



Local sleep episodes during wakefulness and space travel

“SleepSpace”

Final report

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Summary

Astronauts sleep control is a major issue for successful space missions as sleep quality supports human physical and mental performance. A well-adapted wake/sleep routine broadly promoted during space stay does not seem to be conclusive against sleep deficiency on astronauts and it has been reported that sleep medication is administered to most of the ISS crewmembers. It is important to note that the functional cerebral mechanisms underlying the qualitative changes related to space stay have not yet been elucidated. In this context, electroencephalogram (EEG) technique offers the possibility to directly (but not invasively) access to the real global electrical brain activity underlying brain function. EEG in sleep research has allowed the sleep pressure characterization in wakefulness and during sleep states by the power increase of the theta (4-8 Hz) and delta (0.5-4Hz) EEG rhythms respectively (Cajochen et al., 1999 and 1995). The aim of the present study was to assess how space travel modifies local sleep episodes during wakefulness by analysing specific EEG data previously recorded on board of the ISS during our previous Neurospat (NES) experiment (AO-2004, 118). We investigated sleep pressure markers during wakefulness, by studying local sleep-like events in five astronauts throughout a six-month space mission. We show an increase of sleep need markers during space flight, which correlates with a decrease of alertness when undergoing a visuomotor task. The fine characterization of such sleep episodes will allow a better understanding of the cerebral functional mechanisms underlying sleep alterations in microgravity. As adequate sleep quantity and quality is required for vigilance, cognitive and learning processes, these results will support further appropriated sleep promoting methods and their support objective evaluation in order to optimize human performance and adaptation in space.

Introduction

“Sleep is regulated by two oscillatory processes: the circadian process and the homeostatic process. The circadian process oscillates on a near 24 hours rhythm and defines the sleep inclination periods (Dijk and Czeisler, 1995). Under normal conditions, the circadian process is synchronized with the light/dark cycle. Astronauts witness short sunrises 16 times a day, since the international space station (ISS) orbits Earth every 90 minutes. As a countermeasure, an artificial 24 hours sleep/wake routine is established to align astronauts’

circadian rhythms on UTC time. Nevertheless, experimental evidence indicates that astronauts experience sleep deficiency on the ISS (Yamamoto et al, 2015; Flynn-Evans et al, 2016). It has also been reported that a majority of the ISS crew members are using sleep promoting medication in response to a sleep deficiency, before and during their mission (Barger et al, 2014). Sleep quality in space might be impacted by external factors such as microgravity, confinement, circadian misalignment, chronic stress, temperature, light and noise disturbances (Thirsk et al, 2009). So far, experiments have shown sensorimotor and neuro-vestibular adaptation to space environment (Yates and Kerman, 1998; Cheron et al, 2014; Hallgren et al, 2015). Yet, no conclusion on changes in the underlying mechanisms regulating sleep in space could be made. Most related ISS studies focus on sleep quantity and chronobiology (Yamamoto et al, 2015; Flynn-Evans et al, 2016). Human spaceflight all-night sleep recording is hard to achieve and only a few reports from space shuttles and the early days of human space stations contain sleep electroencephalogram (EEG) data (Gundel et al, 1997; Monk et al, 1999; Dijk et al, 2001). Regulated separately but concomitant with the circadian process, the homeostatic process, represented by sleep pressure (i.e. sleep need), builds up with the time spent awake. Scalp EEG measurement allows real-time recordings of the cortical activity and is currently the gold standard for sleep quality analysis. EEG markers of high sleep pressure can be observed during wakefulness, by increased theta activity (5-7 Hz) and while asleep by an increase of slow wave activity (SWA) (0.5-4 Hz) (Cajochen et al, 1999; Finelli et al, 2000; Borbély et al, 2016). Dynamical changes in SWA's topographical distribution have been observed after sleep restriction (Plante et al, 2016). Moreover, the local regulation of SWA seems to be closely related to the capacity for neuroplastic changes (Tononi and Cirelli, 2014). Recently, it has been shown that similar local sleep-like events can be observed in awake rodents (Vyazovskiy et al, 2011). Using high density scalp EEG, local sleep-like events have also been studied in awake humans alongside the increase of sleep pressure (Fattinger et al, 2017b) and after a period of sleep deprivation (Hung et al, 2013; Bernardi et al, 2015).

Here, we analyze how sleep deficiency as reported by astronauts during space flight impacts local sleep-like events and we investigate if it is related to visuomotor performances. This analysis is based on high-density wake EEG data collected between 2011 and 2013, as part of the Neurospat experiment (Cebolla et al, 2016)”: (Petit et al. submitted).

Methods

« Participants and Experiment. Five male astronauts (54.2 ± 2.6 years old) participated in this investigation. They were in excellent health, as regularly determined by a special medical commission throughout the experiment. Each astronaut was tested on the ground before flight, in weightlessness aboard the International Space Station (ISS) and on the ground after his return on Earth. For the present study, the data analysed were those on Earth before the mission (Earth: -62.8 ± 8.0 days), two weeks after the launch (space1: 10.4 ± 1.9 days), and two months after the launch (space2: 56.0 ± 3.4 days). During their six-month mission on the ISS, they reported their medication intake. To ensure comparable levels of sleep quantity, a sleep questionnaire was filled by astronauts assessing the night before each Neurospat recording session. Before each session, all astronauts slept for more than five hours and less than eight hours and the mean time asleep was not different across conditions (Earth: 6.4 ± 0.4 , space1: $7:0 \pm 0:6$, space2: $6:8 \pm 0:4$ hours, linear mixed-effects model. with Earth/space1/space2 as a fixed effect and different random intercepts for each astronaut, $F(2,12)=0.40$, $p=0.679$, $n=15$ recording sessions). Recordings took place at variable times along the day, between two and ten hours after awakening. Thus, to correct for the homeostatic process (buildup of sleep pressure while awake) we wanted to make sure that recording sessions were performed at a similar time for each astronaut. Overall, the amount of time awake at the time of recording was not different across the three conditions: Earth (293 ± 45), space1 (327 ± 77) and space2 (367 ± 76 minutes) (linear mixed-effects model with Earth/space1/space2 as a fixed effect and different random intercepts for each astronaut, $F(2,42)=0.60$, $p=0.564$, $n=15$ recording sessions)”, (Petit et al., submitted) :

