RESEARCH ARTICLE

The influence of microgravity on cerebral blood flow and electrocortical activity

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Abstract

Changes in gravity conditions have previously been reported to influence brain hemodynamics as well as neuronal activity. This paper attempts to identify a possible link between changes in brain blood flow and neuronal activity during microgravity. Middle cerebral artery flow velocity (MCAv) was measured using Doppler ultrasound. Brain cortical activity (i.e., cortical current density) was measured using electroencephalography. Finger blood pressure was recorded and exported to generate beat-by-beat systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), and cerebrovascular conductance index (CVCi). Seventeen participants were evaluated under normal gravity conditions and microgravity conditions, during 15 bouts of 22-s intervals of weightlessness during a parabolic flight. Although MAP decreased and CO increased, MCAv remained unchanged in the microgravity condition. CVCi as the quotient of MCAv and MAP increased in microgravity. Cortical current density showed a global decrease. Our data support earlier data reporting a decrease in the amplitude of event-related potentials recorded during microgravity. However, the general decrease in neural excitability in microgravity seems not to be dependent on hemodynamic changes.

Keywords Parabolic flight · EEG · Transcranial Doppler ultrasound · MCA

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Introduction

In the last decades there has been a number of studies reporting on cognitive impairment during space flight (Fowler and Manzey 2000; Bock et al. 2001; Heuer et al. 2003), (Money and Cheung 1991; Bock et al. 1992, 2003; Lackner and DiZio 1992; Hermsdörfer et al. 1999, 2000; Jüngling et al. 2002; Augurelle et al. 2003). Unfortunately those studies barely differentiated between a primary effect of weightlessness and a secondary effect of the stressful environment. Indeed, deteriorations in cognitive performance were often monitored in transition phases (e.g., start or end) of missions, suggesting a possible impact of stress. In the latter years, experimental protocols on board of the International Space Station (ISS) were adjusted in order to further investigate gravity-related modulation of neural processing, e.g., visual perception: (Cheron et al. 2014). Simultaneously, a number of neuroscientific experiments has been conducted on board of parabolic flight (Saradjian et al. 2014) allowing to discriminate between primary effects of weightlessness and secondary effects of stress and/or isolation. Although parabolic flights are well known to induce stress (Schneider

et al. 2007, 2009), too, an experiment designed to assess performance in the weightlessness (0G) and normal gravity (1G) phase of a parabolic flight, allows to distinguish between primary effects of weightlessness and stress, as the stress level—except of acute motion sickness—will remain constant with these two phases only 20 s apart.

Recently, we were able to show that during short periods of microgravity, the amplitude of event related potentials tend to be lower during microgravity than in normal gravity (Wollseiffen et al. 2015). This was accompanied by a decrease in reaction time, which was found to be more prominent with increasing task complexity, indicating that less cortical resources seem to be necessary to perform a task in 0G in comparison to a 1G condition (Wollseiffen et al. 2015). As these data have been gathered during a parabolic flight comparing 1G and 0G inflight, any possible effect of stress could be ruled out (Schneider et al. 2007), especially as the phenomenon was observable for novices as well as for experienced flyers and was independent on anti-nausea medication (scopolamine).

As brain activity is dependent on oxygen delivery to the brain, one possible explanation for the observed neurocognitive benefit in 0G could be the increase in cerebral blood volume during microgravity which has been shown previously using near-infrared spectroscopy (NIRS) (Schneider et al. 2013). Although there is an increase in cerebral blood volume during microgravity, Ogoh et al reported no increase in cerebral blood flow during microgravity, measured using Doppler ultrasound (Ogoh et al. 2015), indicating a blood pooling in the brain caused by a decreased outflow (drainage).

This study aims to identify a possible relationship between an increase in cerebral blood flow, quantified as middle cerebral artery velocity, and brain cortical activity during microgravity. It is hypothesized that an increase in cerebral blood flow during microgravity will be mirrored by a decrease of brain cortical activity.

