

POTENTIAL FOR CENTRAL NERVOUS SYSTEM EFFECTS FROM RADIATION EXPOSURE DURING SPACE ACTIVITIES PHASE I: OVERVIEW



National Council on Radiation Protection and Measurements



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Preface

In March of 2013, the Board of Directors approved a project to address the potential short- and long-term consequences of space radiation on the central nervous system (CNS). A two-phased effort was envisioned. During the first phase, which resulted in this Commentary, the critical issues surrounding the potential short- and long-term consequences of space radiation on the CNS are described, research needs outlined, and the groundwork provided for a more comprehensive subsequent report (Phase II).

The basis for this effort is a concern that radiation exposures in space may result in acute functional and cognitive CNS effects that could impair missions, and that delayed CNS effects may result in serious cognitive and mental dysfunction in exposed crew members. Radiation-induced damage to the CNS has long been recognized in patients treated with high-dose photon radiation therapy, but recent animal experiments have shown a number of early and delayed deleterious effects following exposures to high atomic number, high-energy particles and at radiation levels lower than previously suspected as being damaging. Permissible exposure limits are currently in place in a National Aeronautics and Space Administration (NASA) standard for cancer and certain noncancer effects, but the need for guidance applicable to CNS and other degenerative conditions needs to be further assessed. Although human data exist following radiation therapy for non-CNS conditions in childhood and in adulthood and subsequent early-onset dementia has been observed, the relevance to space radiation has not been evaluated. Conceivably, risk-limitation strategies to reduce CNS effects may require a distinct strategy that differs from approaches used for cancer and noncancer effects in the past.

Specific topics that were addressed in this Commentary (Phase 1 of the effort) are listed below. The conclusions and recommendations of this Commentary will guide a more complete National Council on Radiation Protection and Measurements (NCRP) report (Phase II).

1. How should clinically or operationally significant CNS effects be defined? This includes the early effects that might occur during a mission and the late effects that might develop years later.
2. Are there clinically or operationally significant CNS effects that can be allowed under controlled circumstances?
3. What behavioral measures should be used in animals to predict human risks?
4. What approach should be used to limit late CNS morbidity and mortality risks? Would these approaches differ from those currently employed to limit late cancer morbidity and mortality risks?
5. What research strategies can be used to understand the short- and long-term CNS risks of radiation exposure? What animal and human research exists today and how might they be enhanced to address the needs of crew members in space?
6. What other space flight factors could influence the impact of significant CNS risks during a mission?
7. What do studies at the NASA Space Radiation Laboratory and at non-NASA facilities indicate on the potential CNS effects from space radiation?
8. Are there any genetic, lifestyle or individual factors that might be important?
9. Are clinical studies with patients exposed to radiation (e.g., proton or carbon therapy; cranial irradiation for non-CNS disorders) of value in interpreting or modeling possible CNS effects from space radiation? Similarly are occupational studies (e.g., workers

exposed to polonium which seeks soft-tissue and exposes brain tissue to alpha particles) or other exposure circumstances (*e.g.*, Japanese atomic-bomb survivor studies) of relevance? Should studies of crew members to evaluate early changes of cognitive function or other conditions be considered?

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John D. Boice, Jr.
President

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1. Executive Summary

The National Council on Radiation Protection and Measurements (NCRP), commissioned by the National Aeronautics and Space Administration (NASA), undertook a study of the effects of radiation in space on the central nervous system (CNS) and potential ways of minimizing the resulting risk to mission objectives and the long-term health of crew members on extended and exploration missions. The objective of the first phase of this study, as reported in this Commentary, is to evaluate whether there is evidence indicating that detrimental effects of radiation on CNS function may be significant and to determine whether there is sufficient information available to support a second phase which would make recommendations about needs for additional research and recommendations about radiation protection relevant to CNS damage.

Nine specific questions, listed in the Preface, were considered. Although complete and detailed answers to each question were beyond the scope of this Commentary, these questions served to focus the evaluations and led to several specific recommendations.

The CNS poses unique challenges for assessing risks associated with exposure to galactic cosmic radiation (GCR) expected during long-duration deep-space travel. The radiation environment beyond the Earth's magnetosphere includes high atomic number, high-energy (HZE) particles and other types of highly ionizing radiations that may pose health hazards that are different from those for low-Earth orbit (LEO) missions. A significant fraction of NASA's space radiation effects research has been directed toward effects on the CNS and has included studies of biochemical mechanisms as well as phenomenological studies. These studies have generally used the same approaches to describing radiation exposure as studies of GCR exposure effects on somatic cells elsewhere in the body, where the focus is on interactions within the cell nucleus that lead to derangements in cellular physiology and chromosomal stability. This established approach to characterizing radiation exposures was developed primarily to address the characteristics relevant to cancer biology. However, this perspective is not suitable for assessing GCR risks relevant to the CNS.

The reasons for this incompatibility arise from the unique structure, organization and function of the brain relative to other organs and tissues elsewhere in the body. The fundamental cellular element of the brain is the nerve cell, or neuron. The adult human brain is comprised of $\sim 10^{11}$ neurons, including $>10^{10}$ in the cerebral cortex, and a larger number of non-neuronal cells, including astrocytes, oligodendrocytes, and microglia (Azevedo *et al.*, 2009; Herculano-Houzel, 2012). Other cell types form CNS-allied structures, including endothelial cells and pericytes at the blood-brain barrier (BBB), ependymal cells in the circumventricular organs, and neurosecretory cells in posterior hypothalamus (Peters *et al.*, 1991).

Neurons are long-lived, post-mitotic (nondividing) cells that derive from the embryonic ectoderm (Nauta *et al.*, 1986).¹ During terminal differentiation and maturation, neurons assume a wide variety of shapes, sizes and specializations (dendrites, soma, axons, synapses, spines, and other morphological and ultrastructural structures) that facilitate a singular function: signal processing. Anatomical connectivity and neurophysiological dynamics involving networks of interacting neuronal systems throughout the brain yield the emergent properties

¹An exception to this rule is the olfactory neuroepithelium, an extension of the CNS that continuously regenerates throughout life.

that we associate with cognition, perception, affect (the experience of feeling or emotion), and consciousness. Ultimately, it is impairment in these higher functions of the CNS that are of concern with respect to GCR effects on human performance, health and disease during and after extended deep-space missions. Although the CNS of mammals share the same basic biochemistry and physiology, they differ in details and degree of sophistication in function. These differences in details make it difficult to extrapolate from observed performance decrement in experimental animals to risk to a space exploration mission or to the mental health of individual crew members. For example it is difficult to relate executive function in human response to an emergency to a test in an experimental animal system.

The significance of these facts is that assumptions and approaches that apply to other organs and tissues in the body are not applicable to the CNS. Stated differently, GCR effects on the brain cannot be appreciated using concepts and strategies borrowed from cancer biology. Rather, understanding and assessing risk associated with acute and delayed effects of any insult to the CNS, including GCR exposure, must be guided by consideration of the unique features of brain structure, function and organization. Furthermore, the multiple levels of brain organization and function that may be affected by injury or disease requires synthesis across a range of basic and clinical disciplines, including neurobiology, neurophysiology, neurogenetics, clinical psychology, neurology, and psychiatry.

In addition, acute and delayed effects on the CNS can be produced by stressors (*e.g.*, microgravity, elevated carbon dioxide levels, sleep deprivation, isolation) other than radiation which are inherent to space missions. These other stressors may produce similar impairment which can mask and dominate over any potential radiation-induced effects. Therefore, it will be problematic to discriminate between potential radiation-induced CNS effects and known CNS effects produced by other stressors during a mission. Many of these effects are meaningful in the sense that they can be measured reliably but, on the other hand, they may not be severe enough to significantly impact mission objectives or safety.

