

Phantom pain reduction by low-frequency and low-intensity electromagnetic fields

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Abstract

Although various treatments have been presented for phantom pain, there is little proof supporting the benefits of pharmacological treatments, surgery or interventional techniques, electroconvulsive therapy, electrical nerve stimulation, far infrared ray therapy, psychological therapies, etc. Here, we report the preliminary results for phantom pain reduction by low-frequency and intensity electromagnetic fields under clinical circumstances. Our method is called as Electromagnetic-Own-Signal-Treatment (EMOST). Fifteen people with phantom limb pain participated. The patients were treated using a pre-programmed, six sessions. Pain intensity was quantified upon admission using a 0-10 verbal numerical rating scale. Most of the patients (n=10) reported a marked reduction in the intensity of phantom limb pain. Several patients also reported about improvement in their sleep and mood quality, or a reduction in the frequency of phantom pain after the treatments. No improvements in the reduction of phantom limb pain or sleep and mood improvement were reported in the control group (n=5). Our non-linear electromagnetic EMOST method may be a possible therapeutic application in the reduction of phantom limb pain. Here, we also suggest that some of the possible effects of the EMOST may be achieved via the redox balance of the body and redox-related neural plasticity.

Keywords: Phantom pain, Low-frequency and intensity electromagnetic fields, EMOST method, Redox-related neural plasticity

Introduction

The amputation of a limb is generally followed by a sensation that the deafferented body part is still present. Phantom limb sensations can be generally perceived by amputees following amputation (Ramachandran and Hirstein, 1998). However, phantom limb sensations can also occur following spinal cord injury, nerve avulsion and in children with congenital limb aplasia (Moore et al., 2000; Melzack, 1992; Melzack et al., 1997). The phantom sensations usually resolve without treatment, except in cases in which phantom pain develops.

When amputees sense an intense pain in their missing body part, the phenomenon is known as phantom pain. Phantom pain is more frequent in patients with preamputation pain and is less likely in cases in which the amputation was performed when the patient was very young. While phantom pain is most common after the amputation of a leg or an arm, it can also occur after the surgical removal of a breast, rectum, testicle, penis, or eye, among others (Flor, 2002). The phantom pain aftereffect occurs in 50-80% of the patients who have undergone this type of surgery, and the most frequently reported types of pain include burning, tingling, and cramping (Sherman, 1994). Various other pains and types of sensation such as shocking, itching, shooting, squeezing, and throbbing, among others, can also occur. Although a high percentage of amputees experience phantom pain, every patient has a unique description concerning his/her particular sensations and the pain experienced, as well as the intensity and frequency of the sensations. Phantom pain generally resolves without treatment, except in cases in which chronic phantom pain develops.

There is increasing evidence that both peripheral and central neural mechanisms are involved in phantom pain, but the pathophysiological mechanisms of phantom pain remain unknown (Devor and Seltzer, 1999; Dhillon et al., 2005; Davis et al., 1998; Mackert et al., 2003; Mercier et al., 2006; Karl et al., 2001). One possible peripheral mechanism is that neuromas (a growth of the nerve tissue) form injured nerve endings at the stump site after the amputation of a limb and fire abnormal action potentials. In addition to peripheral processes, spinal mechanisms have also been considered to influence phantom pain (Bittar et al., 2005). Phantom limb pain is also strongly correlated with changes in the representational plasticity (cortical reorganization) in the somatosensory and motor cortices. According to the neuromatrix theory, there is an extensive, genetically predetermined, network that interconnects the thalamus-cortex-limbic system, and phantom pain could arise from an atypical reorganization of this neuromatrix (Melzack, 1993; Bittar et al., 2005). Psychological factors have also been investigated. Whereas psychological factors do not appear to cause the phantom pain, these factors might affect the severity and the progression of the pain (Sherman et al., 1987).

