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REHABILITATION IN MICROGRAVITY: A NEUROPHYSIOLOGICAL APPROACH

Author: Dr. Irene Lia Schlacht
Design Department, Politecnico di Milano, Italy, irene.schlacht@mail.polimi.it

Prof. Luisa Pizzigalli
Department of Medical Sciences, NeuroMuscular Function Research Group, S.U.I.S.M. - Turin University, Italy
luisa.pizzigalli@unito.it

Prof. Marco Ivaldi
Department of Medical Sciences, NeuroMuscular Function Research Group, S.U.I.S.M. - Turin University, Italy
marco.ivaldi@unito.it

Prof. Melchiorre Masali
Università degli Studi di Torino, Italy, melchiorre.masali@gmail.com

Prof. Bernard Foing
ESA/ESTEC, The Netherlands, bernard.foing@esa.int

Prof. Gennaro Boccia
Department of Medical Sciences, NeuroMuscular Function Research Group, S.U.I.S.M. - Turin University, Italy
gennaro.boccia@unito.it

Dr. Giovanni Cugliari
Department of Medical Sciences, NeuroMuscular Function Research Group, S.U.I.S.M. - Turin University, Italy
gianni.cugliari@icloud.com

Dr. Deborah Gualini
S.U.I.S.M. - Turin University, Italy deborah.gualini@yahoo.it

Dr. Mario Benassai
Altec S.p.A., Italy, mario.benassai@altecspace.it

Mrs. Tanja Lehmann
Mars Society Germany, Verein zur Foerderung der Raumfahrt, Germany, zero_g@gmx.de

Prof. Margherita Micheletti Cremasco
Università degli Studi di Torino, Italy, margherita.micheletti@unito.it

ABSTRACT

Considering that in microgravity, demineralization (calcium loss in particular) occurs with an average of 1-2 % every 30 days, astronauts on a trip to Mars could easily experience osteoporosis and break bones without the possibility of re-entry for physical rehabilitation. Starting with the research done since 2006 by the Microgymn group, this paper present investigations from the field of neurophysiologic applications for physical rehabilitation during long-duration Space travel in microgravity. Experiments in comparative states such as parabolic flight, Earth gravity, and neutral buoyancy are planned to test the exercises for physical rehabilitation. A strong degree of innovation is applied and a new approach is proposed that applies rehabilitation using comfortable, easy-to-use, and non-intrusive equipment based mostly on rehabilitative isometric exercise, without the use of machines. Specific checks are being developed to emphasize changes in the recognition of afferences by the sensory and motor cortex, also using quantitative EEG. Movement capacity is also being investigated. The findings will permit creating rehabilitation protocols that will be helpful for astronauts working in zero gravity conditions.

I. BACKGROUND

Humans are the product of biological and cultural adaptation to our planet achieved in the process of human evolution. Terrestrial models may be hard to transfer to extremely long Space missions in which peculiar environmental conditions may affect locomotion, working capabilities, living conditions, and, particularly, well-being. Spaceflight is a new experience for humans. Manned Space exploration exposes travelers to a variety of gravitational stresses (Stein, 2013). During long-duration spaceflight, the human body is subjected to many risks, including the microgravity-induced risks of muscle atrophy and bone loss (Ohshima, 2010). During this period of physical
deconditioning (decrease in muscular strength and in general physical performances), injuries may occur more frequently and may jeopardize spaceflight mission (Viegas, et al., 2004).

II. PROBLEM

Microgravity causes alterations in the physiological processes and astronauts must understand, anticipate, and deal with these adaptations. It is fundamental to know how these changes are integrated within and expressed throughout the body, so that appropriate clinical decisions can be made. For example, if an astronaut involved in a long journey were to be injured during the mission and require immediate medical attention, not only surgery but also appropriate rehabilitation protocols would be needed, as any return to Earth for physical rehabilitation sessions would be impossible.

