Biological 12-hour rhythm facilitates re-entrainment from circadian desynchrony and promotes psychological resilience during long-duration spaceflight

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Abstract

Heart rate variability (HRV) reflects brain's 'vertical integration' in association with functions of the default mode network (DMN) and salience network (SN). We investigate the role of 12-h components in HRV endpoints in facilitating adaptation to the space environment. Ambulatory 24-h electrocardiograms were obtained from 20 healthy astronauts (47.2 ± 5.9 years) before launch, twice in space (ISS01 on days 21.7 ± 2.9 and ISS02 on days 159.2 ± 46.1), and after return to Earth. Astronauts were classified depending on whether the 12-h amplitude of the TF-component of HRV during ISS01 versus pre-flight increased (Group I, N = 11) or not (Group II, N = 9). In Group I, the circadian acrophases of TF- and ULF-components were delayed during ISS01 versus pre-launch, whereas in Group II, the circadian acrophase of the MF1-band advanced. Lower HRV spectral power indicated psychological resilience during both ISS01 and ISS02 in association with the brain's DMN and SN. Since adverse consequences of circadian desynchrony may be more pronounced due to phase advances than to phase delays, the differential behavior of the 12-h component between Groups I and II suggests its amenability to manipulation in interventions aimed at improving space adaptation.

Introduction

Spaceflight dramatically influences human physiology, resulting in cardiovascular dysfunction, immune suppression and impaired secretion of hormones and neurotransmitters. Microgravity-induced blood volume redistribution is the initial trigger to cardiovascular dysfunction, involving diverse processes and complex mechanisms [1, 2, 3]. Astronauts living on the International Space Station (ISS) experience other unique stressors, including cosmic radiation, noise, social isolation, confinement and factors that can impact aging. It was once widely accepted that the space environment accelerates the aging process [4, 5]. Unexpectedly, however, recent research suggests that long-duration space travel may be associated with anti-aging effects [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19].

Several lessons were learned from our previous investigations [13, 14, 15, 16, 17, 18, 19]. (1) We observed that adaptive processes in space are circadian stage-dependent, starting at night and later spreading to the entire day. (2) The circadian rhythm of heart rate (HR) was strengthened in space, sleep quality was improved, and parasympathetic tone was enhanced at night by activating brain's default mode network (DMN). (3) Magnetic fluctuations in the magnetosphere can affect and enhance endpoints of HR variability (HRV), suggesting anti-aging effects in space, perhaps conveying an increased well-being and psychological resilience. (4) Most strikingly, the 12-h (circasemidian) component could have consolidated the circadian system and contributed to a rapid adaptation to microgravity in space. These studies enabled the formulation of novel hypotheses that the biological 12-h component could play an important role in the adaptation to space, taking advantage of brain's plasticity at night and psychological resilience during daytime [19].

Most life on Earth, from unicellular organisms to humans, including intracellular organelles, is governed by biological rhythms that are defined as self-sustained oscillations, cycling with a specified period [20,

21, 22, 23, 24, 25]. Biological rhythms are thought to give an adaptive advantage as physiology adjusts to recurring daily changes in the external environment. Circadian disruption can lead to cancer, cardiovascular, metabolic, and psychiatric disorders, and to cognitive decline in the aged. An altered 12-h component related to cardiovascular dysfunction [26] may imply that it is potentially important for human health and adaptation to a novel environment, including space. Following the pioneering study by Hughes et al. [27], a series of studies of Pittsburgh's group [28, 29, 30, 31, 32, 33] identified a cell-autonomous 12-h oscillator of nuclear speckle liquid-liquid phase separation dynamics in mammals, including humans, which regulates 12-h rhythms of systemic gene expression and metabolism independently from the 24-h circadian clock. The 12-h oscillation was found to be regulated by the unfolded protein response (UPR) transcription factor spliced form of X-Box Binding Protein 1 (XBP1s) [31, 32, 33, 34, 35].

The human brain oscillates in harmony with frequency-specific subcomponents of several brain regions [36]. The bidirectional heart-brain connection was enunciated by Claude Bernard and confirmed by Thayer and Lane [37]. HRV may serve as a proxy for the brain's 'vertical integration' in association with functions of the DMN and salience network (SN). HRV may thus serve as an adequate substitute to study activity of the coordinating system to obtain information about the extent of adaptive adjustment, including brain plasticity and psychological resilience.

As plans consider inhabiting the Moon or Mars, studying the effect of the space environment on human well-being and aging has increased in interest and medical importance. Astronauts' brain plasticity and psychological resilience during long-duration spaceflight missions are investigated herein by gauging the activity of intrinsic networks of the brain, DMN and SN particularly, by focusing on the biological 12-h rhythm of HRV endpoints.

