on previous studies and meta-analyses (e.g., Lim and Dinges, 2010). Furthermore, due to the decreased efficiency of cognitive processing we expected to see decreased performance measured by accuracy.

5. Hypothesis: Increased go reaction times and SSRT after sleep deprivation.
6. Hypothesis: Decreased go and stop signal accuracy after sleep deprivation.
Third, we predicted changes in the amplitudes and latencies of N200, P300, ERN, and Pe. As we described earlier, the findings regarding ERP components are rather ambiguous. Thus, we examined all four ERP components systematically.

7. Hypothesis: Decreased mean amplitudes of the N200, P300, ERN, and Pe after sleep deprivation.
8. Hypothesis: Prolonged latencies of the N200, P300, ERN, and Pe after sleep deprivation.
2 Methods

2.1 Participants

The participants (N = 24) were recruited through advertisement on social media and they provided their informed consent written after a personal meeting with one of the researchers. The potential participants were screened and excluded if they reported that they suffer from any psychological, neurological or sleep disorder. At the personal meeting, they were informed about the procedure and the potential risks of sleep deprivation. Furthermore, they filled out the Pittsburgh Sleep Quality Inventory (Buysse et al., 1989) to assess their sleep quality. Half of the participants (n = 12) showed good sleep quality (lower general score than 5), while the rest of the participants showed poor sleep quality (Buysse et al., 1989). The participants were instructed to maintain a regular sleep schedule (sleep between 23:00 and 7:00 o’clock) and to refrain from alcohol intake and napping the day before the experiments. Caffeine consumption was also restricted; however, they were allowed to drink the same amount of caffeinated beverage as they usually do on an average day. All participants had normal or corrected-to-normal vision. Overall, twenty-six (14 females) participants went through the personal meeting; however, one of the participants withdrew from the study due to personal reasons and one participant’s sleep deprivation data was not usable because of a misunderstanding of the task requirements. Thus, the final number of participants was twenty-four (12 females; age: 24 ± 3). All participants received 400 NOK compensation after completing the three experimental sessions. Moreover, snacks and beverages were provided in the morning and during the sleep deprivation night. The experiment was approved by the Internal Research Ethics Committee of the Department of Psychology at the University of Oslo and followed the Helsinki Declaration.

2.2 Procedure

Although sleep deprivation has a relatively strong impact on the brain already after only 24 hours, the question what is the ideal control state is important to address. In order to avoid the interaction with the circadian system, we recorded the experiments approximately at the same time in the morning. Moreover, it has been well established that there are individual
differences in vulnerability to the effects of sleep deprivation (e.g. Chuah et al., 2006). Therefore, we used a within-subject design to control for these individual factors.

The experiment involved three separate appointments for each participant. There were two control sessions and one session after sleep deprivation. The sessions were recorded after (1) a normal night of sleep at home, (2) a night sleeping in the laboratory and (3) a night awake in the laboratory to complete a total of 24 hours of sleep deprivation. The order of the sessions were counter-balanced across the participants.

The first control session (Baseline session) was recorded after the participants spent their night at home where they were asked to follow their normal nighttime routine whilst trying to stay within a regular sleep schedule between the hours of 23:00 o’clock and 7:00 o’clock. The participants were instructed to arrive at the laboratory at 8:00 o’clock. Then, following the EEG electrode preparation, which took approximately 45 – 60 minutes, the eyes open and eyes closed resting state EEG was recorded. This part took approximately 5 minutes. Finally, the participant proceeded with the Stop Signal Task, which took 30-45 minutes. A transcranial magnetic stimulation protocol was also included at the end of each session; however, the data is not reported here and we will therefore not elaborate on it. The whole procedure took approximately 150 minutes. For the second control session (Maximally rested session), the participants were asked to spend the night before the experiment in the laboratory where a completely dark room with minimal noise was ensured. They arrived in the laboratory usually approximately 10 minutes before 23:00 o’clock. Then, they were left in the room, instructed to avoid using phones or electric devices, and instructed to fall asleep. In the morning, they were wakened by a researcher at 7:00 o’clock. After a light breakfast the same procedure as described for the baseline session was repeated starting at 7:30 o’clock. Finally, for the sleep deprivation session, the participants were asked to arrive at 23:00 o’clock in the laboratory to spend the night awake accompanied by a researcher. They were allowed to use a computer, watch movies, play games and take short walks during the night. In the morning, the same procedure was conducted as in the maximally rested session. Between each session, there was at least five consecutive nights of resting period scheduled.
2.3 Data acquisition

2.3.1 EEG equipment

The EEG data was recorded with multi-channel EEG amplifiers (BrainAmp, Brain Products GmbH, Germany) using 64 passive electrodes placed according to the international 10-10 electrode placement system. Two EOG electrodes were positioned below the right and beside the left eye to record horizontal and vertical eye movements. The reference and ground electrode were placed on the forehead. The electrode impedances, for all electrodes were kept under 10 kΩ. The data was recorded with an online low-pass filter at 1000 Hz and sampled at 5000 Hz. The BrainVision Recorder (Brain Products GmbH, Germany) software solution was used for recording.

