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.

Keywords: Sleep deprivation; EEG; Steady-state visual evoked potential (ssVEP); Inter trial phase coherence (ITPC)

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).

Several neurophysiological mechanisms have been proposed to underlie the behavioral impairments following sleep loss. These include altered functional connectivity patterns (e.g., Chengyang et al., 2017; De Havas et al., 2012; Lei et al., 2015; Verweij et al., 2014) and reduced 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). For instance, an EEG study (Hoedlmoser et al., 2011) examined the neural response of 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). During task trials, the P100 ERP component demonstrated a progressive decrease with extended wakefulness. The authors further found decreased inter trial phase locking of neural oscillations in the delta and theta frequency ranges during the PVT, which was positively correlated with self-reported sleepiness. This suggests that sleep loss impacts the temporal synchronization of the neural response across different frequencies.

Neural oscillations reflect periodic fluctuations of excitability in local groups of neurons, measurable noninvasively from the human scalp by means of EEG and MEG (Buzsáki and Draguhn, 2004; Buzsáki and Watson, 2012; Cohen, 2017; Thut et al., 2012). Fluctuations between high and low cortical excitability states are represented by the phase of neural oscillations, which is the time-varying angle of the oscillatory signal (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 neural oscillations, also referred to as inter trial phase coherence (ITPC), is a measure of phase consistency of the brain response over experimental trials (van Diepen and Mazaheri, 2018). Phase coherence is 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 the impact of sleep loss on ITPC and specifically, whether the measure of ITPC would demonstrate any sleep sensitivity in paradigms that overtly entrain steady-state evoked responses. Since ITPC reflects the degree of temporal synchronization of the brain response with task-related sensory stimuli, it offers a novel way to examine the neural mechanisms that underlie behavioral impairments following sleep loss, beyond alterations in amplitude or connectivity.

In the present study we investigated the ITPC of steady-state visual evoked responses (ssVEP), that were recorded under total sleep deprivation and after habitual sleep, in the same circadian time. ssVEPs 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. We therefore examined ITPC of ssVEPs along with behavioral performance in the ssVEP task. We further recorded behavioral responses in the psychomotor vigilance task during the same

circadian time, to examine co-occurring changes in vigilance following sleep loss.

Our main hypothesis is that ITPC during the ssVEP task will be reduced in sleep deprivation compared to the sleep rested condition, and that this reduction will be accompanied by a decrease in task performance and in measures of vigilance.

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 normal 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. Behavioral measures of vigilance 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), as described in Ben-Simon et al., 2015.

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 visual detection 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 (Deweese et al., 2014; Müller et al., 2007; Fig 1). Prior studies have demonstrated that such competition between the main flickering stimuli and 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).

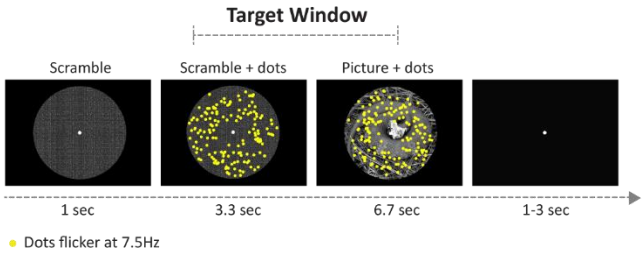

Figure 1. Experimental trial design. Each trial started with 1 s presentation of a scrambled picture, followed by the appearance of flickering dots (at a rate of 7.5 Hz) for 3.3 s. Consequently, a positive, negative, or neutral picture appeared for 6.6 s at the background of the dots. Targets were rare 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.

3.2.1. Picture Stimuli

Distractor pictures were divided into three valence categories, positive, negative and neutral (for details see Ben-Simon et al 2015). 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; $P>0.1$, paired t-tests) or experimental sessions (sleep-rested, 84.09; sleep-deprived, 84.66 trials on average, $P>0.1$, paired t-test). 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 distractor on ssVEP 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 sleep rested (SR) and sleep deprived (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 Inter Trial 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):

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

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. 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.