Conclusions derived from this Phase I effort indicate approaches that can be used to move forward with a comprehensive report. Many of these conclusions suggest approaches to answering the specific questions (indicated in parentheses) enumerated in the Preface. These conclusions are:

- Exploration-mission-relevant doses of HZE particles in animals, environmental exposure to other radiation insults, and clinical effects of therapeutic radiation exposure suggest that significant alteration in brain function can occur due to exposure to radiation. Taken together these findings warrant a detailed Phase II study leading to recommendations for future actions (5, 7).
- The structure and function of the CNS results in damage mechanisms which are different from the mechanisms for cancer induction (4).
- Other sources of stress during space missions may mask or add to any radiation-induced CNS effects (6):
 - Environmental factors, workload, and perceived risk may trigger CNS responses which are independent of, additive to, or synergistic with radiation-induced CNS effects that could affect behavior and impair performance (6)
 - Attempts to mitigate effects of stress, such as the use of pharmaceuticals to improve sleep, may result in additional CNS perturbation (6).
- The nature of CNS damage leading to functional and cognitive effects is significantly different from the cellular damage leading to cancer [cancer can be initiated through a wide range of mechanisms, often involving deoxyribonucleic acid (DNA) changes (mutagenesis), leading to uncontrolled clonal expansion] and therefore effects on the CNS may require a different approach to characterizing radiation exposure (4):

- Functional and cognitive CNS effects can be induced by significant cell damage outside the nucleus (4, 7).
- It is likely that many sequelae do not involve clonal expansion mediated by cell proliferation (7).
- Animal research addressing cell and molecular basis of damage and behavioral outcomes is needed to relate to both simple and complex behaviors relevant to the human risks (5).
 - Relevant animal or cellular models need to be defined based on the questions relevant to the human risks (7).
 - Animal studies should include pathological and morphological endpoints as well as behavioral outcomes including complex responses (executive functions) (3, 7).
 - A Phase II study should include analysis of any available primate data on CNS effects of radiation [e.g., as might come from the evaluation of radiation countermeasures in the Medical Countermeasures Against Radiological and Nuclear Threats Program of the National Institute of Allergy and Infectious Diseases (NIAID, 2012)] (3).
- Methods for assessing the CNS damage and its possible impact on crew-member health and mission objectives need to be developed (5).
- Life-long medical follow-up of crew members to evaluate potential CNS changes is essential (5).
- More research is needed to characterize the interaction of radiation exposure with other aspects of crew-member environment (e.g., sleep, lighting, exercise and diet including micronutrients, supplements) and the pharmaceuticals or other methods used to mitigate these factors (6).
- Transgenic animal studies suggest that inter-individual genetic differences may alter risk (8).
- Clinical studies with patients exposed to high-energy heavy-ion radiation, and occupational studies (e.g., workers exposed to polonium) are very limited but may be useful for evaluating tests for CNS function (9).
- Integration of data across all biological scales (subcellular damage through human behavior) and for all CNS endpoints should be emphasized (5, 6, 7).
- Pre- and post-flight imaging and biomarkers for CNS diseases, including tissue banking should be used to the fullest extent possible (5).
- Systems biology or medicine and animal mechanistic studies are generally considered independent disciplines and do not, in the present environment, inform each other conceptually. Steps should be taken to encourage interacting and integrative work at all levels of conceptualization (6, 7, 8).
- Comparison of the assessment results for exposed crew members with those for other nonexposed groups is essential (providing controls for exposed crew-member follow-up studies) (1, 2, 3).
- Use of autonomic nervous system responses as indication of damage should be evaluated (5).
- Since mechanisms leading to functional and cognitive CNS effects may be different from mechanisms leading to cancer, which underlie current risk mitigation procedures, alternative approaches to risk management should be investigated (4).

The summary recommendations of this Commentary are:

A. Proceed with the Phase II Report.

B. The work of a Phase II committee should summarize and critically review the existing literature on each of the five main topics listed below, and make recommendations for research and other directions needed within each topic.

1. mechanisms for space radiation damage in the CNS;
2. experimental animal research;
3. human data;
4. integration of data across all biological scales (subcellular damage through human behavior); and
5. interactions of radiation with other factors.

Additional detail on the components of research that need to be pursued for each of these five main topics is provided in Section 12.

The Phase II committee should include expertise in a number of fields, as noted in Section 12.

2. Introduction

Exposure to the high-energy charged particles in interplanetary space, and to the secondary products from their interaction with matter, is a major risk to crew members engaged in space exploration. Emphasis on the consequences of exposure to this radiation in space has been, and continues to be, on cancer induction. This emphasis is appropriate because the impact of cancer risk on quality and length of life appears to exceed that of other radiation-induced risks. This dominance is due to the large number of studies indicating a relationship between cancer and radiation at various dose levels. However, cancer risk estimates are affected by significant uncertainties which are likely to persist until a multiscale, integrated understanding of radiation carcinogenesis allows for predictions of cancer risk in living systems that are more accurate than currently possible on the basis of epidemiology alone.

Results of current scientific research point to the possibility that other tissue effects (acute, early delayed, and late delayed) may contribute meaningfully to health risks in space; in particular, the CNS, the subject of this Commentary, may be compromised as a consequence of exposure to space radiation. The CNS is generally found to be relatively resistant to low linear energy transfer (LET) radiation, compared with many other tissues. However, the observation of “light flashes” by astronauts and others exposed to high-energy charged-particle radiation led to the hypothesis that the long, densely ionized, tracks of these particles might produce unique forms of damage in the CNS. This hypothesis has been a subject of study for nearly five decades.

Current understanding of mechanisms underlying radiation-induced cancer and CNS damage suggests that the biological processes leading to these two unique effects are quite different; therefore, the scientific approaches required for studying each and estimating their risks are expected to be different. Cancer is generally attributed to clonal expansion of one or, at most, a few transformed cells. Under that assumption the relevant statistical problem is determining the probability of altering the DNA in a single cell, whether that cell is directly traversed by a charged particle, traversed by delta rays emitted during the passage of the particle, or is influenced by signals produced by cells which received radiant energy.

It is generally assumed that the statistical problem for understanding CNS response to any irradiation is the determination of the number of cells altered by the radiation insult, directly or indirectly, and their locations relative to each other in the highly structured tissues of the CNS. It is important to note that CNS tissues may also be affected indirectly, as a consequence of signals originating as a response to radiation in other tissues.

It is often assumed that the probability that a function associated with a particular structure of the CNS will be compromised depends on the fraction of the structure’s volume compromised by radiation. In some cases, existent tissue repair mechanisms may render any impairment reversible. If the number and distribution of cells affected by radiation is large enough, the tissue response may be described as having exceeded a damage threshold. Radiation damage can, in principle, lead to prompt or delayed expression of damage. The time course of the tissue response may be short (*e.g.*, resulting in inflammation and immediate manifestations of radiation response). If the time course of the tissue response is longer, the radiation response may appear as degenerative damage (*e.g.*, as a more probable incidence of Alzheimer’s disease, or a shortening of its presumed latency). However, alternative mechanisms, such as interference with the cell’s ability to produce the molecules needed for repair, may also contribute to the risk.

Not all CNS responses to radiation will have the same impact on mission objectives. A highly redundant system, such as a team of humans trained to work together, will likely be impervious to many possible manifestations of immediate radiation effects. However, if near-term damage results in major changes in personality in one or more crew members it may disrupt team function. The possibility that long-term degenerative effects may result in similar impairment of all crew members needs to be considered for risk management. In order to develop an appropriate understanding of the risk to CNS from exposure to space radiation, it is necessary to gain a better understanding of the biological mechanisms leading to observable endpoints.

