

Tab 3

Research Statement

A. Integrated Research Plan Risks and Gaps

This Step-2 proposal responds to NRA-NNJ09ZSA001N regarding the critical need for ground-based radiobiological studies to identify long-term effects of space radiation on the central nervous system (CNS). This application address the 2nd category of space radiation risk and gaps outlined in the Human Research Program Integrated Research Plan (HRPIRP): *1.2 Risk of Acute or Late CNS Effects from Space Radiation; specific gaps: CNS-2 and CNS-6 (NRA, pg 33, 37).*

B. Statement of Problem

The long-term risk of neurobiological damage to humans induced by space radiation during deep space travel is the most poorly explored health risk in ground-based studies of space radiobiology. Future deep space missions, such as long-term lunar and Mars missions, require travel beyond the Earth's protective magnetic field. Such continuous exposure leads to different types of space radiation hazards such as galactic cosmic rays (GCRs) and solar particle events (SPEs), which consist of particles of high energy and charge (HZE) and protons. Exposure to these radiations may pose a significant health risk for astronauts and, notably, low doses of GCRs or proton exposure caused by SPEs may be the primary sources of space radiation hazards on long duration missions. Recent studies suggest that the CNS, like the gastrointestinal tract, may be a radiosensitive organ.¹ Thus, exposure to these types of space radiation, in addition to jeopardizing mission success, may cause considerable and potentially long-term damage to the astronaut's normal CNS functioning and overall health. Although astronauts will be exposed to low doses of HZE particles (e.g. ⁵⁶Fe) and protons during deep space travel, studies to date have primarily focused on the short-term CNS effects of high doses of HZE's and protons.²⁻³⁴ Surprisingly little information is available on the long-term CNS consequences of different types of space radiation with exposures that may be more representative of a space radiation environment. This information gap has significantly hindered NASA's ability to realistically estimate radiation risk associated with human space exploration and, consequently, impeded the development of future human deep space missions. The studies proposed in this application will address this information gap by developing a set of *in vivo* procedures in nonhuman primates that will examine the long-term effects of two different dose levels each for ⁵⁶Fe and protons on CNS function.

C. Overall Objectives, Specific Aims and Hypotheses

1. **Program Objective.** The overall objective of our program is to obtain data from studies in nonhuman primates that help predict long-term deleterious effects of space radiation on CNS function in humans. We propose to undertake this effort with neurobehavioral pharmacological studies in monkeys to evaluate the long-term (4 yrs) effects of exposure to two doses of ⁵⁶Fe ion (0.1 or 0.5 Gy) and protons (0.5 or 1.0 Gy).

2. **Specific Aims.** Specifically, we aim to:

a. **Evaluate effects of space radiation on overt behavior.** The dose-related effects of dopaminergic drugs on targeted overt behavior--i.e., visual scanning, eye-blinking, self-scratching--have been used to study CNS dopamine (DA) receptor-mediated mechanisms (D₁, D₂) in monkeys.²⁵⁻²⁷ We will compare pre- and post-radiation exposure effects of

receptor-selective drugs on overt behavior to determine whether DA receptor-mediated function in monkeys is altered by exposure to ^{56}Fe particles and protons.^{2,14,16-18}

b. Assess effects of space radiation on motivational processes. Progressive-ratio (PR) procedures to measure the amount of behavior a subject will emit for food reinforcement provide an established operant index of reinforcement value and permit the study the role of different CNS systems in motivational processes. We plan to assess the effects of drugs that selectively increase or decrease different types of receptor activity implicated in brain reward systems [e.g. DA, cannabinoid CB₁, glutamate (GLU)]⁴⁴ to determine how exposure to ^{56}Fe particles and protons alters their effects on PR behavior.

c. Examine space radiation effects on cognitive processes. Behavioral procedures such as the 'Stop Signal Response (SSR) Task' to measure impulsivity and performance monitoring, and the 'Stimulus Discrimination /Reversal (SD/R) Task' to measure cognitive functions, have been used to study aspects of impulsivity and cognitive function in both nonhuman primates and humans.⁴⁵⁻⁴⁸ We will use these highly translational procedures in squirrel monkeys to determine how ^{56}Fe particles and protons may alter the effects of drugs that target different brain systems implicated in cognitive processes (i.e. cholinergic; DA, cannabinoid CB₁).

d. Develop a 3-D computer model for monkey irradiation to estimate absorbed space radiation doses. Radiation dosimetry will be implemented using a combination of extensively validated physical measurements and independent software models: 3-D MCNPX²⁸, HZETRN2005²⁹, NASA OLTARIS³⁰, TLD dosimeters; standard dosimetric instrumentation; and HZETRN2005 1-D fused with RADCOG code.³¹⁻³² A generic computer model for primates will be developed using magnetic resonance imaging (MRI) scans, 3-D MCNPX software²⁸, Scan2MCNP software³³, and RADCOG code.³¹⁻³²

3. Hypotheses. Although the absence of comparable studies in other species does not permit confident prediction, we anticipate that:

a. studies of overt behavior will reveal long-term alterations in both D₁ and D₂ receptor mechanisms, consistent with a role for DA systems in motivation and cognition.

b. exposure to ^{56}Fe particles and protons will alter the pharmacology of motivational and cognitive processes in nonhuman primates and, in particular, the effects of DA-related drugs on PR behavior and in SSR and SD/R tasks.

c. the combination of experimental dosimetry and dose assessments will reveal meaningful cause-effect relationships between radiation dose and neurobehavioral pharmacological data in monkeys.

D. Relevance, Significance and Feasibility of Proposed Studies

Our overall research strategy is pharmacologically mechanistic. We plan to compare the effects of CNS receptor-selective drugs before and after exposure to evaluate long-term neurobehavioral effects of ^{56}Fe particles and proton. This approach is based on observations that exposure to high doses of GCR and SPE leads to: 1) short-term detrimental effects in some rodent neurobehavioral assays;^{2,15} 2) *in vitro* changes in brain DA striatal tissue;^{2,14,16-18} 3) long-term CNS changes that are comparable to those observed in normal human aging;^{2,15,22} 4) acceleration of the aging process and an increased risk of early onset of neurodegenerative disease^{2,5,15,22} and 5) molecular and cellular damage in CNS.²³⁻²⁴ These findings come mainly from *in vitro* preparations or neurobehavioral assays in rodents, and provide a strong foundation for further assessing

the immediate and long-term CNS effects of space radiation. Cognizant of anatomical and functional variations across species that limit extrapolation of laboratory data from rodents to nonhuman primates or humans,³⁵ our approach will employ well-established procedures in nonhuman primates to study the effects of ⁵⁶Fe and proton radiation on brain systems that may be involved in motivational and cognitive processes.

1. Relevance of Proposed Studies. There presently is little understanding of potential long-term neurobehavioral consequences of exposure to space radiation. In this regard, NASA's Space Radiation Program-HRPIRP has identified studies of immediate and late (i.e., long-term) effects of space radiation on CNS functions as a major research focus (NRA, pg 11):³⁴ The relevance of our proposed research is that we will directly address this need with ground-based studies in monkeys to examine the long-term effects of HZE and proton radiation in neurobehavioral assays of motivational and cognitive processes. This information will help advance NASA's ability to predict the long-term CNS risks of space radiation for astronauts.

2. Significance of Proposed Studies. To our knowledge, the neurobehavioral effects of exposure to space radiation have not been previously examined in nonhuman primates. Overall, a highly significant aspect of our proposal lies in our use of nonhuman primates. Several features of nonhuman primate research facilitate the translation of experimental results to humans with reasonable predictive validity.³⁵⁻³⁸ For example: 1) nonhuman primates and humans are similar in their genetic, physiological, pharmacokinetic, and neurobiological characteristics; 2) within-subject designs similar to those used in human laboratory studies permit meaningful conclusions or inferences to be based on the evaluation of all treatment effects in individuals as well as in groups; and 3) nonhuman primates are reliable subjects in long-term behavioral and pharmacological studies.³⁸⁻⁴⁰ Considerations such as these suggest that nonhuman primates are especially well-suited for ground-based research to study long-term neurobehavioral effects of space radiation.

Previous reports suggest that HZE particle radiation may have deleterious effects on DA function. Thus, we have chosen to first evaluate the long-term consequences of exposure to ⁵⁶Fe and proton radiation on CNS DA-related systems. Studies of overt behavior outlined in Specific Aim 1 (see section G.2.a, G.6.a, and H.1) will enable us to determine whether exposure alters the effects of DA receptor subtype-selective drugs or of drugs that activate DA receptors indirectly. The significance of these studies is that they will advance NASA's Space Radiation Program in a manner that is logically based on previous findings of DA-related abnormalities and that is highly translational.

Under Specific Aims 2 and 3, we will employ operant procedures that are widely acknowledged to measure aspects of motivation and cognition (see sections G.2.b-c, G.6.b-d, and H.2-3). These procedures also have been used to study the effects of receptor-selective drugs that act through CNS systems implicated in these neurobiological processes. Our proposed research will use this pharmacological approach to analyze the long-term effects of exposure to radiation on motivation and cognition by evaluating changes in baseline performance over time, and by comparing pre- and post-exposure effects of receptor-selective drugs. The significance of these studies is that they will provide data in nonhuman primates that will lead to more accurate prediction of long-term effects of space radiation on motivational and cognitive processes.

Finally designing and developing a novel computer model for nonhuman primate irradiation (**Specific Aim 4**: see section G.2.d, G.7, and H.6) will yield estimates of absorbed doses to individual organs and whole body with high degrees of accuracy. The significance of this work is that it will permit meaningful analyses of cause-effect relationships between radiation dose and effects in neurobehavioral studies in monkeys.

Taken together, the results of these studies will provide previously unavailable information on the long-term CNS effects of ^{56}Fe particles and proton radiation in nonhuman primates. Regardless of study outcomes, such quantitative and qualitative neurobehavioral and neuropharmacological data will be uniquely valuable to two stated goals of NASA's Space Radiation Program: a) significant progress toward estimating space radiation risks to humans and b) development of a strong and clear foundation for NASA to successfully design future human deep space missions.

3. Feasibility of Proposed Studies. Given that similar ground-based studies in space radiobiology have not been previously conducted in nonhuman primates, it is important to recognize the feasibility of our planned research. Our research group includes investigators with as much as 30 years of experience in conducting complex behavioral pharmacology studies in nonhuman primates (Drs. Bergman [REDACTED], radiation biology expertise in cellular and molecular CNS effects of space radiation,²³⁻²⁴ [REDACTED], sophisticated understanding of the physical causes of space radiation from GCR's and SPE's,⁴¹ [REDACTED], and expertise in radiation physics with particular emphasis on dosimetry calculations in animals and humans.³¹⁻³² [REDACTED].

With regard to our proposed neurobehavioral studies, we have substantial experience in studying drug effects on overt behavior in squirrel monkeys (**Specific Aim 1**), and we have demonstrated that different types of DA receptor-related drugs exhibit unique and characteristic behavioral profiles (see section G.6.a).^{25,27,42-44} Our laboratory also has extensive experience in training nonhuman primates in complex behavioral tasks that are used to measure both motivational and cognitive processes (**Specific Aims 2 and 3**). For example, we currently are conducting studies in squirrel monkeys using PR performance as an index of motivation and we have recently trained monkeys to leverpress or withhold leverpressing depending on the color of visual stimulus lights as a measure of impulsivity⁴⁹. Except for the use of a touch screen in place of stimulus lights and levers, this task is nearly identical to the SSR task that we will use in our proposed research⁴⁵. Finally, SD/R learning is routinely used in the context of drug discrimination or choice research in our laboratory. Based on our extensive experience in training squirrel monkeys to perform these and other complex behavioral tasks, we do not anticipate methodological problems in achieving the goals of this application. Regarding **Specific Aim 4**, our project team has substantial experience in understanding the causes of particle radiation and in developing novel approaches to radiation dosimetry (section G.7).^{31-32, 41}

Finally, to further ensure that the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL, NY) can support our planned studies in nonhuman primates, we recently visited [REDACTED] (a consultant on our proposal) and [REDACTED] (BNL Animal Facility Manager). Following careful inspection of the NSRL and the animal care facility at BNL, and as well, discussion with [REDACTED] and [REDACTED], we are highly confident that: 1) the irradiation of squirrel monkeys at

NSRL will be conducted without difficulty; and 2) our subjects will be properly housed and maintained at BNL during the irradiation protocol (see section G.2.e and G.3).

E. Future Direction of Planned Nonhuman Primate Studies

Our proposed research in nonhuman primates is designed as an initial set of studies to assess the *in vivo* CNS effects of exposure to relatively low doses of ^{56}Fe particles and protons. We understand that in these initial studies, monkeys will be exposed to particle radiation that does not fully mimic the chronic low dose situation in a mixed radiation field. Based on guidance from NASA, we expect future research to include studies of long-term CNS risks associated with other radiation types, including a combination of ^{56}Fe and proton irradiation. In addition to space radiation, other external stressors also may have detrimental effects on normal CNS function during long-lasting deep space missions. These include microgravity, altered light-dark cycle, elevated CO_2 levels in ambient air, confinement, and high physical and mental workload.⁴⁶ Consequently, future studies in this program also may be designed to evaluate the short- and long-term impact of a combination of ^{56}Fe and/or proton irradiation and external stress factors (e.g., microgravity) on normative behavior in nonhuman primates. Finally, previous work in rodents suggests that we will observe DA-related behavioral effects of exposure in our initial studies. If earlier findings are confirmed in our studies, we are prepared to measure ^{56}Fe and proton radiation-induced changes in DA neurochemistry in monkeys, using *in vivo* microdialysis procedures that are ongoing in our laboratory.³⁹

Although identifying specific studies is premature at this time, we recognize that the major goals of this program will include, first, research into the relationship between molecular and cellular changes in primate brain tissue and neurobehavioral and pharmacological effects of exposure to HZE particles and protons radiation and, second, the development of effective pharmacological and/or dietary countermeasures to lessen the risks of HZE and proton radiation and/or other external stressors to CNS function. Data from our planned studies will provide a strong first step in these directions.

