An Introduction to Behavior Testing for the Radiobiologist

Bernard M. Rabin
Dept. of Psychology, UMBC, Baltimore, MD 21250

Abstract

Exposure to HZE particles produces changes in central nervous system function which may, in turn, affect cognitive performance. The evaluation of the effects of exposure on behavior requires the use of animal models, which can differ in validity and reliability. Also, the disruption of performance can reflect deficits in different factors which can influence behavior: sensory, motor, or integrative components. The present review considers the procedures which must be employed to study the effects of exposure to HZE particles and protons on cognitive performance and how these may be influenced by the use model systems.

Introduction

The central nervous system (CNS) functions to mediate the interaction between the organism and the environment. To the extent that exposure to cosmic rays affects CNS functioning, exposure to HZE particles may impair the ability of astronauts to perform critical tasks during long-term space travel beyond the magnetosphere, or may accelerate aging after returning to earth. Research using animal models has shown that exposure to HZE particles can affect the function of the CNS. Exposure to ^{56}Fe particles affects dopaminergic and glutaminergic neurotransmission (Joseph et al., 1992; Machida et al., 2010), hippocampal neurogenesis (Raber et al. 2004, Casadesus et al. 2005), inflammation (Rola et al., 2005) and oxidative stress (Limoli et al., 2007; Shukitt-Hale et al., 2007). While these changes in CNS function are a potential cause for concern relating to the health and well-being of astronauts on exploratory class missions, an additional concern is that the changes in CNS function will produce changes in cognitive performance that may affect the ability of astronauts to successfully meet mission requirements. However, the observation of changes in CNS function does not, in and of itself, mean there will be corresponding changes in behavioral function. As such, the understanding of the

Table 1
Factors Influencing Cognitive Performance

- Radiation Characteristics
  - Dose and dose rate
  - Effects on central nervous system
    - Changes in neuronal function
    - Relationship to Behavior
- Animal Models
  - Morris water maze
  - Validity
  - Reliability
- Variability
  - Organismic
    - Strain Differences
    - Sex
    - Age
  - Environmental
- Behavior Analyses
  - Sensory Deficits
  - Motor Deficits
  - Cognitive Deficits

effects of exposure to HZE particles and protons requires actually testing cognitive performance.

Whether or not the disruption of neuronal function by exposure to HZE particles will lead to behavioral dysfunction depends upon several factors. The first set of factors is related to the functioning of the CNS itself, and how HZE particles interact with neurons to affect their function. It has been estimated (*e.g.*, Cucinotta & Durante, 2006) that during a 3-year Mars mission astronauts may be exposed to doses of up to 42 cGy of HZE particles and protons. Much of the research on the cognitive effects of exposure to HZE particles has utilized ^{56}Fe particles at doses between 10 and 200 cGy. The focus on the use of ^{56}Fe particles derived from the fact the much of the effective dose from exposure to HZE particles may come from these particles. More recent work has involved a wider range of HZE particles, including ^{48}Ti, ^{12}C and ^{16}O, at doses that fall within the range of doses to which astronauts may be exposed (Britten et al., 2010; Rabin et al., 2011). Rabin et al. (2011) exposed rats to a range of doses of different HZE particles and measured their performance on an operant response. The results showed that there was a significant disruption of performance following exposure to doses of ^{16}O (600 MeV/n) as low as 1 cGy. However, the doses needed to disrupt cognitive performance may vary as a function of specific task: exposing rats to 20 cGy of ^{48}Ti particles (1100 MeV/n) will disrupt performance on the attentional set shifting task (Britten et al., 2010) whereas exposure to 50 cGy of ^{48}Ti particles (1100 MeV/n) is needed to disrupt operant performance (Rabin et al., 2011). These differences in the effectiveness of the same particle in disrupting cognitive performance may reflect differences in the complexity of the task. In addition to the effects of dose on HZE particle-induced alterations in cognitive performance, dose rate may also influence the effects of exposure on performance. In contrast to the procedure used in ground-based studies, which deliver the entire dose within minutes in order to minimize the discomfort to experimental subjects, on exploratory class missions the dose due to exposure to protons and HZE particles will be delivered over the duration of the mission. Whether similar effects will be observed when the dose is spread out over a period of several years remains to be established.