Following this brief Introduction (Section 2), the main body of the Commentary covers:

- Reference Human Extended and Exploration Missions (Section 3) on the characteristics and durations of extended International Space Station (ISS) and potential space exploration missions which may lead to significant radiation exposure.
- Radiation Risk Management at NASA (Section 4) on an example of the current radiation protection standards (in this case for fatal cancer) and the research program intended to improve the understanding of CNS radiation risks.
- Space Radiation (Section 5) and Structure and Function of the Brain (Section 6) on the unique radiation environment in space and the organization and function of the CNS, respectively.
- Evidence of Radiation Effects on the Central Nervous System (Section 7) on the experimental evidence of CNS changes in animals, primarily small rodents, exposed to simulated space radiation, observed effects in people exposed to radiation for therapeutic purposes, and studies of dementia in radiation-exposed populations.
- Examples of Other Known Stressors on the Central Nervous System (Section 8) on other stresses which may exacerbate the effects of radiation on the CNS, or which may produce similar impairment which can mask, and potentially dominate over, the radiation-induced effects.
- Simulation of the Space Radiation Environment (Section 9) on issues in simulating space radiation for use in biological experiments.
- Central Nervous System Function Studies of Crew Members (Section 10) on studies to objectively measure cognitive performance in crew members while on mission.
- Approaches to Limiting Potential Central Nervous System Risks (Section 11) on issues relating to the use of shielding design to minimize the risk to the CNS resulting from radiation exposure in space.
- Conclusions and Recommendations (Section 12) on producing a Phase II Report with more detail on the research that could provide a better understanding of the potential for CNS effects from exposure to the space radiation environment during extended space missions.

3. Reference Human Extended and Exploration Missions

The NASA Human Research Program (HRP) is responsible for investigating and mitigating the highest risks to crew-member health and performance in support of extended ISS and exploration missions (NASA, 2013). Design Reference Missions (DRMs) provide boundary conditions and a framework to identify key capabilities, guiding drivers, and assumptions. In some cases, the details provided by the agency DRMs are not specific enough to assess each of the risks in its portfolio and the HRP makes additional assumptions for research and risk assessment. The extended ISS and exploration missions for which DRMs are currently considered are described in Sections 3.1 through 3.4.

3.1 International Space Station: 12 Months

This DRM involves an extended stay on the International Space Station (ISS) involving two crew members for a minimum duration of 12 months. An additional four ISS crew members will participate with a six month rotation cycle.

3.2 Lunar Outpost and Sortie

The total mission duration can range from approximately three weeks for a sortie mission to approximately six months for an outpost mission. The transit time to or from the Moon will be ~4 d. Surface time for a sortie mission will be approximately two weeks and an outpost mission will last approximately six months. During the entire lunar surface stay, the four crew members are expected to perform multiple extravehicular activities (EVAs). During an EVA sortie, the crew members have the capability to perform EVAs with all crew members egressing from the vehicle through an airlock or suitport-provided capability.

3.3 Near Earth Objects or Asteroids

One proposed design (Stich, 2013) is for a 12 to 13 month mission with ~12 months of transit time and a 30 d stay. During the entire 30 d stay on the near-Earth asteroid surface, the crew members are expected to perform multiple EVAs. During the EVA, the crew members will be augmented with robotic support. More recent designs depict a 21 or 22 d mission with 16 d of transit, orbit around the near-Earth asteroid of 6 d, and EVAs to the asteroid but no surface stay.

3.4 Mars

There are two basic possibilities for a practical Earth to Mars trajectory requiring minimum mission duration: opposition-class and conjunction-class trajectories. The two are so named because they are based on the relative positions of Earth and Mars at launch: opposition occurs when Mars is closest to Earth, and conjunction occurs when Mars is furthest from Earth. These positions can be visualized best when thinking of the Sun, Earth and Mars lying across a straight line. At opposition, the Sun is in the middle, Earth is to the right, and Mars is further right. At conjunction, Mars is on the far left, the Sun is in the middle, and Earth is on the right. These favorable possibilities are repeated approximately every 26 months,

allowing prepositioning of habitat and cargo modules preceding a launch of the crew members by 26 months.

The Mars Exploration DRM-5 (Drake, 2009), often referred to as long-stay missions, are characterized by the need to minimize the exposure of the crew members to the deep-space radiation and zero-gravity environment while, at the same time, maximizing the scientific return from the mission. This is accomplished by taking advantage of optimum alignment of Earth and Mars for both the outbound and return trajectories, and by varying the stay time on Mars, rather than forcing the mission through nonoptimal trajectories. This approach allows the crew members to transfer to and from Mars on relatively fast trajectories, on the order of six months, while allowing them to stay on the surface of Mars for a majority of the mission, on the order of 18 months. The total mission duration from launch to crew-member return is assumed to be ~3 y. Once on the surface, expectations are that the crew members will be required to perform many activities in support of mission objectives and mission success. During the entire 18 month stay on the Martian surface, the six crew members are expected to perform multiple EVAs, assisted by pressurized and unpressurized rovers, to carry out field work in the vicinity of the surface base.

4. Radiation Risk Management at NASA

4.1 Human Research Road Map

NASA human health and performance risk mitigation strategies (including for ionizing radiation) are within the purview of the NASA Human Research Program (HRP). Three core documents describe the HRP; they are the:

- *Human Research Program Requirements Document* (NASA, 2013);
- *Human Research Program Integrated Research Plan* (NASA, 2011); and
- *Human Health and Performance Risks of Space Exploration Missions* (referred to as the *Evidence Book*) (McPhee and Charles, 2009).

The *Evidence Book* is a collection of evidence-based risk reports and journal articles for each individual risk (including ionizing radiation) that is contained within the *HRP Requirements Document* and for which implementation activities are listed in the *HRP Integrated Research Plan*.

4.2 Radiation Risk Perspective

The current radiation risk estimates and associated uncertainties are described in MCPhee and Charles (2009), a collection of the evidence base for potential health and performance risks to crew members on future exploration missions. The book contains risks in 12 different areas, including the following related to radiation exposure:

- radiation carcinogenesis;
- acute radiation syndromes due to solar particle events (SPEs);
- acute or late CNS effects from radiation; and
- degenerative tissue or other health effects from radiation.

Table 4.1 lists the radiation risks considered, and Table 4.2 lists possible health and performance outcomes (McPhee and Charles, 2009).

4.3 Radiation Protection Standards

As an example of the approach NASA has taken previously to manage radiation risks encountered during space missions, the current NASA radiation protection standard for fatal cancer is provided below. The approach to risk management for any potential CNS effects may need to be different from that for fatal cancer because of the differences in the underlying biological mechanisms leading to CNS effects.

4.3.1 Permissible Exposure Limit

The permissible career exposure limit set by NASA is a 3 % risk of exposure-induced death (REID) for cancer at a 95 % confidence level to protect against uncertainties in risk projections (NASA, 2014). The 3 % REID limit for cancer is based on comparisons with risks of fatal accidents in “safe,” “less safe,” and “hazardous” occupations, the middle group of these being preferred because crew members have other additional high risks apart from radiation

TABLE 4.1—*Spectrum of radiation risks to crew members on future exploration missions (adapted from McPhee and Charles, 2009).*

<i>Carcinogenesis (including age and gender differences)</i>
Leukemias
Solid cancer
<i>Degenerative tissue effects</i>
Heart disease
Cataracts
Respiratory disease
Digestive diseases
<i>Damage to the CNS</i>
Cognitive and affective changes
Motor skills
Behavior
Accelerated aging
<i>Acute risks</i>
Death
Vomiting and nausea

TABLE 4.2—*Possible health and performance outcomes for crew members on future exploration missions from exposure to GCRs or SPEs (adapted from McPhee and Charles, 2009),*

Mortality: reduced lifespan (from GCR or SPE)
Mortality: in-flight (acute from SPE)
Performance degradation in-flight (from GCR or SPE)
Morbidity: post-flight (from GCR or SPE)

(NCRP, 1989). Additional support for the choice of a 3 % REID, although perhaps coincidental in nature, is that using the more common (terrestrial) approach, the lifetime risk of radiation-associated fatal cancer is ~3 % (NCRP, 2014). This calculation uses the current NCRP effective dose limit for occupational exposures of no more than 50 mSv y⁻¹ in any 1 y, with a cumulative limit (age × 10 mSv) after 18 y of age (NCRP, 2000). The 3 % REID limit is used to set specific mission and vehicle requirements for shielding, dosimetry, countermeasures, and crew-member selection. A detailed description of the current model used by NASA to calculate cancer risk predictions is contained in Cucinotta *et al.* (2013), which is the updated version produced after review by NA/NRC (2012) of an earlier model (Cucinotta *et al.*, 2011). NCRP Commentary No. 23 (NCRP, 2014) discusses the issues that will need to be considered regarding the applicability of current NASA radiation protection standards to extended LEO and exploration missions. It is noted that NASA is the only organization using a risk-based system for radiation protection in contrast to the systems of dose limits for occupational exposures used by terrestrial-based organizations.