“Set-up. Similar to previous space mission investigation, the participants were told to look straight ahead at a laptop screen through a form-fitting facemask, fitted with a cylindrical viewing tube that removed external visual cues. The screen was centred on the line of sight, at ~ 30 cm from the eyes. The facemask was held firmly in place by a strap that passed behind the head. A joypad was mounted vertically on the right side of the cylindrical tube, allowing the participants to hold on to the entire structure (mask/tube/laptop) with both hands and still manipulate the joystick and press the buttons on the joypad with right thumb and right index finger. On Earth, the participants performed the experiment while seated comfortably in front of the computer, which rested on a support table. The

facemask was at eye level. During weightlessness in space flight, they performed the experiment in a free-floating condition. In order to restrain large shifts of trajectory, a belt was put around the subject's waist and then attached to straps fixed by metal rings to the right and left racks of the Columbus module of the ISS", (Cebolla et al. 2016).

Stimuli and task. "The participants observed a virtual environment displayed on the computer screen that simulated one of two scenarios: that of piloting a space ship towards the ISS or that of controlling a space ship from the ISS. In both randomly presented scenarios, their goal was to match positions between spaceship and ISS. There were 80 trials per session (40 for each scenario) and each trial lasted 15 seconds maximum. The 80 trials were divided in four blocks, which allowed the astronaut can take a break before starting the next block of 20 trials. At the beginning of each trial, the image of the space ship (or ISS) was presented first and the image of the ISS (or spaceship) one second after. One second after, the target deviated from the nominal straight-ahead position for two seconds. Throughout this first period (total duration of 4 seconds), the subject was asked to observe the space ship (or ISS) without performing any movement (...). Six seconds after the presentation of the first image, the centre of the space ship (or ISS) subtly, but quite perceptibly, changed from white to grey, which indicated that the subject was required to take control of the spaceship and perform as quickly as possible (seven seconds maximum), and make the best possible manual adjustment to the space's ship trajectory toward the target by pressing on a small joystick operated with the right index finger. Once the subject considered that he had matched the positions of both craft as closely as possible, he pressed a button on the joypad with his thumb. The centre of the space ship changed from white to blue or to yellow, depending whether the positions were matched acceptably (precision 3 mm) or not. The next trial started two seconds later. The entire second part constituted the "visuo-motor" period", (Cebolla et al. 2016).

Data Trials. "The astronauts could either fail (F) or succeed (S) their recovery manoeuvre and dock the Soyuz capsule. (...). Bringing the total number of artifact free trials to 367. The time point from which the astronauts were allowed to recover the trajectory of the spacecraft until the first movement recorded with the joystick was defined as reaction time. Reaction times above 500 ms were considered as lapses and discarded (Basner and Dingel, 2011; Bernardi et al, 2015). Reaction times below 50 ms were due to anticipated movements and also discarded, reducing the total number of trials to 164. A recording session was used in

our analysis if at least 5 trials were defined as failed and 5 trials were defined as succeeded within the (50-500 ms) time range. Accordingly, we had to exclude two astronauts in space1 and one astronaut in space2 condition for this analysis. The time interval to look for local sleep-like events was defined as 250 ms before stimulus (i.e. motor action planning) and 500 ms after stimulus presentation (i.e. maximal reaction time) (Perfetti et al, 2010)", (Petit et al. submitted).

Wake EEG Recordings. "Each participant, for each session, was recorded with 58 EEG electrodes with the multi-electrode electroencephalogram mapping module (MEEMM) from the European physiology module placed on the ISS Columbus module, at the European Astronaut Centre (Köln, Germany) or at Star City (Moscow, Russia). In addition to the 58 EEG electrodes (10–20 electrode system EEG cap), three electrooculogram (EOG) (allowing horizontal and vertical EOGs), one electrocardiogram (ECG) and one electromyogram (EMG) (recorded at the first interosseous muscle of the right hand) were recorded. Continuous wake EEG was recorded for 70 minutes during each Neurospat session at a sampling rate of 1116 Hz (0.01–558 Hz band width). For all recordings, the reference was placed on the right ear lobe. Scalp electrodes' impedances were measured and kept below 50 KW. EOG, EMG, ECG and derivation P5 and P6 were excluded from further analysis" (Petit et al. submitted).

EEG Pre-processing. "EEG data pre-processing was performed in Matlab (Version R2017b) using EEGLAB toolbox scripts (Version 14) (Delorme and Makeig, 2004) and additional custom-made scripts. EEG data were pass-band filtered [0.1–48 Hz] and down sampled to 512 Hz. Each EEG channel was referenced to the average value across the channels (i.e. average referencing). A first Independent Component Analysis (Delorme et al, 2007) was performed to remove ocular, muscular, and electrocardiographic artifacts (Earth: 2.6 ± 0.7 , space1: 1.0 ± 0.0 , space2: 1.8 ± 0.5 components rejected) as defined by Hulse and colleagues (Hulse et al, 2011). Using the EEGLAB graphical user interface, all movement artifacts in the signal were marked by visual inspection and removed (Earth: 55.3 ± 2.2 , space1: 60.6 ± 2.8 , space2: 64.7 ± 4.4 minutes of recording remaining). The power spectrum was computed for each channel and non-physiologic spectra were excluded from the dataset (Earth: 2.0 ± 0.7 , space1: 1.6 ± 0.8 , space2: 0.8 ± 0.3 channels rejected). A Second Independent Component Analysis was performed on cleaned data to further remove ocular, muscular, and electrocardiographic artefacts (Earth: 4.2 ± 0.9 , space1: 4.0 ± 0.7 , space2: 4.4 ± 0.8

components rejected). For each subject, rejected channels were finally interpolated. We standardized all EEG channels' differences of potentials by applying z-score transformation. For power analysis, the raw signal was phase rectified over 4 second epochs. Phase-rectified signal averaging (PRSA) (Liu et al, 2016) allows to superimpose the oscillations to create an interference and hence reduce the weight of acute noise generators in the signal. The power spectral density was estimated using the Welch's averaged periodograms with a 4 second Hamming window and a frequency resolution of 0.125 Hz. In each frequency bin, the power at each channel was normalized by the average power over the scalp. The theta power band was computed between 5 and 7 Hz. As in previous work (Hung et al, 2013), we define a global increase when more than 50% of the electrodes were involved" (Petit et al. submitted).