F. Background

1. Space Radiation Environment and Risks to Humans. During deep space travel, astronauts are continuously subjected to a hazardous radiation environment that is made up of SPEs, HZE ions (GCRs), and secondary radiation. Whereas SPEs consist mainly of protons, GCRs consist of many different types of HZE particles (i.e. Fe, Ti, or Cl). High radiation doses from GCRs and SPEs arise from protons and high Z nucleons at energies of about ~1000 MeV and ~50-100 MeV per nucleon, respectively.^{1,47-48} SPEs are very intense low energy particles compared to GCRs and occur over relatively short periods of time (i.e., hours to days) which allows their effects to be minimized with effective shielding.⁴⁹⁻⁵⁰ However, the timing of SPEs is difficult to predict, which increases the risk of proton exposure. In contrast, GCRs are less intense, but due to their penetrating and persistent nature, shielding alone is unable to prevent exposure to ionizing HZE particles. For example, during interplanetary travel, each cell within an astronaut's body is likely to be hit by either a proton or secondary particle every few days and by a HZE ion approximately once a month (1-2 mSv/ day whole body accumulation).⁵¹⁻⁵² Over the course of a three year mission to Mars, calculations suggest that brain neural cells will be subject to a direct hit by: a) an HZE particle ($z > 15$; 46% of cells exposed), with 13% of the neurons traversed by an ^{56}Fe ion ($z = 26$); and b) a proton, with all cells being

traversed on the average of once every three days.⁵¹⁻⁵⁴ Even under conditions of low Earth orbit (90 days), an estimated 45% of brain hippocampal cells are likely to be hit by a high linear energy transfer (LET) particle; these numbers rise to >90% of the cells over a one year mission.⁵⁵

It seems clear that exposure to GCRs and SPEs may jeopardize mission success and cause long-term damage to the astronaut's overall health. Ground-based biological studies of space radiation have confirmed that exposure can cause severe damage to all biological processes within the human body, including those mediated within the CNS. Yet, the risk of neurological damage induced by charged particles is among the most poorly understood health risks for humans traveling through space on lengthy missions. Our proposed ground-based studies are intended to address this critical gap in information regarding the long-term effects of exposure to HZE particles and protons on the CNS and, thereby facilitate progress in NASA's deep space program.

2. Molecular and Cellular Effects of Space Radiation in CNS. Although the proposed work does not focus on ⁵⁶Fe and proton radiation-induced changes in molecular and cellular activity, this section provides a brief overview of our current understanding of these effects. Recent studies of neurogenesis in hippocampus suggest that ionizing radiation doses may have damaging biological and molecular effects on brain mitotic and post-mitotic cells.⁵⁶ Studies have demonstrated that the cellular response to ionizing radiation is complex and varies across cell types and forms of radiation.⁵⁷ In neuronal cells, cytotoxic damage is likely to include apoptotic loss of neurons, functionally impaired surviving neurons, and impaired neurogenesis, which may be important in the progression of neuropathological conditions and neurodegenerative diseases.⁵⁸ Furthermore, damage to DNA has been shown to activate the apoptotic process in neurons, leading to the emergence of peripheral neuropathies, neurodegeneration, and neuropathological conditions.⁵⁹⁻⁶⁵ This cascade may involve molecular events, including the regulation of tumor suppressor protein p53, or its target components downstream.^{59,63,66-72} Though this type of research supports the view that ionizing radiation may alter molecular and cellular activity within the CNS leading to cell death, the precise nature of changes in neurons as a consequence of exposure to HZE particle and proton radiation remains to be fully determined.

It is currently unknown whether the above described molecular and cellular changes in CNS translate to functional alterations in CNS function in the whole organism. Our proposed research represents an essential step toward studying and understanding such relationships, and will lead to significant progress in characterizing the underlying neurobiological effects of HZE and proton radiation. Together, such advances will help reduce the uncertainties in assessing the risks of space radiation.

3. Neurobehavioral and Neuropharmacological Effects of Space Radiation. In early behavioral work, exposure to conventional γ radiation was reported to produce dose-related and reversible disruptions in motor function and in operant behavior maintained under a variety of schedule conditions.⁷³⁻⁷⁸ In other studies, radiation exposure also was shown to decrease non-conditioned activity, including aggressive, defensive, ambulatory, and rearing behaviors.⁷⁹⁻⁸³ These early findings indicated that radiation could have important behavioral effects and encouraged further research. More recently, the development of NSRL at BNL and the radiation accelerator at Loma Linda

University, CA, has allowed researchers to directly evaluate the effects of ground-based models of space radiation on different neurobehavioral processes, e.g. reactivity to stimuli, motivation, cognition, and mood.^{2,22,84-101} Generally, these studies have shown that exposure to HZE, but not protons, can produce profound deficits in both simple and complex behaviors that provide a measure of motor and cognitive functioning,^{2-17,84-101} and that these changes may be similar to those observed in aging.^{2,20-22,91,93,98-107} Several studies have related the behavioral consequences of HZE particle and proton radiation exposure to *in vitro* neurochemical changes within the CNS. In particular, studies have examined the relationship between *in vitro* DA neurochemistry and DA-mediated behavioral endpoints that are associated with motoric and cognitive functions.^{2,7,9,11,13-14,18,22,95-96,98,102-103} These studies have yielded mixed results. For example, Rabin and colleagues provide some evidence for a relationship between radiation-induced damage to the brain DA neurotransmitter system (substantia nigra and striatum) and deficits in DA-mediated motor and cognitive behavioral measures.^{2,7,9,11,13-14,22,95,96,98} They report that the observed behavioral and neurochemical deficits are not dose-related but are evident following a threshold radiation dose below which there are no effects. Additionally, these deficits occur quickly following HZE (⁵⁶Fe) radiation and fail to dissipate afterward.^{2,14} These investigators also report a lack of association between the LET (linear energy transfer) of HZE particles and their relative effectiveness in disrupting behavior or DA regulation.⁹²

Although the above findings suggest that irradiation may induce both behavioral and neurochemical deficits in CNS DA function, the results of other studies are not consistent with this view. Thus, exposure to ⁵⁶Fe particles failed to alter the density of DA transporters (midbrain and forebrain regions), and altered cocaine-induced effects on locomotor activity but did not alter other DA-mediated behaviors.^{18,102} The paucity of other data on the behavioral and neurochemical effects of space radiation makes it difficult to reconcile these varying findings, but they may reflect differences in behavioral and neurochemical procedures.

The above studies clearly demonstrate that further neurobiological research on the short- and long-term effects of HZE particle and proton radiation is critical to the advancement of NASA's Space Radiation Program. Notably, the above results have mainly been obtained from rodent studies or *in vitro* tissue preparations. These studies provide a strong initial foundation for further work to effectively and efficiently evaluate the long-term effects of exposure to GCR and SPE radiation on neurobehavioral processes and CNS function. Our ground-based studies in nonhuman primates are designed to provide previously unavailable information and, thereby, yield an improved understanding of the CNS-mediated behavioral effects of space radiation. This will lead to significant progress toward NASA's mission of estimating and reducing the uncertainties associated with space radiation exposure during deep space missions.

4. Computational Models for Radiation Dosimetry. A clear need exists for improved computational models in radiation dosimetry. For example, previous studies have reported dose calculation discrepancies for identical computational models among established software packages and different research groups.¹⁰⁴⁻¹⁰⁵ Along these lines, comparative studies of European and Asian computational human phantoms based on cadavers have demonstrated that the anatomical features of the phantom significantly influence absorbed organ and total body dose estimates. Several studies have reported

variations in the absorbed dose to specific organs by up to 300% for three phantoms with minor anatomical differences.^{104-106,126} For GCRs and SPEs the substantial organ dose variations appear to depend on the precise organ location within the body.¹⁰⁷ The estimates of the mean absorbed dose in organs and tissues, as well as the whole body are affected by several important factors: including overall body size, position relative to the beam during irradiation, position and movement of organs during irradiation; dimensions and densities of the body skeleton components; amount and distribution of fat tissue throughout the body; and other individual anatomical characteristics of the bodies.¹⁰⁸

In summary, our plan to develop computer models for radiation dosimetry in squirrel monkeys will allow more precise measurement of the absorbed dose in specific organs, tissues, and whole body. This will improve our assessment of cause-effect relationships between space radiation dose and long-term neurobiological effects.

G. Research Methods and Procedures

1. Subjects. Experimentally naïve adult male squirrel monkeys (*Saimiri sciureus*, approx. 650 to 800g) will serve as subjects (n=4/radiation type; n=3 for control group). Monkeys will be individually housed in stainless steel cages in a climate-controlled vivarium under an automated 12:12 light-dark cycle. Monkeys will have unlimited access to water and will receive a daily allotment of high-protein monkey chow (LabDiet, Brentwood, MA). All monkeys will be weighed daily and their diets will be adjusted to maintain constant body weights. Experimental sessions will be conducted daily (Monday–Friday) between 10 AM and 6 PM. The study protocols are under review, pending approval by the McLean Hospital (McL) Institutional Animal Care and Use Committee (IACUC; see attached letter from, [REDACTED]). If our proposal is approved, we will apply for approval of our irradiation procedure and protocol by the BNL IACUC. Appendix 1 provides further information regarding use of vertebrate animals.

2. Apparatus. All experimental sessions will be conducted in a specifically constructed ventilated, sound-attenuating chamber provided with white noise to mask extraneous sounds. During all experimental sessions, monkeys will be seated in a customized Lexan chair.¹⁰⁹ The front panel of this chair will differ for each type of experiment depending on the study requirements (see Fig. 1).

a. Overt Behavior. The front wall of the chair will be removed in order to facilitate videotaping with a compact video camera (JVC, GR-AX10). The camera will be located at a distance of approximately 2ft in front of the seated monkey. All behaviors will be scored from videotape by blinded observers.

b. PR Performance. Monkeys will be seated in a chair similar to that shown in Figure 1. While seated, monkeys will face a panel containing colored stimulus lights serving as visual stimuli and two response levers. Reinforced lever presses will activate a syringe pump outside the chamber and deliver 0.2 ml of 30% sweetened condensed milk into a food tray located midway between the two levers (see section G.6.b for details).

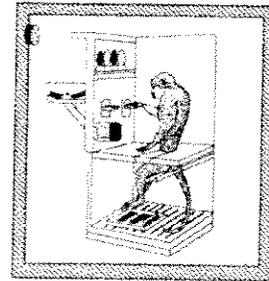


Figure 1. A customized Lexan chair in which squirrel monkeys will be seated during PR-FR experimental sessions. The front panel consists of stimulus lights, two response levers, and a food tray. For overt behavior and the cognitive tasks, the front panel will be removed and replaced with a touch screen, respectively.

c. SSR and SD/R Tasks. During experimental sessions, the front panel will incorporate a touch screen (30cm wide x 22.5 cm high, Elo systems CarrollTouch, Menlo Park, CA) that uses an infrared sensor grid just above the surface to monitor touches. Milk will be used to reinforce behavior and will be delivered by syringe pump into a food tray located on the side wall. E-prime software (Psychology Software Tools, Pittsburgh, PA) will be used for all schedules of stimulus presentation and recording of responses (see section G.6.c for details).

d. Radiation Dosimetry. Standard dosimetric instrumentation available at BNL will be used to measure radiation dose at the location of the subject. Additionally, personal thermoluminescent (TLD) dosimeters will be positioned across each of the squirrel monkey jackets (Lomir, Malone, NY, USA). For proton irradiations, the 3-D MCNPX software code,²⁸ the HZETRN software,²⁹ and OLTARIS³⁰ will be used in parallel. For ⁵⁶Fe irradiations, the 1-D software, HZETRN software,²⁹ and OLTARIS³⁰ will be used. Following irradiations, a combination of computational tools, outputs of the standard dosimetric instrumentation, and TLD dosimeter readings, will be used to assess actual doses. At later stages, geometric framework will be coded by fusing HZETRN2005 1-D capabilities with 3-D capabilities of the RADCOG.³¹⁻³² Appendix 2 provides a detailed description of the software to be used for radiation dose assessment.

e. Irradiation Chamber. During irradiation procedures, freely moving monkeys will be placed individually in a customized, well-ventilated plastic chamber (30 x 30 cm²) that will be positioned inside the radiation field. The chamber will be constructed to meet the requirements of the radiation field.

3. Transportation and Irradiation Procedure. After pre-radiation studies are completed, monkeys will be transported to NSRL/BNL for irradiation. We anticipate three separate trips to BNL (six monkeys pre trip). Prior to each trip, the attending veterinarian at McL. [REDACTED] will conduct pre-transport evaluations of all subjects, including physicals and laboratory tests to establish their pre-radiation clinical profiles, and issue required health certificates. A McLean-approved vendor [REDACTED] will transport monkeys to BNL. In addition to customized travel crates designed for squirrel monkeys and safe passage, food and water will be provided to monkeys *ad libitum* throughout the shipping process. Upon arrival at BNL, monkeys will be transferred to the BNL animal facility under the oversight of [REDACTED]. Subjects will be allowed to acclimate in the BNL animal facility for at least one week prior to radiation exposure. During that time, they will be under the direct care of BNL staff, headed by [REDACTED] (Animal Facility Manager) and [REDACTED] (Attending Veterinarian). Food, enrichment, and all instructions for the proper care of squirrel monkeys will be provided by our laboratory. A BNL IACUC approval for transfer of monkeys and irradiation protocol also will be obtained prior to any treatment exposure. All irradiations will be performed in accord with BNL safety policies and procedures, and guided by BNL scientists.

