VIEWPOINT

A call for research to assess and promote functional resilience in astronaut crews

Mark Shelhamer

NASA Human Research Program, NASA Johnson Space Center, Houston, Texas

TO THE EDITOR: NASA plans to send humans to Mars in about 20 years. The NASA Human Research Program supports research to mitigate the major identified risks to human health and performance on such long-duration missions. However, there will undoubtedly be unforeseen events on any mission of this nature-thus mitigation of known risks alone (4, 9) will not be sufficient to ensure optimal crew health and performance under challenging conditions. Research should be directed not only to mitigating the known risks, but also to providing flight crews with the tools to assess and enhance physiological and behavioral resilience to cope with the unexpected, as a group and individually. A Mars mission-along with parallel studies in simulation and laboratory facilities—can also provide a model for terrestrial health concerns that involve small groups of high-performing individuals in stressful settings where health and fitness are crucial but easily compromised; examples include military special operations, mountaineering, and deepsea exploration. Beyond these specifics, however, the tools and procedures developed in the research program described here could be of value in most any setting where physiological and psychological parameters can be measured and used to guide interventions: hospital ICUs and chronic-care facilities for the elderly, for example.

One approach to this issue is to draw on ideas from complexity theory and network theory to assess crew and individual resilience (3, 8). Depending on whether one considers a physiological or a behavioral view, either an individual crewmember or the entire crew could be treated as a complex system that is composed of many subsystems (physiological subsystems or individual crewmembers), where the interactions between subsystems are of crucial importance for overall health and performance (1). In the case of individual crewmember resilience, one might think of the main physiological subsystems (cardiovascular, sensorimotor, musculoskeletal, etc.) as the nodes of a large network, with natural connections forming linkages between nodes. The ways in which these linkages form-their statistics and distributions, for examplecan lend to the network either rigidity or flexibility in the face of perturbation. These types of self-organization (12) are characteristic of healthy systems of many kinds, and some general rules that enable this form of resilience have been elucidated. An understanding of the structure of these interactions can provide important information even in the absence of complete information on the component subsystems. This is critical in human spaceflight research, because insufficient opportunities exist to elucidate the details of each subsystem in space flight. With eventual linkage of these results to omics approaches now being developed, the connections to personalized medicine on earth are apparent (5). This approach can be extended to include disciplines not typically considered in an integrated fashion with physiology, such as behavior, performance, and human factors. As an example, in the case of multiperson crew resilience, it is likely that individual roles and responsibilities will need to change through different phases of a mission. A strong hierarchical command structure might be needed during dynamic phases of planetary approach, landing, and initial reconnoitering. During extended months-long exploration, a more democratic approach might serve better. Add to this the possible changes in motivation level, mood, and state of health due to the coupled physiological changes, and the desire to have a crew organize itself to changing internal and external demands becomes apparent.

Enabled by recent advances in the noninvasive measurement of physiological and behavioral parameters (EEG, EMG, EKG, body movement, temperature, etc.), continuous subsystem monitoring can be realistically and unobtrusively implemented within a mission and also during preflight training to establish baseline values and ranges for each individual. Coupled with mathematical modeling, this can provide real-time assessment of health and function and detect early indications of imminent breakdown (10). Because the interconnected web of physiological systems (and crewmembers) can be interpreted as a network in mathematical terms, we can draw on recent work that relates the structure of such networks to their resilience (ability to self-organize in the face of perturbation) (3, 12). The term "resilience" has many meanings. In this setting, it is proposed that the human "system" is more than just the sum of its parts, that there are emergent properties that arise from the coupled interactions of physiological subsystems, and that it is these emergent properties (which would not be apparent by a detailed investigation of each subsystem on its own) that lead to resilience. Resilience then means the ability to call on multiple subsystems to different degrees, to maintain health and performance, and to change these interactions as needed when faced with a perturbation such as disease or injury or environmental stressor. The underlying hypothesis is that lessons learned from network theory can be used to understand and evaluate resilience in physiology. This raises the questions of what systems are coupled, how to measure the couplings, and if there is any meaning to them, which are the areas where research is needed.

There are many parameters and interactions that might be amenable to such an approach. Normal variability is an established characteristic of a healthy physiological response (7).

Address for reprint requests and other correspondence: M. Shelhamer, NASA Johnson Space Center, Code SA2, Houston, TX 77058 (e-mail: mark.j.shelhamer@nasa.gov).

Perspectives

472

Healthy coupling has been investigated less extensively (6), but there are cases in which too tight or too loose coupling might be problematic. In the area of physiological systems, examples include:

- cardiorespiratory rhythms;
- circadian rhythms, body temperature, and sleep;
- stress markers and cardiac and immune function;
- stress markers and cognition, sleep, and performance;
- profiles of biochemical markers related to immune function and nutritional status;
- sensorimotor aspects such as motion sickness, ataxia, reaction time, and manual control.

In the area of interindividual behaviors, examples might be: • sleep cycles;

- coordination of work and meal times;
- coupled motions during communication;
- group dynamics of sharing habitable spaces for work and rest.

