Decreased Inter Trial Phase Coherence of Steady-State Visual Evoked Responses in Sleep Deprivation

M Eidelman-Rothman[1], E Ben-Simon[2,3], D Freche[1,4], A Keil[5], T Hendler[2,3,6,7] and N Levit-Binnun[1]

[1]Sagol Center for Brain and Mind, Interdisciplinary Center Herzliya, [2]Functional Brain Center, Wohl Institute for Advanced Imaging, Tel Aviv Medical Center, [3]Sackler Faculty of Medicine, Tel Aviv University, [4]Physics of Complex Systems, Weizmann Institute of Science, [5]Center for the Study of Emotion & Attention, University of Florida, [6]Sagol School of Neuroscience and [7]School of Psychological Sciences, Tel Aviv University

1. Abstract

Sleep loss has detrimental effects on cognitive and emotional functioning. These impairments have been associated with alterations in EEG measures of power spectrum and event-related potentials, however the impact of sleep loss on inter trial phase coherence (ITPC), a measure of phase consistency over experimental trials, remains mostly unknown. ITPC is thought to reflect the ability of the neural response to temporally synchronize with relevant events, thus optimizing information processing.

In the current study we investigated the effects of sleep deprivation (SD) on information processing by evaluating the phase consistency of steady-state visual evoked potentials (ssVEPs) obtained from a group of 18 healthy individuals following 24 hours of total SD and after a night of habitual sleep. An ssVEP task was utilized, which included the presentation of dots flickering at 7.5 Hz, along with a cognitive-emotional task. Our results show that ITPC is significantly reduced under SD relative to habitual sleep. Interestingly, the decrease in ITPC was accompanied by a decrease in behavioral performance in the ssVEP cognitive-emotional task, and the psychomotor vigilance task (PVT) in the majority of our participants.

The results suggest that the capability of the brain to synchronize with rhythmic stimuli is disrupted in SD. Thus, decreased ITPC may represent an objective and mechanistic measure of SD, allowing future work to study the relation between brain-world synchrony and the specific functional impairments associated with SD.

2. Introduction

Sleep is a ubiquitous phenomenon, essential for well-being and for maintaining optimal behavioral performance. At the neural level, it is hypothesized to have a functional role in various restorative processes, including synaptic plasticity and the balance between excitation and inhibition in neural circuits (Meisel et al., 2013; Tononi and Cirelli, 2006). Accordingly, sleep loss adversely affects cognitive and emotional functioning (Krause et al., 2017). It is associated with alterations to sensory perception, decreased performance in cognitive tasks (Killgore, 2010), overall slowing of responses (Lim and Dinges, 2008), disturbed mood, and impaired emotional processing (Kahn et al., 2013; Pilcher and Huffcutt, 1996; Walker and van Der Helm, 2009). Disrupted sleep pattern is present in various mental disorders including schizophrenia (Chouinard et al., 2004), depression (Tsuno et al., 2005) and post-traumatic stress disorder (Kobayashi et al., 2007). Although it is yet unclear whether sleep abnormalities play a causal role in the etiology of these conditions (Goldstein and Walker, 2014), establishing neuromarkers for disrupted sleep is important for the identification of individuals who are at risk and for the development of efficient interventions for those who suffer from it.

Supporting neurophysiological mechanism for sleep loss-related behavioral impairments demonstrated lower event-related potentials/fields (ERPs/ERFs) components associated with sensory stimuli and attention (i.e., N1, P1, P3 e.g., : Boonstra et al., 2005; Hoedlmoser et al., 2011; Lee et al., 2003; Morris et al., 1992) in sleep deprived individuals. In addition, a single night of SD was shown to result in indistinguishable response of the late positive potential (LPP) to affective and neutral stimuli, otherwise enhanced by emotional content (Alfarra et al., 2015). In the same vein, enhanced response to negative compared to neutral distracting pictures during a steady-state visual evoked potential (ssVEP) cognitive-emotional task was found in a group of

individuals after habitual sleep, but not after 24 hours of total SD (Ben-Simon et al., 2015). A lack of neural discrimination between neutral and affective stimuli in limbic and early perceptual regions was also demonstrated in the same group of individuals utilizing fMRI and the n-back memory task (Ben-Simon et al., 2015). In another study (Hoedlmoser et al., 2011), EEG was collected from participants at several time points over a night of SD, while performing a psychomotor vigilance task (PVT), a measure of visual attention and vigilance, highly sensitive to SD (Drummond et al., 2005). In addition to a progressive decrease in the P100 ERP component, this study found decreased inter trial phase locking of neural oscillations in the delta and theta frequency ranges during the PVT, suggesting that sleep loss impacts the temporal synchronization of the neural response across different frequencies. Notably, in the experimental design of the aforementioned study, the EEG and behavioral measurements were obtained in different time points along the sleep-wake cycle and therefore, the results may have been influenced by unspecific factors (e.g., metabolism, circadian effects; Hoedlmoser et al., 2011)

