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CHANGES IN THE CENTRAL NERVOUS SYSTEM DURING LONG-DURATION SPACE FLIGHT: IMPLICATIONS FOR NEURO-IMAGING

A. B. Newberg and A. Alavi

Division of Nuclear Medicine, University of Pennsylvania School of Medicine, 118 Donner Building,
3400 Spruce Street, Philadelphia, PA 19104, U.S.A.

ABSTRACT

The purpose of this paper is to review the potential functional and morphological effects of long duration space flight on the human central nervous system (CNS) and how current neuroimaging techniques may be utilized to study these effects. It must be determined if there will be any detrimental changes to the CNS from long term exposure to the space environment if human beings are to plan interplanetary missions or establish permanent space habitats. Research to date has focused primarily on the short term changes in the CNS as the result of space flight. The space environment has many factors such as weightlessness, electromagnetic fields, and radiation, that may impact upon the function and structure of the CNS. CNS changes known to occur during and after long term space flight include neurovestibular disturbances, cephalic fluid shifts, alterations in sensory perception, changes in proprioception, psychological disturbances, and cognitive changes. Animal studies have shown altered plasticity of the neural cytoarchitecture, decreased neuronal metabolism in the hypothalamus, and changes in neurotransmitter concentrations. Recent progress in the ability to study brain morphology, cerebral metabolism, and neurochemistry *in vivo in* the human brain would provide ample opportunity to investigate many of the changes that occur in the CNS as a result of space flight. These methods include positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI).

INTRODUCTION

As the US approaches the 21st century, there are many plans for the development of longer duration manned space missions and permanent space habitats. These plans include the Space Station, a moon base in which astronauts might stay for as long as a year, and a manned mission to Mars in which astronauts would remain in space for as long as three years. For these plans to be realized, it must be established that human beings can safely live in space. To that end, the effects of long duration space flight on the human central nervous system (CNS) must be determined (Newberg, 1994).

Early in the history of space flight, it was realized that there were a number of factors in the space environment that might have untoward effects on the human nervous system. Initial studies of human performance in space such as during the Mercury, Gemini, and Vostok missions showed that there were no serious, immediate effects of space flight on the human brain (Hawkins and Zieglschmid, 1975, Nicogossian, 1994). However, these early space flights were usually of short duration (less than two weeks). The first concerted effort to study human neurologic function during long term space flight occurred with the advent of space stations. The Russian missions aboard Salyut and Mir have been of the greatest duration, compared to any other country, ranging from 100 days to over 300 days in space (Nicogossian, 1994). The US did most of its long-term studies of space flight during the three Skylab missions (lasting 28, 59, and 84 days). The results from Skylab indicated that there were no gross neuropsychological changes in astronauts (Johnston and Dietlein, 1977).

Alterations in the structure and function of the human brain during space flight requires analysis on several different levels. These levels include gross function (i.e. behavior, performance, and psychology) of the nervous system in space flight, anatomic and structural changes in the brain, cerebral metabolic changes, plasticity of neurons and neural connections, and alterations in the neurotransmitter systems. It is the purpose of this paper to briefly review the effects of various space flight factors on the neurophysiological function of the brain with specific attention focused on clinically relevant phenomena that may lend themselves to neurophysiological analysis. Particular importance will be given to the neurophysiological changes that may be either permanent or pose some danger to human beings in space, specifically during space flight of months to years. This paper will also review the current uses of neuroimaging techniques and how they might be used for the study of the effects of space flight on the central nervous system.

Neurophysiological Changes During Space Flight

Much of the neurological research done on human exposure to space flight has been on the neurovestibular system since space motion sickness (SMS) has been of prime significance, especially to the US space program. While many of these experiments have investigated various clinically relevant vestibular effects, there have been a number of studies related to changes in brain physiology and neurotransmitter activity, particularly involving the neurovestibular organs.