Subjects And Methods

Subjects

Twenty-one healthy astronauts participated in the ISS Japan Aerospace Exploration Agency (JAXA) investigation named "Biological Rhythms 24 Hrs & 48 Hrs" from 2008 to 2016. One astronaut was excluded from this study because the pre-flight record was much shorter than 24 h due to poor contact of the electrodes, preventing a reliable estimation of the reference circadian variation and a rigorous assessment of changes associated with space microgravity. The remaining twenty astronauts (17 men, 3 women) had a mean (± SD) age of 47.2 ± 5.9 years. Their mean stay in space was 172.4 ± 45.0 days.

Astronauts had passed class III physical examinations from the National Aeronautics and Space Administration (NASA). The study was approved by the Institutional Review Boards of NASA, European Space Agency (ESA), Pro0406 (MOD00001598), and JAXA, JX-IRBA-20-084 Amd-10. Informed consent was obtained from all participants. A detailed explanation of the study protocol was given to the astronauts before they gave written, informed consent, according to the Declaration of Helsinki Principles. All methods were performed in accordance with the JAXA/ESA/NASA guidelines and regulations.

Experimental protocol

Ambulatory around-the-clock 24-h electrocardiographic (ECG) records were obtained by using a two-channel Holter recorder (FM-180; Fukuda Denshi, Tokyo, Japan or H12+; Mortara, NY, USA). Measurements were made four times: once before launch (Pre-flight), twice on the ISS (ISS01 and ISS02), and once after return to Earth (Post-flight). The control session was conducted on days 175.6 ± 116.7 (50 to 469) before launch in all but three astronauts who had technical problems with their before-flight record, in which case a replacement control record was obtained 116, 242 or 469 days after return to Earth. The two sessions in space were performed on days 21.7 ± 2.9 (18 to 30, ISS01) and 159.2 ± 46.1 (122 to 326, ISS02) after launch, the latter corresponding to 18.1 ± 3.4 days (11 to 21) before return to Earth. The last measurement session was performed on days 82.9 ± 35.4 (17 to 156 days) after return to Earth (After flight).

Universal Time Coordinated (UTC) is used aboard the ISS. The windows are covered during night hours to give the impression of darkness because the station experiences 16 sunrises and sunsets per day. Astronauts follow a strict 24-h routine, waking up at 06:00 and retiring for sleep at 21:30. At the time of data collection, artificial lighting from both incandescent and fluorescent light sources was used on the ISS; maximal light intensity was 700 lx [15, 16, 17, 18, 19].

Analysis of HRV

Data collection and measurement procedures were conducted as previously reported [13, 14, 15, 16, 17, 18, 19]. Briefly, for HRV measurements, the RR intervals between normal QRS waveforms were extracted as normal-to-normal (NN) intervals, which were A/D converted (125-Hz) with 8-ms time resolution. The authors first confirmed that all artifacts were actually removed and that the data excluded supraventricular or ventricular arrhythmia. Time-domain measures (CVNN, r-MSSD and pNN50), Lorenz plot (Length, Width and Length/Width ratio), and conventional frequency-domain measures (TF-, ULF-, VLF-, LF- and HF-HRV and LF/HF ratio) [38] were determined, as was β, reflecting the intrinsic cardiovascular regulatory system, using the Maximum Entropy Method (MEM) software (MemCalc/CHIRAM, Suwa Trust GMS, Tokyo, Japan) [39]. Time series of NN intervals covering 5-min intervals were analyzed by the MEM to compute the spectral power in different frequency regions.

HRV measures reflecting dynamics of brain functional connectivity [16, 40, 41, 42, 43, 44, 45] were also assessed, as defined in Table 1. Frequency regions examined were 0.01–0.05 Hz (LF-band), 0.05–0.10 Hz (MF1-band), 0.10–0.15 Hz (MF2-band), and 0.15–0.20 Hz (HF01-band), according to Baria et al. [46]; 0.20–0.30 Hz (HF02-band), 0.30–0.40 Hz (HF03-band), and 0.40–0.50 Hz (HF04-band), according to Chen and Glover [47]. Changes in MF2- and HF01-, HF02-, HF03-, and HF04-bands show dynamic interactions among the DMN and SN, i.e., the alerted DMN involved in the adaptation to a novel environment [16, 46, 47].

Low-frequency fluctuations (LFFs) (0.01–0.10 Hz) during daytime were measured as HRV indices reflecting psychological resilience (subjective well-being and/or life-satisfaction) related to brain's DMN

activity, primarily in the orbitofrontal cortex [48, 49, 50, 51]. LFFs include the LF-band, MF1-band and VLF-component (0.003–0.04 Hz). Psychological resilience was estimated from 6:00 to 21:00 in 3-h intervals, where LFFs were averaged over the 5-min estimates (07:30, 10:30, 13:30, 16:30 and 19:30).

Sleep duration at night was estimated by using circadian profiles of RR-intervals and 5-min HF endpoints of HRV [14, 18, 53]. Sleep quality was assessed based on whether a sleep-related increase in RR-intervals and in HRV-HF could be observed [18, 19]. When 48-h ECG were recorded, HRV endpoints and sleep duration were averaged over the two consecutive sleep spans.