Neural oscillations (or “neural rhythms”) reflect periodic fluctuations of excitability in local groups of neurons. These fluctuations are generated by synchronous transmembrane currents that give rise to local field potentials (LFPs), measurable noninvasively from the human scalp by means of EEG and MEG (Buzsáki and Draguhn, 2004; Buzsáki and Watson, 2012; Donner and Siegel, 2011; Thut et al., 2012). The fluctuations of excitability of LFP oscillations are represented by their oscillatory phase, which is the time-variant angle of the oscillatory cycle (Buzsáki, 2010; Buzsáki and Watson, 2012; Klimesch et al., 2007; Lakatos et al., 2007, 2008; Thut et al., 2012). In humans, inter trial phase locking of LFP oscillations, also known as inter trial phase coherence (ITPC), is a measure of phase consistency of the brain response over experimental trials (van Diepen and Mazaheri, 2018). The consistency of phase angles over trials

during rhythmic sensory stimulation has been suggested to serve as a mechanism for optimizing data processing, by tuning the brain response to the temporal structure of task relevant information, such that high excitability phases of oscillations are aligned with the timing of stimulus presentation (Besle et al., 2011; Golumbic et al., 2013; Lakatos et al., 2008; Mathewson et al., 2010; Schroeder and Lakatos, 2009).

Increased phase consistency has been associated with enhanced cognitive performance, including enhanced visual perception (Hanslmayr et al., 2005), attention (Ding et al., 2005; Kim et al., 2007) and performance in memory tasks (Fell et al., 2008; Klimesch et al., 2004), while decreased consistency has been observed in a number of disorders, such as dyslexia (Hämäläinen et al., 2012), attention-deficit/hyperactivity disorder (ADHD; McLoughlin et al., 2014) and schizophrenia (Teale et al., 2008). Currently very little is known about ITPC in SD and specifically, ITPC of steady-state evoked responses. Studying ITPC in sleep deprived individuals is important for the elucidation of brain mechanisms underlying the behavioral impairments associated with sleep loss, and for the identification of neuromarkers for this condition, an essential step towards the development of efficient intervention.

In the present study we investigated the ITPC of steady-state visual evoked responses, that were recorded under total sleep deprivation and after habitual sleep, in similar time points within the sleep-wake cycle. ITPC was examined along with behavioral performance in the PVT and in the ssVEP task. Steady-state visual evoked potentials are continuous EEG responses, generated by delivering a rhythmic stimulus at a known frequency rate (e.g., flickering dots; Norcia et al., 2015). The ssVEPs typically recorded in occipital electrodes and are measured as oscillatory waveforms, stable in phase and amplitude (Regan, 1966), with the same frequency peak as the delivered stimulus. Thus, ssVEPs are relatively narrow band oscillations and are

advantageous in their excellent signal to noise ratio, which is essential for a reliable phase coherence estimation (Tallon-Baudry et al., 1996; van Diepen and Mazaheri, 2018). In addition, ssVEPs can be detected on a single trial level (Vialatte et al., 2010), which empowers their relevance for behavioral performance.

In light of the above, our main hypothesized is that the ITPC of ssVEPs will be reduced in sleep deprivation (SD) compared to the sleep rested (SR) condition, and that this reduction will be accompanied by decreased performance in the cognitive-emotional (ssVEP) and psychomotor vigilance tasks.

3. Methods

3.1. **Participants and Experimental Design**

Participants and experimental design were as described in Ben-Simon et al., 2015. Briefly, 18 healthy adults (age range, 23–32 years; mean, 26.8 ± 3 years; 10 females) participated in two experimental sessions each, in a repeated-measures crossover design: after a night of habitual sleep (sleep-rested condition, SR) and following 24 h of supervised sleep deprivation (SD). EEG was recorded at ~8:00 A.M. (± 30 min) of the following morning of each session while participants were engaged in a steady-state visual evoked potential (ssVEP) task (see section 3.2). Experimental sessions were separated by a mean of 13.8 d with the order of the sleep-rested and sleep-deprived sessions counterbalanced across participants. Normal sleep-wake patterns were validated using actigraphy (movement sensor sensitive to wake–sleep states; Fitbit) and subjective sleep logs. Normal sleep parameters were validated using an ambulatory sleep device (WatchPAT-100; Itamar Medical) during the night of the SR session. Fatigue related behavioral measures were obtained every 2 h during the SD night (from 11:00 P.M. to 7:00 A.M.) and in the

morning of the sleep-rested session (± 8:00 A.M.) and included the Hebrew version of the Stanford Sleepiness Scale questionnaire (SSS; Hoddes et al., 1973) as well as the Psychomotor Vigilance Task (PVT; Drummond et al., 2005). Mood changes after sleep were assessed with the Positive and Negative Affective Scale (PANAS; Watson et al., 1988) questionnaire, every 4 h during the SD night and upon arrival in the SR session.

