Hippocampal volume changes in astronauts and Bilateral Vestibulopathy patients

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Abstract

The hippocampus is a particularly plastic and vulnerable brain structure. Given the modulatory role of the vestibular system on hippocampal function, we hypothesized that altered vestibular stimulation associated with prolonged spaceflight could lead to similar hippocampal volume changes in astronauts after long-duration spaceflight and in individuals with bilateral vestibulopathy (BV), as a ground analog of spaceflight. We quantified hippocampal volumes using magnetic resonance imaging (MRI) in astronauts before and after spaceflight and in BV patients relative to matched healthy controls. MRI analyses revealed a significant decrease in the left hippocampal volume (-2%) and an increase in the total volume of the ventricles (+ 11%) postflight in astronauts. The variations in volume of right and left hippocampus and ventricles were not correlated with each other, suggesting that the cerebrospinal fluid redistribution that occurs with spaceflight does not contribute to hippocampal volume changes. BV patients exhibited reduced hippocampal volumes compared to matched controls (-6% left and − 4% right), suggesting that reduction of vestibular inputs, due either to microgravity or a disease, may contribute to hippocampal atrophy. Furthermore, in both astronauts and BV patients, hippocampal volume correlated negatively with age, suggesting increased vulnerability of older individuals to vestibular-related neurodegeneration. Overall, our findings suggest that hippocampal atrophy in astronauts is not driven by mechanical compression, but it may be affected by reduced vestibular input, aligning with observations in terrestrial vestibular loss.

Introduction

Spaceflight presents one of the most extreme environments humans can experience, exposing astronauts to several environmental stressors including weightlessness. Weightlessness challenges all body systems, and particularly the central nervous system, which must adapt to maintain proper sensorimotor control and cognitive performance during long-duration missions. Indeed, studies report structural and functional changes in the brain after long-term spaceflights [1–5].

One of the major reasons leading to the brain changes due to spaceflight is mechanical. Weightlessness leads to an upward shift of the body fluids, such as blood and the cerebrospinal fluid (CSF), as they are no longer pulled downward by gravity; this is thought to lead to an upward displacement of the brain in the cranium, and increased pressure of the CSF in the head. This increased CSF volume could result in an increase in the ventricular volume and potentially some compression in the brain tissues. Multiple MRI studies report increased ventricular volume [6–9] perivascular space morphological changes [10], and an upward displacement of the brain [9,11–13] after spaceflight. Ventricular volume changes correlate with the flight duration [8,9] and show some recovery several months after the return to Earth [14].

There are other ways in which spaceflight might change the brain. In normal Earth conditions, the brain continuously receives information about gravity and motion through the vestibular system and other graviceptors [15]. The semicircular canals in the vestibular organ detect angular velocity, while the graviceptors including otolithic vestibular organs detect the gravitoinertial acceleration, the summary stimulus resulting from linear accelerations and gravity. This information contributes to sensorimotor function and spatial orientation [16]. In weightlessness, the gravitational part of these signals is absent, so the brain areas usually receiving otolith inputs experience altered afferent signals. Some adaptive changes or even atrophy might be evident in brain areas processing vestibular information[12]. Many studies report significant modifications in global white matter or gray matter volume after

spaceflight [11,17]. Studies often indicate an increase in the gray matter volume in posterior-parietal regions, and a decrease in the cortical thickness in fronto-temporal regions [3]. However, the researchers are cautious of whether the observed changes are due to plasticity or rather linked to the fluid redistribution [3,4,11,14], as the pattern of the modifications can indicate the upward shift of the brain tissue, with the gray matter crowding at the vertex.

A recent study has reported a significant decrease in the left anterior hippocampus in astronauts postflight [18]. The hippocampus plays a central role in spatial navigation and receives vestibular inputs. Moreover, this brain region is known to be particularly plastic, with the hippocampal dentate gyrus being one of the rare regions in the central nervous system where adult neurogenesis has been observed. Otolithic function has previously been associated with hippocampal volume [19] and spatial memory [20]. The hippocampus is also particularly sensitive to various environmental stressors. This makes the hippocampus a good candidate for neuroplastic modifications occurring with spaceflight.

A reduction in hippocampal volume has been found in people with vestibular disorders. The first evidence was from patients following bilateral vestibular neurectomy, who presented a bilateral hippocampal atrophy of approximately 17% [21]. Hippocampal volume decreases have been reported in subsequent studies, with atrophies in different hippocampal subregions [22–25]. This vestibular-related loss of the hippocampal volume suggests that the astronauts might also experience some degree of hippocampal atrophy after spaceflight due to the decrease in vestibular afference in the absence of gravitational stimulation.

Our aim was to determine whether hippocampal volume changes in astronauts after long-duration spaceflight. Moreover, we analyzed differences between bilateral vestibulopathy patients and an age-and sex matched control group. We hypothesized that astronauts postflight compared to preflight and BV patients compared to control subjects would present as diminution in the hippocampal volume.

Results

Hippocampal Volume in Astronauts

The linear mixed model showed a significant effect of session (pre-/post-flight) in the left hippocampus, but not the right hippocampus (Table 1; Figure 1). The left hippocampus showed a volume loss of 2% postflight.