Although various treatments have been presented, there is little clinical proof supporting the benefits of pharmacological treatments, surgery or interventional techniques, electroconvulsive therapy, electrical nerve stimulation, far infrared ray therapy, pulsed radiofrequency ablation, or psychological therapies (for instance, mirror box therapy), among other treatments (Gnezdilov et al., 1995; Rasmussen and Rummans, 2000; Wiech et al., 2004; Irlbacher et al., 2006; Wilkes et al., 2008; Huang et al., 2009; Seidel et al., 2009; de Roos et al., 2010).

Here, we report the preliminary results for phantom pain reduction by Electromagnetic-Own-Signal-Treatment (EMOST) under clinical circumstances. Our EMOST method does not perform any electromagnetic wave modulation or wave inversion (phase shift) of recorded output bioelectric and bioelectromagnetic signals of subjects. EMOST method solely employs filtered, various low-frequency and intensity electromagnetic fields (between 1 Hz - 1 MHz) that is controlled via preprogrammed computer. The EMOST device is based on our new concept, i.e., very fast electromagnetic feedback of recorded bioelectromagnetic signals of subjects without any changes could promote and reinforce intra- and intercellular redox communication. We also discuss that low-frequency and intensity electromagnetic fields (LFI-EMFs) may influence the cortical reorganization and the neurogenesis.

Materials and Methods

Patients

Limb amputees (*with vascular and arterial disease, diabetes and accidents*) were recruited at the National Institute for Medical Rehabilitation in Budapest, Hungary. The limb amputees (experimental amputees (n=10) and control amputees (n=5)) were randomized to receive either an active EMOST treatment or a sham treatment. Our EMOST experiments were performed by permission of the Ethics Committee of the National Institute for Medical Rehabilitation, Budapest, Hungary.

Apparatus

The EMOST device (BioLabor-MCC HI 2.5.2) was used in the experiments. It contains three basic elements: (1) an input electrode, (2) signal-processing circuits and (3) an output electrode. The input and output flat electrodes were placed on the joints of patients. The input signals were originated from bioelectric and bioelectromagnetic signals of patients who were placed in direct contact with the specially designed flat electrodes. The input signals were recorded similarly to extracting information from electromagnetic brain function via electroencephalogram (EEG). Namely, the EMOST device (which is controlled by a personal computer) operates with the non-linear, bioelectromagnetic signals of the patient within preprogrammed frequency ranges (between 1 Hz - 1 MHz). The parameters (input filtered frequency ranges and output intensity) and exposure time can be preprogrammed. The collected input signals of patients can be filtered using pre-programmed, low-frequency ranges (between 1 Hz - 1 MHz) by device circuits. Output, low-frequency electromagnetic signals were emitted by an identical flat electrode. The output electromagnetic intensity range of the device is 0.1-10 microteslas. A photograph of the EMOST apparatus is shown Figure 1.



Figure. 1. The EMOST device (BioLabor-MCC HI 2.5.2) is controlled by a personal computer.

Treatments

The present research conformed to the Helsinki Declaration outlining the principles for medical research involving human subjects. All of the subjects completed an informed consent form prior to participation in the study. The collected bioelectromagnetic input signals of patients were processed by preprogrammed EMOST device. The patients were treated by output preprogrammed signals of EMOST device (frequencies in the range of 1 Hz - 1 MHz; intensity range between 0.1-10 micro Teslas) via a flat electrode (Fig. 2) for six sessions. Each session was approximately 45 min, between all treatments with a one-day pause. Sham exposed patients (control group) were placed in the same conditions as the exposure groups but EMOST device was turned off. Subjects could not notice anything different from active and sham treatments. Pain intensity was quantified upon admission using a 0-10 verbal numerical rating scale (NRS) (Fig. 3). The patients were asked to rate their pain on the verbal NRS prior to the therapy and after they had completed the six treatments. During and after the patients had completed the six treatments, they did not receive any additional treatments related to the reduction or elimination of phantom limb pain.

