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Review Article

# A Consensus Panel Review of Central Nervous System Effects of the Exposure to Low-Intensity Extremely Low-Frequency Magnetic Fields

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*Background:* A large number of studies explored the biological effects of extremely low-frequency (0–300 Hz) magnetic fields (ELF-MFs) on nervous system both at cellular and at system level in the intact human brain reporting several functional changes. However, the results of different studies are quite variable and the mechanisms of action of ELF-MFs are still poorly defined. The aim of this paper is to provide a comprehensive review of the effects of ELF-MFs on nervous system.
*Methods:* We convened a workgroup of researchers in the field to review and discuss the available data about the nervous system effects produced by the exposure to ELF-MFs.
*Main Findings/Discussion:* We reviewed several methodological, experimental and clinical studies and discussed the findings in five sections. The first section analyses the devices used for ELF-MF exposure. The second section reviews the contribution of the computational methods and models for investigating the interaction between ELF-MFs and neuronal systems. The third section analyses the experimental data at cellular and tissue level showing the effects on cell membrane receptors and intracellular signaling and their correlation with neural stem cell proliferation and differentiation. The fourth section reviews the studies performed in the intact human brain evaluating the changes produced by ELF-MFs using neurophysiological and neuropsychological methods. The last section shows the limits and shortcomings of the available data, evidences the key challenges in the field and tracks directions for future research.


## Introduction

A large number of studies explored the biological effects of extremely low-frequency (0–300 Hz) magnetic fields (ELF-MFs) and reported the induction of functional changes in excitable biological tissues such as nervous, muscular and cardiac tissues exposed to fields with an amplitude of the order of up to a few milliTesla. Neurophysiological studies reported measurable changes in brain electrical activity following low-intensity ELF-MF exposure and suggested that they can influence neuronal functions such as motor control, sensory perception, cognitive activities, sleep and mood [1,2].

The purpose of this paper is to summarize and critically review the scientific literature about this topic. Despite the increasing amount of available data, the mechanisms of ELF-MF action on the brain are still poorly defined. Studying such mechanisms is hampered by methodological and technical constraints: 1) the heterogeneity of exposure systems and the low statistical power characterizing most of the experiments in humans have yielded inconsistent results; 2) the development of animal studies is complicated by difficulties in designing suitable exposure systems

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and in finding experimental paradigms comparable to those used in humans.

Although *in vitro* studies have produced interesting data about the possible mechanisms of ELF-MF action on cell physiology, the lack of sufficiently detailed models of the effects of ELF-MF at the cellular level and the huge differences in magnetic stimulation parameters used, make these data hardly applicable to human beings.

This review is composed of five sections. The first section reviews the main devices and exposure systems used in human, *in vivo* and *in vitro* studies. The second section analyses the contribution of computational methods for estimating the electric fields and currents induced by ELF-MFs and describes the state of the art of the modeling of the interaction between ELF-MFs and neuronal cells and networks. The third section is devoted to the experimental results of the interaction of ELF-MFs at cellular and tissue levels. The available data about the effects on distribution and functionality of cell membrane receptors such as adenosine receptor, the influence on intracellular $Ca^{2+}$ signaling and homeostasis and their correlation with neural stem cell proliferation and differentiation are reviewed. The forth section analyses the effects of ELF-MFs at system level reviewing the studies performed in the intact human brain evaluating the changes produced by ELF-MFs using neurophysiological and neuropsychological methods. The last section provides a critical point of view, evidencing the limits and shortcomings of the available data and tracking directions for future research.

The aim is to provide a deeper knowledge of the effects of ELF-MFs on the intact human brain as a non-invasive, anatomically-targeted approach for controlled modulation of regional brain activity that might become a useful tool for the treatment of neurologic and neuropsychiatric disorders.

*Devices and exposure systems:* See Supplemental section 1.

*Methods and models used for investigating the effects of ELF-MFs on the neuronal systems:* See Supplemental section 2.

*Experimental effects of ELF-MFs on cells and tissues:* See Supplemental section 3.

## Possible effects of ELF-MFs on the intact human brain

### *Neurophysiologic evaluation of ELF-MF effects*

Despite the increasing number of studies about the biological effects of ELF-MFs, the influence of this exposure on brain functions remains elusive. Neurophysiologic techniques allow obtaining consistent and reliable measurement of brain activity, thus they have represented the main tool to explore the effects of ELF magnetic fields. The literature on this topic was extensively reviewed by Cook and colleagues [1,2].