Local Sleep-like Events Detection. "To look for evidence of local sleep-like events during wakefulness we combined existing detection_methods (Massimini et al, 2004; Hung et al, 2013; Bernardi et al, 2015; Mensen et al, 2016; Hung et al, 2013; Fattinger et al, 2017b). We used the SWA-Matlab toolbox developed by Mensen and colleagues with the following parameters (Mensen et al, 2016; Mensen, 2018) (Fig. 4). The EEG channels within 3 non-overlapping areas (frontal: Fp1-Fp2-AF3-AFz-AF4-F1-Fz-F2, central: FC1-FCz-FC2-C1-CPz-CP2 and parietal: CP1-CPz-CP2-P1-Pz-P2-PO3-POz-PO4) were averaged and the three outcomes, also called reference signals, were filtered within the theta band using a second order Butterworth band pass filter. A threshold was set at 2 times the median deviation from the median signal for each area reference signal. All negative peaks on the reference signal below this relative threshold were detected and marked as a local sleep-like event (7019 ± 488 events per recording session). To study the size of each local sleep-like event over the scalp, the event's globality was computed by cross correlating the reference signal with each channel across the scalp within the theta range, looking for similar oscillations within a 50 ms time window. For each correlation above 95%, the corresponding channel was marked as involved in the event. As an additional layer of security, we unmarked isolated channels which could represent artifacts by applying a cluster test (Mensen and Khatami, 2013). We further assessed the density of local sleep-like events per minute of recording and the amplitude from the negative peak to the following positive peak, measured at the channel with the median slope across all channels involved in the corresponding event" (Petit et al. submitted).

Statistics. “Data points were reported as mean \pm sem. For mean values comparison, first we assessed normal distribution with a quantile-quantile plot, then we performed a two-tailed paired Student’s *t*-tests ($p=p$ -values, df =degrees of freedom). For topographical analysis we plotted *t*-values for the two tailed paired Student’s *t*-tests and used a non-parametric cluster test (coefficient of variation=2.757, 25 permutations, $n=5$) (Huber et al, 2004; Fattinger et al, 2017a) for multiple comparison corrections (adjusted *p*-values). For repeated measures time series, the mean value for each astronaut was represented by a grey dot, the mean \pm sem across astronauts were color marked as a dot and a line respectively. To deal with missing values, we used mixed-effects analysis to model repeated measures. First, we assessed normal distribution with a quantile-quantile plot. For normal distributions, we performed a linear mixed effects analysis of the relationship between the variable of interest and fixed/random effects. For non-normal distributions (e.g. binomial distributions), we used a generalized linear mixed effects analysis. We used the restricted maximum likelihood estimate method to fit the model and choose the best model based on Bayesian information criterion results. Visual inspection by quantile-quantile plot of the residuals confirmed that homoscedasticity and normality were respected. The influence of the fixed effects on the model were determined by *F*-tests (*F* (degrees of freedom in the numerator, degrees of freedom in the denominator) =*F*-value, $p=p$ -value). We finally reported the estimated differences (mean \pm se) between repeated measures for each fixed effect, together with the two-tailed paired Student’s *t*-tests results ($t=t$ -values, df =degrees of freedom, $p=p$ -values). When no fixed effect could help to fit the model (i.e. best model is the intercept only model), we reported the non-significant results for the *F*-test assessing the influence of each potential fixed effect on the model. If the variable of interest is best modeled by a unique fixed effect without random effects, we used a linear regression model to obtain a *R*² adjusted value which indicates how much of the total variation can be explained by the fixed effect. Finally, we completed a *F*-test (*F*-value, df =degrees of freedom, $p=p$ -value) with the null hypothesis that the slope of the model is equal to zero. All statistical analysis were performed in Matlab” (Petit et al. submitted).

Results

“Theta Power from Earth to Space. All astronauts were recorded in three conditions: on Earth before the mission (Earth: -62.8 ± 8.0 days), two weeks after the launch (space1: 10.4

± 1.9 days) and two months after the launch (space2: 56.0 ± 3.4 days). In a first step we assessed theta power's topographical distribution over the scalp. Theta power appears higher in the central areas, and consistently for the three conditions (Fig. 1.a). In the majority of astronauts, we observe a global increase (i.e. when at least 50% of the electrodes are involved) in theta power from Earth to space (in 5 astronauts out of 5 for space1 and 4 out of 5 for space2). However, by comparing space to Earth (paired t-test) only a few electrodes show a significant increase of theta power ($df=4$, white dots for $p<0.05$ adjusted values, $n=5$ astronauts) (Fig. 1.b) and a high variability can be observed across astronauts (Fig. 1.c).

