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Research paper

Effect of exercise on brain function as assessed by functional near-infrared spectroscopy during a verbal fluency test in a simulated International Space Station environment: A single-case, experimental ABA study in Japan

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ABSTRACT

Over the past few years, the number of Japanese astronauts recruited for a long-term stay in the International Space Station (ISS) has increased. However, no consensus has been reached on a standardized method for measuring psychosocial stress triggered under such confined environment conditions, and on methods to effectively minimize the detrimental effects of such stress. To address this matter, we aimed to inspect stress-related index measurements of frontal brain function in experiments simulating long-term space confinement environment at the Japan Aerospace Exploration Agency (JAXA). Study participants (N = 8, all adult men) were confined in the "confinement environment adaptation training facilities" of the Tsukuba Space Centre for 15 days, in a controlled, confined environment that attempted to closely simulate the conditions experienced by astronauts during the astronaut selection examination and inside the ISS. Frontal brain activation of the prefrontal cortex during a verbal fluency test (VFT) was evaluated as a confinement-related stress index, measured by functional near-infrared spectroscopy (fNIRS), a non-invasive brain-imaging method. An exercise intervention was additionally applied, using a single-case experimental ABA design (Intervention period (B): 5 days, 15 min aerobike daily exercise; Control periods (A): 5 days before and 5 days after intervention period, prohibition of any type of exercise), to observe whether exercise could have an ameliorating effect on the confinement-induced stress. The fNIRS values showed a significant decrease at the beginning of confinement when compared with the before-confinement values, remaining stable during confinement and thus showing no difference between the exercise intervention and control periods, ultimately returning to pre-confinement levels a week after confinement (analyzed using a generalized linear mixed model). The fNIRS-measured initial decrease in prefrontal cortex activity indicates that fNIRS can efficiently detect the confinement-triggered stress. Importantly, the stable fNIRS values during confinement suggest that exercise can maintain the frontal brain function assisting against further deterioration under confinement environment stress. Our results support that exercise can facilitate better prefrontal cortex activity combating the negative effects of confinement-induced stress, and therefore should be beneficial for maintaining good frontal brain function among astronauts in the ISS.

1. Introduction

As focus on exploration missions taking humans to space intensifies, and with hundreds of astronauts having already flown into space, the number of Japanese astronauts recruited for a long-term stay in the International Space Station (ISS) has also increased. The controlled, harsh, confinement environment in space could have negative effects in the astronauts' cognitive function and mental wellbeing, and spending

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Acronyms/abbreviations

(Deoxy-Hb) Deoxyhemoglobin
(DLPFC) Dorsolateral prefrontal cortex
(fNIRS) Functional near-infrared spectroscopy
(FP) Frontal pole
(ISS) International Space Station
(JAXA) Japan Aerospace Exploration Agency
(Oxy-Hb) Oxyhemoglobin
(Total Hb) Total hemoglobin
(VFT) Verbal fluency test

extended periods of time on a mission with the same people in the same room could present an additional psychosocial stressor, possibly causing feelings that can be described as “psychological suffocation”.

Several confinement studies have been conducted as simulations of space-stay environments such as the ISS. The psychology of interpersonal communication of a crew in a confined environment was surveyed for 4 weeks during the Isolation Study for European Manned Space Infrastructures, and for 9 weeks during the Experimental Campaign for the European Manned Space Infrastructure [1]. The Flight of the International Crew on the Space Station simulation used a repertory grid method to assess the participants' psychological dynamics [2]. For other spaceflight studies, cortisol, epinephrine, and catecholamine levels have been measured to assess the astronauts' stress levels resulting from staying in a confined environment [3–7]. However, the optimal method for measuring stress triggered under such conditions has remained a subject of debate, although numerous stress-assessment tools have been used in confinement environment studies.

