Decreased prefrontal connectivity parallels cognitive fatigue-related performance decline after sleep deprivation. An optical imaging study

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ABSTRACT

Fatigue induced by sustained cognitive demands often entails decreased behavioural performance and the unavailability of brain resources, either due to reduced levels or impaired access. In the present study, we investigated the neural dynamics underlying preserved behavioural performance after inducing cognitive fatigue (CF) in a sleep deprivation (SD) condition in which resources are naturally compromised. Using functional near infrared spectroscopy (fNIRS), we recorded cortical brain activity during task-related CF induction in the evening, in the middle of the night and early in the morning. Although cortical oxygenation similarly increased over the 3 sessions, decreased intra-hemispheric connectivity between left anterior frontal and frontal areas paralleled a sudden drop in task performance in the early morning. Our data indicate that decreased sustained attention after the induction of cognitive fatigue in a situation of high sleep pressure results from impaired connectivity between left prefrontal cortical areas rather than from a mere modulation in brain resources.

Keywords: Cognitive Fatigue, Sleep deprivation, connectivity, fNIRS, haemodynamics, human performance

1. INTRODUCTION

Cognitive fatigue (CF) and the associated decreases in cognitive and behavioural performance represent a major societal issue. CF entails loss of productivity (Krueger, 1989; Setyawati, 1995), increased risk of accidents (Lal & Craig, 2001), poor academic performance (Sievertsen, Gino, & Piovesan, 2016) and reduced quality of life in healthy (Akerstedt et al., 2004) and neurological (Pittion-Vouyovitch et al., 2006) populations. Precisely knowing when an individual starts being cognitively less efficient would allow developing better strategies to prevent potential errors. Potential indicators for the triggering of CF have been investigated including changes in biochemical, immunological and physiological biomarkers such as saliva, blood and urine, as well as autonomic nervous system modifications such as heartbeat, pupillary dilation or skin conductance (for a review see Kajimoto 2008). Detecting CF-related changes in brain dynamics is another promising approach (Borghini, Astolfi, Vecchiato, Mattia, & Babiloni, 2012). Transcranial Doppler sonography (TCD; Warm, Matthews, and Parasuraman 2009), functional magnetic resonance imaging (fMRI; Cook et al. 2007) or electrophysiology (EEG; Hopstaken et al. 2015) studies suggest that decreased performance following sustained cognitive demands is associated with the unavailability of brain resources, especially in the context of tasks featuring executive working memory (Cook et al., 2007; Hopstaken et al., 2015) or even simpler attentional (Warm et al., 2009) components. Yet, it remains uncertain whether decreased performance during sustained cognitive demands actually results from a shrinkage of available brain resources (e.g., as postulated in the Malleable Attentional Resources Theory [MART]; Young and Stanton 2002) or, alternatively, whether it is the access to the pool of

resources which is compromised (as proposed by dynamic models of stress and sustained performance; Hockey 1997; Hancock and Warm 1989; Desmond and Matthews 1997). Beyond an apparent reduction in brain activity however, other studies suggest that adequate performance levels could be maintained through time in the context of CF by recruiting additional neural activity (Li et al., 2009; Wang et al., 2016). For a similar performance level, supplementary neural activity would continue increasing through time until a maximal threshold is reached, and then eventually brain activity and performance would decrease in parallel (Wang et al., 2016). This mechanism is viewed as a supplementary allocation of cognitive effort in the compensatory control model of Hockey (1997), who proposed that allocation of extra resources rely on cognitive control areas including the dorsolateral prefrontal (DLFC) and the anterior cingulate (ACC) cortex. Notwithstanding this proposal, different brain areas seem differentially sensitive to the triggering of CF (Lorist, Boksem, & Ridderinkhof, 2005; Wang et al., 2016). In this respect, the interrelated dynamics of brain activity make it necessary to investigate the neural correlates of CF by taking into account the relationships between these different brain areas. Another natural state in which cognitive and brain resources are compromised is sleep deprivation (SD). A meta-analysis conducted over 70 studies indicates that the most disrupted cognitive domains after SD are attention and working memory (Lim and Dinges 2010). Disrupted performance can be accompanied by reorganized patterns of brain activation or deactivation. For instance, in a verbal learning task, activity increased after SD in bilateral fronto-parietal regions, whereas activity decreased in temporal areas (Drummond & Brown, 2001). Similarly, increased prefrontal-thalamic activity together with reduced medial parietal activity was evidenced

after SD during a working memory task featuring high information processing demands (Chee & Choo, 2004). At variance, increased thalamic activation together with lower activity in prefrontal, parietal and occipital cortices was reported during a visual attention task in sleep deprived subjects (Tomasi et al., 2009). Accordingly, a likelihood estimation approach conducted over 11 studies highlighted a predominantly decreased activation within fronto-parietal attentional network accompanied by increased activation in the bilateral thalamus (Ma, Dinges, Basner, & Rao, 2015). The large variability of tasks, experimental protocols and populations used in previously published studies might explain seemingly contradictory reports, and suggest that these parameters are to some extent responsible for variable brain reorganisations patterns following SD (Ma et al., 2015).

Functional near infrared spectroscopy (fNIRS) is a non-invasive neuroimaging technique allowing the measurement of variations in blood oxygenation in cortical areas. Functional NIRS was found to reliably reflect cognitive load (Ayaz et al., 2012; Harrivel, Weissman, Noll, & Peltier, 2013) and can be used in ecological contexts (Piper et al., 2014; Tachtsidis et al., 2004) with acceptable spatial (1-3 cm) and good temporal resolutions (1 - 100 Hz). Functional NIRS was also found appropriate to track changes in brain connectivity (Fishburn, Norr, Medvedev, & Vaidya, 2014; Zhang et al., 2010). The versatility of fNIRS makes it an excellent technique to study brain activity in ecological contexts including test-retests paradigms (Pinti et al., 2018).

In the present fNIRS study, we aimed at investigating the cortical neural compensatory mechanisms acting against CF using a high cognitive-load task paradigm (Borragán, Slama, 2017) in the context of increasingly growing sleep pressure during a

night of total sleep deprivation. The rationale of this experimental setting is based on the induction of a dual fatigue effect due to CF-inducing high cognitive load sessions conducted at three time points during a sleep deprivation protocol in which brain resources are gradually compromised over the course of the night. Considering that SD impacts fronto-parietal activity in particular (Chee & Choo, 2004; Drummond & Brown, 2001; Ma et al., 2015), and that these same fronto-parietal areas are recruited in high cognitive load working memory situations (Owen, McMillan, Laird, & Bullmore, 2005), we hypothesized that the similar task demands will lead to a faster development of task-related CF as the sleep deprivation night progresses. CF-related effects were also investigated analysing post-task effects on resting state cortical activity at each session during the SD night.

2. METHODS

2.1 Participants

Eighteen healthy participants (mean age ± std: 22 ± 2.23 years; 7 men) gave written informed consent to participate in this study conducted in agreement with the Declaration of Helsinki and approved by the Faculty ethics committee of the Université Libre de Bruxelles. They were asked to avoid alcohol for the duration of the entire experiment, and caffeine or stimulant drinks intake for at least 3 hours before any experimental session. All participants received monetary compensation for their participation. Exclusion criteria were signs of depression or anxiety (HAD-anxiety > 8; HAD-depression > 8; Zigmond and Snaith 1983), high levels of cognitive fatigue (FSM cognitive > 28; Penner et al. 2009) and bad sleep quality (PSQI > 7; Buysse et al. 1989) within the last month, and extreme morningness-eveningness chronotype (Horne & Ostberg MEQ score <31 or > 69; Horne and Ostberg 1976). Two participants were excluded for not fulfilling these criteria.

2.2 Procedure

Participants were asked to respect normal sleep schedules during the 6 days preceding the SD night, i.e. to wake up between 7h and 9h and to go to bed before 01h. Compliance was assessed using wrist actigraphy (ActiGraph, wGT3X-BT Monitor, USA) from 5 days before the Pretest session held the day before the day of the SD night until the end of the experiment. The SD experimental night started on Day 6 from 19h to 9h next morning (see Figure 1). Participants were first briefed about the experimental procedure and instructed how to distinguish between sleepiness and cognitive fatigue as reported on

subjective scales (see details below). Every hour during the night (from 20h to 9h), vigilance was assessed using a 5-minutes version of the Psychomotor Vigilance Task (PVT; Dinges and Powell 1985), and subjective scales for sleepiness (VASs, KSS) and fatigue (VASf) were administered (see below). During the SD night, participants were allowed to engage in quiet activities such as talking, watching movies or playing board games, and had access to their personal computers. Neither smoking nor any caffeine or stimulant drink intake was allowed. Water was offered ad libitum, and light snacks made available at regular intervals.

At three times during the course of the SD night, i.e., in the evening (**1EV**, between 20h-22h), in the middle of the night (**2MN**; between 1h30-3h30) and in the morning (**3MO**; between 7h-9h), participants performed for 16 minutes the CF-inducing TloadDback task (see description below), a high cognitive load dual-task which adapts to each individual's maximal cognitive capacity (Borragán, Slama, Destrebecqz, & Peigneux, 2016). Cortical brain activity changes during the TloadDback task were recorded using fNIRS (see below). To assess the impact of induced CF on post-task spontaneous neural activity, cortical brain activity was also recorded during a 4-minutes resting state (Rst) period immediately after the TloadDback (for the sake of conciseness, resting state analyses are presented as supplementary material). Participants were instructed to look at a fixation cross during the Rst period. Subjective feelings of CF and sleepiness were assessed using the scales immediately before (p1) and after (p2) each administration of the TloadDback task, and after the ensuing Rst period (p3). Due to time constraints of fNIRS optodes placement at each of the three recording sessions, only two participants were tested per experimental night. The two participants were tested in succession, always in the same

order within the two hours of testing time. Additionally, each participant's maximal load capacity was assessed during a Pretest session (always taking place between 17h-20h) held the day before the day of the SD night (see Borragán, Slama, 2017 for more details on the task). Experimental room conditions (light and temperature) were kept constant during the whole experiment.

To further investigate the expected dissociation between sleepiness and fatigue levels, thought to represent distinct dimensions (Neu et al., 2010), participants were asked a few weeks later to fill in VASf and KSS scales every hour from 9h to 19h. That is, they reported again on the evolution of their subjective fatigue and sleepiness levels in the context of low to moderate sleep pressure during the regular course of a day, as opposed to the high to extreme sleep pressure experienced in the SD condition. Only participants respecting regular sleep-work schedules were included in this retest session. Eleven out of the 18 participants took part in this delayed phase of the experiment.

