1. WM topic

EMF-based neural repair and regeneration

2. WM subtopics of interest

- Biomedical applications of EMFs combined with co-factors
- Tissue healing using low frequency EMFs
- Neural tissue stimulation
- Functionalized human models
- Neural tissue models

3. WM description

Ischemic stroke is the major cause of adult disability (including paralysis) and cognitive deficits (Burns et al., 2009) and the third main cause of death after heart disease and cancer. While approximately 75% people survive their initial stroke, just one-third of them recover completely. According to the World Health Organization (2007) 15 million people suffer stroke worldwide each year. Of these, five million die and another five million remain permanently disabled. This long-term disability implies that most of the costs of stroke are incurred in supporting stroke survivors whose number is expected to increase due to the natural aging of the population.

Up-to day clinical practice in case of brain damage and in particular in case of stroke is “rehabilitation”, a neural plasticity-exploiting approach that forces undamaged neural circuits to undertake the functionality of the damaged tissue.

However, brain repair instead of rehabilitation should be the best approach for in stroke therapy. Two main approaches are possible for this purpose: grafting or injection of multiple types of stem-cells to enhance regeneration and functional recovery and the stimulation of the nervous tissue through the application of low intensity electromagnetic fields (EMF)

Up-to now, the employment of stem cells did not offer the expected results. On the other side the healing hypothesis by means of EMFs is supported by an extend literature.

Here we propose that neural tissue repair through the application of low intensity electromagnetic fields (EMF) is the correct approach and that specific brain machine interfaces (BMIs) could be designed to achieve this purpose.

4. State-of-the-art

Rehabilitation aims to partial restoration of the neural functions by circuit remodeling rather than by the regeneration of damaged circuits.

Within neural repair, one of the major trends is the grafting or injection of multiple types of stem-cells to enhance regeneration and functional recovery (Borlongan, 2009; Carmichael, 2010). However, for the moment and compared to the initial expectatives, stem-cell-based therapy has reached a relatively modest level of success in clinical trials (Kondziolka et al., 2005; Banerjee et al., 2010).

Today, the most promising approach is to directly act on the causal molecular mechanisms that control tissue regeneration and on the design of pharmacological and stimulation approaches to manage them (Carmichael et al., 2005; Benowitz and Carmichael, 2010, Herrera-Rincon et al. 2011).

With respect to the use of EMF, there is experimental evidence supporting that the weak fields generated in a natural way by the physiological activity of neocortical networks are strong enough to (i) significantly modify the excitability of their own cells and (ii) alter the synchronization of the networks themselves (Fröhlich and McCormick, 2010; Mann and Paulsen, 2010; Weiss and Faber, 2010). Moreover, electric fields and biochemical neural processes are deeply intermingled and, therefore, electric fields are likely to also affect dendritic conductances, transmitter release, and the diffusion of ions and charged neurotransmitters (Weiss and Faber, 2010).

In almost all systems that have been studied, crucial behaviors such as cell division, cell migration, and cell differentiation take place within an extracellular milieu in which standing voltage gradients persist for several hours or even days (McCaig et al., 2005, 2009).

The appearance of electric fields is not a prerogative of the central nervous system. Direct-current (DC) electric fields naturally arise in all developing and regenerating animal tissues although their existence and potential impact on tissue repair and development remain largely unexplored (McCaig et al., 2005, 2009).

5. Gaps and challenges

Gaps and challenges concern processes to induce, augment and/or accelerate self-repair processes of the neural tissue after stroke.

Animal studies indicate that genes and proteins important for the three key aspects in neural repair, namely neural growth, synaptogenesis, and neural sprouting, expressed at their highest levels during early brain development (Hattiangady et al., 2005) are also expressed during a short-lived period that opens immediately after stroke (Murphy and Corbett, 2009). EMF should be employed to stimulate in a controlled manner the initiation and correct advance of such processes.

It has been proved that self-repair processes are accompanied by the spontaneous modulation of extracellular fields (Carmichael and Chesselet, 2002; Carmichael, 2003;

McCaig et al., 2009; Floel and Cohen, 2010) and the emergence of synchronous activity (Carmichael and Chesselet, 2002). We should explore the possibility to induce such a modulation in an artificial manner and become able to use it to control and guide repair processes of the neural tissue.