3.5.4. 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 each subjected to a Hilbert transform and amplitude was extracted as described in the time domain averaged ssVEP amplitude analysis in section 3.5.2.

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 (as 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 the SR and SD conditions 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.

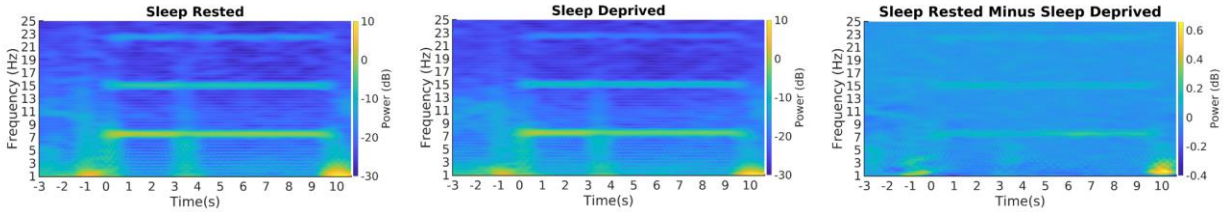

Figure 2. Time-frequency representation of the steady-state visual evoked response. Spectrograms were averaged across visual electrodes (O1, O2, Oz) and across subjects. The steady state visual evoked response is evident at 7.5 Hz and its harmonics, in the sleep rested (SR) and sleep deprived (SD) conditions.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

4.2. Inter trial Phase Coherence 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 throughout the steady state evoked response period (i.e., from dots onset to dots offset; Fig 3a; 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). 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.

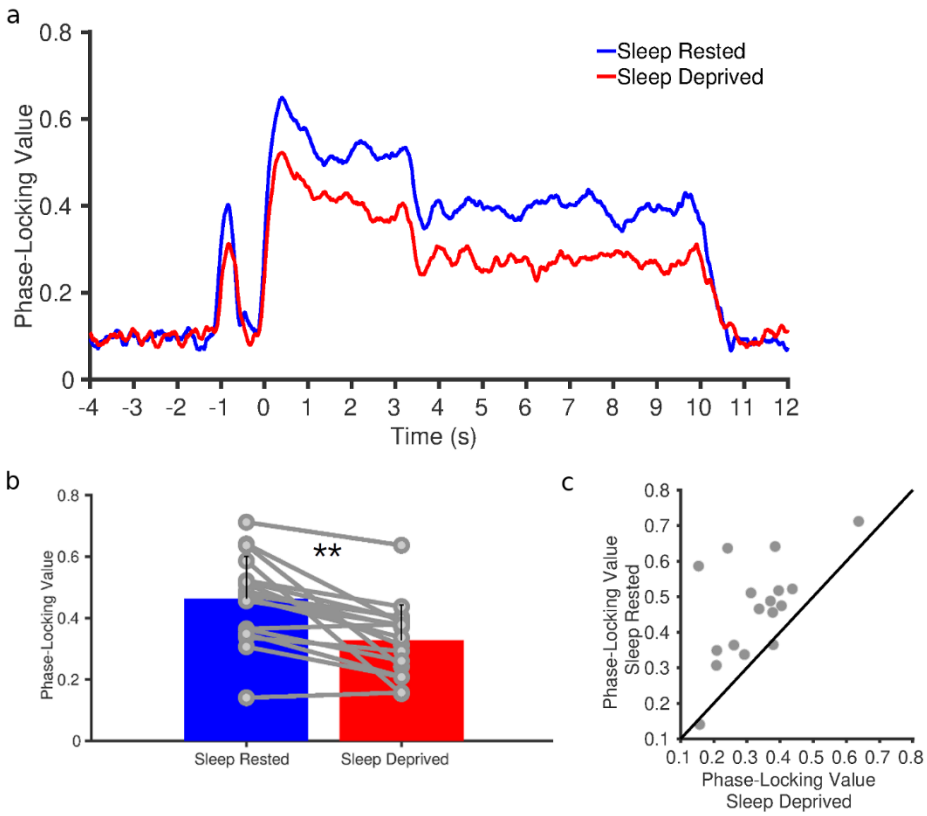

Figure 3. Inter trial phase coherence of the steady-state visual evoked response. (a) PLVs calculated around the stimulation frequency (7.5 Hz), averaged across visual electrodes (O1, O2, Oz), and across subjects. PLVs during the evoked response period (i.e., from dot onset at time zero to dot offset at 10 s) were significantly lower in the sleep deprived (SD) compared to the sleep rested (SR) condition (all p values ≤ 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 needed 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.