2.3.2 Resting EEG

Two minutes of eyes open and eyes closed resting state EEG was recorded in sitting position. During the eyes open condition the participants were instructed to look at one point in front of them and to minimize blinking and eye movements. For the eyes closed condition, the participants were asked to sit still and to resist falling asleep. Nonetheless, after sleep deprivation, several participants had difficulties in staying awake during the eyes-closed measurements and the muscle and eye activity introduced too strong artifacts into the recordings. Thus, in the final analysis we only included the eyes open data.

2.3.3 Stop signal Task

The participants were seated approximately 50 cm away from the computer screen. The stimulation was presented centrally on a 1280 x 1024 resolution screen using the E-Prime 2.0 software (Psychology software tools, Inc.). The task was to respond to a green arrow (go signal) pointing either left or right by pushing one of two buttons on a keyboard accordingly. In 25 % of the cases, a blue arrow (stop signal) followed the green one. In those cases, the participant had to withhold the response. Before the task, the instructions were presented on the screen, which emphasized the importance of both speed and accuracy. After that, a training section was implemented during which the participants were observed by the researcher to see if they understood the task. Further, the EEG recording started and the participants completed 810
trails in nine blocks of 80 trials each, and one block with 90 trials. Between the blocks, the participants were able to take self-paced breaks and drink water to help maintain their attention. After each block, the participants received feedback on their reaction times in the form of a text on the computer screen saying either ‘Well done!’ or ‘Be faster!’ if the average reaction time on the block was more than 500 milliseconds.

Overall, the task included 610 go and 200 stop trails presented in a random order. Every trial began with a grey screen and a black fixation cross in the middle of the screen with duration jittering between 1000 and 1500 ms. The go signal appeared for 100 ms and as a valid response, the participants had to push the correct button within the following 1000 milliseconds. In stop trials, the delay between the stop signal and the go signal is called stop signal delay (SSD). The SSD was manipulated according to the performance in order to achieve an error rate of approximately 50%. The starting SSD was set to 250 ms, and the upper and lower SSD limits were 100 and 800 ms, respectively. If the participant successfully stopped the motor response, the SSD increased in 50 ms steps until an error (false alarm) was committed in which case the SSD started to decrease.

2.4 Data processing

The preprocessing of the EEG data was conducted in MATLAB R2016a (The MathWorks Inc., Natrick, USA) using the EEGLAB v14.0.0 toolbox (Delorme and Makeig, 2004).

2.4.1 Phase lag index

An important advantage of the PLI is that it is not affected by common sources such as the impact of volume conduction (Stam, Nolte and Daffertshofer, 2007). However, the PLI cannot provide information about which source is leading in phase. The values of PLI are between 0 and 1, where 0 indicated no phase-coupling and 1 shows perfect phase-locking.

In order to extract the PLI values, we down-sampled the continuous resting state data from 5000 Hz to 500 Hz, and referenced to the average reference. Then we conducted independent component analysis (ICA) on the data, identified the components representing blinks and horizontal eye movements, and removed them from the data. Since the phase information was in the center of interest, it was important to preserve phase information during
filtering. Thus, we applied the EEGLAB Blackman-window filter, which ensures zero-phase shift and rather strong (-75 dB) stopband attenuation (Widmann, Schröger and Maess, 2015). We filtered the data into delta (0.5 – 4 Hz), theta (4 – 8 Hz) and alpha (8 – 13 Hz) frequency bands, then we created 4 seconds long epochs since they have been shown to be more reliable than similar amount of 12 seconds long epochs (Hardmeier et al., 2014). In the final step, we visually inspected the data and the artifactual epochs were removed. To complete the PLI computation, we randomly selected 10 four seconds long epochs from each. Then we used Hilbert transform on the data and extracted the PLI values by comparing each electrode with each other. The PLI computation script was adapted from the open-source Neurophysiological Biomarker Toolbox (Hardstone et al., 2012). The extracted PLI values were average together across the epochs.

We obtained mean PLI values in the three examined frequency bands by averaging together the PLI-s of each electrode pair. Beside the grand average PLI, we used bipolar electrode montages (Lehembre et al, 2012) to extract the average PLI values of more specific regions. We took the average PLI of the F3, C3, P3 electrodes to account for the left hemisphere and F4, C4, P4 for the right hemisphere, F3, Fz F4 for the frontal region and P3, Pz, P4 for the parietal regions. Moreover, interhemispheric (F3 - F4, C3 - C4, P3 - P4) and anterior-posterior (F3 - P3, Fz - Pz, F4 - P4) electrode montages were also applied and PLI values were averaged together to represent phase synchronization across these regions for all three examined frequency bands. The electrode montages are illustrated of Figure 1.

![Figure 1. a frontal, parietal, left and right hemisphere electrode montages; b interhemispheric electrode montage; c anterior-posterior electrode montage.](image-url)
2.4.2 Stop task

As behavioral data, go reaction times, go accuracies, and stop accuracies were extracted. Furthermore, the SSRT was calculated using the integration method (Verbruggen, Chambers, and Logan, 2013) since the error rates showed high variance in our data and the integration method was reported to be more reliable under such conditions.

