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Minireview

Positive visual phenomena in space: A scientific case and a safety issue in space travel

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Abstract

Most astronauts on Apollo, Skylab, and MIR reported 'flashes of light' occurring in different shapes and apparently moving across the visual field, in the absence of auditory, somatosensory, or olfactory abnormal percepts. A temporal correlation with heavy nuclei or protons has been documented in space and comparable phosphenes were observed by volunteers whose eyes were exposed to accelerated heavy ions at intensities below the threshold for Cerenkov visible radiation. An interaction between heavy ions and the retina was suggested. However, the biophysics of heavy ions or protons action remains undefined, the effects on photoreceptors and neuroretina have not been differentiated, and some direct action on the visual cortex never ruled out. Phosphenes are common in migraine and are known to occur also in response to the electrical stimulation of ganglion cells (in retinas without photoreceptors), optic pathways or visual cortex, with mechanisms that bypass the chemically gated channels. Intrinsic photosensitive ganglion cells exist in the retina of teleost fish and mammals. In the hypothesis of a peculiar sensitivity to subatomic particles of the visual system, phosphenes due to the activation of processes by-passing the photoreceptors would raise questions about human safety in space. The issue is particularly relevant with experiments of increasing duration being now operative in the International Space Station (ISS) and with plans of space travel outside the geomagnetic shield. Research is in progress both in the ISS and on animal models, in the framework of the NASA/ESA actions to improve the astronauts' health in space.

Keywords: Phosphenes; Space travel; Vision; Retina; Astronauts' safety; Heavy ions, protons

1. Positive visual phenomena in space

Beginning with the report by astronaut E.E. Aldrin onboard Apollo 11 to the Moon (1969), crew members on Apollo, Skylab, and MIR missions observed white '*flashes of light*' occurring in different shapes and apparently moving across the visual field or toward the observer. These percepts, that C.C. Tobias had already predicted in the early 1950s for high altitude flights (Tobias, 1952), appear to have been quite common during translunar coast, in lunar orbit, on the lunar surface, and during transearth coast, according to early NASA reports. Over 80% of astronauts serving in today's NASA or ESA (European Space Agency) programs have perceived phosphenes at least in some missions and often over several orbits, according to a recent survey by questionnaire (Fuglesang, Narici, Picozza, & Sannita, 2004). The shapes most frequently reported were "*flash or flashes*, *stripe(s)* or *strike(s)*, *spot(s)*, *supernova*" or the like (Fig. 1). When detected, motion was mainly from the periphery of visual field toward the fixation point; colors (e.g., yellowish, pale green, or blue) were exceptional. Apart from individual differences, phosphenes occurred at average rates that varied depending on the spacecraft shielding, orbital height, and latitude and were correlated to the known flux of cosmic radiation (frequency was up to

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25 times higher near the magnetic poles than in equatorial latitudes and maximum (1.3 ± 0.1/min) outside the geomagnetic shield; the higher frequency of phosphenes when traveling to, than on the way back from the Moon has never been explained (Avdeev et al., 2002; Budinger, Bichsel, & Tobias, 1971; Budinger et al., 1977; Pinsky, Osborne, Bailey, Benson, & Thompson, 1974; Pinsky, Osborne, Hoffman, & Bailey, 1975; see for reference: Horneck, 1992)). A temporal correlation between phosphenes and particles flux (as detected by silicon telescopes also providing information about the particle trajectory and charge) was confirmed in dedicated observation sessions on the MIR station, with indication that heavy nuclei and protons may activate complementary generating mechanisms (Avdeev et al., 2002; Bidoli et al., 2000, 2001; Casolino et al., 2003) (Figs. 2 and 3). The lack of reported auditory, somatosensory or olfactory abnormal percepts either concomitant or unrelated to the *light flashes* (Fuglesang et al., 2004) suggests a peculiar, albeit not necessarily unique, sensitivity of the visual system to particles or microgravity. In general, the suggested explanation for *light flashes* was in terms of interaction between cosmic ray particles and the eye. Visible light due to Cerenkov radiation emitted in the cornea, lens or vitreous,[1] isomerization of rhodopsin molecules, or electric excitation of the retina were the proposed causes of phosphenes.