Table 1: The results of the linear mixed model for the left and right hippocampal volumes in astronauts, including the total brain volume as a covariate and session (pre/post-flight), sex and age as fixed effects.

	LEFT					RIGHT				
	Estimate	SE	df	t	p-value	Estimate	SE	df	t	p-value
(Intercept)	3516.0	935.4	13.0	3.8	0.002	4295.0	944.5	13.1	4.5	0.001
Brain Volume	0.0	0.0	13.5	0.7	0.515	0.0	0.0	13.6	0.0	0.971
Pre/Post flight	-71.9	32.1	14.3	-2.2	0.042	26.0	31.8	14.3	0.8	0.427
Sex M	159.5	195.9	12.0	0.8	0.431	212.6	197.9	12.0	1.1	0.304
Age	-4.1	11.1	11.2	-0.4	0.717	-10.6	11.2	11.2	-0.9	0.363

[insert figure 1 about here]

Ventricular Volume change in Astronauts

The linear mixed model showed a significant effect of the session (pre-/post-flight) in total ventricular volume. The model indicates a significant increase in ventricular volume postflight compared to preflight (Table 2; Figure 2). On average, ventricular volume increased by 11%. Both the left (β = 753, SE = 113, t = 6.7, p<0.001) and the right (β = 802, SE = 99, t = 8.1, p<0.001) lateral ventricles showed increases.

Table 2: the results of the linear mixed model for the total ventricular volume in astronauts, including the total brain volume as a covariate and session (pre/post-flight), sex and age as fixed effects.

	Total ventricular volume				
	Estimate	SE	df	t	p-value
(Intercept)	5727.0	22800.0	20.9	0.3	0.804
Brain Volume	0.0	0.0	23.0	-0.5	0.595
Pre/Post flight	1912.0	252.2	13.1	7.6	0.000
Sex M	3520.0	5717.0	13.8	0.6	0.548
Age	320.1	366.2	10.8	0.9	0.401

[insert figure 2 about here]

Hippocampal Volume - **BV patients *vs* controls**

The linear model showed a significant effect of group (BV/CT), brain volume, and sex in the left and right hippocampi (Table 3, Figure 3). The CT group had a positive effect on the hippocampal volume of both sides, and the male sex had a negative effect on the hippocampal volume. On average, the BV group presented 6% less volume in the left hippocampus and 4% in the right hippocampus.

Table 3: the results of the linear model for the left and right hippocampal volumes in BV patients and control subjects, including the total brain volume as a covariate and group (BV/CT), sex and age as fixed effects.

	LEFT				RIGHT			
	Estimate	SE	t	p-value	Estimate	SE	t	p-value
(Intercept)	1108.0	356.9	3.1	0.003	411.5	390.7	1.1	0.297
Brain Volume	0.0	0.0	8.3	0.000	0.0	0.0	9.6	0.000
Group CT	171.6	50.6	3.4	0.001	114.1	55.4	2.1	0.044
Sex M	-241.2	61.5	-3.9	0.000	-252.2	67.3	-3.7	0.000
Age	-4.5	2.3	-2.0	0.052	-1.4	2.5	-0.6	0.565

[insert figure 3 about here]

Correlation Hippocampal Volume vs Age

Astronauts preflight vs postflight

Left hippocampal volume change pre to postflight was significantly correlated with age in astronauts (Pearson's R = -0.63; p = 0.01; Figure 4). Right hippocampal volume change pre to postflight was not significantly correlated with age in astronauts (Pearson's R = -0.30; p = 0.28).

[insert figure 4 about here]

BV patients VS controls

Left hippocampal volume was significantly correlated with age in BV patients (Pearson's R = -0.59; p = 0.0006, Figure 5), but not in control subjects (Pearson's R = -0.24; p = 0.208). Right hippocampal volume was also significantly correlated with age in BV patients (Pearson's R = -0.47; p = 0.009), but not in control subjects (Pearson's R = -0.14; p = 0.472).

[insert figure 5 about here]

Correlation Hippocampal Volume vs Ventricular Volume changes in Astronauts

The percentage of change in the left hippocampus pre to postflight was not significantly correlated with the percentage of change in the left lateral ventricle (Pearson's R = -0.36; p-value = 0.18). The percentage of change in the right hippocampus pre to postflight was not significantly correlated with the percentage of change in the right lateral ventricle (Pearson's R = 0.21; p-value = 0.45)

Discussion

In this study we investigated changes in hippocampal volume in astronauts after approximately 6 months of spaceflight. We also investigated whether these volume modifications were associated with increased ventricular volume. We also quantified the hippocampal volume of subjects with BV compared to matched controls.

We observed a significant decrease of the left hippocampal volume (-2%) and an increase in the ventricular volume (+ 11%) in astronauts postflight compared to preflight. However, these changes were not correlated with each other. The BV subjects presented a lower hippocampal volume than the control subjects (6% left and 4% right). In astronauts, the degree of loss of the hippocampal volume after the flight correlated with their age. Hippocampal volume also correlated with age in patients but not in controls.