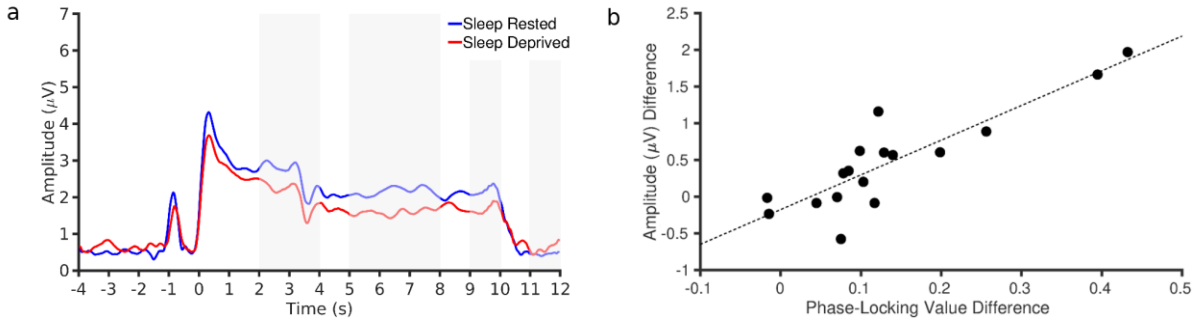

Figure 4. Relation between ssVEP amplitude and ITPC. (a) ssVEP amplitude calculated around the stimulation frequency (7.5 Hz), averaged across visual electrodes (O1, O2, Oz), and across subjects. Amplitudes during the evoked response period (i.e., from dot onset at time zero to dot offset at 10 s) were significantly lower in the sleep deprived (SD) compared to the sleep rested (SR) condition in specific time windows along the time course of the experimental trial (marked in gray shades), starting from 2s following dots onset (all p values ≤ 0.035, FDR corrected). (b) Correlation between the differences in mean PLVs and in mean amplitudes between sleep conditions (SR minus SD; $r = 0.87$, $p < 0.0001$).

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 (SR minus SD) were correlated. A positive correlation was found ($r = 0.87$, $p < 0.0001$; 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 (van Diepen and Mazaheri, 2018), SNR analysis was conducted by calculating the ratio between power at the ssVEP frequency, to power at the average of neighboring frequencies (see section 3.5.3 in Methods). Higher SNR was found in the SR condition compared to SD (mean ± sd, 168 ± 93 and 123 ± 103.5, respectively), however this difference was not significant ($t(16) = 1.69$, $p = 0.1$).

4.2.3. Ongoing Activity is Increased in Sleep Deprivation

Ongoing activity at the stimulation frequency was significantly higher in the SD compared to the SR condition through the entire experimental trial (excluding the 1000 ms time window immediately before scramble picture presentation, in which amplitude differences were not significant; t values ranged from $t(16) = -2.96$ to $t(16) = -4.96$; all p values < 0.01, FDR corrected; Fig 5). Figure 5 also shows the time-locked but not phase locked (i.e., induced) activity in response to the onset and offset of the dots in the two conditions.

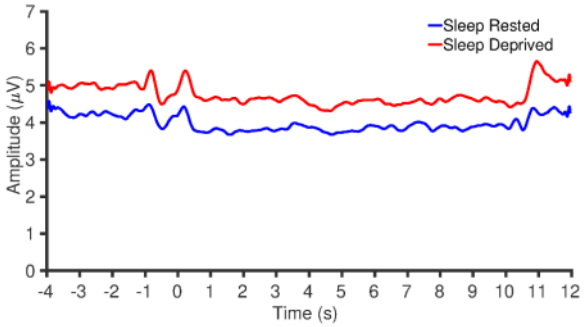

Figure 5. Ongoing activity at the stimulation frequency. Ongoing activity was calculated around the stimulation frequency (7.5 Hz), averaged across visual electrodes (O1, O2, Oz), across trials and across subjects. A significantly increased activity along the experimental trial (excluding the 1000 ms time window immediately before scramble picture presentation) was found in SD ($p<0.01$, FDR corrected).