Materials and methods

Participants and procedure

European Space Agency (ESA) and German Space Agency (DLR) parabolic flights take place at the Bordeaux International Airport (F) aboard the A310 ZeroG. A parabolic flight maneuver is characterized by gravitational changes from 1G to 1.8G, to 0G (weightlessness approximately 22 s), and back to 1.8G, and finally to 1G. One campaign consists of 3–4 flight days, and on each flight day 30 experimental parabolas are completed. During four parabolic flight campaigns scheduled between November 2017 and April 2018, data from 17 participants were recorded [female:

$n = 8$, with a mean age of 37 ± 11 years (mean ± SD), height 170 ± 5 cm, weight 66 ± 12 kg; male: $n = 8$, with a mean age of 36 ± 12 years, height 181 ± 8 cm, weight 83 ± 9 kg]. All participants, either staff members or students of the involved universities, underwent a pre-campaign clinical examination and provided informed consent. The protocol for the study was approved by the Research Ethics Committee of the University de Caen, in accordance with the Declaration of Helsinki.

For the flight phase of the study, participants were seated for 15 parabolas in a relaxed position in front of a 27-in. iMac screen and were firmly and comfortably strapped to the floor in order to avoid artifacts caused by stabilization movements. During the 1G and the 0G phases participants performed a 20-s cognitive task, which consisted of a mental arithmetic task (problem solving). Results of this task are not being reported here.

During the 15 parabolas participants were continuously monitored by electroencephalography (EEG), transcranial Doppler ultrasound and finger blood pressure. Whereas EEG has been established as suitable method to monitor brain electrocortical activity in extreme environments and parabolic flights (Marusic et al. 2014), the combination with Doppler ultrasound so far is unique.

For data analysis, start and end of each task in 1G and 0G was triggered to the EEG as well as the transcranial Doppler. This signal was used offline for identifying the 15 trials of 22 s of relevant data in 1G and 0G that were used for further analysis.

Cerebral blood flow, blood pressure, cerebrovascular conductance and cardiac output

Middle cerebral artery flow velocity (MCAv) was assessed using transcranial Doppler ultrasonography (TCD). A 2-MHz probe (Multi-Dop, Compumedics DWL, Germany) was placed over the right temporal ultrasound window, fixed at a constant angle and secured with an adjustable headband (Spencer Technologies, Seattle, WA). The MCAv signal was identified according to standardized criteria guided by signal depth, velocity and wave characteristics (Aaslid et al. 1982; Willie et al. 2011). Depth, sample volume and signal power remained constant throughout the flight after an optimal MCAv signal was established. Using these guidelines this technique is a valid and reliable index of cerebral blood flow velocity. Mean MCAv was calculated from the envelope of the velocity tracing using a weighted mean (1/3 maximum + 2/3 minimum) (Skow et al. 2013). Due to poor MCAv signal quality, data from two participants could not be included in the analysis. Blood pressure was measured continuously at the left middle finger using photoplethysmography (Finometer MIDI, Finapres Medical Systems, Amsterdam, The Netherlands). Finger blood pressure was

exported to generate beat-by-beat systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP = 1/3 systolic blood pressure + 2/3 diastolic blood pressure), heart rate (HR) and cardiac output (CO) (ADInstrument, PowerLab 8/35, Bella Vista, NSW, Australia). Non-invasive cardiac output was calculated offline from finger BP, where age, gender, body height and body weight were taken into consideration. This technique has been demonstrated to be a valid and reliable index of cardiac output (van Lieshout et al. 2003; Truijen et al. 2010; Bartels et al. 2011). Cerebrovascular conductance index (CVCi) of the MCA flow territory was calculated by dividing MCAv by MAP. End-tidal carbon dioxide, a key driver of MCAv was not collected, as end-tidal carbon dioxide remained unchanged during parabolic flights (Ogoh et al. 2015). MCAv, MAP, HR, CO and a g-force sensor were simultaneously sampled at 1 kHz via an analog-to-digital converter and stored for offline analysis (LabChart Pro v7.3.7 and PowerLab, ADInstruments, Bella Vista, NSW, Australia). Time-aligned signals were resampled using a second-by-second (1 Hz) method for offline analysis. Mean responses for the 0G and 1G phases were calculated for each parabola and the average of all parabolas was used for data comparison.

EEG data collection and analysis

An EEG actiCAP (Brain Products GmbH, Munich, Germany) with 32 Ag–AgCI electrodes, arranged in the international 10–20 system at positions Fp1, Fp2, F3, F4, F7, F8, Fz, FC1, FC2, FC5, FC6, C3, C4, Cz, CP1, CP2, CP5, CP6, P3, P4, P7, P8, Pz, FT9, FT10, T7, T8, TP9, TP10, O1, O2 and Oz, was mounted on the participant's head prior to take off. Each electrode was referenced to a single reference electrode that was mounted in the triangle of FP1, FP2 and Fz. The ground electrode was located next to the reference electrode. Electrodes were filled with Electro-Gel™ (Electro-Cap International, USA) for optimal signal transduction. During the flight, impedance was kept below 10 kilo Ohm [kΩ] by refilling the electrodes with gel. The analog signal of the EEG was amplified, converted to digital signals and stored using a Brain Vision amplifier and RecView software (Brain Products GmbH, Munich, Germany). All recordings were monitored by a trained investigator.