The electroencephalogram (EEG) is the main technique used in the evaluation of physiological effects of weak magnetic fields (MF) exposure. The effect of static MF (0–0.05 Hz) on brain function was studied by Fuller and Dobson [3,4] evaluating the interictal rates of EEG spike discharge in epileptic patients who had underwent electrode implantation for presurgical investigations. They found that weak MFs (0.9–4 mT) increase the epileptiform activity [3,4]. This effect seems to be related to gradient's field and becomes more pronounced at longer exposure times of the order of 10 min [5].

In 1992, Bell et al. compared the effect of static (0.078 mT) and ELF-MF (60 Hz; 0.078 mT) on the EEG power spectrum of 20 subjects [6]. All but one showed changes in EEG: 35% of the subjects responded to static MF while 60 Hz exposure was effective in 80% of them. The main finding was the increase of EEG activity at frequencies within 1–18.5 Hz, more often at the central and parietal regions. The simultaneous application of static and alternating MF did not induce synergistic effects. In order to clarify the role of the exposure frequency, Bell et al. [7] compared the effects of 1.5 and 10 Hz MF (0.02–0.04 mT) on the EEG of 19 subjects. They found that 10 Hz was more effective in increasing EEG power but, more interestingly, the spectral analysis demonstrated that specific frequencies of EEG could be influenced by the same specific frequencies of applied MFs. In order to extend these data, Cvetkovic et al. [8] analyzed the effects of multiple ELF-MF exposures (50, 16.66, 13, 10, 8.33 and 4 Hz) on the power of the corresponding EEG bands. This study partially confirmed the intriguing possibility to induce some form of entrainment of driving alpha and beta EEG bands by alpha and beta sinusoidal MF stimulation.

In the past 20 years, an increasing number of studies have analyzed the effects of ELF-MFs on the human EEG. The results are different and partially contradictory, both for the differences in EEG analysis techniques and for the variations in exposure characteristics. Among this large amount of data, the most consistent finding is the change in the alpha band (8–13 Hz) over occipital–parietal regions of the scalp but the direction of this modification is not clearly defined.

Most of the studies reported an increase in alpha activity [9–11]. Marino et al. [10] showed that exposure to ELF-MF (1.5 or 10 Hz; 0.08 mT) potentiates EEG activity at higher spectral frequencies. In 62 volunteers, Heusser et al. [9] demonstrated that 3 Hz MF (0.1 mT) applied for 20 min produces significant increase of the activity in theta (3.5–7.5 Hz) and beta band (12.5–25.0 Hz) in the occipital regions. Lyskov et al. [11] also found that 45 Hz MF (1.26 mT) applied for 60 min enhances alpha and beta activity and decreases the delta one, mainly in the frontal derivations. Cook et al. [12] demonstrated that 15 min of exposure to a specific pulsed ELF MF (200 μT) produces higher resting EEG alpha activity compared to a sham exposure in 20 subjects. Ghione et al. [13] found a significant increase in alpha activity recorded at medial-occipital site following 50 Hz MF (80 μT; 90 min) in 20 healthy volunteers. Few studies reported opposite results. Bell et al. [7] found that the exposure for 10 min to ELF-MF (10 Hz; 0.1 mT) reduces the 10 Hz spectral power measured from the occipital electrodes during the first minute after the stimulation. Similar results were obtained by Cook et al. [14] who analyzed the EEG changes during the stimulation. They found a decrease in occipital alpha activity after the first 5 min of a 15 min pulsed ELF-MF exposure without any significant increase after the stimulation.

Recently, in order to overcome this controversy and clarify the characteristics that drive the effect of magnetic exposure on alpha band, Cook et al. [15] compared the effects of pulsed ELF MF (200 μT) delivered into two different sequences that differed only in presentation rate (refractory period). Compared to sham exposure, ELF-MF induced significant changes in EEG activity in occipital–parietal regions of the brain after 5 min: in particular, alpha activity was lower after the sequence with a shorter refractory period, while the sequence with a longer refractory period produced an increase in alpha activity over the same regions. Interestingly, they noticed that, in the majority of subjects, their initial exposures determined their subsequent responses when they were exposed to a varied presentation of the original sequence. Discussing these data, they hypothesized that individual differences may play an important role in determining a subject's response to an ELF-MF.

