Evidence for changes in brain synaptic plasticity induced by exposure to extremely low-frequency magnetic fields

Julien Modolo, Alex W Thomas, Robert Z Stodilka, Alexandre Legros
Lawson Health Research Institute, Saint Joseph Health Care
Department of Medical Biophysics, University of Western Ontario
268, Grosvenor Street, London, N6A4V2, Canada

AIM OF WORK

This work aims to provide a theoretical basis for experimentally reported lasting effects induced by extremely low-frequency (ELFs, < 300 Hz) magnetic fields (MF) in humans [1, 2] Specifically, we propose that brain exposure to ELF MF has the potential to induce changes in brain synaptic plasticity, resulting in lasting effects.

MATERIAL AND METHODS

Brain synaptic plasticity refers to the dynamic change in synapses efficiency (efficiency to depolarize/hyperpolarize post-synaptic membranes, also called "weight") perpetually occurring the brain. Synaptic weights can either increase (synaptic potentiation) or decrease (synaptic depression). Different factors can induce changes in synaptic plasticity, a critical one being the timing of action potentials between interconnected neurons. In this work, we have used a mathematical model of spike-timing dependent plasticity (STDP), extensively validated experimentally worldwide [3,4]. In brief, STDP describes how the time interval between pre- and post-synaptic action potentials induces changes in synaptic weights. Let t_{pre}/t_{post} be the times at which pre/post-synaptic spikes occur, and let $\tau = t_{pre} - t_{post}$ be the time difference between pre- and post-synaptic spikes. Let $\frac{dw}{w}$ be the change in synaptic weight *w* associated with a *single synaptic plasticity event* (i.e., reception of a pre-synaptic spike followed by emission of a post-synaptic spike), then the STDP model is [5]:

$$\begin{cases} \frac{dw}{w} = A_p.\exp(-\frac{\tau}{\tau_p}) \text{ if } \tau < 0 \\ \frac{dw}{w} = A_d.\exp(-\frac{\tau}{\tau_d}) \text{ if } \tau > 0 \end{cases} \quad (1)$$

where A_p / A_d are the amplitude of synaptic potentiation/depression, and τ_p / τ_d are the time constants for synaptic potentiation/depression lumping molecular processes into play. It has been demonstrated experimentally and investigated theoretically that neural tissue exposure to weak electric fields (that can be induced by time-varying MF) can modulate spike timing [6,7,8]. In the following, we intent to evaluate the impact of shifts in spike timing in the millisecond range on single synaptic potentiation or depression events.

RESULTS

Let δt be the shift in spike timing for a single potentiation ($\frac{dw}{w} > 0$) or depression event ($\frac{dw}{w} < 0$), and let τ_p^0 / τ_d^0 be the average delay between pre- and post-synaptic action potentials during a single synaptic potentiation/depression event. In the following, we assume that MF exposure results only in spike timing perturbation, and not in any action potential generation (e.g., the MF flux density is sufficiently low so that it does not cause neurons to fire). Therefore, we investigate potential *neuromodulatory* effects, and not neurostimulation effects. In the case of no MF exposure ("sham" condition), $\delta t = 0$ and the average potentiation/depression $\delta W_p / \delta W_d$ in the "sham" condition are directly given by the STDP model (1):

$$\begin{cases} \delta W_{sham}^{p} = A_p . \exp(\frac{\tau_p^0}{\tau_p}) \\ \delta W_{sham}^{d} = A_d . \exp(-\frac{\tau_d^0}{\tau_d}) \end{cases} \qquad (2)$$

First, we treat the case of synaptic potentiation during MF exposure. If $\delta t < -\tau_p^0$, then the perturbation in spike timing induced by MF exposure is such that it results in a modulated potentiation:

$$\delta W_{\exp}^{p} = A_p . \exp(\frac{\tau_p^0 + \delta t}{\tau_p}) \qquad (3)$$

So that the net change between the "exposed" and "sham" condition is:

$$\delta W_p = \delta W_{\exp}^{p} - \delta W_{sham}^{p} = A_p . \exp(\frac{\tau_p^0}{\tau_p}) . [\exp(\frac{\delta t}{\tau_p}) - 1] \qquad (4)$$

However, if $\delta t > -\tau_p^0$, then $\tau = \tau_p^0 + \delta t > 0$, therefore *the synaptic potentiation event becomes a synaptic depression event* (per the STDP model (1)), i.e. an opposite direction of the effect. This point is critical: for small perturbations of spike timing, synaptic potentiation is modulated in amplitude, but for larger perturbations of spike timing, synaptic potentiation is reversed into synaptic depression. In that situation, the change in synaptic weight in the "exposed" condition becomes:

$$\delta W_{\exp}^{p} = A_d . \exp(-\frac{\tau_p^0 + \delta t}{\tau_d}) \qquad (5)$$

And the net change caused by the exposure becomes:

$$\delta W_p = \delta W^p_{\exp} - \delta W^p_{sham} = A_d.\exp(-\frac{\tau^0_p + \delta t}{\tau_d}) - A_p.\exp(\frac{\tau^0_p}{\tau_p}) \qquad (6)$$

Also, if δt becomes large (say, $\delta t \to \pm\infty$), then we obtain $\delta W^p_{\exp} \to 0$. This translates into a cancellation of synaptic potentiation for large values of δt, and presumably large MF flux density values. Therefore, it is theoretically possible that exposure to sufficiently high flux density MF (but lower than the threshold for action potential initiation) might impair synaptic potentiation processes.

