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Title: Extremely low frequency magnetic field exposure and neuromodulation in humans

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Short Abstract (500 characters max): 778 characters (68 words)

A sufficiently strong time-varying magnetic field (MF) can impact the electrical activity of neurons and neuronal assemblies.

However, no consensus exists yet on the MF threshold in the Extremely Low Frequency Range (ELF, < 300 Hz) inducing neuromodulation in humans, and to what extent it translates into objective behavioral outcomes.

Here, we review results suggesting possible ELFMF-induced neuromodulation, and discuss them through the prism of possible synaptic mechanisms.

Long abstract (10,000 characters max): 8779 characters (1302 words)

INTRODUCTION

Many studies suggest neuromodulatory effects due to electric fields induced by time-varying magnetic fields (MF) exposure in the extremely low-frequency range (ELF, < 300 Hz – see [1-3] for review). Let's specify that the concept of neuromodulation refers to: modifications of electrical, metabolic, or chemical processes taking place in the central nervous system as a consequence of an exogenous stimulus (e.g., ELFMF exposure).

Electroencephalography (EEG) is the central nervous system biomarker that has likely been the most studied in the context of ELFMF research. Although the results are very heterogeneous (partially because of the wide variety of protocols used), the most consistently reported effect is an increase the resting occipital alpha EEG rhythm (8-12 Hz) as a consequence of exposure [4, 5]. It is interesting to note here that, since in most cases the EEG cannot be recorded during the ELFMF exposure conditions due to MF-induced artefacts in the signal, these are post-exposure persistent effects. Other studies have focused on human motor or cognitive behaviour and possible exposure effects on physiological baselines and performances. In terms of motor control, results show that an ELFMF exposure can under certain circumstances reduce the normal antero-posterior standing balance [6, 7] or modulate physiological tremor amplitude [7-9] in healthy volunteers. Vestibular-related postural responses and vertigo have also been reported as a consequence of moving the head in the strong static magnetic field of a Magnetic Resonance Imaging (MRI) scanner [10, 11]. In terms of cognition, a disruption in attention and of working memory were reported with exposures as low as 0.6 mT at 50 Hz [12], and our group has also observed an interference in short-term memory performance with a one hour, 3 mT exposure at 60 Hz [13]. More specifically, this last result suggests a cancellation, with ELFMF exposure, of the performance improvement classically associated with the repetition of a task. It is interesting to notice that this same interference in performance improvement has also been observed in a reaction time task when given before and after an exposure of 1 hour to a 1.26 mT MF at 45 Hz [14]. A movement-induced time-varying MF tested in an MRI environment is reported to impact neurocognitive performance as well [15].

Post-exposure persistent effects have also been observed using functional Magnetic Resonance Imaging (fMRI) in a standard finger tapping task: specific brain regions displayed higher levels of activation after one hour of exposure to a 60 Hz, 1.8 and a 3 mT MF (2 different experiments) as compared to after a sham condition [16]. One of the putative mechanisms potentially supporting these observations could involve changes in cortical excitability due to synaptic plasticity processes (i.e., dynamic changes in synaptic efficiency). Capone et al. have tested this hypothesis and have shown that a pulsed MF (peak value 1.8 mT) delivered during 45 minutes can indeed have a persistent effect by increasing cortical excitability [17]. Interestingly, MRI imaging procedures given in a 1.5 and 7T scanner have also been shown to impact cortical excitability in healthy volunteers [18].

Put together, those effects suggest that an ELFMF stimulus is capable of having a persistent effect (in the order of minutes) on neurophysiological processes and behaviours, which could be interpreted as the consequence of synaptic plasticity modulations.