II.a The effects of microgravity on the bone structure

Life on Earth has evolved under the influence of gravity, which acts on the physiological systems of every living being. Any gesture made on our planet, like walking, running, or simply standing still, takes place in a gravitational field, which is characterized by a force of attraction toward the center of the planet: the strength-weight. Such a condition can vary depending on the type of gravity to which the mass is subjected, and it can even change in the absence of gravity, or rather in microgravity.

Indeed, the absence of gravity is the condition in which no kind of force is acting; however, during spaceflights, there is always a little residual acceleration, in the order of 0.001g. For this reason, the use of the term "microgravity" is preferred.

The 1960s marked the beginning of the first human spaceflight missions, but even before this period, the question was how humans could survive in microgravity while staying healthy.

Since then, numerous studies have been conducted concerning the physiological changes experienced by humans or living beings in general (Smith et al., 2014).

Many scientists and researchers have been interested in microgravitational effects on the cardiovascular, respiratory, neurovestibular, and musculoskeletal systems of astronauts and cosmonauts. In particular, this paragraph describes the changes that take place at the level of the human skeleton.

The skeleton plays an essential role in humans: it is a dynamic system, able to adapt to many mechanical stimuli (loads). These adjustments are made possible by bone turnover, marked by continuous bone production and resorption: specifically, the bone is formed by cells called osteoblasts, which are responsible for the production of new bone, and by cells called osteoclasts, with the opposite function.

The activity of each of these cells varies, depending on the mechanical stimuli to which the bones are subjected. In fact, there is greater osteoblastic activity when the bone is subjected to a mechanical load exceeding the daily physiological levels; in contrast, increased osteoclast activity occurs when the mechanical load is below normal levels.

Therefore, considering the possibility of humans living in microgravity, the skeleton is subjected to less mechanical stress, stimulating increased osteoclast activity and a consequent progressive decrease of bone density (Arfat et al., 2014).

During long-duration missions in space, the possibility of experiencing osteopenia or osteoporosis, associated with the probability of bone fractures, are a risk that has existed ever since the duration of space missions gradually expanded over the years (Sibonga, 2013). For this reason, interest in the study of bone changes in microgravity is very important in order to preserve the bone structure of astronauts and cosmonauts more effectively.

The purpose of our study is to identify a protocol of isometric exercises that have the major effects on the structure and bone metabolism under space conditions.

All scientific literature agrees that bones undergo a decrease in bone mineral density or in bone mineral content. This decrease differs depending on the length of a space mission. It also proves to be heterogeneous with respect to the localization of the bone and its parts.

The main skeletal areas analyzed were: the spine, the hip and the femur, in particular the trochanter, femoral neck and proximal epiphysis, the radius and the tibia, and the heel bone. Comparing all these areas, it has been found that the greatest bone loss is observed at the level of the lower limbs and the lumbar spine, as shown by studies done by Sibonga and colleagues and LeBlanc and colleagues.

Unlike during short-duration space missions, greater bone loss is experienced during long-duration (4 to 6 months) space missions. For example, the study by Vico and colleagues compared the effects of microgravity on groups of astronauts who had participated in short-duration missions (1 month) and long-duration missions (6 months). The results showed not only a difference depending on the duration of their stay in space, but also heterogeneity in the marrow in the same areas.

In fact, the trabecular parts (cancellous bone and innermost parts) showed greater decrease compared to the cortical (outer) parts, especially at the level of the tibia. Similar results were also found in the study by Collet and colleagues and Lang and colleagues. In particular, these studies showed a greater decrease at the trabecular level in the hip joint area, stressing the loss especially in the lower limbs.
In fact, studies on the radius showed a lower decrease of BMD components with respect to the lower limbs.

Another important feature to point out is that in many studies, lower BMD values were found after space missions compared to the start; slowing the recovery progress.