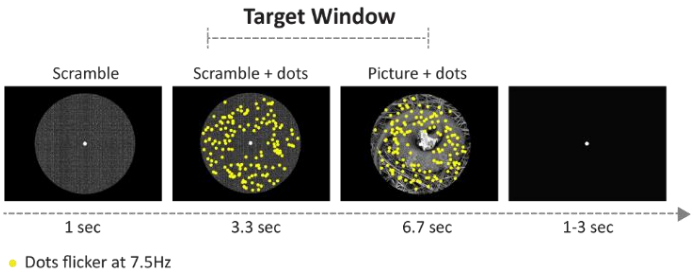

Figure 1. Experimental trial design. Each trial started with 1 s presentation of a scrambled picture, followed by the appearance of flickering dots (at a rate of 7.5 Hz) for 3.3 s. Consequently, a positive, negative, or neutral picture appeared for 6.6 s at the background of the dots. Targets were rare intervals of coherent motion of the dots that could only occur between 1.17 and 7 s after stimulus onset (marked target window). Each trial lasted 10 s, with a variable 1–3 s inter trial interval.

3.2. **ssVEP Task**

ssVEPs were elicited using random-dot kinematograms that consisted of randomly moving dots flickering at a rapid rate (7.5 Hz; Ben-Simon et al., 2015). During the presentation of the dots participants were engaged in a cognitive-emotional task aimed at detecting very short intervals of coherently moving dots, while ignoring task-irrelevant neutral or affective distracting pictures, presented at the background of the dots, as previously described (Deweese et al., 2014; Müller et

al., 2007; Fig 1). Such competition by task-irrelevant distractors can be quantified as an attenuation of task-evoked processing, predominantly evident in visual regions (Ben-Simon et al., 2015; Deweese et al., 2014; Müller et al., 2007).

3.2.1. Picture Stimuli

Distractor pictures were divided into three valence categories, positive, negative and neutral (for details see Ben-Simon et al). Each category included 30 pictures, totaling 90 pictures, selected from the IAPS (Lang et al., 1997) with additional images selected from the public domain to complete balanced human and animal picture categories. All stimuli were grayscale pictures and were controlled for visual complexity (measured as .jpeg size) and matched for luminance using scripts from the MATLAB image processing toolbox (Picture stimuli were circular in nature and were cropped and adjusted such that the defining element of each picture was positioned at the center of a circle (Fig 1).

3.3. **Experimental Trial**

Each trial began with a 1 s presentation of a stimulus image with individual pixels scrambled to avoid contamination of the ssVEP with transient responses to the luminance gradient created by stimulus onset (Ben-Simon et al., 2015). Next, a total of 150 yellow dots (each 0.3° x 0.3° of visual angle) were superimposed on the scrambled image for 3300 ms. The scrambled picture was then replaced by a positive, neutral, or negative image that remained on the screen for the remaining duration of the trial (6600 ms). The flickering dots were distributed randomly across pictures and while remaining inside the circle (6.9° visual angle) at all times. The yellow dots were “on” for six frames and “off” for eight frames. All dots remained in continuous motion throughout the trial, and each dot changed its position by 0.04° in a random direction with every ssVEP cycle (i.e., 7.5 times/s). In a random subset of 50% of the trials, all dots moved coherently

in the same direction (target), and participants were instructed to respond to coherent motion events with a mouse click, as quickly and as accurately as possible. Coherent motion of the targets occurred in one of four diagonal directions (45°, 135°, 225°, and 315°) at random. In an effort to produce a difficult and demanding perceptual detection task, coherent motion lasted for only four successive cycles of 7.5 Hz (i.e., 533.33 ms). For further details, see Ben-Simon et al., 2015. Each trial lasted 10,000 ms, with inter stimulus intervals varying randomly between 1,000 and 3,000 ms, during which a white fixation dot was presented at the center of the screen (Fig 1). Stimuli were presented centrally on an LED monitor, set at a resolution of 1024 x 768 with a refresh rate of 60 frames/s (i.e., 16.66 ms refresh interval).

3.4. **EEG Data Recording and Preprocessing**

The EEG signal was recorded from the scalp using the BrainAmp-MR EEG amplifier (Brain Products) and the BrainCap electrode cap with sintered Ag/AgCl ring electrodes providing 30 EEG channels, one EKG channel, and one EOG channel (Falk Minow Services). The reference electrode was between Fz and Cz. Raw EEG was sampled at 500 Hz and recorded using the Brain Vision Recorder software (Brain Products) with scalp impedance for each electrode kept below 20 kΩ. Signal preprocessing was carried out using MATLAB (The MathWorks) and functions from the EEGlab toolbox (Delorme and Makeig, 2004). The continuous data were bandpass filtered offline in the 0.5-40 Hz range (Hamming windowed sinc FIR filter) and re-referenced to the averaged potential across electrodes. Subsequently, the data were segmented into 13 s epochs (- 1 s before and 12 s after dots onset) and segments with amplitudes exceeding 100 μV were excluded from further analysis. This resulted in an overall retention rate of 84.38 trials, with trial counts not significantly different between conditions (positive, 28.11 trials; neutral, 28.17 trials; negative, 28.08 trials on average; paired t-tests) or experimental sessions

(sleep-rested, 84.09; sleep-deprived, 84.66 trials on average). One participant was excluded from further analysis due to insufficient number of trials following artifact rejection.