Altering excitability and network synchronization are keys to the two synaptic learning rules, known to influence CNS synaptogenesis and plasticity (Murphy and Corbett, 2009): Hebbian plasticity mechanisms that favor the rewiring of neural pathways and homeostatic plasticity mechanisms that ensure that neurons receive an adequate amount of synaptic input. Moreover, the spontaneously appearing synchronous neuronal activity is a signal for axonal sprouting after cortical lesions (Carmichael and Chesselet, 2002).

Axonal sprouting (rewiring) and functional remapping are based on synapse-based learning rules that depends on the existence of synaptic input and the circuitry to route sensory signals to the brain and motor commands out of it. Optimal parameters for the electrical stimulation can be determined from studying and modeling the dynamics of the electric fields and their effects on the central and peripheral nervous system.

EMF parameters should be determined to

- Save penumbra cells from death: This is dependent on early reperfusion further promoted by angiogenesis (the growth of new capillary vessels) as well as by insuring sufficient synaptic
- Send neural input to the penumbra area.
- Promote rewiring and remapping in the penumbra by stimulating synaptogenesis and axonal sprouting.

EMFs could be applied either alone or combined with stem-cells implants and pharmacology.

6. Objectives to be achieved

It is plausible that the same temporal dynamics followed by the electric fields in case of successful spontaneous healing serve to artificially promote neural repair where self-repair does not spontaneously arise or even to increase the effectiveness of the spontaneously arising healing processes.

Obj. 1 Identify and model the dynamics arising in the neural tissue in case of spontaneous healing

Obj. 2 Investigate the relationship between the dynamics of spontaneously emerging electrodynamic fields and the self-induced repair processes (macroscopic-mesoscopic scale) that lead to a complete recovery of the central nervous

Obj. 3 Identify and model cellular, molecular and gene changes in the neural tissue in case of spontaneous healing

Obj. 4 Determine the correct way to stimulate and establish the ranges of the parameters to obtain optimal neural repair by means of artificially generated EMFs.

Obj. 5 Establish the role EMFs play in the functional integration between implanted stem-cells and the ischemic neural tissue and develop mathematical models of such interactions..

Obj. 6 Determine the correct way EMFs should be applied to obtain a functional integration between implanted stem-cells and the ischemic neural tissue.

7. Proposed research activities

RA1: Establish the link between electric field dynamics and neural recovery in animals (rodents)

Methods: 1) Perform extracellular measurements of local field potential (LFPs) and single/multi unit activity (SUA/MUA). 2) Determine anatomical-structural changes in the neural tissue to establish specific links between the naturally occurring electric fields and functional/structural recovery. 3) Correlate specific changes in the electrophysiological recordings with the diverse histochemical measures of network activity and connectivity: amplitude, frequency, hyperexcitability, synchrony, and different functional connectivity measures in the first case and metabolic activity, number of neurons, axonal sprouting, neurogenesis, etc., in the second.

RA2: Correlate frequency specific changes in the core/penumbra with structural/functional and metabolic changes detected from non-invasive neuroimaging techniques such as MRI/PET/fMRI in human subjects.

Methods: 1) Monitor scalp EEG during the acute/post-acute phase of stroke and after the transfer of patients to the rehabilitation unit. 2) Perform a non-invasive estimation of field potentials or currents to assess the properties of ongoing phenomena within the core/penumbra area since scalp EEG lacks the spatial resolution.

RA3: Create information theory models to guide EMFs to induce optimal repair and recovery.

Methods: 1) Perform electrophysiological characterization of electrodynamic phenomena within the core and the penumbra area. 2) Assess EMFs effects on neural repair through: electrophysiology (hebbian plasticity); immunohistochemical/ immunofluorescence analysis of the neural tissue (metabolic activity, number of neurons, connectivity, axonal sprouting, neurogenesis, etc.); behavioral markers (functional performance). 3) Use information theory to: characterize the dynamics of self-repair processes; evaluate which parameters of spontaneous EMFs influence self-repair, as measured by conventional electrophysiological, histochemical, neuroimaging, or behavioral techniques; model the recovery process, for example as Markov stochastic processes.

I accept to l 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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