Local Sleep-like Events. To look more into theta power increase, we detected local sleep-like events. 1) We first defined three areas of interest along the anterior-posterior axis (i.e. frontal, central and parietal) (Fig. 2.a). 2) Then, we defined amplitude detection thresholds according to theta oscillations within each of these areas (Fig. 2.b). The thresholds were computed for all conditions (i.e. Earth/space1/space2) and averaged within each astronaut. As shown earlier, the central area has a higher theta activity, ultimately the threshold for local sleep-like events detection in this area will be set higher (Fig. 2.b). By defining a detection threshold for each astronaut, we expected similar number of local sleep-like events per astronaut. In addition, the number of local sleep-like events detected could not be predicted by the different topographical areas (linear mixed-effects model with frontal/central/parietal as a fixed effect and different random intercepts for each astronaut, $F(2,42)=1.844$, $p=0.171$, $n=45$ measures), nor by the different conditions of recording (linear mixed-effects model with Earth/space1/space2 as a fixed effect and different random intercepts for each astronaut, $F(2,42)=0.28$, $p=0.758$, $n=45$ measures) 3) Finally, we calculated the amplitude of each local sleep-like event and examined how many electrodes were involved in each event, defining this latest property as the globality of an event (Fig. 2.d,e). Our results show that amplitude varies across the topographical areas, with a different baseline level for each astronaut (linear mixed-effects model with frontal/central/parietal as a fixed effect and different random intercepts for each astronaut, $F(2,42)=5.73$, $p=0.006$, $n=45$ measures). The amplitude of the local sleep-like events is higher in the frontal area compared to the central area (z -score : $+1.41 \pm 0.42$, $t=3.43$, $df=42$, $p=0.002$). We also found that globality of the events varies from Earth to space, with a different baseline level for each astronaut (linear mixed-effects model with

Earth/space1/space2 as a fixed effect and different random intercepts for each astronaut, $F(2,42)=21.11$, $p<0.001$, $n=45$ measures). In space local sleep-like events are more global compared to Earth (Earth to space1: $+4:06\%_{0:66}$, $t=6.13$, $df=42$, $p<0.001$, Earth to space2: $+3:26\%_{0:66}$, $t=4.92$, $df=42$, $p<0.001$).

Alertness and Cognitive Performances. The visuomotor task had two outcomes. In one case, the astronauts succeeded to recover and dock the Soyuz capsule, or they failed. By looking into the local sleep-like events, the outcomes of the task couldn't be predicted by the amplitude (generalized linear mixed-effects model with events' amplitude as a fixed effect and different random intercepts for each astronaut, $F(1,365)=3.04$, $p=0.082$, $n=367$ trials), nor by the globality of the events (generalized linear mixed-effects model with events' globality as a fixed effect and different random intercepts for each astronaut, $F(1,365)=0.15$, $p=0.699$, $n=367$ trials) (Fig. 3.a,b). Direct implication of local sleep-like events on cognitive tasks could not be attested. However, we observed a variation in the amount of slow reaction times (i.e. higher than the median reaction time of 231 ms) from Earth to space, with different baseline and different responses for each astronaut (linear mixed-effects model with Earth/space1/space2 as a fixed effect, different random intercepts for each astronaut and by-astronaut random slopes for the fixed effect, $F(2,9)=21.48$, $p<0.001$, $n_{Earth} = 5$, $n_{space1} = 3$, $n_{space2} = 4$ astronauts) (Fig. 3.c). The percentage of slow reaction times increased by $25:58\%_{6:37}$ in space2 compared to Earth ($t=4.01$, $df=9$, $p=0.003$). Moreover, looking at all reaction times across recording sessions, it appears that local sleep-like events are more global during slow reaction times (linear regression model with globality as a fixed effect: $R^2=0.070$, $F=13.2$, $df=162$, $p<0.001$, $n=164$ trials) (Fig. 3.d)" (Petit et al. submitted).

Figures

(from Petit et al. submitted):

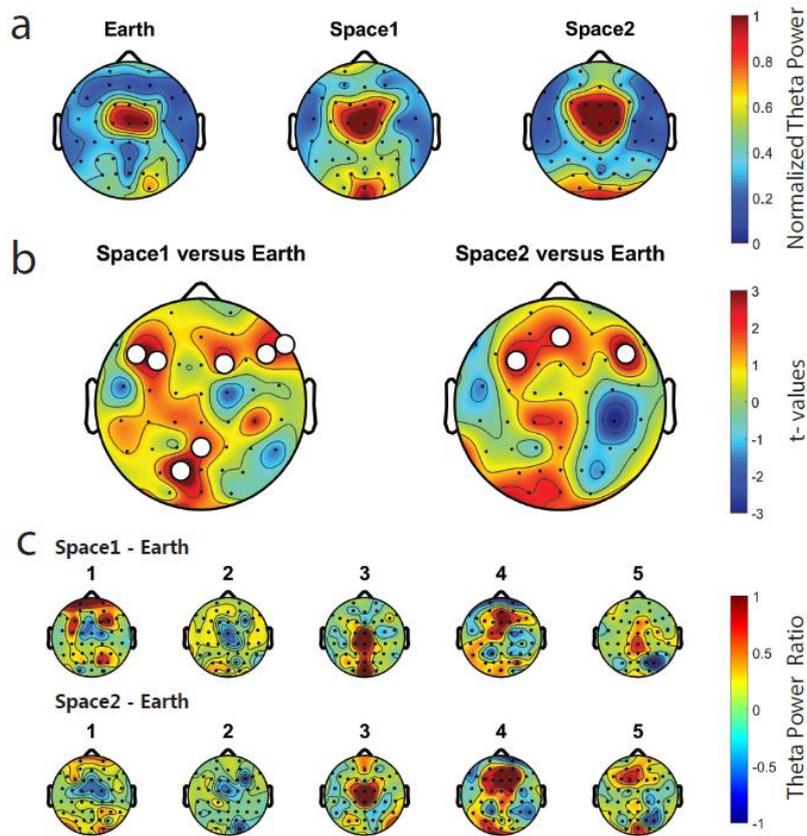


Figure 1: Theta power topographical distribution across the recording conditions. (a) Normalized theta power for Earth, space1 and space2. Consistent central and occipital distribution of the theta power in all conditions for 5 astronauts. (b) In space1 and space2 compared to Earth, theta is globally increased for a majority of astronauts. Red colour indicates an increase of theta power in space compared to Earth (paired t-test t-values, white dots for $p < 0.05$ adjusted values). (c) Space1-Earth and space2-Earth differences in theta power for each astronaut (1-5). Differences in theta power from space to Earth are observed but no clear topographical pattern emerges.