Subjective reports from astronauts and cosmonauts regarding changes in the neurovestibular system during space flight have included postural illusions, tumbling sensation, dizziness, and SMS (Graybiel *et al.*, 1977; Young *et al.*, 1986; Nicogossian, 1994). Proprioceptive illusions have been reported including self-motion or unusual motions of the surroundings such as moving walls (Lackner and Graybiel, 1981; Watt *et al.*, 1985; Reschke and Parker, 1987; Nicogossian, 1994). Most changes have been attributed, to some degree, to the adaptation to microgravity and a reinterpretation of sensory inputs regarding position and orientation. There have also been reports of post-flight neurovestibular disturbances, particularly in the long duration Soviet missions. Cosmonauts have experienced persistent postural instability, dizziness, nausea, and vomiting (Gazenko, 1979).

The attempt at finding therapeutic modalities for SMS has required a combination of clinical and neurophysiogical aspects of SMS. These modalities have included mechanical devices that restrict head movements since SMS is aggravated by such movement (Matsnev *et al.*, 1983), biofeedback to aid astronauts in controlling their symptoms of SMS (Cowings and Toscano, 1982), and pharmacologic therapy consisting of anticholinergic drugs using various routes of administration (Homick *et al.*, 1983; Davis *et al.*, 1993). However, none of the treatment modalities offers a consistently successful method with minimal side effects (Davis *et al.*, 1993; Nicogossian, 1994). Fortunately, SMS usually resolves after several days in space due to the adaptation of the neurovestibular system to the space environment and thus is less of a problem for long-duration space flight.

There have been a number of reports and studies, which have addressed the issue of changes in sensory perception during space flight. Astronauts have experienced changes in the gustation, olfaction, and the somatosensory systems (Nicogossian, 1994). Reports by astronauts have included feelings of diminished hunger and increased fullness in space. Foods tend to taste bland therefore requiring more seasoning in space (Yuganov and Kopanev, 1975). Despite sensory disturbances being somewhat common, there has never been any characteristic pattern with regard to the aggravating or alleviating factors, the time to onset, the duration, or the intensity of these disturbances.

Space flight has been associated with decreases in visual motor task performance, visual fields, and contrast discrimination (Nicogossian, 1994). Even though there are reports of increased visual acuity to the extent that astronauts reported seeing rivers, lakes, roads, automobiles, groups of people, and the wake of moving ships (Sasaki, 1965; Berry, 1970), more objective experiments showed that visual acuity was unchanged in astronauts, that contrast sensitivity was actually decreased, and that the perceived increase in visual acuity is due to a considerable degree of initial acuity of astronauts and the discrimination of objects according to secondary signs such as the wake of a boat

(Yuganov and Kopanev, 1975; Nicogossian, 1994). Another visual problem that has been reported is the intermittent perception of light flashes during flight. This phenomenon was studied on board Skylab and was shown to be caused by heavy ionized cosmic particles passing through the retina (Hoffman *et al.*, 1977).

Another effect of exposure to weightlessness, which may play a role in CNS changes, is the adaptation process that occurs in the musculoskeletal system. It is known that during space flight a significant reduction in muscle mass occurs, especially in the weight bearing muscles (Thornton and Rummel, 1977; Fuchs, 1980; Nicogossian, 1994). It might be expected that during long space flights, the cortical areas responsible for directing, initiating, and coordinating the movements of these muscles would be significantly affected. This might be reflected by metabolic and morphologic changes in the motor and pre-motor cortices as well as in the basal ganglia. These effects may make readaptation to Earth's 1-g environment by astronauts more difficult especially after missions lasting several years such as one to Mars. There may also be changes in neurotransmitters systems, such as dopamine and acetylcholine, which are crucial to the proper functioning of the motor pathways. Preliminary studies of rats flown on Spacelab 3 for 7 days showed that there is down-regulation of the D2 receptors in the striatum compared to ground based controls. This finding suggests increased dopaminergic activity in the striatum during space flight that might result from novel motor stimuli (Miller *et al.*, 1989).