3.5. **ssVEP Analysis**

The analysis was focused on visual electrodes (O1, Oz, O2), where the greatest overall ssVEP amplitudes have been observed (Ben-Simon et al., 2015). The effect of emotional distractors on ssVEPs in the SR vs. SD condition was analyzed and reported in the previous work conducted with the same experimental group (Ben-Simon et al., 2015), and the current analysis was performed on the entire trial pool, with no distinction between distractor type.

3.5.1. Spectral Analysis

To visualize ssVEPs in the SR and SD conditions, a time-frequency analysis was conducted. The spectral analysis was performed for each subject on the time-domain-averaged data (see section 3.4) in each visual electrode. Spectral power was estimated in the 1-25 Hz frequency range using the short-time Fourier transform with a sliding hamming window of 1024 samples length and 1023 overlapped samples. The obtained spectrograms were averaged across visual electrodes and across subjects.

3.5.2. ssVEP Phase Coherence and Amplitude Analysis

The continuous EEG signal was filtered around the stimulation frequency (7.5 Hz ± 0.5; Hamming windowed sinc FIR filter). For inter trial phase coherence (ITPC) analysis, the filtered signal was subjected to Hilbert transform and was subsequently segmented into 16 s epoches (4 s before and 12 s after dots onset). Phase-locking values (PLVs; i.e., the resultant vector length) were calculated for each time point using the following formula, as previously described (Lachaux et al., 1999; Sharon and Nir, 2017; van Diepen and Mazaheri, 2018):

$$ITPC = \frac{1}{N} \sum_{K=1}^{N} e^{i * \phi_k}$$

where N is the number of trials and Φ_k is the angle of the signal relative to the stimulus, in radians. PLVs were calculated as the absolute value of the ITPC, yielding values between 0 (high phase variability across trials) and 1 (uniformity of phase across trials). The PLVs were averaged across electrodes for each participant, and group statistics comparing between sleep conditions was carried out using paired t-tests (implemented in MATLAB). Paired t-tests were conducted in 1000 ms time windows along the experimental trial, with False Discovery Rate (FDR) correction for multiple comparisons (Benjamini and Hochberg, 1995). For ssVEP amplitude analysis, the Hilbert transform was applied to the time-domain averaged filtered-data. The amplitude at each time point was extracted as the absolute value of the Hilbert transformed analytic signal. Group statistics comparing between sleep conditions was conducted similarly to the PLV analysis as described above.

3.5.3. Ongoing Activity Analysis

Decreased phase synchronization during processing of external events is hypothesized to be associated with elevated background noise (Krystal et al., 2017), such as spontaneous activity. We therefore examined ongoing brain activity at the stimulation frequency in SR vs. SD. The ongoing activity was calculated by subtracting the time-domain averaged data from each trial, thus eliminating all evoked (phase-locked) activity. The resulting trials of non-phase-locked activity were subjected to a Hilbert transform and were analyzed similarly to the time domain averaged ssVEP amplitude analysis, as described in section 3.5.2.

3.5.4. ssVEP Signal to Noise Ratio Analysis

To examine whether differences in signal quality exist between the two sleep conditions, a signal to noise ratio (SNR) analysis was conducted. The ssVEP SNR was calculated as the ratio between power at the ssVEP frequency, to power at the average of neighboring frequencies (+/−2 Hz, excluding +/−0.5 Hz around the ssVEP frequency), as previously described (Cohen and Gulbinaite, 2017; Kashiwase et al., 2012). SNR differences between SR and SD were then compared using paired t-test.

3.6. **Correlation Between ssVEP Amplitude and ITPC**

ITPC differences between experimental conditions have been shown to be affected by corresponding differences in amplitude (van Diepen and Mazaheri, 2018). Accordingly, we tested the relation between the differences in ssVEP amplitude and in ITPC as a result of SD. A single value was first calculated for each quantity (amplitude/phase) in each sleep condition (SR/SD), per subject, by averaging the amplitudes/PLVs over all time points along the steady state visual evoked response (i.e., from dots onset to dots offset). The difference between conditions (SR minus SD) in mean PLV was then correlated with the corresponding difference in ssVEP amplitude, using Pearson correlation.