Insert Figure 1 over here

2.3 Material and Tasks

2.3.1 Subjective scales

Self-reported feelings of CF and Sleepiness were assessed during the experimental sessions using visual analogue scales for fatigue (VASf) and sleepiness (VASs) (Lee, Hicks, and Nino-Murcia 1991) and the Karolinska Sleepiness Scale (KSS; Akerstedt and Gillberg 1990).

2.3.2 TloadDback task

As mentioned above, cognitive fatigue (CF) was induced at 3 different times of the night using the TloadDback, a task that can be tailored to each individual's maximal performance level, and was previously shown efficient to induce CF and a decrease of performance (Borragán et Slama, 2017; Borragán et al., 2016). The TloadDback task is a dual working memory task in which letters and numbers are displayed in alternation for 16 minutes. For each number, a parity decision must be made. For each letter, the participant must decide whether it is the same than the last presented letter (i.e., a N-1 back task with an intermediate number stimulus). The stimulus time duration (STD) in the high cognitive load condition is determined in a stepwise procedure during a separate pre-test, calibration session as the shortest possible STD at which the participants' accuracy remains > 85% (see Borragán et al. 2017 for details). In the present study, considering that global cognitive capacity can be altered over the course of the sleep deprivation protocol, a complementary recalibration session was added before each of the three TloadDback sessions, to confirm that the optimal STD determined the day before during the Pretest session still allowed participants to reach accuracy > 85%. During these recalibration sessions, the predetermined STD was slowed down if necessary by steps of 100 msec until participants' performance was > 85%.

2.3.3 Psychomotor vigilance task

The hourly evolution of vigilance during the experimental night was evaluated using a 5-minutes version of the Psychomotor Vigilance Task (PVT-5; Dinges & Powell, 1985). In this monotonous task, participants are instructed to stop as fast as possible a visual countdown starting at random intervals ranging from 2 to 10 seconds, during 5 minutes.

2.3.4 fNIRS acquisition

To record cortical brain activity, we used a multichannel fNIRS system (BrainSight V2.3b16, Rogue Research Inc., Canada) with two continuous wavelengths of 685 and 830 nm. Twenty-four optodes detectors were positioned around 6 optode sources, covering 3 predefined anatomical regions in each hemisphere (thus a total of 4 channels per area). Detector optodes were positioned at a distance of 3 cm from the source optodes using a 3-D coordinates system combined with a Polaris localization device (optodes' positions are visualized Figure 2; see also the transformed mean Montreal Neurological Institute [MNI] coordinates in Table S1). The setting targeted (see Table S2) the Superior/Middle Frontal gyrus (SMFg), the Inferior Frontal gyrus (IFg), and the Angular gyrus/Inferior Parietal lobule (AgIPL), in line with studies showing the impact of SD on these regions (Ma et al., 2015) and their involvement in working memory updating tasks (Owen et al., 2005). Functional NIRS signals were recorded at a sample rate of 20 Hz.

2.3.5 fNIRS analysis

For each participant, raw absorption quantities were first normalized then band-pass filtered (0.009 - 0.08 Hz) for detrending and to reduce high frequency noise due to respiration, cardiac pulsations and optodes' movements (Huppert, Diamond, Franceschini, & Boas, 2009). Signals were then converted into haemoglobin oxygenated (HbO) and de-oxygenated (HbR) components using the modified Beer-Lambert law (Delpy et al., 1988). Both filtering and optical density computations were performed using Homer toolbox functions (Huppert et al., 2009). In order to evaluate HRF responses underlying cortical activation, signals were also filtered using a wider band-pass filtered (0.1 - 0.4 Hz; Herff et al., 2014). To improve signal quality, noisy channels were

automatically detected and processed using global correlations of HbO and HbR signals improved with local information inherent to the experimental paradigm (Guerrero-Mosquera, Borragán & Peigneux, 2016). The signal was then analysed computing two different indicators of brain activity. Cortical activity modifications during practice of the TloadDback task were estimated using Cerebral Oxygen Exchange (COE) values. COE is an indirect measure of brain metabolism (see Yoshino, Oka, Yamamoto, Takahashi, & Kato, 2013), in which negative values reflect higher oxygenation levels (COE = HbR-HbO). Pearson correlation coefficients (*r*) were systematically computed with the time-course of COE during the evolution of the task to assess functional connectivity dynamics. COE values were averaged across detectors linked to a source in each of the 3-targeted areas in each hemisphere. Task-related changes in brain activity during the ensuing resting state period (Rst) were estimated by computing the amplitude of low frequency fluctuations (ALFF; Yu-Feng et al., 2007) within the frequency range between 0.009 and 0.08 Hz of the total haemoglobin concentration. ALFF is reputed a good measure of spontaneous neural activity, appropriate to detect state-dependent resting brain changes associated with CF (Gui et al., 2015).

Insert Figure 2 over here

2.3.5 Statistics

Statistical analyses were computed following Fritz, Morris and Richler (2012) recommendations. Mean (*m*) ± Standard Deviation (*std*) are reported as measures of central tendency, and size effects are reported as partial eta squares ($\square^2$). Mean squared errors (*MSE*) are included in the ANOVAs. Significance level was set at $p < .05$ (two-tailed) and Tukey HSD test was employed for post-hoc corrections. Correlation analyses were conducted using Spearman rank correlation coefficients (Rousselet & Pernet, 2012) and all analysis corrected by multiple comparisons.

3. RESULTS

3.1 Sleep quality and actigraphy recordings during the entire experiment

Separate repeated measure ANOVAs conducted on subjective sleep quality scores (from 1 [bad] to 6 [good]) and sleep duration (hours) as reported in the QSN (Ellis et al., 1981) did not disclose differences between the 7 experimental nights of the experiment (*all ps* > 0.7), suggesting a stable sleep-wake cycle.

Additionally, motor activity recorded using wrist actimetry was hourly averaged over day (16h) and Night (8h) periods. A repeated-measure ANOVA conducted on motor activity with Days (7 levels) and Cycle (Night vs Day) as within-subject factors disclosed a main Cycle effect ($F_{(1, 15)}$ = 151*; p* < .001; *MSE*= 1.64e+09; *partial-*η^2 = .91) with higher motor activity during the day than the night, and a main Day effect ($F_{(6, 90)}$ = 9.5*; p* < .001; *MSE*= 8.4e+08; *partial-*η^2 = .39), with globally higher activity on Day 7 (Days 1-6 < Day 7; *p* < .001). The Days × Cycle interaction was significant ($F_{(6, 90)}$ = 5.56; *p* < 0.001; *MSE* = 5.7e+08; *partial-*η^2 = 0.27). Post-hoc tests showed that equivalent activity levels between the day and the night explained the effect on Day 7, i.e., when the night of sleep deprivation was organized (*p* < 0.05; See Figure S1).

3.2 Hourly evolution of alertness, sleepiness and CF during the SD night

3.2.1 Vigilance

The repeated-measures ANOVA conducted on reciprocal reaction times (1/RT; Basner & Dinges, 2011) in the PVT-5 with Hour (from 20h to 8h00) as within-subject factor was significant ($F_{(12, 180)}$ = 8.2*; p* < .001; *MSE*= .03; *partial-*η^2 = .35). Tukey post-hoc tests indicated higher 1/RT (i.e., faster processing) during the first half of the night (from 20h

to 3h) as compared to the second half (from 4h to 8h; *ps* < .05). Additionally, a clustering analysis of unsupervised k-means performed on 1/RT values grouped hourly data into 3 temporal clusters, from 20h to 24h (cluster 1), for 01h to 03h (cluster 2) and from 04h to 08h (cluster 3). Hence, this independent clustering analysis supports our experimental design and the temporal setup of the three fNIRS sessions at these time periods in the evening, the middle of the night and the morning (see Procedure and figure 3).

3.2.2 Sleepiness

Similar analyses were carried out to assess the subjective evolution of sleepiness. The repeated-measures ANOVA performed on KSS scores with Hour (from 20h to 8h00) as within-subject factor disclosed increased self-reported sleepiness during the experimental night ($F_{(12, 180)}$ = 59,76*; p* < .001; *MSE*= 1.09; *partial-*$\square^2$ = .8; Tukey post-hoc: [20h-22h < (23h-24h < ((1h-2h) < ((3h-7h) < 8h)))]). The clustering analysis also grouped sleepiness levels in three consistent clusters: 20h-23h, 00h-03h and 04h-08h (see Figure 3).

3.2.3 Cognitive Fatigue

Similar analyses were carried out to assess the subjective evolution of fatigue. The ANOVA disclosed increased CF during the night ($F_{(12, 180)}$ = 42*; p* < .001; *MSE*= 2.8; *partial-*$\square^2$ = .74; Tukey post-hoc: [20h-23h < (24h-1h < ((2h-5h) < (6h-8h)))]). The clustering analysis again resulted in three clusters: 20h-24h, 01h-04h and 05h-08h (see Figure 3). Additionally, we computed MANOVAs analyses with the values of these two indexes as dependent variables and Time at the three different night periods (1st period= 20-24h; 2th period= 1-4h; 3th period = 5-8h) as within subject-factor to test whether self-reported CF and Sleepiness can be dissociated. The analysis disclosed increasing values

of CF and Sleepiness with Time (*all Fs* > 8.49; *ps* < .001) but no significant interaction between Sleepiness and CF (*Fs* < 1.23; *ps* > .27).

3.2.4 Relationships between the evolution of vigilance, sleepiness and CF

To probe a potential dissociation between the evolutions of these three parameters all over the night, we ran correlation analyses. The temporal evolution of CF and sleepiness scores was highly correlated (*rho* > .99; *p* < .001), suggesting that both feelings of CF and sleepiness similarly evolved. There was also a strong negative relationship between vigilance levels (1/RT scores on PVT) and CF or sleepiness (*rhos* < -.85; *ps* < .001). Hence these results suggest a lack of dissociation between these measures during our SD protocol.

Insert Figure 3 over here

3.2.5 Evolution of sleepiness and CF under low sleep pressure

In an additional behavioural session, a subset of participants rated hourly their sleepiness and CF levels during the course of a normal waking day, from wakefulness to the end of the day. As done in the SD condition, we investigated the relationship between self-reported CF and sleepiness during the 11 first daytime hours (from 9h to 19h). CF (VASf) and sleepiness (KSS) values were entered in MANOVAs with Time at the three different days periods: Morning (9-12h), Post-lunch dip (Monk 2005; 13-14h) and afternoon (15-19h). In the Morning period, there was a significant interaction effect ($F_{(3, 27)}$ = 3.6*; p* < .05; *MSE*= 1.02; *partial-*$\square^2$ = .28), indicating that self-reported sleepiness

was higher than CF during the first morning hours (9h and 10h: *ps* < .05). No other effects were significant. Hence, these data indicate that CF and sleepiness can be dissociated when accumulated sleep pressure is low, in the first few hours after waking up. See Figure S2.