EEG signals were analyzed offline using Brain Vision Analyzer 2.1 (Brain Products, Munich, Germany). After the application of low and high pass cut-off filters, a frequency range between 3 and 40 Hz remained for analyses (time constant 0.531 s; 48 dB/octave). Single channels exceeding an impedance of 10 kΩ were interpolated (order of splines: 4, maximal degree of Legendre polynomials: 10, default lambda: 1E-05). Following visual inspection, ocular correction using individual component analysis was applied to identify and eliminate blinks and horizontal eye movements.

Data were then segmented into 4-s epochs and an automatic artifact rejection was applied (gradient < 50 µV; max/min amplitude − 200 to 200 µV; lowest allowed activity in intervals 0.5 µV). For each condition and each participant signal-to-noise ratios were calculated (P_{signal}/P_{noise}). The similarity between P_{signal} and P_{noise} never exceeded 2%.

Finally, activity in the four lobes (frontal, parietal, occipital, limbic) and activity in the gyri supplied (Griffiths 2008) by the middle cerebral artery (MCA: inferior frontal gyrus, inferior parietal lobule, middle frontal gyrus, middle temporal gyrus, postcentral gyrus, precentral gyrus, superior temporal gyrus), anterior cerebral artery (ACA: cingulate gyrus, medial frontal gyrus, paracentral lobule, precuneus, superior frontal gyrus, superior parietal lobule) and by posterior cerebral artery (PCA: cuneus, inferior temporal gyrus, lingual gyrus, parahippocampal gyrus, uncus) was extracted and exported by using the built-in LORETA module of Brain Vision Analyzer 2.1 (Brain Products, Munich, Germany). Addressing the idea of an inverse solution, low-resolution electromagnetic tomography (LORETA) provides a three-dimensional distribution of brain electrical activity (the current density field). LORETA computes the smoothest of all possible neural current density distributions, where neighboring voxels have maximally similar activity. LORETA is a linear method; it calculates the current density at each voxel in the brain as the linear, weighted sum of scalp electrical potentials (Pascual-Marqui et al. 1994). The number of 32 electrodes used in this study is considered to be at the lower range necessary to perform a LORETA analysis—however, as we addressed only the major cortices and relevant gyri and did not perform an analysis based on individual voxels the number is considered appropriate.

Statistics

Statistical analyses were performed using STATISTICA version 7.1 (StatSoft, Tulsa, USA). Comparisons of cortical current density were performed using repeated measures ANOVA with the within-group factors of "localization" (frontal, parietal, occipital, limbic, hippocampus, MCA, ACA, PCA) and "gravity" (1G, 0G). Significant ANOVA effects at $p < .05$ were further analyzed using Fisher's least significance difference test (LSD). The effect of gravity on MCAv, MAP, SBP, DBP, HR, CO and CVC were compared using t tests.