2. Experimental studies in particle accelerators

Positive visual phenomena comparable to those described by astronauts were reproduced in experiments carried on in the early 1970s to characterize phosphenes based on the particles physical properties. Under controlled conditions in particle accelerators, the eyes of healthy volunteers (usually the scientists themselves) were exposed to single particles or particle bursts in the hundred MeV energy domain (relativistic muons, pions, neutrons, nonrelativistic helium, nitrogen, carbon ions, etc.). The accelerator beam was collimated and each subject maintained the alignment of his eye to the emerging beam by biting into his personal dental impression plate. Minimally ionizing particles emitting Cerenkov radiation produced visible light and the volunteers reported large phosphenes as expected. However, discrete *light flashes* were observed also upon passage through the posterior portions of the eye of highly ionizing particles (e.g., HZE nuclei) at energies *below* those producing Cerenkov visible light and with negligible fluorescence; no visual perception was reported when the ion beam was passed through the anterior eye. Phosphenes were reportedly short, without after-image, with approximate correlation between the irradiated retina and the portion of visual field in which phosphenes were subjectively located. Motion in the same direction of the beam was often reported: this percept is conceivably due to psychophysical events unrelated to the exceedingly high particle speed through the eye and still needs to be investigated (Budinger, Lyman, & Tobias, 1972; Charman, Dennis, Fazio, & Jelley, 1971; Charman & Rowlands, 1971; McAulay, 1971; McNulty, Pease, & Bond, 1975, 1976; McNulty & Pease, 1978; McNulty et al., 1972; Tobias, Budinger, & Lyman, 1971). The estimated efficiency for the perception of phosphenes following exposure to accelerated nitrogen nuclei below Cerenkov threshold varied between 10 and 40%, with differences among subjects and studies possibly accounted for by the experimental conditions, number of particles, etc. (Budinger et al., 1972; McNulty et al., 1972). The early human observations were in part replicated on anaesthetized adult mice exposed to bursts of ^{12}C ions at energies below Cerenkov threshold (unpublished personal data).

3. Phosphenes and radiation

Cerenkov radiation was observed in accelerator experiments with numbers of particles compatible with the estimated threshold sensitivity to photons of the retina (McNulty et al., 1975). Models of non-Cerenkov phosphenes estimated a threshold number of ionizations per sensitive volume that was understood to suggest some effect of particles on the rod outer segment or photochemical molecules (McNulty, 1996). The evidence suggesting some direct or indirect action of ionizing particles on the retina (photoreceptors) appears compelling. It is neither conclusive nor exclusive, though. The biophysics of particles action and the visual structures/functions eventually involved in the generation of phosphenes remain undefined. Volunteers in accelerator experiments noted brighter phosphenes after dark adaptation (Budinger et al., 1972) and about 70% of astronauts observed phosphenes before going to sleep, in a "dark" environment. Twelve astronauts reportedly could not fall asleep and one astronaut occasionally woke up *because of light flashes* (Fuglesang et al., 2004). However, no inference about the retinal adaptation or sensitivity to light required to perceive phosphenes is possible based on these reports. In fact, about one-fifth of astronauts observed *light flashes* also in dim light and two with bright illumination; one astronaut perceived phosphenes regardless of light and light adaptation

[1] Cerenkov radiation (first described by Pavel Cerenkov in 1934) is emitted by charged particles traveling through a medium at speed higher than the light in the same medium. The light speed throughout any transparent material (such as glass or air) is slightly retarded, while that of high energy subatomic particles (such as the cosmic rays) is not. Fast particles moving e.g., through water polarize the water molecules thus causing distortions in the electrical charge; the molecules tend to revert to their previous orientation and in this process emit pulses of coherent electromagnetic radiation in the form of faint glowing bluish light (of the kind observed in the core of nuclear reactors) known as Cerenkov radiation. Quite several astronomical events can result in the production of Cerenkov radiation and the atmosphere is the largest available medium in which it can occur. It was first suggested that astronauts could perceive in the form of *light flashes* the Cerenkov radiation originating in the cornea, lens or vitreous. This mechanism would better explain the observations of bluish *light flashes* and was documented in volunteers exposed to accelerated particles. In these experiments, however, phosphenes were perceived also at particle intensities too low to generate Cerenkov radiation in the eye media.