Brain plasticity at night and psychological resilience during daytime estimated by HRV

Brain plasticity at night was assessed by (1) changes in circadian amplitude of NN intervals, (2) sleep-related decrease in HR, and (3) HRV increase during spaceflight. Lack of HR drop during sleep was defined as a less-than-10% decrease from the awake span [52], and nocturnal HRV rise was calculated relative to daytime values [18].

Resilience, the ability to adapt to stress, is important for well-being, life satisfaction and health. Since functional MRI showed that higher psychological resilience relates to lower LFFs, we consider herein that lower HRV reflecting DMN or SN activity, which includes LFFs, is associated with higher psychological resilience.

Cosine curve fitting for estimating amplitude and phase by cosinor

Single 24-h, 12-h, 8-h, 6-h, or 90-min cosine curves were fitted independently to the data by cosinor [54, 55, 56] to estimate their respective amplitudes and phases as well as the rhythm-adjusted mean (MESOR). Changes in amplitude and acrophase from pre-flight to ISS01 and/or ISS02 assessed the response of each periodic component to the space environment.

Classification of astronauts into Groups I and II

Twenty astronauts were classified into two groups depending on changes in the 12-h amplitude of their TF-component during ISS01 compared to pre-flight. It increased in astronauts of Group I (N = 11; 47.3 ± 6.1 years; 10 men), but not in those of Group II (N = 9; 47.1 ± 6.1 years; 7 men). Their mean stay in space was similar (177.9 ± 59.3 vs. 165.6 ± 17.9 days, P = 0.5557). Astronauts were monitored at similar stages (in days) before launch (165.3 ± 95.9 vs. 190.4 ± 148.6, P = 0.6764), in space (ISS01: 21.2 ± 2.5 vs. 22.2 ± 3.3, P = 0.4378; ISS02: 163.8 ± 62.7 vs. 154.1 ± 17.4, P = 0.6602), and after return to Earth (77.2 ± 31.8 vs. 90.8 ± 40.7, P = 0.4249). Thresholds distinguishing Group I from Group II were determined from HRV rhythmic endpoints during Pre-flight by Receiver Operating Characteristic (ROC) curve.

Statistical analyses

Estimates of HRV endpoints were expressed as mean ± SD. Changes in each HRV index during ISS01, ISS02 and post-flight were compared to pre-flight by the paired t-test. HRV endpoints averaged over 24 h

were compared between Groups I and II by Student t-test. Circadian stage-dependent changes in LFFs between Pre-flight and space (ISS01 and ISS02) were determined between 06:00 and 21:00 by averaging 5-min endpoints in 3-h intervals. P-values less than 0.05 are considered to indicate statistical significance. The Stat Flex (Ver. 6) software (Artec Co., Ltd., Osaka, Japan) was used.

Results

Changes in heart rate variability during long-duration spaceflights

Changes in 24-h average HRV endpoints between space and Earth and between the two sessions in space are summarized in Table 1. Reflecting the dramatic changes in cardiovascular function taking place in space, parasympathetic activity was statistically significantly decreased during ISS01 and ISS02 compared to pre-flight in the 20 astronauts, as seen from 24-h averages of r-MSSD, pNN50, SDNNIDX5, SDNNIDX30 and HF-component. By contrast, HR (or NN-interval) and sympathetic activity estimated by the LF/HF ratio did not differ. The fractal scaling of HRV (slope β) was statistically significantly less steep in space than on Earth, as shown earlier [14, 15, 19], but did not change from ISS01 to ISS02.

While normal pre-launch, further increases during ISS01 are observed in SDNN (from 143.3 ± 42.5 to 153.4 ± 35.8 msec, P = 0.0681), SDANN5 (from 124.5 ± 37.6 to 133.8 ± 32.6 msec, P = 0.0775) and SDANN30 (from 117.5 ± 37.1 to 131.2 ± 33.3 msec, P = 0.0113), suggesting anti-aging effects, as previously reported [57, 58, 59].

Brain plasticity at night estimated by changed HRV dynamics in space

Changes in the circadian amplitude of NN intervals and the extent of sleep-related HR-dipping and HRV-rising during spaceflight served to assess brain plasticity at night (Table 1, bottom). Compared to pre-launch, the circadian amplitude of NN intervals increased from 116.9 to 134.7 msec (P = 0.0418) during ISS01 and to 132.6 msec (P = 0.1281) during ISS02. The nocturnal HR-dip became deeper during both ISS01 (P = 0.0309) and ISS02 (P = 0.0447), and the nocturnal HRV-rise accentuated during ISS02 in LF-component (P = 0.0454), LF-band (P = 0.1618) and MF1-band (P = 0.0087), which reflects DMN activity. The nocturnal rise in MF1-band and HF-band also increased statistically significantly between ISS01 and ISS02. In concert with the response in brain plasticity, suppression of the parasympathetic activity seen during ISS01 was no longer observed during ISS02 for r-MSSD, pNN50 and HF-component, even though nocturnal HR-dip and suppression of SDNNIDX5 and SDNNIDX30 lasted over both sessions in space (Table 1).