To our knowledge, there has been only one study evaluating hippocampal volume changes in astronauts after the spaceflight [18]. They evaluated 17 astronauts, 8 females, with mean age 45.3 ± 5.8 years old) who participated in ISS missions with an average duration of 189.0 ± 63.2 days. Data were collected on average 224 days before launch and about 13 days after landing as part of the Canadian Space Agency (CSA) 'Wayfinding' project. The study evaluated the whole hippocampal volume and its anatomical (anterior, body, and posterior) subregions and found a significant decrease in the left hippocampus, particularly its anterior part. Our postflight data was collected on average 5 days after the flight and our results corroborate these findings, showing a significant decrease in the left hippocampal volume postflight compared to pre-flight.

Several spaceflight-related stressors could contribute to this loss. For example, previous studies have found that hippocampal atrophy is observed due to isolation [26,27], radiation [28,29], sleep deprivation [30], and emotional stress [31]. However, we also observed the reduction of the hippocampal volume in BV subjects, which indicates that the atrophy might occur due to the altered vestibular inputs. Previous studies on the hippocampal volume in BV provide conflicting results. While the first evidence of bilateral hippocampal atrophy in patients following bilateral vestibular neurectomy was robust [21] and this result was followed by subsequent studies that found with atrophies in different hippocampal subregions [22–25], some studies found no difference in the hippocampal volume of BV patients [32–34]. The difference in the results can be related to the methodology of the study, the exact nature of the vestibular loss, such as partial preservation of the saccular function [19], the time since the loss of vestibular function, and potentially the sex and age of patients in the group. Aging is generally associated with the gradual loss of hippocampal volume [35]. Spaceflight, as an environment full of stress factors, may accelerate this loss. Indeed, in our study, the degree of atrophy of the left hippocampus is correlated with age in astronauts. That is, older astronauts presented a greater degree of atrophy after the spaceflight than younger ones. In patients, the hippocampal size also correlated with age for both right and left hippocampus, but such correlation was not found in the control subjects. This indicates that older individuals presenting the loss of the vestibular function present a greater degree of age-related hippocampal atrophy than the general population [36] without BV. This finding might partially explain the inconsistency of the results in the literature. This finding echoes observations in mice, that showed that the hippocampus of younger mice is more resilient to stressors than in older mice [37]. In humans, such evidence has been less direct, but studies indicate that the concentration of regulators of neurogenesis such as brain-derived neurotrophic factor (BDNF), which is highly associated to the induction of neuron survival and differentiation of hippocampal stem cells, is decreased in older age [38,39]. This might contribute to reduced stress resilience.

The decrease in the hippocampal volume in BV patients was greater than the one found in astronauts. This may be partly explained by a shorter duration of the exposure to the altered vestibular inputs, and by the fact that in weightlessness only the gravitational part of the vestibular information is lacking. This difference between groups might also be related to age. Our data suggests that hippocampal atrophy due to stressors (BV, spaceflight) is more pronounced with older age, and the patient group was on average older than the astronauts.

The hippocampal volume loss observed in this study is asymmetrical. Left hippocampus presents a greater loss in the patients' group and the greater correlation with age, and only the left hippocampus presented a significant loss in astronauts. This lateralized atrophy may have functional implications. The literature supports functional lateralization of the hippocampus, [40,41] with the right hippocampus usually linked to spatial memory and navigation, and the left more involved in verbal memory processing. We would expect the right-side dominance for the vestibular-related atrophy. There are, however, studies suggesting a more nuanced implication of both hippocampal sides for navigation functions [42]. Several factors have shown lateralized effect of the left hippocampus volume. For example, the left hippocampus has been found more vulnerable to stress [43,44]. Physical exercise was associated with increases in left hippocampal volume [45,46]. Vestibular patients present reduced physical activity often linked to the fear of falling [47]. The spaceflight environment imposes numerous stressors and reduced physical activity despite regular exercise. These factors may contribute to the volume loss specifically in the left hippocampus.

We have found a significant increase in the ventricular volume in astronauts after spaceflight. This finding corroborates with the literature and is supported by a large number of previous studies [6–9]. We suggested that if the hippocampal volume change was due to mechanical compression of brain tissues, we would observe an inverse correlation between the percentage of the hippocampus atrophy and the percentage of the increase of the ventricular volume. We observed no correlation between the modifications of these volumes. This supports that the observed atrophy in the left hippocampus is likely to be the result of altered vestibular signaling.

The heterogeneity of the BV group, regarding etiology, residual vestibular function, and time since onset may have contributed to hippocampal volume variability. The MRI acquisitions of astronauts and BV subjects were not performed under identical scanner settings or environmental conditions; however, this study does not directly compare the data from these conditions. Freesurfer's accuracy in identifying the lateral inferior horn of the ventricles has previously been reported not optimal[48,49], which might affect the ventricular volume estimation. We addressed this limitation by thorough manual quality check of the segmentation. Finally, the cross-sectional observation in BV patients and astronauts does not allow for establishing a direct causal link between the loss of a vestibular input and spaceflight-induced hippocampal changes.

