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RESEARCH ARTICLE

Neurophysiological, neuropsychological, and cognitive effects of 30 days of isolation

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Abstract
The increasing demand of space flights requires a profound knowledge of the chronologic reactions of the human body to extreme conditions. Prior studies already have shown the adverse effects of long-term isolation on psycho-physiological well-being. The chronology of the effects and whether short-term isolation periods already lead to similar effects has not been investigated. Therefore, the aim of the current study was to investigate the effects of short-term isolation (30 days) on mood, cognition, cortisol, neurotrophic factors, and brain activity. 16 participants were isolated in the Human Exploration Research Analog at NASA for 30 days. 17 non-isolated control participants were tested simultaneously. On mission days − 5, 7, 14, 28, and + 5, multiple tests including the Positive and Negative Affect Schedule-X and cognitive tests were conducted, and a 5-min resting electroencephalography was recorded. A fasted morning blood drawing was also done. Increased stress was observed via augmented cortisol levels during the isolation period. Activity within the parietal cortex was reduced over time, probably representing a neural adaptation to less external stimuli. Cognitive performance was not affected, but rather enhanced in both groups. No further significant changes in neurotrophic factors BDNF/IGF-1 and mood could be detected. These results suggest that 30 days of isolation do not have a significant impact on brain activity, neurotrophic factors, cognition, or mood, even though stress levels were significantly increased during isolation. Further studies need to address the question as to what extent increased levels of stress do not affect mental functions during isolation periods.

Keywords Isolation · Cortisol · Neurotrophic factors · Brain activity · Mood · Cognition

Abbreviations

HPA	Hypothalamic–pituitary–adrenal axis
BDNF	Brain-derived neurotrophic factor
IGF-1	Insulin-like growth factor 1
LORETA	Low-resolution brain electromagnetic tomography
HERA	Human exploration research analog
IG	Isolation group
CG	Control group
MD	Mission day
PANAS-X	Positive and negative affect schedule-X
GPA	General positive affect
GNA	General negative affect
EEG	Electroencephalography
ACTH	Adrenocorticotropic hormone
PFC	Prefrontal cortex

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Introduction

Since there is an increasing demand of space flights to chart new territories as well as a planned manned mission to Mars, the issues accompanied during long-term space flights have become a central topic in space research (Bachman et al. 2012). Long-term space flights are a significant challenge for crewmembers due to stressful environmental conditions (Basner et al. 2014) which can be described as isolated, confined, and hostile (Palinkas 2007). Even if space flights represent state-of-the-art technological progress, isolation is still a major stressor and, therefore, a justified present concern, as it impairs regulation of mood, cognitive performance, stress hormones, neurotrophic factors, and brain cortical activity (Golden et al. 2009; Friedler et al. 2015; Cacioppo et al. 2015; O'Keefe et al. 2014; Schneider et al. 2010). The current study makes use of a short-term isolation design to overcome several limitations which arise during long-term isolation studies (e.g., very low number of participants, long gaps between time of measurement). Here, we tried to answer the question if 30 days of isolation already have a significant impact on the abovementioned parameters and to further provide essential information about the chronology of potential impairments.

It is already well established that mood is affected during long-term spaceflights representing a form of social isolation (Gabriel et al. 2012). Even if it is difficult to quantify the effects of social isolation during spaceflights (for definition, see Cacioppo and Cacioppo 2014), prior research conducted on this topic revealed that isolation in small groups such as during spaceflights increases the perception of loneliness, which is further related to a decrease in well-being (van Baarsen et al. 2009). Studies investigating the direct effects of social isolation showed impaired self-regulation of hedonistic processes (Baumeister et al. 2005), which is the pursuit of pleasure and positive emotions under the absence of negative emotions (Kringelbach and Berridge 2010). However, positive emotions are a key psychological component, as they enhance the ability to cope with stressful events (Tugade and Fredrickson 2004). Considering this aspect of preserving mood during spaceflight is of high importance. Nevertheless, it is still not known when mood impairments occur and if they are already present during short-term isolation.

However, it is not only the level of emotion that is affected. Mood and cognition are strongly linked, where altered states of mood during isolation, such as feelings of loneliness have been shown to be a predictor for reduced cognitive performance (Tilvis et al. 2004; Wilson et al. 2007). For instance, Cacioppo et al. (2000) found that executive function was impaired in lonely compared to nonlonely individuals. This finding could be supported by a study from Campbell et al. (2006), demonstrating that brain areas related to executive function are less active in socially excluded participants during a math problem task. This is in line with mild decrements reported for problem solving during an 8-month Antarctic analog study (Sauer et al. 1999). Furthermore, working memory, assessed via a classic match-to-sample task, was impaired over the first 4 months of Antarctic residence (Reed et al. 2001). These observations are in line with a non-human isolation study, reporting deficits in spatial working memory (Huang et al. 2011). One of the most regularly mentioned cognitive concern during spaceflights, however, is the reduced ability to pay attention or concentrate. These functions are, among others, fundamental to handle all the necessary tasks during a space mission (Strangman et al. 2014). The Mars 520 isolation study provided additional evidence for attentional performance deficits (Basner et al. 2013). Currently, there is no evidence of the effects of short-term isolation on cognitive function, which, however, is essential to understand to be prepared for appropriate countermeasures during the first weeks of spaceflights.

