B C C 520-D I

Mathias Basner[1]*, David F. Dinges[1], Daniel J. Mollicone[2], Igor Savelev[3,4], Adrian J. Ecker[1], Adrian Di Antonio[1], Christopher W. Jones[1], Eric C. Hyder[1], Kevin Kan[2], Boris V. Morukov[5], Jeffrey P. Sutton[4,6]

1 D t t t, t S M, , , t St t A , **2** I t, , , t St t A , **3** , H t, , t St t A , **4** t S B I tt t, H t, , t St t A , **5** I tt t B , M , **6** C t S M D t t M , B C M , H t, , t St t A

Abstract

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NASA’s recent evidence-based review of the behavioral health risks to crew and mission success during exploration space flight concluded they were among the most serious risks to such missions [6], a view shared by the Aerospace Medical Association [7]. According to NASA [6], ‘‘anecdotal and empirical evidence indicates that the likelihood of a behavioral condition or psychiatric disorder occurring increases with the length of a mission’’ and ‘‘while behavioral conditions or psychiatric disorders might not immediately and directly threaten mission success, such conditions can, and do, adversely impact individual and crew health, welfare, and performance, thus indirectly affecting mission success.’’

There is a critical need to predict the time course, magnitude, and individual variability in behavioral, cognitive, affective and interpersonal reactions of space explorers during long-duration missions. Accurate prediction will inform strategies for crew selection, spacecraft habitability requirements, and behavioral health countermeasures needed for interplanetary missions. High-fidelity simulated space flight has paramount importance in providing data on crew behavioral changes during prolonged confinement and isolation. However, the ecological validity of the simulation depends heavily upon the extent to which it instantiates elements relevant to crew behavior during prolonged confinement in space. These include crew characteristics and size, habitat and habitability, isolation from Earth’s light-dark cycles and weather, mission duration and realistic mission operations, flight simulation with mission controllers, communication delays inherent in interplanetary missions, limited consumable resources, and attention from media and the public.

Antarctic winter-over conditions require groups of subjects to spend prolonged periods of time in confinement and isolation, and they share some of the other environmental and psychosocial stressors inherent to exploration-type space missions (e.g., monotony, threat-to-life, restricted consumables, non-24 h light-dark cycles). They are used by several space agencies as space analog environments. However, these winter-over analogs usually do not extend beyond one year, they do not have a space mission context, and crew composition and size may not generalize to astronauts on long-duration space missions. The greater the fidelity an analog environment has to prolonged space flight, the greater the opportunity to identify the manner in which behavioral health may be affected by prolonged space missions.

Here we report on the behavioral and psychological effects on a 6-person multinational, culturally diverse crew comparable to space fliers, who were participating in the first high-fidelity simulated 520-day mission to Mars. The simulation was developed and operated by the Institute for Biomedical Problems (IBMP) of the Russian Academy of Sciences. We hypothesized that behavioral and psychosocial responses to the prolonged period of confinement, isolation, and space operational requirements, would change systematically with time in mission and related to mission events (e.g., the mid-mission simulated Mars landing). However, due to the uniqueness and unprecedented duration of this simulation, we made no specific hypotheses related to the direction and duration of any systematic trend, but rather formulated our null hypothesis more neutral as ‘‘no difference in responses related to time in mission.’’ Due to the diverse cultural and educational backgrounds of the crew, we expected inter-individual differences in the way individual crewmembers coped with the prolonged period of confinement and isolation.

Materials and Methods

2.1 S j t t

The State Scientific Center of the Russian Federation –IBMP of the Russian Academy of Sciences performed the Mars 500 project at the IBMP in Moscow, which consisted of three isolation studies with six crewmembers each: a 14-day pilot study (completed in November 2007), a 105-day pilot study (completed in July 2009), and the main 520-day study simulating a mission to Mars (completed in November 2011), which is the focus of this manuscript.