A related issue concerns the degree to which nervous system function must be altered before it is reflected as a change in cognitive performance. Although it has been estimated that 8% or 46% of cells will be traversed by an HZE particle with $z \geq 15$ and that every cell will be traversed by a proton once every three days during a 3-year Mars mission (Curtis et al., 1998), it remains to be established whether this will produce enough change in CNS function to produce a corresponding change in behavior, particularly given the concerns presented below.

The first of these concerns relates to the fact that there is a great deal of redundancy in the CNS. As a result of this redundancy unilateral damage to the CNS may not affect behavioral functioning (Meyer, 1958). There is also the possibility of some recovery of function, particularly when the damage occurs over an extended period of time (Corbetta, 2010). A second concern is the fact that specific behaviors

are mediated by specific brain regions. For example, motivational factors depend upon the integrity of the striatum (Salamone, 1994; Salomone and Correa, 2002) whereas spatial learning and memory depend upon the integrity of the hippocampus (Shukitt-Hale et al., 2000; Rola et al. 2004). As such, if there is an asymmetrical distribution of HZE particles passing through the CNS, such as may occur during a mission in space, one behavior may be affected and not another.

Models

In addition to the concerns about the relationships between nervous system function and cognitive performance, there are additional concerns that must be taken into account when behavior is added to the mix. The experimental study of the relationship between HZE particle-induced changes in neuronal function and cognitive performance requires the use of animal models. Animal models are commonly used in behavioral neuroscience to study brain/behavior relationships where human subjects cannot be used, such as attempts to understand the mechanisms underlying neurological and psychiatric disorders (Kaleuff et al., 2007; Cenci et al., 2002; Russell, 1991; van der Staay, 2006). Some of the aspects of behavior and the animal models used to evaluate the effects of exposure to HZE on cognitive performance are outlined in Table 2. Although the use of animal models is an accepted practice, there are concerns about validity and reliability of these models.

A. B.

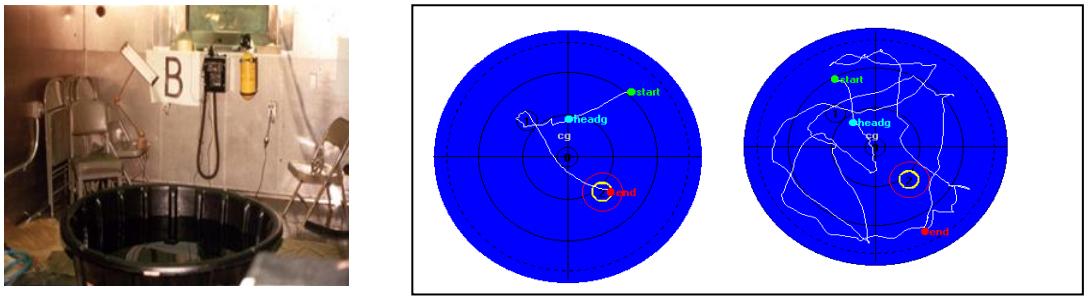

Fig. 1. Performance in the Morris water maze as an animal model for studying the effects of exposure to HZE particles on spatial learning and memory. The rat must locate a hidden platform using visual cues in order to escape from the water. **A**. The apparatus with visual cues for spatial location on the walls surrounding the pool. **B**. Tracings of the performance of the path of rats in locating a hidden platform on the second trial following the reversal of its location; left: a non-irradiated rat; right: a rat exposed to 150 cGy ^{56}Fe particles. Courtesy of Barbara Shukitt-Hale.