Results

MCAv, BP, HR, CO, CVC data

Although 0G leads to a reduction in blood pressure (MAP $p < .001$; SBP $p < .001$; DBP $p < .001$, Fig. 1) and an increase
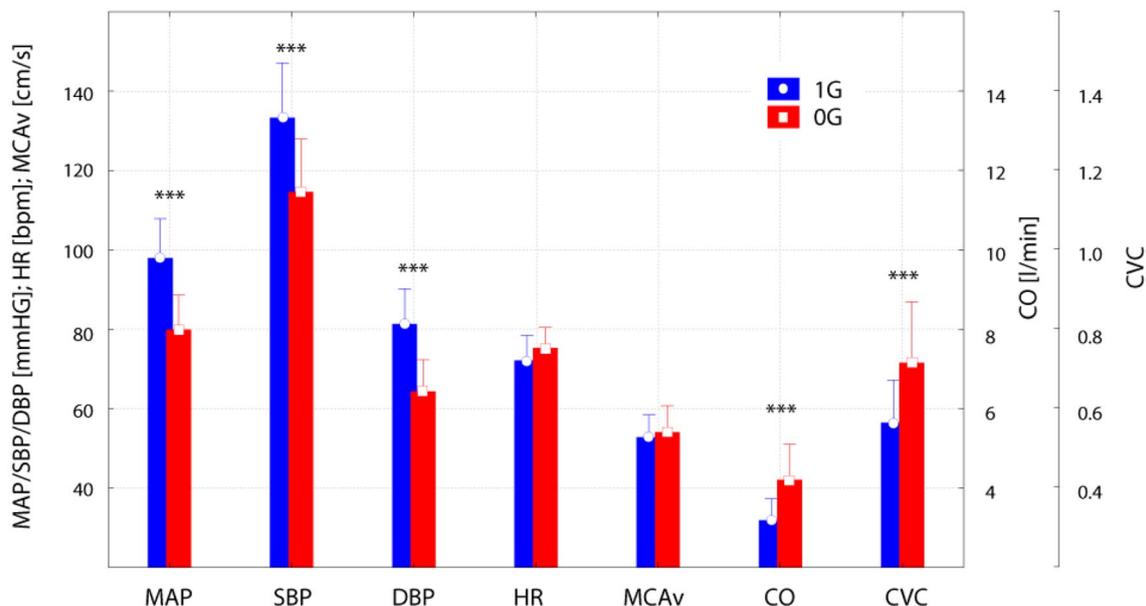
Fig. 1 Mean arterial pressure (MAP), systolic arterial blood pressure (SBP), diastolic arterial blood pressure (DBP), heart rate (HR), medial cerebral artery velocity (MACv), cardiac output (CO) and cerebrovascular conductance (CVC) averaged the 15 trials of 20 s of normal gravity (1G, blue) and microgravity (0G, red). Displayed are means $\pm$ 95% confidence intervals. ***$p < .001$ between 0G and 1G

in CO ($p < .001$, Fig. 1) compared to the 1G phases, the averaged MCAv response during 0G was not different compared to averaged MCAv response during 0G ($p = .28$, Fig. 1). Mean HR remained unchanged for the two gravitational levels ($p = .15$). Cerebrovascular conductance (CVC) as a quotient of MCAv and MAP was significantly increased in 0G ($p < .001$, Fig. 1).

EEG data

Analysis showed that there were statistically significant differences in the amount of regional activity ($F_{(7, 112)} = 98.80$; $p < .001$), and that mean cortical current density was significantly decreased in the 0G condition ($F_{(1, 16)} = 16.25$; $p < .001$). Interaction ($F_{(1, 112)} = 8.54$; $p < .001$) and post hoc analysis revealed that this decrease was not region specific, but a decrease of activity was found in all defined ROIs in the 0G condition (Fig. 2): frontal lobe ($p < .01$), parietal lobe ($p < .01$), occipital lobe ($p < .001$), limbic lobe ($p < .001$), hippocampus ($p < .001$), MCA supplied region ($p < .05$), ACA supplied region ($p < .05$) and PCA supplied region ($p < .001$).

Discussion

This study aimed to identify gravity-induced changes in cerebral blood flow, measured as middle cerebral artery velocity and brain cortical activity. In contrast to our

initial hypothesis, we could not observe an increase in cerebral blood flow during microgravity as MCAv remained unchanged in the 0G condition although mean arterial pressure decreased and cardiac output increased, which are important regulating factors of MCAv increased. Interestingly brain cortical activity was reduced globally in the 0G condition.

Both findings support previous data, describing no gravity-induced changes in MCAv during parabolic flight (Ogoh et al. 2015) and reduced electrocortical activity, specifically the P2 amplitude within the N1/P2 complex during microgravity (Wollseiffen et al. 2015).

Blood flow velocity

It is well known, that during microgravity a redistribution of blood volume causes blood pooling within the brain (Schneider et al. 2013) which most likely causes an increase in intracranial pressure (Lawley et al. 2017). This blood pooling is hypothesized to be dependent on three mechanisms: first an increase in intracranial inflow caused by an increased flow through the carotid arteries as well as extra carotid flow (Ogoh et al. 2015), secondly by an increase in cardiac output during 0G (Norsk et al. 2006) and finally by a missing drainage of blood from the brain due to a loss of the hydrostatic gradient in 0G (Schneider et al. 2013).

