Brain Microstructure and Brain Function Changes in Space Headache by Head-Down-Tilted Bed Rest

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INTRODUCTION: Several astronauts have experienced severe headaches during spaceflight, but no studies have examined the associated brain microstructure and functional changes. Head-down-tilted bed rest (HDBR) is a well-established method for studying the physical effects of microgravity on the ground. In this study, we analyzed the changes in brain microstructure and function during headache caused by HDBR using diffusion tensor imaging (DTI) and resting state functional magnetic resonance imaging (R-fMRI).

METHODS: We imaged 28 healthy subjects with DTI and R-fMRI in the horizontal supine position and HDBR. Using Tract-Based Spatial Statistics, fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity were compared between the headache and non-headache groups. Additionally, an analysis of functional connectivity (FC) was performed, followed by a correlation analysis between FC and numerical rating scale.

RESULTS: HDBR caused headaches in 21 of 28 subjects. DTI analysis showed no significant change in fractional anisotropy after HDBR, whereas axial diffusivity, radial diffusivity, and mean diffusivity increased significantly. R-fMRI analysis showed a significant decrease in FC in several areas after HDBR. The headache group showed significantly higher FC before HDBR, and both groups showed higher FC after HDBR. Correlation analysis showed a positive correlation between FC and numerical rating scale before HDBR but negative after HDBR.

DISCUSSION: We demonstrated the image change in the acute phase of space headache by HDBR using DTI and R-fMRI. Changes in brain microstructure and function specific to patients developing headaches may be evaluated by imaging.

KEYWORDS: space headache, head-down-tilted bed rest, diffusion tensor imaging, resting state functional MRI.

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Many astronauts develop severe headaches during spaceflight. It has been suggested that these headaches are caused by increased intracranial pressure as a result of fluid shift to the head in microgravity, abnormal sensory integration due to changes in the vestibular system and deep senses, and high carbon dioxide (CO_2) concentration in the International Space Station (ISS).[23]

This space headache is newly listed as "spaceflight headache" in Appendix A.10.8 Headache Due to Other Homeostasis Disorders in the International Classification of Headache, Third Edition (ICDH-3).[8] Human space exploration will soon accelerate human expansion into space, and space headaches that degrade astronaut performance and affect mission success will become an important issue.[17] Therefore, further research on the pathogenesis of such headaches is required.

In the first report in 2009, 12 of 17 astronauts (71%) (1 woman and 16 men, aged 28–58 yr) experienced headaches during spaceflight.[24] A total of 21 headaches occurred in 12 astronauts, 2 (9.5%) of which met the diagnostic criteria for migraine based on the International Classification of Headache, Second Edition (ICDH-2); the remaining were tension-type or nonspecific pain. The majority of the pain (71%) was moderate-to-severe, and headaches (76%) occurred independently of space motion sickness symptoms. Moreover, there was no relationship between headache onset and duration of stay in space.

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In a ground-based replication study of space headaches caused by head-down-tilted bed rest (HDBR), 14 of 22 subjects (63.6%) developed headaches, and centrifugal accelerator and aerobic exercise coping strategies during HDBR did not eliminate the headache but decreased its severity, and the headache occurred most frequently on the first day of the experiment.[23]

Moreover, in a study of 12 healthy subjects who also underwent a 5-d −6° HDBR, 7 (58.3%) developed headaches.[5] The results showed that the levels of epinephrine, hematocrit, hemoglobin, and other blood cell components increased, but the levels of salivary cortisol decreased in headache-prone subjects. The levels of zonulin, a tight junction marker, also increased. The study suggests that hemoconcentration occurs in all subjects and that fluid redistribution due to intravascular-to-extravascular water transfer, as well as fluid shift, is the cause of headaches.

HDBR is a well-established method for studying the physical effects of microgravity in space on the ground.[18] In recent headache research, magnetic resonance imaging (MRI) has been used to clarify the pathophysiology of some headaches, and diffusion tensor imaging (DTI) and resting state functional MRI (R-fMRI) can noninvasively evaluate dynamic changes in brain microstructure and functions in real time.[22] Although many findings have been reported on the pathophysiology of primary headaches, such as migraine and cluster headaches, by using these MRI methods,[3,18] there are no reports of such imaging analysis on space headaches.