HRV measures before launch predict change in 12-h amplitude of NN intervals

Thresholds distinguishing Group I from Group II determined by ROC curve before launch were a 12-h amplitude of TF-component of 1529.4 or 2087.9 $msec^2$ (sensitivity = specificity of 0.8182; AUC = 0.9798 ± 0.02604) and a 12-h amplitude of ULF-component of 1321.5 or 1776.2 $msec^2$ (sensitivity = specificity of 0.9091; AUC = 0.9798 ± 0.02596).

Biological rhythm and sleep characteristics of Groups I and II

In Group I, the 12-h amplitude of TF-component increased about 2.4 times from pre-flight to ISS01 (from 801.6 to 1894.5 $msec^2$, P = 0.0001), the 8-h amplitude increased about 1.4 times (P = 0.1130) and the 6-h amplitude about 1.7 times (P = 0.0317), Table 2. Similar changes were not statistically significant during ISS02, except for the 12-h amplitude (P = 0.0663).

By contrast, in Group II, only a decrease of borderline statistical significance in the 12-h amplitude of TF-component is observed from pre-flight to ISS01 (from 4339.3 to 1718.8 $msec^2$, P = 0.0634), perhaps because all amplitudes pre-flight are higher in Group II than in Group I. Indeed, amplitudes (in $msec^2$) in Group II vs. Group I are 5019.2 vs. 1842.6 (P = 0.0525; 24-h), 4339.3 vs. 801.6 (P = 0.0019; 12-h), 2621.2 vs. 1150.6 (P = 0.0589; 8-h), 2222.6 vs. 866.8 (P = 0.0133; 6-h), 533.4 vs. 322.5 (P = 0.0922; 3-h), and 502.8 vs. 196.1 (P = 0.0235; 90-min). During ISS01, differences between the two groups are no longer observed, perhaps due primarily to an amplification of the 12-h amplitude of TF-component in Group I.

Sleep duration (mean ± SD, in min) did not differ between Groups I and II (Pre-flight: 395 ± 86 vs. 410 ± 89, P = 0.7059; ISS01: 395 ± 38 vs. 412 ± 86, P = 0.5432; ISS02: 378 ± 50 vs. 426 ± 59, (P = 0.0685); Post-flight: 392 ± 84 vs. 398 ± 94, P = 0.8835). On average, the time of awakening (mean ± SD, in hr:mn) was also similar between the two groups (Pre-flight: 6:51 ± 1:10 vs. 6:25 ± 0:53, P = 0.3765; ISS01: 6:25 ± 0:48 vs. 6:20 ± 1:08, P = 0.8672; ISS02: 6:18 ± 1:06 vs. 6:18 ± 0:39, P = 0.9962; Post-flight: 7:08 ± 1:05 vs. 7:05 ± 0:57, P = 0.9165).

HRV endpoints of Groups I and II astronauts

A comparison of 24-h averaged HRV endpoints between Groups I and II is shown in Table 3. Pre-flight, SDNN (122.8 vs. 168.4 msec, P = 0.0126), SDANN5 (107.4 vs. 145.3 msec, P = 0.0204) and SDANN30 (101.6 vs. 137.0 msec, P = 0.0292) involving anti-aging effects, were lower in Group I than in Group II, even though all endpoints were within normal limits, as reported previously [38, 57, 58, 59]. Similarly, pNN50 (P = 0.0293) and TF- (P = 0.0082), ULF- (P = 0.0067) and VLF-components (P = 0.0199) were smaller in Group I than in Group II.

In Group I, statistically significant increases during ISS01 were found for SDNN (114.7%; from 122.8 to 140.9 msec, P = 0.0275), SDANN5 (114.2%; from 107.4 to 122.7 msec, P = 0.0493) and SDANN30 (118.9%; from 101.6 to 120.8 msec, P = 0.0201). This result suggests that the amplified 12-h rhythm of HRV may have promoted anti-aging effects in concert with the response in brain plasticity. Consequently, statistically significant differences between Groups I and II, seen during ISS01, are no longer observed during ISS02 since higher measures were maintained without changes in Group II (Table 3).

The fractal scaling of HRV (slope β) was statistically significantly less steep in space, with no changes observed between ISS01 and ISS02. Neither parasympathetic activity reflected by r-MSSD, pNN50 and HF-component, nor sympathetic activity estimated by the LF/HF ratio showed any definite differences between Groups I and II across the two records obtained in space.

12-h rhythm counteracted circadian desynchrony during long-duration spaceflight

Individual changes during spaceflight in the 24-h acrophase of HRV endpoints served to evaluate circadian desynchrony [60, 61, 62]. In Group I, the circadian acrophase of the TF-component was statistically significantly delayed by about 5 h (P = 0.0303) during ISS01 compared to pre-launch, and that of the ULF-component by about 6 h (P = 0.0055), Fig. 1 (upper left). The acrophases partly recovered during ISS02 but were still delayed by about 3 h (P = 0.0450) or 4 h (P = 0.0304), respectively (Table 4). In this group, circadian acrophases of the MF1-band did not differ statistically significantly between the two sessions recorded in space (Fig. 1, lower left).