3.3. Evolution of task-related CF and sleepiness

VASf and VASs scores were entered in a repeated-measure MANOVA with Session (1EV vs. 2MN vs. 3MO) and self-reported measurement Period (i.e. pre- [p1] vs. post- [p2] TloadDback vs. post-Rst [p3]) as within-subject factors (see Table 1). The analysis disclosed a main Session effect ($F_{(2, 60)}$ = 105, 12*;* p < .001; *MSE*= 12.92; *partial-*$\square^2$ = .78). Tukey post-hoc tests confirmed increased levels of CF and Sleepiness during the night (p1 > p2 > p3; *ps* < .001). The main Period effect was also significant ($F_{(2, 60)}$ = 47, 19*;* p < .001; *MSE*= 1.93; *partial-*$\square^2$ = .61). Tukey post-hoc tests disclosed increased self-reported CF and VASs scores at p2 after the TloadDback task (p1 < p2; p < .001), which remained stable after the 4-minutes Rst period (p1 < (p2=p3); p < .001). No other main or interaction effects were significant (*ps* > .36). Raw data are presented in Table 1.

Insert Table 1 over here

3.4 TloadDback performance

3.4.1 Calibration sessions

The minimal STD to ensure task performance >85% was computed for each individual separately. Mean STD was 869 ± 108 msec. A Shapiro-Wilk normality test disclosed a negative skew distribution of STD across participants with a larger number of participants presenting higher STD scores ($p < .05$).

3.4.2 Recalibration sessions

As a reminder, a recalibration block (approximate duration of 3-4 min) was administered at the beginning of each TloadDback session to ensure that increasing sleep pressure during the course of the SD protocol did not compromise the previously estimated participant's cognitive load at the Pretest session the day before the day of the SD night. STD and performance during the recalibration block were not different between the three different sessions (mean ± std STD: 1EV = .89 ± .11, 2MN=.88 ± .10 and 3MO = .89 ± .11; mean ± std accuracy: 1EV = 91% ± .037, 2MN= 93% ± .039 and 3MO = 93%± .037; *ps* > .29) or between these session and the initial Pretest (*ps* > .1).

3.4.3 Evolution of performance accuracy (and CF) during TloadDback performance

To assess session-related changes in the evolution of performance during the course of the 16 minutes of practice on the TloadDback task, mean accuracy was computed over four successive 4-minutes periods (t1, t2, t3 and t4). A repeated-measures ANOVA was conducted on accuracy scores with Session (1EV vs. 2MN vs. 3MO) and Time on Task (ToT: t1 vs. t2 vs. t3 vs. t4) as within-subject factors. The Session × Time on Task interaction was significant ($F_{(6, 90)} = 2.84$; $p < .02$; $MSE = .0014$; $partial\text{-}\eta^2 = .16$). Post-hoc planned comparisons did not evidence differences between sessions at the beginning

of task practice (t1; 1EV = 2MN = 3MO; *ps* > .14). However, accuracy in the morning (3MO) session was significantly lower than in the two other sessions with continued practice at t2 [(1EV = 2MN) > 3MO; *ps* < .02], t3 [(1EV = 2MN) > 3MO; *ps* < .001] and t4 [(1EV= 2MN) > 3MO; *ps* < .001]. As illustrated Figure 4, accuracy monotonically decreased from t1 to t3 in the morning (3MO) condition only ((t1 > (t2 = t3), ps < .01; t3 = t4, p > .99), whereas it remained stable in the evening (1EV) and middle night (2MN) conditions (*ps* > .1)

Insert Figure 4 over here

3.5 fNIRS data

3.5.1 TloadDback: within-task oxygenation changes (band-pass filter range of 0.1 - 0.4 Hz)

In a first step, we investigated the evolution of participant's brain activation patterns under high cognitive load during the sleep deprivation night. COE values in each of the 6-targeted areas were introduced in a repeated-measure ANOVA with Area (SMFg vs. IFG vs. AgIPL), Hemisphere (Right vs. Left), Session (1EV vs. 2MN vs. 3MO) and Time-on-Task (ToT; t1 vs. t2 vs. t3 vs. t4 vs. Rst) as within subject factors. The analysis disclosed a main effect of ToT ($F_{(4, 60)}$ = 22.6; p < .001; *MSE*= 2.34 e^{-10}; *partial-*η^2 = .6). Post-hoc tests disclosed a decreased COE signal (i.e.: increased oxygenation) from the first to next 4-minutes portions of task practice, followed by a significant increase during the subsequent Rst period (t1> (t2, t3, t4, Rst; *ps* < .05), t2> (t3, t4; *ps* < .008), t4 > Rst; *p* < .001).

Besides, analyses also reported a triple interaction between Hemisphere, ToT and Session ($F_{(8, 120)}$ = 4.35; $p < .001$; *MSE*= 2.11 e^{-11}; *partial-*$\square^2$ = .22; see Figure 5). In the right hemisphere, Tukey post-hoc tests evidenced a significant decrease in COE with time on task during the two late sessions in the course of the sleep deprivation (2MN: t1 > t4; $p <$ .001 and 3MO: t1 > (t3, t4); $p < .003$). All *ps* were > .7 for the 1EV condition. At variance in the left hemisphere, COE decreased with ToT with time on task during the first session at the beginning of the sleep deprivation night (1EV: t1 > (t3, t4); $p < .001$) but COE remained stable with ToT in the second session (2MN; all *ps* > .8). During the last 3MO session at the end of the sleep deprivation night, Tukey post-hoc disclosed ToT-related increased oxygenation levels (3MO: t1 > t4; $p < .001$ and t2 > t4; $p < .05$). Resting state post-task activity was similar between sessions (all *ps* >.9). See supplementary information for further analyses computed on Rst.

In order to investigate possible associations between increased cortical activity and performance maintenance, we performed Spearman correlations between the averaged activity in the most activated hemisphere (as given by the prior ANOVA) at the end of the task (t3 and t4) and performance in the TloadDback task at the different sessions, i.e., the left hemisphere during the EV and MO sessions and the right hemisphere during the MN and MO sessions. Only during the last session in the morning, activity in the right hemisphere significantly correlated with TloadDback performance at t3 (rho = -.65; p = .009). However, this result must be considered cautiously since it did not survive correction for multiple comparisons/correlation indices (set at .0041). All other correlations were non-significant (all ps > .01 and rho < -.4). Likewise, no significant

correlations were found between subjective evolution of CF and performance after correction by multiple comparison (all ps > .07 and rho < -.45).

Insert Figure 5 over here

3.5.2 TloadDback: within-task connectivity (band-pass filter range of 0.009 - 0.08 Hz)

To investigate the dynamic interactions in cortical activity that may potentially subtend variations in performance, we computed two connectivity models based on changes in Pearson correlations values between the six areas of interest during the evolution of task practice. The two models investigated intra-hemispheric and inter-hemispheric connectivity patterns, respectively. Changes in intra-hemispheric connectivity patterns were assessed in a repeated-measure ANOVA on correlations values with Session (1EV vs. 2MN vs. 3MO), Connected Areas (IFg-AgIPL vs. IFg-SMFg vs. SMFg-AgIPL), Hemisphere (Right vs. Left) and ToT (t1 vs. t2 vs. t3 vs. t4) as within subject factors. The Session × Connected Areas × Hemisphere interaction was significant ($F_{(4, 60)} = 2.71$; $p < .05$; *MSE*= .016; *partial-*$\square^2 = .15$). Post-hoc tests evidenced stable connectivity over the 3 Sessions in the Right hemisphere in all areas (*all ps* > .9). In the Left hemisphere, connectivity remained stable between fronto-parietal connections (SMFg-AgIPL and IFg-AgIPL; *ps* > .3), but significantly decreased during the morning session in frontal connections (IFg-SMFg; (1EV = 2MN) > 3MO, *ps* < .05; Figure 6).

Changes in inter-hemispheric connectivity patterns between homologous regions (i.e., correlations between Left and Right IFg, SMFg or AgIPL) were assessed with a repeated-measure ANOVA on correlations values with Session (1EV vs 2MN vs 3MO),

Connected Areas ([left-right] IFg vs AgIPL vs SMFg) and ToT (t1 vs t2 vs t3 vs t4). The main Connected Areas effect was significant ($F_{(2, 30)} = 6.6$; $p < .005$; $MSE = .010$; $partial\text{-}\eta^2 = .3$) with higher inter-hemispheric connectivity in SMFg than other regions (SMFg > (AgIPL = IFg); *ps* < .05). As well, there was a ToT effect ($F_{(3, 45)} = 3$; $p < .05$; $MSE = .018$; $partial\text{-}\eta^2 = .17$). Post-hoc tests indicated decreased interhemispheric connectivity from the beginning to the end of the task (t1 > t4; $p < .05$). Finally, there was a trend for a main Session effect ($F_{(2, 30)} = 2.95$; $p = .067$; $MSE = .059$; $partial\text{-}\eta^2 = .16$) with globally lower inter-hemispheric connectivity at the end of the night (1EV = 2MN; 1EV > 3MO; $p < .058$; Figure 6).

Insert Figure 6 over here

Finally, we investigated the association between decreased intra-hemispheric connectivity within the left frontal region (IFg-SMFg) and diminished performance at the end of the night (2MN > 3MO). Correlations computed between delta performance (i.e. 2MN minus 3MO accuracy performance on the TloadDback) and delta connectivity (i.e. 2MN minus 3MO connectivity 3MOvalues) were significant (*rho* = .52; $p < .05$). In addition, we conducted correlation analyses to investigate whether the general reduction in interhemispheric connectivity observed during the course of the TloadDback explained the decrease in performance during task practice, separately at the three sessions (1EV, 2MN and 3MO). No correlation reached significance (*ps* > .5).

4. DISCUSSION

The present study aimed at investigating how the triggering of cognitive fatigue (CF) is modulated in a sleep deprivation (SD) condition in which brain resources are naturally compromised (Ma et al., 2015). Besides changes in performance and subjective scales for CF and sleepiness, we explored using fNIRS the modulations in brain activity and connectivity associated with the induction of CF during the course of a SD night, i.e. in the evening (1EV), in the middle of the night (2MN) and in the morning (3MO). An independent clustering analysis confirmed distinctive alertness, sleepiness and fatigue patterns during these three sessions. In line with prior findings, decreased alertness/vigilance over the night was mirrored by increased self-reported feelings of sleepiness and CF (Thomas et al., 2003). Although CF and sleepiness have been construed as two distinct processes (Neu et al., 2011), their evolution was parallel and indistinguishable during the SD night. However, a follow-up experiment conducted with a subset of the same subjects showed that sleepiness and CF could be dissociated when accumulated sleep pressure is still low, i.e., during the first 6-8 hours after awakening. These observations suggest that CF and sleepiness can be part of a same continuum, which would explain why these concepts are often not clearly distinguished in the literature (Shen, Barbera, & Shapiro, 2006).