The scientific literature also agrees on the change of bone metabolism: the reduction or increase in the activity of formation markers and the markers of bone resorption. The study by Caillot-Augusseau and colleagues has shown that the microgravity conditions affecting the metabolism, resulting in increased activity of resorption markers, correlated to a physiological hormonal decoupling in which a reduction of vitamin D (in the form of calcitriol) prevails, which under normal conditions promotes the reabsorption of calcium in the intestines. A decline, however, promotes bone resorption. In addition, there has been a decrease of calcitonin, which under normal conditions inhibits bone resorption. These decreases were also found in studies done by Smith and colleagues.

Therefore, most of the scientific results seem to be consistent, although some studies have a number of limitations. This is related first of all to the size of the sample, which is obviously always too small for meaningful results. In addition, each study group is representative of the population of astronauts / cosmonauts and their changes related to microgravity may be different than those of a common person, as to be able to deal with the conditions in space requires specific training / physical maintenance and diet. Another important limitation is the protocol used, which proved to be variable depending on the study and depending on the length of the space mission.

Moreover, even the measurements taken on Earth, before and after the missions, were not collected at equal intervals nor shared between the different searches.

In conclusion, all studies have shown that microgravity alters the physiological processes and the bone structure; however, further research should be performed in order to pay closer attention to preventive aspects and to the maintenance of healthy bones in space. To do this, we will require studies of longer duration and more sophisticated equipment that can also be used on board. In addition, all identified countermeasures could be used in the future not only for astronauts, but also for any person remaining too long in a condition of immobility due to bone disease or trauma.

Based on a thorough review of the literature, it is possible to highlight that heavy resistance exercise plus good nutritional and vitamin D status reduce the loss of bone mineral density on long-duration International Space Station missions (Smith et al. 2014).

Some studies have investigated ex vivo the long-term effects of weightlessness (simulated microgravity) on bone tissue (Cosmi et al. 2015). Osteocytes are extremely sensitive to mechanical stress, a quality that is probably linked to the process of mechanical adaptation. It is possible that the mecha-nosensitivity of bone cells is altered under microgravity conditions, and that this abnormal mecha-sensation contributes to the disturbed bone metabolism observed in astronauts (Burger & Klein-Nuleed, 1998).

Losses >10 % of bone mineral density in some astronauts following a typical 6-month mission in space are related to fracture risk; the set of risk factors that may contribute to this bone loss comprises adaptation to weightlessness, suboptimal diet, reduced physical activity, perturbed mineral metabolism (Sibonga, 2013).

To prevent the risk of osteoporosis, one intervention possibility is supplementation. Calcium, vitamin D, and vitamin K are agents that have both potent anti-resorptive and anabolic effects on cancellous and cortical bone and may be needed to stabilize calcium balance and bone metabolism and prevent bone loss in astronauts during space flight (Iwamoto et al. 2005). Another hypothetical intervention possibility is low-magnitude high-frequency loading to stimulate bone formation under microgravity conditions (Torcasio et al. 2014).

In this scenario, skeletal fractures represent an issue that must be taken into account in the design of space missions, such as those proposed for Mars. The risk of skeletal fractures represents the probability of encountering a condition in which the load applied to the bone exceeds its strength. Ideally, to understand the risk of skeletal fractures incurred by crewmembers in these missions, we must understand the variety of potential loading conditions applied to the skeleton during the mission and the strength of the skeleton with respect to those loads. Our knowledge in this area is incomplete and requires much study in terms of modeling the range of mechanical loads associated with excursions onto planetary surfaces, how those loads are modified by spacesuit designs, and which skeletal sites are placed most at risk by those loading conditions. While we are at present far from having such an integrated picture of skeletal fracture risk, considerable effort has been made to understand the effect of spaceflight on some of the elements of bone fracture risk.