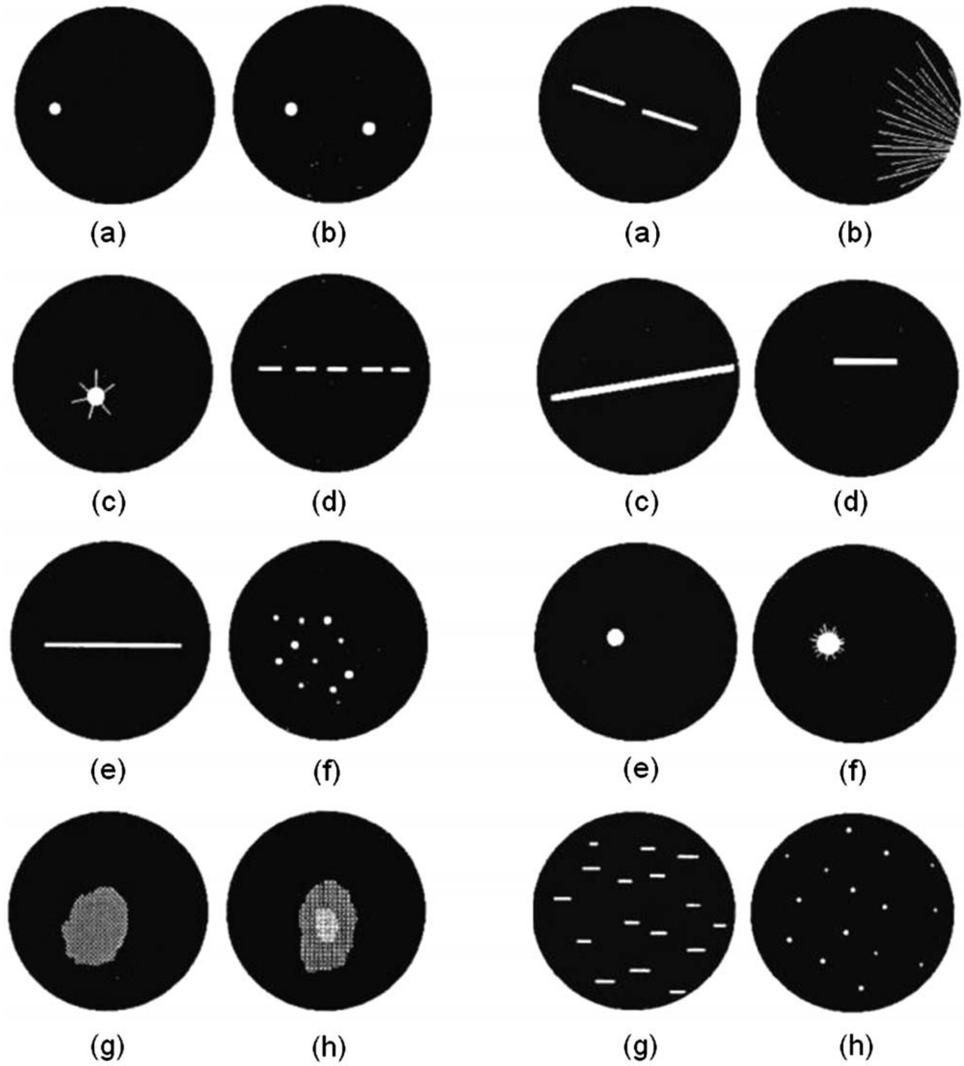

Fig. 1. (Left two columns): Schematic drawings of *light flashes* observed by astronauts on Apollo and Skylab missions; astronauts referred to these different shapes as *star* and *double-star* (a and b), *supernova* (c), *streaks* (d and e), *sky of stars* (f), *clouds* (g and h). (Right two columns): Light flashes described by cosmonauts onboard the MIR space station and during the IL.62 M and TU-144 space missions (from Akatov et al., 1996).

(Fuglesang et al., 2004). It should be noted that illumination is quite constant in space stations, with only dimmer light allowed where astronauts sleep. Moreover, some self-training was reportedly necessary for the astronauts to learn *how* to focus on, and perceive phosphenes in the space station (Fuglesang et al., 2004). Both retinal adaptation to dim light and the lack of operations to attend to may have favored the perception of phosphenes before sleep.

