1. WM topic

EMF modulation of acetylcholine-mediated plasticity in the mammalian cortex. Comparative biophysical study and modeling of tMS and tDCS.

2. WM subtopics of interest

- EMF-induced neural plasticity
- Neural tissue stimulation
- Neural tissue models
- tMS and tDCS-induced neural plasticity
- acetylcholine (ACh)-based plasticity
- EMF modulation of cognitive processes

3. WM description

Acetylcholine (ACh) is one of the most important neurotransmitters of both, the central and peripheral nervous system and plays a key role in arousal, attention, decision making, perception, learning and encoding of new memories (Spehlmann et al., 1971; Foote et al., 1975; Stone, 1972; McGaughy et al., 1996; Hasselmo, 2006). ACh also plays an equally important role in the functional reorganization of adult rat, cat and primate sensory and motor cortices (Golmayo et al., 2003; Rasmusson and Dykes, 1988; Sachdev et al., 1998; Thiel et al., 2002; Weinberger, 2004).

EMFs originated by any type of tanscranial stimulation, either magnetic (tMS), direct current (tDCS) or alternating current (tACS) are able to modulate cortical information processing, neural plasticity and learning (Gillick and Zirpel, 2012; Cheeran et al., 2010; Antal et al., 2011). Moreover, EMF interacts with cortical ACh in several cortical processes (Chaieb et al., 2012).

Up to now, despite many “in vivo” (several of them in humans) and some “in vitro” studies we don’t have any knowledge on the effect of the different types of transcranial EMF applications on the ACh-mediated cortical processes nor on the involved circuit, cellular and subcellular mechanisms.

Here we propose to perform “in vivo” and “in vitro” comparative studies of the three main transcranial EMF generators, namely tMS and tDCS and to develop mathematical models of the applied EMFs and their interactions with cortical dynamics at circuit, cellular and subcellular level.

4. State-of-the-art

Pharmacological studies in human subjects conclusively demonstrate that blockade of muscarinic cholinergic receptors by drugs such as scopolamine impairs the encoding of new memories but not the retrieval of previously stored memories (Atri et al., 2004; Hasselmo and McGaugh, 2004) and impairs working memory for some stimuli (Green et al., 2005). Conversely, drugs which activate nicotinic receptors enhance the encoding of new information (Buccafusco et al., 2005; Levin et al., 2005).

ACh also plays an equally important role in the functional reorganization of adult rat, cat and primate sensory and motor cortices (Golmayo et al., 2003; Rasmusson and Dykes, 1988; Sachdev et al., 1998; Thiel et al., 2002; Weinberger, 2004). ACh enhances neuronal responsiveness as concluded through its involvement in activity-dependent cortical plasticity: First because ACh facilitates responses to visual, auditory, and tactile stimuli and also assists in “unmasking” hidden receptive fields. In the above-cited processes ACh appears either as permissive agent or a facilitator of other acting mechanisms (Casamenti et al., 1986; Celesia and Jasper, 1966) although fundamental questions like when, how or why ACh release is activated are yet to be answered. Second, because peripheral deafferentation directly affects the cholinergic system: sensory deprivation down-regulates cortical ACh through its synthesizing enzyme the choline acetyltransferase (ChAT) from the first days after the injury (Rothe et al., 1990) indicating cholinergic circuits are affected by alterations of the sensory input (Avendano et al., 1995).

Low-intensity currents modify spiking of neural populations (Reato et al., 2010). tAES modifies the neural mechanisms of the cognitive processes (Herrmann et al., 2013) and several of the principal characteristics and molecular mechanisms of tMS-induced plasticity correspond to those of the STDP observed at a cellular level (Feldman, 2012; Müller-Dahlhaus et al., 2010). A very recent research on human subjects demonstrated that a central bottleneck of information processing can be overcome by cathodal but not anodal tDCS of the left pLPFC immediately before the task (Filmer et al., 2013).

EMF and cortical ACh interact in several cortical processes. A differential action of the nicotine (ACh agonist) to paired sensory-tDCS and possible synergies between different cholinergic receptors and non-invasive current stimulation were reported in a study of the motor cortex by (Chaieb et al., 2012). Direct interaction of transcranial electrical stimulation and ACh pharmacology (ACh agonists-antagonists) as well as paired electrical stimulation of a nerve has also been proved (Korchounov and Ziemann, 2011).

ACh is a key factor selectively enhancing the process of thalamic inputs and suppressing the retrieval of internal associations (Sarter et al., 2005; Ramanathan et al., 2009). EMF could have a direct effect on the efficiency of these inputs in cortical plasticity phenomena.

Mathematical models and simulations of TS are very few and mostly limited to a rough description of the direction and intensity of the fields and to the suggestion of optimal placement of stimulation devices (http://biohacksblog.com/tdcs-models-modulations/)

5. Gaps and challenges

Electric fields generated by the tMS either depolarize or hyperpolarize the neural membrane which affects the generation of action potentials. Anodal (V+) tDCS depolarize the membrane of the neurons in the affected area with a consequent increase of the excitability of the neural cells while cathodal stimulation has the opposite effect. Repeated tMS and tDCS both produce long-lasting plastic phenomena equivalent to long term potentiation (LTP) and long term depression (LTD). However the exact details of how these tMS and tDCS function are still to be discovered.