Studies of aging and physical disability indicate that loss of muscle strength and indices of balance are associated with a risk of falling, and that falls are one of the most serious risk factors for bone fractures in the elderly. If muscle atrophy associated with prolonged skeletal unloading in spaceflight has similar effects for the crews of Mars missions, for example, the fracture risk associated with increased skeletal fragility may be
compounded by an increased risk of falling. Declines of muscle mass and muscle strength are associated with spaceflight, and recent studies have shown declines in indices of postural stability, averaging 68%-82% (Lang, 2006).

Musculoskeletal injuries and minor trauma in space were analyzed based on data from the U.S. space program. The incidence rate over the course of the space program was 0.021 per flight day for men and 0.015 for women. Hand injuries represented the most common location of injuries. Crew activity in the spacecraft cabin such as transferring between modules, aerobic and resistive exercise, and injuries caused by the extravehicular activity (EVA) suit components were the leading causes of musculoskeletal injuries. Exercise-related injuries accounted for an incidence of 0.003 per day. Exercise is also the most frequent source of injuries in astronauts living aboard the International Space Station (ISS). Isometric protocols can help to prevent injuries during training and contribute to reduced loss of osteopenia (Scheuring et al. 2009).

In 2009, Nelson and colleagues developed a predictive tool based on biomechanical and bone loading models at any gravitational level of interest. The tool is a statistical model that forecasts fracture risk, bounds the associated uncertainties, and performs sensitivity analysis. The scientists focused on events that represent severe consequences for an exploration mission, specifically that of spinal fracture resulting from a routine task (lifting a heavy object up to 60 kg), or a spinal, femoral, or wrist fracture due to an accidental fall or an intentional jump from 1 to 2 m.

They predicted fracture risk associated with reference missions to the Moon and Mars that represented crew activities on the surface. Fractures were much more likely on Mars due to compromised bone integrity. No statistically significant gender-dependent differences emerged. Wrist fractures were the most likely type of fracture, followed by spinal and hip fractures.
II.b Muscles and bones as an integrated system

Bones and muscles are complementary and essential for locomotion and individual autonomy. In the past decades, the idea of a bone–muscle unit has emerged and numerous studies have confirmed this hypothesis.

Spaceflight, bedrest, as well as osteoporosis and sarcopenia experimentations have allowed accumulating considerable evidence. Mechanical loading is a key mechanism linking both tissues with a central role promoting physical activity. Moreover, the skeletal muscle secrets various molecules that affect the bone, including the insulin-like growth factor-1 (IGF-1), the basic fibroblast growth factor (FGF-2), interleukin-6 (IL-6), myostatin, osteoglycin (OGN), and osteoactivin. Understanding this system will allow defining new levers to prevent/treat sarcopenia and osteoporosis at the same time (Tagliaferri et al. 2015).

Bones and skeletal muscles are both derived from somitic mesoderm and accumulate peak tissue mass synchronously, according to genetic information and environmental stimuli. An understanding of the mechanisms underlying the parallel development and involution of these tissues is critical to developing new and more effective means to combat osteoporosis during space flight (DiGirolamo et al. 2013).

Bone repair is a complex phenomenon involving many cell types and signaling factors. Substantial evidence exists to suggest that stem cells originating from local osseous tissues, particularly the periosteum, can contribute to bone repair. However, there are situations where bone repair involves compensatory secondary systems. One potential alternate source of osteoprogenitors is muscle, which typically suffers trauma during an orthopedic insult. While muscle access is known to be beneficial to bone repair, this is conventionally credited to its high vascularity, and thus its contribution to the local blood supply. However, there is emerging evidence to suggest that progenitors from muscle may directly contribute to bone healing. Defining the role of muscle in bone formation and repair has significant clinical implications particularly in case of space missions (Liu et al. 2010).