The high fidelity of the simulation to actual spaceflight was reflected in the following features of the experiment: (i) a multinational crew of N = 6 healthy adult male volunteers selected by the Russian Federation (N = 3), the European Space Agency (N = 2), and the China National Space Administration (N = 1), who were trained together and who were similar in age (average age at hatch closing 32 years, range 27–38), careers, and education (e.g., engineers, physicians, military backgrounds) to astronauts/cosmonauts living on the ISS; (ii) 520 consecutive days of confinement (3 June 2010 to 4 November 2011) in a 550 m^3 pressurized facility with a volume and configuration comparable to a spacecraft with interconnected habitable modules; (iii) facility modules equipped with life support systems and an artificial atmospheric environment at normal barometric pressure; (iv) activities that simulated aspects of the International Space Station with daily maintenance work, scientific experiments, and exercise; (v) isolation from Earth’s daily environmental light-dark cycles, temperatures and seasonal conditions; (vi) a realistic Mars flight simulation based in orbital mechanics and under the direction of mission controllers, with a 30-day Mars orbiting phase (between mission days 244 and 273) and 3 of the 6 crewmembers simulating egresses on the Martian surface (between mission days 257 and 265); (vii) work throughout the 520-day mission that included both routine and simulated emergency events; (viii) changes in communication modes and time delays between mission days 54 and 470 that would occur in transit to and from Mars; (ix) limited consumable resources (food and water); and (x) the crew awareness of frequent publicity of the mission by media and the public. Thus, Mars 520 had many essential features of an isolated and confined environment (ICE) that had the fidelity necessary to study behavioral and psychological reactions to prolonged space flight.

The crew lived on a 5-day work cycle, with two days off, except for simulation of special situations (e.g., emergencies). For the whole mission operations were organized around 24-h clock time. A typical workday would start with personal hygiene and breakfast at 8:00 followed by operative work (including facility inspection), operative meetings, and the preparation of scientific experiments. After lunch (served between 13:30 and 14:30), the crews performed the scientific experiments and exercised until supper the study, and they were free to discontinue the study at any time. The crewmembers revealed their identities before, during and after the simulation. To ensure confidentiality in this manuscript, results were de-identified (i.e., crewmembers were randomly assigned English alphabetic letters *a f*) and no data were reported relative to crewmembers' nationalities, ages, professions, or roles in the mission.

2.2 E t t

atory variable (MQ1, days 1–130; MQ2, days 131–260; MQ3, days 261–390; MQ4, days 391–520) and with the scores from the mood scales (BDI-II and POMS-SF) and visual analog scales as outcome variables. Although we could have justified many different hypotheses relative to time in mission (e.g., steadily increasing or decreasing effects, third quarter effect), we chose to keep our hypothesis as generic as possible (null hypothesis: no difference between mission quarters). This was partially driven by findings on the activity data that showed a steep decline in activity initially, a slow but steady decline during the second and third mission quarters, and a sharp rise at the end of the mission, which conformed to neither of the two above-stated hypotheses [19]. Our mixed model analyses took the clustered nature of the data into account and used all available data points based on repeated measures within subjects ($N = 444$ for measures sampled only in the morning or in the evening and $N = 888$ for measures sampled both in the morning and the evening). The models for outcomes sampled both in the morning and the evening were also controlled for administration time (morning or evening). If a type 3 test indicated a significant MQ effect ($P<0.05$), post-hoc tests comparing each MQ with each other MQ were performed. Post-hoc tests were Bonferroni corrected for Type I error inflation ($\alpha = 0.05/6 = 0.0083$).

To investigate individual differences between crewmembers, ANOVAs (Proc Mixed in SAS) were performed with crewmember as the only explanatory variable and with the scores from the mood scales (BDI-II and POMS-SF) and visual analog scales as outcome variables. Again, models with visual analog scale variables sampled twice daily were also controlled for administration time (morning or evening). If a Type 3 test indicated a significant crewmember effect ($P<0.05$), post-hoc tests comparing data from each crewmember with data from each of the other crewmembers were performed. Post-hoc tests were Bonferroni corrected for Type I error inflation ($\alpha = 0.05/15 = 0.0033$). For ease of interpretation, all scales were transformed to a 0 to 100 range in Tables 1 and 2.

To investigate changes of individual differences with time in mission, graphs plotting cumulative scores of mood and visual analog scale outcomes relative to time in mission were generated for those variables with a significant ($P<0.05$) main effect for mission quarter. To further investigate individual differences, we calculated intra-class correlations (ICC) for each outcome measure as the ratio of between-subjects variance to the sum of the between- and within-subjects variances. The ICC is based on variance components analysis, involving the explicit separation of within-subjects variance and between-subjects variance in data derived from repeated measurements in individuals. The ICC expresses the proportion of variance in these data that is explained by systematic inter-individual variability. Stability of ICC values was interpreted using the following ranges: ‘‘slight’’ (0.0–0.2); ‘‘fair’’ (0.2–0.4); ‘‘moderate’’ (0.4–0.6); ‘‘substantial’’ (0.6–0.8); and ‘‘almost perfect’’ (0.8–1.0) [20]. We compared actigraphy scorings across subjects on a minute per minute basis. One minute epochs that were classified as missing or off-wrist for at least one crewmember were excluded from the analysis (86,068 min or 11.5% of the 520-day period). For 4os.atto40ForP scores (0.679), POMS ratings of vigor-activity (0.772), confusion-bewilderment (0.632), and total mood disturbance (0.701), and visual analog scale ratings of unhappiness (0.753), sickness (0.671), mental fatigue (0.788), and stress (0.669). On average, more than half (55%) of the variance in self-report outcomes was attributable

Table 2. I t - .