In the present proposal, two doses of each radiation type will be studied. Separate groups of monkeys (n = 4) will be exposed to two doses of protons (0.5 and 1.0 Gy) at a dose rate of 0.25 Gy/min and two doses of ⁵⁶Fe particles (0.1 and 0.5 Gy) at a dose rate of 0.1 Gy/min with energy levels of a 1000 MeV/u; a control group (n = 3) will be subjected to identical experimental conditions, except that they will not be exposed to any particle radiation. The total beam time necessary to conduct irradiations in all 16 subjects will be

approximately 128-min, assuming a 5-min entry and exit time from the NSRL irradiation facility per subject; beam time calculations are based on the above described doses of each particle and its associated dose rate/min. The radiation beams and doses have been selected after consultation with NASA, BNL, and SwRI scientists and will provide information needed to fill critical gaps in NASA's deep space travel data base. Early discussions indicate that, in addition to the standard radiation field (20 x 20 cm²), a 60 x 60 cm² field should be available for irradiation procedures, which are scheduled to begin in year 2 of our protocol. Although either field will be suitable, the larger field allows greater flexibility and likely will be used for our studies. Briefly, monkeys will be placed individually in a custom made plastic chamber (see G.2.e) that will be positioned securely and comfortably inside the radiation field perpendicular to the beam. Freely moving monkeys will receive full body exposure to the different types of particle radiation described above. This is intended to realistically simulate the space radiation environment experienced by astronauts during deep space travel. To accurately calculate the radiation dose absorbed by an internal organ/tissue the position of all subjects will be photographed or video taped during the irradiation procedure. We note that the activation decay times for the highest dose of protons and ⁵⁶Fe particles to be considered non-dispersible are approximately 140 min and 36 min, respectively (see BNL website: <http://www.bnl.gov> for further details on activation decay times). Materials exposed to radiation in the BNL target room will be considered radioactive until surveyed and released by a BNL Radiological Controls Technician. Monkeys will be considered non-dispersible and will require no special radiological handling, after the de-activation time has elapsed following exposure (i.e. after approximately 140 min). Appropriate biological handling techniques including radiological training (Radworker and Radiobiology Users Training) and a radiation work permit will be obtained from BNL by [REDACTED] and trained technicians as needed. All experimental procedures at BNL and at McL will be carried out by [REDACTED] and trained technicians. Following radiation exposure, monkeys will remain at BNL for a period of at least one week. During this time, all monkeys will be monitored by BNL veterinary staff, who will issue health certificates for their return to McL. [REDACTED] will again be present during the transfer of monkeys back to McL, where the attending veterinarian will oversee the re-introduction of monkeys in the vivarium. Once fully re-situated, monkeys will be tested periodically and on a long-term basis, i.e., up to 3-4 years following exposure to ⁵⁶Fe particles and protons.

4. Drugs and Dosing Procedures. Drugs and dose ranges have been selected on the basis of our previous research and other previously published reports (see Table 1). All drugs listed are available from Sigma-Aldridge, Tocris, the NIH/NIDA Supply Program, or the NIH/NIMH Chemical Synthesis Program. The effects of drugs will be studied with single- and cumulative-dosing procedures that are routinely used in our laboratory.^{110,111} Under cumulative dosing procedures, the test session will be divided into four identical components; incremental doses of a test drug will be given intramuscularly (i.m.) prior to each sequential component. In this way, the effects of up to four graded doses can be determined in a single test session. If necessary, overlapping ranges of cumulative doses in separate test sessions will be studied to determine effects of five or more doses of a drug. Under single dosing procedures, a single dose of the test drug will be injected i.m. prior to the start of the first component; injections of vehicle (0.3 ml) will be given prior to each sequential component of the test session.

5. Behavioral Procedures

a. *Studies of Overt Behavior.* We have previously identified overt behaviors in squirrel monkeys that are selectively increased by different types of DA drugs e.g. visual scanning/checking by indirectly-acting agonists such as methamphetamine (MA) or cocaine (Fig. 2A)^{25,112} and eye-blinking or persistent self-scratching by, respectively, directly-acting DA D₁ and D₂ agonists (see Figs. 2B, 2C). Typically, these effects occur at doses of drugs that do not usually produce effects on other observable behaviors.

Experimental sessions will be videotaped and each will comprise a 10-min habituation period followed by four sequential 5-min test components separated by 10-min timeout periods. Injections will be given during timeout periods using procedures described in section G.4. Drugs and vehicle will be tested in random order no more often than twice weekly. Videotapes will be scored by two trained observers who are blinded to test conditions. The following behaviors²⁵ will be measured in each component: a) frequency of visual scanning/ checking (rapid movement of eyes or head from one side to the other or up and down); b) duration of persistent self-scratching (vigorous and rhythmic manipulation of skin or fur with fingers or toes); c) frequency of eye blinking (visible closing and opening of the eyelid); d) duration of huddling (a seated posture in which limbs are drawn close to the body and the tail is curled over the back).

Table 1: DA, cannabinoid, cholinergic, and GLU drugs to be studied under Specific Aims 1-3. Doses for each drug are taken from our own studies and from published reports.^{25-27,39,43-44,110,113-115}

Type	Drug	Drug Dose (mg/kg)
Indirect DA agonist	MA	0.1-3.0
	Cocaine	0.1-3.0
D ₁ agonist	SKF 82958	0.03-1.0
D ₂ agonist	(+)-PHNO	0.0003-0.01
CBI agonist	AM 4054	0.0032-0.1
CBI antagonist	SR 141716A	0.3-18
Cholinesterase inhibitor	Donepezil	0.01-0.3
Muscarinic antagonist	Scopolamine	0.01-1.0
Nicotinic agonist	Nicotine	0.1-1.0
mGluR1 antagonist	CPCCOEt	0.001-1.0
mGluR2 antagonist	LY 379268	0.001-0.1
mGluR5 antagonist	MPEP	0.001-1.0

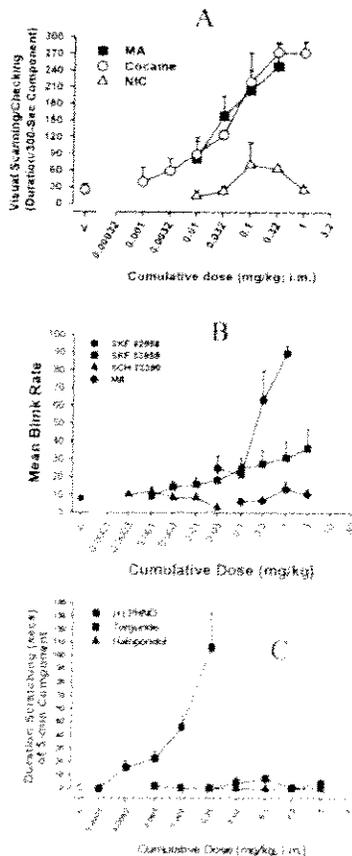


Figure 2. Effects of dopamine-related drugs on overt behavior in squirrel monkeys (n=4 per study)

A. Cocaine and MA dose-dependently increased visual scanning/checking beyond levels observed with nicotine.^{25,112}

B. The DA D₁ full agonist (SKF 82958) and partial agonist (SKF 83959) produced dose-related increases in eye blinking, whereas MA had no effect.^{25,112,113}, and the D₁ antagonist (SCH 23390) decreased it.

C. The D₂-like family full agonist [e.g., (+)-PHNO] produced dose-related increases in self-directed scratching, whereas the D₂-family partial agonist terguride and the D₂-family antagonist haloperidol were without effect on this measure.²⁵

b. Progressive Ratio (PR) Behavior. PR schedules of food reinforcement provide a widely accepted means for studying the motivational value of reinforcing events and how it may be altered by drug treatment. In our laboratory, we have developed and validated a modified PR-FR choice procedure to study the effects of behaviorally active drugs on motivated behavior. Using this procedure, monkeys can press one lever for milk delivery under a PR schedule (the number of required responses increases from trial to trial) or a second lever for delivery of a lesser quantity of milk under a fixed-ratio (FR 30) schedule (the number of responses is constant from trial to trial). Using this procedure, it is possible to determine whether a drug selectively decreases the reinforcing strength of food or, as with cocaine in Fig. 3, has little effect on reinforcing strength even at doses that markedly disrupt FR performance. In our proposed studies, we will use this procedure to systematically compare the pre- and post-exposure effects of drugs that selectively target different neurochemical mechanisms that may mediate motivational processes.

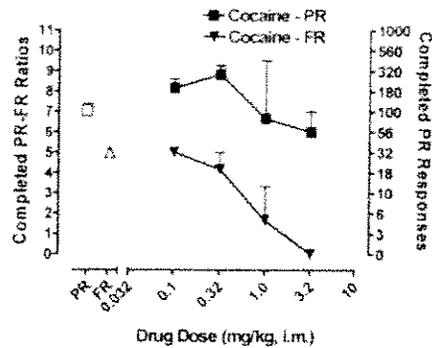


Figure 3. Effects of cocaine on the PR-FR choice schedule of food reinforcement. Cocaine has little effect on PR performance even at dose that significantly disrupt FR performance.⁴⁴

All monkeys will respond on two levers under the modified PR-FR choice schedule of food reinforcement described above. Responding on both levers will be reinforced by milk delivery. However, responses on one lever will be reinforced under a PR schedule with a progressively increasing response requirement (i.e. lever presses per successive milk deliveries = 3, 6, 10, 18, 32, 56, 100, 180, 320, 560, 1000, etc.) whereas, responses on the second lever will be reinforced under a FR 30 schedule. The volume of milk delivered under the PR schedule will be 8x greater than the volume of milk delivered under the FR schedule, and each milk delivery under both schedules will be followed by a 45-sec timeout (TO) period. Daily session will comprise one to four components; five reinforcer deliveries under the FR 30 schedule will turn off all stimulus lights and terminate programmed contingencies for the remainder of the component. Drugs will be studied once or twice per week under identical conditions, using procedures described in section G.4; training session will continue on intervening days.

c. Stop-Signal Response (SSR) Task. This task is a gold-standard assay in human subjects to reveal deficits in impulse control and learning.¹¹⁹⁻¹²² The task measures both impulse control and performance monitoring, which are indicative of broader cognitive functionality¹¹⁹⁻¹²⁰ and has been used with great success to study impulse control in monkeys.^{121,122} We recently have successfully trained monkeys under SSR task contingencies using jeweled stimulus lights and response levers⁴⁵; we anticipate no problems in transferring our training procedures to touch screen technology for our proposed studies. In this regard, touch screen methods have been used both in rhesus monkeys^{121,12} and squirrel monkeys.¹²³

During initial touch screen training, milk reinforcement will be used to train squirrel monkeys to touch an abstract stimuli (i.e. a blue square) in the middle of the

touch screen. Following successful completion of each trial (>90% accuracy), monkeys will be presented with the same abstract stimuli in a random location, and thereafter, the presentation of abstract stimuli will be varied in size and location. Briefly, monkeys will be presented with one of two abstract stimuli at the center of the touch screen. When the stimulus is one color (i.e. a solid green circle, GO trial), the subject can touch the screen over the stimulus for access to milk reinforcement; when the stimulus is another color (i.e. a solid red circle, STOP trial), the subject must withhold a screen-touch for access to the reinforcer. The GO stimulus will remain on the touch screen until the subject touches the screen, whereas the STOP stimulus will be presented on the touch screen only for 1.5 sec. Subjects will only be reinforced for accurately responding (correct trial) on the GO and STOP trials (i.e. touching the green circle and withholding a response for a red circle). Incorrect responses will not be reinforced but, instead, initiate a 10-sec TO during which responding will have no scheduled consequences. Successive approximation will be used to train subjects to track the different types of stimulus presentation.

Under terminal contingencies, sessions will comprise four components including 200 randomly presented trials--135 GO trials and 65 stop trials. Both types of trials will commence with an abstract stimuli (i.e. blue rectangle) in the center of the touch screen. To initiate the trial, subjects will be required to touch and the stimulus continuously for a random duration (200-2000 msec). Once the hold stimulus requirement is met, a GO stimulus (e.g. a green circle) will be presented on the screen with a limited hold of 1.5-sec to touch the green circle in order to obtain reinforcement. During STOP trials, the GO stimulus will change color to the STOP stimulus (e.g. green circle to red circle) after a certain period of time (Stop Signal Delay, SSD). On the first session, SSD will start at zero and thereafter at the mean SSD from the previous session. Each correct response on a stop trial will increase the SSD by 20 ms on the next STOP trial; each incorrect response will decrease the SSD by 20 ms on the next STOP trial after an incorrect response. This staircase procedure allows calculation of a mean SSD from the session that corresponds to the average time at which an individual would fail half the Stop trials. A 50% error rate will be consistently obtained for all individuals after the performance is stabilized. A change in impulsivity, e.g., following radiation exposure, can be inferred by changes in SSD values and generally is calculated for individual subjects.

d. Stimulus Discrimination/Reversal (SD/R) Task. This task will be used to determine the extent to which deficits in inhibitory control observed in the SSR task are accompanied by broader cognitive deficits and temporal cortical dysfunction in monkeys.¹²² This touch screen task is relatively simple and we anticipate no difficulty in

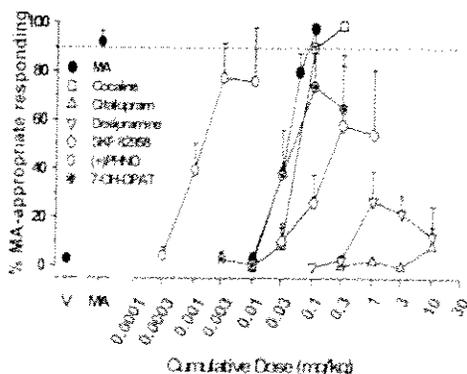


Figure 4. Effects of dopaminergic and non-dopaminergic drugs in squirrel monkeys ($n = 4$) trained to discriminate 0.056 mg/kg MA from saline under a FR 10 schedule of stimulus shock termination. These studies established differences in potency and effectiveness of DA compounds and identified a critical role that DA mechanisms play in mediating the subjective effects of MA.^{26, 27, 10, 11}

training subjects in its performance. We have extensive experience in training monkeys to acquire reliable discriminative stimulus control with different types of stimuli

including visual, food, and psychoactive drugs. For example, we have successfully used drug discrimination procedures to provide information on the mechanisms underlying subjective effects of psychomotor stimulant drugs in humans (Fig. 4).^{26,39,110-113} In this proposal, we will use the SD/R task to systematically study the acquisition of reversal performance as well as the effects of drugs that selectively target different CNS systems implicated in cognitive processes. Comparisons of the acquisition of reversal performance and of the effects of mechanistically-selective drugs before and after exposure will provide critical information on the long-term effects of ⁵⁶Fe and proton radiation on cognitive function.