In principle, ionizing particles at intensities too low to produce Cerenkov light can induce phosphenes by activating the same retinal physiological processes and biochemical cascade that mediate in early vision (see Rodieck, 1998, for a review). However, any interpretation of the effects of ionizing particles at non-Cerenkov energies on the ground of the mechanisms generating retinal responses to light should be cautious. Several events may follow upon the impact of particles on living tissues—with a direct ionization due to energy released by crossing heavy nuclei and/or with indirect effects in a knock-on process involving protons, neutrons, etc., and the tissue nuclei. Interaction among particles is also possible. The reported differences among the effects of distinct ions suggest complex and occasionally peculiar modalities of interaction with living tissues even at potentially damaging linear energy transfer (Krebs, Krebs, Merriam, & Worgul, 1988). For instance, electrode microscope scanning of the mudpuppy *Necturus maculosus* showed morphological retinal alterations after exposure to accelerated neon, but not after fast helium ions at radiation levels at least five times higher (Malachowski, Tobias, & Leith, 1977). Studies using oxygen nuclei radiation in vivo (*Macaca mulatta*) and iron particles in retinal explants indicate a low rad equivalent dose for ganglion cell impairment as compared to e.g., X-ray. In contrast, ultrastructural retinal changes were not detected and the spatial cellular densities of pigment epithelial and photoreceptor cells were within the normal range at 24 h and 6 months after irradiation with accelerated argon (Bonney, Beckman, & Hunter, 1974; Vazquez & Kirk, 2000).