Second, we treat the case of synaptic depression similarly to the case of synaptic potentiation. If $\delta t < -\tau^0_d$, then in the "exposure" condition, a single synaptic depression event is modulated and the resulting amplitude in synaptic depression becomes:

$$\delta W^d_{\exp} = A_d.\exp(-\frac{\tau^0_d + \delta t}{\tau_d}) \qquad (7)$$

Resulting in a net change compared to the "sham" condition:

$$\delta W_d = \delta W^d_{\exp} - \delta W^d_{sham} = A_d.\exp(-\frac{\tau^0_d}{\tau_d}).[\exp(-\frac{\delta t}{\tau_d}) - 1] \qquad (8)$$

However, if $\delta t > -\tau^0_d$, $\tau = \tau^0_d + \delta t < 0$, then *the synaptic depression event becomes a synaptic potentiation event* (again, a change in the direction of the effect). In this case, the synaptic change is:

$$\delta W^d_{\exp} = A_p.\exp(\frac{\tau^0_d + \delta t}{\tau_p}) \qquad (9)$$

Resulting in a net change compared to the "sham" condition:

$$\delta W_d = \delta W^d_{\exp} - \delta W^d_{sham} = A_p.\exp(\frac{\tau^0_d + \delta t}{\tau_p}) - A_d.\exp(\frac{\tau^0_d}{\tau_d}) \qquad (10)$$

Finally, if δt becomes large (say, $\delta t \to \pm\infty$), then we obtain $\delta W^d_{\exp} \to 0$, implying that exposure to MF with high flux density values might cancel synaptic depression processes as well. Consequently, large δt values theoretically result in a cancellation of both synaptic potentiation and depression processes.

The explicit formulas (4,6,8,10) that we derived define the relationship between the spike timing shift induced by ELF MF exposure and its impact on a single synaptic plasticity event (synaptic potentiation or depression). This relationship is presented in Figure 1, both for synaptic potentiation and depression.

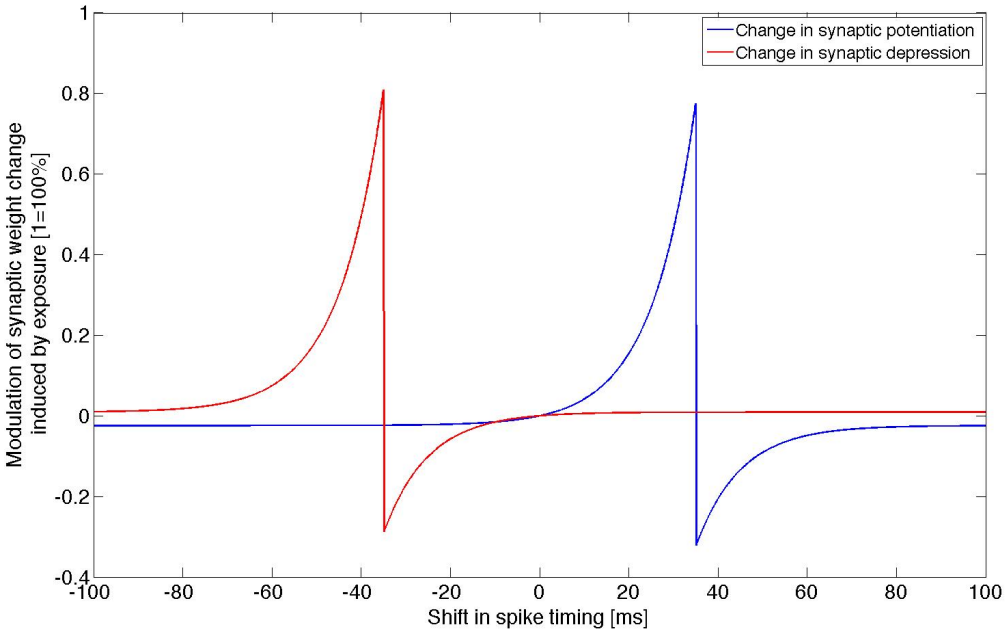

Figure 1. Relationship between the amplitude of spike timing (e.g., induced by MF exposure) and its impact on synaptic plasticity changes (changes in synaptic potentiation, blue; changes in synaptic depression, red). A "window effect" depending on δt values appears, as a consequence of the nonlinear system of equations that describe STDP processes. Standard parameter values were used for STDP: $A_p = 0.8$, $A_d = -0.3$, $\tau_p = \tau_d = 10$ ms [4]; and the average delays between pre- and post-synaptic spikes were $\tau_d^0 = -\tau_p^0 = 35$ ms. Let us note that different values for τ_d^0, τ_p^0 will result in different curves (not affective qualitatively the results).