However, the mechanisms underlying cognitive impairment during spaceflights are still not well understood. One potential explanation for cognitive impairments might be disrupted stress hormonal regulation via an overstimulation of the hypothalamic–pituitary–adrenal axis (HPA axis) during longer periods of isolation. This has already been shown in prior long-term isolation investigations (Jacubowski et al. 2015; Chouker et al. 2002). The relevant question, up to which point of isolation hormonal regulation is intact and when it becomes disrupted, is still a matter of debate. This question becomes even more important in regard to the adverse effects of psychosocial stress on neurotrophic factors which are highly associated with cognitive function. There is growing evidence that psychosocial stress can cause damage and atrophy in certain brain areas, such as the hippocampus and the prefrontal cortex (PFC) (Duman and Monteggia 2006); Liston et al. 2009). One underlying mechanism might be due to a decrease of brain-derived neurotrophic factor (BDNF) in these areas, which is an important regulator for neurogenesis and neuroplasticity. Different studies could demonstrate reduced BDNF levels during social isolation (Barrientos et al. 2003; Gong et al. 2017). Insulin-like growth factor 1 (IGF-1), a polypeptide hormone, showed positive effects on cell proliferation and neurogenesis in the adult brain (Anderson et al. 2002). However, psychosocial stress might also decrease expression of IGF-1 via inhibiting effects of upregulated glucocorticoid levels (Anderson et al. 2002; Epel 2009). If neurotrophic factor regulation is already disturbed during short periods of isolation still needs to be investigated.

Changes within the brain have not only been proven on a molecular level. Cortical activity has been shown to be altered when individuals are isolated (Schneider et al. 2010). These observed changes during isolation have been related to the adaption of the brain to less sensory input. For instance, Schneider et al. (2010) reported a depression of cortical activity as a result of long-term confinement. These changes have been reported on a more global level and gave a first understanding to what happens in the brain during long-term isolation. Nevertheless, to draw inference about emotional and cognitive processes in regard to altered brain activity, a more specific localization to certain brain areas is required. Therefore, we focused on the effects of short-term isolation on both prefrontal and parietal cortex because of their high contribution in emotional processing and integrating different sensory modalities to form multiple cognitive functions (Andersen 1997; Brodt et al. 2016).

In consideration of the abovementioned physiological and (neuro)psychological risk factors of isolation and the increasing demand of space flights to chart new territories, investigation of neuropsychological and neurophysiological effects of spaceflight is essential in regard to astronauts´ health. Although a lot of research on this issue has been conducted, it is limited by the very low number of human subjects participating in most of the (long-term) studies. In addition, comparison of the previous studies showed that the replicability of the results is a huge issue, making a generalizability and practical implications for space missions difficult. Therefore, a larger data base is necessary to gather a better understanding of the human body and its reaction to isolation and confinement. Furthermore, the chronology of the effects during the initial days/weeks has barely been considered and it is unclear if impairments are already detectable within the first few days after exposure to isolation. It can be speculated that the first days and weeks of space and space-analog missions are even more sensitive or prone for health or performance issues due to multiple adaptation processes. Furthermore, taking previous observations and theories, like the third-quarter phenomenon into account, it seems reasonable to investigate if such quarters or reversal timepoints also occur within shorter periods of time. This would provide important information on the periodic pattern of stress markers, for example. Since most long-term studies are designed with a large time interval between the different points of measurement, important information on what happens in between might be already excluded just by the experimental design. If, however, changes occur already during the first few days after exposure to isolation, countermeasures could be provided at earlier stages to prevent health deteriorations or performance decrements.

Therefore, the aim of the current study was to assess the effect of 30 days of isolation in 16 human subjects on mood, cognitive performance, blood stress markers, neurotrophic factors, and cortical activity localized to prefrontal and parietal cortices. It was hypothesized that 30 days of isolation will lead to (1) decreased subjective well-being (mood), (2) decreased cognitive performance (problem solving, working memory, and attention), (3) increased secretion of cortisol as a chronic stress marker, (4) decreased level of both BDNF and IGF-1, and (5) increased prefrontal and decreased parietal cortex activity.

Materials and methods

Participants

The isolation group was selected by the HERA team (Human Exploration Research Analog) after an open call following astronaut selection criteria as a guideline (Cromwell and Neigut 2014). To approximate the stereotypical characteristics of an astronaut, requirements for subjects to participate were quite strict. Candidates were required to hold a bachelor's degree in a natural-science-related field and must have shown the motivation to and "work ethic similar to the astronaut stereotype" (Cromwell and Neigut 2014). Furthermore, to be considered as a potential mission candidate, subjects had to pass the the NASA long-duration space flight physical which includes that participants had normal or corrected-to-normal visual acuity and that their resting state blood pressure did not exceed 140/90 mm Hg.

The study was part of the HERA program campaign 3, sustained by the National Aeronautics and Space Administration (NASA, Houston, USA).