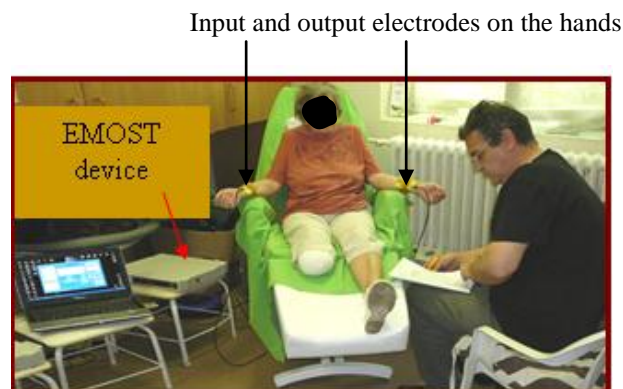


Figure. 2. Photograph of an amputee undergoing an EMOST treatment. While the operator was collecting patients' reports he was blind to the type of treatment (i.e., active or sham treatments).

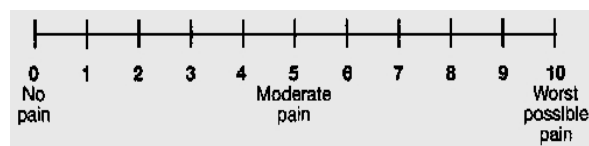


Figure. 3. Verbal numerical rating scale.

Results

The Student's t-test was used to analyze the data. The reduction of phantom limb pain by EMOST was statistically significant (*P < 0.05) as compared to the controls. Although our goal was to reduce phantom limb pain (or reduction in the frequency of phantom pain (PP↓)) via EMOST treatments, most of the patients also reported a marked improvement in their sleep and mood quality after the treatments. No improvements in the reduction of phantom limb pain or sleep and mood improvement were reported in the control group. The results obtained after six EMOST treatments are summarized in Table 1. All patients were followed for 2 weeks following their completed six treatments and there were no major differences in terms of phantom pain relief during this time.

	Patients	Phantom pain intensity before the treatments	Phantom pain intensity after six completed EMOST treatments	Interval between the amputation date and the EMOST treatments	Additional improvements reported by patients after six EMOST treatments	Disease or Accident
Patients with EMOST treatments	I.	6	0	1 month	Sleep	Diabetes
	II.	7	3	1/2 year	Sleep	Arterial
	III.	8	4	2 years	Mood	Diabetes
	IV.	6	2	1 month	Sleep, Mood	Arterial
	V.	1	0	8 years	Sleep, Mood	Arterial
	VI.	3	2	1 month	Sleep, Mood PP frequency↓	Arterial
	VII.	7	2	1 month	Sleep, Mood	Diabetes
	VIII.	7	4	1 month	Mood	Accident
	IX.	7	0	3 years	Sleep PP frequency↓	Diabetes
	X.	7	6	5 years	Mood	Diabetes and arterial

Table 1. This table summarizes the phantom pain intensity observed after completion of six EMOST treatments and additional improvements reported by the patients (The control group is not shown).

Discussion

Some possible effects of LFI-EMFs on cellular processes

Living cells display a particularly weak non-linear electromagnetic activity in a wide spectrum of frequencies - from Hz to THz, in cells (Fraser and Frey, 1968; Levin and Korenstein, 1991; Isojima et al., 1995; Cohen and Popp, 1997; Kobayashi et al., 1999; Pokorný et al., 2001; Lipkova and Cechak, 2005; Pelling et al., 2005) - that can be generated by diverse cellular mechanisms that are associated with biochemical processes.

Although the health effects of low-frequency and intensity electromagnetic fields (LFI-EMFs) are controversial, increasing evidence suggests that non-ionizing LFI-EMFs can influence numerous cell functions and are capable of initiating various healing processes, such as the delay of fractures, induction of analgesia, acceleration of wound re-epithelialization, inhibition of inflammatory processes, reduction of fatigue, improvement of multiple sclerosis and chronic pulmonary disease, among others (Orgel et al., 1984; Selvam et al., 2007; Reiter 1993; Satter Syed et al., 1999; Lappin et al., 2003; Kumar et al., 2005; Alfieri et al., 2006; Zhang et al., 2007; Markov 2007a; Tsang et al., 2009; Huo et al., 2009; Sutbeyaz et al., 2009; Mach and Persinger, 2009; Mancuso et al., 2007; Jing et al., 2010; Patruno et al., 2010).