We hypothesized that patients with space headache would have some alterations in brain microstructure and that there would be differences in brain function between the patients with and without space headache. These differences might be useful in predicting the onset of space headache. Therefore, to clarify these hypotheses, we performed HDBR on healthy subjects and analyzed how their brain microstructure and function differed according to headache occurrence.

METHODS

Subjects

There were 28 healthy adult volunteers, 11 men and 17 women, with a mean age of 47.7 ± 11.7 yr, participating in this study from March 2021 to December 2021. The inclusion criteria were as follows: 1) had no primary headache and 2) had no organic intracranial lesions. Participants' medical history included overactive bladder, hyperuricemia, anemia, sinusitis, duodenal ulcer, dermatomyositis, spinal canal stenosis, and diabetes. The exclusion criteria were as follows: 1) pregnancy; 2) had been enrolled to participate in other clinical trials; and 3) had claustrophobia, a pacemaker, and/or other medical issues causing them to be inappropriate for MRI imaging. Written informed consent was obtained from all subjects.

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association, the Ethical Guidelines for Clinical Research, and related laws and guidelines such as the Pharmaceutical Affairs Law. The study protocol was approved by the Ethics Committee of Mito Kyodo General Hospital (No. 20-52) and was registered in the University hospital Medical Information Network trial registry (ID: UMIN000043583).

Procedure

This was a single-arm study. All subjects were first imaged in the horizontal supine position with R-fMRI and DTI. Then, HDBR was performed in the supine position by lowering the head 10° from the horizontal position, and the subjects were observed for 10 min. Next, the same MRI imaging was performed again in HDBR. Before the start of imaging, the patient's physical condition was thoroughly confirmed by interview.

Headache was assessed 10 min after starting HDBR and again after the second MRI, which was performed under HDBR conditions. Headache symptoms and headache intensity were evaluated. Headache symptoms were classified into "congestion," "heavy feeling," and "pressing" based on the subject's representation. Subjects were also asked about the presence or absence of accompanying symptoms such as nausea. Headache intensity was evaluated objectively using the numerical rating scale (NRS), which is a well-established method for the quantitative assessment of pain in headache research,[1,4] and was also assessed on a three-point scale of "mild," "moderate," and "severe" in accordance with prior reports of space headaches (**Fig. 1**).[5,23,24]

Image Acquisition

Data were acquired with a 3.0-Tesla MRI scanner (Siemens, Erlangen, Germany) using a 3-channel head coil. Our routine protocols included: T1-weighted volume with the magnetization-prepared rapid acquisition with gradient echo (sagittal), R-fMRI and DTI. T1-weighted imaging parameters were as follows: repletion time (TR)/echo time (TE) = 2300/2.32 msec, FOV = 240 mm, 192 sagittal slices, slice thickness = 0.9 mm, and base resolution = 256 × 256. Diffusion-weighted acquisition using spin-echo planar imaging parameters were as follows: TR/TE = 7500/95 ms, matrix size = 128 × 128, 65 axial slices, and b values of 0, 1000, and 2000 s · mm^{-2}. R-fMRI parameters were as follows: TR/TE = 2500/35 ms, FOV = 192, slice thickness = 4 mm, slice axial = 40, matrix = 64 × 64, and voxel size = 3.0 × 3.0 × 4.0.

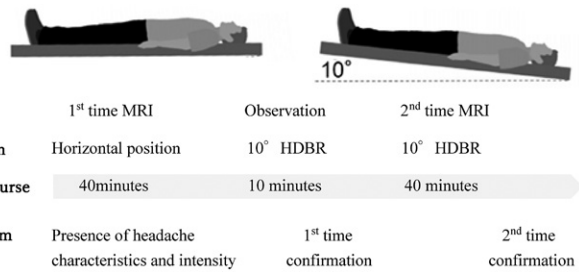

Fig. 1. All subjects underwent R-fMRI and DTI on a 3.0-T MRI scanner in the horizontal supine position and HDBR for 40 min each. First, imaging was performed in the horizontal position, followed by 10 min of observation as HDBR, and if there were no problems, a second imaging was performed as is. Headache symptoms and intensity were evaluated 10 min after the start of HDBR and after the second MRI under HDBR.