If these multiple couplings and interactions can be placed into a network context, several advantages accrue, such as the ability to call on established metrics for self-organization and resilience that represent robustness and the ability to selforganize in the face of perturbation. Within this framework, tools for resilience are then the means to measure and analyze these physiological and behavioral parameters, incorporate them into models of normal variability and interconnectedness (2), and recognize when parameters or their couplings are outside of normal limits. What to do when a problem is identified depends on its nature: changes might be made to crew procedures, work pacing, interpersonal interactions, sleep cycles, meal timing and content, as guided by the model. Furthermore, this approach could provide guidance on whether other targeted interventions are needed during a mission, such as nutritional or pharmaceutical.

Human spaceflight research is an ideal setting in which to carry out this type of work. There is a need for such an integrated approach to efficiently address the physiological and behavioral problems encountered by humans in long-duration flight (11). Another benefit is that the in-flight use of these methods could provide meaningful autonomous work for the crew on an extended flight, such as during the return phase of a Mars mission when the anticipation of the outbound journey and the excitement of planetary exploration have subsided. (In fact the in-flight data might be made available solely to the crew for their own benefit. This could help offset concerns about privacy of medical data and the intrusive aspect of continuous monitoring.) Moreover, the International Space Station is a near-perfect laboratory for this research: the environment is self-contained and heavily monitored, and the astronaut crew (test subjects) is relatively homogeneous, healthy, and highly motivated. Many confounds that would complicate an integrative approach in terrestrial populations are avoided. It is also worth noting that the strategy proposed here would lead to individual characterization of each astronaut crewmember, in the form of a physiological "signature" of normal responses, interactions, and alterations under various stressors. This would allow for the eventual implementation of personalized countermeasures for the deconditioning effects of extended space flight, tailored to the individual. This would provide a savings in crew time and other resources, which are in short supply on space missions.

The NASA Human Research Program (HRP) provides opportunities to conduct the types of research described here. Although the release of a specific grant solicitation for a wholesale integrative-physiology and modeling initiative is not imminent, other possibilities exist. Solicitations are released regularly for research in analog facilities: controlled environments that mimic key aspects of extended spaceflight such as isolation, confinement, and an extreme environment. HRP makes use of a number of such facilities, in which small groups of test subjects are confined for various periods of time. (Perhaps most notable of these was a 520-day mission; see Ref. 13.) In addition to the psychological stress induced by these analog studies, some of them involve extended duration headdown bed rest, which mimics some aspects of fluid shift and muscle disuse as seen in space flight (and has been used to reproduce some effects of ageing). Because these are controlled environments in which subjects are closely monitored and various perturbations and interventions can be produced, they provide excellent settings for the research promoted here.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.S. drafted manuscript; M.S. edited and revised manuscript; M.S. approved final version of manuscript.

REFERENCES

- Barabási AL. Network medicine from obesity to the "diseasome". N Engl J Med 357: 404–407, 2007.
- Barzel B, Liu YY, Barabási AL. Constructing minimal models for complex system dynamics. *Nat Commun* 6: 7186, 2015; doi: 10.1038/ ncomms8186.
- Boccaletti S, Latora V, Moreno Y, Chavez M, Hwang DU. Complex networks: structure and dynamics. *Physics Rep* 424: 175–308, 2006.
- Buckey JC. Space Physiology. New York, NY: Oxford University Press, 2006.
- Chen R, Snyder M. Promise of personalized omics to precision medicine. Wiley Interdiscip Rev Syst Biol Med 5: 73–82, 2013; doi: 10.1002/ wsbm.1198.
- Glass L. Synchronization and rhythmic processes in physiology. *Nature* 410: 277–284, 2001.
- Goldberger AL, West BJ. Chaos in physiology: Health or disease? In: Chaos in Biological Systems, edited by Degn H, Holden AV, Olsen LF. New York: Springer, 1987.
- Newman MEJ. The structure and function of complex networks. SIAM Rev 45: 167–256, 2003; doi:10.1137/S003614450342480.
- Piantadosi CA. Mankind Beyond Earth: The History, Science, and Future of Human Space Exploration. New York: Columbia University Press, 2012.
- Saria S, Rajani A, Gould J, Koller D, Penn A. Integration of early physiological responses predicts later illness severity in preterm infants. *Sci Transl Med* 2: 48ra65, 2010.
- White RJ, Averner M. Humans in space. *Nature* 409: 1115–1118, 2001; doi:10.1038/35059243.
- Yates FE. (editor). Self-Organizing Systems: The Emergence of Order. New York: Springer, 1988.
- Yi B, Rykova M, Feuerecker M, Jäger B, Ladinig C, Basner M, Hörl M, Matzel S, Kaufmann I, Strewe C, Nichiporuk I, Vassilieva G, Rinas K, Baatout S, Schelling G, Thiel M, Dinges DF, Morukov B, Choukèr A. 520-d isolation and confinement simulating a flight to Mars reveals heightened immune responses and alterations of leukocyte phenotype. *Brain Behav Immun* 40: 203–210, 2014; doi: 10.1016/ j.bbi.2014.03.018.