Many potential causes have been suggested to explain the influence of LFI-EMFs in living systems, for example, Eddy electric currents, classical and quantum oscillator models, by the help of biomagnetites, cyclotron resonance, the interference of quantum states of bound ions and electrons, coherent quantum excitations, stochastic resonance, parametric resonance, bifurcation, and magnetosensitive free-radical and redox processes, among others (Binhi, 1999; Bókkon and Salari, 2010). Despite these explanations, the primary effect of LFI-EMFs on cell functions remains unclear. However, several effects of extremely low-frequency electromagnetic therapies may be explained (or connected) by redox regulations and membrane processes (Patruno et al., 2010; De Nicola et al., 2006; Di Loreto et al., 2009; Morabito et al., 2010).

Numerous experiments have provided evidence that reactive oxygen species (ROS) and reactive nitrogen species (RNS) and their derivatives act as fundamental signals (secondary messengers) during physiological (and pathophysiological) processes in intracellular signaling and intercellular communication processes (Hidalgo et al., 2000; Hancock et al., 2001; Dröge, 2002; Kamsler and Segal, 2007; Valko et al., 2007; Kishida and Klann, 2007; Forman et al., 2008; Bókkon and Antal, 2010). Because several effects of LFI-

EMFs can be explained by redox regulation and membrane processes, LFI-EMFs may have an important effect on redox mechanisms.

A growing body of evidence indicates that cell membranes play a key role in the transduction and amplification of LFI-EMF field signals (Bauréus et al., 2003; Foster, 2003; Mathie et al., 2003). Specifically, LFI-EMFs can affect the length of cell membranes and the number and variety of membrane-bound receptors. However, the activation of many cell surface receptors (for example, G protein-coupled receptors and receptor tyrosine kinases, among others) induces an influx of Ca^{2+} into the cells and the release of Ca^{2+} from the endoplasmic reticulum. Because ROS and calcium signals are intimately interconnected and calcium and ROS constitute the most significant intracellular signaling molecules in the regulation of various cellular functions (Gordeeva et al., 2003; Yan et al., 2006; Feissner et al., 2009), the effect of LFI-EMFs on cell membranes and membrane-bound receptors may cause these radiations to stimulate Ca^{2+} -related pathways and free radical and redox-regulated processes. Several cell surface receptors are regulated by redox processes (Dröge, 2002; Bókkon and Antal, 2010; Choi and Lipton, 2000; Nakashima et al., 2002; Kishida et al., 2005; Yang et al., 2006; Monteiro et al., 2008; Shi et al., 2010). Figure 4 shows some possible effects of LFI-EMFs on cellular processes.

In addition, LFI-EMF can have effects on the molecular transition states and can affect the kinetic processes of enzymes without thermodynamic kT energy. Importantly, magnetic fields are more effective when the tissue is out of equilibrium (Markov, 2007b). Consequently, LFI-EMFs experiments in healthy individuals do not reflect the potential response of patients who have endured an injury or disease. Because the cell type-specific redox status is responsible for the effects of diverse electromagnetic exposures (Simkó, 2007), it is possible that the effects of diverse electromagnetic fields are dependent on the cell type and the temporary spatiotemporal redox (and free radicals) patterns of cells.