3.7. **Correlation Between ITPC and Behavioral Measures**

As reported in Ben-simon et al., 2015, sleep deprivation resulted in increased subjective and objective assessments of sleepiness (the Stanford Sleepiness Scale questionnaire and the psychomotor vigilance task, respectively) and in decreased performance in the ssVEP task. The association between SD-related alterations in ITPC and in behavioral measures was tested by correlating the difference between conditions (SR minus SD) in mean PLV (calculated in section 3.6) with the corresponding difference in the behavioral measures, using Pearson correlation.

4. Results

4.1. **ssVEP Spectral Analysis**

Group averaged time-frequency representations of the ssVEPs in SR and SD are presented in Fig 2. The ssVEP in 7.5 Hz and its harmonics are clearly seen in the two conditions. As demonstrated by the difference of the two spectra (SR minus SD), the ssVEP power in SD is reduced compared to SR. The reduction of the ssVEP signal was further inspected and statistically tested at the stimulation frequency, as detailed in section 4.2.1 and Fig 4.

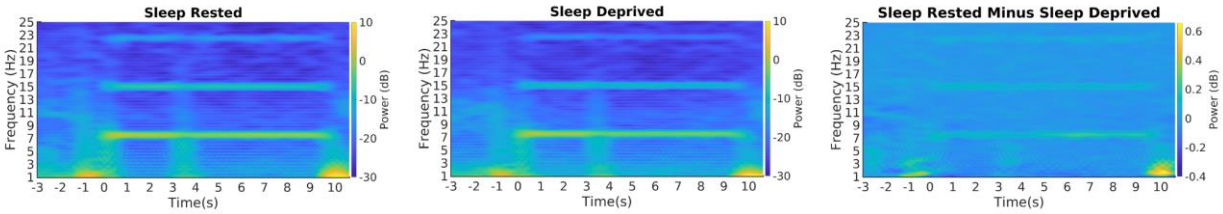

Figure 2. Time-frequency representation of the steady-state visual evoked response. Spectrograms were averaged across visual electrodes (O1, O2, Oz) and across subjects. The steady state visual evoked response is evident at 7.5 Hz and its harmonics, in the sleep rested (SR) and sleep deprived (SD) conditions. As revealed by the difference plot (SR minus SD), ssVEP power in SD was reduced compared to the SR condition.

4.2. **Phase-Locking of ssVEPs is Decreased in Sleep Deprivation**

Our inter trial phase-locking analysis revealed a significant reduction in PLVs in the SD compared to the SR condition (t values ranged from $t(16) = 3.25$ to $t(16) = 5.39$ across the tested time windows; all p values < 0.008, FDR corrected) throughout the steady state evoked response

period (i.e., from dots onset to dots offset; Fig 3a). This was the case for the vast majority of the participants as demonstrated in Fig 3b and 3c. These findings indicate that SD is associated with increased variability in the timing of the ssVEP responses, which can be seen on the individual subject level, suggesting that decreased ITPC may be used as a reliable indicator of SD.

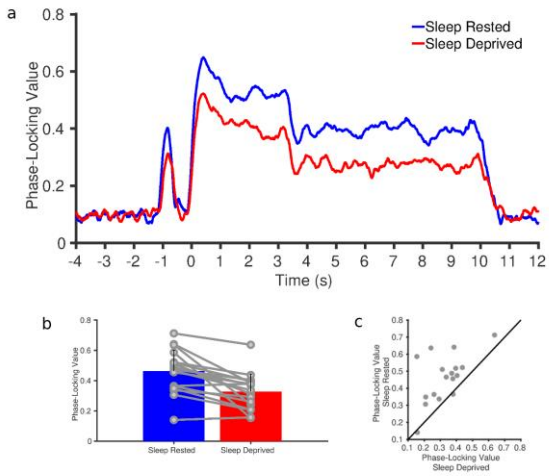

Figure 3. Inter trial phase coherence of the steady-state visual evoked response. (a) PLVs calculated around the stimulation frequency (7.5 Hz), averaged across visual electrodes (O1, O2, Oz), and across subjects. PLVs during the evoked response period (i.e., from dot onset at time zero to dot offset at 10 s) were significantly lower in the sleep deprived (SD) compared to the sleep rested (SR) condition ($p<0.008$, FDR corrected). (b) Group level (bar graph) and individual level (circles) differences between SR and SD in mean PLVs, calculated per individual as the averaged values over all time points within the steady-state evoked response. Error bars represent standard deviations. (c) Mean PLVs in SR and SD plotted against each other. Each circle represents one subject. As indicated by the position of most circles above the 45-degree diagonal line (i.e., equality of PLVs in SD and SR), decreased inter trial phase coherence is evident at the individual level for almost the entire sample.