In order to link the changes in EEG activity with those observed in brain functions, some authors analyzed the effects of ELF-MFs on event related potentials (ERPs). Indeed the ERPs derive from the EEG signal and represent voltage changes in the brain associated with specific processes or events such as visual, auditory, somatosensory and olfactory stimuli. The ERP waveform consists of a sequence of positive and negative voltage fluctuations. They are called with a P (positive) or N (negative) followed by either latency.

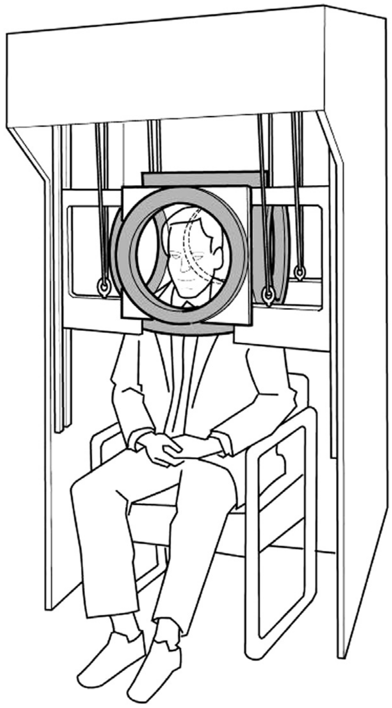

**Figure 1.** An example of device for sinusoidal magnetic stimulation. The exposure system consists of six Helmholtz coils in three orthogonal directions forming a cubic structure. Modified from Crasson et al. [19].

**Figure 2.** Exposure system used to evaluate the effect of PEMF on cortical excitability. The custom coil wrapped around (1400 turns of copper wire, 0.2 mm) a flexible plastic support is positioned to orient the positive pole of the magnetic field toward the top of the skull and connected to the pulse generator (B-01; IGEA, Carpi, Italy). Modified from Capone et al. [25].

Amplitude, latency, and scalp distribution are the measurable features of the ERP [16].

In 1992, Cook et al. [17] examined the effects of combined 60 Hz electric (9 kV/m) and magnetic (20 μT) field compared to sham exposure in 30 voluntaries. They found an increase of P300 amplitude in auditory but not in visual ERP. Similar results were obtained by Graham and colleagues [18]. Under double-blind control conditions, they recorded visual and auditory ERP before, during and after exposure to electric and magnetic field (60 Hz) at different intensities [18]. They demonstrated that specific exposure (9 kV/m, 20 μT) produces replicable effects on P300 only for the auditory ERP. Lyskov et al. found a decrease in N100 amplitude and latency after exposure for 15 min to an intermittent ELF-MF (45 Hz; 1.26 mT; 1 s on/off) [11]. Crasson et al. [19] analyzed the effects of continuous and intermittent ELF-MFs (50 Hz; 100 μT) on several psychological and electrophysiological parameters (Fig. 1). Compared to sham, a brief (30 min) magnetic exposure induced slight but significant changes in ERP. In particular, on a listening task involving selective attention, the N100 amplitude was reduced by intermittent stimulation and increased by continuous exposure. Moreover, in the oddball paradigm (a visual discrimination task), they demonstrated slowing in P2 latency and reaction time.

In order to confirm such conclusions, Crasson et al. [20] tried to replicate these data using the same paradigms with another group of healthy volunteers. The study, double-blind and counter-balanced in the exposure order, did not show any difference among the conditions regarding the performance and electrophysiological measures [20]. They argued that individual susceptibility to MF exposure could explain the lack of reproducibility.

An additional way to investigate the effects of ELF-MFs on brain activity is represented by the evoked potentials (EP). They are currently used in the clinical practice as useful and non-invasive tools to study the function of the somatosensory (SEP), motor (MEP), visual (VEP) and auditory (BAEP) pathways. The effect of ELF-MF on pain-related-evoked potentials (EP) was assessed by Sartucci et al. [21] in a sham controlled study on 11 healthy volunteers. They showed that 2 h exposure to oscillating MFs (+70 to −20 μT; 0.026, 0.043, 0.067 Hz) significantly reduces EP amplitude (N150, P250). On the contrary, Graham and Cook [22] found no effect on the visual evoked potentials (VEPs), brainstem auditory evoked response (BAER) and somatosensory evoked potentials (SEPs). They evaluated 32 subjects after 45 min of MF exposure (60 Hz; 14.1 or 28.3 μT) or an equivalent sham-exposure control period.