There have been both subjective reports and objective studies regarding sleep disturbances during space flight. Sleep disturbances have been reported by both US and USSR astronauts during both short and long space flights. Cosmonauts in long term flight have often used hypnotics and have been vulnerable to fatigue. They have sometimes required 12 hours of sleep per day by mission end (Czeisler *et al.*, 1991). Sleep disturbances have even been reported after many months in space during Russian space station missions, suggesting that alterations in sleep patterns might be more persistent. Similar problems have been found during US Shuttle missions in which 30% of the astronauts requested sleep medications while in space (Santy *et al.*, 1988). Changes in sleep may be caused by various factors in the space environment such as weightlessness, spacecraft noise, SMS, and unusual work shifts. Even astronaut anxiety and excitement have been implicated (Yuganov and Kopanev, 1975; Frost *et al.*, 1977 Santy *et al.*, 1988). It has also been suggested that the sleep disturbances during space flight might share similar mechanisms with the type of sleep disturbances associated with aging (Czeisler *et al.*, 1991). However, more studies will be needed to elucidate the precise mechanisms underlying sleep disturbances during space flight.

Radiation exposure is a potentially significant problem during space flight. Studies on earth have shown that ionizing radiation can affect most cells in the human body including those in the CNS (Nicogossian, 1994). However, it has been difficult to determine the effects of prolonged exposure to radiation (Joseph *et al.*, 1992), especially in conjunction with other factors that might be experienced during long term space flight (Antipov *et al.*, 1991a, 1991b). A number of US and Russian animal studies have described the neurophysiological effects of radiation. The results of such studies clearly indicate that changes occur in the brain with exposure to radiation, and that there is a need for more extensive and rigorous studies in order to determine the behavioral and performance problems that radiation exposure might cause for long duration space flights.

Joseph *et al.* (1992) reported that rats irradiated with ^{56}Fe particles had significant performance deficits compared to controls regardless of the level of radiation (0.1, 0.25, 0.5, or 1.0 gray 1 gray equals 100 rad). However, the greater the radiation dose, the poorer was the performance. These effects were observed to occur within 12 hours after irradiation and were sustained for at least 14 days. This study also examined the enhanced release of dopamine from striatal tissue slices and found significant decreases in all the irradiated groups compared to controls. This study used radiation doses which are particularly relevant for space flight exposure. However, a number of the other studies have used much higher radiation doses. In a related study, Rabin *et al.* (1989) showed that there is a dose dependent behavioral toxicity from exposure to high energy iron particles, and that this type of radiation is more toxic than similar levels of gamma or electron radiation.

Several investigators (Gitsov *et al.*, 1990; Joseph *et al.*, 1992) have suggested that changes in the neurons after exposure to both carbon ions and gamma radiation may be a sign of premature aging. Thus, it is possible that the degeneration described in the radiation exposure studies may result in long term behavioral and psychological effects on astronauts who may be in space for many years, such as during a Mars mission (although no studies to date have reported how radiation affects behavior and performance). This might result in physiological, and later, morphological changes in brain parenchyma. Several animal studies using brain imaging techniques have examined the morphologic and functional changes that are related to radiation exposure. These will be described in the section below on "Current Neuroimaging Applications." For example, if the effects of radiation to the hippocampus accumulate during a long term mission, astronauts may possibly develop dementia-like symptoms. However, it is not known if such exposures to radiation would affect behavior and performance.

Many of the above mentioned neurological sequellae of space flight eventually result in, or from, alterations in the activity and concentrations of neurotransmitters. Further, long term alterations in the activity of various neurotransmitters might result in such phenomena as up or down regulation of receptors leading to reversible and, possibly irreversible neurophysiological changes (Miller *et al.*, 1989). One study determined the levels of serotonin in various brain structures in Earth based rats exposed to vibration (Dmitriyev and Tropnikova, 1988). In control rats, who underwent a vibration test, there was increased utilization of serotonin in the hippocampus and hypothalamus, regions which modulate the stress response in rats. Rats exposed to long term vibration were found to have undergone an adaptation response reflected by an increase in serotonin levels in the parietal cortex, while levels in the caudate nucleus and hypothalamus were decreased. There was also evidence of increased serotonin utilization in the pons and thalamus. It was suggested that astronauts might experience similar changes due to the vibrational forces experienced during space flight.