Validity is concerned with the degree to which the test measures what it purports to measure and may involve one of several criteria. The first of these is "face validity", the degree to which the test appears to be superficially similar to the behaviors that will be expected of astronauts. The tests that are typically used to study brain/behavior relationships (*e.g.*, operant performance in rats using a bar-pressing response [Rabin et al., 2005]) typically lack face validity. However, they do

show "concurrent validity"; that is different measures consistently show a disruption of cognitive performance. Following exposure to HZE particles, deficits have been shown in spatial learning and memory using the Morris water maze in rats (Shukitt-Hale et al., 2000) and mice (Raber et al., 2004; Rola et al., 2004; Villasana & Raber, 2010b) and using a novel spatial recognition task (Rabin, unpublished results). Changes in emotional responding have been shown using the elevated plus-maze to measure anxiety (Rabin et al. 2007) and in fear conditioning (Villasana et al. 2010b) following irradiation. The similarity in results across different tests of cognitive function provides evidence of concurrent validity. A third type of validity, "content validity", is shown by the psychomotor vigilance tests employed by Heinz (Davis et al., 2011) following exposure to protons, in that the similar tests have been used with astronauts on the International Space Station as well as with rats. Whether these tests will ultimately show "predictive validity" (that is, predict the effects of exposure to HZE particles on astronaut performance during exploratory class missions) remains to be established. Thus, despite some concerns about the relevance of specific models for the human performance, the general consensus is that well-chosen models can provide relevant information for the human condition (Kaleuff et al., 2007; Cenci et al., 2002; Russell, 1991; van der Staay, 2006).

Table 2
Behavioral Tests Used to Evaluate the Cognitive Effects of Exposure to HZE Particles

Motor Performance
- Wire Hang Time (Upper Body Strength)
- Rotorod
- Accelerating Rotorod

Learning & Memory
- Novel Object Recognition

Spatial Learning & Memory
- Morris Water Maze
- Barnes Maze
- Radial Arm Maze
- Novel Spatial Location

Motivation
- Fixed-Ratio Operant Responding

Emotion
- Elevated Plus-Maze (Anxiety)
- Fear Conditioning
- Forced Swim Test (Depression)

Attention
- Attentional Set Shifting
- Psychmotor Vigilance Test
- Prepulse Inhibition of Acoustic Startle

In addition to concerns about the validity of animal models, there are also concerns about the reliability of our models and measures. Reliability refers to the reproducibility of the results: the degree to which results are consistent across repeated tests. Testing for reliability requires several replications of the experiment in which possible sources of error (but see below) are minimized. Given the costs associated with HZE particle research and the reluctance of Institutional Animal Care and Use Committees to approve animal experiments that repeat previous research, it is hard to determine the reliability of the cognitive deficits obtained using animal models. Nonetheless, in a preliminary study of the reliability of the thresholds for the disruption of operant responding following exposure to different HZE particles, Rabin *et al.* (2009) have reported that the specific dose of a particle (*e.g.*, ^{48}Ti, ^{12}C, ^{28}Si) needed to disrupt performance varied across the different

replications. However, the general pattern was constant across the different replications, such that a lower dose of ^{12}C particles was needed to disrupt performance compared to ^{28}Si or ^{48}Ti. As such, these results suggest that, despite experimental variability, there is sufficient reliability to determine the relationship between exposure to HZE particles and the disruption of cognitive performance.

Variability

When an experiment involves live animals, individual differences must be taken into account. There are two sources of variability that may affect cognitive performance: organismic and environmental. Organismic variability may reflect strain, sex and age differences. The effects of these factors can be minimized by holding them constant. Thus, experimenters will work with only a single strain of rats, such as Sprague-Dawley (S-D) or Fischer (F-344) rats; or a single strain of mice, such as C57BL6 or DBA/2J. A problem arises because certain strains of rats and mice constitute the standard animal models for studying the relationship between specific organismic characteristics and behavior. Thus, most research on the behavioral toxicity of various stimuli, including HZE particles, has utilized S-D rats. However, F-344 rats are the standard animal model for studying aging because, unlike S-D rats, they do not continually gain weight as they age. Also, unlike S-D rats, they do not show much exploratory behavior in the open field, and cannot therefore be used to test for HZE particle-induced deficits in learning and memory using the novel object recognition task (Rabin et al., unpublished).