By contrast, in Group II, during ISS01 compared to pre-launch, the circadian acrophase statistically significantly advanced by about 7.5 h in MF1-band (P = 0.0012) and by about 3 h in HF-component (P = 0.0095), r-MSSD (P = 0.0274) and pNN50 (P = 0.0318). Further advances were observed during ISS02, now averaging about 8 h (P = 0.0012) in MF1-band and 3.5 h in HF-component (P < 0.01), r-MSSD (P = 0.0221) and pNN50 (P = 0.0257) compared to pre-flight, Table 4. Then, the circadian acrophase of the LF-band and LF-component also advanced significantly by about 1.5 h (P = 0.0052) and 6.5 h (P = 0.0141), respectively (Table 4). The circadian phase advance in MF1-band of Group II is depicted in Fig. 1 (lower right). In this group, the ULF-component did not show any statistically significant phase shift between the two sessions recorded in space (Fig. 1, upper right).

12-h rhythm facilitates psychological resilience during daytime in space missions

Since neuroimaging studies showed that activity in low-frequency fluctuations corresponding to the DMN or SN was negatively associated with psychological resilience, the state of psychological resilience during daytime was assessed herein by changes in those HRV endpoints reflecting DMN or SN activity.

First, a comparison of Groups I and II during pre-launch shows that LF-, MF2- and HF01-bands and LFFs of Group I were statistically significantly lower than those of Group II, Table 5 (top). During ISS01 and ISS02, these HRV endpoints as well as HF01-, HF02-, HF03-, HF04-bands are also lower in Group I than in Group II. These differences are statistically significant in the case of MF2-band and HF01- and HF02-bands during ISS01 and of LF-, MF2-, HF01-, HF02-, HF03-, HF04-bands and LFFs during ISS02. The MF2-band in Group I remains lower than in Group II post-flight. These results suggest that Group I astronauts may have had higher psychological resilience than Group II astronauts.

Next, a comparison of ISS01 and ISS02 versus pre-flight in Group II shows that psychological resilience improved in space. During ISS01, LF- and HF03-bands and LFFs decreased to 71.8% (P = 0.0194), 79.6% (P = 0.0311) and 78.9% (P = 0.0378) of pre-flight values, respectively, and during ISS02, LF- and MF1-bands and LFFs decreased to 79.6% (P = 0.0322), 78.3% (P = 0.0325) and 79.1% (P = 0.0271) of pre-flight values, respectively (Table 5, top). In Group I also, MF1-band decreased to 90.1% (P = 0.0435) and 82.6% (P = 0.0365) of pre-flight values during ISS01 and ISS02, respectively, while during ISS01, MF2-, HF01- and HF03-bands decreased to 85.3% (P = 0.0737), 84.8% (P = 0.0834) and 67.8% (P = 0.0699) of pre-flight values, respectively.

Finally, psychological resilience, including life-satisfaction, was assessed in 3-h intervals from 06:00 to 21:00. LFFs improved mostly in the morning, Table 5 (bottom). During ISS02, LFFs in Group II decreased at 07:30 (i.e., between 06:00 and 09:00), 10:30 and 13:30 to 70.6% (P = 0.0433), 56.8% (P = 0.0387) and 74.8% (P = 0.0251) of pre-flight values, respectively, while during ISS01, LFFs decreased only at 07:30 (67.2%, P = 0.0198) and 13:30 (79.2%, P = 0.0497). In Group I, however, LFFs only decreased statistically significantly at 16:30 during ISS02. These observations suggest that Group II astronauts may have felt a sense of fulfillment during ISS01 and ISS02 and gained a great sense of satisfaction on days 159.2 (122 to 326) after launch (during ISS02), particularly in the morning.

Discussion

Twenty healthy astronauts who spent about 6 months in space gave us a unique opportunity to examine the adaptive process of neuro-cardiovascular coordination. We obtained new evidence that the 12-h biological rhythm facilitated the rapid adaptation to microgravity in space (Table 1), supporting results from our previous case report [19], while the circadian system plays a key role in the adaptation to the novel space environment [14, 15, 17, 18]. The response of the 12-h rhythm appeared early, after about 21 days in space (ISS01), and it was larger than the circadian response (Table 2). The biological 12-h rhythm reflects both the function of “endogenous endoplasmic reticulum (ER) stress and unfolded protein response (UPR^{ER}) cycle” and the reaction of “mitochondrial stress response pathway and unfolded protein response (UPR^{mt})”, which can protect cells from widespread proteome stress in both central and peripheral tissues. This may be why the biological 12-h rhythm was first activated, to consolidate a stronger circadian system in space.