4.2.1. Relation Between ssVEP Amplitude and ITPC

ITPC estimation has been shown to be affected by the amplitude and quality of the signal, such that significant power is need for reliable phase calculation (van Diepen and Mazaheri, 2018; VanRullen et al., 2011). Therefore, as a first step we examined whether significant amplitude differences exist between SR and SD at the ssVEP stimulation frequency. Fig 4a presents the group averaged ssVEP amplitude, indicating that ssVEP amplitude in the SR condition was higher compared to the SD condition. These differences were statistically significant in specific time windows along the time course of the experimental trial, starting from 2s following dots onset (t values ranged from $t(16) = 2.7$ to $t(16) = 3.7$;all p values < 0.035, FDR corrected). In the next step, the differences in mean PLVs and mean amplitudes between sleep conditions were correlated. A positive correlation ($r = 0.87$, $p < 0.0000$) was found (Fig 4b), indicating that higher decrease in ITPC was associated with higher decrease in the signal amplitude.

4.2.2. ssVEP Signal to Noise Ratio Analysis

To evaluate differences in signal quality between the two sleep conditions that may have affected ITPC estimation, SNR analysis was conducted. Fig 5 shows higher SNR in the SR condition compared to SD, however this difference was not significant ($t(16) = 1.69$, $p = 0.1$).

4.2.3. Ongoing (Non-Phase-Locked) Activity is Increased in Sleep Deprivation

Ongoing activity at the stimulation frequency was significantly higher in the SD compared to the SR condition throughout the entire experimental trial (excluding the 1000 ms time window immediately before scramble picture presentation; t values ranged from $t(16) = -2.96$ to $t(16) = -4.96$;all p values < 0.01, FDR corrected; Fig 6). Fig 6 also demonstrates the time-locked but not phase locked (i.e., induced) activity in response to the onset and the offset of the dots.

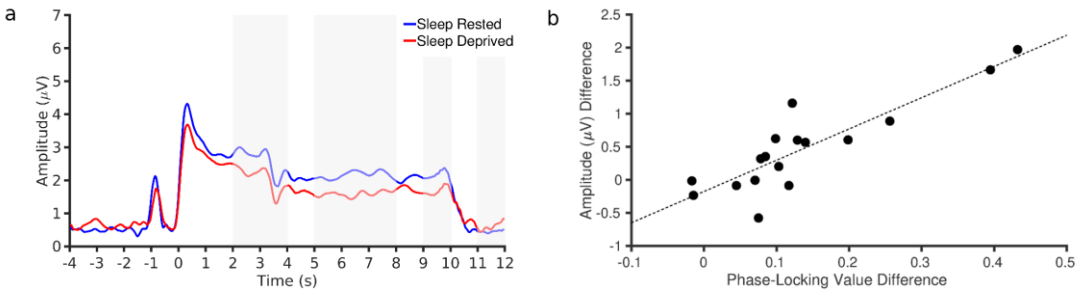

Figure 4. relation between ssVEP amplitude and ITPC. (a) ssVEP amplitude calculated around the stimulation frequency (7.5 Hz), averaged across visual electrodes (O1, O2, Oz), and across subjects. Amplitudes during the evoked response period (i.e., from dot onset at time zero to dot offset at 10 s) were significantly lower in the sleep deprived (SD) compared to the sleep rested (SR) condition in specific time windows along the experimental trial (marked in gray shades), starting from 2s following dots onset ($p<0.035$, FDR corrected). (b) Correlation between the differences in mean PLVs and in mean amplitudes between sleep conditions (SR minus SD; $r = 0.87$, $p < 0.0000$).

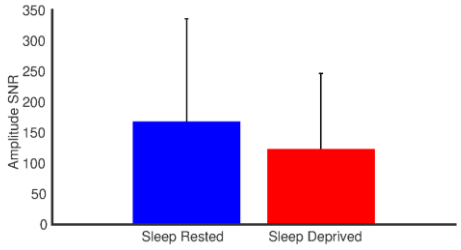

Figure 5. ssVEP signal to noise ratio analysis. Group averaged SNR calculated as the power at the stimulation frequency relative to the power of neighboring frequencies. No significant difference was found between conditions. Error bars represent standard deviation.

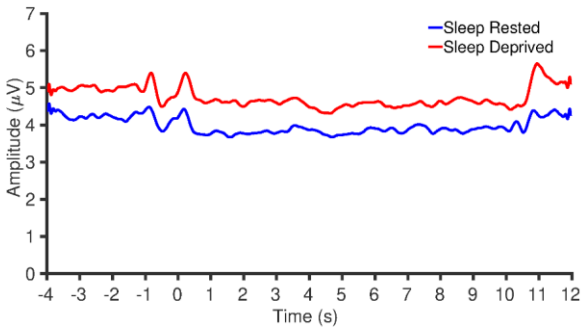

Figure 6. Ongoing activity at the stimulation frequency. Ongoing activity was calculated around the stimulation frequency (7.5 Hz), averaged across visual electrodes (O1, O2, Oz), across trials and across subjects. A significantly increased activity along the experimental trial (excluding the 1000 ms time window immediately before scramble picture presentation) was found in SD ($p<0.01$, FDR corrected).