16 participants (age$_{mean}$: 36.3 ± 7.2; 7 females, see Table 1) served as the isolation group (IG) and were isolated for 30 days inside the NASA HERA module at the Johnson Space Center in Houston, USA. The study was divided into 4 missions with 4 crewmembers each (January 2016–June 2017). There was a fixed daily and weekly schedule for the participants, which they were asked to follow, to align as closely as possible to the typical ground work on the ISS. For further details on the daily schedule and the routine of the participants within the HERA module, a detailed description is provided by Cromwell and Neigut (2014). A non-isolated control group (CG) at the German Sport University Cologne, Germany, consisted of another 18 participants (Age$_{mean}$: 31.9 ± 8.5; 8 females, see Table 1). Participants were tried to match the isolation group as close as possible to overcome confounding effects on our dependent variables. To account for the effect of education, participants for the control group were also required to hold at least a bachelor's degree. Furthermore, to match the subjects in regard to their physical health status, control subject needed to perform at least 3 times of physical activity per week which was monitored via pulse monitors and training documentation. This group was asked to continue their normal living routine. One participant did not finish the study due to private reasons, so that data from a total of 17 participants were included in the data analysis (Table 2).

Table 1 Characteristics of participants

N = 33	Isolation group	Control group
N	16 (7 females)	17 (9 females)
Age (years)	36.3 ± 7.2	31.8 ± 8.7
Weight (kg)	73.7 ± 15.8	72.7 ± 14.3
Height (cm)	172.8 ± 10.3	175.9 ± 9.1
BMI (kg/m^2)	24.6 ± 3.37	23.27 ± 2.7

Data are presented as mean ± standard deviation (SD)

BMI Body Mass Index, *N* number of participants

Table 2 Statistical results

Parameter	Group (*N*)	MD pre 5	MD 7	MD 14	MD 28	MD post 5	Group effect	Time effect	Interaction effect
Cortisol (µg/dL)	Isolation (16)	12.5 ± 3.73	19.5 ± 1.91	18.8 ± 2.75	18.5 ± 2.29	13.6 ± 2.38	**< 0.001*** **	**< 0.001*** **	**< 0.001*** **
	Control (17)	12.1 ± 4.03	13.2 ± 4.44	12.4 ± 4.26	13.0 ± 3.16	12.9 ± 3.24			
IGF-1 (µg/L)	Isolation (16)	186.6 ± 48.54	183.5 ± 51.17	191.6 ± 58.77	199.4 ± 54.34	171.9 ± 48.59	0.094	0.074	0.175
	Control (17)	162.7 ± 50.30	146.6 ± 62.37	156.29 ± 64.92	158.24 ± 54.41	157.18 ± 53.75			
BDNF (ng/mL)	Isolation (16)	25.8 ± 5.55	27.6 ± 7.15	25.9 ± 6.34	24.5 ± 6.79	25.2 ± 6.54	0.920	0.635	0.571
	Control (17)	26.3 ± 6.90	25.2 ± 4.99	25.8 ± 8.31	25.3 ± 6.40	25.4 ± 6.06			
LORETA frontal ($\mu A^2/mm^4$)	Isolation (11)	0.0023 ± 0.0006	0.0020 ± 0.0005	0.0019 ± 0.0006	0.0019 ± 0.0003	0.0020 ± 0.0004	0.228	0.112	0.740
	Control (13)	0.0021 ± 0.0006	0.0018 ± 0.0004	0.0018 ± 0.0004	0.0020 ± 0.0003	0.0019 ± 0.0005			
LORETA Parietal ($\mu A^2/mm^4$)	Isolation (11)	0.0059 ± 0.0019	0.0051 ± 0.0017	0.0045 ± 0.0019	0.0038 ± 0.0011	0.0048 ± 0.0018	**< 0.001*** **	**< 0.05***	0.154
	Control (13)	0.0038 ± 0.0011	0.0030 ± 0.0007	0.0033 ± 0.0009	0.0034 ± 0.0008	0.0040 ± 0.0016			
GNA (Points)	Isolation (15)	10.7 ± 1.28	10.7 ± 1.22	11.5 ± 1.77	10.4 ± 0.63	11.1 ± 1.36	**< 0.001*** **	0.188	0.203
	Control (14)	17.1 ± 6.53	14.5 ± 5.45	15.9 ± 6.8	15.0 ± 4.47	14.2 ± 2.72			
GPA (Points)	Isolation (15)	38.5 ± 9.05	40.8 ± 7.88	33.5 ± 10.74	33.7 ± 8.67	35.1 ± 7.64	0.381	0.063	0.389
	Control (14)	35.7 ± 3.81	35.7 ± 3.43	34.9 ± 3.80	34.0 ± 5.19	34.6 ± 7.93			
Speed match (points)	Isolation (16)	20,717 ± 5131.2	20,753 ± 3770.1	21,597 ± 4339.6	22,527 ± 4403.1	23,713 ± 2981.3	0.185	**< 0.001*** **	0.682
	Control (17)	18,115 ± 4043.2	18,912 ± 4771.7	20,768 ± 5467.9	21,247 ± 4132.7	21,641 ± 3777.9			
Memory matrix (points)	Isolation (16)	29,426 ± 4507.7	32,296 ± 5752.8	31,603 ± 5873.3	32,723 ± 6566.0	32,446 ± 5818.5	0.492	**< 0.001*** **	0.368
	Control (17)	28,462 ± 4102.9	29,062 ± 5433.6	30,318 ± 5445.0	32,559 ± 7867.0	31,968 ± 6398.6			
Chalkboard challenge (points)	Isolation (16)	9750 ± 5221.0	11,000 ± 6158.0	11,638 ± 7318.9	12,706 ± 7280.4	12,686 ± 7247.8	0.626	**< 0.05***	0.423
	Control (17)	12,218 ± 4561.3	11,753 ± 4484.6	12,918 ± 5320.9	12,488 ± 5852.0	13,058 ± 6348.4			