The EEG data was first low-pass filtered with 200 Hz, re-referenced to average reference and down-sampled to 500 Hz sampling rate. As band-pass filter, the EEGLAB built-in basic finite response filter was applied between 0.1 and 40 Hz. Then, 3 seconds long epochs were extracted, visually inspected, and cleaned from extensive amount of noise. To clean the data from eye movements, ICA was applied. Trials were considered as valid if the participant pushed the correct button in case of a go trials and if the participant successfully withheld the response in case of stop trials. Finally, valid go, valid stop, and false alarm trials were extracted from -200 to 800 ms around the stimulation of interest, which was go stimulus for valid go trials, stop signal for valid stop trials and erroneous response in stop trials for false alarm trials. Baseline correction was computed for the 200 ms pre-stimulus interval.

Then, all trials were averaged together and the mean amplitudes and the 50% absolute area latency values of N200, P300, ERN and Pe were obtained based on the recommendations of Luck (2014). To extract the mean amplitudes, we determined the local minima or maxima depending on the polarity of the components in a predefined time window. Then, a 40 ms long section was averaged together around the peak of each component. The peaks were assessed in each channels separately. According to the previous literature, the following windows were used to find the peak for the above-mentioned components: 200 – 350 ms for the N200, 300 – 450 for the P300 (Huster et al., 2014), 1 – 150 ms for the ERN and 150 – 400 for the Pe (Herrmann et al, 2004).

It has been proposed that the 50% fractional area latency is a more robust and more reliable technique to estimate the latency of ERP components (Luck, 2014). Since sleep deprivation has been reported to reduce the amplitudes of the components, one could argue that the local minimum or maximum do not necessarily reflect the latency of the component accurately. Therefore, by determining when the 50% of the component is reached, we might be able to gain more reliable information on timing of the component. The area of the components was calculated using the sum of the amplitudes. In order to account for the activity above/below the baseline, the component was shifted with the maximum value for negative and minimum value for positive ERPs. We determined the negative area for potentials with negative polarity.
and positive area for potentials with positive polarity. For the 50% fractional area latencies, we used the grand mean ERP of all subjects to determine such windows that include the whole components. Thus, the windows for latencies are 150 – 400 for the N200, 225 – 500 for the P300, 1 – 150 for the ERN and 100 – 400 for the Pe.

2.5 Statistical analysis

The statistical analysis was completed with the IMB SPSS Statistics 22 software. Due to the within-subject design, the data was analyzed with repeated-measures analysis of variance (ANOVA). In cases of violations of the sphericity assumption measured by Mauchly’s test, Greenhouse–Geisser corrections were applied and the corrected p-values are reported. We used pairwise comparisons based on the estimated marginal means as post hoc test on the within-subject factors to interpret the significant main effects and interactions in case of multiple factors. For post hoc tests, a Bonferroni correction was applied to correct for multiple comparisons.

2.5.1 PLI

The grand average PLI values of delta, theta and alpha bands were compared across the three session (sleeping at home or baseline session (B), sleeping in the laboratory or maximally rested session (MR) and sleep deprivation (SD) session). Thus, we used sessions as one factor in the repeated-measures ANOVA.

The electrode montages were separated into local and global connectivity measures. The group of local measures included the left hemisphere, right hemisphere, frontal region and parietal region while the inter-hemispheric and anterior-posterior electrode montages were considered as global indexes. In the analysis of the local connectivity, 3 X 4 factorial repeated-measures ANOVA was applied, in which the three session and the four local montages were used as factors. In case of the global connectivity, sessions and global montages were compared in a 3 X 2 factorial model. The three examined frequency bands were analyzed according to this set-up separately.
2.5.2 Behavioral data

The same set-up was applied on the behavioral data as on the grand PLI. We examined the go reaction times, the SSRT, the stop signal delay (SSD), and the go and stop accuracies.

2.5.3 ERPs

The mean amplitudes and the 50% area latencies of the ERP components were also examined with repeated measures ANOVA. For the mean amplitudes of N200 and P300, we used a 3 X 2 X 3 X 3 factorial model in which the three sessions (B, MR, SD), trials (go and stop), anterior-posterior (frontal, central, parietal electrodes) and left-right (left, midline, right electrodes) factors were included. Into the anterior-posterior and left-right factors the following electrodes were selected: F3, Fz, F4, C3, Cz, C4, P3, Pz, P4 (Figure 2). The mean amplitudes of ERN and Pe were tested within 3 X 3 X 3 model, where the sessions, the anterior-posterior, and the left-right factors were included.