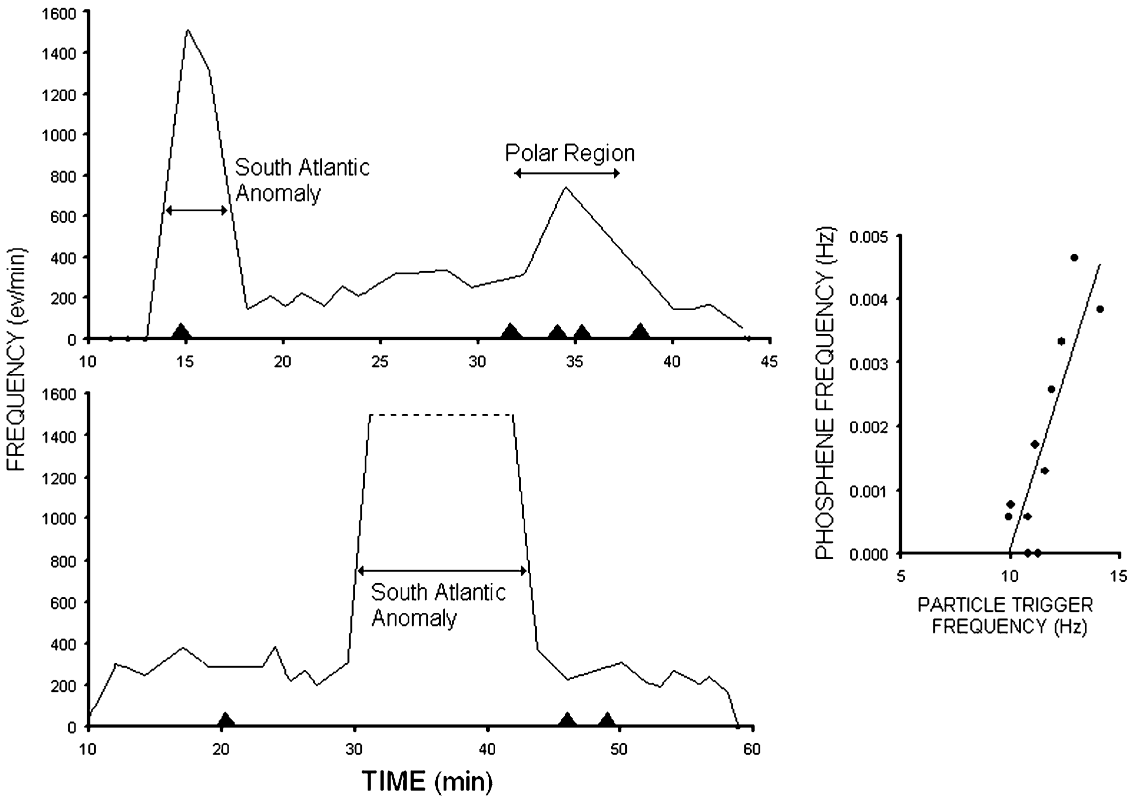

Fig. 2. Incidence of phosphenes in space. SilEye experiment performed in the MIR station. (Left) Two out of 25 observation sessions in different days: reported phosphenes (triangles on abscissas) and flux over time (averaged values over 60 s intervals) of cosmic particles at the astronaut's eye (dotted lines). Cosmic particles are more frequent near the magnetic poles and the occurrence of phosphenes appeared to follow the particle flux. Most of the flux in the South Atlantic Anomaly (SAA) is composed of low energy protons, that may interact with the visual system with modalities differing from high energy particles (such as those at polar regions) (see Fig. 3). (Right) Correlation between particles and phosphenes outside the SAA; averages on eleven 90-min orbits (three astronauts). Particles were detected by advanced silicon telescopes. Note that protons inside the SAA exceeded the maximum acquisition rate of detectors, with saturation above 25 Hz or 1500 ev/min (bottom left). Reprinted from *Adv. Space Res.*, Vol. 25, V. Bidoli et al., Study of cosmic rays and light flashes onboard space station MIR: the SilEye experiment, pp. 2075–2079, 2000, with permission from Elsevier.

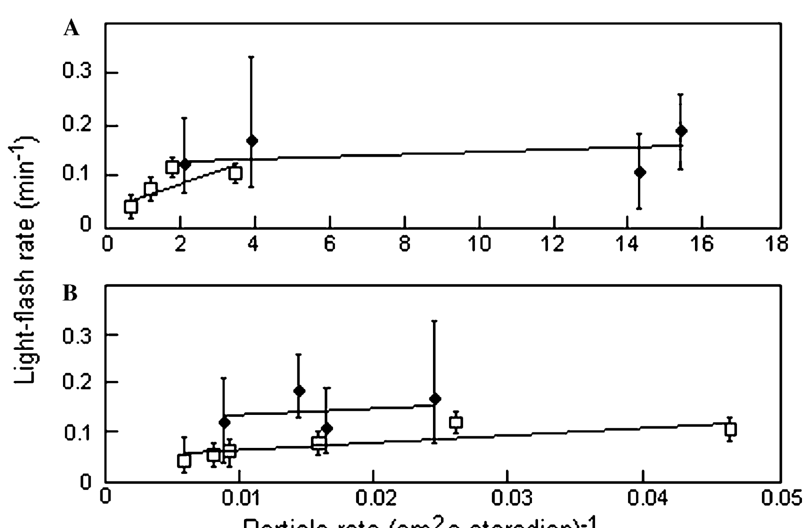

Fig. 3. Incidence of phosphenes in space (SilEye experiment). Rate of occurrence of phosphenes versus the rate of protons (A) and of particle with linear energy transfer >20 keV μm^{-1} (B). Circles and squares represent measurements inside and outside the SAA, respectively. Two different mechanisms are needed to model these data, namely heavy nuclei interacting directly through ionization or direct excitation of the retina, and proton-induced knock on particles in the eye. Reprinted by permission from Macmillan Publishers Ltd: *Nature*, Vol. 422, Casolino et al., Space travel: dual origins of light flashes seen in space, p. 680, copyright 2003.