Values for the assessed parameters are presented for control group and isolation group. Means ± standard deviation (SD) are presented for each parameter at each timepoint

Significance level: $p < 0.05$ = *; $p < 0.01$ = **; $p < 0.001$ = ***

Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Study design

The study design is pictured in Fig. 1. Participants of both IG and CG completed 5 measurement sessions. A test run of questionnaires and cognitive tasks was conducted beforehand for familiarization. Baseline measures were recorded 5 days prior to the start of isolation [Mission Day − 5 (MD − 5)]. Within the 30 days of isolation, measurements were carried out on Mission Days 7, 14, and 28 (MD 7, 14, 28). A post-test was carried out 5 days after the end of the isolation period [Mission Day + 5 (MD + 5)].

The measurements included a resting electroencephalography recording (EEG) with eyes closed, a questionnaire concerning subjective mood [Positive and Negative Affect Schedule-X (PANAS-X)] and a cognitive test battery. All

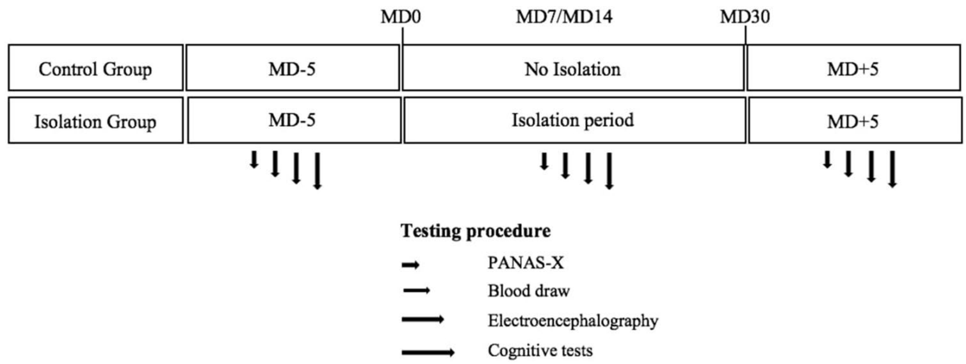

Fig. 1 Study design. Experimental design of the Human Exploration Research Analog (HERA); *MD* Mission Day, *PANAS-X* Positive and Negative Affect Schedule-X (Watson and Clark 1999)

tests have been executed at about the same time of day to avoid day-time effects. Furthermore, a fasting blood sample was taken in the morning of each assessment day. To avoid any kind of confounding social experiences during isolation, participants always accomplished the measurements in pairs. Therefore, they were given detailed instructions on how to conduct the different measurements before the beginning of the study period. For the blood drawing during isolation, participants were asked to pass their arms through a curtain, while the medical staff was asked to not speak with the subjects. This was done, because any kind of social experience, except the inter-individual interaction between subjects, was to be avoided.

Positive and negative affect schedule-X

The PANAS-X is a widely used self-report measure (Watson and Clark 1999) to assess the specific distinguishable states that emerge from the general dimension of positive and negative emotional experiences. The general positive affect (GPA) and the general negative affect (GNA) have been identified in both intra- and inter-individual analyses and emerge in a consistent way across sets, time frame, response formats, language, and culture. The PANAS-X is a 60-item expended version of the PANAS. In addition to the two original higher order scales, the PANAS-X measures 11 specific affects: fear, sadness, guilt, hostility, shyness, fatigue, surprise, self-assurance, joviality, attentiveness, and serenity. Participants had to rate adjectives based on their own feelings on a five-point Likert scale from 1 (“not at all”) to 5 (“extremely”). The results of all subscales are computed via the sum of the respective items.

Participants were asked to complete an electronic version of the PANAS-X on MD-5, 7, 14, 28, and +5 by indicating their average feeling during the past week.

Unfortunately, due to technical backup problems, data were not complete for 3 subjects in the CG and for 1 subject in the IG. Therefore, for the PANAS-X, only 29 data sets ($N_{CG} = 14$; $N_{IG} = 15$) were included into further statistical analysis.

Cognitive tests

Cognitive performance was assessed using three different cognitive tasks (see below) from a commercial brain game (lumosity.com) that participants were asked to perform on an iPad (Apple, California, USA). These same tests have been used in the previous confinement investigations (Abeln et al. 2015; Schneider et al. 2013). All tasks were performed for familiarization during the training session prior to isolation. Participants were free to test multiple times until they felt familiar with the task (1–3 times).

Memory matrix This task tests the visuo-spatial working memory as well as spatial imagination. Based on the variant of a one-up one-down staircase method (Levitt 1971), the subject’s memory threshold could be defined. In this game, pattern of tiles was presented on a grid; then, disappeared and participants were subsequently asked to recall the exact pattern. The difficulty rose by increasing the number of tiles every time the participant responded correctly and decreased after incorrect attempts. Participants earned a number of points increasing with the pattern difficulty for each correct answer. The game stopped after 12 trials.

