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Microgravity effect and efficacy of high intensity jump training on default mode network alterations during light sleep on extreme environments

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Introduction

Human ambition to explore the outer space is expected to result soon in manned missions to Mars. However, such long-term spaceflights pose significant challenges regarding adaptation of human physiology on isolated and extreme environments [1]. Cognitive performance and mental well-being are key factors for the accomplishment of such missions and they are both found to be dependent on sleep quality [2]. Previous studies have demonstrated that sleep duration is decreased due to increased arousal and awakening events, leading to a reduction of deep sleep and rapid eye movement (REM) sleep stages [1, 3]. These findings altogether result in deterioration of sleep efficiency which may lead to fatigue, irritation or even to decline of cognitive performance, jeopardizing thus the crew health.

Space agencies and academia lately began to investigate the detrimental effects of microgravity and whether a countermeasure would neutralize its impact on central nervous, neuromuscular and cardiovascular system through a timely efficient manner [4]. Efficient sleep in space remains a research topic of great interest but also an unresolved challenge. Sleep macro-architecture (duration, efficiency, stage cyclicity and duration) is often examined through bed-rest studies and more scarcely by actigraphy or even polysomnographic recording during space missions [3]. However, contemporary mathematical tools derived from statistics and graph theory could expand our knowledge on sleep dynamics and help the neuroscientific to understand how the microgravity influences sleep and whether a potential countermeasure may induce neuroplasticity effects in order to compensate for weightlessness. So, functional neuroimaging analysis may track the co-operative activity of brain regions and networks activated during sleep [5].

Among them the Default Mode Network (DMN) has been on the focus of several studies, since it is activated during resting-state conditions. It is consisted of several anterior and posterior nodes located in the cerebral cortex. The precuneus, posterior cingulate cortex, parietal regions, parahippocampal gyri, medial prefrontal (MPFC) and orbitofrontal (OFC) cortices, are the most important DMN sub-systems [6]. Some of the aforementioned nodes have been found to be important during both normal sleep and sleep disorders such as insomnia [7, 8].

Aiming to investigate how sleep is affected by microgravity effect and whether an exercise-based (high intensity jumps) countermeasure would minimize the impact of weightlessness, we studied the sleep macro-architecture of participants involved in a head-down tilt (6°) bed-rest study. We gathered polysomnographic (PSG) data and we estimated the cortical activations of the DMN regions of interest (ROIs) during light sleep (N1 and N2 NREM sleep stages). Our hypotheses would be that the microgravity would change the intra-network (DMN) functional connectivity (FC) by sustaining activation of specific ROIs, which are also active in sleep disorders. The countermeasure would provide only partial efficacy by relative amelioration of the previous hypothesis in the training group. These assumptions would be tested on both alpha (8-12 Hz) and beta (18-22 Hz) waves. We focused on these rhythms because alpha activity during N1 reflects the drowsiness level due to sleep onset and the feasibility to transit to deeper sleep stages. Beta waves are indicative of the arousal level and would quantify sleep quality deterioration. We tested our hypotheses under a novel framework of identifying statistically significant edges and quantifying optimal network performance through graph metrics.

Materials and Methods

The project aimed to investigate the microgravity effect and the robustness of reactive sledge jumps (RSL countermeasure) on sleep quality. It was part of an ESA funded, head down tilt (HDT) of 6° bed rest study that was hosted in the ‘envihab’ premises of the German Aerospace Center (DLR) in Cologne, Germany [4]. The project investigated the impact of long-term space flights (60 days) on 23 healthy male adults ranging from 23 to 45 (mean: 29±6 years). They were assigned either to a control or training group and were healthy as confirmed by detailed medical and psychological examination. They were informed for the study and signed a written informed consent form (Kramer et al, 2017). The ethics committee of the Northern Rhine Medical Association (Arztekammer Nordrhein) in Duesseldorf, Germany Strahlenschutz) approved the study.

The present study employed PSG entire night recordings obtained during baseline (14 days before study onset /BDC-14) and the 21st night after the head down tilt period (HDT21). We employed different recording mo- modalities such as electroencephalography (EEG), electrocardiography (ECG), chin electromyography (EMG), vertical & horizontal electrooculography during sleep. The EEG was obtained through 19 electrodes placed according to the 10-20 international system. Bipolar ECG electrodes were placed below and above the chest. Two EMG electrodes were placed on the masseter muscles and there were two bipolar electrodes placed above/below the right eye and on the outer acanthus of both eyes.