Based on prior reports, it could be expected that sustained exposure to high cognitive task demands would be paralleled by progressively increasing brain activity to keep stable performance levels (Wang et al., 2016). In line with this assumption, brain oxygenation increased (i.e. COE decreased) in frontal areas while performance remained

stable during the second half of TloadDback practice in the evening (1EV), middle of the night (2MN) and morning (3MO) sessions. Increased brain activity with time on task was found in analogous locations in other EEG and fNIRS studies (Li et al., 2009; Wang et al., 2016), providing support to the hypothesis that frontal areas contribute to maintain performance during high cognitive demands, which might lead to CF (Hockey, 1997). Activity in frontal areas has been repeatedly related to the prospective use of information to guide behaviour (Blumenfeld & Ranganath, 2006; Passingham & Sakai, 2004), given its strategic position to integrate reward prediction (Kahnt, Heinzle, Park, & Haynes, 2011; Tsujimoto & Sawaguchi, 2005). Consistently increased activity within this region might be interpreted as the theorized control mechanism that regulates effort to protect from performance decline (Hockey, 1997, 2013).

Nevertheless, contrary to our expectations, a similar pattern of brain oxygenation was found within the angular gyrus and the inferior parietal lobule (here referred as SMFg), which in its turn appeared to sustain (at least partially) performance maintenance during the morning session (3MO). Therefore, our fNIRS study evidenced a pattern of increased brain activity within fronto-parietal cortices. This might be expected since the targeted areas in our experiment are consistent with the defined task-positive network responsible for supporting control and integrating information from one trial to the next; i.e. maintaining performance (Clare Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Dosenbach et al., 2007).

It is worth noticing here that a limitation inherent to the fNIRS technique is that we recorded brain activity only at the cortical level. However, other structures such as the anterior cingulate cortex or the thalamus have also been associated with action

monitoring during fatigue (Lorist et al., 2005), as well as with compensatory processes during SD (Tomasi et al., 2009). Lack of or specific effects observed at the cortical level thus do not preclude the possibility that performance maintenance is further modulated through subcortical activity and/or connectivity.

The current study disclosed an apparent hemisphere dissociation of brain activity during task practice. Whereas we observed a significant increase in left hemisphere cortical activity at the end of the evening 1EV session, cortical activity mostly increased in the right hemisphere during the middle night 2MN session. Furthermore, higher activity was observed at the end of the late night 3MO session in both hemispheres. Bilateral patterns of increased over-activation following sleep deprivation have been previously described in the literature (Drummond, Gillin, & Brown, 2001; Drummond, Brown, Salamat, & Gillin, 2004). However, the evolution of cortical brain activation patterns during the current sleep deprivation study suggests a prior involvement of the right hemisphere (as shown by increased activation during the 2MN session) then followed by bilateral over-activation.

A prior study reported a major involvement of the right hemisphere during a sustained attention task when task demands remained relatively low. At variance, when the difficulty of the task increased, unilateral activation during task performance was replaced by a bilateral activation (Helton et al., 2010). These results are congruent with the results of the current study in which bilateral over-activation at the end of the sleep deprivation night (3MO) contrasts with unilateral dominance observed during the previous sessions (1EV and 2MN). These results are also in line with reduced TloadDback performance during the 3MO session. Finally, cortical oxygenation tended

to decrease again during post-task resting states, further indicating that extra resources were allocated in responses to task needs, and are dismissed afterward.

Does decreased performance stem from compromised resources?

In line with prior studies (Ma et al., 2015), we could hypothesise that decreased fronto-parietal activity at the end of the night (3MO) contributes to a faster triggering of CF, as measured through self-reported scales and a drop in accuracy during the task. Contrarily however, we observed cortical over-activation patterns developing with time on task, differently between the two cerebral hemispheres. On the other hand, subjective CF and sleepiness were higher at the end of the night and performance markedly dropped with time on task in the morning (3MO) but not in the middle of the night (2MN). Performance in the morning (3MO) period was stabilized during the second half of task practice, even if at a lower performance level. This suggests that participants did not disengage from the task, but rather continued to try performing as requested in a straining situation (Hockey, 2013). Since we used a task in which cognitive load is individually adapted to the individual's maximal capacity, task disengagement caused by too low (Saxby, Matthews, Hitchcock, & Warm, 2007) or too high (Schulz & Schönpflug, 1982) demands may have been limited. Besides relative changes in oxygenation levels, we found that decreased performance in the morning session (3MO) was associated with disrupted connectivity between left prefrontal regions. This result might be interpreted in the context of the cost-benefit model of Kurzban (Kurzban, Duckworth, Kable, & Myers, 2013), who proposes an adaptive approach as the most suitable way for understanding subjective effort and performance achievement. According to this model, the brain performs cost-benefit calculations in order to

determine the amount of effort/resource expenditure at any given moment. In the context of this experiment, brain connectivity changes might reflect a higher cost of resource consumption when sleep pressure is high. Indeed, when activity in left SMFg and IFg starts being desynchronized in the morning as a result of extended sleep deprivation, performance is readjusted at a lower rate. These results additionally fit well with a top-down signalling role of the frontal areas to regulate/control activity within related brain areas (Curtis & D'Esposito, 2003). It should be noticed that the impact of IFg on cognition has been linked to its intrinsic connectivity with other cortical and subcortical regions (Dosenbach et al., 2007; Petrides & Pandya, 1994). In light of these findings, we propose that performance levels are readjusted when the availability of brain resources becomes compromised by the sleep deprivation situation. Nonetheless, it should be reminded that this evidence is by itself insufficient to infer possible causal relationships between a drop in regional connectivity and decreased performance.

One could argue that our results could at least be partially explained by task-automatisation or learning effects from one session to another. We argue against these possibilities for the following reasons. First, the presence of a pre-test session for the TloadDback task held the day before the experiment, likely limited the impact of potential learning effects over the three night sessions. Second, the task involves working memory components that cannot be predicted and thus could hardly be automatized (Rankin et al., 2009). The fact that performance decreased with time on task during the three sessions (and more so in the last session) also argue against automatisation (Rankin et al., 2009). Third and most importantly, hemodynamic patterns increased with time on

task in fronto-parietal regions, suggesting the development of compensatory mechanisms necessary to maintain performance.

Finally, we acknowledge the limited spatial resolution of the fNIRS technology, which might be a limiting factor. Although we used of a 3-D coordinates system combined with a Polaris localization device that significantly improved spatial resolution, the localization of the optodes does not allow determining with high precision the underlying brain structures. To circumvent this potential issue, we projected the average of the optodes' coordinates across all participants on an IRM template. However, using individual IRM acquisitions would have resulted in better accuracy. Therefore, the anatomical names given to our regions of interest should be seen as tentative. Similarly, although fNIRS represents nowadays an interesting technology to investigate the relationship between brain activity and cognitive processes in ecological contexts, recordings are limited to cortical areas. As stated above, it means that the differential impact on cortical networks observed in this experiment are possibly mediated by connectivity between cortical and subcortical areas that could not be recorded here, e.g. the thalamus. Future studies using whole-brain neuroimaging techniques are needed to investigate further this issue. Finally, associations with cognitive fatigue have been made with lifestyle and physical factors such as BMI, diet style or physical activity (Resnick, Carter, Aloia, & Phillips, 2006), that were not explicitly considered in the present study.

Conclusion

We investigated the triggering of CF at three different moments during a night of sleep deprivation, a situation in which available resources are naturally compromised. Results showed on the one hand, increased oxygenation levels appearing with time on task,

suggesting the existence of compensatory mechanisms. Besides, reduced connectivity between the left IFg and SMFg regions at the end of the night was associated with readjusted performance at a lower rate. Altogether, our results suggest the hypothesis that rather than from a reduction in brain activity levels per se, it is a readjustment mechanism, possibly regulated by left prefrontal connectivity, which is responsible for a reduced performance in the current experimental protocol.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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FIGURES LEGEND

Figure 1: Experimental procedure. During the 13 hours of sleep deprivation (SD), participants were administered hourly a vigilance task (5-minute version of the PVT) and cognitive fatigue (CF) and sleepiness self-report scales. CF was induced during the TloadDback task (duration 16 minutes) at 3 different moments of the night (inter-session interval +/- 4.5 hours): Evening (1EV), Middle of the Night (2MN) and Morning (3MO). A 4-minute resting state (Rst) period followed the TloadDback task. Cortical oxygenation/deoxygenation changes were assessed during the TloadDback and the Rst periods using functional near infrared spectroscopy (fNIRS). The day before the day of the SD night, a pretest session was conducted to determine the participant's individual maximal cognitive capacity (i.e., fastest processing speed allowing performance accuracy > 85%), and a short recalibration was performed before each session in the SD night to ensure that initial processing capacity remained at the same level.

Figure 2: Rendering of the estimated optodes positions on a template brain. Red and blue numbers represent sources and detectors respectively. Yellow lines sketch out the channels created by the combination of every detector with its corresponding source. Created using Homer2-AtlasViewer (Aasted et al., 2015).

Figure 3: Evolution of vigilance (PVT), self-reported sleepiness (KSS) and cognitive fatigue (CF) during the SD night (from 20h to 08h). Blank-spaces indicate the grouping of time slots as highlighted by cluster analyses. Correlations illustrate relationships between the three variables. All data are normalized, and vertical bars are standard errors scores.

Figure 4: Evolution of performance during TloadDback practice in the evening (1EV), the middle of the night (2MN) and the morning (3MO). Grey rectangles encompass time points in which performance is equal. Asterisks indicate significant p-values after Tukey post-hoc correction: * = $p < .05$; ** = $p < .01$ and *** = $p < .001$. *n.s*: non-significant.

Figure 5: Cerebral oxygen exchange (COE) values during the TloadDback and subsequent resting states in the right and left hemispheres. Note that negative and positive COE values indicate increased and reduced oxygenation, respectively.

Figure 6: Intra- and inter-hemispheric connectivity. Blue circles indicate the regions of interest where activity was recorded using fNIRS. Green Xs indicate inter-hemispheric connections in which connectivity decreased from the beginning (t1) to the end (t4) of the TloadDback task (bottom right panel) during the 3 sessions. Red Xs indicates the intra-hemispheric connection (on the left SMFg - IFg) in which connectivity decreased in the morning (3MO) session as compared to the evening (1EV) and middle night (2MN) sessions (bottom left panel).

SUPPLEMENTARY INFORMATION

Table S1: Averaged Montreal Neurological Institute (MNI) coordinates for the optodes positions.

Table S2: Estimated MNI location of the cortical areas measured through the light diffusion pattern created between each source and its associated detectors. Locations were computed using the Anatomy software (Eickhoff et al., 2005), an SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data.