Scales	Crewmember							ANOVA
	a	b	c	d	e	f	ICC	P-value
Social Desirability								
S D t S -17	81	69	56	56	25	81		
Depression								
B D I t -II	0 ′*	0 ′*	0 ′*	0.4 (0.1)	12.1 (0.9) ′ ′ ′ ′	0.5 (0.1)	0.679	<0.0001
Mood								
MS D -D j t	0.0 (0.0)	0.0 (0.0)	0.1 (0.1)	0.1 (0.1)	4.6 (0.8) ′ ′ ′ ′	0.8 (0.3)	0.251	<0.0001
MS -A t t	41.3 (2.4) ′ ′ ′ ′	48.8 (0.7) ′ ′ ′ ′	77.0 (0.7) ′ ′ ′	72.2 (1.0) ′ ′ ′	22.0 (1.4) ′ ′ ′ ′	28.5 (1.6) ′ ′ ′ ′	0.772	<0.0001
MS C -B √ t	0 ′ ′ ′*	13.2 (0.3) ′ ′ ′	6.8 (0.8) ′ ′ ′	0.5 (0.2) ′ ′	13.8 (0.9) ′ ′ ′	1.4 (0.5) ′ ′	0.632	<0.0001
MS -A t	0 ′*	0 ′*	0.9 (0.4)	0.7 (0.3)	7.5 (1.0) ′ ′ ′ ′	1.7 (0.5)	0.322	<0.0001
MS A -H t t	0.1 (0.1)	0 ′*	0.2 (0.1)	0.4 (0.3)	6.7 (1.0) ′ ′ ′ ′	1.9 (0.5)	0.293	<0.0001
MS F t -I t	1.3 (0.5)	0.2 (0.2) ′	3.2 (0.6) ′	1.8 (0.6)	12.0 (1.2) ′ ′ ′ ′	1.4 (0.4)	0.376	<0.0001
MS t M D t S	9.7 (0.4) ′ ′ ′	10.1 (0.1) ′ ′ ′	5.3 (0.3) ′ ′ ′	5.0 (0.3) ′ ′ ′	19.6 (0.8) ′ ′ ′ ′	12.8 (0.3) ′ ′ ′ ′	0.701	<0.0001
Visual Analog								
H -	0.5 (0.5) ′ ′ ′	9.8 (0.3) ′ ′ ′ ′	20.9 (0.7) ′ ′ ′ ′	2.6 (1.0) ′ ′ ′	49.8 (1.4) ′ ′ ′ ′	35.1 (1.1) ′ ′ ′ ′	0.753	<0.0001
H t -S	0.0 (0.0) ′ ′	0.5 (0.3) ′ ′	15.2 (0.5) ′ ′ ′	0.7 (0.5) ′ ′	35.2 (1.2) ′ ′ ′ ′	14.8 (1.3) ′ ′ ′	0.671	<0.0001
E t - E t	9.1 (1.2) ′ ′ ′	11.4 (0.3) ′ ′ ′	23.6 (0.8) ′ ′ ′ ′	3.6 (0.7) ′ ′ ′ ′	41.3 (1.2) ′ ′ ′ ′	34.3 (1.6) ′ ′ ′ ′	0.587	<0.0001
M t S -M t F t	0.8 (0.7) ′ ′	1.5 (0.7) ′ ′	31.8 (0.6) ′ ′ ′ ′	1.0 (0.5) ′ ′	44.1 (1.3) ′ ′ ′ ′	40.0 (1.2) ′ ′ ′ ′	0.788	<0.0001
t St - St	0.0 (0.0) ′ ′	0.3 (0.1) ′ ′	21.5 (0.8) ′ ′ ′ ′	1.1 (0.6) ′ ′	31.1 (1.3) ′ ′ ′	31.5 (1.5) ′ ′ ′	0.669	<0.0001
t G -	10.1 (1.4) ′ ′	12.2 (0.3) ′ ′	41.8 (1.1) ′ ′	8.7 (0.9) ′ ′	37.2 (1.6) ′ ′ ′	42.3 (1.4) ′ ′ ′	0.563	<0.0001
G S t - S t	9.2 (3.1) ′ ′	12.3 (1.1) ′ ′	22.2 (1.5) ′ ′ ′ ′	5.4 (1.6) ′ ′	41.1 (2.0) ′ ′ ′	47.3 (2.1) ′ ′ ′	0.508	<0.0001