Touch screen training has been described above in detail. During experimental sessions, each trial will begin with an abstract stimulus (i.e red square) in the middle of the screen. Touching this stimulus will lead to a random and simultaneous presentation of two images on the touch screen (either side of midline). Touching one image will be reinforced by milk delivery (correct); touching the second image (incorrect) will result in a blank screen and a 5-sec TO. A 10-sec timeout period during which responding has no scheduled consequences (TO) will follow each milk delivery. Daily training sessions will consist of one to four components with each component consisting of 30 trials. Testing will only be initiated after criteria for acquiring stimulus discrimination (i.e 27/30 consecutive correct responses for 4 successive training sessions) are met. Components of test sessions will be preceded by 10-min TOs during which vehicle or test drug will be injected. Drug testing will be conducted once or twice weekly using procedures described in section G.4., with training sessions on intervening days. Upon completion of SD/R studies, reward values will be reversed and, once performance is stable, the effects of drugs will be re-determined.

Findings from neurobehavioral pharmacological studies in nonhuman primates should provide clear indications of long-term consequences of ⁵⁶FE and proton radiation on CNS mechanisms that may be involved in motivational or cognitive processes. In providing important quantitative and qualitative data, these studies should lead to significant improvements in predicting the CNS risks associated with space radiation exposure during space travel.

7. **Absorbed Dose Assessment.** To investigate dose-effect relationships we will calculate the absorbed doses in relevant regions within the primate brain, other organs, tissues, and whole body using extensively validated 1-D and 3-D radiation dose assessment models and software described above (section E.2.d; see Appendix 2). For whole-body proton and ⁵⁶Fe irradiations, we will develop generic full-body 3-D computer models based on MRI scans of three monkeys (600g–900g). Specifically, we will convert the images for input into the computer codes MCNPX and RADCOG^{39,40} using Scan2MCNP⁴¹ and a proprietary file converter module, respectively. The model will be the basis for establishing a dose-response relationship, and will be customized for each monkey to reflect actual weight, height, fat content, organ and size. This will allow for accurate calculations of dose to specific organs for the particular subject. We will develop these generic primate models, for each of software packages (HIZETRN³⁷, NASA OLTARIS³⁸, MCNPX³⁹, and RADCOG^{39,40}). To enhance the computational model and reduce the likelihood of potential biases, omissions, and errors in calculating absorbed doses, we may obtain specific organ and tissue weight information from monkeys that may unexpectedly die over the course of the project or, upon recommendation of our

veterinarian, non-study monkeys that are scheduled for euthanasia. This approach will allow us to obtain subject-specific dose information to the whole body and to each organ of interest. Using the output from standard dosimetric instrumentation positioned at the location of the subject and personal thermoluminescent dosimeters (TLDs) placed on the bodies of primates we will calibrate the dose output of our computer models. The radiation sources, their housings, spectra, actual beam shape and intensity, collimators, shielding, and dosimeters will be accurately modeled based on the available information. The dosimeter readings will be used to calibrate the computational models.¹⁰⁸ The output of these models will contain computed readings of the modeled dosimeters and absorbed doses in organs, tissues, and whole bodies of the irradiated squirrel monkey subjects. This approach to the dosimetry will reduce, eliminate, or compensate for bias in our dose data.

8. **Data Analysis.** In observational studies, the effects of vehicle and each drug dose will be determined by calculating the average group frequency or duration of target behaviors during a 5-min observation period. For cumulative dosing procedures, data from the test component immediately following injection will be used to express the effects of the administered dose, and for single dosing procedures, data from all four test components will be averaged and used to express the effects of the administered dose. For PR responding, the measures for each monkey will be: a) the value of final ratio completed, the break point; b) the total number of lever presses for each component; and c) the mean response rate. In the SSR Task, impulsivity will be measured by the stop signal response time (SSRT) determined for each session (i.e. SSRT = mean Go reaction time - mean SSD). Performance monitoring will be the Post-Stop trial Slowing (PSS) determined as: mean of the individual values of: PSS = Go reaction time of the first Go trial following a Stop trial - Go reaction time of the last Go trial prior to that Stop trial. Data for the SD/R Task will be expressed as the number of stimulus discriminations divided by the total number of trials. All results will be presented as group means (\pm S.E.M.). Where possible, data will be analyzed using analysis of variance followed by *post hoc* tests for specific comparisons (significance will be set at $P < 0.05$). Dose-effect curves will be analyzed with standard parallel-line bioassay techniques.¹²⁴ ED₅₀ values and their 95% confidence limits will be determined and pairs of ED₅₀ values will be considered to be significantly different if their 95% confidence limits do not overlap.¹²⁵

H. Research Design and Plan of Experiments

This proposal is designed to obtain critical information on the long-term effects of space radiation on the CNS in squirrel monkeys. The intended studies will utilize neurobehavioral pharmacological procedures with which we have extensive (>30 years) experience.^{25-27, 9, 10, 113} Using a within-subjects design, data for all studies will be obtained before and after exposure to two different doses of ⁵⁶Fe particles and protons each (n=4/radiation type); a separate control group of squirrel monkeys (n=3) also will be tested but will not be exposed to any radiation particles. Initially, each monkey will be trained under the PR-FR choice procedure (see section G.2.b). When criterion levels of performance are stable, training under the PR-FR choice procedure will be suspended and, instead, using touch screen technology training under the SSR and SD/R Tasks will begin (see section G.6.c). Distinctive stimuli (color and shape) will be used in each of the operant tasks to facilitate the development of stimulus control during training.

Subsequently, training under the PR-FR choice procedure will be re-introduced, and the operant condition will vary daily in a random sequence. During this time, subjects also will be habituated to the chair and conditions used for studying overt behavior. Testing will begin when stimulus control and stable performance are evident for each of the operant tasks over a 3-4 week period. During pre-exposure testing, the operant condition will remain constant for each monkey in each of three rounds of testing; in the first round, the effects of drugs on overt behavior will be studied one week and the effects of drugs on PR-FR performance will be studied the following week, until all drug effects have been determined in both experiments. Subsequently the effects of drugs will be re-determined on the SSR Task, and thereafter, on the SD/R Task. In each operant condition, drug test sessions will follow two or more control sessions of stable performance. Drug effect will be studied as described above in section G.4. After initial testing of a drug, its effects will be re-determined in subjects for which data lie outside the 95% confidence interval of grouped values. Based on previous experience, we expect that the effects of each drug will be reproducible in individual subjects over time and repeated testing (i.e., limited, if any, sensitization or tolerance). Following completion of these studies, we will expose subjects to ^{56}Fe ion and proton radiation (see section G.3) After radiation exposure and return of subjects to the vivarium, behavioral experiments will resume and the effects of all drugs on each behavioral endpoint will be periodically re-determined. Data with each drug under all behavioral procedures will be obtained prior to exposure and at least twice during the remainder of the project period (i.e. Years 2-4) following exposure. The proposed hypotheses and related studies are designed to systematically evaluate the following specific aims, which will comprise our basic research framework:

- i. **Specific Aim 1. Long-term effects of ^{56}Fe particles and protons on overt behavior in squirrel monkeys**
 - a. **Hypotheses.** 1) Exposure to ^{56}Fe particles will alter targeted brain DA mechanisms involved in overt behavior in a dose-related manner, leading to changes in dose-effect relationships for DA-related drugs. 2) Exposure to protons will not alter targeted brain DA mechanisms involved in overt behavior: dose-effect relationships for DA-related drugs will be unchanged.
 - b. **Studies of Overt Behavior.** In these studies, we will use receptor-directed pharmacology to assess changes in the effects of DA-related drugs on overt behavior following exposure to ^{56}Fe and protons. The effects of DA indirect agonists and direct agonists (see Table 1, section G.5) will be studied by measuring the effects of: a) MA and cocaine on visual scanning/checking; b) SKF 82958 on eye blinking; and c) (+)PHNO and 7-OH-DPAT on self-directed scratching. Effects of all drugs will be systematically determined before and after exposure to ^{56}Fe particles and protons. Cumulative dosing procedures will be used to study a full range of doses of each drug in all subjects; dose ranges are given in Table 1 (see section G.5) and are based on our previous studies. The effects of sequential injections of vehicle also will be determined at least twice over the course of experiments in each monkey (see section G.6.a). Based upon previous studies employing cumulative dosing procedures, we estimate that approximately 6-8 weeks will be required to complete observational experiments during this phase of our studies.
 - c. **Expectations.** Based on our previous work, we anticipate that prior to ^{56}Fe and proton exposure, MA and cocaine will produce dose-related increases in visual scanning/

checking, and that DA D₁ agonist will increase eye-blinking behavior. Both D₂ and D₃ agonist will produce dose-related increases in self-directed scratching. We expect ⁵⁶Fe particles, but not protons, to modify these effects of DA agonists, revealing exposure-induced changes in CNS DA function.

2. **Specific Aim 2. Long-term effects of ⁵⁶Fe particles and protons on motivational processes in squirrel monkeys**

a. **Hypotheses.** 1) Exposure to ⁵⁶Fe particles will dose-relatedly modify brain systems involved in motivational processes involved in PR performance, revealed by systematic changes in receptor-directed pharmacology. 2) Exposure to protons will not produce changes in brain systems involved in motivation; dose-effect relationships for drugs that target DA, GLU, and CB1 systems will be unchanged following exposure.

b. **Studies of Progressive-Ratio Performance.** In these studies, we will evaluate the pre- and post-exposure effects of receptor-selective drugs on PR-FR choice performance to assess changes in motivation-related processes induced by exposure to ⁵⁶Fe particles and protons. In addition to DA-related drugs listed under Specific Aim 1, we also will study the effects of a CB1 agonist (AM 4054), a CB1 antagonist (SR 141716A), and GLU receptor antagonists (mGluR1: CPCCOEt; mGluR2: LY 379268; mGluR5: MPEP), listed in Table 1 (see section G.5). As in studies of overt behavior, we will examine the effects of a full range of doses of each drug in each subject, using drug treatment procedures described in sections G.4 and H.1.b. Doses of CB1 and GLU ligands are based on previous studies in our laboratory (CB1 ligands) or published literature (GLU ligands) (see section G.5). Based upon previous studies employing single and cumulative dosing procedures, we estimate that approximately 8-12 weeks will be required for this phase of the study. Because observation studies and PR-FR studies will be conducted in tandem, we conservatively estimate that approximately 12-16 weeks will be needed to complete both these sets of studies.

c. **Expectations.** Based on our previous and ongoing research, we anticipate that, prior to ⁵⁶Fe and proton exposure, MA and cocaine will dose-dependently decrease FR performance over a range of doses that do not decrease PR responding. On the other hand, other DA-related and CB1 ligands should dose-dependently decrease both PR and FR performance over the same range of doses. Although we have not studied the effects of GLU compounds under these behavioral conditions, we anticipate that the Glu ligands also will produce dose-related decreases in PR and FR performance with comparable potency. We expect ⁵⁶Fe particles, but not protons, to alter DAergic, cannabinoid, and GLU systems within the brain, as revealed by changes in baseline PR performance and/or changes in drug potency under the PR and FR schedules.

3. **Specific Aim 3. Long-term effects of ⁵⁶Fe particles and protons on cognitive processes in squirrel monkeys**

a. **Hypotheses.** 1) Exposure to ⁵⁶Fe particles will dose-dependently modify brain systems involved in cognitive processes involved in SSR and SD/R tasks, revealed by systematic changes in receptor-directed pharmacology. 2) Exposure to protons will not produce changes in brain systems involved in cognitive processes; dose-response relationships for drugs that target DA, CB1, and cholinergic systems will be generally unchanged following exposure.

b. SSR and SD/R Tasks. As in studies described above under Specific Aims 1 and 2, we will evaluate the pre- and post-exposure effects of receptor-selective drugs using performance in SSR and SD/R tasks to evaluate changes in cognitive processes (including learning in the stimulus discrimination/reversal procedure) induced by exposure to ^{56}Fe particles and protons. In addition to studying changes in DA and CBI systems with DA-related and CBI ligands listed under Specific Aims 1 and 2 (see Table 1 in section G.5), we also will assess changes in cholinergic systems that are implicated in cognitive processes by studying the effects of a cholinesterase inhibitor (donezipil) and cholinergic receptor ligands including a muscarinic antagonist (scopolamine) and a nicotinic agonist (nicotine) (see Table 1 in section G.5). Doses of these drugs will be based on data from [REDACTED] ongoing studies of nicotine pharmacology in our laboratory. As in studies of overt behavior and PR performance, we will examine the effects of a full range of doses of each drug in each subject, using drug treatment procedures described in sections G.4 and H.1.b. Based on previous studies^{121,122}, we estimate that approximately 32-36 weeks will be required for this phase of our studies.

c. Expectations. Based on previous research, we expect DA agonists to selectively increase impulse control and decreased performance monitoring but, in the absence of published literature, it is difficult to predict whether CBI or cholinergic ligands will have similar effects. However, we do anticipate that ^{56}Fe particles, but not protons, will have a long-lasting impact on CNS DA, cannabinoid, and cholinergic systems and that this will modify the effects of receptor-selective ligands on measures of impulsivity in the SSR task and learning in the SD/R task.