Figure S1: Actigraphy recordings. Averaged motor activity over the 7 nights and 7 days of the experiment. Sleep deprivation was organized on Day 7, resulting in comparable levels of motor activity between day and night on this experiment day.

Figure S2: Evolution of self-reported feelings of sleepiness and cognitive fatigue (CF) during normal waking hours (low sleep pressure). The hours are divided into three different periods: Morning (from 9h to 12h), Post dip lunch (from 13h to 14h) and Afternoon (from 15h to 19h). Asterisks indicate the presence of significant differences between sleepiness and CF feelings; n.s = non-significant. Error bars represent standard errors.

Post-CF inducing task changes in the resting state (band-pass filter range of 0.009 - 0.08 Hz)

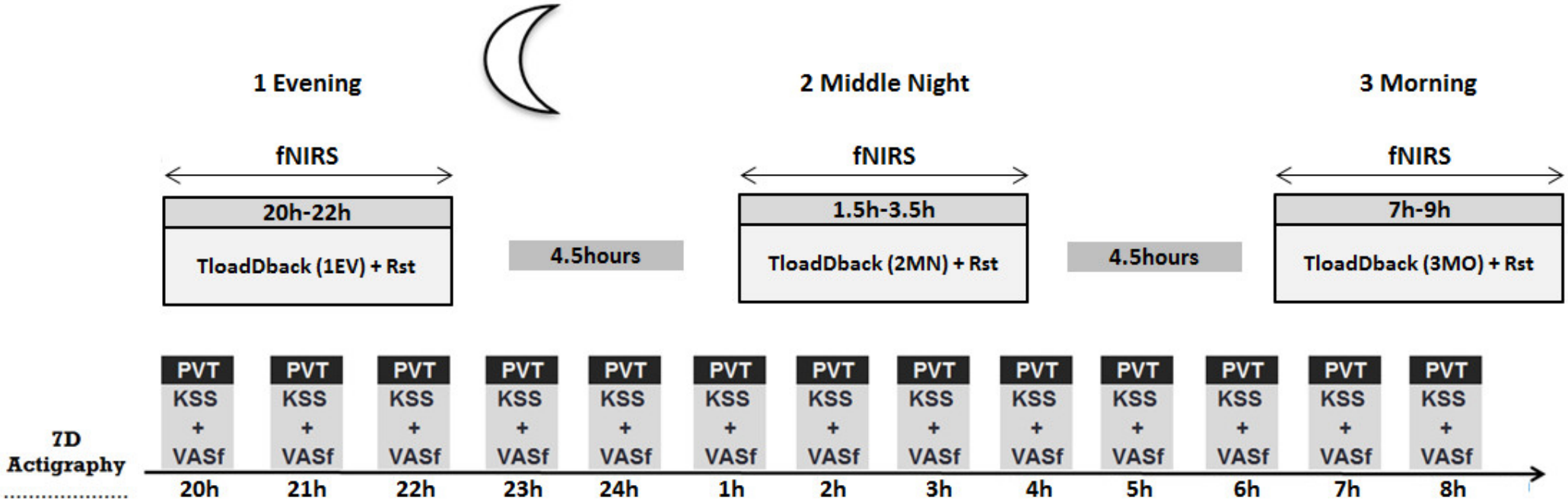
In addition, to investigate how task-related CF induction changed post-task brain oxygenation and whether it changed to the same extent during the course of the SD night, we investigated COE variations during post-task resting state (Rst) periods. A repeated-

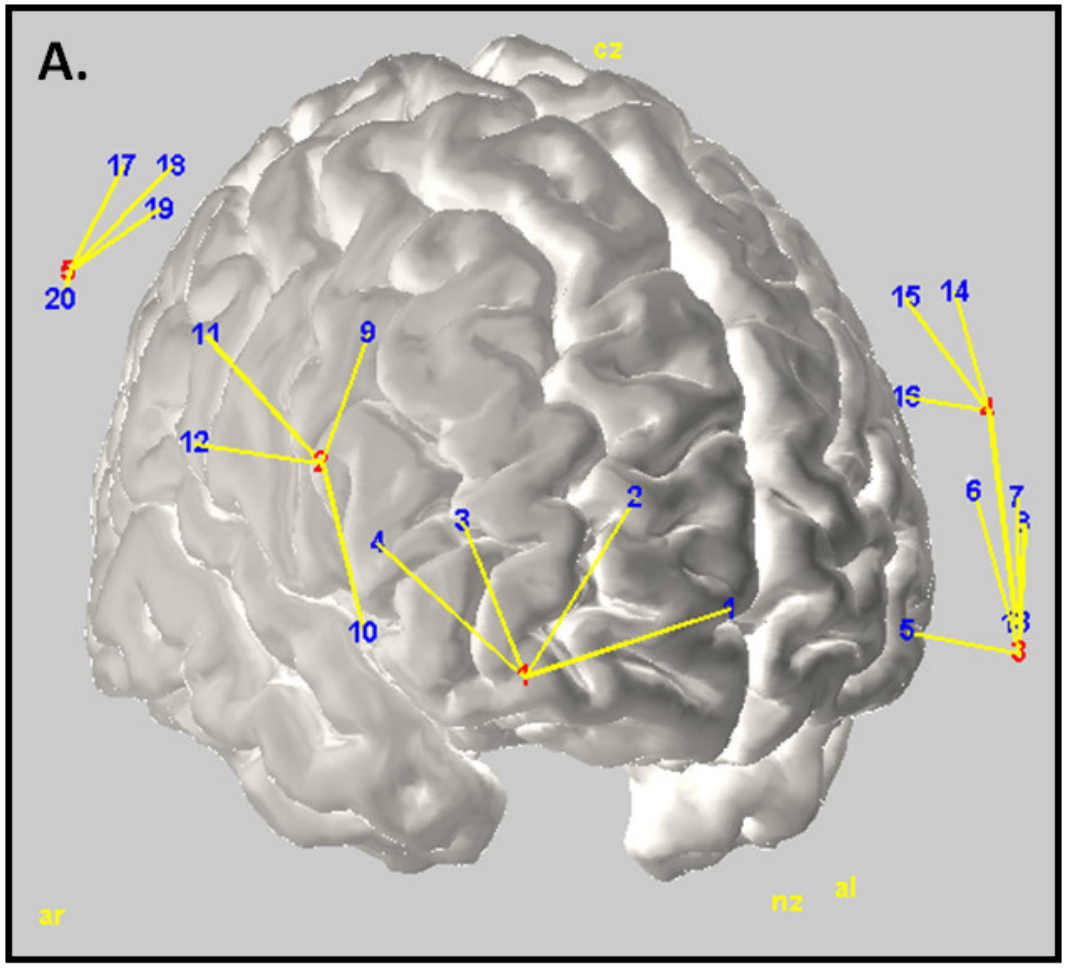
measure ANOVA was conducted on averaged COE values during Rst periods with Area (SMFg vs IFg and AgIPL), Hemisphere (Right vs. Left) and Session (1EV vs. 2MN vs. 3MO) as within subject-factors. There was a main Area effect ($F_{(2, 30)} = 8.5$; $p < .005$; $MSE = 5.92\ e^{-11}$; $partial\text{-}\eta^2 = .36$) with lower COE (i.e., higher oxygenation levels) in frontal areas ((SMFg = IFg) > AgIPL; $ps < .05$). There was also a main Hemisphere effect with higher oxygenation in the Right than the Left hemisphere ($F_{(2, 30)} = 6.83$; $p < .01$; $MSE = 2.62\ e^{-11}$; $partial\text{-}\eta^2 = .31$).

Finally, we also computed analyses on the Amplitude of Low Frequency Fluctuations (ALFF), an index of spontaneous neural activity deemed sensitive to activity changes during resting state sessions (Yu-Feng et al., 2007). A repeated-measure ANOVA was conducted on ALFF values with Area (SMFg vs IFg and AgIPL), Hemisphere (Right vs Left) and Session (1EV vs 2MN vs 3MO) as within subject-factors. The analysis disclosed an Area × Hemisphere interaction effect ($F_{(1, 15)} = 6.77$; $p < .005$; $MSE = .09$; $partial\text{-}\eta^2 = .31$). Post-hoc tests evidenced apparently similar ALFF between hemispheres in the SMFg and IFg areas ($ps > .6$), but higher ALFF in the Right than the Left AgIPL ($p < .005$). The Area × Session interaction was also significant ($F_{(4, 60)} = 4.91$; $p < .005$; $MSE = .056$; $partial\text{-}\eta^2 = .25$). Post-hoc tests showed decreased ALFF over the night (1EV > (2MN = 3MO); $p < .05$) in the SMFg, whereas it remained stable in the IFg and AgIPL (1EV= 2MN = 3MO); $ps > .13$).

To sum up, functional connectivity analyses on brain activity in the resting state period (4 minutes) immediately after task practice disclosed overall higher activation in frontal cortices as compared to the other targeted areas. This is in line with prior findings showing that measured activity within resting state networks reflects a dynamic image of

the existing brain state (Waites, Stanislavsky, Abbott, & Jackson, 2005). Higher oxygenation levels were also found in the right as compared to the left hemisphere during this post-task period. These results might reflect a dominance of the right hemisphere in processes underlying the regulation of attention during the resting state (Helton et al., 2010). Furthermore, a decrease in the amplitude of ALFF was also observed within the sleep deprivation night (1EV> (2MN, 3MO)) in the anterior frontal areas, which might illustrate an effect of sleep deprivation over cognitive control-related brain areas (Jackson et al., 2013).