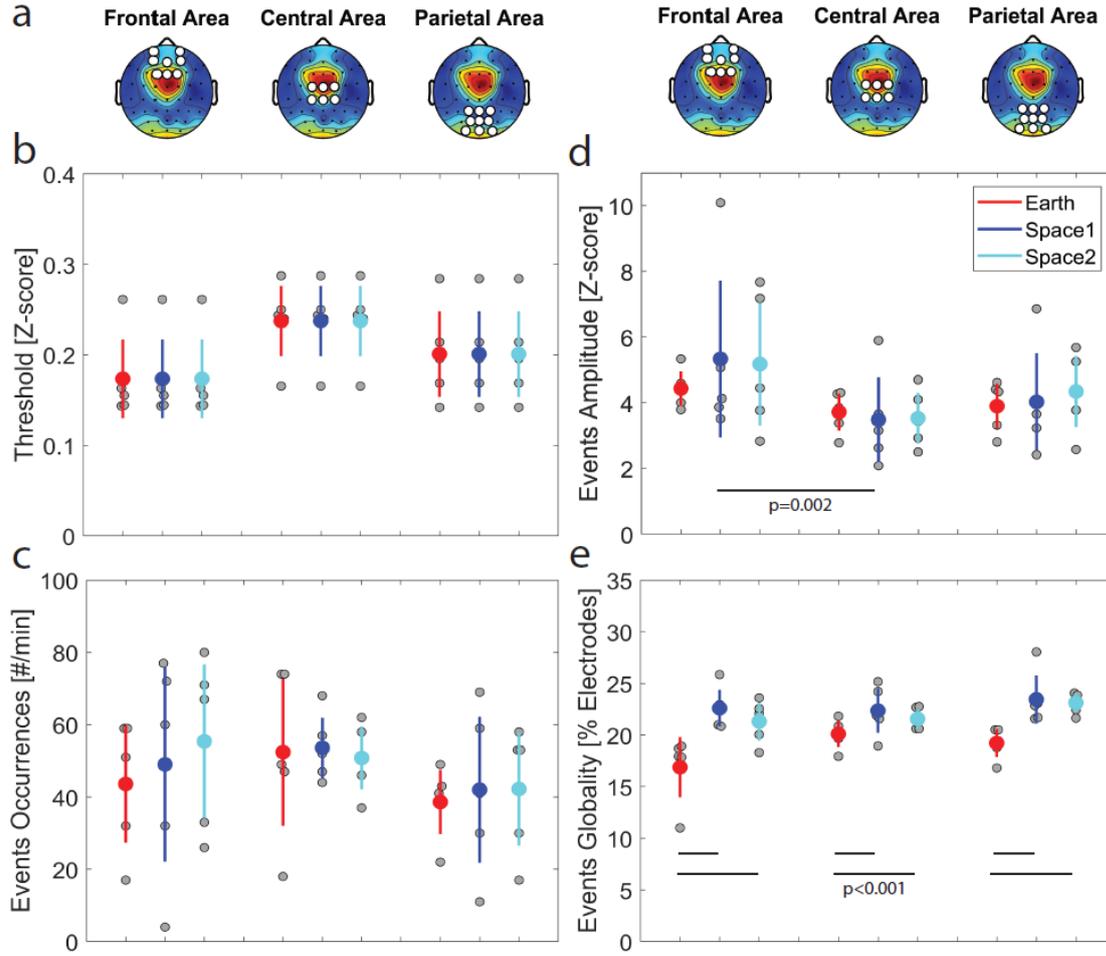


Figure 2: Local sleep-like events in the frontal, central and parietal areas. (a) Topographical distribution of theta power in space2. The white dots define the three non overlapping areas (frontal, central and parietal) used for the detection of local sleep-like events. (b) The voltage at each channel is standardized by z-score transform. A detection threshold is defined for each astronaut within each area (i.e. frontal, central or parietal area). Each grey dot represents the mean value for one astronaut and the $mean \pm sem$ across astronauts are color marked as a dot and a line respectively. (c) Similar number of local sleep-like events selected in each area and across conditions. (d) Increase of the amplitude for local sleep-like events in the frontal area compared to the central area. (e) Increase of the globality for local sleep-like events from Earth to space.