An elaborate pre-processing pipeline was adopted in order to obtain high quality, artifact-free data. So, we first removed baseline and then digitally filtered the biosignals through Butterworth filters of 2nd order filters as described in [9]. The filters retained frequencies ranging from 0.5-50 Hz. Industrial noise centered at 50 Hz and their harmonics were also rejected. Then, we performed Independent Component Analysis (ICA) for identifying and eliminating artifactual sources. These steps were performed through the EEGLAB graphical interface ran under Matlab environment [10]. Artifact-free data were epoched and staged by two sleep experts according to the suggestions of the American Association of Sleep Medicine [11]. Some participants were excluded from further analysis due to excessive noise particularly on N1 stage, resulting in 18 participants (8 in control group).

Estimation of cortical activity was performed through the Brainstorm interface [12]. Firstly, generic anatomy head modeling was performed by means of Open MEEG Boundary Elements Method (BEM head model). Then inverse solution through sLORETA was performed by 15000 fixed dipoles. Based on a-priori knowledge from previous neuroimaging studies we defined 18 DMN ROIs, whose activations were used for further analysis (see Figure 1). These data were then subjected to FC analysis through the Phase Lag Index (PLI) implemented by the HERMES toolbox [13]. Then, FC matrices were used as input in both Network Based Statistics (NBS) [14] and Brain Connectivity Toolbox (BCT) [15]. Finally, visualization of brain networks was performed through the BrainNet software [16].

Region	Label	X	Y	Z	Nodes
Left Posterior Inferior Parietal Lobe	LpiPL	-51	-67	26	N1
Right Posterior Inferior Parietal Lobe	RpiPL	52	-64	27	N2
Orbitofrontal Cortex	OFC/vACC	-2	62	-17	N3
Brodmann Area 8	dMPFC BA8	-16	49	43	N4
Brodmann Area 9	dMPFC BA9	19	54	36	N5
Left Dorsolateral Prefrontal Cortex	L DLPFC	-45	19	44	N6
Right Dorsolateral Prefrontal Cortex	R DLPFC	45	18	43	N7
Left Parahippocampal Gyrus	L PHG	-13	-35	-5	N8
Right Parahippocampal Gyrus	R PHG	12	-35	-5	N9
Left Inferior Temporal Cortex	L ITC	-62	-16	-20	N10
Right Inferior Temporal Cortex	R ITC	62	-15	-22	N11
Medial Prefrontal Cortex	MPFC	-1	49	-5	N12
Posterior Cingulate Cortex	PCC	-6	-52	-40	N13
Precuneus	Precuneus	0	-56	28	N14
Left Precuneus/Posterior Cingulate Cortex	3IL	-10	-66	24	N15
Right Precuneus/Posterior Cingulate Cortex	3IR	10	-66	24	N16
Left Lateral Parietal	LLP	-46	-70	36	N17
Right Lateral Parietal	RLP	46	70	36	N18

Figure 2: Description of DMN ROIs

The BCT contains scripts for quantifying optimal network performance (small-world property, efficiency), local information processing (mean cluster coefficient) and information flow (characteristic path length). Data were analyzed using SPSS Version 23. As the normality assumption was met, we conducted two-way repeated measures ANOVA with group (controls & sledge) as the between subject factor, sleep stages (N1 & N2) and time phases (BDC-14 & HDT21) as the within subject factors. Using Pillai' trace, we tested if there were statistically significant main effect of time and time by group interaction ($p<0.05$) . Then we performed Bonferroni post hoc comparisons between stage-time and group-time respectively.

Results

Regarding the N1 stage, there was a statistically significant interaction (p=0.0014) in alpha waves among the experimental phase (BDC-14 vs HDT21) and the experimental group (control vs sledge). There were 58 statistically significant edges. Further analysis revealed that this finding was due to functional reorganization of the control participants (p=0.028), since 89 edges were found to statistically increase their strength during the HDT21 phase. Moreover, there was an increase in FC for 21 edges for both groups (main effect of time) during HDT21 in beta waves (p=0.007) These findings are visualized in Figure 2.