A promising stress-related index that has yet to be surveyed thoroughly in confinement is frontal brain function. The prefrontal cortex is the frontal brain area that controls cognitive skills, including working memory, problem-solving, planning, judgment, reasoning and decision-making, as well as social cognition, emotional expression, behavioral control, and personality [8]. An undoubtable connection has been established between the prefrontal cortex function and psychological disorders, including depressive and mood disorders, although there is still a lot to be unveiled regarding the mechanisms underlaying that mental health - prefrontal cortex interrelation [9–11].

Functional brain imaging has been an invaluable tool for recognizing and further studying cerebral function. In recent years, researchers have focused on the use of functional near-infrared spectroscopy (fNIRS), which can evaluate cortex function by detecting oxygenation and hemodynamic changes in oxygenated and deoxygenated hemoglobin (Oxy-Hb and Deoxy-Hb, respectively), providing a respectable amount of evidence on its usefulness and credibility [12]. Prefrontal cortex function has been studied by fNIRS in a series of psychiatric disorders [13–18]; fNIRS has been reported to detect a decrease in prefrontal function among patients with major depressive disorder [19]; and could also be used as a marker to predict the clinical response to antidepressants [20]. Interestingly, a previous study reported that elevated job-related stress was associated with decreased frontotemporal activation among workers, providing pre-clinical evidence using fNIRS [21]. Thus, stress reactivity of the prefrontal cortex during confinement could present an intriguing insight.

In the present study, we investigated changes in stress-related cerebral function measured by fNIRS under the stress of being in an ISS-simulating confinement environment [22]. To accurately replicate the ISS conditions and to study possible countermeasures against the stress experienced by the astronauts, exercise intervention was also implemented. Medium-intensity exercise of 50% maximum oxygen uptake for 10 min has been shown to enhance extremely detailed brain function of overcoming Stroop interference. It has also been shown that improved brain function involves an increase in activity in the left front prefrontal cortex [23].

Although the clinical use of fNIRS and the improvement in brain function from exercise have been reported, experiments on preclinical psychological states remain limited. We previously examined the effect of exercise on cognitive brain function in confinement experiments in Japan [24], as there was little fNIRS data involving exercise in confinement experiments. The aim of the present single-case, experimental ABA study (where in a single experiment we apply exercise intervention [B] in between two no-exercise control periods [A]) was to assess prefrontal cortex function in reaction to stress due to confinement using fNIRS, also evaluating the effects of exercise. The results could contribute to the development of psychological assessment tools and countermeasures for inflicted stress among astronauts.

2. Methods

The present study attempted to confirm the effects of exercise on cognitive brain function measured by fNIRS in response to a verbal fluency test (VFT) during confinement.

The experiment consisted of three phases: pre-confinement phase (pre-confinement days: L-7 ~ L-1), confinement phase (confinement days: C1 ~ C15), and post-confinement phase (post-confinement days: R + 1 ~ R + 7).

2.1. Confinement environment

The experiment was carried out in the long-term confinement facilities [25] (space residence environment simulation) of the Japan Aerospace Exploration Agency (JAXA) in Tsukuba, Japan (December 2017). The isolation complex consists of an experiment module that is a mock-up of the interior of the Japanese experiment module for the ISS. ISS-conditions simulating daily schedule and work-load were applied during confinement. Preceding confinement experiments were conducted in the same facilities under the same conditions, described also in our previous reports [22,24].

2.2. Participants

Eight healthy Japanese men (20–50 years of age) voluntarily participated in this study. All participants were right-handed. During their stay, they underwent several group and personal tasks, assessment by a psychiatrist, and medical checkups, among other tests [14].

2.3. Exercise intervention (C6~C10)

We designed an ABA single experiment study, conducted over 15 days of confinement (C1~C15) divided into three periods (5 days each) over which, exercise intervention and control periods were applied as follows:

A (C1~C5): No exercise
B (C6~C10): Exercise
A (C11~C15): No exercise

Exercise protocol:

- Tools: two aerobikes (EZ101; KONAMI Holdings Corporation, Tokyo, Japan) for eight persons
- Exercise time: 15 min/day
- Exercise intensity: VO2max 50%*
- Intensity setting: estimation method using predicted maximum heart rate based on age (simple method)

* On the day before the confinement (L-1), experts made load adjustments on-site for each participant.