The hemodynamic responses presented in this study allow to further discriminate between these effects. The blood pooling in the head (Schneider et al. 2013) reduces

Fig. 2 Cortical current density over the 15 trials of 22 s of the cognitive task performed in 0G (red) and 1G (blue). Displayed are means ± 95% confidence intervals. *$p < .05$, **$p < .01$, ***$p < .001$ between 0G and 1G. *MCA* middle cerebral artery, *ACA* anterior cerebral artery, *PCA* posterior cerebral artery
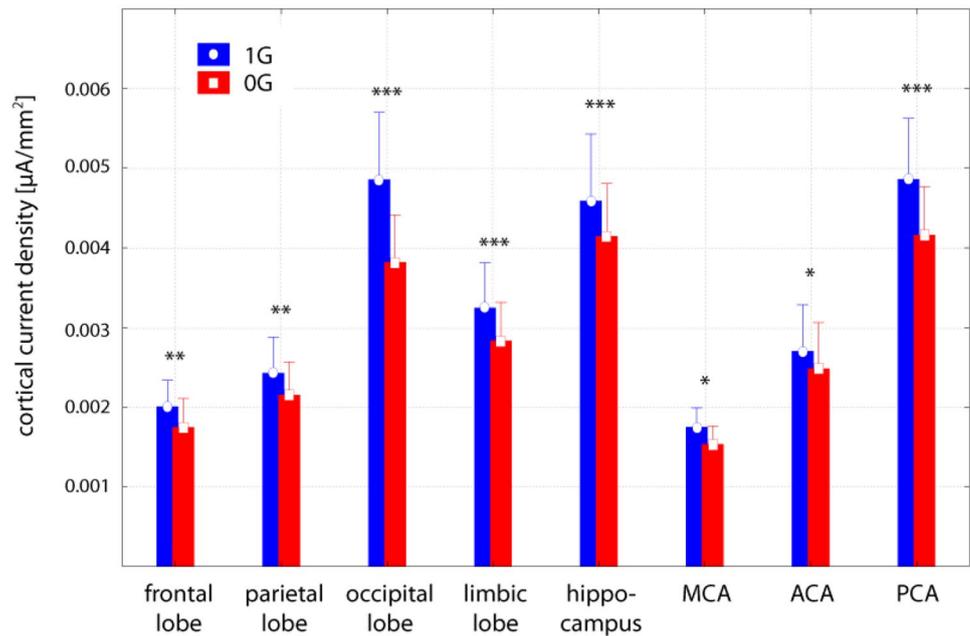
the amount of blood volume in the upper and lower extremities and leads to a reduction in MAP measured at heart level. Due to an increased venous return in microgravity, CO increased. Interestingly these two adaptations, a decrease in MAP and an increase in CO thwart each other, so that MCAv remains unchanged during 0G compared to 1G, which is in accordance with previous experiments (Ogoh et al. 2015). As a consequence of the reduction in MAP and the need for preservation of MCAv, cerebrovascular conduction was increased during 0G.

From the data presented here, it might be concluded, that measuring inflow of blood to the brain might not be an appropriate method to quantify the volume of blood that is available within the brain. Although MCAv is not increasing, the volume of blood within the brain and therefore intracranial pressure is increasing (Lawley et al. 2017), which is probably due to the loss of the hydrostatic gradient and the missing drainage from the blood.

Electrocortical activity

The decrease in electrocortical activity across all brain regions is completely uncoupled from the inflow to the brain. Unfortunately, at this stage possible explanations can only be speculative and further research is necessary to untangle this phenomenon. Wollseiffen et al. (2015) discussed a possible influence of task complexity or motivational aspects of performance. Given the global and task-independent decrease of electrocortical activity, this explanation can be ruled out. Further experiments should aim to identify the role of an increased intracranial pressure on neuronal activity especially as in vivo and in vitro experiments (Kohn and

Ritzmann 2018) identified changes in membrane viscosity caused by increased pressure as a source of a reduced resting potential of approximately 3 mV (Kohn 2013), which reduces the action potential difference between the resting potential and the AP threshold.

Conclusion

Data presented here allow a complete new view on the effects of weightlessness on neurocognitive performance. Together with the previous publication of Wollseiffen et al. (2015), there is good reason to speculate that the central nervous system benefits from a weightlessness situation. However: the underlying mechanism as well as possible long-term effects remain unknown and need further research. Also the role of exercise needs to be considered within this context.

Compliance with ethical standards

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