4.3.2 Safe Days in Space

The risk calculations allow NASA to estimate “safe days in space,” the number of days that a crew member may spend in space with 95 % confidence that he or she will not exceed the

career REID limit of 3 % for cancer. Given the inherent uncertainties in the risk calculations, to assure that the permissible exposure limit will not be exceeded may require designing for a 1 % or even smaller REID for cancer. Examples of the results of such a calculation are given in Table 4.3. For comparison the ages of astronauts at time of selection has ranged from 26 to 46 y, with the average being about 34 y. Several years training is required before their first flight, and between flights.

As seen in Table 4.3, the number of safe days in space for this example is considerably less than the time required for a mission to Mars. The estimates given in Table 4.3 are for a hypothetical Mars mission under specified conditions; other missions with different specified conditions would produce different estimates of safe days in space. NASA has embarked on a long-term research program intended to reduce the uncertainties inherent in these based on a better understanding of the mechanisms leading from radiation exposure to cancer. Some results of this ongoing research, including the effects of considering different models for radiation quality and different assumptions on allowable uncertainties, are presented by Cucinotta *et al.* (2015).

TABLE 4.3—*Estimates of safe days in deep space, defined as the maximum number of days with 95 % confidence level to be below the 3 % REID limit for cancer. Calculations are for a hypothetical mission to Mars at average solar minimum with 20 g cm⁻² aluminum shielding. Values in parenthesis are for the case of the deep solar minimum of 2009 (Cucinotta et al., 2013).*

Age (years)	Safe Days in Space	
	Using Risk Model for the U.S. Average Population	Using Risk Model for Never-Smokers
Males		
35	209 (205)	271 (256)
45	232 (227)	308 (291)
55	274 (256)	351 (335)
Females		
35	106 (95)	187 (180)
45	139 (125)	227 (212)
55	161 (159)	277 (246)

5. Space Radiation

5.1 Radiation in Space

The ionizing radiation environment in space has two origins, GCR and solar emissions. The primary radiations from these sources interact with material in space to produce additional types of radiation and to modify the radiation spectrum in terms of particle fluence and energy. The Earth's magnetic field deflects charged particles in space, creating trapped radiation belts surrounding the planet and reducing the dose rate in LEO relative to that outside the influence of the local magnetic field. NASA has extensive documentation on radiation protection policies and dose monitoring requirements both for ISS and for exploration missions (Turner, 2012). The properties of the space radiation environment have been reviewed in previous NCRP (2000; 2006) reports and by others (Durante and Cucinotta, 2011; ICRP, 2013) and will be described only briefly here.

5.1.1 Galactic Cosmic Radiation

Galactic cosmic radiation (GCR) appears to originate throughout the universe and consists of atomic nuclei that travel at very high velocities in all directions. It is believed that outside the influence of a solar system the GCR spectrum is essentially time independent and omnidirectional (NCRP, 2006). The GCR spectrum includes all atomic nuclei, approximately in proportion to their abundance in the universe. Thus, hydrogen nuclei (*i.e.*, protons) make up a large majority of the spectrum. Particles heavier than iron occur at much lower fluence than iron and lighter ions because of the limits of the nuclear fusion processes in stars.

GCR particles are not uniformly distributed in the solar system because the Sun emits a wide range of charged particles, and one class of these particles, the solar wind, creates a magnetic field throughout the solar system. This magnetic field deflects the GCR particles, preventing some lower-energy ones from reaching the inner planets, but higher-energy particles are not deflected as much. Thus in the vicinity of Earth and Mars the energy spectrum of each particle type extends over several orders of magnitude, from a few to thousands of megaelectron volts per nucleon (MeV n^{-1}),² with a peak fluence in the vicinity of 300 to 700 MeV n^{-1} . In terms of contributions to the absorbed dose the median energy is $\sim 1,500 \text{ MeV n}^{-1}$.

5.1.2 Solar Radiation

The Sun emits a wide range of materials, some of which are charged particles. The majority of these particles are relatively low-energy protons that constitute the solar wind. The Sun also displays several types of transient activity including sun spots and coronal mass ejections. Solar emissions have been reviewed by NCRP (2006) but will be briefly described here. The rate of transient solar events, as well as the magnitude of the solar wind, varies with

² MeV n^{-1} : Since the unrestricted electronic (collision) stopping powers (*i.e.*, LETs) of charged particles of equal velocity are proportional to the effective Z^2 of the particle, it is convenient, and customary, to describe particles in terms of energy per atomic mass unit since particles of equal megaelectron volts per atomic mass unit have the same velocity. Generally this is approximated by energy per nucleon. The effective Z is equal to the atomic number Z for fully stripped particles, which is characteristic of most cosmic-ray particles until they have lost most of their energy.

time, primarily on an 11 y cycle, but can be modified by superimposed cyclic variations with other periods. SPEs, including impulsive events (related to some sun spots) and coronal mass ejections, produce bursts of charged particles, nearly all protons, with widely varying fluence rates, energy spectra up to a few hundred megaelectron volts, and random initial trajectories. Impulsive events typically last no more than a few hours or days with the fluence rate rising to a maximum in a few hours and then falling off. The dose rate produced by a coronal mass ejection typically rises more slowly, with the peak lasting for several hours. The probability of an SPE is approximately proportional to other activity during the solar cycle, but a large SPE can occur at any time in the solar cycle.

5.1.3 *Typical Dose Rate outside the Earth's Magnetosphere*

Outside the Earth's magnetosphere the absorbed dose rate due to GCR particles is modified by the solar wind, with the maximum dose rate occurring at solar minimum and decreasing to approximately half of the maximum dose rate at solar maximum. However, the increase in SPEs as the solar activity increases results in the annual absorbed dose being approximately constant, but with large variations near solar maximum since the frequency and magnitude of SPEs vary dramatically from one solar cycle to the next. Furthermore, it is not possible to predict the maximum annual absorbed dose with any certainty since the maximum dose during an SPE remains uncertain. During 2011 to 2012 an absorbed dose rate of 0.45 mGy d^{-1} was recorded in transit between Earth and Mars (Zeitlin *et al.*, 2013). For comparison, the average dose rate on the ISS ranges from 0.12 to 0.29 mGy d^{-1} depending on location within the vehicle (NASA, 2015).

5.2 Characteristics of Energy Depositions

5.2.1 *Electronic Interactions*

Ionizing charged particles, such as in GCR and SPEs, interact with matter primarily by inelastic collisions with atomic nuclei and Coulombic interactions with the electrons of the atoms they pass. Inelastic nuclear interactions are relatively rare, so most energy deposition is through electronic interactions. Depending on the ionizing particle's charge, velocity, and distance from the atom it can transfer any amount of energy to an electron, from a fraction of an electron volt up to a maximum, determined by conservation of energy and momentum, which gives the electron a velocity up to twice the velocity of the incident particle. Because of geometric considerations, interactions which transfer a small amount of energy, resulting in excitation of the atom, are most common. Interactions which transfer enough energy to ionize the atom are less common, but the total amounts of energy resulting in excitations and ionizations are approximately the same. Interactions which result in ionization produce a free electron which can have any energy up to the maximum which can be transferred.