It is important to note the role of exposure time during LFI-EMF therapies is especially critical. Radiations with a short-term exposure (according to our experience, less than 45 min) can facilitate (for example, through redox activation processes) the immune system and cellular processes, but a long-term or continuous exposure to LFI-EMFs results in a decline in cytoprotection (Regoli et al., 2005; Di Carlo et al., 2002). Long-term electromagnetic radiations may shift the redox and calcium balance, which could cause additional cellular malfunctions. For example, NMDA receptors can be redox modulated by

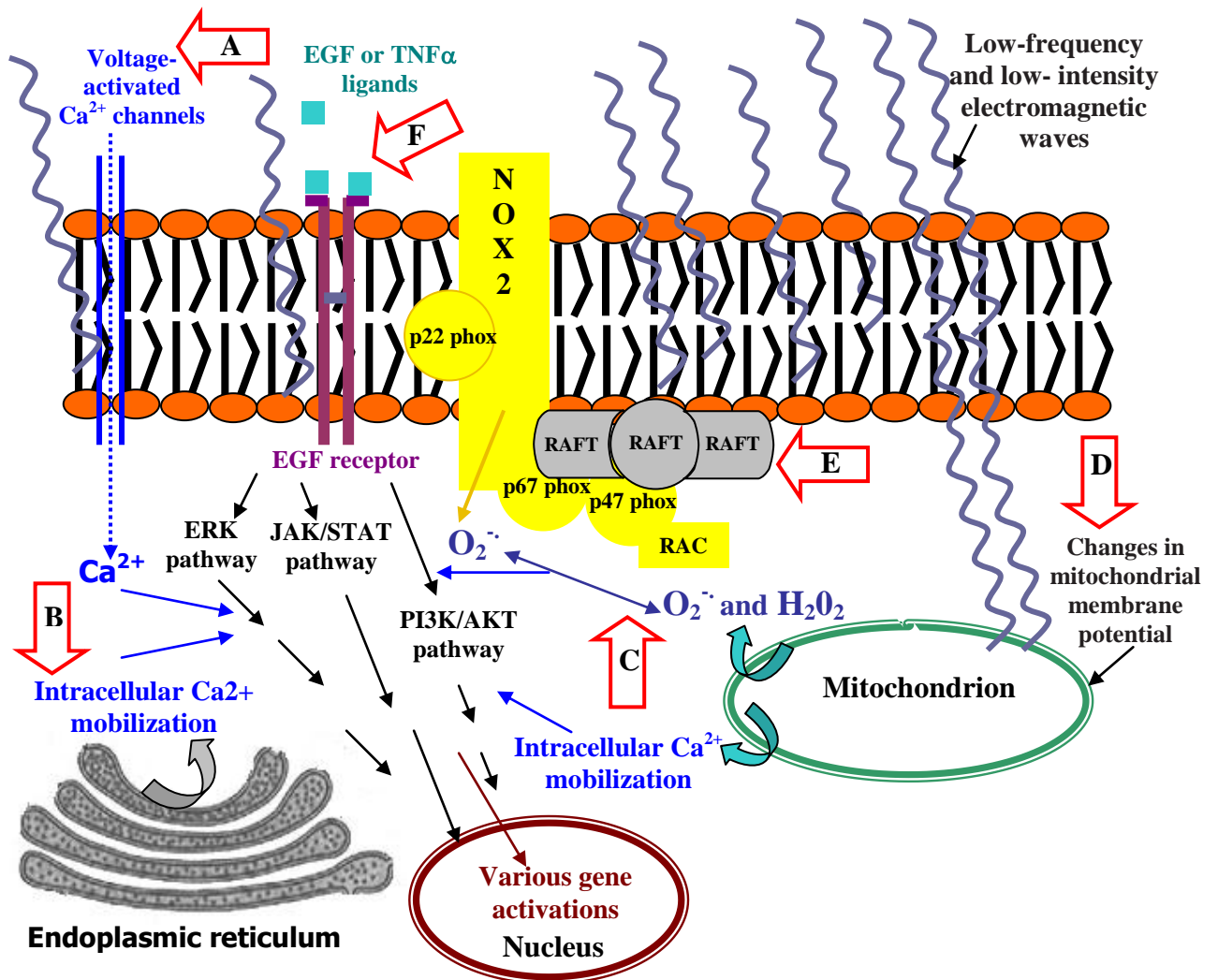


Figure 4. Some possible effects of LFI-EMF fields on cellular processes. A growing body of evidence indicates that cell membranes, mitochondria, Ca²⁺ and ROS play key roles in the transduction and amplification of LFI-EMF field signals. ELF-EMFs may be capable of inducing a shift in cell status to an “activated” state. Lipid rafts (RAFT, membrane microdomains) can play essential roles during the activation of membrane-bound receptors and enzymes by ELF-EMFs. **A.** Increases the open-channel probability. **B.** Intracellular Ca²⁺ mobilization. **C.** Increased intracellular O₂^{•-} and H₂O₂ levels. **D.** Changes in mitochondrial membrane potential. **E.** Facilitation of NADPH oxidase (NOX) aggregation by membrane lipid drafts. **F.** Facilitate assembly and activation of membrane-bound receptors.

hydroxyl radicals (Aizenman, 1995), but long-term or continuous exposure to LFI-EMFs provoke aberrant NMDA receptor activities (Manikonda et al., 2007).

In most LFI-EMF experiments or treatments, various devices employ diverse artificial frequencies, which are waveforms that are modulated with respect to the frequency or the amplitude. LFI-EMFs with different characteristics, including different waveforms, frequencies and modulations, can have diverse (*or even opposing*) effects on biochemical signal processes during experiments. In other words, the effects of electromagnetic fields are associated with the type of electromagnetic field that is applied (Walther et al., 2007).

During various diseases, cells not only demonstrate altered biochemical processes but also produce altered non-linear electromagnetic complex patterns. Because it is impossible to investigate the whole range of artificial LFI-EMFs for potential therapeutic applications, it seems reasonable to use non-linear bioelectric and bioelectromagnetic signals from cells of the body for potential therapeutic applications that may be more effective than the diverse, artificial types of LFI-EMFs signals. However, the EMOST method is based on the utilization of the non-linear, bioelectric and bioelectromagnetic signals of the patients without any electromagnetic wave modulation or wave inversion of recorded output signals of subjects.