![Figure 2](image.png)

**Figure 2.** a electrodes in the anterior-posterior axis; b electrodes in the left-right axis.

The latencies were compared in a similar fashion as the mean amplitudes, except the analysis only included those electrodes where the components were the most pronounced. Thus, Fz was used in the analysis in case of the N200 and Cz for the P300. Thus, the tests of the N200 and P300 only involved the sessions and trials (go, stop) factors in 3 X 2 model. In case of latencies of the ERN and Pe, the same frontal and central electrodes were applied respectively. Therefore, in the analysis of ERN and Pe latencies, sessions was used as a factor in repeated-measures ANOVA.
3 Results

3.1.1 PLI

The grand average PLI showed no significant differences in the examined frequency bands across the three sessions (Table 1). Regarding the electrode montages (Table 2), sessions had no significant main effects. Although we find the significant main effect of the localization in case of the local electrode montages of the alpha frequency band (F (3, 69) = 2.885, p = .042, \( \eta^2_p = .111 \)), which showed that the frontal regions had lower average phase synchronization then the right hemisphere; however the difference was no longer significant after the Bonferroni adjustment (p = .072). Overall, phase synchronization was not affected significantly by sleep deprivation.

Table 1. Means and standard deviations of the grand average PLI values.

<table>
<thead>
<tr>
<th></th>
<th>Baseline session</th>
<th></th>
<th></th>
<th>Sleep deprivation session</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean  ± SD</td>
<td>Mean  ± SD</td>
<td>Mean  ± SD</td>
<td>Mean  ± SD</td>
</tr>
<tr>
<td>Grand Average Delta PLI</td>
<td>0.20  ± 0.01</td>
<td>0.20  ± 0.01</td>
<td>0.20  ± 0.02</td>
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</tr>
<tr>
<td>Grand Average Theta PLI</td>
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<td>0.17  ± 0.01</td>
<td>0.18  ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Grand Average Alpha PLI</td>
<td>0.18  ± 0.02</td>
<td>0.19  ± 0.04</td>
<td>0.18  ± 0.02</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Means and standard deviations of the PLI values in the examined electrode montages for delta, theta, and alpha frequency bands.

\(^a\) = significant main effect (uncorrected)

<table>
<thead>
<tr>
<th></th>
<th>Baseline session</th>
<th></th>
<th>Maximally rested session</th>
<th></th>
<th>Sleep deprivation session</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Frontal region</td>
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<td>0.20 0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal region</td>
<td>0.21 0.04</td>
<td>0.19 0.03</td>
<td>0.21 0.03</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>0.21 0.02</td>
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<td>0.20 0.04</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Right hemisphere</td>
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<td>0.20 0.03</td>
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<td></td>
<td></td>
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<tr>
<td>Inter-hemispheres</td>
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<td>0.20 0.03</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anterior-posterior</td>
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<td>0.20 0.03</td>
<td>0.21 0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal region</td>
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<td>0.18 0.03</td>
<td>0.17 0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal region</td>
<td>0.17 0.03</td>
<td>0.18 0.03</td>
<td>0.17 0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>0.18 0.03</td>
<td>0.18 0.03</td>
<td>0.18 0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>0.17 0.03</td>
<td>0.18 0.04</td>
<td>0.17 0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0.17 0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0.18 0.03</td>
<td>0.18 0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal region (^a)</td>
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<td>0.18 0.05</td>
<td>0.17 0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal region</td>
<td>0.18 0.05</td>
<td>0.19 0.05</td>
<td>0.19 0.04</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>0.18 0.05</td>
<td>0.20 0.09</td>
<td>0.19 0.04</td>
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<tr>
<td>Right hemisphere</td>
<td>0.18 0.04</td>
<td>0.21 0.07</td>
<td>0.18 0.04</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Inter-hemispheres</td>
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<td>0.19 0.04</td>
<td>0.18 0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior-posterior</td>
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<td>0.19 0.05</td>
<td>0.18 0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.1.2 Behavioral data

Although the go reaction times increased after sleep deprivation compared to the two control conditions, the effect was not significant (F (1.42, 32.68) = 2.349, p = .125, $\eta^2_p = .093$). The go accuracy, on the other hand, showed significant main effect of the sessions (F (1.15, 26.46) = 13.229, p = .001, $\eta^2_p = .365$). The post hoc test revealed the accuracy decreased significantly after sleep deprivation. Compared to both baseline (p = .001) and maximally rested sessions (p = .009). No significant difference was found in the case of stop accuracy, SSD and the SSRTs. Table 3 provides the means and standard deviation of the reaction times and accuracies.

Table 3. Means and standard deviations of the examined behavioural data.

* = significant main effect.