Sex differences in cognitive performance may result from activational and organizational effects of gonadal hormones (McCarthy, 2010; Mitsushima et al., 2009). Activational effects refer to contemporary correlations between gonadal hormones (estrogen or testosterone) and cognitive performance. Organizational effects refer to differences in brain organization resulting from hormonal differences in the perinatal hormone environment. Both effects of gonadal hormones can affect cognitive performance (Rabin et al., in preparation; Villasana et al., 2010a). Consequently, male subjects are typically used in order to minimize the effects of changing levels of gonadal hormones on performance. Similarly, only rats of a single age will be used because of potential declines in cognitive performance as a function of increasing age (Mendez-Lopez et al., 2009; Rabin et al. 2007; Shukitt-Hale et al., 2007). While this approach minimizes variability, it also limits the generalizability of the experimental results. Results obtained using male rats may not be generalizable to females and the use of rats of a single age may not be generalizable to subjects of different ages. This means that understanding how these factors may interact with exposure to HZE particles to affect cognitive performance will require the use of subjects that have these specific characteristics.

Organismic variability may also affect cognitive performance following irradiation because of differences in the sensitivity of individuals to the effects of exposure to HZE particles. Using the psychomotor vigilance test, Davis et al. (2011) reported that irradiated rats could be divided into two groups: one group which showed a disruption of performance following exposure to protons; and a second

group which was less sensitive to the effects of irradiation on performance. Compared to non-irradiated control and radiation-insensitive rats, the radiation-sensitive rats showed a disruption of performance on the psychomotor vigilance test following exposure to protons. The differences in behavior were correlated with differences in neurochemical functioning such that the radiation-sensitive rats had significantly higher levels of dopamine D_2 receptors and dopamine transporter. Given the asymmetric distribution of HZE particles in terms of parts of the CNS affected, individual differences in sensitivity to potentially disruptive effects of exposure to protons and HZE particles may add to observed variability in neurocognitive performance during exploratory class missions.

Even with organismic factors held constant, environmental factors will affect cognitive performance. This occurs because the environment, even within the same laboratory, is only imperfectly under the control of the experimenter. Thus, the experimenter cannot completely control how a rat interacts with its cage mates, handling by different experimenters, or testing procedures. All of these factors can influence cognitive performance (van der Staay, 2006), resulting in error bars (standard deviation or standard error of the mean) that may be quite large. This means that the statistical analysis of the results and the selection of the most appropriate statistical tests assume an important role in evaluating the effects of exposure to HZE particles on behavior.

These problems are increased when we attempt to compare results of similar experiments conducted in different labs. Under these conditions we not only have variability resulting from intra-individual differences in our subjects, but also from differences in housing, feeding and testing conditions between the different laboratories. For example, the experiments on the effects of exposure to HZE particles on baseline anxiety reported by Rabin et al. (2007) make use of rope lights located under the open arms of the plus-maze, which mimics nighttime conditions. If rats were tested in a plus-maze using overhead lighting, it is possible that the results would be different. Milena et al. (2005) have reported differences in the performance of rats tested in the elevated plus-maze as a function of ambient illumination level. Similarly, unexpected changes in ambient light can affect attentional mechanisms measured using prepulse inhibition of the acoustic startle response (Schmajuk et al., 2009).

Behavior

Exposure to HZE particles can affect the function of the CNS, disrupting dopaminergic and glutaminergic neurotransmission (Joseph et al., 1992; Machida et al., 2010), hippocampal neurogenesis (Casadesus et al. 2005, Raber et al. 2004), inflammation (Rola et al., 2005), and oxidative stress (Limoli et al., 2007; Shukitt-Hale et al., 2007). Exposure to HZE particles also disrupts cognitive performance (Britten et al., 2010; Davis et al., 2011; Raber et al. 2004; Rabin et al. 2005, 2007; Rola et al. 2004; Shukitt-Hale et al., 2000, 2007; Villasana & Raber, 2010a).