4. General mechanisms of phosphenes

The general mechanisms of phosphenes are poorly understood (Delbeke, Oozeer, & Veraart, 2003; Normann, Maynard, Rousche, & Warren, 1999). The possibility that heavy ion interaction with the photoreceptors or the neuroretina may result in substantially different mechanisms of activation of the visual system has not been explored yet (Vazquez & Kirk, 2000). Neurons of the retina and cortex are sensitive to ionizing agents, to which can respond with transient functional changes. Phosphenes and changes in retinal sensitivity have been observed after exposure to low doses of X-rays (Doly, Isabelle, Vincent, Gaillard, & Meyniel, 1980a, 1980b; Lipetz, 1955a, 1955b; Tobias et al., 1971). Phosphenes can occur following electrical stimulation of the retina, optic nerve or visual cortex, and systematic studies on their size, luminosity and position in visual space are instrumental in the development of prostheses for the blind (Margalit et al., 2002; Zrenner, 2002). In early studies, electrical stimulation of discrete points of the human visual cortex produced corresponding punctuated sensation of light in both sighted and blind subjects (Dobelle & Mladejovsky, 1974; Dobelle, Mladejovsky, & Girvin, 1974). Subretinal micro-photodiodes or epiretinal electrodes stimulating the bipolar and ganglion cells, self-seizing spiral cuff electrodes around the optic nerve, and cortical (surface or intracortical) stimulation devices have been tested thus far. Some correlation between phosphenes and the stimulus intensity and location in the visual field has been reported with all prostheses. The spatial resolution of cortical activation by electrical subretinal stimulation has been estimated to be as high as $\sim 1°$ based on multi-electrode cortical recordings from the cat. Cortical electrophysiological responses to the retina or optic nerve electric stimulation have been recorded in animals and man (Chow et al., 2004; Delbeke et al., 2001, 2003; Dobelle, 1994, 2000; Eckhorn et al., 2001; Fang et al., 2005; Schwahn et al., 2001; Veraart, Wanet-Defalque, Gerard, Vanlierde, & Delbeke, 2003; Weiland, Liu, & Humayun, 2004; Zrenner, 2002).

The electric stimulation of the retina or visual cortex is thought to evoke phosphenes by opening voltage-sensitive ion channels and by-passing the chemically gated channels in the stimulated cell (Margalit et al., 2002). This condition may not be unique. Reportedly, patients with ocular pathology did not perceive phosphenes during proton therapy at 60 MeV (with intensity of 10^8–10^9 particles s^{-1} cm^{-2}) (G. Cuttone, personal communication). However, patients undergoing ^{12}C ion therapy of skull tumors also involving the anterior optic pathways (e.g., chondromas, chondrosarcoma, malignant schwannoma, atypical meningeoma of the clivus) at the Gesellschaft für Schwerionenforschung facilities in Darmstadt (FRG) reported clearly visible *light flashes* during irradiation at 200–250 MeV (with intensity of about 10^8 particles s^{-1} cm^{-2}). Phosphenes were similar in shape to those described by astronauts and volunteers in accelerator experiments (e.g., showers of light or streaks traversing the visual field like shooting stars over a preferential direction). Treatment doses were delivered point-by-point by moving a narrow beam over the tumor target volume and phosphenes were correlated with the instantaneous beam position and corresponding local dose deposited near the optic pathways or the eye (Schardt & Krämer, 2003). Further research is in progress in the attempt to locate the origin of phosphenes by electrophysiological techniques.

Electrophysiological studies on patients with retinitis pigmentosa and mutant mice have documented activation of visual cortex in response to light also after substantial damage of photoreceptors (Claes et al., 2004; Kanda et al., 2004; Ren, LaVail, & Peachey, 2000; Strettoi, Porciatti, Falsino, Pignatelli, & Rossi, 2002). Studies on rodents lacking rod and cone photoreceptors and teleost fish have identified subsets of intrinsically photosensitive retinal ganglion cells. The function of these cells appears to be limited to e.g., the photoentrainment of the circadian clock and pupil light reflex, with no transfer of light information able to produce images. In primates, however, these cells project to the LGN and seem to merge with the retinal pathways to cortex that transfer visual information to be processed into visual images (Dacey et al., 2005; Foster et al., 2003; Van Gelder, 2005); some role of these cells in the generation of phosphenes is therefore possible in principle.