<table>
<thead>
<tr>
<th></th>
<th>Baseline session</th>
<th>Maximally rested session</th>
<th>Sleep deprivation session</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go reaction time</td>
<td>Mean 489.18 ± 131.77</td>
<td>Mean 512.15 ± 170.99</td>
<td>Mean 531.25 ± 146.00</td>
</tr>
<tr>
<td>SSRT</td>
<td>213.41 ± 27.78</td>
<td>230.81 ± 108.39</td>
<td>199.31 ± 47.18</td>
</tr>
<tr>
<td>SDD</td>
<td>260.55 ± 139.21</td>
<td>281.45 ± 167.59</td>
<td>306.71 ± 170.47</td>
</tr>
<tr>
<td>Go accuracy *</td>
<td>95.62 ± 7.62</td>
<td>94.49 ± 12.22</td>
<td>82.89 ± 13.92</td>
</tr>
<tr>
<td>Stop accuracy</td>
<td>42.67 ± 14.45</td>
<td>45.40 ± 13.46</td>
<td>43.87 ± 13.13</td>
</tr>
</tbody>
</table>

3.1.3 ERPs

We examine the mean amplitudes and the 50% fractional area latencies of the N200, P300, ERN and Pe event-related potentials. Figure 3 and 4 show the topographies of N200, P300 and ERN, Pe, respectively. The average ERPs are presented on Figure 5 to 7.
Figure 3. Topographies of N200 and P300 corresponding to the peaks of the components.

Figure 4. Topographies of ERN and Pe corresponding to the peaks of the components.
Figure 5. ERP time courses in go trials at Fz, Cz and Pz electrodes.

Go trials

Figure 6. ERP time courses in stop trials at Fz, Cz and Pz electrodes.

Stop trials
The mean amplitudes of the N200 demonstrated that the potential activity was the highest on the frontal region by the significant main effect of the anterior-posterior axis (F (1.37, 31.62) = 13.944, p < .001, η^2_p = .377) and the post hoc comparison which showed that the frontal region differed significantly from the central (p < .001) and parietal areas (p = .005). The mean amplitude of N200 in go trials was significantly more negative than in stop trials (F (1, 23) = 24.879, p < .001, η^2_p = .520). Furthermore, the N200 showed no significant main effect of the sessions; however, there was a significant interaction between the sessions and the left-right axis (F (4, 92) = 4.066, p = .004, η^2_p = .150). While the midline and right side showed smaller N200 in the sleep deprivation session, the mean amplitudes on the left side were barely affected, and showed slightly more negative N200 in the sleep-deprived state. Thus, the hemispheres were affected asymmetrically by the lack of sleep.

In case of the P300, the sessions had significant main effect on the mean amplitudes (F (2, 46) = 17.346, p < .001, η^2_p = .430). According to the post hoc test, the P300 was significantly smaller on the sleep deprivation session compared to both baseline (p < .001) and maximally

Figure 7. ERP time courses in false alarm trials at Fz, Cz and Pz electrodes.
rested sessions (p = .001). The P300 was significantly larger (p< .001) in stop trial compared to go trials in line with the main effect (F (1, 23) = 18.219, p < .001, η²_p = .442). Moreover, the component showed a central-parietal position based on the post hoc test of the main effects of the anterior-posterior axis (F (1.58, 36.36) = 19.708, p < .001, η²_p = .461) and the left-right axis (F (2, 46) = 40.314, p < .001, η²_p = .637). The effect of the sleep deprivation occurred in a significant interaction between sessions and trials (F (2, 46) = 7.414, p =.002, η²_p = .244), which showed that the P300 in stop trails are more strongly affected by sleep deprivation than in go trails.

**Figure 8.** The mean amplitudes with the corrected 95% confidence intervals of N200 and P300. The presented mean values are extracted from the Fz electrode in case of N200, and from Cz in case of P300.

** = significant main effect. (p < .01).

The main effect of the sessions was significant in the case ERN mean amplitudes as well (F (2, 46) = 4.175, p =.022, η²_p = .154). The post hoc test showed that ERN was significantly smaller after sleep deprivation compared to the maximally rested session (p = .034) while the baseline session displayed no significant difference (p = .607). The fronto-central position of the ERN was also demonstrates by the data. The main effect of anterior-posterior axis (F (1.36, 31.40) = 10.091, p =.001, η²_p = .305) revealed that the mean amplitudes...
of ERN were significantly more negative at the frontal (p = .001), and at the parietal region (p < .001) than at the central electrodes. The mean amplitudes of Pe have also revealed the significant main effect of the sessions (F (2, 46) = 14.566, p < .001, $\eta^2_p = .388$). The Pe components of sleep deprivation session were significantly smaller than in the other two conditions (baseline: p < .001; maximally rested: p < .001). Similar to P300, the central position of Pe was supported by the significant main effects of the anterior-posterior axis (F (1.51, 34.94) = 25.850, p < .001, $\eta^2_p = .529$) and the left-right axis (F (2, 46) = 63.247, p < .001, $\eta^2_p = .733$). On the anterior-posterior axis, the Pe mean amplitudes displayed the larger values at the central region compared to frontal (p = .013) and parietal areas (p < .001). Moreover, the midline region showed significantly larger Pe compared to the left (p < .001) and right sides (p < .001). The mean amplitudes of ERN and Pe are illustrated on Figure 9.

**Figure 9.** The mean amplitudes with corrected 95% confidence intervals of ERN and Pe. The presented mean values are extracted from the Fz electrode in case of ERN, and from Cz in case of Pe.

* = significant main effect. (p < .05).