Electrons which receive enough energy to produce several additional ionizations along their paths are referred to as delta rays. Delta rays are emitted approximately perpendicular to the primary particle trajectory, but scatter in random directions due to their low mass. The maximum path length for delta rays can be millimeters in water (Table 5.1), but because of the scattering their maximum distance from the primary particle trajectory is generally much less. The delta ray fluence as a function of radial distance from a charged particle track can be determined using Monte-Carlo methods and extensive data on electron interaction cross sections.

Since the Monte-Carlo calculations are time-consuming, approximations which estimate the average energy deposited per mass as a function of radial distance from the charged particle's path (Butts and Katz, 1967; Kobetich and Katz, 1968) are often used. These models show

TABLE 5.1—Primary energy, maximum delta-ray energy, maximum continuous slowing down approximation delta-ray range in water, and Chatterjee model penumbra radius.

Particle Energy (MeV n ⁻¹)	Maximum Delta-Ray Energy (MeV)	Range of Maximum Energy Delta Ray (μm)	Estimated Delta-Ray Cutoff Radius (μm) (Chatterjee and Holley, 1993)
10	0.0219	10.2	1.8
100	0.229	568	39
1,000	3.339	17,100	269

that the delta-ray fluence decreases rapidly with radial distance, and because the mass in cylindrical shells increases with increasing radius, the energy per mass decreases even more rapidly.

For purposes of estimating radiation chemistry reactions, another approximation describing the track as a core surrounded by a penumbra where energy is deposited by delta rays (Chatterjee and Holley, 1993) was developed. In this approximation to track structure, a cutoff radius, which is actually much less than the maximum delta-ray penetration that would be found in Monte-Carlo results, is used because the fluence of delta rays at distances greater than the cutoff is so low that it has been assumed to be insignificant. However, at very low doses, where primary-ion tracks are separated by much more than the cutoff distances assumed in this model, the small numbers of delta-ray events at larger distances may become significant for some biological processes.

Because of the large number of low-energy delta rays that are produced, targets which are close to the track core have a much higher probability of a delta-ray event, and depending on the target size and the ion charge there may be more than one delta-ray event per target. The distribution of energies deposited by individual delta rays, at any distance from the particle path, ranges from relatively low values produced when high-velocity electrons pass through a target to relatively high values when an electron stops in the target.

A different approach (Cucinotta *et al.*, 2000), using a combination of an analytical calculation of delta ray fluence and Monte-Carlo results for energy deposition in small sites, avoids use of an arbitrary cutoff of delta ray penetration, but shows that energy deposition by delta rays is extremely unlikely at large radial distances, for example, delta ray interactions in ~1 in 10⁷ nucleosomes at 1 mm from a 1,000 MeV n⁻¹ iron-ion track.

For particles of equal velocity, the energy distribution of delta rays produced is the same, and therefore the maximum penetration of the delta rays is the same, but the number of delta rays produced per micrometer of primary ion path length is proportional to the primary particle's stopping power and therefore to Z^2 .

5.2.1.1 Linear Energy Transfer and Biological Effectiveness.³ Although heavy ions have very high linear energy transfer (LET) values for short distances near the ends of their tracks, for most of the energy deposited the LET produced by GCR and SPE particles is roughly the same as the range of LET produced by particles with terrestrial origins, alpha and beta particles from radionuclides, recoil protons produced by neutrons and recoil electrons from gamma-ray

³Biological effectiveness is used in the general sense, referring to differences in effect for similar exposures, measured in any way. The term "relative biological effectiveness" (RBE) refers to one precisely defined measure of biological effectiveness (see Glossary).

irradiation, a fraction of a kiloelectron volt per micrometer to well over $100 \text{ keV } \mu\text{m}^{-1}$. However, the distribution of energy deposition in small objects such as molecules and cells, and the spatial distribution of the small objects with energy deposited, differ substantially from the distributions produced by more conventional radiations.

High-energy delta-ray production results in two differences. The delta rays produced by high-velocity particles carry part of the energy that was lost by a particle, while it was in a small site, across the site boundary and deposit it in other small sites. Consequently, the energy deposited in a small site is significantly less than the particle's stopping power times its path length in the site, and there are a large number of sites which receive energy deposition by a delta ray, even though they were not touched by the primary ion. The other main difference is due to the long range of the high-velocity heavy ions. An alpha particle with stopping power of $100 \text{ keV } \mu\text{m}^{-1}$ has enough energy to penetrate a few cells before it stops. However, an iron ion with the same stopping power has sufficient energy (on the order of $1,000 \text{ MeV n}^{-1}$) to pass through tens of thousands of cells before coming to a stop.

Equal doses of particles with equal stopping powers will result in roughly the same number of cells hit by the charged particles.⁴ The tracks of alpha particles emitted by a radionuclide will be short, producing strings of a few hit cells, and those strings will be distributed randomly through a tissue uniformly labeled with the radionuclide. In contrast the same dose will be delivered by a few GCR tracks which will produce long strings of traversed cells, surrounded by cylindrical volumes (with radius equal to the maximum delta-ray penetration) where a small fraction of the cells have been hit by a delta ray.

In tissues where cells can be reasonably represented by simple spheres, homogeneous track-based estimates (Brooks *et al.*, 2001; Cucinotta *et al.*, 1998) indicate that the number of cells hit by a delta ray, per cell hit by the primary ion, can be relatively large, on the order of 32 for $1,000 \text{ MeV n}^{-1}$ iron ions, but is still a small fraction (0.7 %) of the cells within range of the delta rays. The energy deposition events produced by delta rays are similar to those produced by low-energy x rays (Metting *et al.*, 1988) and may result in a relatively low biological effectiveness for that part of the energy deposited by delta rays. The number of delta-ray traversals of cells which are near the primary-ion track depends very strongly on the size of those cells, but at radial distances more than only a few cell diameters, the probability of two delta rays from a single primary-ion track interacting in the same cell is very low.

In tissues with complex cell shapes, such as the CNS, this simple estimate of event frequencies is not valid. In the CNS, detailed models of cell structure will have to be used with Monte-Carlo track simulation in order to determine the energy deposition distributions and frequencies. A recent such study of energy deposition by ^{56}Fe , ^{12}C , and ^1H ions in neurons of the mouse hippocampus (Alp *et al.*, 2015) shows that at 0.1 Gy of 600 MeV n^{-1} Fe ions essentially all of the soma are hit, but only 11 % of the dendrites, 0.6 % of the spines, and 0.6 % of the filopodia are hit by a primary ion or a delta ray.

Returning to the simple spherical cell model, the long string of adjacent damaged cells may result in a change in the local extracellular environment that could not be produced by the short strings of damaged cells produced by low-energy ions with the same LET. Furthermore, differences in biological processes may result in different ratios of relative biological effectiveness (RBE) in different tissues or for different biological effects. Thus, for example, the RBE for liver cancer due to iron ions may be higher than for alpha particles of the same LET but the RBE for leukemia due to iron ions may be less than that for alpha particles. There is some evidence for large differences in RBE in different tissues for HZE particles (Weil *et al.*, 2014).

⁴Actually, since the stopping power increases as the particle slows down, alpha particles will have a higher average stopping power than GCR particles that started with the same stopping power, and therefore will produce less total path length.

Tissues with complex cell structures are likely to also show effects of extracellular environment and cellular repair processes, but it is unlikely that results for tissues with simple cell geometries will be directly applicable to tissues with more complicated intercellular associations.