Speed match In this game, a single symbol appeared briefly in the center of the screen and was then replaced by another. Participants were requested to respond as fast as possible to whether the current symbol matched the previous one. Scores were calculated by summing the number of correct responses within 45 s. This task assesses visuo-perceptual attention as well as working memory and decision-making. The task requires fast sensory processing, analysis, and integration of the visual input. This ability depends to a large extent on the working memory ability, as one has to remember the previous symbol and compare it to the present stimuli to decide whether both are coherent or incoherent.

Chalkboard challenge In this game, two simple arithmetical equations were placed on the screen. Participants were asked to decide as quickly as possible which equation was the largest or whether they were equal. The initial duration of the task was 50 s, but a set of 5 correct answers gave a time bonus of 10 s and each incorrect answer withdrew

3 s. The complexity of the arithmetical equations increased throughout the challenge. Scores were computed via the total number of correct responses as well as the highest level achieved. This task tests executive function via mathematical problem solving and quantitative reasoning. Problem solving is said to depend on working memory (Swanson and Sachse-Lee 2001). In this task, the subject's ability to ignore irrelevant information (e.g., a higher number in the one equation did not imply that this equation was larger than the other one) and to concentrate on the target or goal (fast processing of equations) was tested.

Blood analysis

Blood was drawn by venipuncture in the morning after at least 8 h of fasting. During isolation, the arm of the participant was passed through a curtain, while the executing medical staff was not allowed to talk. Blood was processed immediately afterwards and stored at − 80 °C. After the campaign, all blood samples were sent to a partner laboratory for analysis of BDNF, IGF-1, and cortisol.

Immunoassay procedures were performed to evaluate the BDNF, IGF-1, and cortisol levels in participants' plasma. BDNF levels were evaluated using the Human Neurodegenerative Bead Panel 3 (EMD Millipore's MILLIPLEX MAP) and biotinylated antibodies detection. Cortisol levels were evaluated with micro-particles immunoassays via the Architect Cortisol kit. Levels of IGF-1 were evaluated via a solid-phase enzyme labelled chemiluminescent immunometric assay (IMMULITE 2000 IGF-1 kit).

Electroencephalography (EEG)

EEG recording EEG activity was continuously recorded using an electrode cap (ActiCap EEG Active Electrode System combined with V-Amp Amplifier, Brain Products GmbH, Gilching, Germany) with Ag/AgCl electrodes located at 16 scalp sites (*Fp1*, *Fp2*, *Fz*, *F3*, *F4*, *F7*, *F8*, *C3*, *Cz*, *C4*, *P3*, *Pz*, *P4*, *O1*, *Oz*, *O2*) based on an international 10–20 system (Jasper 1958). Crewmembers of the IG have been trained to mount the EEG cap and to assist recording pairwise in a training session prior to the mission. Brain cortical activity was measured for 5 min in a relaxed, seated position with eyes closed. Participants were asked to concentrate on themselves, relax, and not to move. The conductivity of the electrodes was enhanced by adding gel (SuperVisc, EasyCap GmbH, Herrsching, Germany). The sample frequency was set at 500 Hz.

EEG analysis Raw data were filtered utilizing a Butterworth zero phase filter including a notch filter at 50 Hz for the CG and at 60 Hz for the IG. Low cutoff and high cutoff were set at 1 Hz and 30 Hz. The 5-min recordings were segmented into segments of 2000 ms. Semi-automatic artifact rejection algorithm was applied on each segment. Segments were marked and removed if the difference between the minimum and maximum amplitude in a single segment exceeded 100 µV. The maximal allowed voltage step was set to 50 µV/ms. The lowest allowed activity was set to 0.5 µV. If an artifact was detected, the algorithm marked the event 200 ms before and 200 ms after the exact artifact occurred to control for the source of noise. Marked segments were untagged manually only if large portions of clearly visible alpha were marked automatically due to their passing of the applied threshold. In addition, Independent Component Analysis (ICA) was used to remove ocular, pulse-related, or movement-related artifacts not being coded by semi-automatic artifact algorithm. Data were then baseline corrected over 2000 ms and LORETA analysis (Pascual-Marqui et al. 1994) applied to our regions of interest (PFC and parietal cortex) and averaged across remaining segments for each participant at each timepoint (at least 60 segments needed to be included for analysis).

Due to insufficient signal quality (artifacts, slow voltage drifts, impedance exceeding 10 kΩ) in some EEG recordings, a total of 24 data sets (13 CG, 11 IG) were included into analysis.

Statistics

All statistical analyses were conducted using IBM SPSS Statistics Version 24. To assess the differences between the groups and the time course for the different variables in each group, a repeated-measures analysis of variance (ANOVA) was calculated including the between-subject factor group (*IG* vs. *CG*) and the within-subject factor time (*MD − 5*, *MD7*, *MD14*, *MD28*, *MD + 5*) as well as the interaction of time and group. Greenhouse–Geisser corrected *p* values were reported if sphericity assumptions were violated. *p* values were adjusted using Bonferroni correction. The Shapiro–Wilk test for testing normal distribution revealed that variables were normally distributed, permitting the use of parametric tests. Furthermore, effect sizes were computed using eta-squared (η_p^2).