From a biophysical point of view main unanswered questions in transcranial stimulation concerns the way such a broad EMF can induce very localized and specific changes in the synapse and the neural activity of the cortical networks. Gaps and challenges include

- Development of mathematical models capable to predict the action of the EMFs at both, macroscopic and microscopic level taking into account that: dimensions of stimulation devices differ considerably from case to case; device location and orientation is highly variable across studies; acting EMFs are severely distorted and filtered by scalp, bones, dura and cerebrospinal liquid.
- Discover how EMFs specifically act on plasticity inducing neurotransmitters and in particular on ACh mechanisms. Investigate the interactions with synaptic activity and local learning rules (i.e. hebbian) of individual neurons, most of which are mediated by ACh. (Rasmusson and Dykes, 1988; Weinberger, 2004; Hasselmo, 2006)
- Determine how EMFs act on the rhythmic activity of the cortical circuits at microscopic level. Neural oscillations and spike-timing-dependent-potentiation are fundamental mechanism for cortical information processing at both, microscopic and macroscopic level (Panetsos and Sanchez-Jimenez, 2010; Feldman, 2012; Sanchez-Jimenez et al., 2013; Ozen et al., 2010).

6. Objectives to be achieved

We hypothesize that transcranially-delivered EMFs interfere with the biomolecular mechanisms of ACh-mediated hebbian plasticity rules through modifications of intracellular cAMP and calcium levels. This should be carried out either with or without interaction with ACh-potentiation mechanisms.

Obj. 1 Identify and model the effect of tMS and tDCS on neural dynamics at cellular and subcellular level and the induction of LTP-LTD (by pairing EMFs and sensory stimulation).

Obj. 2 Identify and model tMS-ACh and tDCS-ACh interactions at cellular and subcellular level and ACh-mediated LTP-LTD (by pairing EMFs and sensory stimulation and delivering ACh agonists-antagonists).

Obj. 3 Identify and model cellular, molecular and gene changes in the neural tissue related to the tMS-tDCS effects on ACh-mediated plasticity/learning

Obj. 4 Identify and model of tMS-ACh and tDCS-ACh interactions at circuit and cellular level correlated to behavioral performance (by pairing EMFs and sensory stimulation and delivering ACh agonists-antagonists).

Obj. 5 Identify and model of tMS-ACh and tDCS-ACh interactions at circuit and cellular level correlated to sensory deprivation-induced plasticity (by pairing EMFs and sensory stimulation and delivering ACh agonists-antagonists).

Obj. 6 Determine the correct way to stimulate and establish the ranges of the parameters to obtain optimal neural plasticity/learning by means of transcranially applied EMFs.

7. Proposed research activities

Research activities will focus on how both, tCS and tCS-ACh interactions affect LTP-LTD processes. Three main research activities are foreseen dealing with “in vitro” studies, “in vivo” animal studies in rodents and “in vivo” studies in humans. Possibly we should also investigate the application of sinusoidal EMFs (also tACS?) at 50Hz and 60Hz since gamma range neural oscillations (voltage changes) are thought to play a key role in both neural information processing and learning processes in the cortex.

RA1: “in vitro” studies in rodent cortical slides (rats). For our purposes we can employ either intracellular, patch clamp or two-photon imaging recordings.

Methods: 1) Perform “in vitro” recordings of slides of motor cortex, prefrontal cortex and/or hippocampus before, during and after the application of EMFs by both, tMS and tDCS. To mimic transcranial stimulation EMF devices should be separated from the nervous tissue by a shield having filtering and distortion characteristics similar to the bone-dura-fluid in the head. Study LTP-LTD mechanisms by means of electrical stimulation of the afferents and pharmacological manipulation of ACh receptors (agonists-antagonists). 2) Employ a wide spectrum of stimulation parameters i.e. intensity, direction, distance of the source, and correlate the resulting biomolecular and electrophysiological changes with the physical characteristics of the applied EMFs and the pharmacological manipulations. 3) Identify the type of the recorded cells by means of well-established immunohistochemical or immunofluorescence techniques. 4) Develop of a thorough mathematical model these long-term phenomena.

RA2: “in vivo” studies in rodents (rats). For our purposes we can employ either two-photon calcium imaging techniques, optogenetic techniques and multiprobe extracellular recordings. “in vivo” intracellular or patch clamp recordings could possibly be useful for ”in vivo” testing of the results of RA1.

Methods: Combine behavioral tests with “in vivo” recordings in motor, somatosensory and prefrontal cortices and/or hippocampus before, during and after the tMS and tDCS and ACh manipulations. 1) Use split attention/central bottleneck behavioral paradigms

for the motor and prefrontal cortices. 2) Use sensory deafferentation and neuroprosthetic stimulation for the somatosensory cortex and 3) Use a memory paradigm for the hippocampus. Study LTP-LTD mechanisms by means of single-task and dual-task training and electrical stimulation of the somatosensory afferents combined with pharmacological manipulation of ACh receptors (agonists-antagonists) and/or the electrical stimulation of the nucleus basalis magnocellularis, the main provider of ACh to the cortex. Similarly to RA1 we will test a wide spectrum of stimulation parameters i.e. intensity, direction, distance of the source, and correlate the resulting behavioral performances and neural activity recordings with the physical characteristics of the applied EMFs and ACh manipulations. 3) Test the outcomes of RA1 in “in vivo” conditions and improve and refine the mathematical models developed in RA1.

RA3: “in vivo” studies in humans.

Methods: Combine behavioral tests and EEG-fMRI recordings in transcranially stimulated subjects with simultaneous cholinergic manipulations of ACh by systemically delivering ACh agonists-antagonists.

I don’t have the necessary knowledge to propose the concrete experiments.

I accept to I give a presentation of the above proposal at Split joint WG meeting (1st WGMs and 2nd MCM, 2-3 October 2014).

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