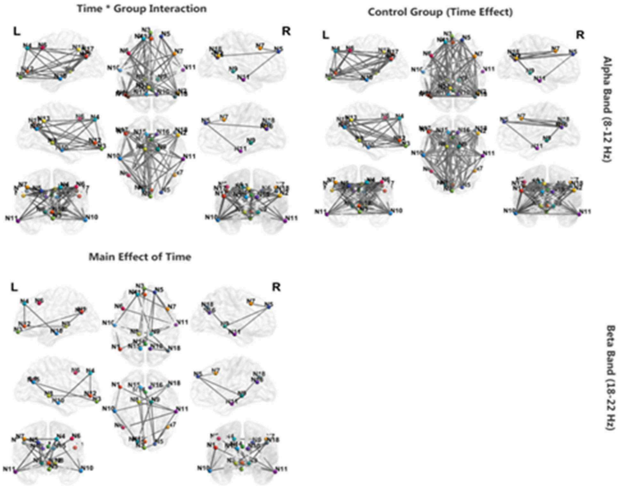

Figure 1: Statistically significant edges on N1 sleep stage for alpha (upper row) and beta band (lower row)

Regarding the N2 stage, there was no difference in alpha activity. However, there was a statistically significant time × group interaction for beta rhythm (p=0.0303) for a sub-network of 56 DMN edges. Post-hoc analysis for the control group revealed a significant (p=0.0464) decrease for 9 edges. On the contrary, there was an increase for 42 edges (p=0.0048). These results are displayed in Figure 3.

There were also statistically significant differences (main effect of time) in network properties within alpha rhythm, regarding the characteristic path length [F (1, 16)= 7.608; p=0.014; n_p^2 =0.322]. Bonferroni post-hoc comparisons for the N1 stage showed significant differences between

BDC-14 (21.130) and HDT21 (16.853) for characteristic path property, p=0.009. Regarding beta rhythm, there was also a statistically significant main effect of time in characteristic path length [F (1, 16)= 13.916; p=0.002; n_p^2=0.465]. Bonferroni post-hoc comparisons for the N1 stage showed significant differences between BDC-14 (23.835) and HDT21 (18.982) for characteristic path property, p=0.012. There were also statistically significant main effects of time in density, efficiency, mean cluster coefficient & small-world properties [F (1, 16)= 11.749 ; p=0.003; n_p^2=0.423], [F (1, 16)= 11.398; p=0.004; =0.416], [F (1, 16)= 10.813 ; p=0.005; n_p^2=0.403] and [F (1, 16)= 4.573; p=0.048; n_p^2=0.222] respectively. Bonferroni post-hoc comparisons for the N1 stage showed significant differences between BDC-14 (0.041) and HDT21 (0.056), p=0.014, BDC-14 (0.053) and HDT21 (0.070), p=0.022, BDC-14 (0.033) and HDT21 (0.046), p=0.011, BDC-14 (44.765) and HDT21 (34.154), p=0.005 for density, efficiency, mean cluster coefficient and small world property respectively.

Regarding alpha rhythm, there was a statistically significant time by group interaction in characteristic path length [F (1, 16)= 5.270 ; p=0.036; n_p^2=0.248]. Bonferroni post-hoc comparisons for controls showed significant differences between BDC-14 (21.931) and HDT21 (17.776) for characteristic path property, p=0.004. Regarding beta rhythm, there was a statistically significant time by group interaction in small world property [F (1, 16)= 4.720 ; p=0.045; n_p^2=0.228]. Bonferroni post-hoc comparisons for sledge showed significant differences between BDC-14 (60.945) and HDT21 (47.081) for small world property, p=0.005.