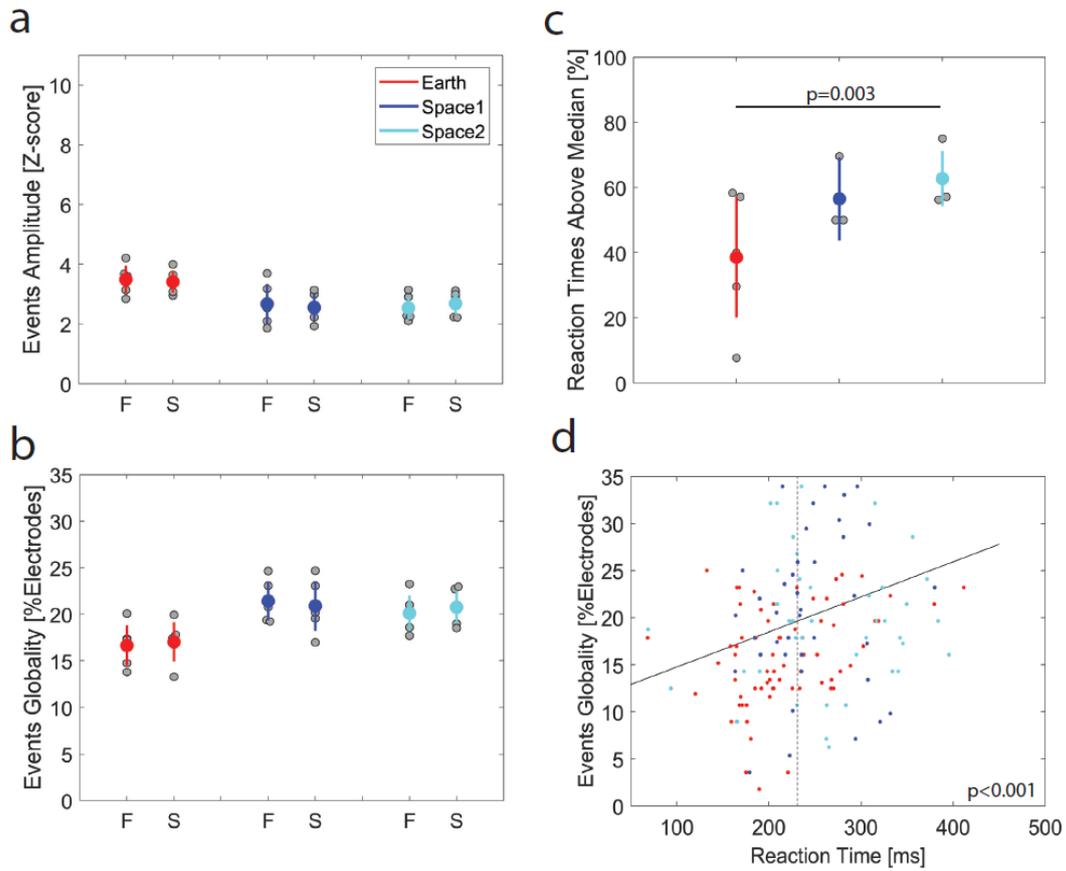


Figure 3: Local sleep-like events impact on cognitive tasks and alertness. (a)(b) During the 10 seconds of the recovery manoeuvre, the astronauts either Failed (F) or Succeeded (S) to dock the Soyuz capsule. The local sleep-like events properties could not predict the two outcomes of the visuomotor task. Each grey dot represents the mean value for one astronaut and the $mean \pm sem$ across astronauts are color marked as a dot and a line respectively. (c) Reaction time until first movement while performing the recovery manoeuvre. There is a higher percentage of slow reaction times in space2 compared to Earth. (d) The full line illustrates the positive correlation between the local sleep-like events' globality around the starting point of the recovery manoeuvre (-250 ms 500 ms) and the reaction times across all trials. The median reaction time is marked by a dotted line at 231 ms.

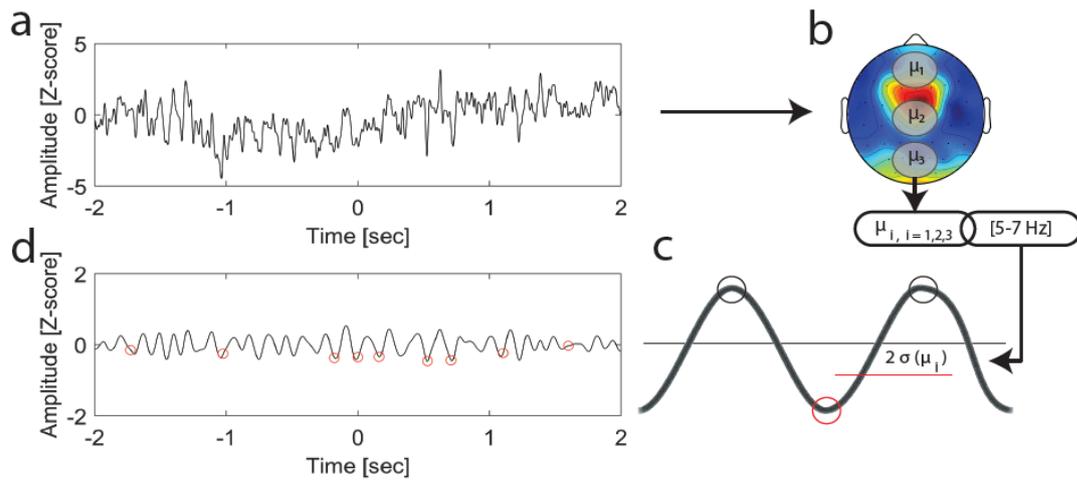


Figure 4: Local sleep-like event detection method (a) Difference of potential at the derivation C3. (b) Signal average within 3 non overlapping areas (frontal, central and parietal) and filtered within the theta band. (c) Detection threshold at 2 times the median deviation from the median signal within each area. All negative peaks on the reference signal below this relative threshold were detected and marked as a local sleep-like event. (d) Red circles mark the local sleep-like events involving the derivation C3.

Discussion

“In this study, we observed a global increase of theta power in space compared to the Earth condition, but no consistent topographical pattern could be defined. In previous work, theta power after sleep deprivation was distributed in the frontal midline areas (Cajochen et al, 1999; Hung et al, 2013). To further analyses sleep need markers and reveal sleep deficiencies on the ISS, we detected local sleep-like events. Since the amplitude detection threshold was set higher in the central area, we were expecting higher amplitudes for the events in the central area. Yet, we showed a higher amplitude for local sleep-like events in the frontal area. In previous work performed by Hung and colleagues (Hung et al, 2013), higher amplitudes for local sleep-like events were observed after sleep deprivation over a left frontal cluster after a listening task and over a parietal cluster after a visuomotor task. Implying that the amplitude of local sleep-like events is task dependent. In our study, local sleep-like events were detected while performing a visuomotor task. Hence, an increase of amplitude in the frontal area could be related to working memory and alertness instead of being task specific. On Earth, an increase of local sleep-like events’ globality is an indication for higher sleep pressure (Fattinger et al, 2017b). In microgravity, potential differences in