Conclusion

Our findings demonstrate a significant postflight decrease in left hippocampal volume and a concurrent increase in ventricular volume in astronauts after approximately six months in space. The absence of a correlation between these changes suggests that hippocampal atrophy is not primarily due to mechanical compression from CSF redistribution. We suggest that this loss is rather related to the decrease of the vestibular input caused by prolonged weightlessness. This interpretation is supported by the reduced hippocampal volume observed in individuals with bilateral vestibular loss. The correlation between age and hippocampal atrophy in astronauts and patients suggests that older individuals may be more vulnerable to vestibular-related hippocampal degeneration, which supports similar findings in animals. Together, these results provide new evidence linking vestibular input to hippocampal integrity in both terrestrial and microgravity conditions.

Methods

Participants

Astronauts

We analyzed the brain scans of 15 astronauts (47.3 ± 6.5 years old; 4 women) who completed 6-month or 12-month missions (average 191 days) on the International Space Station. The MRI sessions were done 66.9 ± 25.0 days before launch and 4.8 ± 1.3 days after return from the ISS.

Patients and controls

We recruited 30 patients with Bilateral Vestibulopathy (BV) (58.8 ± 12.9 years old; 17 women) from the Association Française de Vestibulopathie Bilatérale [50] and tested in the COMETE Laboratory at the University of Caen. Age and sex-matched control (CT) subjects (58.9 ± 13.5 years old) participated in a control study in the COMETE

Laboratory. The groups were also matched by the study level (2.8 ± 2.5 years after high school level for BV; 2.8 ± 2.2 for CT).

The diagnostic criteria for the BV subjects strictly followed the guidelines outlined in the consensus document by the Classification Committee of the Bárány Society [51]. In addition, we excluded patients with hearing loss or neurological symptoms, whether central or peripheral. The BV subjects in this study experienced the condition for an average of 8 ± 2 years. The caloric nystagmus velocities of all subjects were below 6°/s. Most of the BV subjects (90%) showed deficits in the video head impulse test, with no compensatory eye movements and multiple catch-up saccades. Twenty-three of the BV subjects had reduced utricular responses (ocular vestibular evoked myogenic potential (oVEMP) amplitude below 100 μV), although 16 of these subjects retained cervical vestibular evoked myogenic potential (cVEMP) responses, indicating preserved saccular function. None of the BV subjects experienced positional vertigo or exhibited signs of cerebellar ataxia. An etiology of BV was found in 7 patients (ototoxic drugs for 4 patients and genetic causes for 3 patients), the others being considered idiopathic and degenerative in nature, which is in line with the literature given the exclusion criteria we used [52].

The astronaut study protocol was reviewed and approved by the NASA (Pro0252), University of Michigan (HUM00050878), and University of Florida (IRB201701528) IRBs. The patients' and controls' protocol was approved by the French Ethical Committee (Comité de Protection des Personnes de la Région Ouest I, No: ID-RCB 2022-AO1513-40). All subjects provided written informed consent before participating in the study. The test procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

MRI acquisition

Astronauts

T1-weighted anatomical MRI scans were acquired using a 3.0 T Siemens Magnetom Verio scanner at the University of Texas Medical Branch, Victory Lakes, TX. Acquisition parameters were as follows: magnetization-prepared rapid gradient-echo (MPRAGE) sequence, repetition time (TR) = 1900 ms, echo time (TE) = 2.32 ms, flip angle = 9°, field of view (FOV) = 250 × 250 mm, slice thickness = 0.9 mm, 176 sagittal slices, matrix size = 512 × 512, and voxel dimensions = 0.49 × 0.49 × 0.9 mm^3 (0.22 mm^3) [6,53].

Patients and controls

All patients' and controls' data were collected using a 3T MRI scanner (MRI GE 3T SIGNA Premier) at Cyceron, Caen, France. T1-weighted anatomical MRI images were acquired using a 3D magnetization-prepared rapid gradient-echo sequence (3D MPRAGE) sequence (TR = 2339 ms, TE = 3.088 ms, flip angle = 8°, FOV = 256 × 256 mm, slice thickness = 1 mm, 178 slices, matrix size = 256 × 256, and voxel dimensions = 1.0 × 1.0 × 1.0 mm^3). T2-weighted 2D-FSE oblique coronal scan perpendicular to the main hippocampus axis were performed with the following parameters: TR = 8000 ms, TE = 47.568, flip angle = 122°, FOV = 176 × 176 mm, slice thickness = 2 mm, 35 slices, matrix size = 448 × 448, voxel dimensions = 0.3929 × 0.3929 × 2.0 mm^3.

MRI preprocessing

Preprocessing and parcellation of all images were conducted using the recon-all pipeline implemented in FreeSurfer (version 7.4.0; [54]), including motion correction, nonparametric nonuniform intensity normalization, computation of the Talairach transform, global intensity normalization, and skull stripping. FreeSurfer's hippocampal subfields toolbox was used to extract hippocampal volume (Fig. 6) [55]. Manual inspection for each hippocampus extraction was done to check the quality of hippocampal segmentation (P.K.). Total brain volume, total ventricular volume and right and left lateral ventricular volumes were extracted using Freesurfer's segmentation.