** = significant main effect. (p < .01).
The latencies of the N200 showed the main effect of the sessions (F (2, 46) = 19.923, p < .001, \( \eta^2_p = .464 \)). The latency of N200 was significant prolonged in sleep deprivation session compared to the baseline (p < .001) and maximally rested (p = .001) sessions. The trials were also significantly different (F (1, 23) = 66.146, p < .001, \( \eta^2_p = .742 \)). The N200 in the go trials appeared to be prolonged compare to stop trails (p < .001). Regarding the P300, the sessions had no significant effect on the latencies; however, the trials differed significantly (F (1, 23) = 32.746, p < .001, \( \eta^2_p = .587 \)). The post hoc comparison revealed that the P300 displayed prolonged latencies in the go trials (p < .001) relative to stop trails.

The ERN component latencies were not affected by sleep deprivation (F (1.43, 33.03) = 1.88, p = .177, \( \eta^2_p = .076 \)). Finally, the Pe latencies have displayed the significant main effect of the sessions (F (2, 46) = 3.27, p = .047, \( \eta^2_p = .125 \)). The latencies showed an increase between baseline and sleep deprivation sessions, but the difference was not significant after Bonferroni correction (p = .055). The mean latencies are presented on Table 4.

Table 4. Means and standard deviations of N200, P300, ERN and Pe.
* = significant main effect.
a = significant main effect (uncorrected).

<table>
<thead>
<tr>
<th></th>
<th>Baseline session</th>
<th>Maximally rested session</th>
<th>Sleep deprivation session</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>N200 (Go)*</td>
<td>286.75 ± 17.93</td>
<td>285.50 ± 18.86</td>
<td>298.67 ± 12.96</td>
</tr>
<tr>
<td>N200 (Stop)*</td>
<td>245.25 ± 19.07</td>
<td>254.75 ± 25.58</td>
<td>263.67 ± 23.89</td>
</tr>
<tr>
<td>P300 (Go)*</td>
<td>419.00 ± 26.80</td>
<td>425.75 ± 34.86</td>
<td>417.17 ± 34.04</td>
</tr>
<tr>
<td>P300 (Stop)*</td>
<td>380.75 ± 34.01</td>
<td>383.00 ± 30.54</td>
<td>394.75 ± 39.36</td>
</tr>
<tr>
<td>ERN</td>
<td>53.42 ± 12.88</td>
<td>56.00 ± 18.47</td>
<td>49.92 ± 12.40</td>
</tr>
<tr>
<td>Pe a</td>
<td>230.58 ± 27.86</td>
<td>236.17 ± 29.46</td>
<td>242.42 ± 36.81</td>
</tr>
</tbody>
</table>
4 Discussion

4.1 Primary results

We examined the effects of 24 hours of sleep deprivation on functional connectivity, response inhibition and performance monitoring. It was demonstrated that sleep loss has an impact on response accuracies and ERP components related to cognitive control showed significant alterations indicating that the temporal course of cognitive processing was also affected by the lack of sleep.

The PLI as marker of functional connectivity measures the synchronous activity in the brain; therefore, it can provide information about the interactions of cortical networks (Lee et al., 2013). We calculated the grand average PLIs for delta (0.5 – 4 Hz), theta (4 – 8 Hz) and alpha (8 -13 Hz) frequency bands since these oscillations showed changes after sleep deprivation in previous studies (Bernardi et al., 2015, Verweij et al, 2014, Hoedlmoser et al., 2011, Finelli et al., 2000, ). The PLI values were not affected significantly by sleep deprivation. The results raises several questions regarding how fMRI and EEG connectivity measures correspond to each other. The functional connectivity literature using fMRI (e.g., Ben Simon et al., 2017, Yeo, Tandi and Chee, 2015, Sämann et al., 2010), have consistently showed that sleep deprivation induces decreased integration with the functionally connected regions and declining separation among the functionally disconnected networks. Connectivity changes have been reported in the study of Verweij and colleagues (2014); however, the changes were only reported for eyes-closed resting state data. The authors examined eyes-open resting state data as well, and they have not found any significant changes. From this aspect, our findings are in line with the results of Verweij and colleagues (2014). Since the quality of our eyes-closed data was questionable due to the difficulties of the participants in staying awake, those datasets were not included in the analysis. However, one could ask if the connectivity changes only occur in eyes-closed state, what kind of impact does this have on our daily life? Barry and colleagues (2007) have systematically compared EEG data from eyes-open and eyes-closed resting state specifically focusing on delta, theta, alpha, and beta power. They reported that all of the frequencies showed reduction in eyes-open condition compared to eyes-closed. Furthermore, Tan and colleagues (2013) compared synchronization likelihood as a marker of connectivity in eyes-open and eye-closed state and they applied graph theory to analyze the data. They revealed that connectivity markers significantly differ in the two states. Additionally, frontal theta and
posterior alpha connectivity was significantly reduced in eyes-open condition (Tan et al., 2013). Thus, one could speculate that the connectivity changes induced by sleep deprivation in eyes-closed state become less apparent when the eyes are open.