4.3. **Relation Between Inter Trial Phase-Locking and Behavioral Measures in SD**

To further evaluate the measure of ITPC in SD, we examined the relations between the observed reduction in phase coherence, the increase in self-reported fatigue and the decrease in task performance under SD. The difference between the mean PLV (calculated in section 3.6) in SD and SR was correlated with the corresponding differences in the scores of the sleepiness scale (level of fatigue), the PVT (number of lapses) and the ssVEP task (accuracy). While no significant correlations were found ($r = -0.09$, $r = -0.09$, and $r = 0.23$, for correlation with Stanford Sleepiness Scale, PVT and ssVEP, respectively, n.s), inspection of all measures at the individual subject level clearly revealed a common trend (Fig 7 and table 1). Specifically, figure 7 presents the percent change from SR to SD (normalized by the maximal absolute change observed per measure), revealing that out of 15 subjects who showed decreased PLV in SD, 13

also showed an increase in the number of lapses in the PVT. Similarly, 13 subjects showed decreased accuracy in the ssVEP task and 14 increased sleepiness along with the decreased PLVs. This points at the possibility that similar to the PVT, known for its high sensitivity to SD, and in line with the increased sleepiness and the decreased cognitive performance typical to SD, (demonstrated here by low accuracy scores in the ssVEP task) PLV may serve as an informative measure for assessing SD.

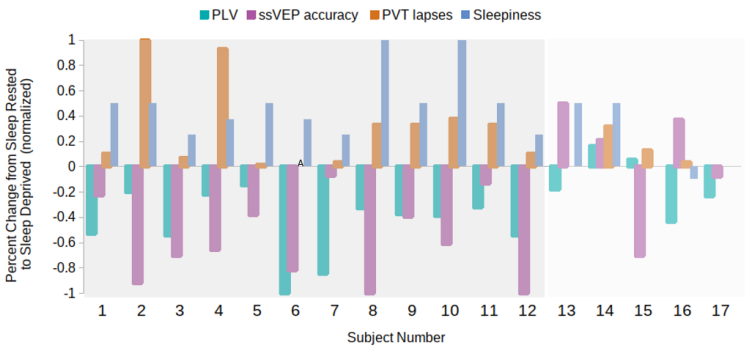

Figure 7. Effects of SD on phase-locking values and behavioral measures. For each subject, normalized percent changes from SR to SD are presented for mean phase-locking value (PLV), for performance in the psychomotor vigilance task (PVT; number of lapses) and in the ssVEP task (accuracy), and for self-reported sleepiness. Decreased task performance and increased sleepiness accompanied the decreased PLV in the majority of the sample. [A] in this subject the original value in the sleep rested condition was zero, however the number of lapses increased in the sleep deprived condition.

Table 1. Effect of SD on phase-locking values and behavioral measures. The table shows for each subject whether a decrease in mean phase-locking value (PLV), in task performance and an increase in self-reported sleepiness were found under SD (indicated by '+'). [A] in this subject the original value in the sleep rested condition was zero, however the number of lapses increased in the sleep deprived condition.

Subject	PLV decrease	ssVEP task accuracy decrease	PVT number of lapses increase	Sleepiness increase
1	+	+	+	+
2	+	+	+	+
3	+	+	+	+
4	+	+	+	+
5	+	+	+	+
6	+	+	+[A]	+
7	+	+	+	+
8	+	+	+	+
9	+	+	+	+
10	+	+	+	+
11	+	+	+	+
12	+	+	+	+
13	+	-	-	+
14	-	-	+	+
15	-	+	+	-
16	+	-	+	+
17	+	+	-	-

5. Discussion

Our findings demonstrate that inter trial phase coherence of steady state visual evoked potentials is reduced after one night of total sleep deprivation, in comparison to habitual sleep. A significant decrease in ssVEP amplitude was also found under SD in specific time windows and was highly associated with the overall degree of ITPC reduction. We thus demonstrate that SD can be reliably assessed by means of ssVEP paradigms, shown to be sensitive to a wide range of tasks used in cognitive and clinical neuroscience (Norcia et al., 2015; Vialatte et al., 2010; Wieser et al., 2016).These results are in line with findings from a previous study, which similarly showed decreased phase consistency across trials in SD (Hoedlmoser et al., 2011), and extend

them by utilizing rhythmic stimulation in an experimental design that minimizes potential effects of nonspecific factors related to the sleep-wake cycle (see section 2).

The phase and amplitude of oscillatory signals play an important role in perceptual and cognitive processing (Donner and Siegel, 2011; Thut et al., 2012; VanRullen et al., 2011; Ward, 2003), and both measures have been shown to be affected by fatigue (Cao et al., 2014; Hoedlmoser et al., 2011). Interestingly, a recent study in healthy humans found attenuated ssVEP responses and decreased ITPC during sleep when stimulating at the alpha (8 and 10 Hz) frequency range (Sharon and Nir, 2017). This finding raises the possibility that the reduced phase locking of ssVEPs around 7.5 Hz observed in our study indexes increased sleep propensity following a sleepless night. No correlation was found however, between the reduction in ITPC and the self-reported increase in fatigue from SR to SD. Yet, the possibility exists that the relationship between ITPC and fatigue level is more complex and may not be captured by a simple correlation test. Future research should examine the association between these measures in further detail.