As only T1 weighted images were available for the astronauts, while both T1 and T2 images were obtained for the BV and CT groups, we opted for a tool that could reliably extract hippocampal volumes both using only T1 weighted images, and T1 + T2 weighted images. We performed a test study comparing the T1-only based analysis and the T1 + T2 based analysis using different segmentation tools and concluded that Freesurfer segmentations of the whole hippocampus with T1 only images as well as with both T1 and T2 are well correlated (see Supplementary materials Fig. 1s).

[insert Fig. 6 about here]

Analysis

The left and right hippocampal volumes were compared between patients and control subjects using a linear model with the group, brain volume, sex and age as factors. In astronauts, the left and right hippocampal volumes were compared between preflight and postflight using linear mixed model, with the session (pre-post), brain volume, sex and age as factors.

We calculated the Pearson's correlation of the hippocampal volume with age for the patients and the controls, and the hippocampal volume change (%) calculated as postflight – preflight divided by preflight volume, for astronauts. Pearson's correlation was also calculated between the changes (%) in the hippocampal and ventricular volumes in astronauts.

All statistical analyses were performed in R [56] using the *stats* and *lmerTest* packages [57]. Data visualization was conducted in Python (Python Software Foundation, version 3.14) using the *matplotlib* [58] and *seaborn* [59] libraries.

Declarations

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Author Contributions

Astronauts study: S.W. and R.S. conceived the study and obtained funding. T.W. performed the data preprocessing. Patients and controls study: P.D. conceived the study and obtained funding. O.E., M.N., and R.S. designed the experiments. O.E., M.N., O.K., performed the experiments. P.K., conducted data preprocessing. O.K. and P.K.

performed data analysis. O.K. and O.E. interpreted the results. O.K. drafted the manuscript. All authors reviewed and approved the final manuscript.

Competing Interests Statement

The authors declare no competing interests.

Data Availability Statement

The code used for the analysis in this manuscript will be made available upon request. Data from the MRI data of astronauts must be requested through the NASA Life Sciences Portal. ((R. Seidler, Spaceflight effects on Neurocognitive performance: Extent, longevity, and neural bases. NASA Life Sciences Portal. https://nlsp.nasa.gov/view/lsdapub/lsda_experiment). Due to privacy and ethical restrictions, the MRI data of patients will not be shared.