4. Potential Limitations of Behavioral Studies. One potential limitation may be the complex neurobehavioral and pharmacological design of our proposed studies. However, this type of longitudinal approach in which a number of drugs are studied under different behavioral conditions is common in single-subject research with nonhuman primates. In view of our considerable hands-on experience in successfully conducting this type of behavioral pharmacology in monkeys^{27,42-45,110-113,116}, we do not anticipate great difficulties in performing the proposed work and obtaining meaningful data on the long-term effects of exposure to ^{56}Fe and proton radiation. In the event that studies do become stalled for technical reasons we are prepared to reduce the number of tasks in the research plan (e.g. by studying only SSD under Specific Aim 3). The lack of information regarding the neurobiological effects of exposure to ^{56}Fe particles and proton radiation in squirrel monkeys is another potential limitation in the proposed studies. With this in mind, we have planned our studies to obtain that information. Regardless of outcomes, our proposed ground-based studies of space radiobiology in nonhuman primates will provide important information on whether exposure to two different doses of ^{56}Fe particles and protons induce neurobehavioral changes in primates that are mediated by their impact on neurochemical CNS systems.

5. Outcome and Future Directions for Behavioral Studies. Our proposed observational and operant studies are designed to determine whether exposure to ^{56}Fe ions and protons will have a long-term impact on DA, CBI, GLU, or cholinergic systems in the CNS that are involved in motivation and cognition. Such long-lasting effects should be revealed by changes in the effects of receptor-selective drugs following exposure to radiation. These ground-based studies in space radiobiology will provide

unique information regarding the long-term effects of ^{56}Fe ions and protons on CNS-mediated neurobehavioral processes and, therefore, will be extremely relevant for assessing health risks that may be associated with NASA's future deep-space missions. Depending on the outcome of our planned research, future studies will further explore the effects of ground-based models of space radiation as discussed above in section E.

6. **Specific Aim 4. Develop a computational model for squirrel monkey space radiation dosimetry.**

a. **Hypothesis.** The multiple-code approach to the dosimetry of proton and ^{56}Fe ion radiations in combination with data from the standard dosimetric instrumentation and personal dosimetry will reduce, eliminate, or compensate for bias in the absorbed dose results. This will permit meaningful cause-effect relationships between space radiation dose and behavioral and pharmacological data in squirrel monkeys.

b. **Computational Models for Monkey Radiation Dosimetry.** Three generic primate models will be developed for whole-body proton irradiations, one for each of the three software packages (1-D HZETRN²⁹ and NASA OLTARIS³⁰ and 3-D MCNPX²⁸). Each model will be developed in three stages. First, we will obtain MRI scans and organ weight information which will be used to develop a generic model based on average organ, tissue, and body sizes. Next, each model will be compared to the other two models to ensure consistency across models and/or to determine reasons for discrepancies. Finally, for each subject, the results of all three generic models will be tested and compared using subject-specific organ and tissue weights and body sizes. The generic models will then be used to calculate doses to each subject involved in the proton irradiations. To develop the computer model for a generic squirrel monkey, full-body, high-resolution MRI scans will be obtained for three primates with different body weights ranging from approximately 600g to 900g (e.g. 650g, 750g, 850g). The resulting MRI scan, in digital format, will contain information on individual characteristics and relative positions of the subject's organs. For development of proton models this digital information will be converted into voxel models suitable for input to the computer code MCNPX²⁸ using the Scan2MCNP³³ software package. For the ^{56}Fe irradiations, information from the MRI scans also will be converted for input into the 3-D computer code RADCOG³¹⁻³² using a proprietary file converter module. The computational models in 1-D HZETRN²⁹ and/or NASA OLTARIS³⁰ will be developed based on the same MRI digital information. Some representative subjects will be sacrificed to obtain specific organ and tissue weight information. The obtained information will enhance the computational modeling by allowing the model to account for differences in individuals. The multiple-code approach to the dosimetry of proton radiation in this proposal is considered necessary to reduce, eliminate, or compensate for bias in the dose results. Previous data^{104,105} illustrate the discrepancies in dose calculations for identical computational models among well-established software packages and among different research groups. The nature of these discrepancies can be very complex, and may be inherent in the underlying software models. Moreover, a potential bias may be introduced into the computational output if only one software package is used by a single modeler. Further, the modeler's inadvertent omissions or errors can also be introduced into the model. To reduce the likelihood of such potential biases, omissions, and errors in our proposed studies we will use three independent models to calculate absorbed space

radiation doses. The use of independent software models will provide confidence in the obtained dose calculation results.

c. **Expectations.** Combination of experimental dosimetry, dose assessments obtained by the extensively validated 1-D and 3-D software codes with 3-D MRI imaging implemented in the newly developed 3-D software geometry framework should provide a robust and flexible set of tools for animal (i.e. squirrel monkey) in experimental irradiation dose assessments.

d. **Potential Limitations and Alternatives.** A potential limitation of the proposed dose modeling approach is that the accuracy of the dose calculation depends on the degree of discretization of the geometric elements comprising the dose receptor model bodies. A higher degree of discretization provides better dose estimates but requires more computational and modelling resources. Due to their stochastic nature, MCNPX and RADCOG codes also require more computational time for relatively smaller organs to ensure accuracy. In virtual radiation transport simulations, the intersection of particles and organs of interest and consequently, contribution to absorbed dose decreases with organ size; yet, more computational resources are required to track particles that would never intersect organs of interest. In order to minimize the impact of this potential limitation, we have planned to first develop simplified models of each subject, and, subsequently, refine these models using more detailed MRI-based information. If necessary, instead of using the detailed MRI-based receptor body models, we may alternatively use (1) simplified generic computational non-MRI-based models with fewer details, or (2) rely on standard dosimetry instrumentation located on-site and/or on the personal TLD and plastic dosimeters placed on the animal bodies during irradiations.

e. **Outcome and Future Directions.** These studies are designed to estimate absorbed organ and whole body doses with a high degree of precision. The detailed MRI-based computational models will be developed and methodologies for their development will be refined. Results of our studies will provide information on the distribution of the absorbed doses among different organs for these types of beams. This information will benefit future animal irradiation experiments by providing a sufficiently detailed framework that is extensively tested with the aid of three different state-of-the-art radiation transport codes. Future work could also encompass automatization of the MRI file conversion to the desirable level of details and expansion of the approach to wider range of particles, energies, beam geometries, subjects, and media.

i. **Time Schedule**

Year 1: All pre-irradiation behavioral and pharmacological studies outlined in **Specific Aims 1-3** will begin in Year 1. Preliminary computational models for dose assessment will be developed in Year 1 before monkeys are exposed to the different types of space radiations. We anticipate all pre-irradiation studies to be completed by the end of Year 1.

Years 2 - 4: Upon completion of all pre-irradiation studies, all monkeys will be exposed to their respective space radiation types at the beginning of Year 2. After irradiation, post-exposure studies (**Specific Aims 1-3**) will be conducted and repeated as indicated in Years 2, 3, 4 and, if necessary, Year 5. This will allow us to monitor radiation associated long-term changes in CNS function over a 3-4 year period post-radiation. More sophisticated 3-D computational models for dose assessment will also be developed in parallel with the neurobehavioral and neuropharmacological studies and validated by experimental dosimetry.

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BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
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1995- Consultant, Medications Development Division, NIH/NIDA
 1997-1999 President, Behavioral Pharmacology Society
 1998-2001 Merit Review Subcommittee for Alcoholism and Drug Dependence (Clinl Pharmacol) Dept of Veteran Affairs
 1999 Organizer, Boston '99 (International Conference of the Behavioral Pharmacology Society and the European Behavioural Pharmacology Society)
 1999- Executive Committee, European Behavioural Pharmacology Society
 2000-2002 Chairman, Division of Behavioral Pharmacology, ASPET
 2001-2002 Organizer, New Advances in the Understanding and Treatment of Addictions. European Behavioural Pharmacology Society/British Association for Psychopharmacology, Brighton, UK
 2001 Chair, P.B. Dews Award Committee, ASPET
 2002- North American Editor, Behavioural Pharmacology
 2004-2005 Reviewer, NIH Integrative, IFCN1, Center for Scientific Review
 2004- Representative, FASEB Research Conferences Advisory Committee, ASPET
 2004- Editorial Board, Biochemical Pharmacology
 2005- Program Committee, Chair, ASPET
 2005- Member, Neurobiology of Motivated Behavior Study Section, NIH Center for Scientific Review
 2006- Nominating Committee, Member, ASPET
 2006- Editorial Board Member, Journal of the Experimental Analysis of Behavior
 2009- Editorial Board Member, Pharmacological Reviews

SELECTED RECENT PUBLICATIONS

Bergman, J., Rosenzweig-Lipson, S., Spealman, R.D.: Differential effects of dopamine D₁ and D₂ receptor agonists on schedule-controlled behavior of squirrel monkeys. *J. Pharmacol. Exp. Ther* 273:40-48, 1995. PMID: 7714795
 Liguori, A., Morse, W.H., Bergman, J.: Ventilatory depressant and behavioral effects of μ and mixed-action opioids. *J. Pharmacol. Exp. Ther* 277:462-472, 1996. PMID: 8613955
 Bergman, J., Spealman, R.D., Madras, B.K., Rosenzweig-Lipson, S.: Agonist efficacy and the behavioral effects of D₁ receptor ligands: drug interaction studies in squirrel monkeys. *J. Pharmacol. Exp. Ther* 276:942-950, 1996. PMID: 8786574
 Grech, D.M., Spealman, R.D., Bergman, J.: Self-administration of dopamine D₁ receptor agonists by squirrel monkeys. *Psychopharmacology* 125: 97-104, 1996. PMID: 8783382
 Carey, G J., Bergman, J.: Discriminative-stimulus effects of clozapine in squirrel monkeys: comparison with

conventional and novel antipsychotic drugs. *Psychopharmacology* 132: 261-269, 1997.

- Bergman, J., Katz, J.L.: Behavioral pharmacology of cocaine and the determinants of abuse liability. In: Higgins, S., Katz, J.L. (eds.), *Cocaine Abuse: Behavior, Pharmacology, and Clinical Applications*, New York:Academic Press. pp. 51-79, 1998.
- Tidey, J.W., Bergman, J.: Drug discrimination in methamphetamine-trained monkeys: agonist and agonist effects of dopaminergic drugs. *J.Pharmacol. Exp. Ther.* 285:1163-1174, 1998. PMID: 9618419
- Paronis, C.A., Bergman, J.: Apparent pA₂ values of benzodiazepine antagonists and partial agonists in monkeys. *J. Pharmacol. Exp. Ther.* 1999;290(3): 1222-1229. PMID: 10454498
- Caine, S.B., Negus, S.S., Mello, N.K., Bergman, J.: Effects of dopamine D₁-like and D₂-like agonists in rats trained to discriminate cocaine from saline. *Exp. Clin. Psychopharmacol.* 8:404-414, 2000.
- Bergman, J., France, C.P., Holtzman, S.G., Katz, J.L., Koek, W., Stephens, D.N.: Agonist efficacy, drug dependence, and medication development: preclinical evaluation of opioid, dopaminergic, and GABA_A-ergic ligands. *Psychopharmacol* 153:67-84, 2000. PMID: 11255930
- Carey, G.J., Bergman, J.: Enadoline-discrimination in squirrel monkeys: Effects of opioid agonists and antagonists. *J. Pharmacol. Exp. Ther.* 297:215-223, 2001. PMID: 11259547
- Bergman, J., Yasar, S., Winger, G.: Psychomotor stimulant effects of β-phenylethylamine in monkeys treated with MAO-B inhibitors. *Psychopharmacology*, 159(1):21-30, 2001. PMID: 11797065
- Paronis, C.A., Cox, E.D., Cook, J.M., Bergman, J.: Different types of GABA_A receptors may mediate the anticonflict and response rate-decreasing effects of zaleplon, zolpidem, and midazolam in squirrel monkeys. *Psychopharmacol* 156:461-468,2001. PMID: 11498724
- Mutschler, N.H., Bergman, J.: Effects of chronic administration of the D1 partial agonist SKF 77434 on cocaine self-administration in rhesus monkeys. *Psychopharmacol*, 160:362-370, 2002. PMID: 11919663
- Dews, P.B., O'Brien, C.P., Bergman, J.: Behavioral effects of caffeine: dependence and related issues. *Food Chemical Toxicology* 40(9):1257-1261, 2002.
- Neumeyer JL, Kula NS, Bergman J, Baldessarini RJ: Receptor affinities of dopamine D₁ receptor-selective novel phenylbenzazepines. *European Journal of Pharmacology*, 474:137-140, 2003. PMID: 12921854
- Czoty P, Makriyannis A, Bergman J. Methamphetamine-discrimination and in vivo microdialysis in monkeys. *Psychopharmacology*, 2004;175:170-178. PMID: 15064912
- Czoty P, Ramanathan CR, Mutschler NH, Makriyannis A, Bergman J: Drug discrimination in methamphetamine-trained monkeys: effects of monoamine transporter inhibitors. *J. Pharmacol Exp Ther* 311(2):720-727, 2004. PMID: 15240827
- Gasior M, Paronis C, Bergman J: Modification by dopaminergic drugs of choice behavior under concurrent schedules of i.v. saline and food delivery in monkeys. *J. Pharmacol. Exp. Ther.* 308:249-259, 2004. PMID: 14563783
- Gasior M, Bergman J, Kallman MJ, Paronis: Evaluation of the reinforcing effects of monoamine reuptake inhibitors under a concurrent schedule of food and i.v. drug delivery in rhesus monkeys. *Neuropsychopharmacology*, 30:758-764, 2005. PMID: 15526000
- Jutkiewicz E, Bergman, J. Effects of dopamine D1 ligands on eyeblinking in monkeys: efficacy, antagonism, and D1/D2 interactions. *J Pharmacol Exp Ther* 2005;311(3):1008- 1015. PMID: 15292458
- Yasar S, Gaal J, Justinova Z, Bergman J. Discriminative-stimulus and reinforcing effects of p-fluoro-deprenyl in monkeys. *Psychopharmacology*, 2005; 182:95-103. PMID: 15990999
- Paronis CA and Bergman J: Measuring the reinforcing strength of abused drugs. *Molecular Interventions*, 6(5):271-281, 2006. PMID: 17035668
- Desai RI, Neumeyer JL, Paronis CA, Nguyen P, Bergman J: Behavioral effects of the R-(+)- and S-(-) enantiomers of the D1-like partial receptor agonist SKF 83959 in monkeys. *European Journal of Pharmacology*, 558:98-106, 2007. PMID: 17207791
- Desai RI, Neumeyer JL, Paronis CA, Bergman J: Pharmacological characterization of the effects of dopamine D₁ agonists on eye blinking in rats. *Behavioural Pharmacology*, 2007; 18:745-754. PMID: 17989512
- Bergman J: Medications for stimulant abuse: agonist-based strategies and preclinical evaluation of the mixed-action D² partial agonist aripiprazole (Abilify®). *Exp Clin Psychopharmacol*, 2008; 16(6):475-483.
- Bergman J, Delatte MS, Paronis CA, Vemuri K, Thakur GA, and Makriyannis A: Some effects of CB1 antagonists with inverse agonist and neutral biochemical properties. *Physiology & Behavior*, 2008; 93:666-700.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME [REDACTED]		POSITION TITLE Instructor of Psychobiology/Psychiatry	
eRA COMMONS USER NAME (credential, e.g., agency login) [REDACTED]			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of Nottingham, Nottingham, UK	B.S.C.	1995	Neuroscience
University of Birmingham, Birmingham, UK	Ph.D.	2001	Psychology/Neuroscience
National Institute on Drug Abuse/NIH	Research Fellow	2002-2005	Pharmacology

Please refer to the application instructions in order to complete sections A, B, and C of the Biographical Sketch.