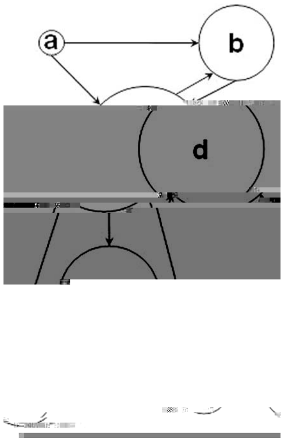

Figure 3. Crew interactions were facilitated by a core group. D - , √ √ t t t t √ √ t t √t t t t . A √ t t √ t t t √ t t ; t t √ t √t √ t t t t t . C t t √t √ √ √ t t t √t t t .
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hypostimulation and restricted social contacts during long-duration missions [2].

A modest increase in depressive symptoms and psychological distress was observed in the second compared to the first half of the mission, but this effect was largely contributed to by crewmember *e*. A higher frequency of crew-perceived conflicts with mission control was reported in the first relative to the second half of the mission (being maximal during the period of the simulated landing on Mars). According to Shved et al. [25], both the number of crew interactions (overall amount of communication) with mission control and the number of negative and critical statements in crew messages increased during the simulated landing period. We did not find a third quarter effect [26] in any of the psychological or behavioral outcomes. The fact that conflicts with mission control were reported by crewmembers five times more often than conflicts among themselves highlights the importance of a good relationship between the crew and mission controllers and the need for a greater involvement of mission controllers in pre-mission training, as has been noted by others [27]. Additionally, greater crew autonomy might reduce conflicts between the crew and mission control.The 520-day simulated Mars mission was completed without any of the crewmembers discontinuing the study prematurely. Moreover, our data and debriefs of the crew data revealed no signs of major behavioral emergencies or serious unresolved conflicts during the mission. This overall mission success is reflected in average scores across crewmembers for many of our outcomes (e.g., sufficiently long sleep, high levels of psychomotor vigilance performance, no indication of depression, low levels of psychologic distress, high ratings of happiness, health, energy, and low ratings of stress, mental fatigue, and tiredness). These results may have been the effect of the psychological support the crew received throughout the mission [24]. However, such findings do not indicate the mission was without behavioral distress for individual crewmembers, as our results also indicated stable inter-individual differences among crewmembers for practically all behavioral health outcomes. This finding is in contrast with an earlier isolation study that was performed at IBMP in Moscow (SFINCSS-99) and included 3 crews of 4 crewmembers each that were confined for 240 days (group 1, 4 Russians) and 110 days (group 2, 1 German and 3 Russians; and group 3, 1 Russian, 1 Austrian, 1 Japanese, and 1 Canadian). Group 3 entered and shared the facility with group 1 after the study ended for group 2. The crew was all male except for one female crewmember. One crewmember of group 3 discontinued the study prematurely on mission day 63, likely as a consequence of a conflict between crewmembers at a New Year's celebration [2,3]. In contrast to Mars 520, the 3 groups involved in SFINCSS-99 did not know each other and did not perform joint training prior to the mission.

There were many examples of inter-crew differences in coping with the prolonged isolation and confinement of the 17-month high-fidelity mission. Crewmember *b* was behaviorally free-running with a dominant period of 24.98 h, and thus his sleep was approximately equally distributed over the 24-h day throughout the mission [19]. Crewmember *a* manifested a split-sleep pattern with frequent naps during the day that lengthened towards the end of the study. As a consequence, crewmembers *a* and *b* would have been at risk for performing suboptimal on mission tasks that were scheduled during the daytime. Also, as both crewmembers were frequently sleeping when the rest of the crew was awake (and vice versa), the time for interaction with the rest of the crew was also reduced [19], which is probably one reason for the lower frequency at which crewmembers *a* and *b* were mentioned by other crewmembers relative to frequency of communication (Figure 3). Crewmember *f* had the lowest average sleep time in mission (6.54 h), and the highest mission average ratings of tiredness, physical exhaustion, stress and poor sleep quality [19]. The sleep-wake data indicated crewmember *f* experienced a worsening sleep onset insomnia across the mission, which resulted in his being the only crewmember averaging less than 7 hours sleep a day in the across the mission [19]. Six or fewer hours of sleep a day on a chronic basis has been shown to lead to escalating errors in psychomotor vigilance performance [28–30]. This was the case for crewmember *f*, who had the majority of PVT-B errors of omission and commission among the crew. This degradation of behavioral alertness could be detrimental during critical periods of the mission (e.g., docking maneuvers, extra-vehicular activities, or emergencies).