DISCUSSION

We have proposed that, by modulating spike timing, MF exposure can result in synaptic plasticity changes with a "window effect". Overall, we can identify three different domains of effects: 1) for small spike timing perturbations, synaptic potentiation and depression are modulated; 2) for higher spike timing perturbations, there is a reversal of synaptic plasticity (synaptic potentiation events become synaptic depression events, and vice-versa); and 3) if spike timing perturbation are too high, then both synaptic potentiation and depression processes tend to cancel.

It is now a consensus in the neuroscience community that synaptic plasticity is a major neurobiological substrate for memory and learning. Therefore, if MF exposure has indeed the potential to modulate synaptic plasticity processes, it is possible not only that observed lasting effects can be explained at least to some extent, but also that possible effects on memory and/or learning could be observed. In a recent study by our group [2], we have found that a one-hour exposure to a 60 Hz, 3000 microtesla MF had an effect on 1 out of 10 different cognitive tests (cancellation of the learning effect in the exposed group in a memory task). Even if, of course, these results need replication, it might be experimental evidence that MF exposure has the potential to impact, to some extent, memory processes, presumably by a modulation of synaptic plasticity induced by the MF.

One possible experimental verification of our theory would consist *in vitro* to use blockers of NMDA receptors, that are involved in the influx of calcium that regulate the presence of AMPA receptors at the dendritic spine level. Indeed, the synaptic weight for a single synapse is proportional to the number of AMPA receptors at the post-synaptic dendritic spine. Such blockade of this critical synaptic plasticity pathway should decrease, if the model is correct, neural tissue sensitivity to external electric fields. Another possibility of testing *in vivo* would be to expose healthy human subjects to MF of gradually increasing MF flux density at a given frequency, and to quantify the performance of cognitive testing involving memory and learning processes. If our proposed mechanism is correct, then different outcomes on the performance, with a reversal in the direction of effects above a certain threshold, should be observed with increasing MF flux density.

The implications of synaptic plasticity as a mechanism of interaction between ELF MF and brain tissue are twofold. First, if correct, knowledge of this mechanism will improve our understanding of lasting ELF MF exposure effects from a regulatory perspective. Second, this mechanism could be exploited to develop innovative, therapeutic neuromodulation protocols, based on magnetic stimulation, that would specifically aim at modulating synaptic plasticity in neurological disorders characterized by impaired synaptic plasticity (e.g., Parkinson's disease [9], epilepsy [10]).

CONCLUSIONS

Using a robust and validated model of synaptic plasticity process taking place *in vivo*, we have shown that small perturbations in the timing of action potentials by MF exposure can result in subtle modulations of synaptic plasticity processes. This suggests that functional effects take time to buildup, and last after cessation of MF exposure. Importantly, these results explain why there might be a specific "window" in MF amplitude resulting in lasting effects of MF exposure. The perturbation of synaptic regulation processes such as STDP provides a biologically plausible explanation of MF exposure lasting effects. Future work will focus on the detailed relation between ELF MF characteristics (flux density, frequency) and the average shift in spike timing, but also how to quantify cumulative effects of the synaptic

plasticity modulation that we have presented in this work. Consequences on neural network dynamics will also have to be investigated.

ACKNOWLEDGEMENTS
This work is supported by a MITACS Elevate Post-Doctoral Fellowship, the Canadian Institute of Health Research (CIHR), Hydro-Québec/Électricité de France/Réseau de Transport d'Électricité, and the Lawson Health Research Institute.

REFERENCES
[1] Legros et al., Eur J Appl Physiol, epub ahead of print (2011).
[2] Corbacio et al., Bioelectromagnetics, 32(8):620-33 (2011).
[3] Gerstner W. et al., Nature, 386:76-78 (1996).
[4] Bi G.Q. and Poo M.M, J Neurosci, 18:10464-72 (1998).
[5] Song et al., Nat Neurosci, 3:919-26 (2000).
[6] Reato et al., J Neurosci, 30(45):15067-79 (2010).
[7] Modolo et al., IEEE 5th international conference on bio-inspired computing, Liverpool (2010).
[8] Stodilka et al., Neurocomputing, 74(12-13), 2164:2175 (2011).
[9] Calabresi P0 et al., Parkinsonism Relat Disord, 13 S3:S259-62 (2007).
[10] Ben-Ari Y., Dialogues Clin Neuosci, 10(1):17-27 (2008).