4.3. Relation Between 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 and the changes in self-reported sleepiness or task performance under SD. These behavioral measures were shown to be affected by SD as studied and reported in Ben-Simon et al., 2015 (see also section 3.7). The difference between the mean PLV (calculated in section 3.6) in SR and SD 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, $P > 0.1$), inspection of all measures at the individual subject level clearly revealed a common trend (Table 1). Specifically, Table 1 demonstrates that out of 15 subjects who showed decreased PLV in SD, 13 also showed decreased accuracy in the ssVEP task. Similarly, in 14 subjects increased subjective

sleepiness was found along with decreased PLVs. Finally, an increase in the number of lapses in the PVT was found in 13 out of 15 subjects showing decreased PLV (not shown). 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 increased sleepiness scores and by the lower accuracy in the ssVEP task), PLV may serve as an informative measure for assessing SD.

Table 1. Effect of sleep deprivation on phase-locking values and behavioral measures.

The table shows for each subject whether a decrease in ssVEP task performance or an increase in self-reported sleepiness were found under SD along with a decrease in mean phase-locking value (PLV; indicated by '+').

Subject	PLV decrease	ssVEP task accuracy decrease	Sleepiness increase
1	+	+	+
2	+	+	+
3	+	+	+
4	+	+	+
5	+	+	+
6	+	+	+
7	+	+	+
8	+	+	+
9	+	+	+
10	+	+	+
11	+	+	+
12	+	+	+
13	+	-	+
14	+	-	+
15	+	+	-

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. Together, these findings suggest that SD disrupts the capability of the neural response to temporally synchronize with external stimuli. They further demonstrate that SD can be reliably assessed by means of ssVEPs 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 prior findings that demonstrate decreased phase consistency in SD (Hoedlmoser et al., 2011), as well as studies that demonstrate the impact of fatigue on the amplitude of ssVEPs (Cao et al., 2014).

A desynchronized neural response to external stimuli could reflect impairments in information processing following sleep loss, possibly due to the limited ability to align the excitability phases of the neural response with stimuli presentation. Interestingly, a recent study demonstrated attenuated ssVEP responses and decreased ITPC during sleep when stimulating at the alpha (8 and 10 Hz) frequency range (Sharon and Nir, 2017). These findings raise 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 and generally points to the impact of sleep and sleep loss on neural responses to external stimuli.

Decreased temporal synchronization with external stimuli has further been suggested to reflect increased background noise, such as spontaneous neural activity (Kashiwase et al., 2012; Krystal et al., 2017). In accordance, previous studies found higher spontaneous activity 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).

A failure to suppress such background noise was theorized to produce impaired behavioral performance, for example due to reduced precision of information representation (Krystal et al., 2017). Our finding of increased ongoing activity following SD (Fig 5) 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 numerous 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 network architecture shifts towards a random-like organization, leading to impaired functional segregation in regions of the limbic, salience and default mode networks (Ben-Simon et al., 2015). These alterations were further associated with impaired task performance elicited by SD.

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). We therefore tested the association between ITPC reduction and task performance. While no significant 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). These results suggest that ITPC may serve as a reliable, noninvasive indicator of SD and the associated behavioral impairment, though profound research on the relation between ITPC and behavioral performance under sleep deprivation is still needed.

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 finding 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 only 2 s after the dots onset (Fig 4a). 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.

Our findings suggest that ITPC may represent an objective and mechanistic measure of SD. Further research is needed to better understand the relation between alterations in ITPC and behavioral impairments in SD. In addition, as sleep-related ITPC patterns were demonstrated to differ depending on the stimulation frequency used to elicit ssVEPs (Sharon and Nir, 2017), future 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. Finally, integrating phase analysis with resting state data is needed to understand the mechanisms of ITPC in SD in a more mechanistic level.