II.c The effects of microgravity on the muscle structure

We already explained above that spaceflight involves musculoskeletal atrophy; a loss in strength and power; and, in the first few weeks, preferential atrophy of extensors over flexors. This atrophy primarily results
from a reduced protein synthesis that is likely triggered by the removal of the antigravity load. Contractile proteins are lost out of proportion to other cellular proteins, and the thin actin filament is lost disproportionately to the thick myosin filament. The decline in contractile protein explains the decrease in force per cross-sectional area, whereas the thin-filament loss may explain the observed postflight increase in the maximal velocity of shortening in the type I and IIa fiber types. Importantly, the microgravity-induced decline in peak power is partially offset by the increased fiber velocity. Muscle velocity is further increased by the microgravity-induced expression of fast-type myosin isozymes in slow fibers (hybrid II/I fibers) and by the increased expression of fast type II fiber types. Spaceflight increases the susceptibility of skeletal muscle to damage, with the actual damage elicited during postflight reloading (Fitts et al. 2000).

After about 270 days, the muscle mass attains a constant value of about 70% of the initial one, even if it is interesting to note that atrophy as a result of at least two weeks of spaceflight varied among individuals and muscle groups and that the degree of atrophy appeared to be greater than that induced by 20 days of bedrest (Akima et al. 2015). The maximal force of several muscle groups showed a substantial decrease (6–25% of pre-flight values). The maximal power during very short “explosive” efforts of 0.25–0.30 s showed an even greater fall, being reduced to 65% after 1 month and to 45% (of pre-flight values) after 6 months. The maximal power developed during 6–7 s “all-out” bouts was reduced to a lesser extent, attaining about 75% of pre-flight values, regardless of the flight duration. It seems that a substantial fraction of the observed decreases of maximal power is probably due to a deterioration of the motor coordination brought about by the absence of gravity (di Prampero, & Narici, 2002), although the adaptation to sustained weightlessness might have led to a microgravity-specific motor strategy, which was not focused on -center of mass- strategy (center of mass strategy is the balance strategy used by human beings on Earth) (Pedrocchi et al. 2001).

Many studies investigate such phenomena with the obvious conclusion that the exercise countermeasures employed have to attempt to provide the high intensity needed to adequately protect fiber and muscle mass in order to avoid seriously compromising the crew’s ability to perform strenuous exercise. The results highlight the need to study new exercise programs that employ high resistance and contractions over a wide range of motions to mimic the range occurring in Earth’s 1 g environment (Fitts et al. 2010).

Other observations indicate that exercise protocols need to be carefully assessed in terms of intensity, that the number of exercises needs to be maximized, and that the loads need to be increased compared to the current levels (Gopalakrishnan, 2010).

The limited access to microgravity environments for investigating muscle adaptation and evaluating countermeasure programs has necessitated the use of ground-based models to conduct both basic and applied muscle physiology research. Published results from ground-based models of muscle unweighting were presented and compared with the results from related spaceflight research by Adams and colleagues in 2003.

The models of skeletal muscle unweighting found in a sufficient body of literature included bedrest, cast immobilization, and unilateral lower limb suspension.

**Fig. 8 Explicative diagrams taken from Adams et al. 2003**

### III PROCEEDURES IN THE HABITAT

Currently, the most common exercises used by astronauts are part of a countermeasure program for bone loss and muscle atrophy used to prepare the musculoskeletal system (pre-flight) and to strengthen it (post-flight) (Ohshima, 2010). For this reason, both American and Russian Space missions have included cycle ergometers, treadmills (active and passive), as well as aerobic and resistive exercise equipment (Hagan, 2002; Trappe, et al., 2009).
IV DESIGN STUDY

Our research is oriented to evaluate specific rehabilitation protocols during space missions. Starting from the research done since 2006 (Schlacht at al., 2009, Masali et al., 2009) by the CROMOS team (ESA student parabolic flight campaign 2007) and by the ZER0gYMN group (Tinto et al., 2011; 2012) this presentation sets up possible rehabilitation exercises, applying rehabilitation with comfortable, easy to use and non-intrusive equipment mostly based on rehabilitative isometric exercise.

Training protocols will be characterised by simplicity, safety, functionalism, adaptability and they will take into account the optimisation of the space in the recreational area of the spacecraft.