Image Analysis

DTI is a method to analyze the amount and direction of diffusion of water molecules by applying a tilted magnetic field in six directions. The amount of diffusion in the direction of the long axis of the molecule is known as axial diffusivity (AD), the amount of diffusion perpendicular to AD is known as radial diffusivity (RD), and the average of the three directions is known as mean diffusivity (MD). Fractional anisotropy (FA) is an indicator of the directionality of diffusion, and its value is 0 for all isotropic directions in free water and 1 when restricted to only one direction.[22] In this study, Tract-Based Spatial Statistics (TBSS) was performed by aggregating the voxel unit values of the whole brain into a mean white matter skeleton, with standardized brain morphology, and comparing them in the horizontal supine position and HDBR to perform whole-brain analysis. The FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl) was used to create FA, AD, RD, and MD skeletons for each subject. From these white matter skeletons, we extracted regions of interest (ROIs) in the knee and body and the splenium of corpus callosum, where several significant differences between subjects with migraine and healthy subjects have been reported in previous studies[25–27] using the ICBM-DTI-81 white-matter labels atlas.[15]

Functional MRI (fMRI) is an imaging method that captures changes in the amount of oxidized hemoglobin associated with increased brain activity as blood-oxygenation-level-dependent.[6] Although fMRI is usually performed with some tasks, R-fMRI which explores brain activity at rest without a task, is highly reproducible and reliable and is suitable for observing network changes during headaches. In the present study, we used R-fMRI and the subjects were asked to keep their eyes closed and not to think during the 7-min imaging period. We selected 30 ROIs, including the frontal cortex, cingulate cortex, insular cortex, bridges, and cerebellum, which have been reported to change functional connectivity (FC) in many studies of headache.[21]

Statistical Methods

All analyses were performed using SPSS version 28.00 (IBM, Armonk, NY), with Fisher's exact test for gender and a two-sample unpaired *t*-test for age between the two groups of headache and non-headache subjects. Mean FA, MD, AD, and RD in the ROIs of the corpus callosum of all 28 subjects were calculated using the paired *t*-test program, MATLAB (R2017a). Non-parametric tests (permutation test; 5000 times) and family-wise error correction were performed for each voxel using the randomized program, with a significance level of < 5%. CONN was used in the R-fMRI analysis, and a paired *t*-test was conducted before and after HDBR in all 28 cases for each of the mean FC values in 30 ROIs, viz., the above-described pain-related regions. Next, FC comparisons were performed between the headache and non-headache groups using *t*-tests in the same 30 ROIs. In both analyses, $P < 0.05$ was considered significant using multiple comparison corrections for the false discovery rate (FDR). Correlation analyses were performed between NRS and all FCs obtained from the 30 ROIs before and after HDBR. The Pearson correlation coefficient was determined. The significance level was set at $P < 0.05$.

RESULTS

Of the 28 subjects in this study, 21 developed headaches and 7 did not. The mean age was 44.3 ± 11.6 yr in the headache group and 54.7 ± 10.9 yr in the non-headache group ($P = 0.05$). Headache intensity was mild in 13 patients, moderate in 7 patients, and severe in 1 patient, with a median NRS of 1.5 at 10 min after the start of HDBR and 1.5 at the end of the second MRI. Headache symptoms included a sense of heavy feeling in 12 patients, congestion in 7 patients, and pressing in 2 patients. None of the subjects complained of nausea or other associated symptoms (**Table I**). After the second MRI with HDBR, the condition of the patients in the headache group immediately recovered, and no patient had a prolonged headache.

DTI analysis showed no significant difference in FA values between before and after HDBR. On the other hand, AD, RD, and MD significantly increased in the genu of the corpus callosum after HDBR. AD and MD also increased significantly in the body and splenium of the corpus callosum after HDBR (**Fig. 2**, **Table II**).