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. ITPC may serve as a useful and non-invasive method to investigate the effects of SD on brain and behavior in healthy individuals and in conditions associated with disrupted sleep.

6. References

Alfarra, R., Fins, A. I., Chayo, I., and Tartar, J. L. (2015). Changes in attention to an emotional task after sleep deprivation: neurophysiological and behavioral findings. *Biol. Psychol.* 104, 1–7.

Beattie, L., Kyle, S. D., Espie, C. A., and Biello, S. M. (2015). Social interactions, emotion and sleep: A systematic review and research agenda. *Sleep Med. Rev.* 24, 83–100.

Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B Methodol.*, 289–300.

Bernardi, G., Siclari, F., Yu, X., Zennig, C., Bellesi, M., Ricciardi, E., et al. (2015). Neural and behavioral correlates of extended training during sleep deprivation in humans: evidence for local, task-specific effects. *J. Neurosci.* 35, 4487–4500.

Besle, J., Schevon, C. A., Mehta, A. D., Lakatos, P., Goodman, R. R., McKhann, G. M., et al. (2011). Tuning of the human neocortex to the temporal dynamics of attended events. *J. Neurosci.* 31, 3176–3185.

Boonstra, T. W., Daffertshofer, A., and Beek, P. J. (2005). Effects of sleep deprivation on event-related fields and alpha activity during rhythmic force production. *Neurosci. Lett.* 388, 27–32.

Buzsáki, G. (2010). Neural syntax: cell assemblies, synapsembles, and readers. *Neuron* 68, 362–385.

Buzsáki, G., and Draguhn, A. (2004). Neuronal Oscillations in Cortical Networks. *Science* 304, 1926–1929.

Deweese, M. M., Bradley, M. M., Lang, P. J., Andersen, S. K., Müller, M. M., and Keil, A. (2014). Snake fearfulness is associated with sustained competitive biases to visual snake features: hypervigilance without avoidance. *Psychiatry Res.* 219, 329–335.

Ding, J., Sperling, G., and Srinivasan, R. (2005). Attentional modulation of SSVEP power depends on the network tagged by the flicker frequency. *Cereb. Cortex* 16, 1016–1029.

Donner, T. H., and Siegel, M. (2011). A framework for local cortical oscillation patterns. *Trends Cogn. Sci.* 15, 191–199.

Drummond, S. P., Bischoff-Grethe, A., Dinges, D. F., Ayalon, L., Mednick, S. C., and Meloy, M. J. (2005). The neural basis of the psychomotor vigilance task. *Sleep* 28, 1059–1068.

Fell, J., Ludowig, E., Rosburg, T., Axmacher, N., and Elger, C. E. (2008). Phase-locking within human mediotemporal lobe predicts memory formation. *Neuroimage* 43, 410–419.

Golumbic, E. Z., Cogan, G. B., Schroeder, C. E., and Poeppel, D. (2013). Visual input enhances selective speech envelope tracking in auditory cortex at a "cocktail party." *J. Neurosci.* 33, 1417–1426.

Hämäläinen, J. A., Rupp, A., Soltész, F., Szücs, D., and Goswami, U. (2012). Reduced phase locking to slow amplitude modulation in adults with dyslexia: an MEG study. *Neuroimage* 59, 2952–2961.

Hanslmayr, S., Klimesch, W., Sauseng, P., Gruber, W., Doppelmayr, M., Freunberger, R., et al. (2005). Visual discrimination performance is related to decreased alpha amplitude but increased phase locking. *Neurosci. Lett.* 375, 64–68.

Henry, M. J., Herrmann, B., and Obleser, J. (2014). Entrained neural oscillations in multiple frequency bands comodulate behavior. *Proc. Natl. Acad. Sci.* 111, 14935–14940.

Hoddes, E., Zarcone, V., Smythe, H., Phillips, R., and Dement, W. C. (1973). Quantification of sleepiness: a new approach. *Psychophysiology* 10, 431–436.