Results from this study are several-fold. (1) The amplified 12-h rhythm of HRV-TF promoted anti-aging effects in concert with the response in brain plasticity. Indeed, during ISS01, the 12-h amplitude was amplified in SDNN, SDANN5 and SDANN30, which involve anti-aging effects (Table 3). (2) Unexpectedly, we found that the amplified 12-h amplitude counteracted circadian desynchrony, as phase delays rather than phase advances occurred during spaceflight, accelerating its recovery (Table 4 and Fig. 1). (3) Psychological resilience was increased in space mostly in the morning, influencing subjective well-being and life satisfaction (Table 5).

Brain plasticity at night counteracts spaceflight-induced cardiovascular dysfunction

Brain plasticity refers to the inherent ability of the central nervous system to change its existing structures and functions in response to experience. This property is fundamental for the adaptability of behavior, for learning and memory processes. Exposure to stimulating environments has repeatedly been shown to strongly influence brain plasticity. It is thus a crucial underlying component of the enormous challenge of space adaptation for astronauts. The increase in brain plasticity was determined herein as an increase in the circadian amplitude of NN intervals, a deeper HR drop and larger HRV rise at night in space compared to pre-launch. As a result, suppression of the parasympathetic activity observed during ISS01 was no longer observed during ISS02, at least in r-MSSD, pNN50 and HF-component (Table 1, bottom).

Role of biological 12-h rhythm in potentially facilitating anti-aging effects

Recent evidence suggests that biological rhythms have expanded beyond the circadian system [24, 63]. A 12-h oscillator independent from the 24-h circadian clock is thought to be regulated by the unfolded protein response (UPR) transcription factor spliced form of X-Box Binding Protein 1 (XBP1s) [27, 28, 29, 30, 31, 32, 34, 35]. The 12-h rhythm provides an evolutionary advantage in mammals, including humans [25, 28, 30, 33, 63, 64]. Previously, we reported that the 12-h component can be important for the rapid adaptation to microgravity in space [19]. Herein, we observed how the 12-h rhythm participated in anti-aging effects, contributing to an amplified circadian rhythm of HR (Table 1), increases in SDNN, SDANN5 and SDANN30 (Table 3), counteracting internal desynchrony (Table 4, Fig. 1), and fostering psychological resilience in space (Table 5). It should come to no surprise since an XBP1s-SON axis implies a cell-autonomous 12-h rhythm of nuclear speckle liquid-liquid phase separation (LLPS) dynamics [33, 65]. A large protein called Son is essential for appropriate subnuclear organization of pre-mRNA splicing factors and for promoting normal cell cycle progression [66, 67]. An evolutionarily conserved XBP1s-SON axis coordinates a rapidly functioning feedforward loop connecting nuclear speckle LLPS and proteostasis, resulting in a highly efficient genetic information transfer functioning at multiple temporal scales,. At the molecular level, it modulates the rates of chemical reactions; at the mesoscale, it organizes large structures within cells; and at the cellular level, it facilitates the localization of cellular materials and homeostatic responses [33, 64, 65].

Anti-aging effects mediated by the 12-h component observed herein are supported by recent studies [31, 33, 68]. (1) In XBP1s liver-specific knockout ($XBP1^{LKO}$) mice, ablation of the 12-h clock accelerates liver aging and fatty liver disease [31]. Clear 12-h transcriptional rhythms are detected in the liver, but also in the lung, kidney, adrenal gland, heart, and even in the hypothalamus of the central nervous system [27]. (2) The nuclear speckle, a direct transcriptional target gene of XBP1s, amplifies p53-mediated gene expression, which is part of the DNA damage response as one of the tumor suppressor genes. It may facilitate adaptive stress responses and enhance overall anti-aging effects [68]. (3) The biological 12-h clock, transcriptionally regulated by 12-h rhythms of XBP1s, mediates the hormetic response, an adaptive cellular response whereby exposure to low doses of stress activates protective mechanisms, attributed to the actions of both ER (for ER hormesis) and mitochondria (for mitohormesis) [30, 69, 70, 71, 72]. Both ER hormesis and mitohormesis are known to positively associate with adaptation to novel environments, stress resistance, anti-aging and longevity. We also observed enhancements of 8-h and/or 6-h rhythms, together with an amplified 12-h rhythm of the TF-component, about 20 days after launch (ISS01) (Table 2), suggesting the additional involvement of the immune function by means of NF-kB signaling [27, 34] and/or of the hypothalamic-pituitary-adrenal (HPA) axis [74, 75] in anti-aging effects in space.

12-h rhythm modifies phase-shift and promotes recovery from circadian desynchrony

We uncovered herein for the first time that an amplified 12-h rhythm can help speed-up re-entrainment from circadian desynchrony. (1) The amplified 12-h rhythm observed in Group I associated with phase delays instead of phase advances observed in Group II (Table 4 and Fig. 1) about 21 days after launch

(ISS01). (2) It was accompanied with a faster re-entrainment after circadian desynchrony. The phase delay of the ULF-component in Group I led to recovery from 14:11 to 12:38, as opposed to the phase advance of the MF1-band in Group II, which led to a further advance from 02:50 to 02:30 163.8 days after launch (ISS02) (Fig. 1).