5. Phosphenes and human safety in space

The evidence that phosphenes can originate from direct stimulation of neurons in the retina, optic nerve, or cortex raises questions that directly relate to the visual positive phenomena (*light flashes*) observed in space. In this regard, the phosphenes described by astronauts could be compared to those experienced by the totally blind and by sighted subjects with migraine or epileptic seizures originating in visual cortex. Migraneurs experiencing phosphenes or photopsia report that these phenomena interfere with reading and driving and, ultimately, with normal visual function (see Celesia, 2005, for a review). The issue does not appear to have been addressed by astronauts. Further to this, the extent to which the perception of phosphenes in space only depends on the high energy deposited by HZE particles virtually absent on Earth surface remains undefined. Functional brain adaptation to microgravity could affect sensitivity as well and may account for some enhanced response of the visual system to particles (or other factors) otherwise ineffective at ground level. Effects on other higher brain functions (such as cognitive processes related or unrelated to vision) would also be possible, at additional astronauts' risk. Experiments of increasing duration and complexity are in progress or scheduled onboard the International Space Station (ISS). Long travels outside the shielding magnetosphere are also being considered, with the Moon and Mars as next plausible targets. Extensive programs to make the astronauts' life and health safer in space are operative under control by NASA and ESA (European Space Agency) (see the NASA and ESA official websites). Health risks due to microgravity and cosmic radiation should nevertheless be expected to increase (Townsend, Cucinotta, & Wilson, 1992). It should be noted that the available methods to project risks from low-earth orbits to exploration missions suffer from limited radiobiology data and knowledge of galactic heavy ions, which may cause estimates of the risk of late effects to be highly uncertain (Cucinotta et al., 2004). Research is therefore also due to focus on the hazard potentially posed by the enhanced or distorted (albeit transient) stimulation by heavy ions of photoreceptors, photopigments, and/or neurons in the retina or elsewhere in the visual system. In this framework, phosphenes can be regarded as possible indicators of abnormal activation of visual mechanisms and—at large—of brain dysfunction that would be potentially critical in conditions where efficiency and reliability of sensory information processing is mandatory. The issue needs to be explored in greater detail also for possible countermeasures to be implemented (e.g., selective spacecraft shielding). Further studies are in progress to document the electrophysiological concomitants of the *light flashes* observed by astronauts onboard the ISS and to investigate the biophysics of particles interaction with the retina (photoreceptors membrane, photopigments, or inner neurons), optic nerve and cortex in animal models and humans[2].

[2] The ALTEA research project investigates the effects of particles on the visual function in space. A facility of the International Space Station (ISS) to be made available to the international scientific community (for human electrophysiological and psychophysics experiments, studies on particle flux, and dosimetry), ALTEA combines a multi-channel electrophysiological recording system, a computer-assisted visual stimulator, and a whole-head large solid angle silicon detector identifying particles charges, trajectories, and transferred energy at discrete locations in the eye and brain. Experiments are scheduled to: 1. test visual functions by sequences of stimulus conditions; 2. collect and store for offline analyses the characteristics of particles and the changes in retinal and brain electrophysiology occurring spontaneously or in concomitance with phosphenes; 3. allow functional recording of brain signals under stimulus conditions and operational tasks involving a wide range of visual and cognitive processes in dedicated sessions; 4. measure the particle flux inside the ISS, with nuclear discrimination. ALTEA is supported by the Italian Space Agency (ASI), the Italian National Institute for Nuclear Physics (INFN) and participating universities. The facility, engineered by Laben (Milan, Italy), is scheduled to be transferred on the ISS in the Spring–Summer 2006. Experiments are tentatively scheduled for the Fall–Winter 2006. Parallel sub-projects are investigating the electrophysiological concomitants of heavy ion therapies in patients and the effect of heavy ions on the retina and visual cortex of normal and transgenic mice. Work is in progress in the accelerator facilities of the Brookhaven National Laboratory (Upton, NY, USA) and Gesellschaft für Schwerionenforshung mbH/Biophysik (Darmstadt, FRG), with ions control and electrophysiological signal recording procedures comparable to those set for human studies in the ISS. The accelerator beam is set to control the location and intensity of particle impact on the retina and sensitive brain structures. Measures of transient electrophysiological change as a function of the particle type and released energy and threshold estimates will allow extrapolation for the space study. Transgenic mice with retinal receptors degeneration are compared to normal animals to tentatively attribute the particle effect to retinal receptors or neuronal structures. Research on the biophysics and biochemistry of the heavy ion action on neuronal and photoreceptor structures (including rhodopsin and messengers) of the retina and cortex is in progress (see Narici et al., 2003; Sannita et al., 2004 for detailed information).

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