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Harnessing the power of the multidimensional signal: Quantitative electroencephalographic analysis to infer state and trait signatures from polysomnography

- Thesis booklet -

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Introduction and main objectives

Sleep can be defined behaviorally as a reversible state of perceptual disengagement from the environment during which we are unresponsive to external stimuli (to a given extent) and usually entails a species specific posture (lying down in humans) combined with closed eyes and limited amount of movements (Pelayo, 2017). Since the first recording of human electroencephalography (EEG) (Berger, 1929) we also know that these behavioral characteristics are accompanied by state specific brain activity, which activity pattern is complementary to, but also highly divergent from activity patterns during wake. Even though almost a hundred year passed, in the field of sleep research EEG is still a necessary tool being the only device that can measure and define sleep with a 100% accuracy. However, it is important to know how to fully exploit this multidimensional signal. The conservative way of sleep scoring (a.k.a. qualitative EEG analysis) leads to a massive loss of information, because the EEG signal contains a lot more than the synchronous and cyclic changes in the oscillatory patterns translated into rigid categories. This traditional view of the EEG signal compartmentalize the dynamic signal into separate stages, which are usually analyzed independently by the researcher. Exceeding sleep macrostructure using quantitative EEG analysis (microstructural and spectral analysis) can help us better comprehend the dynamic changes in the data and to better understand cognitive processes during sleep.

Quantitative EEG analysis is a way to examine EEG data numerically by transforming the raw signal from the time to the frequency domain and relating these frequency characteristics to different behavioral and conscious states (Cohen, 2014). This approach gives us the tool to 'dig deeper' into this multidimensional signal and by adapting complex signal processing and statistical methods from neighboring scientific fields it's enabling us to simultaneously investigate dynamic task or more stable group related changes in the power spectrum as well as state specific changes in the communication between groups of neurons.

In my thesis I present five papers all using the most common quantitative EEG analysis methods (power spectral analysis, phase synchronization) to investigate state and trait signatures from polysomnography (PSG). We used power spectral analysis to zoom in on potential state-like changes related to selective memory processing during an afternoon nap. Furthermore, we used the same 'tool' to uncover potential trait-like changes associated to frequent nightmare experiences. Last but not least connectivity analysis was applied to further our knowledge of the differences between tonic and phasic REM sub-states. The results presented in these papers help us better understand information processing during sleep by focusing on the dynamicity and the periodicity of this unconscious state and shedding light on the importance of the combination of qualitative and quantitative EEG analysis.

1. Thesis point 1: NREM specific oscillations and following REM sleep collectively participate in the facilitation of selective, declarative memory processing.

Ever since Jenkins and Dallenbach (1924) reported that memory retention was better after a night of sleep compared to the same amount of wake following learning, researchers are trying to understand what makes some periods more preferable to some types of memories over others and what neural processes can be hidden behind these important sleep stages (Gais & Born, 2004). It is also an open question how sleep selects some memories to keep/strengthen over others from the millions and millions of information we encounter during a day (van Dongen, Thielen, Takashima, Barth, & Fernández, 2012). Previous studies found evidence supporting selective enhancement of stimuli with emotional valence compared to neutral stimuli (Hu, Stylos-Allan, & Walker, 2006; Payne, Stickgold, Swanberg, & Kensinger, 2008) and with weakly encoded memories benefiting more from sleep, than strongly encoded (Diekelmann, Wilhelm, & Born, 2009). Furthermore, rewarding the correctly retrieved words (Oudiette, Antony, Creery, & Paller, 2013), as well as expectance of future retrieval (van Dongen et al., 2012) also selectively increase the beneficial effect of sleep on memory consolidation. These results support the idea that sleep has a beneficial effect on memories, especially on memories that are considered to be relevant for the future (e.g. emotional valence, reward at retrieval).