Animal studies have been done to investigate changes in the serotonin, dopamine (D2), alpha 1 and 2 noradrenergic, muscarinic, and gamma-aminobutyric acid (GABA) neurotransmitter systems in rats flown in space (Miller *et al.*, 1985, 1989; Morey-Holton and Tischler, 1988; Horowitz and Horwitz, 1988-1989). Miller *et al.* (1985, 1989) studied neurotransmitter changes in six rats flown in space for 7 days on board Spacelab-3 (the animals were sacrificed 13.5 hours after landing) compared to ground based control rats. found that there were no changes observed in receptor affinity for any of the neurotransmitters studied. There was an increase in the number of serotonin (5HT-1) receptors in the hippocampal membrane, corroborating the previously mentioned report (Davydov *et al.*, 1986). This may be particularly important since this region is involved not only with body cycle regulation, but also with memory and learning. D2 receptor number was shown to decrease in the striatum during space flight. However, there were no changes seen in D2 receptor number in the prefrontal cortex (Miller *et al.*, 1985, 1989). The authors concluded that the changes observed in the serotonin receptors in the hippocampus and D2 receptors in the striatum likely reflected the transition from a 1-g to a 0-g environment with a subsequent need for changing the spatial map of the environment (hippocampus) and the response to novel motor activity (striatum). Further, these studies showed no neurotransmitter changes in the centers for reflex control (cerebellum) or for the sleep-wake cycle (pons-medulla) even though there are observed clinical changes in these systems.

Miller *et al.* (1985, 1989) also found no significant changes in the brain regions associated with stress response, such as the prefrontal cortex (dopamine receptors), the forebrain (adrenoreceptors), and the midbrain (opiate pain receptors). It was suggested that this might reflect sufficient adaptation to the weightless space environment after seven days (which was the duration of the study). This result also suggested that the space environment is not particularly adverse to the rat CNS after sufficient exposure for adaptation. While Miller *et al.* found no changes in the GABA system, Kovalev and Enes (1988) reported that during adaptation periods, there is increased CNS activation which is linked to the GABA system as reflected by increased L-cystathionine. The conclusions drawn from these neurotransmitter studies must be carefully considered due to the small number of animals studied and the effects of the period of readaptation after landing. Miller *et al* . (1985, 1989) suggested that larger studies need to be done in order to replicate the current findings as well as explore other neurotransmitter systems in more detail.

There have been only a few human studies, and none that have measured neurotransmitter levels in specific brain regions in subjects undergoing either space flight simulation or actual space flight. In a head-down tilt study by Davydov *et al.* (1986) on human subjects, it was found that hypokinesia resulted in an initial increase in serotonin system activity (as measured by serum levels of serotonin and various serotonin metabolites) that was followed by a decrease after 70 days of hypokinesia compared to the subject's baseline level. The increase was believed to be caused by the adaptation period to the head-down tilt while the subsequent decrease reflected a completed adaptation to hypokinesia and a response to decreased afferent stimulation. Histamine levels, on the other hand, increased throughout hypokinesis, although no hypothesis was given for the mechanism of this increase. Both serotonin and histamine levels returned to baseline 25 days post-hypokinesis.

There are also many psychological and behavioral alterations that might occur in astronauts during long term space flight. Furthermore, these disturbances may caused by or reflected in changes in neurophysiological parameters previously mentioned in this paper. Among the psychological and behavioral changes that have been investigated and considered are: disruption of cognitive and memory functions; stress and anxiety states induced by concern for a successful mission, fear of the physical dangers encountered during space flight, social isolation, decreased personal space, sensory deprivation or overload in a space craft design, interpersonal difficulties among crew members, familial problems, and sleep disturbances; depression that could be caused by any of the above mentioned factors; and personality changes that might occur as a result of space flight factors or via intrinsic mechanisms (Christensen and Talbot, 1985; Nicogossian, 1994).