R-fMRI analysis showed a significant decrease in FC after HDBR between the left cerebellum and bilateral inferior frontal gyrus (pars opercularis and triangularis) as well as

Table I. Characteristics of All Subjects Included in the Study.

CHARACTERISTIC	HEADACHE GROUP (*N* = 21)	NON-HEADACHE GROUP (*N* = 7)	*P*-VALUE
Mean of age, yr ± SD.	44.3 ± 11.6	54.7 ± 10.9	0.05*
Gender, women/men	14/7	3/4	0.381**
Basic disease (%)			
Overactive bladder	0	1	NA
Hyperuricemia	1	0	NA
Anemia	2	0	NA
Sinusitis	1	0	NA
Duodenal ulcer	0	1	NA
Dermatomyositis	0	1	NA
Spinal canal stenosis	1	1	NA
Diabetes	0	1	NA
Median NRS (percentile)			
10 min after starting HDBR	1.5 (0.00-3.00)	—	NA
After HDBR imaging	1.5 (0.25-4.00)	—	NA
Severity			
Mild	13	—	NA
Moderate	7	—	NA
Severe	1	—	NA
Character			
Heavy feeling	12	—	NA
Congestion	7	—	NA
Pressing	2	—	NA

SD = standard deviation; NA = not applicable.
*Two-sample unpaired t-test.
**Fisher's exact test.

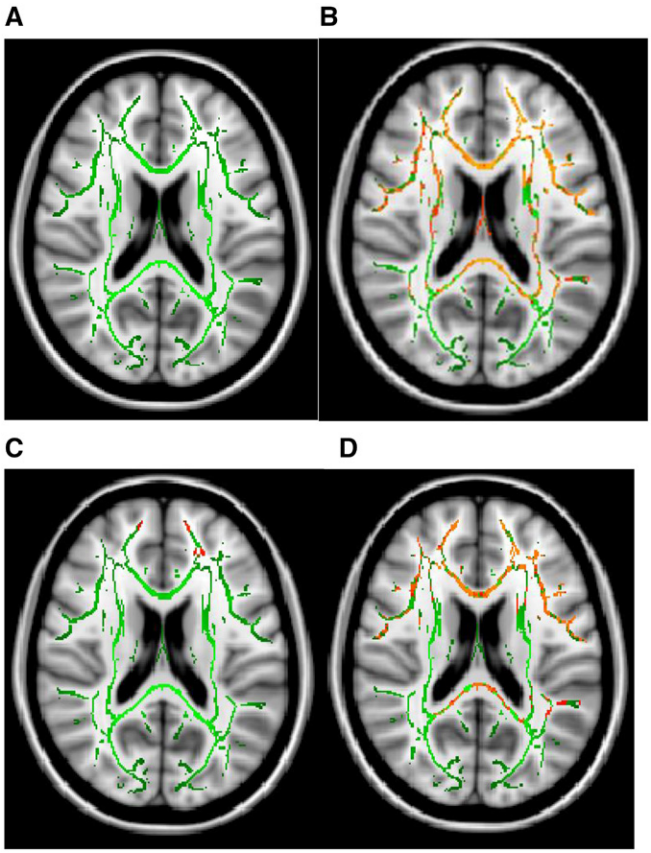

Fig. 2. TBSS shows changes in FA, AD, RD, and MD before and after HDBR. The orange part shows a significant increase in AD, RD, and MD after HDBR. AD and MD also increased significantly in the body and splenium of the corpus callosum after HDBR.