1 Evening
2 Middle Night
3 Morning
fNIRS
fNIRS
fNIRS
20h-22h
TloadDback (1EV) + Rst
4.5hours
1.5h-3.5h
TloadDback (2MN) + Rst
4.5hours
7h-9h
TloadDback (3MO) + Rst
7D Actigraphy
PVT KSS + VASf
20h
21h
22h
23h
24h
1h
2h
3h
4h
5h
6h
7h
8h


A.
cz
17
18
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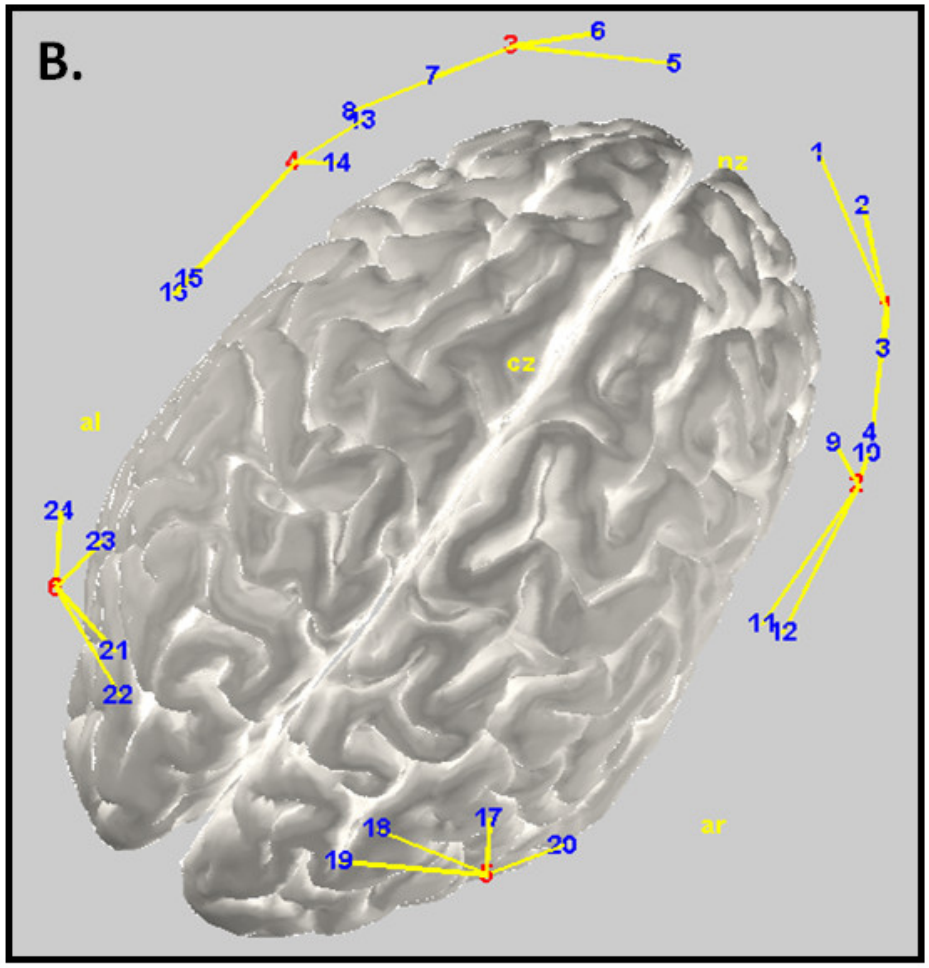