Motor evoked potentials (MEPs) can be obtained by recording the muscle responses evoked by transcranial magnetic stimulation (TMS) of the brain. TMS is a non-invasive technique that allows studying the corticospinal motor pathway and, using suitable protocols, to investigate mechanisms of cortical physiology [23,24]. Using TMS, Capone et al. [25] studied non-invasively the effect of pulsed ELF-MFs (75 Hz; 1.8 mT; 45 min) on several measures of cortical excitability in 22 healthy volunteers (Fig. 2). Compared to sham field exposure, the ELF-MFs produced a significantly increase of the intracortical facilitation that is a physiological parameter related to cortical glutamatergic activity. Other parameters of cortical excitability remained unchanged. These results suggest that pulsed MFs exposure may produce a selective enhancement in cortical excitatory neurotransmission.

*The effects of ELF-MF on brain functions*

The effects of ELF-MFs on human pain perception was investigated by Papi et al. [26] who found a significant increase in pain sensitivity (hyperalgesia) after exposure to oscillating MFs (+70 to −20 μT; 0.026, 0.043, 0.067 Hz). This finding was confirmed by subsequent studies of Ghione and colleagues [27] (Fig. 3). In 10 subjects, the nociceptive sensitivity, evaluated by electrical cutaneous threshold, was increased following magnetic exposure (37 Hz; 80 μT; 60 min) [27]. This effect was associated with significant changes in cardiovascular regulation such as slight increase in blood pressure and abnormal response of heart rate variability. They also evaluated the effect of 50 Hz MF (40 μT and 80 μT; 90 min) compared to sham treatment in 40 healthy volunteers [13]. EEG was affected by 80 μT exposure while 40 μT

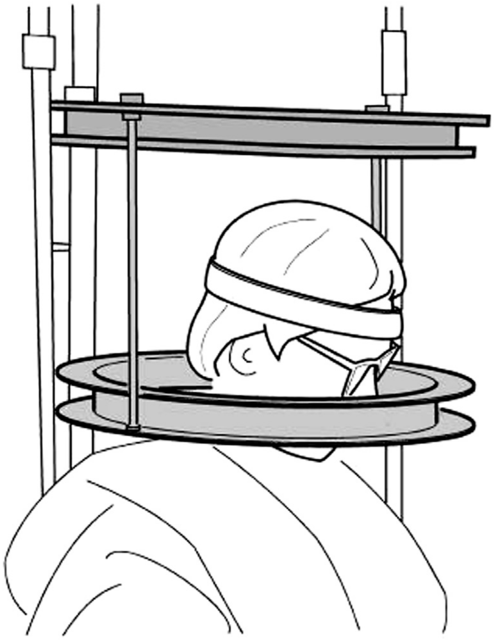

**Figure 3.** PEMF device for human head exposure to a 37 Hz magnetic field. Two circular Helmholtz coils (35 cm in diameter, each composed of an aluminum ring on which 100 copper coils of 0.8 mm of diameter were wound) are connected to the generator. Modified from Ghione et al. [27].

exposure enhanced pain sensitivity assessed by determining dental pain threshold. Cardiovascular parameters remain unchanged in both conditions. Shupak et al. [28] found opposite results when they examined the effects of pulsed MFs (0–500 Hz; 200 μT; 30 min) on thermal sensory and pain thresholds. Compared to sham, the magnetic exposure produced a significant reduction in pain sensitivity (hypoalgesia) but did not affect the sensory threshold. This incongruence could be related to the different experimental conditions such as the magnetic exposure parameters and the kind of pain-protocol used (electrical vs. thermal stimulation). However, the effect of ELF-MF on pain perception seems to be consistent and could be related to changes in opioid system as suggested by animal studies [29].

The motor system can also be modulated by ELF-MF. Thomas et al. and Prato et al. [30,31] evaluated the standing balance recording the normal postural sway with a forceplate that measures the center of pressure and its dynamics. They found that specific pulsed MFs (200 μT; 2 min) produce a significant improvement of the standing balance and this effect is dependent on light-intensity conditions. With eyes closed, the postural sway is increased under low light-intensity and decreased under high light-intensity. The authors hypothesize that, as observed in animals [32], also in humans the magnetic field detection process could be influenced by light.