This new rehabilitation approach will be tested in three comparative states:
- Microgravity in Parabolic flight
- Water Neutral Buoyancy
- Earth gravity

Laboratory tests may be performed as:
- Ground terrestrial tests
- Tests at high altitude
- Tests in water neutral buoyancy
- Tests in Mars and Moon gravity during parabolic flights.
Fig. 12 Parabolic flight (©ESA) & G-force diagram of a typical parabola, generated from the aircraft’s accelerometer data. During hypergravity, gravity (G) values reach approximately 1.8G. During the 20 s microgravity phase (Zero G), gravity remains below 0.05G (Schneider et al. 2015).

Fig. 13 Neutral Buoyancy Test Facility NBTF, Advanced Logistics Technology Engineering Centre ALTEC, Torino, Italy (©ALTEC)

IV.a Role of exercise to prevent bone osteopenia and muscle deconditioning and to accelerate the process of resolution of non-displaced fractures

Many studies have aimed at examining the effects of a high-intensity concurrent training program using a single gravity-independent device for maintaining musculoskeletal function (Cotter et al. 2015). Some of them have focused on the role of exercise and protein supplementation to prevent loss of muscle strength and lean tissue mass loss during 60 days of bedrest, with the hypothesis that bedrest is equal to long-duration space missions. An exercise protocol combining resistive and aerobic exercise training protects against losses in strength, endurance, and lean mass, whereas nutritional countermeasures without exercise are not effective (Lee et al. 2014). Nowadays exercises and training protocols need to consider some peculiar aspects of movement in 0g and the relative motor control strategy realized to reprogram movement. Previous spaceflights have shown that astronauts in orbit adapt their motor strategies to each change in their gravitational environment. A training program for astronauts might be designed to encourage fine-control motions as these increase controllability (Stirling et al. 2009). Such strategies include management of the inertial effects of the segments in terms of total angular momentum or the control of the body’s center of pressure (Pedrocchi et al. 2003). Another important aspect is lower back pain; for spaceflights, the hypothesis was formulated that muscle atrophy in the absence of gravity loading destabilizes the lumbopelvic area (Snijders & Richardson, 2005). Moreover, in microgravity, the body lengths by 4-6.0 cm (normal diurnal increase is 1-2 cm on Earth). This large increase is attributed to disc swelling from the reduced spinal forces, and also to reduced spinal curvature. Second, without cyclic mechanical loading on the spine, there can be decreased cellular anabolic activity and accelerated disc degeneration. A third possibility may involve trunk muscle deconditioning.
and dysfunction. These etiologies can contribute to altered spinal column biomechanics (i.e., stiffness and compressibility), injury, and pain. It is necessary for this reason to create a training program aimed at decreasing back pain and related disability such as pain, sleep disruption, and mental distraction (Chang et al. 2014). It has been demonstrated that isometric exercises are an adequate stimulus for strengthening the muscled of the neck, back, upper and lower extremities, and are capable of enhancing bone formation (Swezey et al. 2000). These effects are increased even more if during isometric exercise, vibration stimulation is performed (Mischi & Cardinale 2015). For all these reasons, a series of isometric exercises to be carried out as part of a training program for astronauts during space travel is briefly described below.

V EXERCISE DESCRIPTION
“Static action training”, also known as static strength training, is based on isometric exercises and involves muscular actions in which the length of the muscle does not change and there is no visible movement at the joints (Fleck, 2004). This kind of training is also recommended in rehabilitation where strengthening the muscles without placing excessive stress on the joint is preferred. It consist of exercises incorporating the major muscle groups of the chest, shoulders, back, upper arm and legs in order to strengthen the muscles that do not get much use in space. A subject-loading device around an astronaut’s feet and chest secures him/her to the floor.

It is important to breathe continuously throughout the exercises. Apnoea will only increase blood pressure without any other improvement. Moreover, during “static action training”, it is essential to pay attention to maintaining a correct posture and constant tension in the abdominal region. The selected exercises are described below.