Hoedlmoser, K., Griessenberger, H., Fellinger, R., Freunberger, R., Klimesch, W., Gruber, W., et al. (2011). Event-related activity and phase locking during a psychomotor vigilance task over the course of sleep deprivation. *J. Sleep Res.* 20, 377–385.

Hung, C.-S., Sarasso, S., Ferrarelli, F., Riedner, B., Ghilardi, M. F., Cirelli, C., et al. (2013). Local experience-dependent changes in the wake EEG after prolonged wakefulness. *Sleep* 36, 59–72.

Kahn, M., Sheppes, G., and Sadeh, A. (2013). Sleep and emotions: Bidirectional links and underlying mechanisms. *Int. J. Psychophysiol.* 89, 218–228.

Kashiwase, Y., Matsumiya, K., Kuriki, I., and Shioiri, S. (2012). Time courses of attentional modulation in neural amplification and synchronization measured with steady-state visual-evoked potentials. *J. Cogn. Neurosci.* 24, 1779–1793.

Killgore, W. D. S. (2010). "Effects of sleep deprivation on cognition," in *Progress in Brain Research*, eds. G. A. Kerkhof and H. P. A. van Dongen (Elsevier), 105–129.

Kim, Y. J., Grabowecky, M., Paller, K. A., Muthu, K., and Suzuki, S. (2007). Attention induces synchronization-based response gain in steady-state visual evoked potentials. *Nat. Neurosci.* 10, 117.

Klimesch, W., Sauseng, P., Hanslmayr, S., Gruber, W., and Freunberger, R. (2007). Event-related phase reorganization may explain evoked neural dynamics. *Neurosci. Biobehav. Rev.* 31, 1003–1016.

Klimesch, W., Schack, B., Schabus, M., Doppelmayr, M., Gruber, W., and Sauseng, P. (2004). Phase-locked alpha and theta oscillations generate the P1–N1 complex and are related to memory performance. *Cogn. Brain Res.* 19, 302–316.

Krause, A. J., Simon, E. B., Mander, B. A., Greer, S. M., Saletin, J. M., Goldstein-Piekarski, A. N., et al. (2017). The sleep-deprived human brain. *Nat. Rev. Neurosci.* 18, 404.

Krystal, J. H., Anticevic, A., Yang, G. J., Dragoi, G., Driesen, N. R., Wang, X.-J., et al. (2017). Impaired tuning of neural ensembles and the pathophysiology of schizophrenia: a translational and computational neuroscience perspective. *Biol. Psychiatry* 81, 874–885.

Lachaux, J.-P., Rodriguez, E., Martinerie, J., and Varela, F. J. (1999). Measuring phase synchrony in brain signals. *Hum. Brain Mapp.* 8, 194–208.

Lakatos, P., Chen, C.-M., O'Connell, M. N., Mills, A., and Schroeder, C. E. (2007). Neuronal oscillations and multisensory interaction in primary auditory cortex. *Neuron* 53, 279–292.

Lakatos, P., Karmos, G., Mehta, A. D., Ulbert, I., and Schroeder, C. E. (2008). Entrainment of neuronal oscillations as a mechanism of attentional selection. *science* 320, 110–113.

Lang, P. J., Bradley, M. M., and Cuthbert, B. N. (1997). International affective picture system (IAPS): Technical manual and affective ratings. *NIMH Cent. Study Emot. Atten.*, 39–58.

Lee, H.-J., Kim, L., and Suh, K.-Y. (2003). Cognitive deterioration and changes of P300 during total sleep deprivation. *Psychiatry Clin. Neurosci.* 57, 490–496.

Lim, J., and Dinges, D. F. (2008). Sleep deprivation and vigilant attention. *Ann. N. Y. Acad. Sci.* 1129, 305–322.

Mathewson, K. E., Fabiani, M., Gratton, G., Beck, D. M., and Lleras, A. (2010). Rescuing stimuli from invisibility: Inducing a momentary release from visual masking with pre-target entrainment. *Cognition* 115, 186–191.