5.2.1.2 Biological Effectiveness and Dose Rate. For many consequences (e.g., cell death, mutation, and malignant transformation) the biological effectiveness of radiation depends strongly on the dose rate, that is, the average time between energy deposition events in the relevant target, if that time is less than a few hours or days. One way to determine the frequency of events per time is to compare the frequency mean single-event specific energy, $z = \varepsilon/m$, where ε is the mean energy imparted in a single event, to the absorbed dose, $D = d\varepsilon/dm$, the expectation value for energy deposition per mass. The number of events (energy depositions in individual cells) is $n = D/z$ and varies widely for the different GCR particles. The probability density and mean value of z depends strongly on the shape and size of the target cell, but the relationship between the number of events, the dose and z is the same, even for cells with very irregular shapes.

Assuming an absorbed dose rate of $450 \mu\text{Gy d}^{-1}$ during transit from Earth to Mars (Zeitlin *et al.*, 2013), and that about 5 % of the absorbed dose is due to GCR particles with lineal energy y (where $y = \varepsilon/d$, and d is the mean chord length of the site) of $\sim 100 \text{ keV } \mu\text{m}^{-1}$, the (average) frequency of such an event in a $8 \mu\text{m}$ spherical diameter cell nucleus is $0.7 \times 10^{-4} \text{ d}^{-1}$ (0.026 y^{-1}). If the site is larger, say $20 \mu\text{m}$ in diameter, the frequency increases to $4.9 \times 10^{-4} \text{ d}^{-1}$ but if the site is much smaller, say $0.1 \mu\text{m}$, the frequency is only $1.1 \times 10^{-8} \text{ d}^{-1}$. However, these “cell hit” events are not randomly distributed in time or space. In addition, the spatial and temporal distributions of hits are quite different from those produced by alpha particles with the same lineal energy. For cells with long extensions, such as neurons, the distribution of z is likely to be heavily weighted by small values (due to small energy depositions occurring when the ion path through the cell body is short) and the mean value is likely to be much less than for the same radiation in a tissue like liver. Again, Monte-Carlo calculations using detailed cell models will be required to determine actual interaction frequencies.

If a target is hit by an HZE particle, thousands of additional targets in line with it will also be hit at essentially the same time. A string of targets along the trajectory of the HZE particle will receive relatively large energy depositions, roughly proportional to the length of the HZE particle trajectory in the target, while a fraction of the cells within a cylinder defined by the penetration of the delta rays will receive energy-deposition events comparable to those produced by low-energy (roughly 30 kV) x rays.

The number of particle tracks per mass can be derived from the definition of absorbed dose and the particle energy. If the dose rate due to HZE particles with an average energy of $1,000 \text{ MeV n}^{-1}$ (total energy of $56,000 \text{ MeV}$) and stopping power of $100 \text{ keV } \mu\text{m}^{-1}$ was $22.5 \mu\text{Gy d}^{-1}$, the average number of HZE-particle tracks per gram of tissue per day would be 14. The situation is quite different for conventional irradiation; it would require 25,000 alpha-particle (average total energy 5.6 MeV each) tracks per gram of tissue to deliver the same dose. The mean number of GCR proton hits per day, about six for an $8 \mu\text{m}$ diameter site, is $\sim 8,000$ times higher than the number of HZE-particle hits.

If radiation-induced changes in the cellular microenvironment, or signaling between hit and unhit cells, modifies a tissue’s response to energy deposition, the distances over which those are effective, and the time that the changes persist, will influence the dose-rate effect. For example, if a specific effect can be caused only by the interaction of the products of two (or more) large energy depositions in a single cell within 24 h, the mean number of GCR events per day (0.7×10^{-4}), makes this interaction extremely unlikely. However, if damage to a cell can be influenced by damage to cells up to 1 cm away within 24 h, such an interaction is almost certain at $22.5 \mu\text{Gy d}^{-1}$.

5.2.2 Nuclear Interactions

As charged particles, such as protons, helium nuclei, and heavier ions, travel through materials, they undergo a myriad of Coulomb interactions with the orbital electrons of the atoms comprising the materials they are traversing. These Coulomb interactions slow the propagating ions and ultimately determine their ranges in the materials. Occasionally, the heavy charged particles will undergo nuclear collisions, resulting in either elastic or inelastic reactions. The inelastic cross sections for these nuclear collisions are relatively small, on the order of a few barns or less [one barn = 10^{-24} cm² (for comparison the electron ionization cross section of carbon is on the order of 20,000 barns)]. Even so, since the range of HZE particles is quite large, their nuclear collision mean free paths are often shorter than their ranges. Elastic nuclear collisions transfer energy to target nuclei and result in some loss of kinetic energy of the incident ion, whose isotopic identity, however, is not altered by the collision. Inelastic nuclear collisions, at energies relevant for space radiation protection, usually result in the fragmentation (breakup) of both the target and projectile nuclei involved in the collision.

The resulting distribution of fragment species and energies depends partly upon nuclear structure and mainly upon collision geometry. If there is complete or nearly complete overlap of the projectile and target nuclear volumes as the collision occurs, the resulting fragments will be primarily protons, neutrons, mesons, and helium nuclei. Such collisions are referred to as “central collisions.” If there is little overlap between the nuclear volumes when the collision occurs, which is more likely, the resulting collision can produce mesons and fragments having any mass number less than the parent nucleus. Such collisions are referred to as “peripheral collisions.” When initiated by a high-energy heavy ion some of the secondary fragments have lighter masses, lower atomic number (Z), and velocities comparable to that of the incident heavy ion that produced them. Since stopping power is proportional to Z^2 , their ranges will exceed the range of the heavy ion that produced them. If the interaction is initiated by a high-velocity, relatively light ion, the fragments will have lower velocities and smaller ranges. Those fragments whose kinetic energies are large may also undergo further nuclear interactions with the target medium and generate additional particles (called *tertiaries*), which in turn interact and produce more particles.

From a space radiation shielding perspective, the overall result of these collisions is to produce radiation fields within a shielded spacecraft volume and inside crew members’ bodies that are depleted of much of their heavy ion content, but are composed of larger numbers of particles of lower stopping power. However, due to the increased ranges of these lighter mass fragments, they are more penetrating and harder to shield against.

The effect of shielding is then decreased absorbed dose and generally a decrease of the biological effectiveness of the radiation, but the volume irradiated is increased due to the longer range. A few cells near the location of the fragmentation event may be traversed by two or more of the fragments produced. However, the paths of the fragments diverge and relatively few cells are directly influenced by more than one fragment.

Since the complex GCR environment consists of naturally occurring elements with kinetic energies spanning many decades, it is virtually impossible to measure such an overwhelming number of individual particle production cross sections in laboratory experiments for all spacecraft materials and human tissue constituents (Norbury *et al.*, 2012). Instead, theoretical models of nuclear collision cross sections are used to provide the input nuclear databases needed in space radiation transport and shielding codes (Adamczyk *et al.*, 2012). These models are validated and subsequently improved in accuracy by comparing their cross section predictions to experimental measurements for a variety of collision systems (projectile-target-energy combinations) relevant to space radiation protection.

6. Structure and Function of the Brain

6.1 Structure of the Brain

The central nervous system (CNS) consists of three distinct parts: the brain, spinal cord, and retina. The brain is contained inside the skull; the spinal cord is encased within the vertebral column; and the retina is formed as outwards extension from the brain and is at the back of the eye. Together, these three parts of the CNS process sensory information, control movements, regulate many aspects of physiology of the body, and enable us to react to what is going on around us and to think. For the purposes of this Commentary, which is concerned with changes in brain function during or after a space exploration mission, the remainder of this section will focus on the brain. Furthermore, the description is limited to the general characteristics which provide a basis for comparison of the physical characteristics of radiation with observed consequences. A more detailed description of the fine structure of the brain can be found in the work of Allen (2015).