Another possible target to probe the influence of ELF-MF on the motor system is represented by tremor, defined as a rhythmical, involuntary oscillatory movement of a body part. Physiological tremor is a normal finding in man and it is thought to be a peripheral manifestation of a central oscillatory activity [33]. A study of Legros and Beuter [34] on 24 healthy volunteers revealed that, compared to sham, magnetic exposure (1 mT; 50 Hz) enhances the proportion of low-frequency (2–4 Hz) oscillations in postural tremor. In order to extend these data, Legros [35] and Pavlov [36] studied the effect of the same exposure system (1 mT; 50 Hz) using the wavelet transform, a technique that allows to analyze transient changes of non-stationary signals in the time-frequency domain. Their results confirmed the previous finding and showed that ELF-MFs can modify the postural tremor features (increase in regularity and homogeneity of energy distribution), facilitating the decrease of tremor intensity over time in a manner that could be comparable to the relaxation. Some subjects seem to be more responsive than others [37], however these effects were very slight.

The possible influence of ELF-MFs on melatonin metabolism has been widely discussed in the last 20 years. Melatonin is a hormone produced by the pineal gland under the influence of the dark/light cycle. Besides the ascertained role in the regulation of sleep and circadian rhythms, recent research suggests an involvement of melatonin in other relevant biological processes such as immunomodulation, antioxidant pathways and oncogenesis [38]. Although the first studies by Stevens [39] and Wilson [40] on diseases like cancer and depression suggested a possible role of MF-induced pineal gland dysfunction, a large amount of subsequent data has ruled out this possibility. Studies on humans demonstrated that neither acute [41,42] nor chronic [43–46] exposure to ELF-MFs could produce substantial changes in melatonin secretion. One study by Wood et al. [47] found some effect but only in a specific phase of melatonin profile and, however, their data did not reach the statistical significance.

Despite the large number of publications about melatonin, few studies have analyzed the effects on sleep induced by ELF-MF. In 18 healthy volunteers, Akerstedt and colleagues [48] demonstrated that magnetic exposure (50 Hz; 1 μT) produces significant changes in subjective and neurophysiological sleep parameters (total sleep time, sleep efficiency, slow wave sleep and slow wave activity), but not in melatonin blood concentration. Graham confirmed these data in a double-blind study on 24 healthy young men exposed to a 60 Hz ELF-MF (28.3 μT) [22]. They found that intermittent, but not continuous or sham exposure reduced total sleep time, sleep efficiency and REM sleep duration. These findings were replicated in a subsequent study [49] on 46 older volunteers. Interestingly, older women, but not men showed the above-mentioned pattern of disrupted sleep. This effect, however, could be related to a pre-existing difference between the two populations.

There are several studies regarding the influence of ELF-MFs on cognitive functions, and to the best of our knowledge, there are three reviews that analyzed this topic [1,2,50]. Comparing the results is very difficult because every study evaluated the effects of different exposure systems on many different cognitive tasks. Moreover, the performance in a task is dependent on different cognitive functions. So, we have decided to organize this large amount of data discussing them on the basis of the cognitive task performed.