Concerning our hypotheses, we did not see synchronization changes in any of the examined frequency bands. Moreover, there was no significant effect of sleep loss within the examined sub-regions either. Thus, we need further investigation to identify the extent of the effect of sleep deprivation on cortical connectivity.

Among the behavioral measures of the stop signal task, only the go accuracy was significantly changed by sleep deprivation. Contrary to our hypotheses, go reaction times, SRTTs and stop accuracies did not show significant alterations. Although several studies have demonstrated that the reaction times are detrimentally affected by sleep deprivation (see Lim and Dinges, 2010), there are several papers reporting the lack of significant effect on reaction times in response inhibition tasks such as the go/ no-go task or the stop signal task (e.g., Acheson, Richards and de Wit, 2007, Bocca, Marie and Chavoix, 2014, Jin et al., 2015). Nonetheless, the declined performance was confirmed by the decreased go accuracy after sleep deprivation. Interestingly, nor the stop accuracy nor the SSRT showed sensitivity to sleep loss. This result may support the Controlled Attention Hypothesis among the earlier described explanations of cognitive impairments related to sleep deprivation (Lim and Dinges, 2010). Since the stop accuracy was not affected by the lack of sleep, the decreased vigilance does not seem to be the probable reason behind the worsening of the performance because that would have an impact on both go and stop. Moreover, Lim and Dinges (2010) concluded that short-term (approx. 24 hours) sleep deprivation has a smaller effect on higher cognitive function on the behavioral level. Thus, response inhibition might elicit such compensatory processes, which can conceal the insufficiencies of the cognitive system.

The consequences of sleep deprivation were more apparent on the electrophysiological measures. In line with our hypotheses, three out of the four examined components showed decreased mean amplitudes after sleep deprivation. Thus, we were able to replicate previous results (e.g., Qi et al., 2010) that showed decrease in the P300 amplitudes after 24 hours of prolonged wakefulness. Furthermore, our findings on ERN and Pe implied that both components are affected by sleep loss. Since previous studies have shown the effect of sleep deprivation on only one of the two ERPs (Murphy, Richard, Masaki and Segalowitz, 2006, Renn and Cote, 2013), our results provided novel insight into the processes of cognitive control.
The attenuation of N200 was not significant on the level of the main effect, which contradicts the findings of Jin and colleagues (2015). However, there was a significant interaction between sleep deprivation and the laterality of N200. The N200 amplitudes were smaller on the right side and around the midline after sleep deprivation while the left side showed no attenuation. Some authors have argued that the N200 originates from the activity of the right inferior frontal cortex (e.g., Fisher, Aharon-Peretz and Pratt, 2011), which would explain the asymmetric impact that we found. The study of Chuah and colleagues (2006) aimed to explore the individual vulnerability to sleep loss during go/no-go task, and they found that the event-related activation in the right ventrolateral prefrontal cortex was increased for those participants who exhibited lower vulnerability. Thus, they proposed that the activity of the region might be a compensatory process to the decreased tonic activation in the bilateral anterior and ventral prefrontal areas. The involvement of the right hemisphere in compensatory processes might influence the changes in the amplitude of N200. Nonetheless, it needs further clarification how this component is affected by sleep deprivation.

Regarding our hypotheses about the prolonged latencies of the examined components, we, indeed, found that the latencies increased after sleep deprivation in case of N200 and Pe. Interestingly, we did not see significant changes in the latencies of ERN and P300 ERP components, which contradicts previous findings (Qi et al., 2010). There are different approaches for the calculation of peak latencies. The one that is used quite often is finding the local maxima or minima within a certain time window and using that point as the peak of the ERP component. However, this method has several shortcomings (see Luck, 2014) such as sensitivity to the noise level in the data. Therefore, we used 50% fractional area latency measures to assess the timing of the components since we expected that the ERPs would be smaller or even completely disappear after sleep deprivation. The fact that we did not find changes in the latencies of ERN and P300 might raise a methodological question about the ideal measure of latencies.

Taken together, we have demonstrated that sleep deprivation leads to attenuated and in some cases prolonged ERP components. What does it mean regarding the cognitive functions? It has been proposed that N200 is associated with conflict monitoring, whereas P300 might be related to updating and inhibition ongoing neural processes (Huster et al., 2013; Wessel and Aron, 2015). On the other hand, P300 has been connected to other cognitive processes such as novelty detection and attentional allocation (Polich, 2007). ERN has been also connected to conflict monitoring in terms of stimulus-response mismatch (Gruendler, Ullsperger and Huster,
and Pe was characterized as component of error awareness which can contribute into error detection though an updating process similar to P300 (Taylor, Stern and Gehring, 2007). Another argument for the phenomenological connection between P300 and Pe is the similarity between the topographies of the two components (Taylor, Stern and Gehring, 2007). Sleep deprivation had a more pronounced effect on these two components, which might indicate that updating processes are more sensitive to sleep loss. However, such specificity in the effect of sleep deprivation seems unlikely. Another possible explanation is that sleep deprivation causes overall less effective information processing in the brain and the malfunctioning of certain components accumulates. Therefore, the later processes are more strongly affected. As we described earlier, lack of sleep leads to increased excitability and growing need for synaptic pruning (Tononi and Cirelli, 2014). This suboptimal state on the cellular level might translate into decreased segregation among the neural networks. Ultimately, information processing becomes more random resulting in declining cognitive functioning.