Factors which may affect human behavior and performance in space are extensive. Psychological and psychosocial variables include decision making abilities, motivation, adaptability, leadership, productivity, human emotions, attitudes, mental and physical fatigue, crew composition and compatibility, psychological stability of individuals, social skills, human reliability, and other physiological changes that occur in space. All of these factors can have a significant impact on behavior and performance (Christensen and Talbot, 1985). There is likewise, a long list of environmental factors that will effect human performance and behavior. These include, spacecraft design and habitability, confinement, isolation, lack of privacy, noise, life support, circadian rhythm changes, hazards, and boredom. Space system characteristics identified as potential factors in human behavior include mission duration and complexity, division of work, information load, task load, crew autonomy, quality of life, communication between crew members and with Earth, and time compression.

The ability and success of various therapeutic interventions is partly determined by the ability to identify psychological problems during space flight. A number of studies have analyzed various methods of detecting stress, diminished performance, and psychological instability. The Russian space program has utilized speech analysis to determine the level of stress and emotional state of cosmonauts (Simonov and Frolov, 1973). However, the success of these studies has not been reproduced by later studies. The issue of psychological and behavioral aspects of long term space flight will certainly need to be addressed in order to determine how and why they might occur, how to prevent them, and how to treat them if they occur. In order to accomplish these objectives, a thorough understanding of the neurophysiological mechanisms underlying these changes will be needed.

Current Neuroimaging Applications

Today's neuroimaging technologies provide the opportunity to observe many of the structural and functional changes in the central nervous system *in vivo* in human beings and animals. Anatomical imaging using x-ray computerized tomography (CT) and magnetic resonance imaging (MRI) yields detailed anatomical images with high resolution. MRI has better resolution than CT and MRI has no associated radiation exposure. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are functional imaging techniques that have been used extensively and safely in the study of various diseases and activation states of the brain. These techniques can measure a number of functional parameters in the brain including metabolism, blood flow, and the activity of various neurotransmitter systems. Numerous studies have been performed using the above mentioned imaging techniques. In considering the use of brain imaging technologies for the study of the effects of the space flight environment on the human CNS, it is important to briefly review some of the current literature regarding the study of various activation states and neuropsychiatric disorders that are potentially relevant to the study of space flight.

In the study of degenerative disorders such as Alzheimer's disease (AD), both qualitative and quantitative CT and MRI findings have shown ventricular and cortical enlargement which are more pronounced than that found in normal aging (Gado *et al*., 1983; Damasio *et al*., 1983; Tanna *et al*., 1991). Furthermore, the brains of AD patients atrophy quicker than age matched controls (Gado 1983). Temporal lobe atrophy may be particularly prevalent in AD patients (George *et al.*, 1987). Further, the degree of atrophy has been found to correlate with certain neuropsychological deficits (Pfefferbaum *et al.*, 1990).

In PET and SPECT studies, the "typical" pattern of regional cerebral blood flow in AD patients is hypoperfusion of the temporo-parietal areas. Bonte *et al.* (1986) indicated that the criteria for the diagnosis of AD included decreased blood flow in one or both temporo-parietal regions. PET studies have described a typical pattern of bilateral parietal hypometabolism (using [18F] fluorodeoxyglucose to measure glucose metabolism) in patients with AD (Jamieson *et al.* 1987; Jagust et al. 1988; Kumar et al. 1991). Furthermore, in a study of 26 patients with cognitive dysfunction, bilateral parietal hypometabolism was successful in predicting AD as much as 13 months prior to the clinical diagnosis of AD by NINCDS-ADRDA criteria (Kuhl *et al.*, 1987).