To investigate whether differences between the consolidation of relevant and irrelevant stimuli can be captured in state-like temporary changes during sleep, we used a quantitative EEG analysis method (power spectrum analysis). Power spectral analysis is one of the most frequently used spectral analyses method, capable of assessing spectral characteristics of NREM and REM sleep (Berry, 2018) but also enables us to investigate state related increase in so called traditional frequency bands (delta, theta, alpha, sigma, beta, gamma), which frequency components are hypothesized to be connected to different functions during sleep (Halász, Bódizs, Parrino, & Terzano, 2014; McKinney, Dang-Vu, Buxton, Solet, & Ellenbogen, 2011; Schönauer, 2018).

In our first study we aimed to examine the consolidation of relevant and irrelevant information – determined by the directed forgetting paradigm – after a 2-hour delay spent either awake or with an afternoon nap. In this paradigm the participants had to learn two separate word lists and the given instruction between these two lists (to forget or to remember the first list) determined their subgroup membership. We found, that the so called directed forgetting effect – relative decrease in the retention of the first list and relative increase in the retrieval of the second list of words – appeared after the 2 hour delay spent awake. This effect was even more pronounced when the participants spent the 2 hours between learning and recall with an afternoon nap. Furthermore, power spectral analysis of the sleep EEG within the nap group showed significant differences between the forget (distinction between relevant and irrelevant stimuli) and remember subgroups (no difference in future relevance between the stimuli) in specific oscillatory patterns during NREM sleep and REM duration. We found that the recall rate of to-be-remembered (future relevance tagged) words in the forget group was predicted by higher amplitude of sleep spindles and higher sigma power during NREM sleep as well as longer REM duration, whereas the recall rate of the to-be forgotten words (irrelevant for the future tagged) only correlated with higher sleep spindle amplitude.

To the best of our knowledge this was the first study that examined the directed forgetting effect (using a list-based paradigm) after a daytime nap in relation to sleep stages and sleep-specific cortical oscillations. Our results seem to be consistent with the re-conceptualized version of the active system consolidation theory (Diekelmann & Born, 2010) advocating for the idea of NREM and REM sleep playing different but equally important roles in declarative memory consolidation. NREM sleep being primarily important for reactivating and 'tagging' newly acquired memories which processes could be captured in the correlations with sleep spindle activity and REM sleep being responsible for the selective retention or 'rejection' of these previously tagged memory elements.

Related article:

Blaskovich, B., Szőllősi, Á., Gombos, F., Racsmány, M., & Simor, P. (2017). The benefit of directed forgetting persists after a daytime nap: the role of spindles and rapid eye movement sleep in the consolidation of relevant memories. *Sleep, 40*(3), zsw076.

2. Thesis point 2: Hyperarousal model of nightmare disorder

Submerging below the surface level of macrostructure during sleep can also help to investigate trait like differences related to various disorders. Hyperarousal related disorders such as Insomnia, PTSD or Nightmare disorder could serve as perfect candidates for this type of analysis. All three of these disorders are hypothesized to have a disrupted balance in wake (arousal) – sleep promoting system in the background, however these theories are mostly based on animal studies or subjective reports of patients (Gieselmann et al., 2019; Riemann et al., 2010; Weston, Stewart Weston, Davin Norrholm, & Piece, 2014; Woodward, Arsenault, Murray, & Bliwise, 2000). Objective measurements of cortical hyperarousal are highly limited in humans since measuring activity of arousal regulating small deep brain structures such as the locus coeruleus (LC) is almost impossible with most of the currently used imaging techniques. However, quantitative EEG analysis can help to measure changes in the high (beta, gamma) and low- frequency (delta) power which based on animal studies (Berridge & Foote, 1991; Cape & Jones, 1998) could be interpreted as indicators of cortical hyperarousal.

2.1. Previous literature suggests abnormal arousal processing in nightmare disorder

In our mini review (Study 2) we aimed to summarize previous literature using quantitative EEG analysis supporting the hyperarousal account of nightmare disorder to advocate for a paradigm change in the diagnosis and definition of nightmare disorder just as it has been happening in the field of insomnia research. Even though the majority of the quantitative EEG studies on the field of nightmare disorder seems to point congruently in the direction of hyperarousal, the indirect measures of cortical hyperarousal within these studies seems to be pretty incongruent.