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Figures

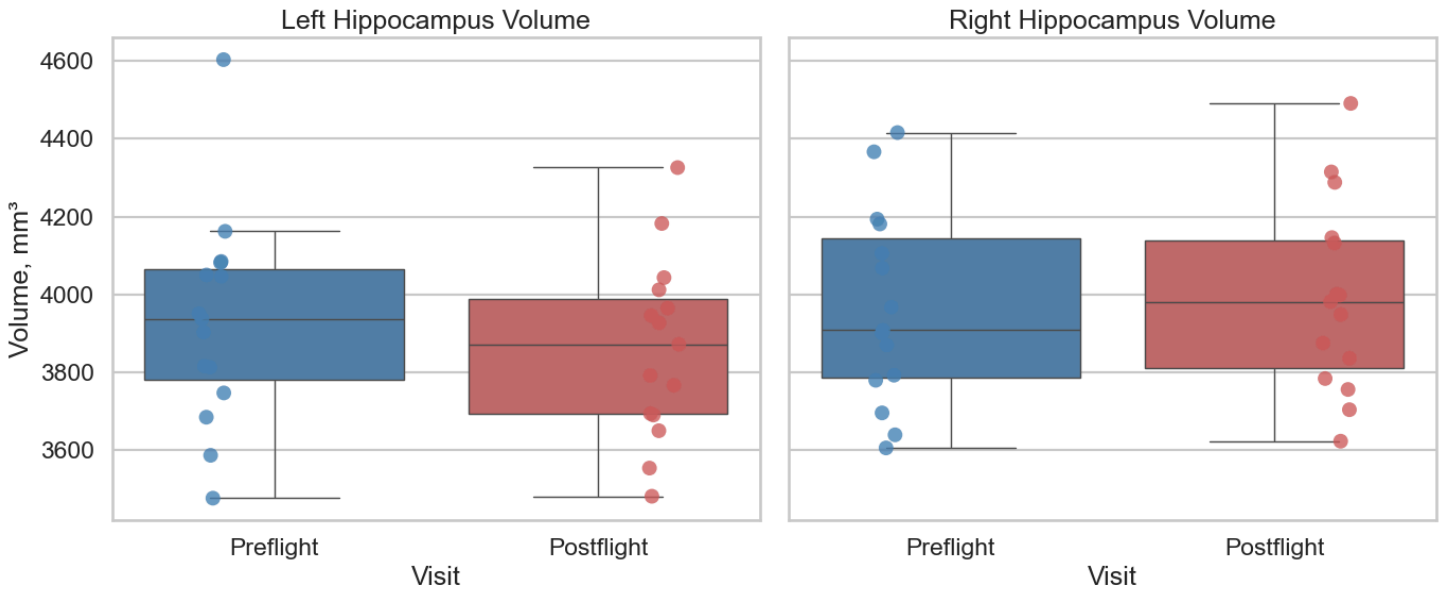

Figure 1

Left and right hippocampal volumes in astronauts preflight and postflight

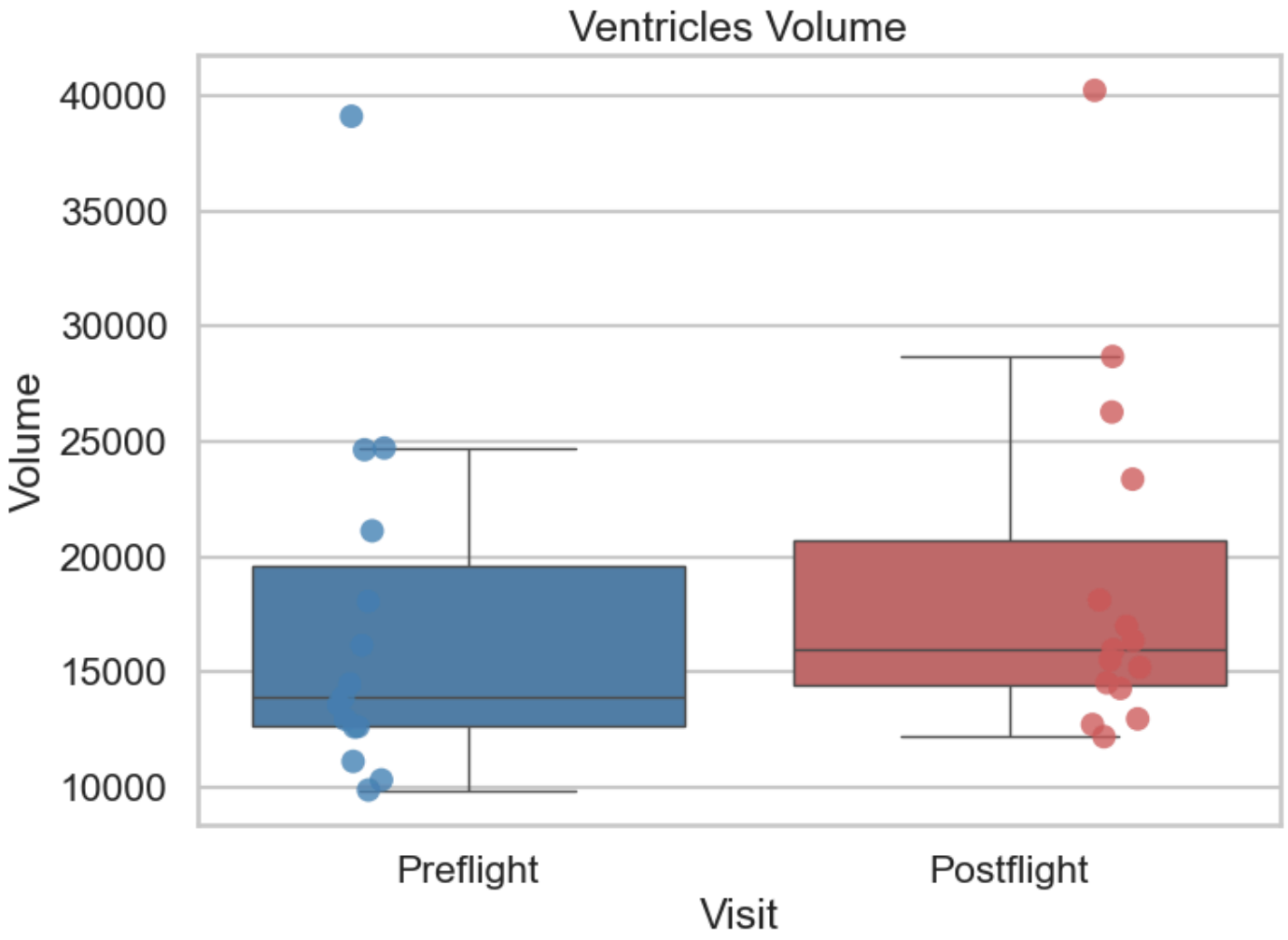

Figure 2

Total ventricular volume in astronauts preflight and postflight.