Results

Mood

GNA was not affected by isolation. Neither an effect of time ($F_{2.169,\ 58.568} = 1.707$, $p = 0.188$) nor an interaction between time and group ($F_{2.169,\ 58.568} = 1.629$, $p = 0.203$) were observed, but a main effect of group was observed with an overall higher negative affect in the CG ($F_{1,27} = 15.799$, $p < 0.001$, $\eta_p^2 = 0.369$). This effect, however, was not caused by isolation, but rather by highly significant baseline differences between the groups.

GPA revealed a different course during isolation. The main effect of time was not significant ($F_{4,108} = 2.308$, $p = 0.063$), but a tendency towards less positive affects in the IG was observed. Neither a group ($F_{1,27} = 0.794$, $p = 0.381$) nor an interaction ($F_{4,108} = 1.042$, $p = 0.389$) effect was revealed.

Cognitive tests

For each cognitive test, an overall time effect with progressively increasing scores could be observed (speed match: $F_{4,124} = 9.049$, $p < 0.001$, $\eta_p^2 = 0.226$; chalkboard challenge: $F_{4,124} = 2.461$, $p < 0.05$, $\eta_p^2 = 0.074$; memory matrix: $F_{4,124} = 6.309$, $p < 0.001$, $\eta_p^2 = 0.169$). No group or interaction effects were found (speed match$_{group}$: $F_{1,31} = 1.834$, $p = 0.185$; chalkboard challenge$_{group}$: $F_{1,31} = 0.242$, $p = 0.626$; memory matrix$_{group}$: $F_{1,31} = 0.484$, $p = 0.492$; speed match$_{interaction}$: $F_{4,124} = 0.574$, $p = 0.682$; chalkboard challenge$_{interaction}$: $F_{4,124} = 0.976$, $p = 0.423$; memory matrix$_{interaction}$: $F_{4,124} = 1.082$, $p = 0.368$).

Blood parameter

Cortisol

Levels of cortisol (see Fig. 2) increased significantly during the isolation period compared to pre- and post-measurement ($F_{4,124} = 19.090$, $p < 0.001$, $\eta_p^2 = 0.381$). Levels differed significantly between the two groups during the period of isolation ($F_{1,31} = 17.675$, $p < 0.001$, $\eta_p^2 = 0.363$). Furthermore, a time × group interaction effect was demonstrated ($F_{4,124} = 14.234$, $p < 0.001$, $\eta_p^2 = 0.315$).

Neurotrophic factors

Neurotrophic factors were not significantly affected. BDNF did not reveal significant time ($F_{4,124} = 0.645$, $p = 0.631$), group ($F_{1,31} = 0.009$, $p = 0.925$), or interaction effects ($F_{4,124} = 0.735$, $p = 0.570$) in response to 30 days of isolation. IGF-1 did not change over time ($F_{4,124} = 2.186$, $p = 0.074$). Furthermore, neither a main effect of group ($F_{1,31} = 2.983$, $p = 0.094$) nor a time × group interaction effect could be observed ($F_{1,124} = 1.612$, $p = 0.175$).

Cortical activity

PFC activity did not change over time ($F_{4,88} = 1.931$, $p = 0.112$) or differ between groups ($F_{1,22} = 1.541$, $p = 0.228$). No time × group interaction could be found ($F_{4,88} = 0.495$, $p = 0.740$). Activity within the parietal lobes (see Fig. 3) showed a significant effect of time ($F_{4,88} = 2.862$, $p < 0.05$, $\eta_p^2 = 0.115$). Differences between groups were significant ($F_{1,22} = 26.116$, $p < 0.05$, $\eta_p^2 = 0.543$). These significant differences, however, already existed at baseline. No time × group interaction was found for activity in the parietal lobe ($F_{4,88} = 1.716$, $p = 0.154$).

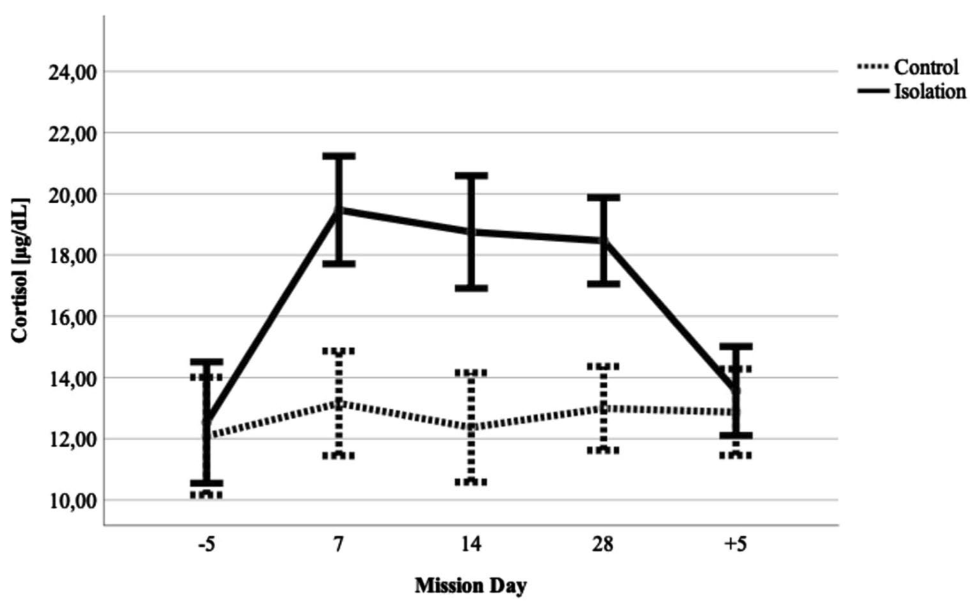

Fig. 2 Cortisol. Levels for cortisol (µg/dL) are presented. Graph is presented in means ± 0.95 confidence interval. significance level: $p < 0.001 = {***}$