Since each patient with phantom pain has a unique description concerning his/her particular sensations and the pain experienced, and the effects of external electromagnetic fields are related to the type of electromagnetic field applied, it is possible that the treatment of particular phantom pain sensations will require specific method. Our EMOST device may guarantee this specific method, because it is based on the bioelectromagnetic fields of the patients' own living systems.

Phantom pain, neuromatrix theory, representation of body image, visual dreams, redox processes, EMOST treatment

The precise cause of phantom pain is incompletely understood, but most researchers agree that phantom pain and phantom sensations could originate from the central nervous system. LFI-EMFs can affect the length of cell membranes and various membrane-bound receptors as well as free radical and redox processes. During several years of EMOST application, we have found that our method generally affects the quality of sleep and mood in subjects. However, EMOST treatments not only significantly reduced phantom pain, but that most of the patients also reported these additional benefits (mainly about improvement of their sleep and mood quality) after six treatments (Table 1).

Recently, Ikeda et al. (2005) suggested that brain oxidation could be an initial process in sleep induction. They proposed that a mild enhancement of reactive species during wakefulness in the neuronal network that regulates sleep might trigger sleep induction. In other words, reactive species-related redox homeostasis plays an essential role in sleep/wake regulation.

Phantom limb pain can also occur in individuals who are born without limbs. Neurologists have hypothesized that the perception of our limbs can be hard-wired into our brain. According to the neuromatrix theory (Melzack, 1990), the representation of body image is genetically determined and can be modified by sensory input to generate a neurosignature. The regular neurosignature may be responsible for painless phantom limb sensations, whereas phantom pain could be due to an anomalous reorganization of the neuromatrix.

Michael Jouvet (1998) suggested that during sleep, an iteration process occurs at the DNA level that maintains and programs hereditary behavior. His notion may be related to the neuromatrix theory. Namely, during sleep, a neurocomputational process can maintain and reinforce the neurosignature and complex neuro-DNA patterns.