THRESHOLDS FOR INDUCED ELECTRIC FIELDS IMPACTING NEURONAL ACTIVITY

ELFMF exposure induces an electric field from Maxwell-Faraday's law. This induced electric field results in an additive cell membrane potential perturbation [19, 20], dependant on neuronal morphology and electric field orientation [21]. For ELFMF exposure in the low mT range, this membrane perturbation is insufficient to trigger action potentials, but might play a role in synaptic communication [22-24]. Synaptic processes can indeed be affected by modulating the presynaptic membrane potential by 1 mV, while a depolarization as little as 60 μV seems to be capable of affecting the synapses in the retina [25-27], and give rise to the perception of phosphenes. Magnetophosphenes are described as flickering visual perceptions and are the most well-established and consistent biological effect of ELFMF on human neurophysiology [24, 28, 29]. Following the work from Lövsund et al. [30], Silny reported human perception of magnetophosphenes induced by an intermittent one hour ELFMF between 10 and 20 mT (frequency range = 5-60 Hz) [31]. In the same study, it is reported that there is an effect of the exposure on visual evoked potentials (VEP) lasting past the end of the exposure period, suggesting a persistent effect and thus a potential impact on synaptic plasticity.

Another suitable approach offering the opportunity to approach the mechanisms of action from another perspective is using available mathematical models mimicking the activity of specific brain structures. Such models describe neuronal electrical activity (e.g., generation and propagation of action potentials) using validated equations simulating synaptic communication [32]. This approach enables the simulation from small-scale (e.g., local field potentials) to large-scale (e.g., EEG) of brain electrical activity, and had recent successes in improving understanding biological mechanisms at work of brain interaction with ELFMF [19]; or therapeutic brain stimulation [33]. We have already initiated mathematical modeling work to explore the interaction between ELF MFs and brain activity [20, 34, 35], showing that lasting changes may be induced in neuronal activity using specific stimuli [35], and that ELFMF exposure impacts single neurons' activity predominantly in two frequency bands: 60-70 Hz and 100-120 Hz, confirming earlier findings [19]. Also, an *in vitro* study (on hippocampal slices) combined with modeling has shown that sub-mV membrane depolarization induced by an AC electric field has an impact on spike timing and rate on a neuronal population [36]. Another study using a similar approach suggested that the effect of a small membrane depolarization induced by the electric field is amplified by non-linear membrane properties, resulting in effects on spike timing [37]. These are converging evidence of the theoretical capability of an ELFMF in the mT range (10 mT and higher) to sufficiently depolarize neuronal membranes to impact their spike timing. This is of crucial importance, since a well-characterized form of synaptic plasticity, termed 'spike-timing dependent plasticity' (STDP) is critically dependent on the timing between pre-/post-synaptic spikes [38]. A spike timing shift of only a few milliseconds can significantly change the synaptic efficacy, and even turn a synaptic potentiation into synaptic depression or vice-versa [39]. Therefore, there is a plausible chain of events leading induced electric fields from ELFMF causing membrane depolarization, and a change in spike timing and synaptic plasticity.

IMPLICATIONS AND DIRECTIONS

It appears that lasting effects observed in human neurophysiology due to ELFMF exposure are compatible with a modulation of synaptic plasticity. If this hypothesis can be further confirmed, it opens the door to one 'skilled-in-the-art' in terms of medical and performance-related translational applications. Indeed, It is already proposed to treat specific neurologic or neurodegenerative diseases by targeting this plasticity [40-42], and we could envision the potential use specific ELFMF stimuli targeting pre-determined changes in synaptic plasticity in order to relieve specific symptoms. To move in this direction, an exciting avenue of research consists of: proposing human experiments guided by results from previous experimental studies and biophysical modeling, and further confronting this synaptic plasticity hypothesis to experimental results (e.g. using learning, memory or cortical excitability protocols).

CONCLUSIONS

It appears from the recent experimental and theoretical literature that ELFMF have the potential, *via* identified and validated biophysical mechanisms, to induce changes in synaptic plasticity processes, which might have implications in, and not limited to, effects on memory and learning performance in humans. Also, although the flux density for reproducible results seems to stand above 10 mT, further knowledge is needed regarding the true ELFMF flux density threshold at which objective biological effects can be detected. This is the goal we are currently pursuing by studying the threshold for magnetophosphenes perception and associated objective neurophysiological responses to 50 and 60 Hz MF of up to 50 mT.

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