There are between 10 and 20 billion (*i.e.*, $\sim 10^{10}$) neurons in the cerebral cortex portion of an adult human brain) and there are 5 to 10 times as many glial cells (Blinkov and Glezer, 1968). Although glial cells certainly contribute in important ways (Kuffler *et al.*, 1984), it is the diversity in shape, form and interconnections of the neurons that is ultimately responsible for the ability of the CNS to process all of the various sorts of information that it confronts.

The two largest areas of the brain are the cerebral cortex and the cerebellar cortex (Figure 6.1). The cerebral cortex is by far the largest subdivision of the human brain. It is involved in processing and analyzing sensory and motor information, and, most importantly for the purposes of this Commentary, cognition. The cerebral cortex is usually described as having six layers of neurons. The layers form a large plate that folds during development to form the sulci and gyri seen in Figure 6.1. The cerebellar cortex is involved in controlling coordinated motor behaviors (*e.g.*, Eccles *et al.*, 1967) and has a regular, almost rectilinear, organization, containing only five types of neurons that are found in discrete laminae (Palay and Chan-Palay, 1974). More details on the subdivisions and cell types of the brain are given in Sections 6.2 and 6.3.

6.2 Subdivisions of the Brain

The nervous system is the most complicated of all of the organs of the body. It has been estimated that >50 % of the genome is involved in nervous system development and function. The nervous system has two components, the CNS and the peripheral nervous system (PNS); they have a different embryological origin and differ in a variety of ways. During development the CNS originates from the walls of the neural tube that differentiates to form two major subdivisions: the spinal cord and the brain. The PNS originates from the neural crest and is comprised of the cranial and spinal nerves that connect the CNS to the muscles and other organs of the body and of collections of nerve cell bodies called *ganglia*, which are associated with these nerves.

The brain is frequently thought of as consisting of gray matter and white matter. Structures comprised of neuronal cell bodies and their processes are called *gray matter*. Gray matter is organized into layers, laminae or nuclei. Structures comprised exclusively of axons (Section 6.3.1) are called *white matter* because of the glistening, white appearance of the myelin (Section 6.3.2.1) sheath in fresh specimens. White matter structures also have a variety of

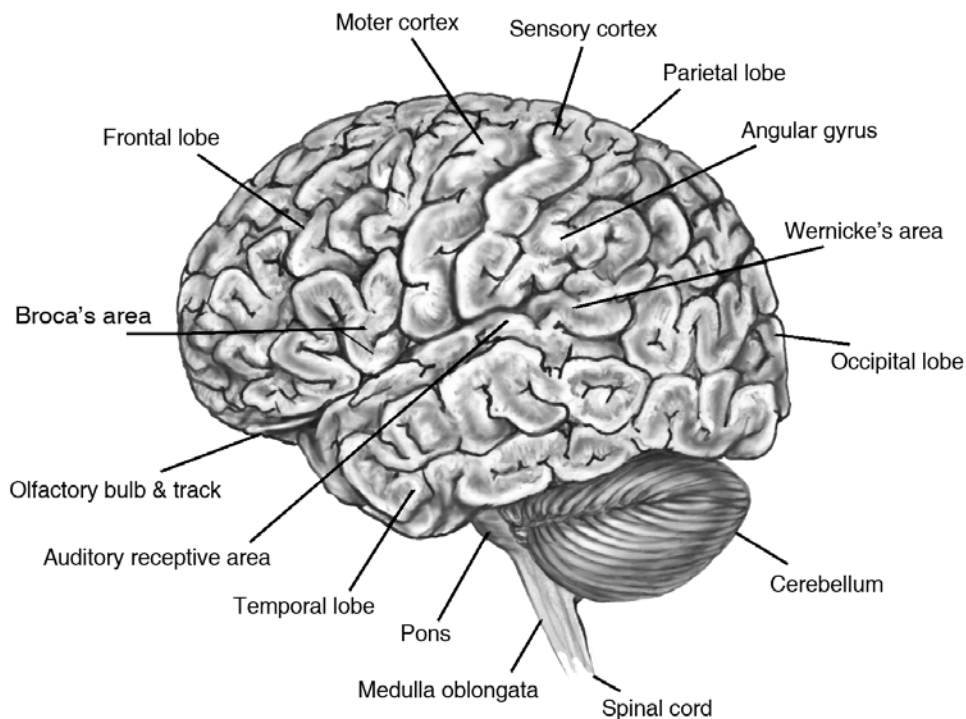


Fig. 6.1. A schematic diagram of the lateral view of the human brain, including brainstem (BIRC, 1998).

names usually related to their shape. Thus, a bundle of axons might be called a fasciculus (bundle), lemniscus (ribbon), or a column. A collection of axons traveling together in the CNS (a fascicle) may cross the midline; a commissure interconnects homologous structures on both sides of the CNS while a decussation connects nonhomologous structures on the two sides of the CNS.

Each area of the CNS has its own set of specialized functions. The major structure/function relationships of each of the major neocortical subdivisions are given in Table 6.1. The function of each area of the CNS is determined by a combination of the connections it makes with other areas of the CNS and with the periphery and its own internal organization. Localized damage can lead to quite specific functional losses. The CNS is also a bilaterally symmetrical structure. While functional differences and some anatomical differences between right and left sides exist, all anatomical features are present on both sides. Functional asymmetry is most obvious in the cerebral cortex. In most people speech and language processing is found on the left side of the brain; other cognitive functions such as music, map reading, and facial recognition are also distributed asymmetrically with one side or the other taking a dominant role in the function. The main significance of the asymmetrical distribution of functions is that damage to one side of the brain can produce functional deficits that similar damage to the other side does not produce.

6.3 Cell Types and Cellular Organization of the Brain

The brain is generally considered to be a static organ (*i.e.*, there is little cell proliferation except in a few specialized areas and in response to an injury). In particular, the neurons of the bulk of the brain are all made during the developmental period (*i.e.*, by the end of the first few months of postnatal life) and no new neurons are made even in response to an injury (Nowakowski, 2006). An exception to this is the hippocampus, which shows significant

TABLE 6.1—*Major lobules and functional areas of the cerebral cortex.*

Lobe	Lobule or Gyrus	Cortical Area	Function
Frontal lobe	Precentral gyrus	Area 4	Primary motor area
	Inferior frontal gyrus	Prefrontal (premotor) area	Language execution (Broca's speech area, in dominant hemisphere)
	Superior frontal gyrus, medial aspect	Supplementary motor area	Complex, patterned movements
	Middle frontal gyrus	Frontal eye fields	Voluntary, conjugate eye movements
Parietal lobe	Superior parietal lobule	Areas 5 and 7	Spatial orientation
	Inferior parietal lobule	Supramarginal and angular gyri	Sensory association area, multisensory perception, recognition of spatial relationships, language (<i>e.g.</i> , naming), mathematic calculation
	Postcentral gyrus	Areas 3, 1 and 2	Primary somatosensory area
Temporal lobe	Superior temporal gyrus, upper bank	Transverse gyri of Heschl	Primary auditory area
	Superior temporal gyrus, posterior region	Wernicke's speech area (in dominant hemisphere)	Language comprehension
	Parahippocampal gyrus, uncus	Limbic lobe	Learning and memory, primary olfactory area
Occipital lobe	Portions of the cuneus (upper) and lingual gyrus (lower) of occipital lobe	Upper and lower banks of calcarine fissure	Primary visual area

deficits in neurogenesis following damage by HZE irradiation (Rivera *et al.*, 2013). Glial cells (Section 6.3.2) can and do proliferate in response to injury and in response to changes in the brain. Tumors in the adult brain involving neurons are unknown, and CNS tumors are derived from glial cells or glial cell precursors. Most notably, the brain does not repair itself after an injury the same way that damage to the liver or skin or many other organs is repaired. The damaged neurons are generally not replaced and the functions that they participate in can be restored only by reprogramming other neurons. Reprogramming is often not possible and the functional losses that result are permanent. This means that emphasis, for everyday life as well as during space flight, needs to be placed on prevention of damage to the brain.