McLoughlin, G., Palmer, J. A., Rijsdijk, F., and Makeig, S. (2014). Genetic overlap between evoked frontocentral theta-band phase variability, reaction time variability, and attention-deficit/hyperactivity disorder symptoms in a twin study. *Biol. Psychiatry* 75, 238–247.

Meisel, C., Olbrich, E., Shriki, O., and Achermann, P. (2013). Fading signatures of critical brain dynamics during sustained wakefulness in humans. *J. Neurosci.* 33, 17363–17372.

Morris, A. M., So, Y., Lee, K. A., Lash, A. A., and Becker, C. E. (1992). The P300 event-related potential. The effects of sleep deprivation. *J. Occup. Med. Off. Publ. Ind. Med. Assoc.* 34, 1143–1152.

Müller, M. M., Andersen, S. K., and Keil, A. (2007). Time course of competition for visual processing resources between emotional pictures and foreground task. *Cereb. Cortex* 18, 1892–1899.

Müller, M. M., Malinowski, P., Gruber, T., and Hillyard, S. A. (2003). Sustained division of the attentional spotlight. *Nature* 424, 309.

Neuling, T., Rach, S., Wagner, S., Wolters, C. H., and Herrmann, C. S. (2012). Good vibrations: oscillatory phase shapes perception. *Neuroimage* 63, 771–778.

Nir, Y., Andrillon, T., Marmelshtein, A., Suthana, N., Cirelli, C., Tononi, G., et al. (2017). Selective neuronal lapses precede human cognitive lapses following sleep deprivation. *Nat. Med.* 23, 1474.

Norcia, A. M., Appelbaum, L. G., Ales, J. M., Cottereau, B. R., and Rossion, B. (2015). The steady-state visual evoked potential in vision research: a review. *J. Vis.* 15, 4–4.

Pilcher, J. J., and Huffcutt, A. I. (1996). Effects of sleep deprivation on performance: a meta-analysis. *Sleep* 19, 318–326.

Regan, D. (1966). Some characteristics of average steady-state and transient responses evoked by modulated light. *Electroencephalogr. Clin. Neurophysiol.* 20, 238–248.

Schroeder, C. E., and Lakatos, P. (2009). Low-frequency neuronal oscillations as instruments of sensory selection. *Trends Neurosci.* 32, 9–18.

Sharon, O., and Nir, Y. (2017). Attenuated fast steady-state visual evoked potentials during human sleep. *Cereb. Cortex*, 1–15.

Ben-Simon, E. B., Oren, N., Sharon, H., Kirschner, A., Goldway, N., Okon-Singer, H., et al. (2015). Losing neutrality: the neural basis of impaired emotional control without sleep. *J. Neurosci.* 35, 13194–13205.

Tallon-Baudry, C., Bertrand, O., Delpuech, C., and Pernier, J. (1996). Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. *J. Neurosci.* 16, 4240–4249.

Teale, P., Collins, D., Maharajh, K., Rojas, D. C., Kronberg, E., and Reite, M. (2008). Cortical source estimates of gamma band amplitude and phase are different in schizophrenia. *Neuroimage* 42, 1481–1489.

Tononi, G., and Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Med. Rev.* 10, 49–62.

Van Diepen, R. M., and Mazaheri, A. (2018). The Caveats of observing Inter-Trial Phase-Coherence in Cognitive Neuroscience. *Sci. Rep.* 8, 2990.

Vialatte, F.-B., Maurice, M., Dauwels, J., and Cichocki, A. (2010). Steady-state visually evoked potentials: focus on essential paradigms and future perspectives. *Prog. Neurobiol.* 90, 418–438.

Walker, M. P., and van Der Helm, E. (2009). Overnight therapy? The role of sleep in emotional brain processing. *Psychol. Bull.* 135, 731.

Watson, D., Clark, L. A., and Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *J. Pers. Soc. Psychol.* 54, 1063.

Wieser, M. J., Miskovic, V., & Keil, A. (2016). Steady-state visual evoked potentials as a research tool in social affective neuroscience. Psychophysiology, 53, 1763–1775.