Under usual conditions, the circadian system synchronizes behavior and physiology to the environmental 24-h cycle. It is hierarchically organized by a central clock in the suprachiasmatic nuclei, which sends diverse signals throughout the organism to maintain internal synchronization. Facing a sudden change in the 24-h routine when arriving on the ISS (or after return to Earth), the astronauts' circadian system has to "reset" to the new phase (Table 4). Differences in the rate of adjustment by different tissue clocks means that any abrupt shift is accompanied by internal desynchrony. Many studies led to the widespread belief that internal desynchrony plays a major role in the development of adverse health consequences of circadian disruption [76, 77, 78, 79, 80, 81]. Importantly, recent studies showed that adverse consequences of circadian desynchrony are more pronounced with phase advances than with phase delays [82, 83, 84]. The phase delays facilitated by an amplified 12-h rhythm, contrasted with phase advances when unchanged or weakened, may hence indicate a better adaptation in space.

12-h rhythm facilitates psychological resilience during long-duration spaceflight

While all HRV measures of all 20 astronauts were normal according to the standards of the Task Force report on HRV [38], astronauts of Group I, who saw their 12-h TF-component rhythm amplified in space, had lower HRV endpoints pre-launch (Table 5). Since HRV activity is negatively associated with subjective well-being and life satisfaction, they may be considered to have enjoyed particularly favorable psychological states.

High psychological resilience influencing subjective well-being and life satisfaction was related to brain regions including the DMN, SN and OFC in astronauts of Group I in the morning as well as in the evening (Table 5, left). In Group II, psychological resilience was observed later in the mission, associated mainly with LF- and MF1-bands and LFFs, which corresponds to the DMN, including the OFC, as seen from a comparison of ISS01 and ISS02 versus pre-flight (right part of Table 5, right).

Limitations

This investigation has several limitations. **First**, ECG records only covered 24 h and were obtained only twice during a 6-month space mission. Longer ECG records are desirable, as shown by our 7-day/24-h investigations on Earth [85, 86, 87, 88, 89]. Adaptation of human neuro-cardiovascular coordination in space remains a challenge, as mechanisms are diverse and complex, and factors other than adaptation to the space environment (such as exercise, nutrition, mission tasks, and interpersonal stress) likely contributed in part to the results. **Second**, brain oscillatory activity data are lacking. Several studies, however, have shown that HRV is associated with structures and functions of the neural network. HRV can thus be considered a biomarker reflecting activities of the brain's integration system [16, 37, 40, 41, 42, 43, 44, 45]. These associations are extremely complex, however, and have not yet been fully

confirmed. Future investigations are needed to directly assess brain oscillatory activity in space. **Third**, no direct measures of aging were obtained in this investigation. Future studies are needed to verify our interpretations, which were reached indirectly from a chronobiologic perspective. Future studies could include measures of telomere length and DNA methylation, which are generally accepted indicators of aging, as a complement to the increased prominence of circadian rhythms and the increase in HRV measures related to anti-aging. **Fourth**, we used HRV indices related to brain's DMN activity on subjective well-being and/or life-satisfaction, focusing particularly on LFFs (0.01–0.10 Hz) in order to assess psychological resilience. Future studies would benefit from including questionnaires scoring specifically for resilience, until fMRI neuroimaging become feasible in space to assess resilience more directly.

Conclusions

Our study shows that the biological 12-h rhythm contributes to the consolidation of the circadian system and to a rapid adaptation to microgravity in space. First, we provided new evidence that an amplified 12-h rhythm can change circadian phase advances to phase delays about 21 days after launch, and efficiently help counteract circadian desynchrony from an about 6-h (ISS01) to a 4-h phase-delay (ISS02) (Table 4 and Fig. 1). Second, we showed that an amplified 12-h rhythm facilitated higher psychological resilience, thereby ameliorating subjective well-being and life satisfaction during daytime in space (Table 5).

While the circadian clock is considered to have evolved separately in different lineages [90], the 12-h clock may be even more ancient and having evolved earlier than the circadian clock, because 12-h clock genes are conserved in even more divergent species. Additionally, the circadian and 12-h clocks are detected both on Earth and in Space together with other (e.g., 8-h, 6-h, 3-h and 90-min) components, Table 2.

Multiple biological clocks may endow organisms with more flexibility and the heightened ability to adapt to different environments, including space, thereby increasing survival advantage. If so, it may not be a dream for humans to live on Mars. Multiple clock components operating in concert with changes in brain–heart activity are an enormous challenge that may shape the future of science and medicine. Our results herein constitute the start of a catalog of measurable components of brain plasticity and psychological resilience that may help guide effective ways to adapt to the space environment and to slow down or even reverse the aging process, thus offering an unprecedented opportunity for human advancement.

Declarations

Data availability

Restrictions from Japan's Aerospace Exploration Agency (JAXA) apply to the availability of the data supporting the findings of this study. The data were used under license for the current study. Although data are not publicly available, they are available to collaborating parties under ethical approval from JAXA, contact address: frtotk99@ba2.so-net.ne.jp.