However, the observation of a disruption of cognitive performance does not necessarily provide information about the nature of the deficit for several reasons.

The first consideration is that the deficit in performance can result from the selection of an inappropriate task for the subject. For example DBA/2J mice cannot be used to study the effects of exposure to HZE particles on spatial memory using the Morris water maze because this strain of rats typically will not swim and make an effort to find the hidden platform; they will just float until they are "rescued" by the experimenter (Fisch, 2009). Spatial learning and memory must be tested in these mice using the Barnes maze. In contrast, spatial learning and memory following irradiation can be testing in the Morris water maze using C57BL/6J mice (Fisch, 2009). A further complication is that radiation-induced deficits in spatial learning and memory are not always observed with C57BL/6J mice tested in a Morris water maze, but may be observed when the mice are tested in the Barnes maze (Raber et al., 2004).

A second consideration is that the disruption of performance can occur on many levels: sensory, motor or cognitive. For example, when a rat or a mouse is exposed to ^{56}Fe particles, it shows a deficit in spatial learning and memory measured using the Morris water maze (Shukitt-Hale et al., 2000). The deficit in performance may occur because irradiation produced a change in the sensory ability of the subject so that it can no longer see the visual cues needed to guide its behavior. Alternatively, it is possible that the irradiation has affected the motor system (Joseph et al., 1992) impairing the ability of the subject to perform the task. Sensory and motor deficits are relatively easy to test for by using a different stimulus, such as auditory or tactile stimulus, and by using a task that requires a different response, such as a head-turning response.

Cognitive factors that may be affected by exposure to HZE particles include motivation and learning and memory. Motivation is concerned with the arousal of goal directed behavior, which can be defined in terms of the approach or avoidance of a particular goal. The motivation to approach or avoid is a function of the conditions of reinforcement. Reinforcement can be either positive or negative. Positive reinforcement occurs when the subject is given a reward for making a response; negative reinforcement occurs when an aversive stimulus is terminated following the performance of a response. Both types of reinforcers are utilized to study the effects of exposure to HZE particles on performance. Positive reinforcers, such as food, are used where previous research has established that the specific manipulation, exposure to HZE particles, does not affect the responsiveness of the subject to the reinforcer; *i.e.*, irradiation does not affect food intake (Rabin, unpublished). The use of positive reinforcement has been utilized by Britten *et al.* (2010) in studies of attentional set shifting which is a measure of cognitive impairment following exposure to HZE particles; and by Rabin *et al.* (2005, 2011) in studies measuring the activational aspects of motivation and decision making as it relates to the willingness of the organism to expend of energy to achieve a specific goal. Where there is reason to suspect that exposure to HZE particles may affect the

responsiveness of the subject to positive reinforcement, the use of negative reinforcement may be satisfactory. This approach underlies the use of the Morris water maze to study spatial learning and memory (Shukitt-Hale et al., 2000, 2007) in which the motivation is to find a hidden platform and escape from the aversive water. As with positive reinforcement, the use of a negative reinforcer requires the appropriate controls to determine the extent to which irradiation affects the motivation to perform the specific task or the extent to which irradiation affects other cognitive processes.

Conclusions

Although exposure to HZE particles affects the functioning of the nervous system, the effects of altered neuronal function on cognitive/behavioral processes is not straightforward. The reasons for this are complex, involving the characteristics of the nervous system as well as the requirements of behavioral testing. The limitations of behavioral testing derive from the need to use models to study brain/behavior relationships; from organismic and environmental variability which is only incompletely under the control of the experimenter; and from the complexity of the behavioral processes that determine if and how an organism will respond to a stimulus. Nonetheless, understanding the effects of exposure to HZE particles and protons on the performance of astronauts during exploratory class missions can only be determined by behavioral testing.

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