In Study 3 and Study 4 we aimed to investigate cortical hyperarousal in participants with frequent nightmares by trying to account for most of the variables hypothesized to be behind the above mentioned incongruity. By looking at nightmare disorder and frequent nightmares as a spectrum-like disorder we aimed to include a bigger part of the spectrum, hence clinically significant nightmare distress was not a necessary criteria of inclusion. Furthermore, we acquired information about life-long traumatic experiences and PTSD symptomatology to be able to see more nuanced differences in spectral characteristics possibly resulting from increased PTSD probability. And to be able to use our data to its fullest potential we focused our attention on NREM to REM transition (pre- REM) and compared them with REM to NREM transitions (post-REM). Since pre-REM phases are considered to be the most fragile periods of sleep and post-REM phases are considered one of the most stabile periods (Halász, Terzano, Parrino, & Bódizs, 2004). Focusing our analysis on them and directly comparing them gave us the possibility to capture the smallest imbalance between the sleep- and wake promoting systems.

2.2. NM participants are characterized by reduced slow frequency and increased fast frequency power during pre-REM phases

In Study 3 we analyzed sleep macrostructure, psychometric and spectral characteristics of participants with frequent nightmares (NM participants) and based on the above mentioned literature hypothesized a globally distributed reduction in slow-frequency (delta) power during NREM sleep which difference was expected to be present primarily during pre-REM periods. On the macrostructural level we found significantly reduced SWS in NM participants compared to controls. On the spectral level this result was supported by a significant reduction of low-frequency (within delta band) power which was accompanied by increased high-frequency activity (within beta, gamma bands) during pre REM phase compared to post-REM periods in the NM group. This sharp difference between the two groups completely disappeared during post-REM phase. Furthermore, the only significant difference in psychometric measurements were in PTSD symptomatology (measured by PCL-5), which showed significantly higher PCL-5 scores in the NM group and with combination of the LEC-5 answers a potential subgroup of NM participants with high probability of PTSD. Ancillary analysis comparing the spectral characteristics of the three groups (control, NM with high probability of PTSD and NM without high probability of PTSD) indicated, that the reduction of low-frequency power during these vulnerable pre-REM states was associated with having frequent nightmares and the additional increase in high-frequency power was attributed to high PTSD probability. In accordance with this finding we also observed a significant correlation between gamma power during pre-REM periods and PCL-5 scores only in the NM group.

2.3. NM participants are characterized by increased amount of arousals during pre-REM phase

Since an increase in higher frequencies during NREM sleep and pre-REM sleep is only indicative of increased activity of the arousal system and therefore of increased arousal, in Study 4 we aimed to investigate sleep microstructure characteristics of individuals with frequent nightmares by calculating arousal (number and length) the most conservative, well accepted and commonly used measurement of hyperarousal. We found that when compared to control participants, increased amount of arousal events only characterize the sleep of NM participants during the vulnerable pre- REM periods. All in all arousal seem to be a much more straightforward marker, even visible to the human eye, and as a consequence, a robust validation of the previous indirect lines of evidence in Study 3.

Related articles:

Simor, P., & Blaskovich, B. (2019). The pathophysiology of nightmare disorder: Signs of impaired sleep regulation and hyperarousal. *Journal of Sleep Research*, *28*(6), Article e12867.

Blaskovich, B., Reichardt, R., Gombos, F., Spoormaker, V. I., & Simor, P. (2020). Cortical hyperarousal in NREM sleep normalizes from pre-to post-REM periods in individuals with frequent nightmares. *Sleep*, *43*(1), zsz201.

Blaskovich, B., Reicher, V., Gombos, F., Spoormaker, V. I., & Simor, P. (2019). Hyperarousal captured in increased number of arousal events during pre-REM periods in individuals with frequent nightmares. *Journal of Sleep Research*, e12965.