"Simple/choice reaction time" tasks evaluate the attention toward a target stimulus focusing on reaction speed and accuracy of the performance. Cook [17] and Graham [18] examined the effects of combined electric and magnetic field (9 kV/m; 20 μT) so their results cannot be directly compared to the others. However, Graham found significant decrements in reaction time and in performance accuracy on a time estimation task [18] while Cook observed decreased errors with unchanged reaction time [17]. In 1996, Whittington et al. [51] performed a double blind, placebo-controlled study on 100 subjects to evaluate the influence of 50 Hz (100 μT; 9 min) on cognitive performances. They used a visual duration-discrimination task with three levels of difficulty. Compared to sham, ELF magnetic exposure produced a small but significant decrease in reaction time, only on the hardest level of the performance task [51], the accuracy remained unchanged. Kazantzis et al. [52] studied in 99 healthy volunteers the effect of the same magnetic exposure (50 Hz; 100 μT; 9 min) on the same cognitive task, at two different times of the day. They found that ELF-MFs did not influence the reaction time but produced a small improvement in accuracy, independently from the time of day at which the study was performed [52]. As reported by Whittington, the effect was evident only at the most difficult level of the task [51]. In order to clarify these data, in 2002 Podd et al. [53] attempted again to replicate the experiment on 80 subjects. Surprisingly, using the same exposure system and the same discrimination task of Whittington and Kazantzis, they did not find changes nor in reaction time neither in accuracy. Preece et al. [54] compared the effects of 50 Hz and static (0.6 mT) MF on several cognitive function tests in 16 subjects. They found that oscillating but not static MFs reduce the accuracy in a "choice reaction time" task. Under specific circumstances of sustained attention, a significant slowing in reaction time on a visual discrimination task was found by Crasson et al. [19] who evaluated the effects of ELF-MF exposure (50 Hz; 100 μT; 30 min) on several psychological and electrophysiological parameters. These results were not confirmed by a subsequent study of the same authors who studied different subjects with the same paradigm [20]. Several papers have addressed the influence of ELF-MFs on memory. Memory is the capacity to acquire, store, retain and later retrieve information. It is commonly divided into short-term (or working memory) and long-term memory. The term working memory refers to the ability to temporarily store and manipulate data subserving performance in cognitive activities [55]. Preece et al. [54] showed that 50 Hz (0.6 mT) MFs reduce the accuracy in a numerical working memory task. Keetley and colleagues [56] analyzed the effect of ELF-MFs (50 Hz; 28 μT; 50 min) on the cognitive performances of 30 human volunteers. They found significant reduction in short-term memory of words (Rey Auditory Verbal Learning Test) and worsening of the performance in the Trail-making B test. However, this task is not specific for the working memory because it involves also the executive functioning. Podd et al. [53] showed that 50 Hz (100 μT; 11 min) MF affect recognition memory producing a reduction in accuracy. Corbacio et al. [57] reported that ELF-MFs (60 Hz, 3 mT) induce an abolition of the improvement associated with practice on the digit span forward test. They speculated that ELF-MFs may interfere with the neuropsychological processes responsible for short-term memory. However there are studies that found no influence of magnetic exposure on any of the above-mentioned cognitive functions. In 1995, Podd et al. [53] evaluated the effects of different ELF-MFs (0.1 and 0.2 Hz, 1.1 mT; sham, 0.2 and 43 Hz, 0.1 mT) on simple reaction time. They found no significant changes. Kurokawa [58] explored the effects of 50 Hz (20 μT) MF on 20 subjects. Simple and choice reaction times, accuracy, time perception and figure perception were not affected by 55 min magnetic exposure. Delhez et al. [59] demonstrated in 32 volunteers that ELF-MF (20 and 400 μT; 50 Hz; 65 min) do not modify the performance in neuropsychological tests (digit span, digit span with articulary suppression, divided attention, flexibility, memory updating and time perception). In 74 subjects, Nevelsteen and colleagues [60] found that 50 Hz magnetic fields (400 μT; 30 min) do not produce effects on tasks evaluating flexibility, divided attention, working memory and cross-modal integration. Interestingly, their double-blind placebo-controlled study demonstrated that expectancies and pre-existing beliefs about the potential effects of MFs (enhancement or impairment of the performance) do not influence the results.

Recently, Barth et al. [61] tried to overcome the uncertainty about the potential cognitive effects of ELF-MFs by carrying out a meta-analysis on the topic. They reviewed the literature published from 1986 to 2007 and they selected 9 studies (including 445 subjects) that fulfilled the inclusion criteria. All these studies analyzed the effects of 50 Hz MF using a double-blind protocol. They found little but significant changes in two cognitive dimensions: visual discrimination and flexibility. In the visual duration discrimination task, the performance of the exposed subjects was better in the hard level of the test and worse at the intermediate level. The cognitive flexibility could be measured as the skill to shift from a type of target to another. The meta-analysis showed that magnetic exposure induced a significant increase of the correct responses in a flexibility task. In conclusion, this study seems to suggest that ELF-MFs could have effects on some specific cognitive functions but considering the very limited number of the included studies, these findings should be considered with caution.

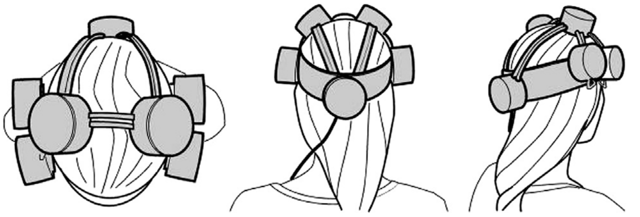

**Figure 4.** PEMF exposure system for the treatment of depression. The treatment helmet comprises 7 coils connected in parallel with the pulse generator, in particular: 2 coils in the anterior and the posterior temporal regions, 1 coil (both sides) in the upper parietal one, and 1 coil in the center of the lower occipital region. Modified from Martiny et al. [65].