A. Positions and Honors.

Positions and Employment

1996–2000 Graduate Teaching Assistant, School of Psychology, University of Birmingham, UK
1998–2000 Clinical Scientist, Queen Elizabeth Psychiatric Hospital, Birmingham, UK
2006– Instructor of Psychobiology, Dept. of Psychiatry, Harvard Medical School, USA

Other Experience and Professional Memberships

1999–2003 European Behavioural Pharmacology Society (EBPS)
2003–2005 Society for Neuroscience (SfN)
2003– Behavioral Pharmacology Society (BPS)
2003–2005 American Society for Pharmacology and Experimental Therapeutics (ASPET)

Honors

1998 British Psychological Society Post-graduate Study Abroad Visit Scheme 1998
2001 EBPS Travel Award
2003 Behavioral Pharmacology Division of ASPET Post-Doctoral Paper Award
2003 EBPS Travel Award
2004 Behavioral Pharmacology Division of ASPET Post-Doctoral Paper Award

B. Selected peer-reviewed publications (in chronological order).

- [REDACTED] Barber DJ, Terry P. Asymmetric generalization between the discriminative stimulus effects of nicotine and cocaine. *Behav Pharmacol.* 1999; 10(6–7):647–56. PMID: 10780506
- [REDACTED] Terry P. Evidence of cross-tolerance between behavioural effects of nicotine and cocaine in mice. *Psychopharmacology* 2003; 166(2):111–119. PMID: 12545328
- [REDACTED] Barber DJ, Terry P. Dopaminergic and cholinergic involvement in the discriminative stimulus effects of nicotine and cocaine in rats. *Psychopharmacology.* 2003; 167(4):335–343. PMID: 12684733

4. [REDACTED] Terry P, Katz JL. Comparison of the discriminative-stimulus effects of SKF 38393 with those of other dopamine receptor agonists. *Behav Pharmacol*. 2003; 14(3):223–228. PMID: 12799524
5. [REDACTED] Terry P, Katz JL. A comparison of the locomotor stimulant effects of D1-like receptor agonists in mice. *Pharmacol Biochem Behav*. 2005; 81(4):843–848. PMID: 16000217
6. [REDACTED] Kopajtic TA, Koffarnus M, Newman AH, Katz JL. Identification of a dopamine transporter ligand that blocks the stimulant effects of cocaine. *J Neurosci*. 2005; 25(8):1889–1893. PMID: 15728828
7. [REDACTED] Kopajtic TA, French D, Newman AH, Katz JL. Relationship between in vivo occupancy at the dopamine transporter and behavioral effects of cocaine, GBR 12909 [1-{2-[bis-(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine], and benztropine analogs. *J Pharmacol Exp Ther*. 2005; 315(1):397–404. PMID: 16014753
8. Zou M-F, Cao J, Kopajtic TA, [REDACTED] Katz JL, Newman AH. Structure–Activity Relationship Studies on a Novel Series of (S)-2-Substituted 3-[Bis(4-fluoro- or 4-chlorophenyl)methoxy]tropane Analogues for in vivo investigation. *J Med Chem*. 2006; 49(21):6391–6399. PMID: 17034144
9. [REDACTED] Neumeyer JL, Bergman J, Paronis CA. Pharmacological characterization of the effects of dopamine D1-like agonists on eye blinking in rats. *Behav Pharmacol*. 2007; 18(8):745–754. PMID: 17989512
10. [REDACTED] Neumeyer JL, Paronis CA, Nguyen P, Bergman J. Behavioral Effects of the R-(+) and S-(-) enantiomers of the D1-like partial agonist SKF 83959 in squirrel monkeys. *Eur J Pharmacol*. 2007; 558(1–3):98–106. PMID: 17207791
11. Loland CJ, [REDACTED] Zou M-F, Cao J, Grundt P, Gerstbrein K, Sifted HH, Newman AH, Katz JL, Gethera U. Relationship between conformational changes in the dopamine transporter and cocaine-like subjective effects of uptake inhibitors. *Mol Pharmacol*. 2008; 73(3):813–823. PMID: 17978168
12. Terry P, Doumas M, [REDACTED] Wing A. Dissociations between motor timing, motor coordination and time perception after the administration of alcohol or caffeine. 2008; Accepted for Publication in *Psychopharmacology*.

Co-Investigator: [REDACTED]
Institution: Southwest Research Institute, San Antonio, TX

Education:

BSc, University College London, UK, 1991.
PhD, University of Birmingham, UK, 1996.

Professional Background:

Staff Scientist, Southwest Research Institute, San Antonio, June 2009 – present
Also Lead Adjoint Associate Professor, Physics & Astronomy, University of Texas at San Antonio, April 2007 – Present
Principal Scientist, Southwest Research Institute, San Antonio, June 2005 – present
Also Adjoint Associate Professor, Physics & Astronomy, University of Texas at San Antonio, Jan 2006 – April 2007
Associate Research Scientist, University of Maryland, July 2004 – June 2005
Assistant Research Scientist, University of Maryland, July 2001 – June 2004
Research Associate, University of Maryland, Feb. 1998 – June 2001
Research Fellow, ESTEC, European Space Agency, Jan. 1996 – Dec. 1998
Research Assistant, University of Birmingham, Sept. 1991 – Dec. 1996
Student Trainee, Lucas Electrical Systems, UK, Sept. 1986 – Aug. 1987

Relevant Experience:

Extensive experience in analyzing and interpreting energetic particle, solar wind plasma, and magnetic field data from the Ulysses, ACE, and Wind spacecraft. Experience in understanding novel composition measurements obtained by instruments on board NASA's ACE and Wind spacecraft during solar energetic particle events and interplanetary shock events associated with coronal mass ejections. Authored or co-authored over 50 publications in refereed scientific journals. Co-Investigator on NASA's Living with A Star Strategic Capability project entitled "Earth Moon Mars Radiation Environment Module." Served on numerous NASA and NSF review panels. Working group leader for Working Group 3 - Solar Energetic Particles at the Solar, Heliospheric, and Interplanetary Environment (SHINE) Workshops. Team Leader for NASA's LWS TR&T 2005 focused science topic (T3d) on Solar Energetic Particles. Steering Committee member of NASA's LWS TR&T ROSES 2006 and NSF's SHINE.

Selected Recent Relevant Publications (from over 50):

1. [REDACTED] G. M. Mason, J. R. Dwyer, J. E. Mazur, C. W. Smith, and R. M. Skoug, "Acceleration of ^3He Ions at Interplanetary Shocks," *Astrophysical Journal (Letters)*, 553, L89-L91, 2001.
2. [REDACTED] G. M. Mason, J. R. Dwyer, J. E. Mazur, R. E. Gold, S. M. Krimigis, C. W. Smith, and R. M. Skoug, "Evidence for a suprathermal seed population of heavy ions accelerated by interplanetary shocks near 1 AU," *Astrophysical Journal*, 588, 1149-1162, 2003.
3. [REDACTED] G. M. Mason, M. E. Wiedenbeck, C. M. S. Cohen, J. E. Mazur, J. R. Dwyer, R. E. Gold, S. M. Krimigis, Q. Hu, C. W. Smith, and R. M. Skoug, "Spectral properties of heavy ions associated with the passage of interplanetary shocks at 1 AU," *Astrophysical Journal*, vol. 611, pp 1156-1174, 2004.
4. [REDACTED] G. M. Mason, J. E. Mazur, and J. R. Dwyer, "Solar Cycle Variations in the Composition of the Suprathermal Heavy Ion Population Near 1 AU," *Astrophysical Journal (Letters)*, vol. 645, L81-L84, 2006.

5. [REDACTED] G. M. Mason, R. E. Gold, S. M. Krimigis, C. M. S. Cohen, R. A. Mewaldt, J. E. Mazur, and J. R. Dwyer, "Heavy Ion Abundances in Large Solar Energetic Particle Events and Their Implications for the Seed Population." *Astrophysical Journal*, vol. 649, 470-489, 2006 ²

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME [REDACTED]		POSITION TITLE Associate Scientist	
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
St. John's University, Jamaica, NY	B.S.	1990	Biology
Albert Einstein College of Medicine, Bronx, NY	M.S.	1996	Microbiology and Immunology
Albert Einstein College of Medicine, Bronx, NY	Ph.D.	1999	Developmental and Molecular Biology
Brookhaven National Laboratory, Upton, NY	Post Doc	2003	Radiobiology

- 1990-1994 Research Associate, Laboratory Manager, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
- 1994-1999 Ph.D. candidate, Departments of Microbiology/Immunology and Developmental/Molecular Biology, Albert Einstein College of Medicine, Bronx, NY
- 2000-2003 Postdoctoral Research Associate, Brookhaven National Laboratory, Upton, NY
- 2003-2005 Assistant Scientist, NASA/NSRL Beam Line Scientist, Medical Department, Brookhaven National Laboratory, Upton, New York
- 2005- Associate Scientist, Medical Department Liaison Scientist for NASA/NSRL, Brookhaven National Laboratory, Upton, New York

Honors

- 1990 Golden Key National Honor Society
- 1994 Received Honors, Biochemistry, Albert Einstein College of Medicine
- 1995 Received Honors, Molecular Genetics, Albert Einstein College of Medicine
- 1996 Received Honors, Immunology, Albert Einstein College of Medicine
- 1996 M.S. degree awarded with Honors, Albert Einstein College of Medicine

Publications

- Tonks, N., Yang, Q., and [REDACTED] (1991). Structure, regulation and function of protein tyrosine phosphatases. *Cold Spring Harbor Symposia on Quantitative Biology* 56: 265-273.

Dyson, N., [REDACTED] McCall, C., and Harlow, E. (1992) Adenovirus E1A makes two distinct contacts with the retinoblastoma protein. *J Virol.* 66(7): 4606-4611.

Dyson, N., [REDACTED] Munger, K., and Harlow, E. (1992) Homologous sequences in adenovirus E1A and human papillomavirus E7 proteins mediate interaction with the same set of cellular proteins. *J Virol.* 66(12): 6893-6902.

Schreiber-Agus, N., Chin, L., Chen, K., Torres, R., Rao, G., [REDACTED] Skoultchi, A.I., and DePinho, R.A. (1995) An amino-terminal domain of Mxi1 mediates anti-Myc oncogenic activity and interacts with a homolog of the yeast transcriptional repressor SIN3. *Cell* 80(5): 777-786.

Rao, G., Alland, L., [REDACTED] Schreiber-Agus, N., Chen, K., Chin, L., Rochelle, J.M., Seldin, M.F., Skoultchi, A.I., and DePinho, R.A. (1996) Mouse Sin3A interacts with and can functionally substitute for the amino-terminal repression of the Myc antagonist Mxi1. *Oncogene* 12(5): 1165-1172.

[REDACTED] and Zhu, L. (1999) DP1 phosphorylation in multimeric complexes: weaker interaction with cyclin A through the E2F1 cyclin A binding domain leads to more efficient phosphorylation than stronger interaction through the p107 cyclin A binding domain. *Biochem. Biophys. Res. Commun.* 258(3): 596-604.

Jiang, H., Karnezis, A.N., Tao, M., [REDACTED] and Zhu, L. (2000) pRB and p107 have distinct effects when expressed in pRB-deficient tumor cells at physiologically relevant levels. *Oncogene* 19(34): 3878-3887.

Sutherland, B.M., Bennett, P.V., Cintron, N.S., [REDACTED] and Laval, J. (2003) Low levels of endogenous oxidative damage cluster levels in unirradiated viral and human DNAs. *Free Radical Biology and Medicine* 35(5): 495-503.

[REDACTED] Vazquez, M.E., and Otto, S. (2005) Cytotoxic Effects of low- and high-LET radiation on human neuronal progenitor cells: induction of apoptosis and TP53 gene expression. *Radiation Research* 164(4): 545-551.

[REDACTED] Vazquez, M.E. (2007) Cytotoxic and cell cycle effects in human neuronal progenitor cells exposed to 1 GeV/n Fe ions. *Advances in Space Research* 39(6): 1004-1010.

Roy, D., [REDACTED] Zhou, G., Echiburu-Chau, C. and Calaf, G.M. (2008) Gene expression profiling of breast cells induced by X-rays and heavy ions. *International Journal of Molecular Medicine* 21(5): 627-636.

Recent Invited Talks

[REDACTED] "Biological and Molecular Effects of Radiation on Human Stem and Neuronal Cells". Brookhaven National Laboratory Medical Department's Post-Doc Forum, March 2003.

[REDACTED] Vazquez, M. and Green, L. "Cytotoxic Effects of HZE Radiation on Human Neural Stem and Neuronal Cells". 3rd International Workshop on Space Radiation Research and 15th Annual NASA Space Radiation Health Investigator's Workshop, May 16-20, 2004, Port Jefferson, NY. Sponsored by NASA, DOE, BNL/BSA and USRA.