3. Thesis point 3: Tonic and phasic REM sleep are differentiated by distinct inter- and intra-hemispheric synchronization patterns

There has been numerous studies presenting a base for a meaningful and necessary distinction between phasic and tonic REM periods. Even though they used different measurements such as focusing on pre-awakening mental experiences (Molinari & Foulkes, 1969), ERP responses (Sallinen, Kaartinen, & Lyytinen, 1996), power spectral analysis (Ermis, Krakow, & Voss, 2010) or combined fMRI-EEG method (Wehrle et al., 2007), the results all seem to point into the same direction: There are differences in sleep depth within REM phase, with phasic REM being a deeper sleep stage than tonic REM.

To further investigate these differences we used the phase information gained after transforming the EEG signal from time to the frequency domain. The basic assumption behind using phase information is, that it can reflect communication between distinct neuron populations. These so called neural assemblies have reciprocal connections within and between areas organized in a web-like fashion (connections to the same and different levels as well). These connections have a dynamic nature (feed-back and feed-forward relations emerging and disappearing). All in all the to be forwarded information is hypothesized to be encoded by the firing patterns of these assemblies and the communication assumed to happen through synchronization between the separate regions in the web (Varela, Lachaux, Rodriguez, & Martinerie, 2001).

The importance of analyzing phase information in this case is supported by the observations that Wake, NREM and REM states can be differentiated not only by power spectrum but also by changes in cortical synchronization. Wake is mostly characterized by high synchronization in the alpha and gamma bands (Achermann, Rusterholz, Dürr, König, & Tarokh, 2016). NREM sleep seem to be characterized by high coherence in delta and sigma bands (Achermann et al., 2016; Pérez-Garci, del-Río-Portilla, Guevara, Arce, & Corsi-Cabrera, 2001), moreover since NREM is a heterogeneous state each sub-state have different synchronization characteristics. For example spindle frequency (in the sigma band) synchronization seems to be the highest during NREM 2 compared to all the other stages (Achermann et al., 2016). Notwithstanding, differentiating between NREM 1, NREM 2 and SWS is a highly accepted and mostly necessary part of sleep research and sleep analysis. REM sleep on the other hand is often described as the most desynchronized homogeneous state during sleep, however there is evidence supporting the contrary. Alpha, beta and gamma coherence seems to be actually higher during REM phase than during NREM phase when measuring global field synchronization index (Achermann et al., 2016) and even though long-range intra hemispheric fast activity (27-48 Hz) seems to reduces during REM phase, short range intrahemispheric fast activity stays at the same synchronization level as during wakefulness (Pérez-Garci et al., 2001). However as mentioned earlier it has already been proposed, that REM – just as NREM – should be considered a heterogeneous phase, which made the investigation of sub-state specific synchronization patterns an important issue.

Our aim in Study 5 was to investigate the differences between phasic and tonic REM states by examining inter-areal (inter- and intrahemispheric) EEG synchronization. Based on the aforementioned studies we hypothesized, that tonic REM sleep has more wake-like characteristic such as enhanced alertness, reinstated attentional processes, which make it more susceptible for environmental stimuli. We were expecting this 'system level openness' to be reflected in increased long-range alpha synchrony, which has been shown to play key role in arousal, alertness and attention during awake (Sadaghiani et al., 2010; Varela et al., 2001). We found increase in long- range inter- and intrahemispheric synchronization in both alpha and beta frequency bands during tonic REM compared to phasic REM. Furthermore, there was an increase in short-range gamma synchrony during phasic REM periods, which also differentiated the two REM sub-states.

Related article:

Simor, P., Gombos, F., Blaskovich, B., & Bódizs, R. (2018). Long-range alpha and beta and short-range gamma EEG synchronization distinguishes phasic and tonic REM periods. *Sleep*, *41*(3), zsx210.

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