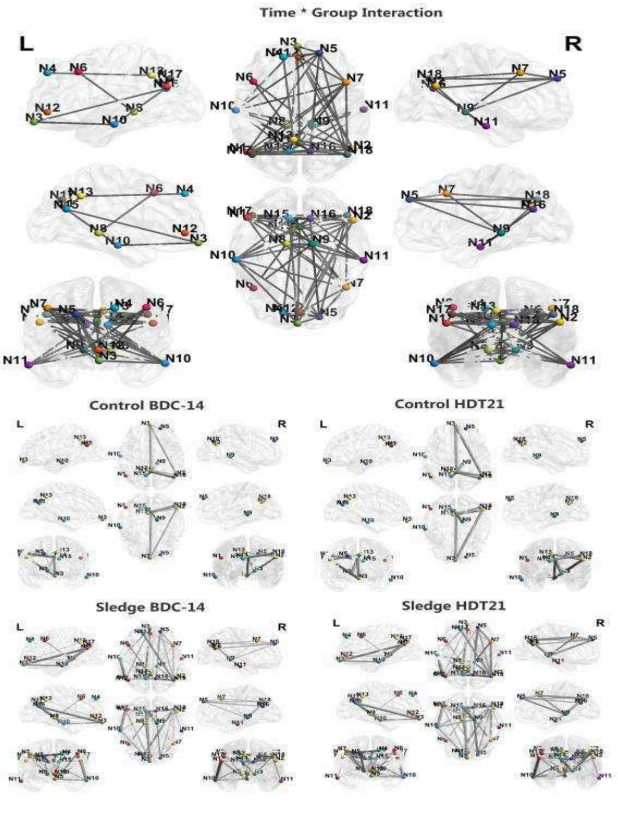

Figure 3: Statistically significant edges on N2 sleep stage for beta waves regarding time ×group interaction (first row) , control (second row) and sledge group (third row)

Discussion

The study findings are in line with previous clinical research on insomnia patients demonstrating sustained activation of anterior cortical regions [7]. More specifically, the participants of the training group did not increase their DMN connectivity values for the alpha band during HDT21, whereas the opposite pattern was observed for the control group, in which there was preserved activity of anterior regions (e.g. OFC, MPFC, dMPFC) either to themselves or with posterior regions (e.g. precuneus and PCC) [8]. This finding is of particular importance since prefrontal regions are among the first ones that inhibit their activity during sleep onset [17], providing evidence for the partial efficacy of the proposed countermeasure.

Sleep disorders such as insomnia and increased number of awakening events are associated with hyperarousal and elevated activity in the beta rhythm [18]. Similarly we observed for that frequency band a significant main effect of time, regardless the group assignment. This finding may indicate a detrimental microgravity impact on sleep quality which could not be reversed by the proposed training. So, investigation of robust countermeasures especially in case of long-term spaceflights remains an unresolved challenge.

Brain network analysis through graph theory indicated that sleep onset (N1 stage) was affected by weightlessness (main effect of time) through shortest characteristic path length in both alpha and beta range. Alterations within the beta band involve increases in density, efficiency and mean cluster coefficient. There was also a prominent decrease in small-world property. The findings support the hypothesis that microgravity increases arousal events through increases DMN activation within the beta band [7, 18]. The partial efficacy of the sledge training was also demonstrated by the time × group interactions showing decrease of characteristic path length for the control group in alpha band and for the sledge in the beta band. So, there is a first evidence that exercise has a beneficial role on sleep onset and transition to N2 stage but then fails to prevent arousal and awakening events.

Our analysis was based on the computation of the inverse solution from 19 electrodes directly located on the participants' head according to the 10-20 International System. Then we modelled the head anatomy with a generic model consisting of 15000 dipoles. The aforementioned approach is usually avoided in modern neuroimaging research since it involves the ill-posed solution of too many equations with data derived from only a few electrodes. Therefore, it is preferable either to employ high-density EEG or to recruit functional Magnetic Resonance Imaging (fMRI). However, preserving sleep quality during these examinations may be unrealistic. On the other hand the present study involves an extreme environment, which poses additional limitations for instrumentation. The experimental framework motivated us to employ a cost-effective approach. Previous studies have also performed cortical estimation through a small number of electrodes and have published results of considerable scientific merit [19-21]. Our findings are also verified by previous studies investigating sleep disorders in clinical populations on earth, enhancing thus the validity of our methodology. However, we should be conservative in their interpretation.

The novelty of the proposed methodological framework is the investigation of the DMN activity during light sleep at extreme environments. DMN is regarded as an important network for cognitive functioning, whereas sleep is a basic physiologic procedure which is directly related to mental and physical well-being. Therefore, early identification of diminished DMN activity may be a valuable biomarker of sleep quality. Our approach indicated DMN disturbances on the light sleep which is regarded as a hallmark of the transition to slow-wave and REM stages. However, it should be further expanded by deep sleep stages to acquire a more concrete view of the training and microgravity effect on sleep quality. Finally, we should note that the DMN activity was assessed by two independent analysis approaches. The first one employs a general linear model (GLM) to find network edges that differ in a statistically significant way between experimental conditions. The second approach uses graph theory to quantify the network performance. Results from both approaches are similar, enhancing thus the validity of our findings.

Concluding, we aim to establish a neuroscientific framework for either validating the efficacy of potential countermeasures for long-term spaceflights or early identifying sleep disorders in space crews or clinical applications on earth. The proposed framework employs contemporary tools derived from functional connectivity and statistics in order to shed light into the effect of microgravity and/or training on the DMN during sleep.

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