B.
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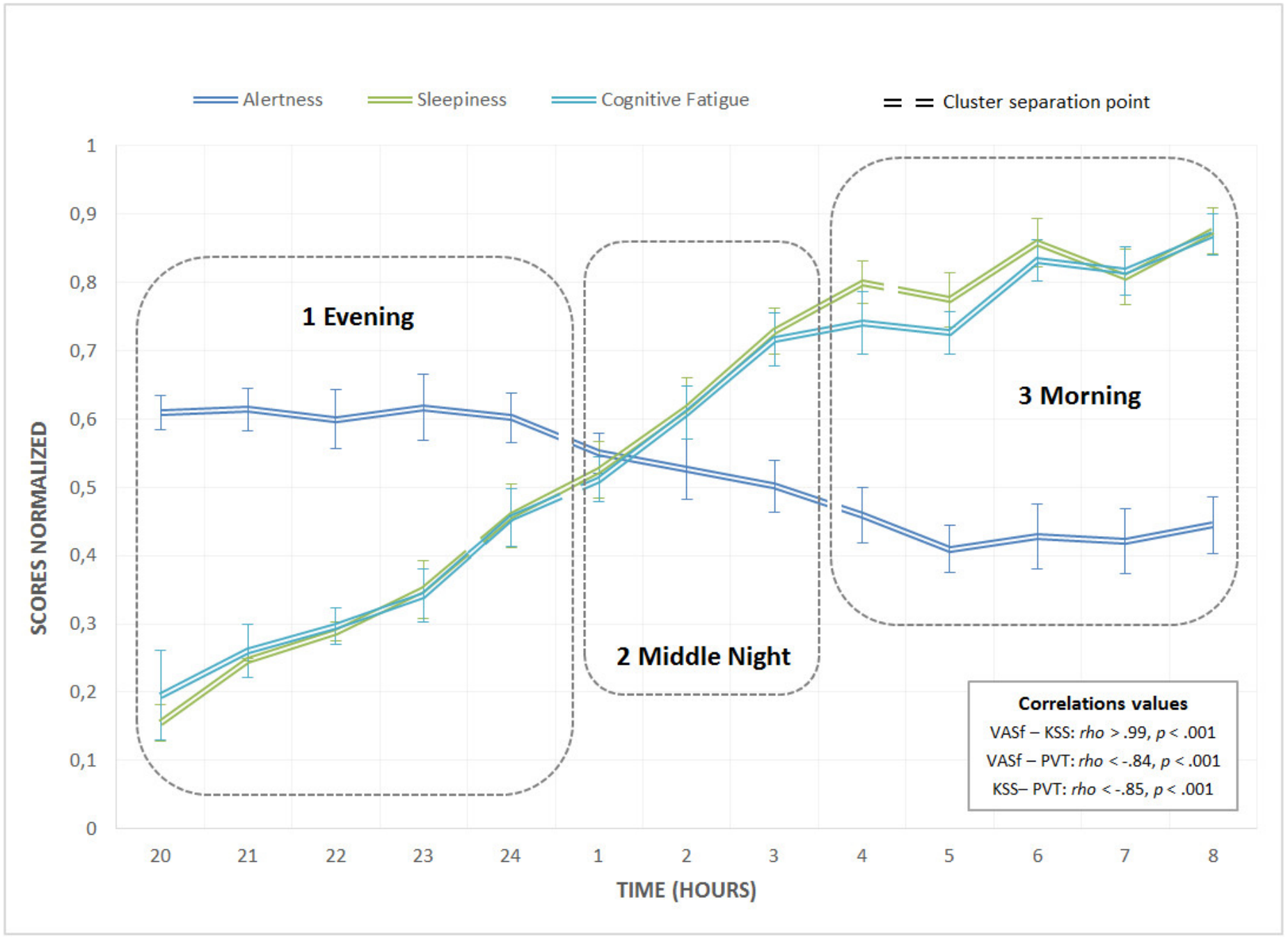
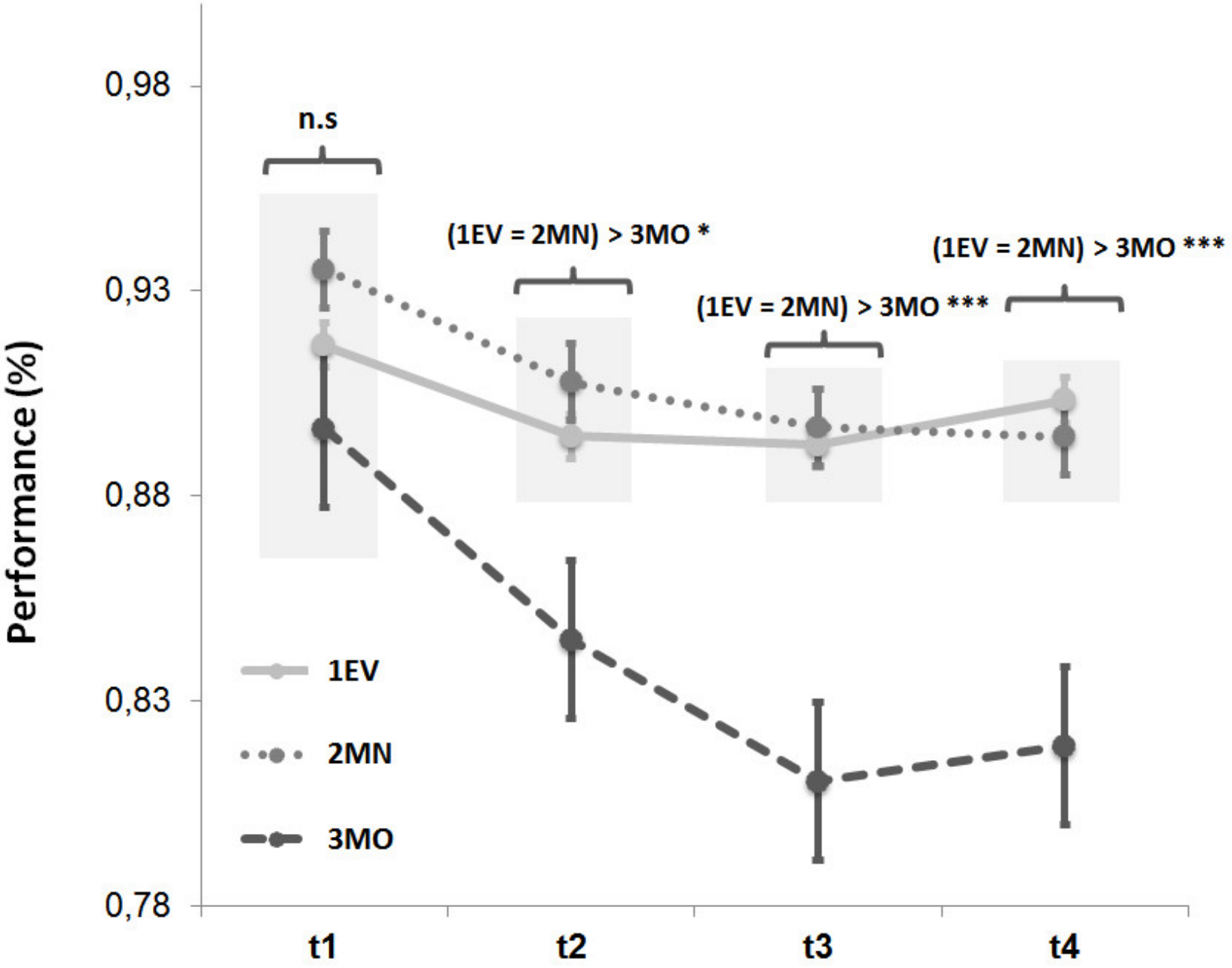
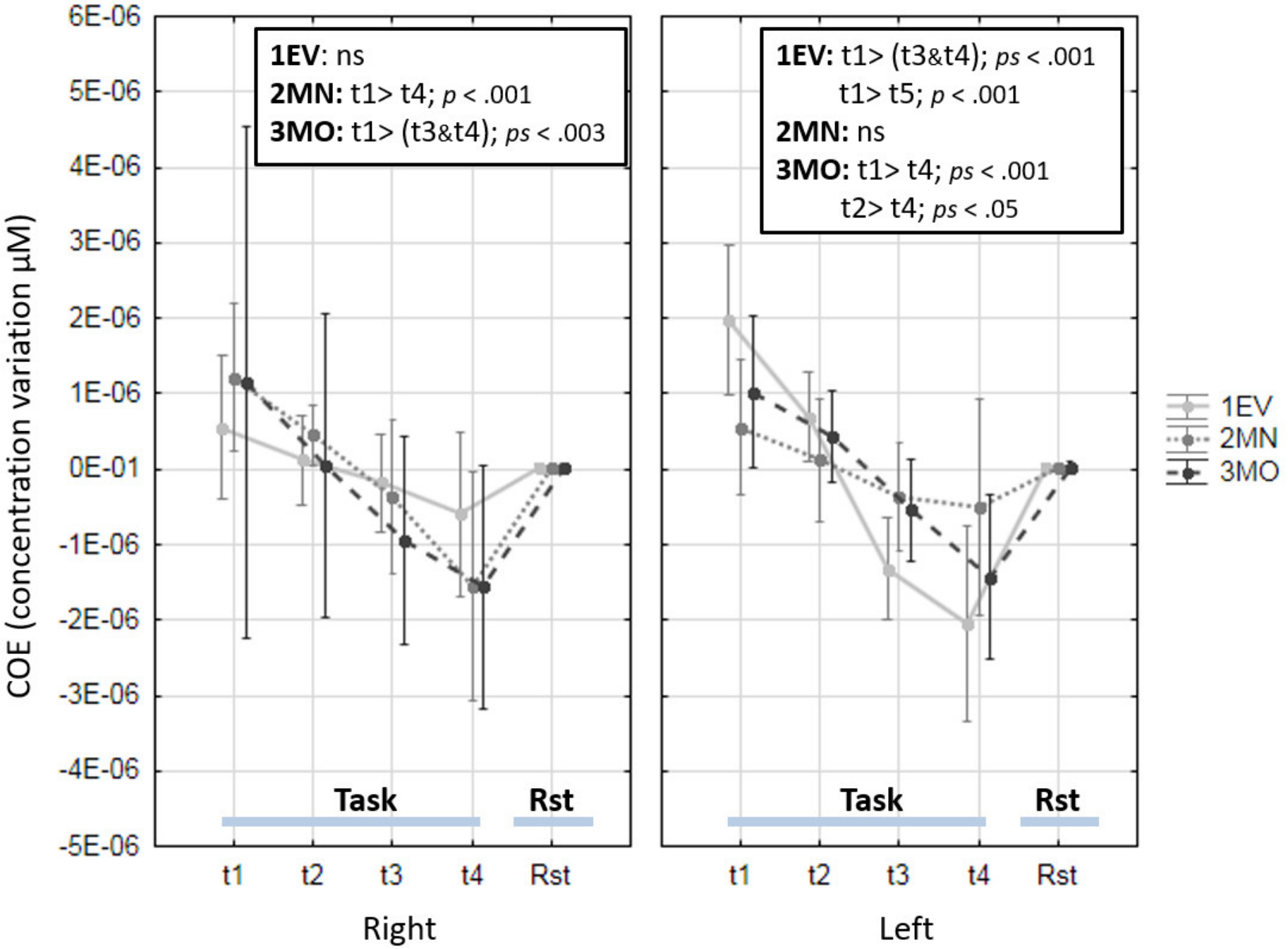
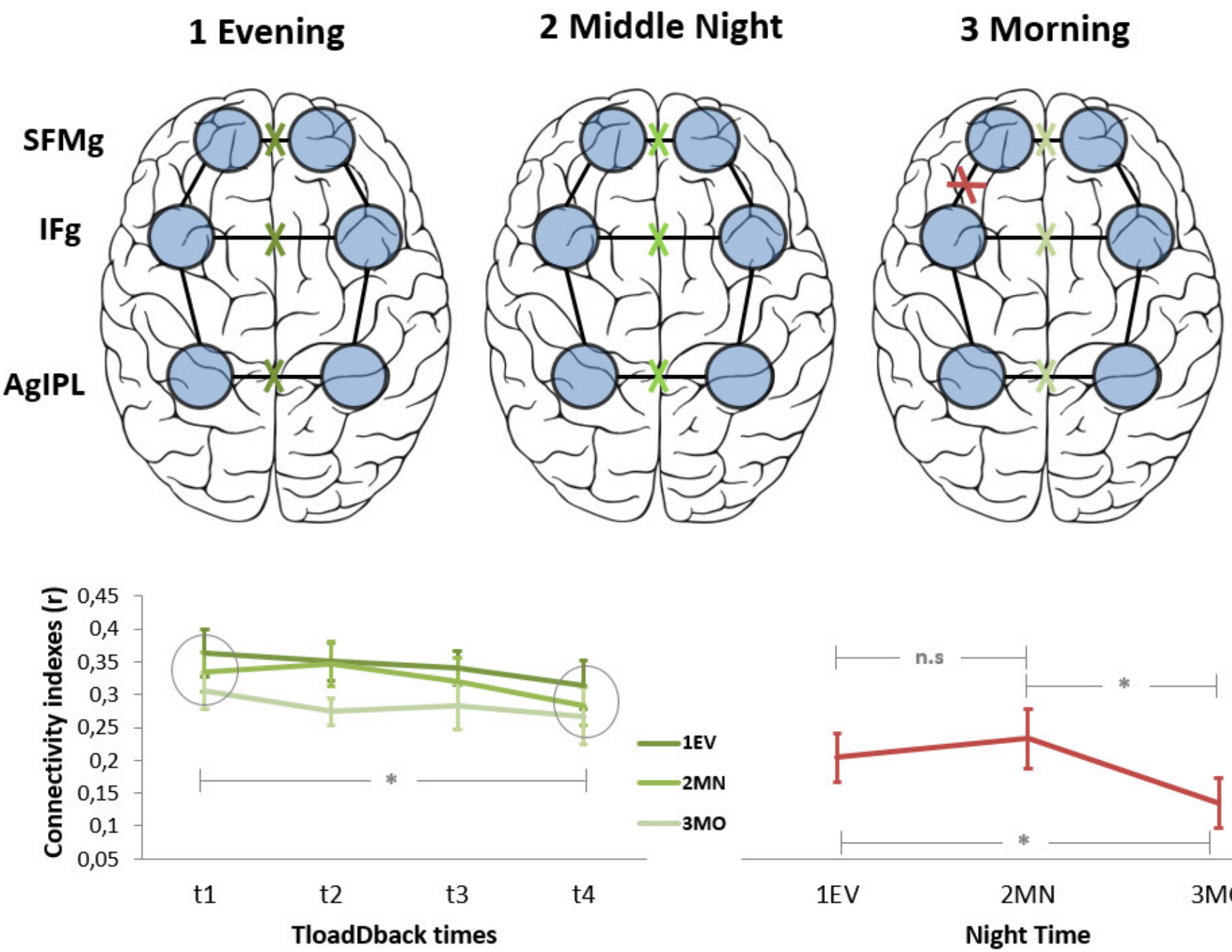
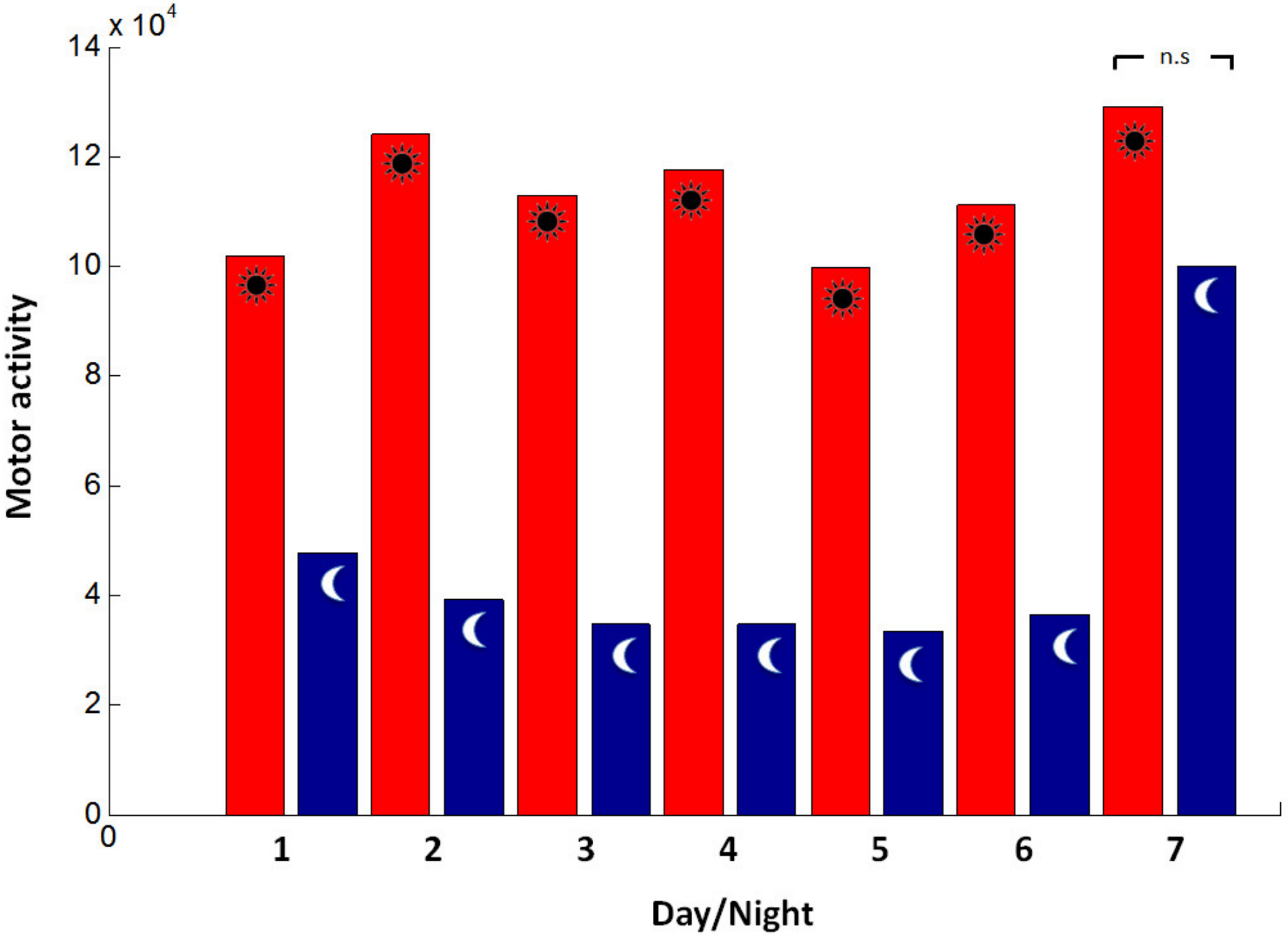
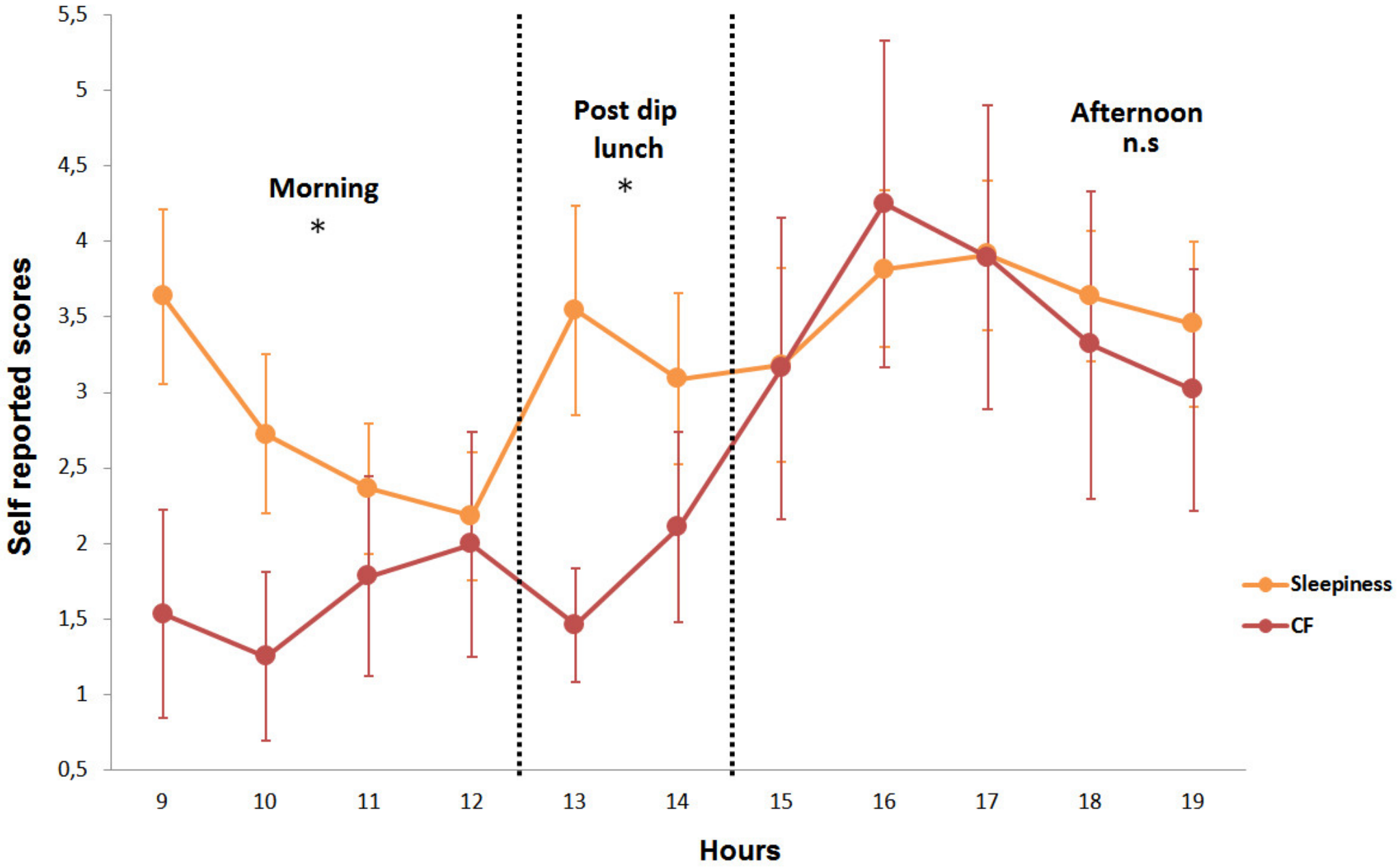