bilateral frontal orbital cortex (family-wise error corrected, $P < 0.05$). FC also significantly decreased between the right cerebellum and right inferior frontal gyrus (pars triangularis), as well as right frontal orbital cortex and between the frontal medial cortex and cingulate gyrus (posterior division). There was no increase in FC after HDBR in all regions (**Fig. 3A**). In comparison between the headache and nonheadache groups, FC was significantly higher between the right inferior frontal gyrus and left cerebellum in the headache group before HDBR, i.e., before headache onset (Family Wise Error corrected, $P < 0.05$, **Fig. 3B**). After HDBR, FC was significantly higher between the brainstem and left inferior frontal gyrus (pars opercularis, triangularis), left hypothalamus, and left cerebellum in the headache group. FC was significantly higher between right frontal eye field and right cerebellum in the nonheadache group (uncorrected, $P < 0.01$, **Fig. 3C**). Correlation analysis of NRS and all FCs obtained from the 30 ROIs revealed a positive correlation between NRS and FC related to the "hypothalamus" before head down (Pearson correlation coefficient 0.448, $P = 0.017$). In other words, the higher the FC associated with the hypothalamus at rest, the stronger the headache at head down (**Fig. 4A**).

After head-down, we detected a negative correlation between NRS and FC related to the thalamus and cerebellum (Pearson correlation coefficient −0.541, $P = 0.003$). In other words, the higher the headache intensity, the lower the functional coupling related to the thalamus and cerebellum (**Fig. 4B**).

Table II. DTI Values Before and After HDBR.

DIRECTION OF DTI IN AREA OF CORPUS CALLOSUM	PRE-HDBR ($mm^2/s \times 10^{-3}$)	POST-HDBR ($mm^2/s \times 10^{-3}$)	*P*-VALUE
AD			
Genu	0.974 ± 0.058	1.012 ± 0.087	0.0227*
Body	1.005 ± 0.053	1.049 ± 0.086	0.00915*
Splenium	0.999 ± 0.055	1.031 ± 0.092	0.0467*
RD			
Genu	0.238 ± 0.049	0.246 ± 0.051	0.0273*
Body	0.279 ± 0.047	0.287 ± 0.054	0.169*
Splenium	0.190 ± 0.029	0.195 ± 0.033	0.214*
MD			
Genu	0.483 ± 0.045	0.501 ± 0.054	0.0206*
Body	0.521 ± 0.039	0.541 ± 0.055	0.0266*
Splenium	0.460 ± 0.028	0.473 ± 0.046	0.0735*

*Two-sample paired t-test.

DISCUSSION

We were able to capture the acute change in brain microstructure due to headache that occurs during a short HDBR. A study reported that increases in FA, MD, RD, and AD were observed in the optic nerve sheaths of 5 head-down tilt conditions in 9 subjects: (−6°, −12°, −18°, −12°, and 1% CO_2, and −12° + lower body negative pressure) after 4.5 h, which were reported to be due to increased perioptic cerebral spinal fluid hydrodynamics during head-down tilt.[8] Another report indicated that at −6° HDBR for 30 d, FA increased in some areas and decreased in others, and it was concluded that increased FA might reflect the strengthened connectivity in microgravity conditions, and that decreased FA was linked to an increase in the extracellular space (dysmyelination, axonal degeneration, and release of white matter fibers) and a decrease of the intracellular space (edema) in the white matter.[11]

Other headache pathophysiology studies have also reported fluctuations in these diffusions, with reports of decreased AD, RD, and MD in the corpus callosum in idiopathic intracranial hypertension.[19] Idiopathic intracranial hypertension is a disease of unknown pathogenesis characterized by headache, nausea, and optic papillary edema, which is thought to be caused by excessive cerebrospinal fluid production and absorption and venous return disorders.[13]

In idiopathic intracranial hypertension, axonal degeneration due to long-term intracranial hypertension and ventricular size enlargement may have resulted in decreased water molecule diffusion, whereas in the present study, acute white matter compression due to head-down tilt may have resulted in increased diffusion per unit volume. Thus, microstructural changes can be detected even in acute headaches due to HDBR and may represent anatomical changes similar to those in space headaches.