2.4. fNIRS measurements

Localized blood oxygenation levels (Oxy-Hb, Deoxy-Hb, Total Hb) in the brain were measured by near-infrared light diffusion to monitor activity in response to the given cognitive task (VFT).

We employed a 22-channel LIGHTNIRS portable fNIRS system (Shimadzu Corp., Kyoto, Japan) to detect hemoglobin signal changes derived from local vascular reactions coupled with neuronal activation at the cortical surface. In the present study, 5-ms pulses of near-infrared light at wavelengths of 780, 805, and 830 nm were emitted from each of the emitter fibers. There is a total of 22 channels (upper row: 7 ch, middle row: 8 ch, lower row: 7 ch), covering the frontal pole (FP) and dorsolateral prefrontal cortex (DLPFC) regions of the prefrontal cortex.

Referring to precedent studies [16–18,26], we calculated the integral and centroid values for both the FP and DLPFC. The integral value of the fNIRS signal indicates oxygenation demand: changed amount of Oxy-Hb ≒ required amount of Oxy-Hb, whereas the centroid value indicates oxygenation response: changed speed of Oxy-Hb ≒ response speed to Oxy-Hb request.

To monitor the prefrontal cortex activity and evaluate the effect of exercise under confinement, fNIRS measurements in response to VFT were taken in specified days of the experiment according to the ABA design, and always on the same time of the day, as follows:

- pre-confinement phase: days L-7 and L-1
- confinement phase:
  control period (A): day C4
  exercise intervention period (B): day C9
  control period (A): day C14
- post-confinement phase: days R+1 and R+7.

2.5. Verbal fluency test (VFT)

VFT was used as the cognitive task initiating cognitive activity during measurements [27]. For the VFT (letter version), we used the methods described by Kameyama et al. and Takizawa et al. [16,17]. Each participant took a seat in front of a table on which a laptop computer had been placed. A black cross was displayed in the centre of the screen. The distance from the participant's eyes to the screen was set at approximately 50 cm. A single trial consisted of three periods, namely, a pre-task period, a task period, and a post-task period, lasting 20, 60, and 20 s, respectively. During the task period, the participants were instructed to generate as many Japanese words beginning with a given initial syllable (e.g.,/a/,/ka/, and/sa/) as possible. Each of the three initial syllables were employed in order and changed every 20 s during the 60-s task. There were four different patterns of syllable combinations, used alternately in each different measurement-day. During the pre- and post-task periods, which served as baselines, the participants were instructed to repeat slowly the basic Japanese vowels (/a/,/i/,/u/,/e/, and/o/). fNIRS measurements (one continuous trial-set) were taken throughout the whole VFT, from the beginning of the pre-task period to the end of the post-task period.

VFT word-count (the total number of words produced by each participant during each VFT session) was used as a performance index.

2.6. Statistical analysis

In the statistical analysis, the fNIRS signals were averaged across each task and non-task period (sum of the pre- and post-periods), and then the increase or decrease in task-induced brain function was determined. The data are shown as mean ± standard error.