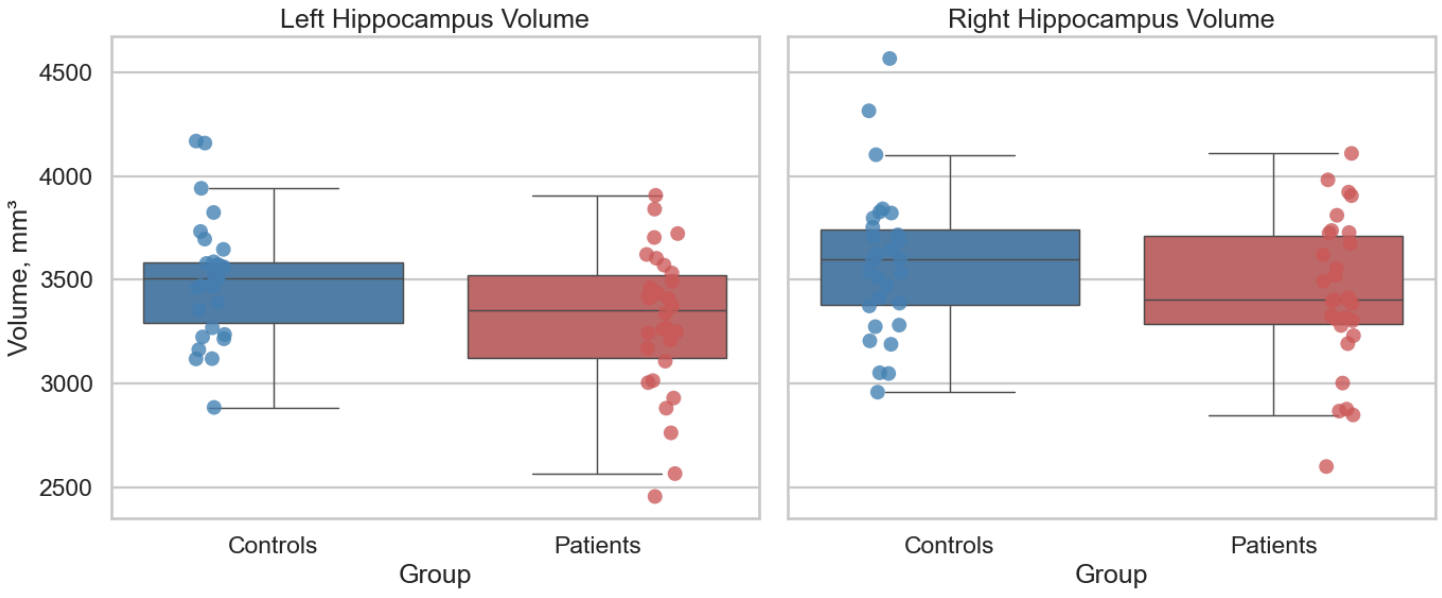

Figure 3

Left and right hippocampal volumes in BV patients and CT subjects.

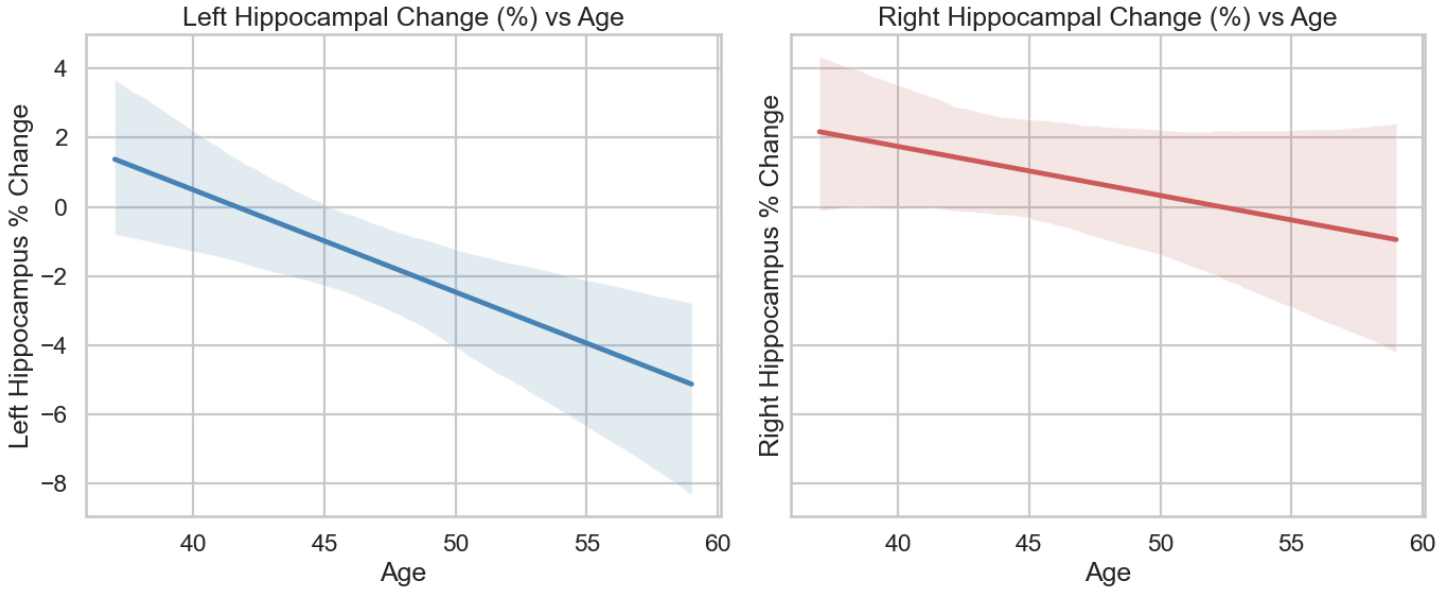

Figure 4

Correlation of the left and right hippocampal volume change (%) in astronauts pre- to post-flight with age, the gray area indicates a 95% CI. Individual data cannot be shown for the reasons of anonymity.