The astronaut has to play a workout with this exercise about 3 times a day; all positions should be maintained pushing for 5/10 seconds with 5 seconds of rest, for 3 series, each series consists of 10 pressures.

The use of a mechanical dynamometer in this position is also possible in water to record the developed strength.

Fig. 15 Isometric exercises for shoulder muscle and rotator cuff

Fig. 16 Isometric exercises for shoulder muscles and rotator cuff

Fig. 17 Isometric exercises for neck muscles
Fig. 18 Isometric exercise for arms muscles (flexors and extensors)

Fig. 19 Isometric exercise for legs and arms: the astronaut can be tied to the floor, or to any flat surface in microgravity or in a state of buoyancy (for the training, obviously), pushing at the maximal for both arms and legs.

Fig. 20 Isometric exercise for hands

V.a Frontiers and future studies based purely on neurophysiological aspects

Among the most exciting frontiers of scientific research that have emerged mostly in recent decades is the analysis of brain changes and the effects on the sensory and motor cortex due to stays in space in microgravity.

The proposed protocol of isometric exercises is designed to counter the negative effects on the musculoskeletal structure using an innovative approach, without the use of machines. It is effective in cases of compound fractures and can be used in synergy by two astronauts at the same time and obviously without any intrinsic costs. This approach also aims to promote greater awareness of the body as isometric exercises, by their very nature, are characterized by a situation of stasis, which also favors a meditative approach alongside the merely conditional aspect.

This last aspect is of particular interest in our work group: what are the changes in the analysis of one’s own body and movements by the Central Nervous System (CNS) while in microgravity? What brain changes occur in relation to the control body and the image that the brain has of its own structure and its own actions?

These analyses and these changes are extremely interesting and relevant, and allow opening up a window on in-depth understanding of the functioning of the CNS in relation to the peripheral body, even under normal circumstances.

However, we would like to particularly dwell on two main issues: motor imagery and the cortical homunculus.

Before participating in a space mission, astronauts undergo parabolic flights and buoyancy training to facilitate their subsequent adaptation to weightlessness.

It would be interesting to set up a simple and inexpensive approach that can be used to prepare astronauts both for the absence of gravity and the subsequent presence of gravity after astronauts return on Earth.

This approach is based on motor imagery (MI), a process in which actions are produced in the working memory without any overt output. Training protocols based on MI have repeatedly been shown to modify brain circuitry and to improve motor performance in healthy young adults, healthy seniors, and stroke victims, and are routinely used to optimize the performance of elite athletes (Bock et al., 2015).

We propose using similar protocols specifically to train the brain to interpret the weightlessness in space and the subsequent presence of gravity after astronauts return on Earth.

As for the cortical homunculus, one must consider that the cortical homunculus is a physical representation of the human body that is located within the brain. A cortical homunculus is a “map” of the neurological anatomical divisions of the body. There are two types of cortical homunculus; sensory and motor (Schott, 1993).

How does this representation vary in microgravity? To date, this question has never been investigated by
Fig. 21 The motor and sensory homunculus: the first map. Penfield and Rasmussen, 1950.

the scientific community. In our opinion, it is one of the most interesting discoveries that could be made in the field of aerospace medicine and neurophysiology of the movement.

The challenge is: how to measure the variation of the representation in a quantitative way? Those who manage to find a way to obtain this measurement and the subsequent description will have the key to unlock the door to the understanding of the sensory and motor representation of the human body in microgravity.

CONCLUSIONS

This research project is part of a long term development of learning consequent of the cooperation between our Research Group and the most advanced Turin Space Industry. The main purpose of this Research program is to analyze the most popular physical exercises used by astronauts during flight, in order to develop rehabilitation protocols. These effective training will permit astronauts to recover their physical characteristics to carry on their missions in Space.

Fig. 22 Walking on the Moon (©NASA)

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