6.3.1 Neurons

The neuron is the key functional unit of the nervous system. All information processing within the nervous system is carried out by neurons organized into systems and pathways of varying complexity. There is considerable diversity among neurons with respect to size, shape, location, and neurotransmitter, yet all neurons share certain essential features.

A typical neuron in the vertebrate CNS (Figure 6.2) has three major parts: (1) the soma or cell body, (2) a dendritic tree, and (3) an axon. The function of a neuron is to receive and transmit information from and to the periphery and other neurons. The soma and dendritic tree comprise the receptive area, where signals are received and integrated, and the axon is the transmission area which sends the message on. The soma of a neuron consists of the nucleus, with prominent nucleolus, and its surrounding cytoplasm, which contains a substantial portion of the biosynthetic machinery of the neuron. Most protein and other macromolecular synthesis occurs in the soma, which has abundant rough endoplasmic reticulum and Golgi apparatus. In the adult mammalian CNS the size of the soma ranges from ~3 to 150 μm in diameter; its shape may vary from fusiform to round to ovate to pyramidal.

The dendritic tree consists of one or more rather large diameter processes that exit from any portion of the neuronal soma and branch at acute angles within the immediate surroundings of the neuron. Each dendrite usually branches several times and is frequently covered with small protuberances called *spines*. Both the spines and the shafts of the dendrites receive synaptic input from axons (and occasionally dendrites) of other neurons.

The axon is a narrow (1 to 20 μm) cylindrical process that exits from the soma (or, less frequently, from a dendrite, close to the soma). It can extend for long distances, often without branching or with some fine caliber branches at right angles to the shaft; usually it branches profusely as it terminates. Along its length, but particularly in its terminal arbor, the axon has swellings or boutons that mark the location of synapses, which are the structures by which the neuron transfers its message to the next neurons in the chain or to muscle. Depending on its function, the axon of a single neuron may form synapses with as few as one other neuron or as many as several thousand other neurons.

Primary afferent neurons of the spinal and cranial ganglia and of the special sense organs differ slightly from this generalized model. With two exceptions (neurons of the mesencephalic nucleus of the trigeminal nerve and the retina) these neurons have their cell bodies in the PNS and extend a peripheral process to innervate a sensory receptor and a central process which enters the CNS and synapses on another neuron. Sensory ganglion cells are pseudounipolar neurons with a round soma connected by a short T-shape connection to a single process which extends from a peripheral receptor to a central neuron. Bipolar neurons of the retina,

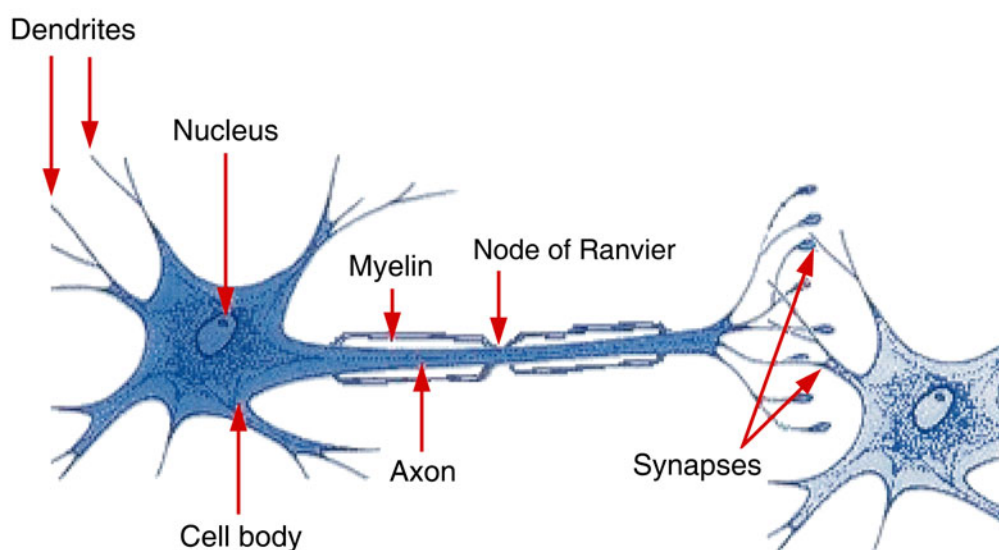


Fig. 6.2. Components of a typical neuron (BR, 2006).

inner ear, and olfactory epithelium extend a peripheral process from one side of the soma to innervate a receptor and a centrally directed process from the opposite side of the soma to synapse on another neuron.

In both the CNS and PNS many axons are invested with a myelin sheath which helps to increase the conduction velocity of the axon. The myelin sheath is comprised of concentric layers (lamellae) of glial cell membrane from which the cytoplasm has been excluded. The myelin sheath begins distal to the axon initial segment, a transient narrowing of the axon cylinder just distal to the axon hillock (the point at which the axon leaves the soma), and extends along the entire length of the axon. The myelin sheath consists of short segments called *internodes*, each supplied by a single glial cell. The short, unmyelinated areas between the myelin segments are known as nodes of Ranvier. The concentration of Na⁺ channels in the axon membrane (axolemma) is much higher in the nodal regions than in the internodal membrane. This concentration of ion channels together with the insulating property of the myelin sheath is believed to be the underlying basis of saltatory conduction whereby the electrical signal (action potential) “jumps” from node to node of myelinated axons many times more quickly than it could be propagated through the axolemma of a similar, unmyelinated axon.

It is the myelin that makes white matter white because of the high content of lipid from the membranes. Thus, white matter and gray matter differ in water content and density. This simple fact may be important for the localization of damage in the brain from radiation exposure.

Throughout the nervous system, neurons are kept separate from one another by intervening glial cells. Unmyelinated axons are, therefore, cradled within folds of glial cell membrane. Several unmyelinated axons can be surrounded by a single Schwann cell in the PNS or astrocyte in the CNS.

In each region of the brain, neurons have specialized shapes and forms that allow them to carry out the specific functions of that region of the nervous system. Variations in the morphology of the soma, axon and dendrites are all used to classify neurons (Allen, 2015).

Neurons are categorized as either projection neurons (or relay neurons) or intrinsic neurons (or interneurons, internuncial neurons) depending on whether they synapse primarily on other neurons in other CNS structures or within the same structure. Projection neurons include the long axon neurons which contribute to the major ascending and descending sensory and motor pathways. In addition they include association neurons (such as commissural neurons) which interconnect structures closely related in position and function (*e.g.*, cortical regions). Intrinsic neurons synapse only on neurons within their own nervous system structure. Because they function to process information in a small functional area they are also referred to as local circuit neurons.

6.3.1.1 Synaptic Structure and Function. The synapse is the structure by which one neuron passes its message to another neuron (or muscle or gland). Thus, these are small but significant structures. Each neuron in the brain can have as many as 10,000 synapses on its surface. However, there are two basic kinds of synapses: chemical and electrical. In the vertebrate nervous system the overwhelming majority of synapses are chemical synapses which have a complicated structure and considerable diversity. Electrical synapses are indistinguishable from gap junctions.

Synaptic junctions generally are quite restricted in size, typically being characterized by a dimension of contact 1 μm or less. Each chemical synapse has a presynaptic component, which usually arises from an axon (or less commonly from a dendrite) and a postsynaptic component, which is usually a dendrite or dendritic spine but which may be a soma or another axon. The space separating these two structures is the synaptic cleft. The direction of information transfer is from presynaptic to postsynaptic.