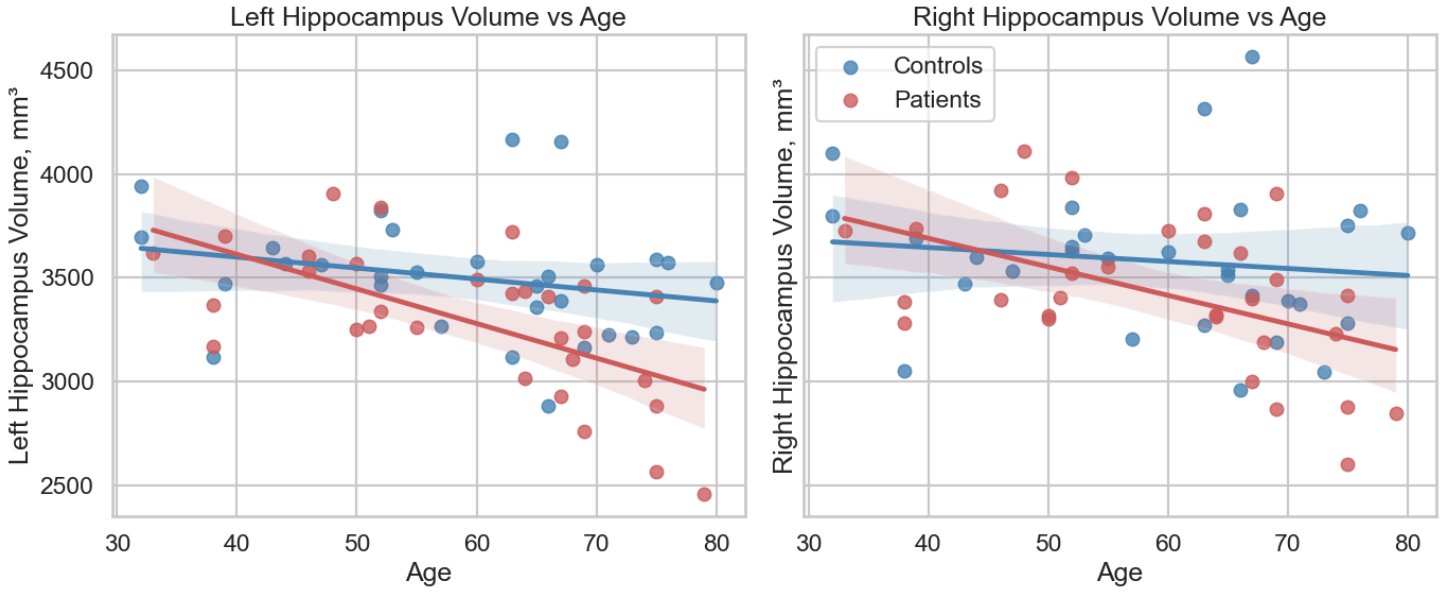

Figure 5

Correlation of the left and right hippocampal volume change (%) in BV patients and CT participants with age.

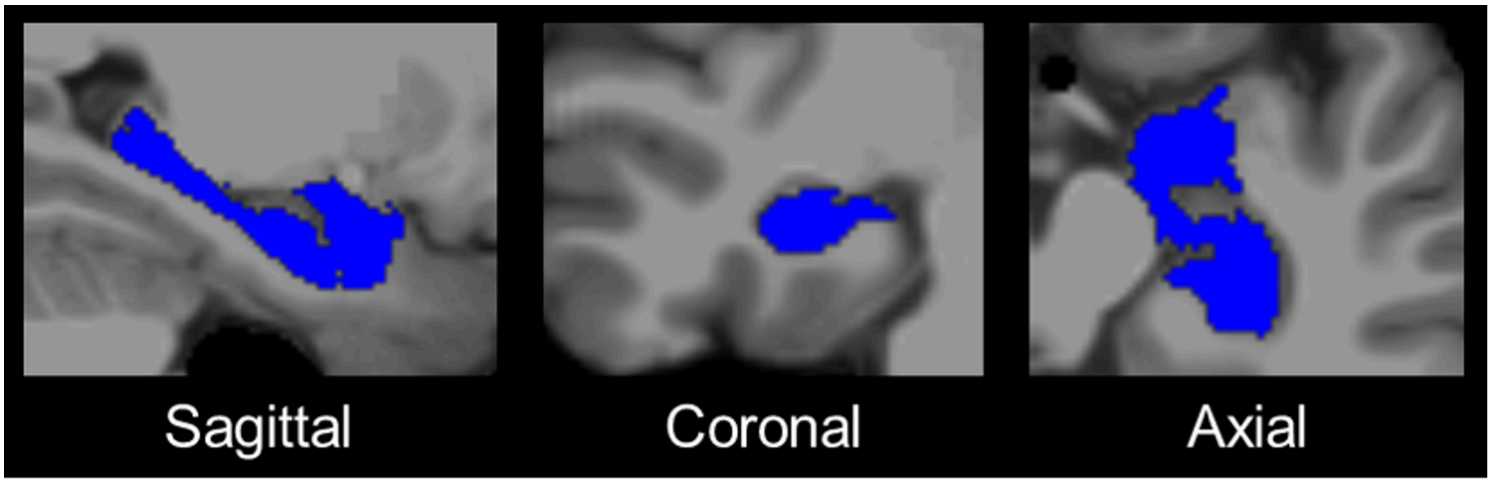

Figure 6

Example of the hippocampal segmentation with the Freesurfer's hippocampal toolbox in different views.

Supplementary Files

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- SupplementaryMaterials1.docx