Neuroimaging studies are also useful in the study of degenerative diseases such as Parkinson's disease (PD) and Huntington's disease. SPECT studies have shown that patients with PD show a mild diffusely decreased blood flow throughout the cortex sparing the cerebellum (Smith *et al.*, 1988; Nagel *et al.*, 1991). It is still controversial whether or not there is hypoperfusion in the basal ganglia in PD (Smith *et al.*, 1988). Several PET studies have reported hypermetabolism in the basal ganglia in early, untreated PD (Rougemont *et al.*, 1984; Eidelberg *et al.*, 1990). Using PET, PD patients have been shown to have mild diffuse cortical hypometabolism that worsens with the severity of bradykinesia (Rougemont *et al.*, 1984). [^{18}F] fluorodopa has been used for PET imaging in PD to evaluate presynaptic dopaminergic function and studies found defective uptake in the nigrostriatal dopaminergic projection (Martin *et al.*, 1986; Brooks *et al.*, 1990) as well as reduced basal ganglia activity (Leenders *et al.*, 1990). PD patients have been followed longitudinally and were found to have a steady decrease in the accumulation of fluorodopa which correlates with worsening bradykinesia scores (Leenders *et al.*, 1990; Eidelberg *et al.*, 1990). Fluorodopa PET studies have also found abnormalities in the nigrostriatal projection in asymptomatic patients with increased risk of developing Parkinson's disease such as co-twins of patients with PD (Brooks *et al.*, 1991; Sawle *et al.*, 1992) and first degree relatives in families with inherited PD (Sawle *et al.*, 1992).

Another use of neuroimaging that might be related to space flight is in the study of patients with normal pressure hydrocephalus (NPH). NPH can be observed on both CT and MRI as increases in the ventricular CSF spaces (Kunz *et al.*, 1989; Becker *et al.*, 1995). However, functional studies allow for a better assessment of the flow of cerebrospinal fluid (CSF) which may help determine which patients might improve after shunt operation for treatment. Studies with both PET and SPECT have demonstrated abnormalities in cerebral blood flow and metabolism in the cortical and subcortical structures in patients with NPH (Brooks *et al.*, 1986; Waldemar *et al.*, 1993). Recent studies have also indicated that NPH might be associated with different degenerative disorders and therefore, may be a more heterogeneous syndrome than previously thought (Tedeschi *et al.*, 1995).

Neuroimaging techniques may be particularly useful in the study of the effects of radiation on the brain. Several animal studies which have explored the consequences of exposure to radiation. Lo *et al.*, (1989) showed that rabbits that had left partial hemibrain irradiation with 30 Gy (230 MeV/u helium ions) had damage to the white matter tracts and thalamic regions observed on MRI. PET studies demonstrated widespread decreases in cerebral glucose metabolism in the cortex and thalamus. Interestingly, these rabbits did not show any signs of neurological deterioration. Rabbits irradiated with 15 Gy did not demonstrate any changes on MR images or PET scans. In a similar study on dogs (Brennan *et al.*, 1993), those that received between 7.5 and 11 Gy of spread Bragg peak neon did not develop radiation necrosis and were found to have no abnormalities on PET or MR images. Neon doses of 13 and 15 Gy did induce radiation necrosis from which the animals ultimately died. However, the abnormalities did not appear on imaging studies until 3-6 weeks prior to the animal's death. Functional changes preceded anatomical findings. In human studies, PET, unlike CT or MRI, is capable of distinguishing radiation necrosis from tumor recurrence (Doyle *et al.*, 1987; Valk *et al.*, 1988). In general, radiation necrosis areas are hypometabolic and tumor recurrence areas are hypermetabolic on FDG-PET. PET has also been used to determine tumor response to radiation and chemotherapy and eventual patient survival (Ogawa *et al.*, 1988). Unfortunately, there have been no studies which have explored the effects of long term exposure to lower doses of radiation. Such studies may be useful in determining the effects of radiation in the space flight environment on the central nervous system.

PET has been widely used in the study of the functional abnormalities in various psychological disorders including schizophrenia (Sedvall, 1992; Cleghorn et al., 1991), depression, bipolar disorder, obsessive-compulsive disorder, and anxiety disorder (Newberg and Alavi, 1996). Each of these disorders has demonstrated unique findings on PET imaging. However, more investigations are necessary to elucidate the underlying neurophysiology of these disorders.