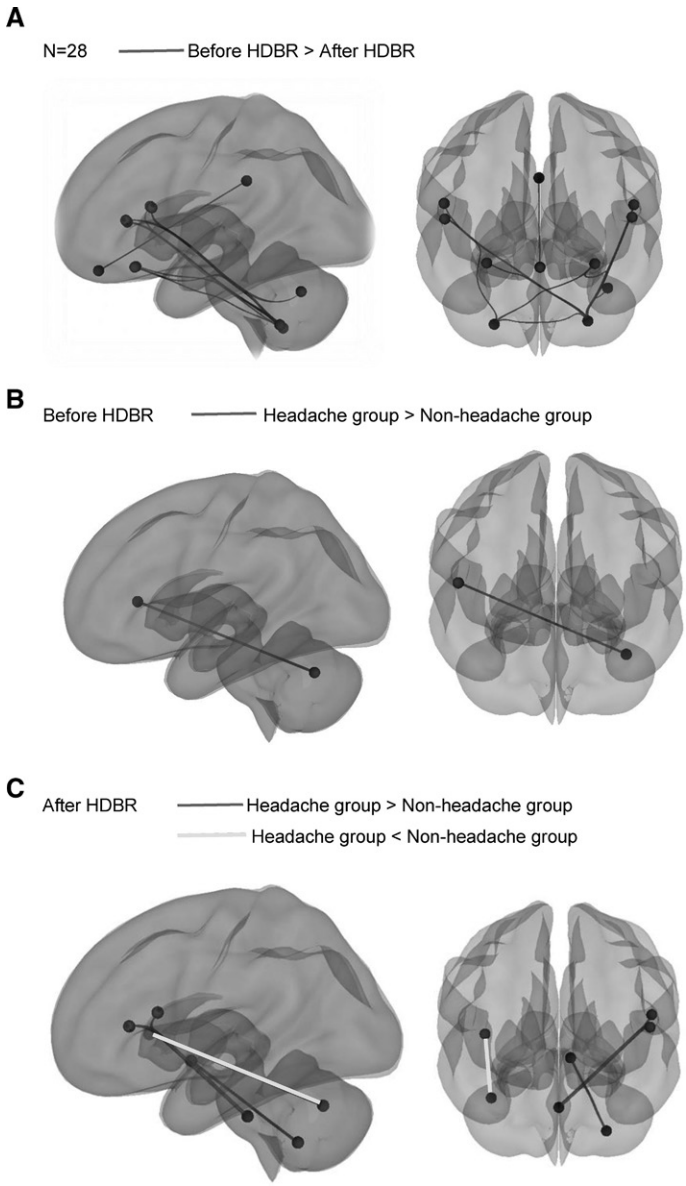

Fig. 3. Comparison of FC in 28 subjects before and after HDBR and comparison of FC between the headache and non-headache groups. A) The gray lines show that FC decreased significantly after HDBR in comparison to before HDBR. B) The gray line shows that FC significantly increased before HDBR between the right inferior frontal gyrus and left cerebellum in the headache group, in comparison between the headache and non-headache groups. C) The gray lines show that FC significantly increased after HDBR between the brainstem and left inferior frontal gyrus valgus and triangle, and between the left hypothalamus and left cerebellum in the headache group, in comparison between the headache and non-headache groups. The white line shows that FC significantly increased after HDBR between the right frontal eye field and right cerebellum in the non-headache group, in comparison between the headache and non-headache groups.

Regarding the relationship between headache and FC, it has been reported that FC in the brainstem and hypothalamus increases during migraine attacks.[15] But in the present study, the R-fMRI analysis revealed a significant decrease in FC after HDBR, and there was no increase in FC after HDBR. These results indicate that headache due to HDBR is associated with reduced brain function. In other words, the ability to control pain may be transiently reduced. Comparing the headache and non-headache groups, FC was significantly higher in the headache group before and after HDBR. In comparison with normal subjects, migraine patients in the interictal period showed higher connectivity between the periaqueductal white matter of the midbrain and right dorsolateral prefrontal cortex, right superior border gyrus, right anterior insular cortex, bilateral precentral gyrus, right postcentral gyrus, right thalamus, left angular gyrus, left supramarginal gyrus, and parietal opercular part.[12] The periaqueductal gray matter of the midbrain is known as a descending pain suppression pathway in the central nervous system, which descends from the insula and hypothalamus to the trigeminospinal tract nucleus.[16] It is possible that the brain activity in these regions is higher in the headache group than in the normal group from normal times. In a comparative study of migraine patients during the paroxysmal phase with healthy controls, migraine patients showed increased