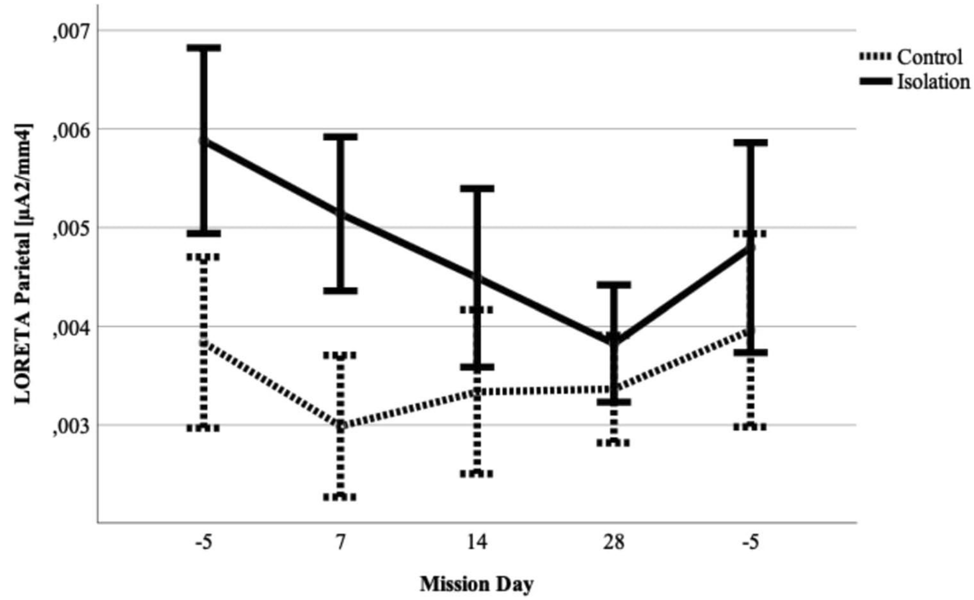

Fig. 3 Cortical activity. Neural current density ($\mu A^2/mm^4$) is presented for parietal cortex. Graph is presented in means ± 0.95 confidence interval. Significance level: $p < 0.05 = *$; $p < 0.01 = **$; $p < 0.001 = ***$

Discussion

The main purpose of the present study was to determine the effects of short-term isolation on (neuro)physiological and (-)psychological parameters. In general, it was hypothesized that short-term isolation already has a negative impact on mood and cognition which should be supported by the physiological data of blood markers and cortical activity.

The major effect of isolation was shown via the significant accumulation in cortisol levels along the isolation period. This observation is consistent with the previous studies investigating the effect of longer isolation periods on cortisol levels (Jacubowski et al. 2015; Chouker et al. 2002). Our results indicate that 30 days of isolation already affect the regulation of the HPA axis, suggesting that stress-related processes were stimulated via increasing synthesis of corticotropin-releasing factor triggering the production of adrenocorticotropic hormone (ACTH) and finally cortisol (Tsigos and Chrousos 2002). This hormonal response might be referred to adaptational processes of the physiological mediators to maintain homeostasis, a procedure called allostasis (McEwen 2004). This hypothesis can be further strengthened by the rapid decrease of cortisol levels immediately after the isolation period at MD + 5, meaning that the cumulative changes were reversible and did not impair the physiological system. Furthermore, we could show that cortisol already increased just a few days after exposure to isolation when compared to studies with longer isolation periods, which gives important insights into the rapid activation of the HPA axis.

We expected that these elevated stress levels would also be reflected in alterations of cortical activity. It was hypothesized that the PFC would elucidate increasing activity in reaction to cumulative stress and negative emotions due to its particular involvement in emotional processing (Etkin et al. 2011; Golkar et al. 2012). This assumption did not appear to be affirmed in the present study. Activity localized within the PFC did not show significant changes, but instead a slight tendency towards a reduction in current density over time. Although contradictive to our hypothesis, similar results found for the relationship between cortisol and PFC activity suggests that activity, particularly in the medial dorsal PFC, is inversely associated with stress-induced cortisol concentrations, whereas more lateral areas exhibit positive associations (Kern et al. 2008). In a different study of Al-Shargie et al. (2017), this theory of subregion-specific response of the PFC upon stress induction could be supported. They showed that alpha activity decreases especially in right lateral areas of the PFC. Due to the limitation of a 16-electrode channel EEG, a more accurate localization cannot be made in the present study. Further studies need to clarify which areas of the PFC mediate ACTH secretion and whether distinct patterns of activity can be detected in different areas of the PFC. With regard to our data, which provides a rough estimation of cortical activity within the PFC, we can conclude that the PFC was not globally affected by 30 days of isolation. Considering the stimulus-reduced environment, the slight reduction of prefrontal activity might reflect an adaptational process of the brain leading to a downstate of the brain due to reduced external input to the cortex (Abeln et al. 2015).