A variety of studies have measured cerebral activation in response to somatosensory and sensory stimulation as well as motor, thought, and language tasks. One group (Alavi *et al.*, 1981; Greenberg *et al.*, 1981) found an increase in the metabolism of the contralateral postcentral gyrus cortex when a subject's hand was stroked with a brush. Another group (Phelps and Mazziotta, 1985) found a 19% increase in metabolism in the contralateral precentral and supplementary motor cortices in subjects who performed the motor task of unilateral finger movements. Grafton *et al.* (1992) found increased rCBF, as measured with $^{15}O\ H_2O$, in the left primary motor cortex, the left supplementary motor cortex, and the left pulvinar thalamus in subjects during the early learning phase of a pursuit motor task with the right hand. Friston *et al.* (1992) showed that with repeated practice of a specific motor task, the subject had decreased activation in the cerebellum (activation measured by an increase in rCBF), while there was no change in the activation of the primary sensorimotor cortex. This decrease is believed to represent the cerebellum adapting to a motor task that was performed by the subject over many trials. Kushner *et al.* (1988) used FDG-PET to study the retinotopic organization in the primary visual cortex. The results from this study showed that visual stimulation of either hemifield resulted in increased metabolism in the contralateral striate cortex. Further, there was a slight increase in metabolism in the right frontal and parietal cortices compared to the left suggesting that the right hemisphere might be more specialized for visual processing.

Neuroimaging in the Study of Space Flight

The effects on the central nervous system that result from space flight might be reflected in both morphological and functional changes. Brain and cerebrospinal fluid (CSF) volume for both the entire cranium and for specific brain regions can now be accurately quantitated using new computer techniques. This ability might be useful for measuring brain volume changes related to long duration space flight. For example, using MRI, an astronaut could be studied before and after a mission on a space shuttle or space station in order to determine if there is any expansion of the CSF volume during space flight that may result from microgravity or radiation exposure. In addition to brain volume quantitation, MRI or CT can detect various brain lesions including those related to tumors and cerebrovascular disease.

Functional changes will likely occur during long duration space flight because of : 1) changes in the neurovestibular and proprioceptive system; 2) changes in the sensory cortex in response to novel stimuli; 3) disturbances in sleep and circadian rhythms; 4) exposure to radiation; 5) behavioral and cognitive changes arising from long durations of isolation; and finally 6) an overall adaptive response to the space environment. Perhaps one might envision the ability to measure cerebral blood flow and metabolism at certain points in time during a long duration space flight. This might allow for the determination of new space flight set points for cerebral function.

Further, if there are decrements in cognitive function with extended stays in space, these might be reflected in metabolic changes before clinical symptoms occur. Another important use for PET and SPECT is in physiological activation studies. For example, one could investigate the changes in metabolism that occur in response to various sensory stimuli or could measure changes that occur while astronauts perform cognitive tasks or while they are subjected to stimuli to provoke motion sickness. With regard to neurotransmitter changes, labeled tracers of many neurotransmitters are now available at a number of institutions for use with either SPECT or PET (see Tables 1 and 2). These imaging techniques may be useful for measuring changes in the neurovestibular system, the sensorimotor cortices, the higher cognitive centers, and could be applied to the study of space flight.

The techniques presented in this paper can be readily used to study astronauts. SPECT, in particular, might have applications in space flight since the instrumentation requires a modest amount of space and weight and the radiopharmaceuticals might be easily synthesized in space without presenting any hazard to the astronauts. We might expect that a flight-ready gamma camera could be a conceivable technological development. This would require minimizing the weight of the camera, which would likely be possible since the size of the mounting and motors would be markedly reduced in a microgravity environment. Also, adequate shielding would need to be used in order to block out incident radiation from the environment. However, the cameras are usually set for specific energies, and the counts that would be emitted from the subject would likely overwhelm any background radiation during the scanning procedure. If a SPECT camera could not be available to fly in space, then it would still be useful to study neurological changes during spaceflight. Certain compounds remain "fixed" in their initial distribution sites in the brain so that the state of brain function at the moment of injection can be imaged up to 24 hours later. The equipment necessary for synthesizing these radiopharmaceuticals is readily available, is small in size, is well shielded from the environment and is of relatively light weight (approximately 100 to 150 pounds). For example, a technetium generator which is widely used in SPECT blood flow imaging uses a generator that can last up to two weeks. Thus, animals or astronauts may be injected in space and imaged upon return to Earth so that the imaging instruments need not be taken into space. Another modality, functional MRI, has potential use for determining cerebral activity during various sensory, motor, and cognitive tasks. However, this technology is still relatively new and its applications to space flight have yet to be determined.