The ability to synchronize with rhythmic stimuli, which are ubiquitous in our natural sensory environment (Kim et al., 2007; Müller et al., 2007), has been demonstrated to have an important role in perception and behavioral performance (Henry et al., 2014; Neuling et al., 2012; Schroeder and Lakatos, 2009). Accordingly, we tested the association between ITPC reduction in task performance. While no correlations were found, our analysis revealed that for most participants, decreased ITPC co-occurred with decreased performance in the ssVEP and in the psychomotor vigilance tasks, the latter known for its high sensitivity to SD (Drummond et al., 2005). Although profound research on the relation between ITPC and behavioral

performance under sleep deprivation is needed, these results suggest that ITPC may serve as a reliable, noninvasive indicator of SD and the associated behavioral impairment.

The decreased phase consistency observed here in nearly all participants suggests that SD disrupts the capability of the neural response to temporally synchronize with external stimuli. This points at a mechanism for the impaired information processing typical to SD, possibly due to the limited ability to align the excitability phases of the neural response with stimuli presentation. Decreased temporal synchronization with external stimuli has been suggested to reflect increased background noise, such as spontaneous neural activity (Kashiwase et al., 2012; Krystal et al., 2017). A failure to suppress such noise was theorized to produce impaired behavioral performance, for example due to reduced precision of information representation (Krystal et al., 2017). The increase in ongoing, non-task evoked activity found in SD around the stimulation frequency may thus represent a state of impaired noise suppression, which may have affected the ability of the neural response to synchronize with presented stimuli. Support for this proposition comes from resting state fMRI studies, which suggest that SD triggers a breakdown in network integrity that may negatively affect, and possibly predict, task related responses in this condition (Krause et al., 2017). For example, a graph theoretical analysis applied on a resting state fMRI data obtained from the currently tested cohort showed that under SD the spontaneous brain activity architecture shifts towards a random-like organization, leading to functional segregation in regions of the limbic, salience and default mode networks (Ben-Simon et al., 2015). These alterations were associated with behavioral impairments elicited by SD. Finally, the increased non-task-evoked activity we found in SD is in line with previous reports of higher spontaneous activity in similar frequencies under SD, which also indicated elevated sleep pressure (Bernardi et al., 2015; Nir et al., 2017) and impaired behavioral performance (Bernardi

et al., 2015; Hung et al., 2013; Nir et al., 2017). Considering the above, it would be informative in future work to examine EEG resting state data along with alterations in ITPC and behavioral measures under SD.

A reliable inter trial phase coherence estimation requires sufficient power of the oscillatory signal, since lower signal amplitudes may lead to lower measures of ITPC (van Diepen and Mazaheri, 2018; VanRullen et al., 2011). Our analysis revealed that both the amplitude and the phase coherence of the ssVEP response were decreased under SD, and that this decrease was highly correlated among the two measures. This raises the possibility that the observed reduction in ITPC results from the weaker signal measured in SD compared to SR. However, following the inspection of the time course of the SD-related ITPC and amplitude changes, we suggest that the reduction in ITPC cannot be trivially explained by the reduction in amplitude. Specifically, the significant ITPC reduction was evident from stimulation onset (i.e., appearance of the dots) throughout the experimental trial time course, and preceded the reduction in amplitude, which appeared significant only 2 s after the dots onset. In addition, SNR levels in both sleep conditions were high and comparable, suggesting that the lower ITPC in SD does not simply reflect SNR differences between conditions.

In summary, our main finding indicates that SD decreases ITPC of steady state visual evoked responses. This suggests that in SD, responses from a large population of neurons (combined in the ssVEPs) become less synchronized with external stimuli, affecting the excitation state of the brain at the time of stimulus occurrence, which ultimately, leads to suboptimal information processing in SD. Although further research on the relation between phase and amplitude as well as the relation between ITPC and behavior in SD is needed, our study suggests that ITPC may serve as a useful and non-invasive method to investigate the

effects of SD on the brain in healthy individuals and specifically, to address questions related to excitation and inhibition balance in this condition. As sleep-related ITPC patterns were demonstrated to differ depending on the stimulation frequency used to elicit ssVEPs (Sharon and Nir, 2017), future SD research utilizing ssVEPs paradigms should examine phase-locking in various stimulation frequencies to better understand the neurobiological mechanisms of SD and its association with fatigue levels and behavioral performance. In addition, integrating phase analysis with resting state data is needed to understand the mechanisms of ITPC in SD more fully.

6. References

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