Alertness
Sleepiness
Cognitive Fatigue
Cluster separation point
SCORES NORMALIZED
TIME (HOURS)
1 Evening
2 Middle Night
3 Morning
Correlations values
VASf – KSS: rho > .99, p < .001
VASf – PVT: rho < -.84, p < .001
KSS– PVT: rho < -.85, p < .001


0,98
0,93
0,88
0,83
0,78
Performance (%)
n.s
(1EV = 2MN) > 3MO *
(1EV = 2MN) > 3MO ***
(1EV = 2MN) > 3MO ***
1EV
2MN
3MO
t1
t2
t3
t4


6E-06
5E-06
4E-06
3E-06
2E-06
1E-06
0E-01
-1E-06
-2E-06
-3E-06
-4E-06
-5E-06
COE (concentration variation µM)
1EV: ns
2MN: t1> t4; p < .001
3MO: t1> (t3&t4); ps < .003
Task
Rst
t1
t2
t3
t4
Rst
Right
1EV: t1> (t3&t4); ps < .001
t1> t5; p < .001
2MN: ns
3MO: t1> t4; ps < .001
t2> t4; ps < .05
Task
Rst
t1
t2
t3
t4
Rst
Left
1EV
2MN
3MO


1 Evening
2 Middle Night
3 Morning
SFMg
IFg
AgIPL
Connectivity indexes (r)
0,45
0,4
0,35
0,3
0,25
0,2
0,15
0,1
0,05
t1
t2
t3
t4
TloadDback times
1EV
2MN
3MO
*
n.s
*
*
1EV
2MN
3MO
Night Time


x 10^4
14
12
10
8
6
4
2
0
0
Motor activity
n.s
1
2
3
4
5
6
7
Day/Night


5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
Self reported scores
Morning
*
Post dip
lunch
*
Afternoon
n.s
9
10
11
12
13
14
15
16
17
18
19
Hours
Sleepiness
CF

Night Period		1 Late afternoon			2 Middle night			3 Early morning		
TloadDback/Rst		p1	p2	p3	p1	p2	p3	p1	p2	p3
CF	Mean	1.85	4.24	3.84	7.01	8.56	8.9	9.42	10.79	10.61
	Std	1.84	2.81	2.64	2.25	2.23	2.48	2.56	1.63	1.59
	CI	[.87 - 2.8]	[2.7 – 5.7]	[2.4 – 5.2]	[5.8 – 8.2]	[7.4 – 9.7]	[7.6 – 10]	[8 – 11]	[9.9 – 11.6]	[9.8 – 11.4]
Sleepiness	Mean	1.76	2.99	3.31	6.94	8.6	9.26	9.29	10.84	10.844
	Std	2.99	3.11	2.89	2.32	1.84	2.33	2.49	1.33	1.35
	CI	[.16 - 3.3]	[1.34 - 4.6]	[1.76 - 4.8]	[5.7 - 8.18]	[7.6 - 9.59]	[8 - 10.5]	[7.9 - 10.6]	[10.1 – 11.5]	[10.1 – 11.6]

Optode position	Hemisphere	X	Y	Z	X (sd)	Y (sd)	Z (sd)
Source 1	Right	36,9	66,3	-2,5	1,8	1,5	4,7
Source 2	Right	51	34,9	21.7	2,3	3,1	4,5
Source 3	Left	-30,3	62,8	-3,3	2,3	2,4	4,4
Source 4	Left	-46,4	33,2	20,8	2,1	3,5	3,3
Source 5	Right	54,7	-66,7	40,54	3,4	4,4	7,8
Source 6	Left	-55,8	-69,3	43,6	3,1	6,6	8,5
Detector 1	Right	16,5	74,3	5,9	2,6	1,5	4,6
Detector 2	Right	24,3	65,9	21	2,6	2,4	3,6
Detector 3	Right	41,8	54,7	15,8	2,6	2,9	4,0
Detector 4	Right	49,7	46,1	10,5	2,2	3,0	4,7
Detector 5	Left	-9,5	73,8	5,3	2,3	1,9	5,8
Detector 6	Left	-17,4	65	19,5	2,5	2,8	4,2
Detector 7	Left	-34,8	53,6	13,6	1,9	3,2	4,5
Detector 8	Left	-43,1	43,9	9,29	1,6	3,2	4,3
Detector 9	Right	41.9	35,6	37,09	3,3	3,6	3,6
Detector 10	Right	52,9	46,9	-4,7	1,4	2,2	5,0
Detector 11	Right	54,6	7,2	37	3,0	4,1	3,7
Detector 12	Right	60,7	9,3	21,4	1,8	2,8	4,1
Detector 13	Left	-44,2	46,7	-3,8	1,6	3,3	4,3
Detector 14	Left	-36	34,2	38,4	2,9	3,6	3,3
Detector 15	Left	-50,3	9,2	38	3,1	4,6	3,9
Detector 16	Left	-58,3	8,7	22,9	2,1	3,9	4,1
Detector 17	Right	48,3	-53,3	56,6	3,8	5,3	5,1
Detector 18	Right	35,8	-73,2	59	4,1	6,6	5,8
Detector 19	Right	34,1	-85,3	49	3,8	6,5	8,6
Detector 20	Right	61,6	-49,6	36,2	2,3	3,7	6,9
Detector 21	Left	-30,8	-72,9	61,5	2,9	7,1	5,4
Detector 22	Left	-25,7	-86	52,6	2,9	7,8	7,6
Detector 23	Left	-46,6	-53,5	60,3	4,1	6,7	4,2
Detector 24	Left	-64	-49,5	38,9	3,3	4,7	7,3

Source/Detector	Hemisphere	X	Y	Z	Brain area
S1D1	Right	27	70	2	Superior Frontal Gyrus
S1D2	Right	31	66	9	Superior Frontal Gyrus
S1D3	Right	39	61	7	Middle Frontal Gyrus
S1D4	Right	43	56	4	Middle Frontal Gyrus
S3D5	Left	-20	68	1	Superior Frontal Gyrus
S3D6	Left	-24	64	8	Superior Frontal Gyrus
S3D7	Left	-33	58	5	Middle Frontal Gyrus
S3D8	Left	-37	53	3	Middle Frontal Gyrus
S2D9	Right	47	35	30	Middle Frontal Gyrus
S2D10	Right	52	41	9	Inferior Frontal Gyrus
S2D11	Right	53	21	30	Inferior Frontal Gyrus
S2D12	Right	56	22	22	Inferior Frontal Gyrus
S4D13	Left	-45	40	9	Inferior Frontal Gyrus
S4D14	Left	-41	34	30	Inferior Frontal Gyrus
S4D15	Left	-48	21	29	Inferior Frontal Gyrus
S4D16	Left	-52	21	22	Inferior Frontal Gyrus
S5D17	Right	52	-60	49	Angular Gyrus
S5D18	Right	45	-70	50	Angular Gyrus
S5D19	Right	44	-76	45	Angular Gyrus
S5D20	Right	58	-58	38	Inferior Parietal Lobule
S6D21	Left	-43	-71	53	Angular Gyrus
S6D22	Left	-41	-78	48	Inferior Parietal Lobule
S6D23	Left	-51	-61	52	Angular Gyrus
S6D24	Left	-60	-59	41	Angular Gyrus