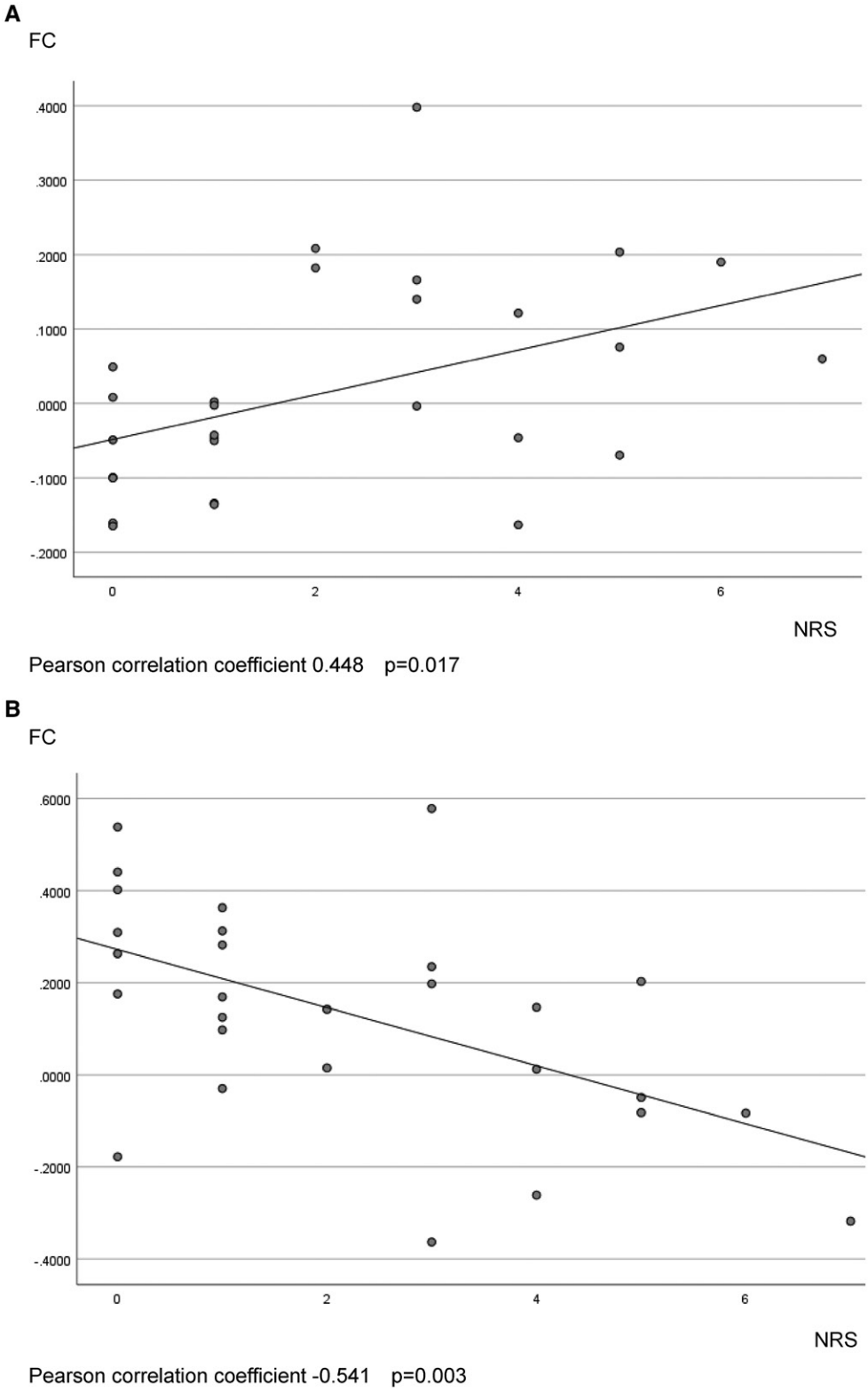

Fig. 4. Correlation analysis of NRS and all FCs obtained from the 30 ROIs. A) Positive correlation between NRS and FC related to the "hypothalamus" before head-down. B) Negative correlation between NRS and FC related to the "thalamus and cerebellum" after head-down.