Crewmember *e* was the only crewmember to frequently report symptoms of depression that increased during the second half of the mission. He also had the highest ratings of psychological distress and of feeling unhappy, sick, physically exhausted and mentally fatigued. Although crewmember *e* was the only subject to report these symptoms, it is unclear whether he was the only subject that experienced them, as the other subjects showed much higher social desirability bias scores (SDS-17) compared to crewmember *e*. Thus, crewmember *e* had the lowest pre-mission bias in presenting himself ideally, while some other crewmembers (e.g., *a* and *f*) had much higher SDS-17 scores indicating a tendency to present themselves more ideally. This bias may have resulted in their misreporting negative symptoms during the mission. This reporting bias could also be based in cultural differences among crewmembers [31]. Crewmember *e* (together with crewmember *f*) reported most of the conflicts with mission control and other crewmembers. Comparable to crewmembers *a* and *b*, crewmembers *e* and *f* had a lower frequency at which other crewmembers mentioned them relative to frequency of communication (Figure 3). In contrast, crewmembers *c* and *d* were notable for showing no signs of behavioral changes or psychological distress during the mission; they were most often mentioned as the two people with whom the rest of the crew interacted; and they were the only two crewmembers to suffer no changes in sleep duration, sleep-wake timing or sleep quality during the 520-day mission.

When all Mars 520 behavioral and psychological data are considered in aggregate, only two of the six crewmembers (*c* and *d*) showed neither behavioral disturbances nor reports of psychological distress during the 17-month period of mission confinement. This meta- finding highlights the importance of identifying behavioral, psychological, and biological markers of the characteristics that predispose prospective long-duration space exploration crewmembers to both effective and ineffective neurobehavioral and psychosocial reactions to the prolonged confinement required for exploration missions. Such predictors and biomarkers are needed to inform crew selection, training, and individualized countermeasures. This conclusion and the findings of this study are consistent with recent reviews of the psychological effects of polar expeditions and other analogs for space flight [2,32,33,34].

The age of exploration space missions will require the ''right stuff'' for prolonged confinement and isolation, which the Mars 520 ICE experiment indicates means good insight into one's capability, behavioral health, biological adaptability, environmental coping, mental endurance, and salutogenic responses to stressors [35]. This conclusion is not only consistent with findings from polar research as a space analog [21,33,34,36], but they should also be priorities in crew selection and training in confined environments for the mission to Mars and beyond.

Finally, we note that the vast majority of both adequate and inadequate psychological and behavioral reactions we observed in Mars 520 crewmembers appeared to be phenotypic (as evidenced by high ICCs, Table 2). Moreover, they appeared relatively early in the mission and sustained unabated throughout it. It suggests that it may be possible to detect individual psychological and behavioral vulnerabilities in periods that are significantly shorter than the 520 days employed in the IBMP study. This would enhance capability to efficiently select and train crew before, and monitor and provide them with adequate, individualized countermeasures during a long-duration mission.

Limitations

This study has several limitations. Naturally, microgravity, radiation and threat-to-life–, three important physiological and psychological stressors that will be encountered during exploration-type missions– could not be simulated in Mars 520, which restricts the generalizability of the findings to long-duration space missions [37]. We only had limited access to the crew before and after the 520-day mission, and thus cannot infer about their psychological status before and after the mission. The medical and psychological selection and screening of the crew was conducted by the space agency responsible for each study participant, making it uncertain to what extent it was comparable. The crew was male only, so we cannot make inferences about female only or mixed crews. Our assessment of performance was limited to psychomotor vigilance testing. It cannot therefore be assumed that other aspects of cognitive performance were not changed across time in mission. We want to stress that we did not measure physiological or endocrine markers of stress, limiting our ability to detect stress reactions not revealed in the behavioral responses of crewmembers. Finally, our protocol was one of at least 90 other protocols carried out in the quasi-operational environment of the 520-day Mars mission simulation. We had no control over the other protocols that may have introduced unexplained variance in our outcome measures.

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Author Contributions

Conceived and designed the experiments: MB DFD DJM IS AJE ADA CWJ ECH KK BVM. Performed the experiments: MB DFD DJM IS AJE ADA CWJ ECH KK BVM. Analyzed the data: MB DFD DJM ADA CWJ ECH KK. Contributed reagents/materials/analysis tools: MB DFD DJM ADA CWJ ECH KK. Wrote the manuscript: MB DFD ADA CWJ ECH JPS.

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