the underlying mechanisms regulating local sleep-like events require further investigation. Nevertheless, in this study we show that local sleep-like events are more largely spread over the scalp (i.e. increased globality) in space compared to Earth. Moreover, we observed an increase of slow reaction times in space compared to Earth and overall slower reaction times when local sleep-like events are more global. In the literature, slow reaction times are usually associated with a decrease of alertness (Basner and Dinges, 2011). What compels a local sleep-like event to involve larger cortical areas is not clear yet, but it has been shown to impact performances on Earth (Fattinger et al, 2017b). In this study, we noticed an association between reaction times and the globality of the local sleep-like events before the visuomotor task's first movement. In previous work performed by Perfetti and colleagues (Perfetti et al, 2010), an increase of theta power was observed in the central areas after a motor task stimulus was presented and before the first movement was executed. For this reason, we defined the same (-250 ms 500 ms) time window of interest around the stimuli. Our results are in alignment with previous findings, showing slower reaction times when sleep pressure is higher (Fattinger et al, 2017b) or when sleep is restricted (Hung et al, 2013; Bernardi et al, 2015). Even though effects of chronic sleep restriction on cognitive performances has been well established (Van Dongen et al, 2003; Maric et al, 2017), direct implication of local sleep-like events' globality on cognitive tasks would need to be further explored on a larger sample population.

Long-term space flight missions raise concerns about chronic effects of microgravity and ionizing radiation on the human central nervous system (Clément and Ngo-Anh, 2013). It would be interesting in future studies to see whether these findings are related to task performance. With the advent of long-term space travel, improving sleep quality will be key for maintaining astronauts' cognitive functions and improving missions' success rate" (Petit et al. submitted).

Conclusions and future perspectives

We show an increase of sleep need markers during space flight, which correlates with a decrease of alertness when undergoing a visuomotor task (Petit et al. submitted). Continuing these promising results, it would be interesting to characterize sleep-like events around the motor response precisely related to the docking motor response and to study the potential link between sleep-like events and succeeded/failed docking. The fine characterization of

such sleep need will allow a better understanding of the cerebral functional mechanisms underlying sleep alterations in microgravity. This will support further appropriated sleep promoting methods and their objective evaluation in order to optimize human performance and adaptation in space.

References

- Barger, L.K., Flynn-Evans, E.E., Kubey, A., Walsh, L., Ronda, J.M., Wang, W., Wright Jr, K.P., Czeisler, C.A., 2014. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. *The Lancet Neurology* 13, 904–912.
- Basner, M., Dinges, D.F., 2011. Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. *Sleep* 34, 581–591.
- Bernardi, G., Siclari, F., Yu, X., Zennig, C., Bellesi, M., Ricciardi, E., Cirelli, C., Ghilardi, M.F., Pietrini, P., Tononi, G., 2015. Neural and behavioral correlates of extended training during sleep deprivation in humans: evidence for local, task-specific effects. *Journal of neuroscience* 35, 4487–4500.
- Borbély, A.A., Daan, S., Wirz-Justice, A., Deboer, T., 2016. The two-process model of sleep regulation: a reappraisal. *Journal of sleep research* 25, 131–143.
- Buzsáki, G., Draguhn, A., 2004. Neuronal oscillations in cortical networks. *science* 304, 1926–1929.
- Cajochen, C., Foy, R., Dijk, D.-J., others, 1999. Frontal predominance of a relative increase in sleep delta and theta EEG activity after sleep loss in humans. *Sleep Res Online* 2, 65–69.
- Cebolla, A., Petieau, M., Dan, B., Balazs, L., McIntyre, J., Cheron, G., 2016. Cerebellar contribution to visuo-attentional alpha rhythm: insights from weightlessness. *Scientific reports* 6, 37824.
- Cheron, G., Leroy, A., De Saedeleer, C., Bengoetxea, A., Lipshits, M., Cebolla, A., Servais, L., Dan, B., Berthoz, A., McIntyre, J., 2006. Effect of gravity on human spontaneous 10-Hz electroencephalographic oscillations during the arrest reaction. *Brain research* 1121, 104–116.
- Cheron, G., Leroy, A., Palmero-Soler, E., De Saedeleer, C., Bengoetxea, A., Cebolla, A.-M., Vidal, M., Dan, B., Berthoz, A., McIntyre, J., 2014. Gravity influences top-down signals in visual processing. *PLoS One* 9, e82371.
- Clément, G., Ngo-Anh, J.T., 2013. Space physiology II: adaptation of the central nervous system to space flight—past, current, and future studies. *European journal of applied physiology* 113, 1655–1672.
- Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of neuroscience methods* 134, 9–21.
- Delorme, A., Makeig, S., Fabre-Thorpe, M., Sejnowski, T., 2002. From single-trial EEG to brain area dynamics. *Neurocomputing* 44, 1057–1064.
- Delorme, A., Sejnowski, T., Makeig, S., 2007. Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. *Neuroimage* 34, 1443–1449.