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Author Contributions

K.O. and G.C. wrote the first draft of the manuscript and prepared the figures. K.O., H.O. and C.M. designed the study, and S.F., K.M., T.A. and H.O. contributed to the acquisition of data. K.O. and G.C. analyzed the data, and K.O., G.C., S.F., Y.K., K.S., K.M., T.A., H.O. and C.M. contributed to the writing and editing of the manuscript. All authors read and contributed to the final version of the manuscript.

Declaration of interest statement

The authors declare no competing financial and non-financial interests.

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

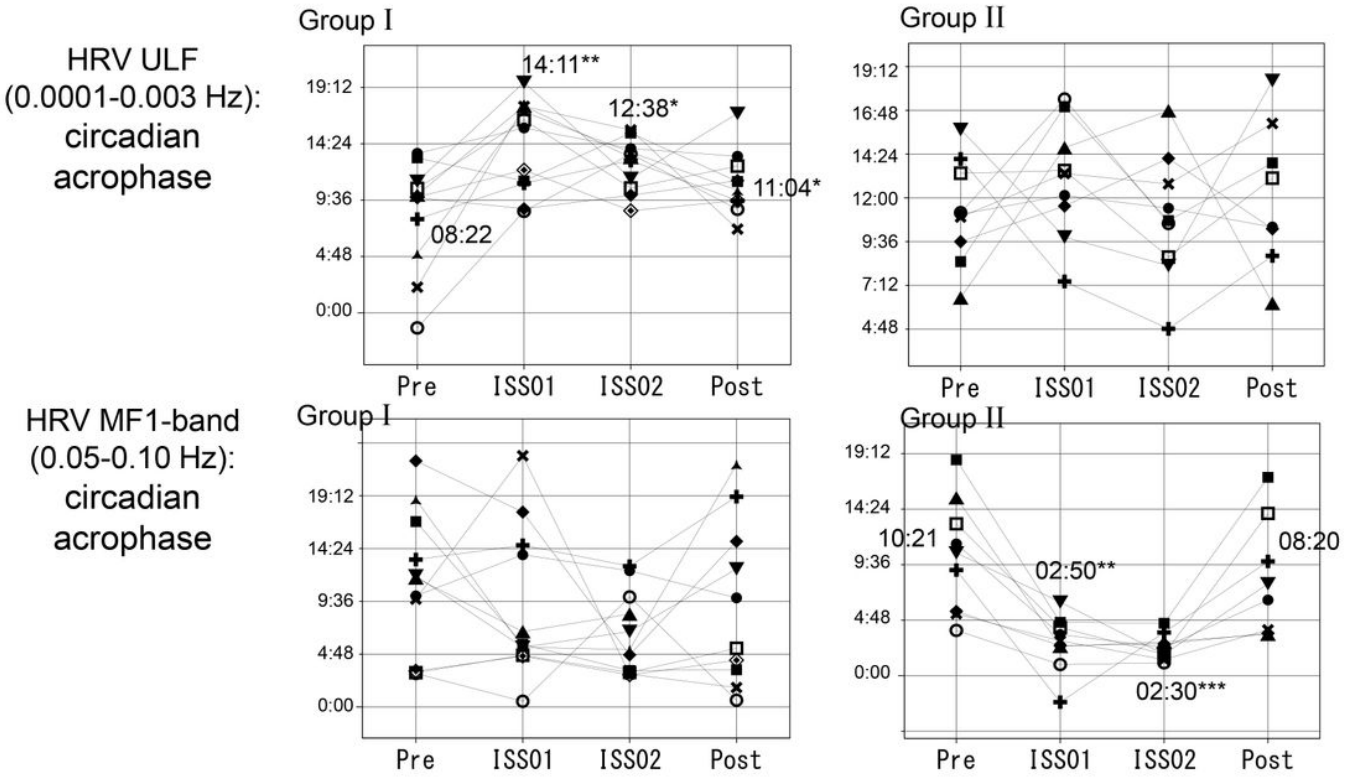

Figure 1

Circadian desynchrony of HRV endpoints during long-duration spaceflights

Group I astronauts showed circadian phase delays of the ULF-component during ISS01 (top left), whereas Group II astronauts showed circadian phase advances of the MF1-band during ISS01 (bottom right). The phase delay observed during ISS01 in Group I recovers during ISS02, from 14:11 to 12:38 (top left), whereas the phase advance observed during ISS01 in Group II is enhanced during ISS02, from 02:50 to 02:30 (bottom right), albeit changes from ISS01 to ISS02 are not statistically significant. As for MF-1 band, LF-band and LF-component are also phase-advanced during ISS02 in Group II. Note that in Group II astronauts, the circadian phase of HRV indices reflecting parasympathetic activity, including r-MSSD, pNN50, LF- and HF-components, is statistically significant advanced during ISS01 and/or ISS02, Table 4.

Supplementary Files

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- Table1.xlsx
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- Table3.xlsx
- Table4.xlsx
- Table5.xlsx