Few studies have investigated the influence of ELF-MFs on mood and emotions. Persinger et al. [62] investigated the effects of localized MF (1 μT; 20 min) on the emotive state of 40 healthy subjects. They found that those who received the stimulation over the right hemisphere rated their experience as significantly more pleasant than those who received the same stimulation over the left hemisphere. Stevens [63] analyzed the effect of 20 Hz MF (50 μT) on perception of visual stimuli. Skin conductance, affective and arousal content rating were measured in 29 subjects. Their results showed that the images viewed under magnetic exposure were perceived as having a more positive affect. In 2007 Stevens [64] performed a pseudo-randomized, double-blind study on 20 volunteers to assess the changes in the emotional state induced by sinusoidal MF (0–5 μT; 8–12 Hz). The frequency of the ELF stimulation differed among the subjects and was chosen to correspond to the mean peak frontal frequency of the EEG previously recorded for each subject during autobiographical recall of emotional states. Compared to sham, the magnetic exposure produced an improvement in emotional state and a significant decrease in cortical activity measured by EEG power spectrum. However, considering the lack of "experiencing emotional state" typical EEG features ($\alpha$ frontal asymmetry), Stevens considered unlikely a direct influence of ELF-MF on brain emotional circuits. Other authors [19,60] found no changes in mood following magnetic exposure. Recently, Martiny et al. [65] evaluated the effectiveness of pulsed ELF-MF (1.9 mT; 55 Hz) in the treatment of drug-resistant depression in a sham-controlled double-blind study (Fig. 4). Fifty patients were randomized into active or sham group and came for daily sessions for 5 weeks. Compared to sham, the pulsed EMF therapy produced a significant better outcome both in clinician rated scales and in patient rated questionnaires, with the onset of the effect within the first weeks of treatment. Side effects were few and mild.

## Conclusions and future perspectives

Taken together, the studies above reviewed suggest that ELF-MFs might exert a slight influence on human brain activity. In particular, the experimental data suggest that weak magnetic exposure could affect almost all cerebral functions such as motor control, sensory perception, cognitive activities, sleep and mood. These findings are supported by the results of the neurophysiological studies that revealed measurable changes in

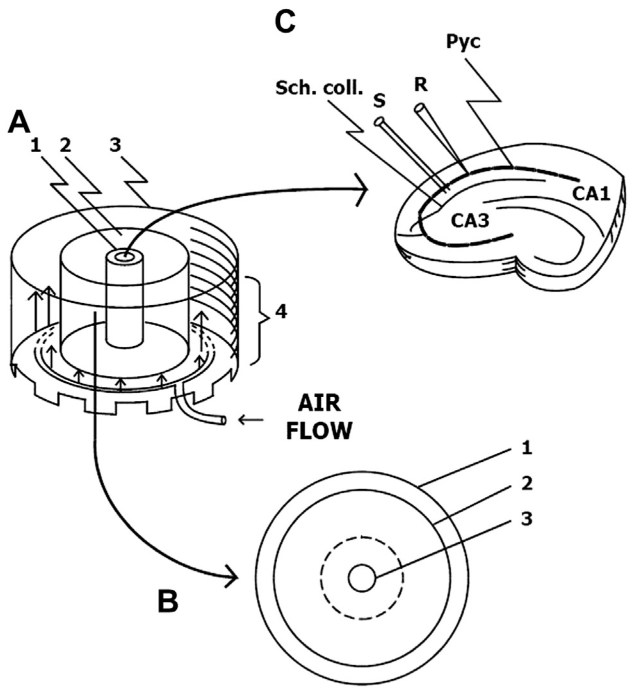


**Figure 5.** Experimental apparatus to study the influence of PEMFs on hippocampal neurons. (A) a side view of the experimental setup. The slice chamber (1), surrounded by a water-containing chamber (2) is inserted into a circular acrylic frame (3) containing magnetic coils (4) placed orthogonally to the plane of the slice. A constant flow of cooling air moved upward. (B) a top view of the apparatus. (C) the hippocampal slice. Electrode (S) stimulated Schaffer collaterals (Sch. Coll.) in CA3 region and electrode (R) recorded extracellularly the activity of CA1 pyramidal cells (Pyc). Modified from Wieraszko [78].

brain electrical activity following ELF-MF exposure. Moreover, the experimental data at cellular and tissue level showing the effects on cell membrane receptors and intracellular signaling suggest possible mechanisms for ELF-MF action on the brain. However, despite the large number of studies performed so far, the reproducibility and specificity of the effects of ELF-MFs are still poorly defined (see Supplemental section 4).