- Dijk, D.-J., Czeisler, C.A., 1995. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *Journal of Neuroscience* 15, 3526–3538.
- Dijk, D.-J., Neri, D.F., Wyatt, J.K., Ronda, J.M., Riel, E., Ritz-De Cecco, A., Hughes, R.J., Elliott, A.R., Prisk, G.K., West, J.B., others, 2001. Sleep, performance, circadian rhythms, and light-dark cycles during two space shuttle flights. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 281, R1647–R1664.
- Fattinger, S., de Beukelaar, T.T., Ruddy, K.L., Volk, C., Heyse, N.C., Herbst, J.A., Hahnloser, R.H., Wenderoth, N., Huber, R., 2017a. Deep sleep maintains learning efficiency of the human brain. *Nature communications* 8, 15405.
- Fattinger, S., Kurth, S., Ringli, M., Jenni, O.G., Huber, R., 2017b. Theta waves in children’s waking electroencephalogram resemble local aspects of sleep during wakefulness. *Scientific Reports* 7, 11187.
- Finelli, L., Baumann, H., Borbély, A., Achermann, P., 2000. Dual electroencephalogram markers of human sleep homeostasis: correlation between theta activity in waking and slow-wave activity in sleep. *Neuroscience* 101, 523–529.
- Fisher, S.P., Cui, N., McKillop, L.E., Gemignani, J., Bannerman, D.M., Oliver, P.L., Peirson, S.N., Vyazovskiy, V.V., 2016. Stereotypic wheel running decreases cortical activity in mice. *Nature communications* 7, 13138.
- Flynn-Evans, E.E., Barger, L.K., Kubey, A.A., Sullivan, J.P., Czeisler, C.A., 2016. Circadian misalignment affects sleep and medication use before and during spaceflight. *npj Microgravity* 2, 15019.
- G. Petit, AM. Cebolla, S. Fattinger, M. Petieau, L. Summerer, G. Cheron and R. Hubert “Local sleep-like events during wakefulness and their relationship to decrease in alertness in 5 astronauts on the international space station”. (*Submitted to npj Microgravity*)
- Gundel, A., Polyakov, V., Zulley, J., 1997. The alteration of human sleep and circadian rhythms during spaceflight. *Journal of sleep research* 6, 1–8.
- Hallgren, E., Kornilova, L., Fransen, E., Glukhikh, D., Moore, S.T., Clément, G., Van Ombergen, A., MacDougall, H., Naumov, I., Wuyts, F.L., 2016. Decreased otolith-mediated vestibular response in 25 astronauts induced by long-duration spaceflight. *Journal of neurophysiology* 115, 3045–3051.
- Hallgren, E., Migeotte, P.-F., Kornilova, L., Delière, Q., Fransen, E., Glukhikh, D., Moore, S.T., Clément, G., Diedrich, A., MacDougall, H., others, 2015. Dysfunctional vestibular system causes a blood pressure drop in astronauts returning from space. *Scientific reports* 5, 17627.
- Huber, R., Ghilardi, M.F., Massimini, M., Tononi, G., 2004. Local sleep and learning. *Nature* 430, 78.
- Hulse, B.K., Landsness, E.C., Sarasso, S., Ferrarelli, F., Guokas, J.J., Wanger, T., Tononi, G., 2011. A postsleep decline in auditory evoked potential amplitude reflects sleep homeostasis. *Clinical Neurophysiology* 122, 1549–1555.
- Hung, C.-S., Sarasso, S., Ferrarelli, F., Riedner, B., Ghilardi, M.F., Cirelli, C., Tononi, G., 2013. Local experience-dependent changes in the wake EEG after prolonged wakefulness. *Sleep* 36, 59–72.
- Liu, Q., Chen, Y.-F., Fan, S.-Z., Abbod, M.F., Shieh, J.-S., 2016. Improved spectrum analysis in EEG for measure of depth of anesthesia based on phase-rectified signal averaging. *Physiological measurement* 38, 116.

- Maric, A., Lustenberger, C., Werth, E., Baumann, C.R., Poryazova, R., Huber, R., 2017a. Intraindividual Increase of Homeostatic Sleep Pressure Across Acute and Chronic Sleep Loss: A High-Density EEG Study. *Sleep* 40.
- Maric, A., Montvai, E., Werth, E., Storz, M., Leemann, J., Weissengruber, S., Ruff, C.C., Huber, R., Poryazova, R., Baumann, C.R., 2017b. Insufficient sleep: Enhanced risk-seeking relates to low local sleep intensity. *Annals of neurology* 82, 409–418.
- Massimini, M., Huber, R., Ferrarelli, F., Hill, S., Tononi, G., 2004. The sleep slow oscillation as a traveling wave. *Journal of Neuroscience* 24, 6862–6870.
- Mensen, A., 2018. Swa-Matlab. GitHub.
- Mensen, A., Khatami, R., 2013. Advanced EEG analysis using threshold-free cluster-enhancement and non-parametric statistics. *Neuroimage* 67, 111–118.
- Mensen, A., Riedner, B., Tononi, G., 2016. Optimizing detection and analysis of slow waves in sleep EEG. *Journal of neuroscience methods* 274, 1–12.
- Monk, T.H., Buysse, D.J., Rose, L.R., 1999. Wrist actigraphic measures of sleep in space. *Sleep* 22, 948–954.
- Perfetti, B., Moisello, C., Landsness, E.C., Kvint, S., Pruski, A., Onofrij, M., Tononi, G., Ghilardi, M.F., 2010. Temporal evolution of oscillatory activity predicts performance in a choice-reaction time reaching task. *Journal of Neurophysiology* 105, 18–27.
- Plante, D.T., Goldstein, M.R., Cook, J.D., Smith, R., Riedner, B.A., Rumble, M.E., Jelenchick, L., Roth, A., Tononi, G., Benca, R.M., others, 2016. Effects of partial sleep deprivation on slow waves during non-rapid eye movement sleep: a high density EEG investigation. *Clinical Neurophysiology* 127, 1436–1444.
- Thirsk, R., Kuipers, A., Mukai, C., Williams, D., 2009. The space-flight environment: the International Space Station and beyond. *Canadian Medical Association Journal* 180, 1216–1220.
- Tononi, G., Cirelli, C., 2014. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron* 81, 12–34.
- Van Dongen, H., Maislin, G., Mullington, J.M., Dinges, D.F., 2003. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 26, 117–126.
- Vyazovskiy, V.V., Harris, K.D., 2013. Sleep and the single neuron: the role of global slow oscillations in individual cell rest. *Nature Reviews Neuroscience* 14, 443.
- Vyazovskiy, V.V., Olcese, U., Hanlon, E.C., Nir, Y., Cirelli, C., Tononi, G., 2011. Local sleep in awake rats. *Nature* 472, 443.
- Yamamoto, N., Otsuka, K., Kubo, Y., Hayashi, M., Mizuno, K., Ohshima, H., Mukai, C., 2015. Effects of long-term microgravity exposure in space on circadian rhythms of heart rate variability. *Chronobiology international* 32, 327–340.
- Yates, B., Kerman, I., 1998. Post-spaceflight orthostatic intolerance: possible relationship to microgravity-induced plasticity in the vestibular system. *Brain research reviews* 28, 73–82.