In all statistical tests, we used mixed model analysis. P values less than 0.05 were regarded as indicating statistical significance. IBM SPSS for Mac (version 24.0; IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

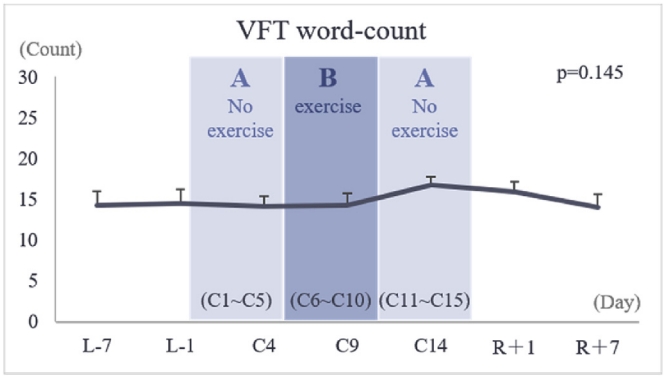

Fig. 1. Comparison of the Verbal Fluency Test (VFT) word-count with/without the exercise intervention within the time course, tested statistically by a mixed model in the ABA single-experiment design.

2.7. Ethical approval

The participants were informed of the purpose and safety of the experiments, and informed consent was obtained prior to participation. This study was performed in accordance with international guidelines of biomedical research involving human subjects, including the Declaration of Helsinki. To pursue the experiments, approval was granted from both the University of Tsukuba Medical Ethics Committee (No. 1022) and the JAXA Ethical Review Board (No. 29-2-1).

3. Results

The results of the VFT word-count showed no significant changes over the time course (Fig. 1). Performance (based on word recall) was stable during the confinement experiment.

The integral values (brain oxygenation demand) of the fNIRS signals in both the FP and DLPFC had significant differences within the time course (Figs. 2 and 3, Supplementary Table S.1). Pairwise comparisons of each measurement item with the others, showed that the ones presenting a significant difference were as follows:

The fNIRS integral values in the FP area:

- L-7 and C4 (*p = 0.012),
- L-7 and C9 (*p = 0.024),

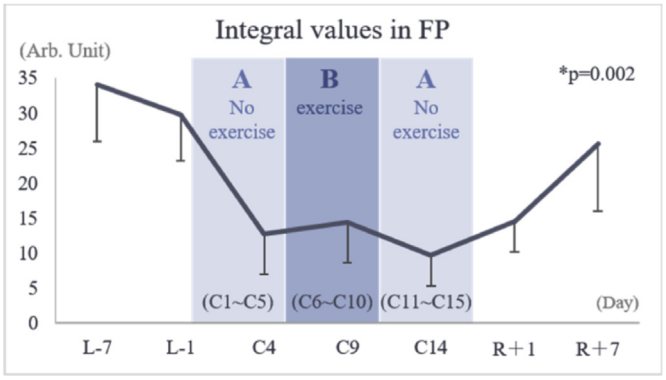

Fig. 2. Time-course comparison of the fNIRS integral values in the frontal pole (FP) with/without the exercise intervention, tested statistically by a mixed model in the ABA single-experiment design (*p = 0.002, mixed model time-series). Specifically, pairwise comparisons showed that L-7 values were significantly different from C4, C9, C14, and R+1 (*p < 0.05, paired comparison).

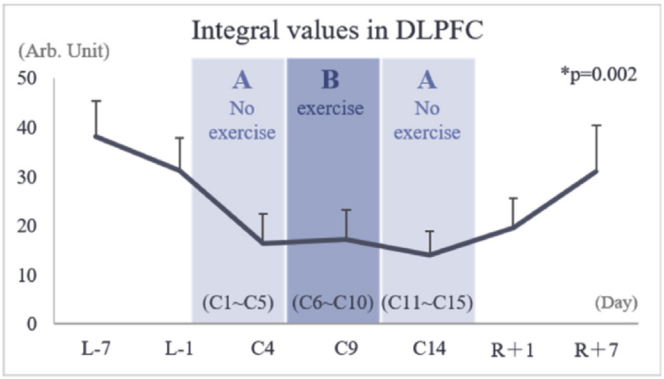

Fig. 3. Time-course comparison of the fNIRS integral values in the dorsolateral prefrontal cortex (DLPFC) with/without the exercise intervention, tested statistically by a mixed model in the ABA single-experiment design (*p = 0.002, mixed model time-series). Specifically, pairwise comparisons showed that L-7 values were significantly different from C4, C9, C14, and R+1 (*p < 0.05, paired comparison).