connectivity between the medial prefrontal cortex (MPFC) and the insula and posterior cingulate gyrus.[2] The brainstem, cerebellum, and hypothalamus, which had significantly higher FC in the headache group after HDBR, have been recognized as pain-related regions in known headache studies, including migraine,[16] suggesting that these regions are also activated in this headache. Regarding the correlation analysis between FC and NRS, previous migraine studies have reported that the

hypothalamic activity increases 48 h before an attack and that the hypothalamus and areas with high FC change from the aura period to the attack period.[20] The positive correlation between FC and NRS associated with the hypothalamus before head-down in the present study suggests that the hypothalamus is also more active than normal in the headache group.

Furthermore, the thalamus and cerebellum are pain-related regions in headache. The thalamus transmits pain signals from the trigeminal nerve to the cerebral cortex in migraine. The cerebellum is one of the ascending tracts where pain is transmitted from the trigeminal spinal nucleus to the hypothalamus and brainstem (parabarachial nucleus and solitarius of the midbrain and pons).[16] The negative correlation between FC and NRS associated with the thalamus and cerebellum after head-down in the present study suggests that the higher the headache intensity, the lower the function of the thalamus and cerebellum. However, it is unclear from the present study whether the functional decline was the cause of the headache or the result of the headache and requires further investigation.

There are several limitations to this study. First, it is a single-arm study with a small population of 28 participants. Second, the HDBR time is short, approximately 50 min. Several previous studies using HDBR, not only headache studies, have performed HDBR from a few hours to 30 d.[7,11] In this study, due to the limitation of the examination schedule, the imaging analysis captured only the acute changes immediately after HDBR. Analysis of the microstructure of headache produced by prolonged HDBR is a subject for future study. Third, ROIs were placed in 30 locations and we did not devise detailed segmentation, including a breakdown of the interior of the brainstem. Similar studies on headaches (such as migraine) have measured FC in detailed ROIs (such as the trigeminal nucleus),[20] but the CONN used in this study automatically obtains ROIs covering the entire brainstem, including the midbrain, pons, and medulla. Therefore, analysis including detailed brainstem segmentation is a topic for future research.

In this study, the most fundamental limitation is that HDBR does not reproduce the complete space environment. Although HDBR studies have been considered as established models to mimic the physiological effects of outer space microgravity on the human body,[5] in addition to fluid shifts due to microgravity, other effects of the space environment on the human body include galactic cosmic rays and localized high CO_2 effects in the ISS. It has been reported that CO_2 concentration is higher on the ISS than on the ground, and that the higher the concentration, the higher the frequency of headaches.[10] It has also been noted that high CO_2 concentrations in the ISS affect the ability to regulate cerebral blood flow.[28] Previously, HDBR has been mainly performed at −6°,[5,11,23] but a recent study reported that a combination of mild hypercapnia (exposure to 3% CO_2, which increases end-tidal CO_2 to 6 mmHg) and −10° HDBR affected dynamic cerebral autoregulation and cerebral blood flow.[9] In the present study, we employed −10° HDBR only to investigate the effect of fluid shift alone (excluding the CO_2 effect) on headache onset. Studying the effects of combined exposure to fluid upward shift and high CO_2 on space headache is a subject for future study.

Although there have been imaging studies using DTI and fMRI during HDBR,[11,14] there have been no previous studies using MRI to analyze microstructural and brain function changes during HDBR-induced headache, which we believe is highly novel.

In this study, we reproduced the pathophysiology of space headache by using HDBR to simulate the space environment and revealed acute changes in brain microstructure and function. The results suggest that changes in brain microstructure during headache onset and the strength of FC characteristic of patients who develop headaches may be evaluated by imaging. These results may be useful for predicting the onset of space headaches and for health management during human space exploration.

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