The slight decrease in PFC activity, however, converges with the findings of the alterations of current density over the parietal cortex. Although there was just a significant time effect and no interaction effect for the parietal cortex activity, a slight decrease of activity within the isolation group could be observed. As the parietal cortex plays a fundamental role in integrating information from various sensory modalities (Balestrini et al. 2015), isolation periods, characterized by reduced external stimulus input, might lead to a transient hypoactivation of the parietal lobe. Our data, however, suggest that there was no effect of short-term isolation on the parietal cortex activity due to the lack of interaction effects. It would be of interest to see whether these changes would further decrease as a function of isolation time. Because the parietal cortex, in particular, the posterior parietal cortex (PPC), is associated with a variety of cognitive functions, such as attention, spatial processing, or episodic memory retrieval (Sestieri et al. 2017), we expected a deterioration of cognitive function. However, cognitive performance was not impaired or reduced over time. Performance was rather significantly increased in both groups. This progressive increase might be attributed to a usual learning effect. The training (familiarization session) should have taken this into account.

It was hypothesized that cognitive function is reduced due to stress-related structural changes in the brain (Liston et al. 2009). This cognitive decline was expected to be reflected by a decrease of neurotrophic factors BDNF and IGF-1, because both are highly associated with cognitive function (Sungkarat et al. 2018; Prokopova et al. 2017; Saatman et al. 1997). Our analyses of BDNF and IGF-1, however, did not show significant changes during isolation. Meanwhile, there is evidence that prolonged stress periods or chronic stress adversely affects neurotropic factors (Licinio and Wong 2002; Sävendahl 2009). Our results suggest that 30 days of isolation do not affect regulation and expression of neurotrophic factors. This is convergent with our findings in cognitive function, even if it is open to the question of whether more sensitive cognitive tests would detect impairments in higher cognitive domains.

It was expected that GNA would increase and consequently GPA decrease during the isolation period. The analysis of both items did not reveal significant changes over time, although GPA showed a tendency towards less positive affects during 30 days of isolation. The significant group effect for GNA, which was already present at baseline, demonstrates less perception of negative affect in the IG compared to the CG. This might be attributed to the effect of social desirability of the screened and monitored IG. The fact that most of the participants of the IG participated in the study to increase their chance of becoming an astronaut might have influenced their answers due to their desire to appear capable of facing stress during space missions. Prior studies using a space-analog environment reported mood deteriorations. However, compared to the present design, isolation periods were much longer (e.g. 9 month, Abeln et al. 2015). Similar results support the assumption that longer periods of isolation adversely affect mood (Palinkas and Houseal 2000; Schneider et al. 2010). Palinkas and Houseal (2000) demonstrated an interesting behavior in their study, in which a deterioration of mood within the first half of isolation was then recuperated close to the end of isolation. This alteration in mood is defined as the "third-quarter phenomenon" which was first described by Bechtel and Berning (1991). In this study, we showed a similar trend in the GPA. Deterioration in mood continued to decrease until MD14 and then remained stable or moderately enhanced until post-mission, although not significant.

Taken together, the present findings indicate that short-term isolation (30 days) has no significant effect on cortical activity, neurotrophic factors, cognition, and mood, even though cortisol levels were significantly increased during isolation.

Limitations

A limitation of space-analog isolation studies is the number of imbedded tests and goals. It exceeds the scope of this manuscript to consider all possible influencing factors, such as group cohesion or crew compatibility, sleep, etc., and it remains difficult to determine the pure effect of isolation or the pivotal factor contributing to the high stress level. There is a need for further investigations systematically examining the effect of various factors of isolation and spaceflight to finally develop efficient countermeasures against psychophysiological impairments. Furthermore, although both groups were matched in regard to confounding parameters, such as age, weight, physical activity, and educational status, there might still be confound in regard to the fact that the participants in the isolation group to some extent participated to increase their chances to be considered for further astronaut selections. Therefore, answers to the questionnaires, such as the PANAS-X, might have been influenced by this purpose, making it more difficult to clearly interpret the null effects for the subjective affects.

Another concern of this study and isolation studies in general is the lack of high power, as the still relatively low number of participants might lead to a higher type II error rate. A priori analyses are difficult to conduct due to the prescribed number of participants allowed to participate. To overcome at least the lack of limited control over confounding variables as well as the lack of power, future investigations should incorporate collaboration and stronger integration of data sharing to allow for more precise implications which are needed for future projects and space missions.

Conclusion

This study provided important insights into the reaction of (neuro)physiological, as well as (-)psychological parameters to short-term isolation periods. The present findings demonstrate that 30 days of isolation do not have a significant impact on cortical activity, neurotrophic factors, cognition, and mood, even though stress levels were significantly increased during isolation.

The present findings and understandings of how several parameters react to isolation and confinement are an important contribution to the future plans in the space community, especially for the manned mission to Mars.

Future studies need to clarify whether higher cognitive processes are affected by short-term isolation, and if so, whether these effects have underlying neurophysiological components (e.g., event-related potentials).

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Compliance with ethical standards

Conflict of interest There is no conflict of interest.

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