- L-7 and C14 (*p = 0.003), and
- L-7 and R+1 (*p = 0.026).

The fNIRS integral values in the DLPFC area:

- L-7 and C4 (*p = 0.011),
- L-7 and C9 (*p = 0.015),
- L-7 and C14 (*p = 0.004), and
- L-7 and R+1 (*p = 0.043).

All the other pairwise comparisons of the fNIRS integral values in both FP and DLPFC showed no significant differences, including, importantly, between the exercise (C6~C10) and no-exercise periods (C1~C5 and C11~C15) (during ABA exercise intervention in confinement). Notedly, the fNIRS integral values increased after confinement.

These data show that fNIRS integral values, which represent brain oxygenation demand (thus prefrontal cortex activation), were significantly higher before confinement (L-7), were reduced significantly during confinement (C4~C14, R+1), but increased back after confinement (R+7). At the same time, these data point that fNIRS integral values were stable during confinement and throughout the ABA exercise intervention.

The centroid values (brain oxygenation response) of the fNIRS signals in both the FP and DLPFC showed no significant change within the time course (Fig. 4 and Fig. 5, Supplementary Table S.2).

4. Discussion

No significant differences were seen in the VFT word count, which suggested an almost stable level of performance in the function of prefrontal cortex. Thus, the exercise intervention period might have had little effect on improving performance in terms of word recall. A precedent study [23] using the Stroop task as a cognitive test showed that medium-intensity exercise, the same as that used in the present study, improved executive function. This difference might the result of the different cognitive tests. The Stroop task is considered more difficult than the VFT because it requires higher brain function. As this factor reflects brain oxygen demand, the Stroop task could require more brain oxygen than the VFT. Our results, which showed no significant differences in the VFT word-count with medium-intensity exercise, suggest that brain oxygen demand during the VFT might be too low to maintain the word recall performance with/without exercise.

When looking into the prefrontal cortex activity, reflected by the measured fNIRS integral values (the oxygenation demand of the cortex), we saw significant differences between pre- (and after-) confinement, and during-confinement values in both FP and DLPFC. Specifically, fNIRS detected that prefrontal cortex activity declined when confinement started (when comparing the pre-confinement measurements [L-7] to all measurements taken during confinement [C4~C14], as well as immediately after confinement [R+1]) but increased again back to pre-confinement levels a week after confinement (R+7). This declining trend in the integral values before the exercise-intervention period (B section) observed in the present study supports the findings of our prior research, where we showed that prefrontal cortex function declines because of the confinement-induced stress [22]. Our current results support again that fNIRS efficiently detects the stress inflicted when entering a confinement environment, reflected by the declined prefrontal cortex activation, and also detects the improvement of frontal brain function after the end of confinement.

We previously found that the integral values of fNIRS signals showed a declining tendency [22] after repeated measurements in short intervals of less than 4 days in a confinement environment. In a preceding study, the integral values were reported to have decreased when measured at 3-week intervals, but then recovered after 1 year [28]. The measurement interval in the present study was 5 or 6 days, which is shorter than that in that precedent study.

Interestingly, our current results point that fNIRS-measured prefrontal cortex activity remained stable during confinement and throughout the ABA exercise intervention. Previously we had reported a continuous deterioration of frontal brain function during confinement that only improved after confinement, when exercise was not applied mandatorily [22]. Here, we observed that when exercise was implemented during confinement (B) the prefrontal cortex activity was stabilized (similar C4~C14, R+1 integral values), and even slightly improved, though not significantly (increasing tendency of integral values after exercise intervention at C9). This indicates that exercise at least prevents the further deterioration of prefrontal cortex function under confinement stress. This finding suggests that medium-intensity exercise in a confinement environment might exert a positive effect on higher brain function.