In general, the effects of sleep deprivation seem to influence several aspects of the cortical system from the functional connectivity to cognitive processing. However, the explanation integrating the findings from molecular level to behavior is still missing. Our experiment confirmed that only 24 hours of sleep deprivation is able to change the normal functioning of the brain in healthy adults. Additionally, we demonstrated that the effect of sleep loss on the behavioral and electrophysiological level as well.

4.2 Limitations

Current experiment has several limitations that we have to address. From methodological aspect, sleep deprivation can be a challenging topic since its prevalence is quite high. Therefore finding a reliable way to ensure appropriate control measures is crucial. Several studies have applied smart watches to record sleep length or used sleep diaries during the experiments. Our study, on the other hand, have not involved ongoing documentation of sleeping behavior, which can be a shortcoming. However, we used a general sleep quality questionnaire. Furthermore, we applied two control sessions. Therefore, the potential disturbances during the nights, when the participants slept at home, were also controlled by the maximally rested session when the participants spent the night in the laboratory in a room that ensured maximally calm environment. Potentially, one could argue that sleeping in the laboratory might also have a negative impact on sleep quality due to the unfamiliar
The “first night effect” is a well-known construct in sleep research. It has been reported that the combination of sleeping in a new environment and sleep recoding with polysomnography can lead to worse sleep quality (Agnew, Webb and Williams, 1966). However, it is challenging to estimate the effect of purely the new environment, since the equipment and the ‘feeling of being observed’ are important components of the first night effect (Kim and Dimsdale, 2007). Since we have not done any kind of observation during the laboratory nights, it is less likely that the first night effect was strongly influencing the outcome of the experiment. Overall, we did not find any systematic difference between the two control sessions. Thus, sleeping at home seems to be sufficient as control, but the ideal solution would involve the usage of a smart watch or phone application that provide direct information on the sleeping behavior of the participants.

Even though we asked the participants to limit their caffeine intake according to their habitual consumption, we did not follow up with questionnaires what was their daily caffeine intake during the days of the experiment. Thus, direct monitoring of the caffeine intake and other factors, such as the usage of nicotine or calorie intake, would be beneficial for future studies.

Moreover, we did not separate the participants according to the individual vulnerability to sleep loss. This individual vulnerability has been described as a trait-like factor (Yeo, Tandi and Chee, 2015) and it can strongly influence the effects of short-term (24 hours) sleep deprivation. As we aim to investigate higher cognitive functions, the individual differences become increasingly important. The negative impact of sleep deprivation was demonstrated on several distinct aspects of cognition such as working memory, decision-making or learning (Alhola and Polo-Kantola, 2007). However, as the complexity increases, the results become more diverse. Studies showed that problem solving, reading comprehension and logical reasoning are not necessary affected by acute sleep loss (Kerkhof and Van Dongen, 2010). Since these functions require several sub-functions and involve a wide range of brain regions, the cortical compensatory processes are likely to be able to support and sustain the performance.

Another challenge regarding the cognitive measures is the problem of task impurity. The sleep deprivation has a strong impact on attentional processes, which can be a mediating variable in higher cognitive functions (Whitney and Hinson, 2010). Therefore, we would need further investigations to describe the role of attention in the cognitive consequences of sleep loss.
4.3 Future studies

Current study was able to provide further evidence for the complexity of the effects induced by sleep deprivation. However, there are several new perspectives to explore. For one, the relationship between the functional connectivity alterations and different frequency bands needs additional investigations. Furthermore, by analyzing the time-frequency decomposition of the EEG from the stop signal task, we might be able to describe the effect of sleep deprivation on the task-related induced activity that may be specific to certain frequency bands. This approach would be also able to test the hypothesis of Bernardi and colleagues (2015) regarding the role of theta activity in erroneous responses. Future studies could benefit from an experimental design that uses selective REM and NREM sleep deprivation to test their role in the functional connectivity changes and in the cognitive performance. Moreover, the inclusion of individual vulnerability as a factor could provide higher validity for the interpretation of the findings. In general, studying sleep deprivation allow us to examine the malfunctioning of the cortical system in a well-controlled design with relatively low risks. Thus, by exploring how sleep deprivation affects the brain, we might be able to gain a deeper understanding about psychological and neural disorders as well.
5 Conclusion

The effects of sleep deprivation on the cortical system extend from the molecular changes in excitability to the altered functioning of larger neural networks. Current experiment investigated the consequences of 24 hours sleep deprivation on cortical connectivity and cognitive processes such as response inhibition and performance monitoring. We reported declining performance during stop signal task. Furthermore, N200, P300, ERN and Pe displayed attenuated amplitudes after sleep deprivation. The latency of N200 and Pe was also prolonged. These findings highlights the role of sufficient amount of sleep in the normal functioning of the brain.


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Attachment