Vazquez, M., [REDACTED] Green, L., Chang, P. and Otto, S. "Cellular and Molecular Effects of High-LET Radiation on Human Neural Precursor Cells and Neurons". 35th COSPAR Scientific Assembly, July 18-25, 2004, Paris, France.

Vazquez, M., [REDACTED] and Kim, A. "Cellular and Molecular Effects of Ionizing Radiation on Human Neurons and Progenitor Cells: Cytotoxicity, Cell Cycle Response, Role of p53 and Countermeasures". 4th International Workshop on Space Radiation Research, 17th Annual NASA Space Radiation Health Investigator's Workshop, June 5-9, 2006, Moscow-St. Petersburg. Sponsored by NASA, DOE, BNL/BSA and USRA.

Vazquez, M., Kim, A. and [REDACTED] "Cellular and Molecular Effects of 1GeV/n Iron Ion Exposure on Post-mitotic Human Neurons". 37th COSPAR Scientific Assembly, July 13-20, 2008, Montreal, Canada.

Recent Posters

Sutherland, B.M., Bennett, P.V., Cintron, N., Georgakilas, A., [REDACTED] Hada, M., Paul, S., Schenk, H. and Laval, J. Clustered DNA Damages. DOE-NASA Workshop, Washington, D.C., June 26-29, 2001.

Stanislaus, M.A., Bennett, [REDACTED] Sutherland, B. and Gewirtz, A.M. Effect of Low Dose Gamma Radiation on Hematopoietic Stem and Progenitor Cells. NASA-National Space Biomedical Research Retreat, Houston, Texas, January, 2002.

Stanislaus, M.A., Bennett, P., [REDACTED] net, G.H., Luongo, J.L., Sutherland, B. and Gewirtz, A.M. Effect of Deep Space Radiation on Human Hematopoietic Stem Cell Function. International Society of Experimental Hematology, 31st Annual Meeting, Montreal, Canada, July 5-9, 2002.

Vazquez, M., Otto, S., [REDACTED] ena, L. and Anderson, C. Effects of Low- and High-LET Radiation on Neural Cells in Culture: Apoptosis Induction, Cell Toxicity and Gene Expression. Bioastronautics Investigator's Workshop, Galveston, Texas, January, 2003.

Vazquez, M., [REDACTED]tto, S., Pena, L. and Anderson, C. Cytotoxicity of Low- and High-LET Radiation on Neural Cells. 14th Annual Space Radiation Health Investigator's Workshop, League City, Texas, April, 2003.

Vazquez, M.E., [REDACTED]ellular and Molecular Effects of Space Radiation on Human Neural Cells and Protection. Bioastronautics Investigator's Workshop, Galverston, Texas, January 11, 2005. Sponsored by USRA.

[REDACTED] Vazquez, M., Kahanda, R., Kim, A. and Anderson, C. Effects of HZE Radiation on Human Neuronal Progenitor Cells: Role of p53, Cell Cycle Responses and Countermeasures. 16th Annual NASA Space Radiation Health Investigator's Workshop, May 15-18, 2005, Port Jefferson, NY. Sponsored by NASA, DOE, BNL/BSA and USRA.

Vazquez, M.E. and [REDACTED] Risk Assessment and Chemoprevention of HZE Induced CNS Damage. National Space Biomedical Research Institute Investigator Retreat, February 27-March 1, 2006, League City, Texas. Sponsored by NSBRI.

Vazquez, M., [REDACTED] and Kim, A. Neurotoxicity of Human Neural Cells Induced by Space Radiation: In Vitro Risk Assessment and Countermeasure. Committee on Space Research, 36th COSPAR Scientific Assembly, July 16-23, 2006, Beijing, China.

Kim, A., Vazquez, M.E. and [REDACTED] HZE Radiation Induced DNA Damage and Its Repair Have Different Kinetics in Human Neuronal Progenitor Cells versus in Post-mitotic Neurons. 18th Annual NASA Space Radiation Investigator's Workshop. July 13-15, 2007, Rohnert Park, CA. Sponsored by NASA.

Hienz, R.D., Weed, M.R., [REDACTED] Vazquez, M.E., Gooden, V.L and Brady, J.V. Impaired Neurobehavioral Function Following Radiation Exposure. NASA Human Research Program Investigator's Workshop, Feb. 4-6, 2008, League City, TX.

Blakely, E., Nelson, G., [REDACTED]usek, A., Sutherland, B., Forrette, E. and Rogers, K. 5th NASA Space Radiation Summer School-June 2008. NASA Human Research Program Investigator's Workshop, Feb. 4-6, 2008, League City, TX.

Ponomarev, A., Sundaresan, A., Kim, A., Vazquez, M.E., [REDACTED] Kim, M.-H. and Cucinotta, F.A. A 3D Monte Carlo Model of Radiation Affecting Cells, and Its Application to Neuronal Cells and GCR Irradiation. 37th COSPAR Scientific Assembly, July 13-20, 2008, Montreal, Canada.

Hienz, R.D., Weed, M.R., Roma, P.G., [REDACTED] Gooden, V.L. and Brady, J.V. Detecting the Effects of Neurobehavioral Function to Space Radiation. NASA Human Research Program Investigator's Workshop, Feb. 2-4, 2009, League City, TX.

Consultant [REDACTED]

Institution: University of Texas at San Antonio & Southwest Research Institute, San Antonio, TX

Education:

M.S. Leningrad Polytechnic Institute, Russia, 1987.

PhD, Oregon State University, USA, 2001.

Professional Background:

Independent Consultant, May 2009 – present

Senior Research Engineer, Southwest Research Institute, San Antonio, 2005 – May 2009

Research Engineer, Southwest Research Institute, San Antonio, Jan 2001 – 2005

Research Assistant, Teaching Assistant, Oregon State University, Corvallis, Oregon, June 1996 – Jan. 2001

Radiological Engineer, Kaskad Ltd, St-Petersburg, Russia, Aug. 1991 – Sep. 1992

Research Engineer, Krylov Shipbuilding Research Institute, St-Petersburg, Russia, May 1987 – Aug. 1991

Dosimetry Technician, Chernobyl Accident Emergency Commission, St-Petersburg, Russia, May 1986 – Jan. 1987

Intern, Industrial Cyclotron Laboratory, St-Petersburg, Russia, June 1985 – Sep. 1985

Research Assistant, Leningrad Polytechnic Institute, St-Petersburg, Russia, Sep. 1983 – May 1987

Relevant Experience:

Extensive experience in radiation dose modeling and radiation measurements. Extensive experience in criticality and radiation safety and accident analyses, radiation protection, dosimetry, and shielding. Lead the development of the software based on a new hybrid approach for rapid radiation dose assessment of complex source/media/receptor geometries.

Selected Recent Relevant Publications and Presentations :

[REDACTED] Chaley, A. Kouznetsov. "Neutronic Reactivity Effect of Removed Neutron Absorber Plates." Presented at the American Society of Testing and Materials meeting on ASTM C26 - Nuclear Fuel Cycle, Denver, CO, June 24, 2008.

[REDACTED] "An Analysis of External Radiation Dose Fields in an Underground Facility at the Potential High-Level Radioactive Waste Geologic Repository at Yucca Mountain, Nevada." Nuclear Technology, Vol. 163, No. 1, pp. 31 – 37. 2008.

[REDACTED] K. Kouznetsov, S. Golikov, R. Benke. "Testing of a Hybrid Approach for Rapid Direct Radiation Gamma Dose Assessments for Complex Source/Receptor Geometries." Presented at the Health Physics Society 52nd Annual Meeting, Portland, Oregon, July 8 – 12, 2007.

4. [REDACTED] "An Independent Analysis of External Radiation Dose Fields in the Operational Facilities at the Potential High-Level Waste Geologic Repository at Yucca Mountain, Nevada." Presented at the International High-Level Radioactive Waste Management Conference, Las Vegas, Nevada, April 30 – May 4, 2006.

[REDACTED] and K.A. Higley. "Application of Autoradiographic Methods for Contaminant Distribution Studies in Soils." Journal of Radioanalytical and Nuclear Chemistry, Vol. 248, No. 3, pp. 561-564. 2001.

6. [REDACTED] K.A. Higley. "Application of Autoradiographic Methods for Contaminant Distribution Studies in Soils." Presented at the Fifth International Conference on Methods and Applications of Radioanalytical Chemistry, Kailua-Kona, Hawaii, April 9 – 14, 2000.



Facilities and Resources

Laboratory:

A vivarium for approximately 90 squirrel monkeys and eight rooms designed for neurobehavioral research is available at the Mailman Research Center, McLean Hospital, Belmont, MA. Four rooms contain behavioral testing chambers and equipment. The other rooms contain control systems, recording equipment and a workshop. A necropsy room is available for harvesting of tissues and dissection. There are currently 16 behavioral testing stations available as needed for operant and observational behavioral studies.

Animal Facility:

Living quarters for animals used in daily experiments are located within the Mailman Animal Facility as described above. Additional facilities there include surgical suites and quarantine rooms. A part-time veterinary medicine staff is available for medical consultation and assistance; supervised technicians are responsible for daily care of animals with the laboratory.

Computer:

Med Associates equipment and microprocessor control units (PC-compatible computers) and electromechanical equipment adapted for neurobehavioral research are available within the laboratory. PC-compatible Pentium IV computers with a hard disk drive, enhanced graphics adaptor, and a high resolution printer with graphics capacity are available for data analysis (including ESA 501, EBDA, KINETIC, LIGAND). Excel, Powerpoint, Prism, Sigma Plot, and SPSS software are also available. We plan to purchase four touch screens for our proposed studies in Year 01 (Elo systems CarrollTouch, Menlo Park, CA). E-prime software (Psychology Software Tools, Pittsburgh, PA) will also be purchased in Year 01 to conduct cognitive and learning tasks.

Office:



Sufficient office space is available for research and support staff at McLean Hospital; a library provides additional room for quiet work. Copy machines and fax machines are available as needed.

Other:

A machine and electrical shop for construction and repair of items used in the neurobehavioral studies is available as needed and includes heavy-duty saws, drills and other mechanical repair equipment.



Budget Justification – McLean Hospital

Personnel

Jack Bergman, Ph.D., Principal Investigator, (1.80 person months) will be responsible for overall project direction and progress, and for final publication of research data.

[REDACTED] Co-Investigator/Science PI, (5.40 person months) will be responsible for overseeing, coordinating, and conducting all neurobehavioral and pharmacological studies of ⁵⁶Fe particles and proton exposure in squirrel monkeys and preparing research data for final analysis and presentation.

Research Technicians (2), *TBA*, (12.00 person months) will conduct daily behavioral studies in squirrel monkeys, prepare data for spreadsheet analysis, and manage the inventory of laboratory supplies and ordering.

[REDACTED] (3.60 person months) will be responsible grant-related correspondence and for the overall management of funds including budget planning and oversight, payroll, purchasing, coordination of travel, and all other related expenses.

All salaries are commensurate with levels recommended by McLean Hospital for respective academic positions and are calculated on the basis of weighted averages of projected levels for FY2010. Fringe benefits are 29%. Increases in salary and other costs for subsequent years are calculated as 3% per annum in accordance with current guidelines of McLean Hospital.

Travel

Travel budgets are calculated on the basis of NASA guidelines which require travel to annual Space Radiation Investigators meeting and strongly encourage presentation of data at professional society meetings. Funds are requested for the PI and/or Co-Investigator/Science PI to attend the annual Investigators meeting and at least one national or international scientific meeting. International travel will be limited to one meeting per annum unless otherwise approved by the NASA Grant Officer. Domestic travel will include planned society meetings for presentation of data, scheduled trips to NSRL/Brookhaven National Laboratories during irradiation protocols, and meeting with collaborators in San Antonio, Texas.

Other Direct Costs

Materials and Supplies: Funds are requested for necessary laboratory, surgical, electronic, and office supplies. These costs are calculated on the basis of laboratory budgets during the previous calendar year and include standard laboratory supplies such as gloves, syringes, vials, saline, alcohol, Plexiglas and tools to maintain laboratory equipment. Costs also include the purchase and installation (Year 01) and maintenance (Years 01-04) of electronic touch screens and software for behavioral studies.

Animal Care: Expenses are based on current and projected McLean Hospital per diem rates for 24 squirrel monkeys, NSRL/Brookhaven National Laboratories per diem rate (Year 02), veterinary expenses, and husbandry supplies (including primate enrichment devices such as puzzle feeders or tech board).

Animal Purchases: Costs are based on current purchase prices. We currently have eight squirrel monkeys that can be dedicated to this project. Funds are requested to purchase an additional 10 squirrel monkeys (\$3000/monkey) in Year 01.

Service Contract: Expenses are requested for animal transportation between McLean Hospital and NSRL Brookhaven National Laboratories (Year 02) based on estimates provided by [REDACTED]

**BERGMAN, J.**ACTIVE

R01 DA 10566 Bergman (PI) Period: 9/30/96 -- 6/30/09 1.20 CY
NIH/NIDA
Cocaine Addiction: Medication Strategies and Evaluation

Studies are proposed using new procedures that will permit full and reproducible dose-effect functions for cocaine self-administration within one or two consecutive sessions.

N01 DA 8876 Mello (PI) Period: 7/7/08 -- 6/30/13 6.00 CY
NIH/NIDA \$734,317
Assessment of Potential Treatment Medications in Non-Human Primates

This contract evaluates coded compounds that have potential for the treatment of drug abuse.

R01 DA 015723 Paronis (PI) Period: 5/14/04 -- 3/31/10 1.20 CY
NIH/NIDA \$185,843
Opioids: Relative Reinforcing Strength and Dependence

The major goal of this project is to examine the role of contextual, pharmacological, and physiological variables in the reinforcing strength of self-administered opioids.

R01 DA 019205 Bergman (PI) Period: 9/30/04 - 8/31/09 1.20 CY
NIH/NIDA \$298,452
CB-1 Antagonists for Cannabis Addiction

The major goal of this project is to develop neutral CB-1 antagonists.