The fNIRS oxy-Hb value was also measured under the premise that it reflected the degree of activation of brain function upon loading on a given cognitive task. It was considered that the decrease of the integral value in this study might have occurred because of the relative decrease of the degree of cerebral function activation in the VFT task. However, the increasing trend in the integral value after the medium-intensity exercise period (B section) observed in the present study is a new finding that also supports the observations of our previous research [24].

In addition, we found that medium-intensity exercise with an aerobike for 15 min/day might prevent a decrease in frontal higher brain function in a confined environment. We consider that the factor difference in the integral values between the intervention B and control

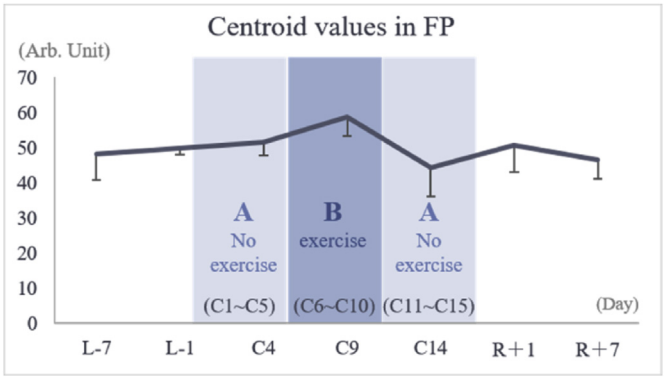

Fig. 4. Time-course comparison of the fNIRS centroid value in the frontal pole (FP) with/without the exercise intervention (N.S., mixed model time-series).

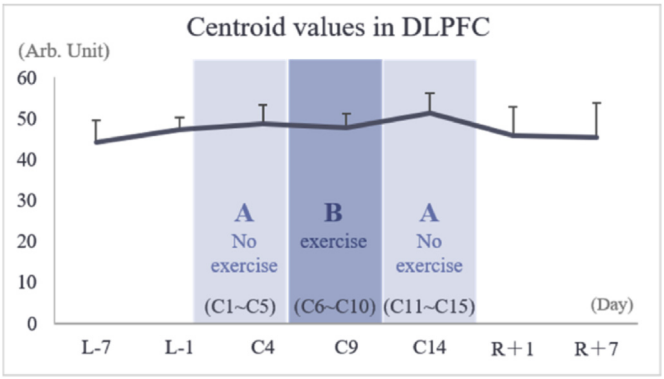

Fig. 5. Time-course comparison of the fNIRS centroid value in the dorsolateral prefrontal cortex (DLPFC) with/without the exercise intervention (N.S., mixed model time-series).

A sections observed in this study might have been the effect of the "medium-intensity exercise intervention" on prefrontal cortex function. Precedent studies have reported a significant positive effect of aerobike exercise on frontal brain function in daily life measured by fNIRS using the Stroop task [23,29]. If medium-intensity exercise is recommended for ISS crews on space missions to prevent decreases in higher brain function in the future, exercise periods of 15 min/day might be appropriate. However, for that purpose, further verification with longer measurement periods and intervals, as well as more evidence, such as from randomized controlled trials, would be necessary.

The centroid value was considered to reflect the speed of response to a request for oxy-Hb, but no obvious differences were observed. However, different results may be obtained in longer experiments or those with higher stress intensities.

5. Conclusions

The present study suggests the efficiency of fNIRS in detecting changes in prefrontal cortex activation under confinement environment stress. Additionally, our results indicate the possible effectiveness of exercise in maintaining better frontal brain activity in such stressful confinement conditions. As good frontal brain function is crucial for cognitive and executive functions in general, and mild exercise has been shown to exert positive effects on frontal brain function, it could be hypothesized that this type of exercise would be advantageous for astronauts in the ISS to retain good frontal brain function.

Declaration of competing interest

We declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.actaastro.2019.10.013.

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