In light of its possible effects on neuronal cells and networks, ELF-MF exposure could represent a potentially valuable approach for controlled modulation of regional brain activity that might become a useful non-invasive tool for the treatment of neurologic and neuropsychiatric disorders.

For instance, the effects on adult hippocampal neurogenesis (see Supplemental section 3.3) suggest that ELF-MF exposure could be useful for improving the function of this brain area, which is primarily involved in learning and memory, and for facilitating functional compensation for age- or disease-related neuronal loss. Hopefully, these findings will be exploited in the near future to develop novel and more effective therapeutic strategies in the field of regenerative medicine, based on combined exposure to electromagnetic and other stimuli (pharmacological or physical) with validated proneurogenic efficacy. Within the preceding context, the protective action of an electromagnetic treatment may also depend on its influence on the metabolic processing of amyloid precursor protein APP. Indeed, this is an integral membrane protein whose non-amyloidogenic processing produces physiological metabolites implicated in synapse formation and in neural plasticity, whereas its amyloidogenic pathway generates pathological products involved in the genesis of the amyloid plaques [66].

Another interesting field of research is the effect of ELF-MFs on glutamatergic neurotransmission because of the ascertained role of glutamate in the pathophysiology of several neuropsychiatric disorders. *In vitro* works have demonstrated that ELF-MFs influence the neuronal activity inducing changes in function and distribution of membrane proteins of exposed cells [67]. In hippocampal glutamatergic synapsis, the group of Wieraszko showed that pulsed ELF-MFs (15 mT; 30 min) produced frequency dependent amplification of evoked potentials mediated by an increase of cAMP in neurons [68] and glutamate concentration in synaptic cleft [69] (Fig. 5). Varani et al. [70–72] found that pulsed ELF-MFs (75 Hz; 1.8 mT; 30 min) produce a specific increase in density and functionality of adenosine receptors (A2A and A3) expressed by nonneuronal cells. Adenosine is a neuromodulator of CNS that acts by four types of G-protein coupled receptor (A1, A2A, A2B, A3) [73]. In particular, A1 and A2A modulate glutamatergic transmission with opposite effects: A1 receptor activation reduces glutamate release and hyperpolarizes neurons, while A2A activation potentiates neurotransmission [74]. Interestingly, Capone et al. [25], using ELF-MF with identical field characteristics of the Varani's studies, found an increase in intracortical facilitation produced by paired pulse TMS. Intracortical facilitation is a cortical phenomenon: the neurophysiological basis is still unclear [23,75] but pharmacological studies suggest that it reflects excitatory neurotransmission largely mediated by NMDA receptors [23]. In agreement with experimental data, this finding suggests that the modulation of neurotransmitters receptors such as adenosine and glutamate could represent a possible explanation for the effect of ELF-MF. A growing body of evidence suggests that glutamatergic abnormalities are involved in the pathophysiology of mood disorders [76] and could be a novel therapeutical target [77]. This possibility was explored by Martiny et al. [65] who demonstrated the effectiveness of pulsed ELF-MF in the treatment of drug-resistant depression in a sham-controlled double-blind study on 50 patients. To the best of our knowledge, this is the only study that has tested the potential therapeutic role of ELF-MFs.

In conclusion, considering the effects of such fields on several brain functions, there is great interest about the ELF-MFs potentialities in the treatment of other neuropsychiatric diseases. Future research should be designed using comparable exposure conditions both *in vitro* and *in vivo*. To this end, the electric field and current distribution inside the exposed target should be evaluated through dosimetric models. Experimental investigations at different levels of biological complexity, coupled with modeling studies, will allow to link the behavioral findings in humans to the changes in cell physiology in order to provide rationale and reliable basis for the use of ELF-MFs in therapy.

## Supplementary material

Supplementary data related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.brs.2013.01.004.

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