In terms of future studies in space flight, NASA has stated that there is a need for studies which combine physiologic and metabolic data with other information in the evaluation of behavior and performance (Christensen and Talbot, 1985). The report by the NASA Life Sciences Strategic Planning Study Committee entitled "Exploring the Living Universe: A Strategy for Space Life Sciences" (1988) indicated that there is a need for the development of advanced technology in the areas of minimally invasive biomedical instrumentation in order to accomplish the above mentioned goal. Johnson and Arno (1989) have suggested that space life science priorities should include the investigation of structural and sensory changes to the CNS in 0 g, including measurements of brain metabolism, the effect of aging on space adaptability, and alterations in the neurotransmitter systems. The ability of SPECT and PET to investigate cerebral function (and in conjunction with anatomical imaging) might satisfy all of the above described goals and play a major role in preparing astronauts for future space flights as well as monitoring them during flight. However, these existing technologies will need to be further developed in order to be used safely and effectively during space flight.

Table 1: A Partial Listing of Radiotracers used in Neurological SPECT Imaging

Compound	Application
HMPAO, ECD	Cerebral blood flow
3-quinuclidinyl benzilate (IQNB)	Muscarinic cholinergic receptor
Iodopride, IBZM, iodospiperone	Dopamine receptor
AMIK, DOI	Serotonin receptor
Iomazenil	Benzodiazepine
2-iodomorphine	Opioid receptor
I-d(CH2)5[Tyr(Me)2, Tyr(NH2)9]AV	Vasopressin

HMPAO = Technetium 99m hexamethyl propylene amine oxime, **ECD** = N,N'-1,2-Ethylenediyl-bis-L-cysteine diethylester
IBZM = 3-iodo-N-[(1-ethyl-2-pyrrolidinyl)] methyl-2-hydroxy-6-methoxybenzamide, **AMIK** = 7-amino-8-iodo-ketanserin
DOI = 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, **IMP** = Iodine-123-N-N', N, -trimethyl-N'-[2-hydroxyl-3-methyl-5-iodo-benzyl]- 1, 3 propane diamine

Table 2: A Partial Listing of Radiotracers Used in Neurological PET Imaging

Compound	Application
[^{15}O] H2O	Cerebral Blood Flow
[^{18}F] fluorodeoxyglucose	Glucose metabolism
$^{15}O_2$	Oxygen metabolism
[^{11}C] raclopride, [^{11}C] methylspiperone, 6-[^{18}F] fluorodopamine, [^{18}F] spiperone,	Dopamine receptor activity
[^{11}C] carfentanil, [^{11}C] etorphine	Opiate receptor activity
[^{11}C] flunitrazepam	Benzodiazepine receptor activity
[^{11}C] scopolamine, [^{11}C] quinuclidinyl benzilate	Muscarinic cholinergic receptors

CONCLUSION

The results from the neurological and neurophysiological studies to date clearly indicate that the human central nervous system undergoes a number of changes when exposed to the space environment. Some of these changes are adaptions to the space environment, but some changes are maladaptive such as those that disrupt circadian rhythms or cause neuronal damage. Many of the environmental factors such as weightlessness, radiation, vibration, and noise all impact on the physiology, morphology, and neurotransmitter activity of the CNS. In short duration flights, changes in neuronal integrity, neural architecture, and neurotransmitter receptors have already been observed in animals. However, if the changes that occur during short term flights continue throughout exposure to the space environment, one might expect to see more extensive and persistent changes occurring with extended stays in space.

Recent progress in the ability to study morphology, metabolism, and neurochemistry *in vivo* in the human brain using current neuroimaging techniques would provide the opportunity to investigate many of the changes that may occur in the CNS as a result of space flight.

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