R37 DA 023142 Makriyannis, (PI) Period: 5/1/07-4/30/12 1.20 CY
NIH/NIDA \$224,234
Cannabinergic Medications for Methamphetamine Addiction

The purpose of this work is to identify CB1 ligands -- with a focus on neutral antagonists and partial agonists -- that may be useful medications for the management of methamphetamine addiction.

PENDING

Makriyannis (PI) Period: 11/1/09 -- 10/31/11 1.20 CY
NIH/NIDA \$253,164
CB1 Receptor antagonists in Drug Abuse

OVERLAP

There is a potential for over-commitment of Dr. Bergman's time during periods of applications and the application under consideration. If applications are funded Dr. Bergman will adjust his percent effort on each pending project so as not to exceed 100% effort overall.



[REDACTED]

ACTIVE

R01 DA 019205 Bergman (PI) Period: 9/30/04 - 8/31/09 6.0 CY
NIH/NIDA \$298,452
CB-1 Antagonists for Cannabis Addiction

R21 DA026548 [REDACTED] (PI) Period: 6/20/09 - 5/31/11 6.0CY
NIH/NIDA
Nicotinic Modulation of Methamphetamine's Behavioral and Neurochemical Effects

Current and Pending Support

Co-Investigator. [REDACTED]

A. Current Support

Title: High Temporal Resolution Suprathermal Ion Spectrometer Concept for Future Heliospheric Missions

Sponsoring Agency: NASA (SR&T), Earth-Sun Division, NASA HQ

Point of Contact: Dr. W. J. Wagner (202) 358 0911

Period of performance: Oct 1, 2006 to Sep. 30, 2009

Budget: \$210,000 (SwRI portion)

Work Year Commitment: 0.05/year

Title: Earth-Moon-Mars Radiation Exposure Module (EMMREM)

Sponsoring Agency: NASA LWS/ NSF Strategic Capability Partnership

Point of Contact: NASA: Dr. Madhulika Guhathakurta (202) 358-1992

NSF: Dr. Kile Baker (703) 292-8519

Period of Performance: 3/1/07 to 2/28/12

Budget: \$610,000

Work Year Commitment: 0.12/year

Title: Interplanetary Sources and Influences of Energetic Proton Populations in the Earth's Magnetosphere

(Subcontract through Univ. of Colorado Boulder -- LASP)

Sponsoring Agency: NASA -- HGI 2006

Point of Contact: Dr. William Wagner (202) 358-0911

(email: William.J.Wagner@nasa.gov)

Period of Performance: 3/1/07 to 2/28/10

Budget: \$177,522

Work Year Commitment: 0.09/year

Title: An Advanced Mass and Ionic Charge Composition Experiment (AMICCE) for NASA's Heliophysics Missions

Sponsoring Agency: NASA -- SHP SR&T 2006 Heliophysics Division

Point of Contact: Dr. William Wagner (202) 358-0911

(email: William.J.Wagner@nasa.gov)

Period of Performance: 10/1/2007 to 9/31/2010

Budget: \$357,027

Work Year Commitment: 0.055/year

Title: Understanding Propagation Characteristics of Heavy Ions to Assess the Contribution of Solar Flares to Large SEP Events

(Subcontract through JHU/APL)

Sponsoring Agency: NASA -- LWS TR&T 2006

Point of Contact: Dr. Glenn M. Mason (240) 228-2805

(email: glenn.mason@jhupl.edu)

Period of Performance: 1/1/2007 to 12/31/2009

Budget: \$117,438

Work Year Commitment: 0.065/year

Title: Suprathermal and Energetic Particle Studies with ACE/ULEIS

(Subcontract through JHU/APL)

Sponsoring Agency: NASA -- MODA

Point of Contact: Dr. Glenn M. Mason (240) 228-2805
(email: glenn.mason@jhuapl.edu)

Period of Performance: 5/1/2007 to 5/1/2010

Budget: \$30000K

Work Year Commitment: 0.03/year

Title: Longitudinal Distribution of Suprathermal and Energetic Particles Around Earth Orbit: New Insights from ACE, Wind, & STEREO

Sponsoring Agency: NASA – Heliophysics STEREO-G1

Point of Contact: Dr. Arik Posner (202) 358 0727
(email: aposner@swri.org)

Period of Performance: 10/1/2007 to 9/30/2010

Budget: \$375,000

Work Year Commitment: 0.04/year

Title: Strofio: Exospheric Sampling of Mercury's Surface Composition – NASA's contribution to the European Space Agency's BepiColombo Mission to Mercury

Sponsoring Agency: NASA – SALMON

Point of Contact: Dr. James Green (202) 358-1588 (email: james.green@nasa.gov)

Period of Performance: 10/2009 to 2/2022

Budget: \$31.8M

Work Year Commitment: 0.25/year

B. Pending Support

Title: Corotating Interaction Regions and Relativistic Electrons in the Earth's Magnetosphere

(Subcontract through Univ. of Colorado Boulder – LASP)

Sponsoring Agency: NASA – NNH09ZDA001N-CMSC

Point of Contact: Dr. Shri Kanekal (303) 554 0917
(email: shrikanth.kanekal@lasp.colorado.edu)

Period of Performance: 1/10 to 12/12

Budget: \$167,624

Work Year Commitment: 0.04/year

This proposal

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SPACE SCIENCE & ENGINEERING DIVISION
DEPARTMENT OF SPACE SCIENCE

June 25, 2009

Dr. Jack Bergman
Preclinical Pharmacology Laboratory
Harvard Medical School/McLean Hospital
115 Mill Street,
Belmont, MA, 02478, USA

Dear Dr. Bergman

I acknowledge that I am identified by name as Co-Investigator to the investigation entitled, "LONG-TERM EFFECTS OF SPACE RADIATION IN NONHUMAN PRIMATES," that is submitted by you to NASA NRA-NNJ09ZSA001N entitled, "Ground-based Studies in Radiation Biology," and that I intend to carry out all responsibilities identified for me in this proposal. I understand that the extent and justification of my participation as stated in this proposal will be considered during peer review in determining in part the merits of this proposal.

Sincerely,


[REDACTED]
Staff Scientist



HOUSTON, TEXAS (713) 477-1377 • WASHINGTON, DC (202) 881-2226



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SPACE SCIENCE & ENGINEERING DIVISION
DEPARTMENT OF SPACE SCIENCE

June 20, 2009

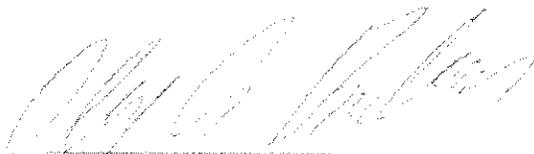
Dr. Jack Bergman
Preclinical Pharmacology Laboratory
Harvard Medical School/McLean Hospital
115 Mill Street,
Belmont, MA, 02478, USA

Dear Dr. Bergman



I acknowledge that I am identified by name as a Consultant to the investigation entitled, "LONG-TERM EFFECTS OF SPACE RADIATION IN NONHUMAN PRIMATES," that is submitted by you to NASA NRA-NNJ09ZSA001N entitled, "Ground-based Studies in Radiation Biology," and that I intend to carry out all responsibilities identified for me in this proposal. I understand that the extent and justification of my participation as stated in this proposal will be considered during peer review in determining in part the merits of this proposal.

Sincerely,







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[REDACTED]

BROOKHAVEN
NATIONAL LABORATORY

Office of the Associate Scientist, Brookhaven
University of Maryland System
Department of Biology

www.bnl.gov

June 16, 2009

[REDACTED]

Harvard Medical School/McLean Hospital
115 Mill Street
Belmont MA 02478

Dear [REDACTED]:

This letter is to confirm my support to serve as a Consultant with you on your research project entitled "Long Term Effects of Space Radiation in Non-Human Primates", which is being submitted in response to a NASA request for applications.

The space radiation environment is quite harsh, and consists of energetic charged particles with mass. NASA identifies radiation-induced adverse effects to the central nervous system as a major potential critical risk. Your animal model system is very well suited to address the important issue of how sophisticated behavioral responses may be affected by space radiation. The studies proposed will also provide insight into the mechanisms of these charged particle radiation induced effects at the molecular and pharmacological level.

As such, I eagerly look forward to working with you on these exciting studies.

Sincerely,



[REDACTED]

Associate Scientist
Brookhaven National Laboratory

[REDACTED]

Appendix I
Vertebrate Animals

1. Approximately 24 adult experimentally naïve squirrel monkeys (*Saimiri sciureus*), available within our colony or purchased from a vendor [REDACTED], will serve as subjects during the four-year period. Eighteen monkeys will participate in behavioral studies; the remaining 6 monkeys will be available for study if necessary. During experimental sessions (<4 hr/day, Monday--Friday), monkeys will be seated comfortably in a custom-constructed primate chair, and will be loosely restrained at the waist and, in some observational procedures, neck.

2. The proposed research is not ethically permissible in human subjects. However, under the experimental conditions described in this application, the effects of drugs in non-human primates can be associated meaningfully to their effects in humans. Squirrel monkeys have been selected for the proposed studies because: a) they adapt well to laboratory environment and can be handled easily and safely by experienced staff members; b) they have been studied previously under experimental conditions similar to those detailed in this application; and c) an extensive literature regarding the physiological and pharmacological effects of drugs in this species is available for reference. This information allows us to conduct our research efficiently and is fundamental to a constructive assessment and interpretation of data. We recognize that non-human primates are a valuable resource, and our research is designed to minimize the number of subjects. The within-subject design used in the proposed research, in which each animal serves as its own control, allows for scientifically meaningful results to be obtained with fewer animals (usually four subjects per experiment) that would be necessary with other experimental designs.

3. The proposed research will be conducted in a facility designed to comply with the current recommendations of the Committee on the Care and Use of Laboratory Animals (NIH Publ. No 85-23). The facility is licensed to the U.S. Department of Agriculture. Animal maintenance and research is conducted in accordance with the guidelines provided by the Committee on the Care and Use of Laboratory Animals (NIH Publ. No. 85-23). The laboratory is periodically inspected by the U.S. Department of Agriculture (USDA) and the McLean Hospital Institutional Animal Care and Use Committee (IACUC). Experimental protocols will be approved by the McLean Hospital and the BNL IACUCs, and animal care procedures will be in accordance with the Guide for the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council (1996). The McLean Hospital Animal Welfare Assurance (Number A-3685-01) is on file with the office of Protection from Research Risks, NIH. Except during testing, monkeys will be housed in individual stainless steel cages in a vivarium in which temperature, humidity, light-dark cycle are controlled. Supervised technicians will provide daily care and feeding of all monkeys and IACUC-approved protocols will be used to provide enrichment. Monkeys will have unlimited access to water at all times and will be given nutritionally balanced diet consisting of LabDiet high protein monkey diet, supplemented with fresh fruit and vegetables daily and trail mix three times a week. Access to food will not be restricted except during experimental sessions. To ensure proper health, monkeys will be examined and weighed daily by the investigator or staff. Living cages will be cleaned and absorbent

bedding material will be changed at least once a week. When required and for routine medical evaluation, veterinary staff is available for diagnosing and treating sick animals.

4. Investigators, laboratory personnel and animal technicians that will participate in the proposed research have had training or demonstrated their competence in the care, use, and handling of laboratory animals. We give assurance that potential discomfort, distress, pain, and injury will be minimized throughout the course of studies. Analgesic, anesthetic and tranquilizing drugs will be used where appropriate to minimize potential discomfort and pain to animals. Although euthanasia is not part of our planned research, ill health or pathology may occur over the course of behavioral or radiological studies and be diagnosed as a terminal condition. If recommended by the veterinarian, euthanasia by pentobarbital overdose (200 mg/kg) will be performed in a humane manner by trained staff.

Appendix 2

Software to be Used for Radiation Dose Assessment

1. MCNPX Version 2.5.0 code uses the Monte Carlo stochastic transport technique to simulate radiation transport in matter.²⁸ Monte Carlo is a pseudo-realistic technique (a numerical experiment) that consists of following large numbers of simulated particles from a source from the emission of the particle to its ultimate termination (i.e., absorption or escape). Distributions of interaction probabilities are randomly sampled to determine the distance between interactions and the type of interaction for many interactions along the transport path. The Monte Carlo technique has been used to theoretically duplicate a statistical process, including interactions of radiation with matter, and is particularly useful for problems involving complex geometry that cannot be accurately modeled using deterministic methods.^{31-32,127-129} In stochastic methods, individual particles of radiation are simulated and some aspects of their average behavior, requested by the user, are recorded, or tallied. Examples of tallies important in dose calculations are total particle fluence at a point, across a surface, or through a volume, and average energy deposited within a specified volume.

2. RADCOG³¹⁻³² is a computational framework developed by SWRI (<http://www.swri.org/3pubs/IRD2006/Synopses/209570.htm>) in the Microsoft Visual Studio programming environment and tested for accuracy and computational speed. The framework approach incorporates recent advances in three-dimensional object representation methods and novel approximations in geometrical and physical models to compute absorbed dose in complex geometries in a fraction of the time required by the MCNP family of codes. The method uses a chord distribution approach to accelerate computation of absorbed dose inside a receptor body. Several generations of scattered and emitted particles are simulated to model secondary radiation. The method then uses stochastic simulation on the chord distribution using particle interaction data from the ENDF/B-VI library to compute radiation absorbed dose.¹³⁰

3. Scan2MCNP³³ converts MRI scan data to a file suitable for input to MCNP and MCNPX. The result file contains only the geometry and materials of the scan region. A three-dimensional model is constructed from the MRI usage file.

4. HZETRN²⁹ is a 1-D deterministic code based on a space-marching formulation of the Boltzmann transport equation with a straight-ahead approximation. The code provides solution for the heavy high-energy ion propagation in media. The code is in continuous development and has been extensively verified and validated by NASA for the tasks similar to the proposed application in this study.¹³¹⁻¹³⁶

5. NASA OLTARIS³⁰ is a web-based tool implementing HZETRN features on-line.²⁸