Mulder et al. (2008) reported that a large number of amputees continue to experience a body with all of the limbs intact during in their dreams. The visual perception from the eyes or the imagination generated internally employs the same (or a very similar) neural substrate in the visual cortex (Ganis et al., 2004; Slotnick et al., 2005; Borst and Kosslyn, 2008). In addition, in dream images, deficits occur that correlate with the damaged visual areas of the cortical brain. These phenomena indicate that the same (or a very similar) neural substrate of the visual cortex is used for the visual content of the dream image (Llinas and Pare, 1991). Such findings suggest that during sleep, visual dreams continue and/or reinforce the representation of a missing limb. After a limb has been amputated, the visual system from the eyes recognizes the lack of the limb, but the subconscious proprioceptive system and visual dreams (which are also produced by the subconscious) do not, because the subconscious brain mechanisms (proprioceptive system, neurosignature) have not yet changed.

According to the latest results of Morabito et al. (2010), low frequency and low intensity electromagnetic fields modify the cellular redox state. Thus, it is possible that one of the important effects of the EMOST method (that is based on the non-linear, bioelectromagnetic fields of the subject) is to influence redox processes in cells and tissues. However, reactive species and their derivatives act as fundamental signals (secondary messengers) in physiological (and pathophysiological) processes and are particularly important in redox signal systems. During EMOST treatments, the feedback of non-linear,

extra weak electromagnetic could strengthen the cellular redox communication between cells and can influence the redox balance of the entire body via the circulating blood. One outcome of these processes is that EMOST affects sleep and mood processes.

There are converging lines of evidence to support the hypothesis that sleep promotes brain plasticity. Glutamate is one of the main excitatory neurotransmitters in the visual cortex (Baughman and Gilbert, 1980), and the NMDA glutamate receptor is the most important molecular structure in controlling synaptic plasticity and memory functions. However, redox modulation has been recognized as a fundamental system in the regulation of the NMDA receptor (Bókkon and Antal, 2010; Choi and Lipton, 2000; Aizenman, 1995). In addition, glutamate receptors are reactivated during sleep-associated consolidation processes (Gais et al., 2008). It is possible that some of the important effects of the EMOST method are achieved via the redox balance of the body and redox-related plasticity during sleep.

In addition, weak magnetic fields with an optimal frequency and intensity have ameliorating effects on melatonin-related diseases (Persinger, 2006). However, melatonin is involved in the regulation of sleep, and can modulate hippocampus NMDA receptors, as well as brain and blood oxidative stress levels in ovariectomized rats. Furthermore, melatonin improves the antioxidant status (balance of the oxidant-antioxidant status) in the brain and liver (Subramanian et al., 2007; Dilek et al., 2010). According to Huse et al. (2001), opioids are effective in the treatment of phantom limb pain and may influence the cortical reorganization. Del Seppia et al. (2007) reported that non-ionizing electromagnetic fields could affect the nociceptive sensitivity and analgesia via opioid-mediated responses. Recently, Cuccurazzu et al. (2010) showed that extremely low-frequency electromagnetic fields can enhance the hippocampal neurogenesis in C57BL/6 mice.

Summary

We presented our preliminary results regarding the effectiveness of the EMOST method (which utilizes the non-linear, electromagnetic fields of the subjects) for the reduction of phantom limb pain under clinical circumstances. Because LFI-EMFs may affect cell membranes, membrane-bound receptors and free radical and redox processes, the cell type-specific redox status is likely responsible for the effects of various LFI-EMFs. Therefore, the EMOST method potentially can affect redox processes. For the reasons that redox homeostasis plays a fundamental role in physiological/ pathophysiological processes and sleep/wake regulation, and the brain oxidation can be an initial process in sleep induction, and

also because sleep promotes the brain plasticity, we hypothesize that some possible effects of EMOST improve redox and redox-related plasticity (*reorganization*).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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FIGURE 5 Treatments of amputees by EMOST in the clinic. (A.Erdöfi-Szabó and I.Bókkon)

