Abstract

Objectives: We consider two consequences of brain capillary ultra-structure in neuromodulation. First, blood-brain-barrier (BBB) polarization as a consequence of current crossing between interstitial space and the blood. Second, interstitial current flow distortion around capillaries impacting neuronal stimulation.

Materials and Methods: We developed computational models of BBB ultra-structure morphologies to first assess electric field amplification at the BBB (Principle 1) and neuron polarization amplification by the presence of capillaries (Principle 2). We adapt neuron cable theory to develop an analytical solution for maximum BBB polarization sensitivity.

Results: Electrical current crosses between the brain parenchyma (interstitial space) and capillaries, producing BBB electric fields (E_{BBB}) that are $> 400\times$ of the average parenchyma electric field (E_{BRAIN}), which in turn modulates transport across the BBB. Specifically, for a BBB space constant (λ_{BBB}) and wall thickness (d_{th-BBB}), the analytical solution for maximal BBB electric field (E_{BBB}^A) is given as: $(E_{BRAIN} \times \lambda_{BBB}) / d_{th-BBB}$. Electrical current in the brain parenchyma is distorted around brain capillaries, amplifying neuronal polarization. Specifically, capillary ultra-structure produces $\sim 50\%$ modulation of the E_{BRAIN} over the $\sim 40 \mu m$ inter-capillary distance. The divergence of E_{BRAIN} (Activating function) is thus $\sim 100 \text{ kV/m}^2$ per unit E_{BRAIN} .

Conclusions: BBB stimulation by principle 1, suggests novel therapeutic strategies such as boosting metabolic capacity or interstitial fluid clearance. Whereas the spatial profile of E_{BRAIN} is traditionally assumed to depend only on macroscopic anatomy, principle 2 suggest a central role for local capillary ultra-structure - which impact forms of neuromodulation including Deep Brain Stimulation (DBS), Spinal Cord Stimulation (SCS), transcranial Magnetic Stimulation (TMS), Electroconvulsive Therapy (ECT), and transcranial Electrical Stimulation (tES)/transcranial Direct Current Stimulation (tDCS).

Keywords: Blood-brain barrier, Electric field amplification, Neurovascular coupling, Neuron polarization

P3.007

THE INFLUENCE OF SAMPLE AND TREATMENT CHARACTERISTICS ON THE EFFICACY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN DEPRESSION: A META-ANALYSIS AND META-REGRESSION

Iris Dalhuisen^{1,2}, Suzanne van Bronswijk^{3,4}, Jeanine Bors¹, Filip Smit^{5,6}, Jan Spijker^{7,8}, Indira Tendolkar^{2,1}, Henricus G. Ruhé^{1,2}, Philip van Eijndhoven^{1,2}. ¹Radboudumc, Nijmegen, The Netherlands; ²Radboud University Donders Institute for Brain Cognition and Behaviour, Nijmegen, The Netherlands; ³Maastricht University, Maastricht, The Netherlands; ⁴Maastricht University Medical Centre+, Maastricht, The Netherlands; ⁵Amsterdam UMC VUMC Site, Amsterdam, The Netherlands; ⁶Trimbos-institute, Utrecht, The Netherlands; ⁷Pro Persona Mental Health Care, The Netherlands; ⁸Radboud University, Nijmegen, The Netherlands

Abstract

Background: In the largest meta-analysis on the effectiveness of rTMS to date and driven by a priori hypotheses we identified population and treatment characteristics that impact on change in depressive symptom severity, treatment response and remission.

Methods: We searched four databases for randomized controlled trials (RCTs) reporting on the therapeutic efficacy of high-frequency, low-frequency, or bilateral rTMS for depression compared to sham. Study and sample characteristics as well as rTMS parameters and outcome variables were extracted. We calculated standardized effect sizes (hedge's g) for change in depression severity, and risk ratios (RR) for response and remission.

Results: Fifty-seven RCTs with a total of 2564 subjects were included in the meta-analysis. We found a large effect size for reduction in depression severity after active compared to sham rTMS (Hedge's $g = 0.832$). Risk ratios for response and remission were also large with 2.264 and 2.303 respectively. Although we found no significant effect of population and treatment characteristics on rTMS efficacy, a trend was seen for worse outcomes in psychotic depression, but better outcomes in bipolar

depression. We conducted various sensitivity analyses that demonstrated the robustness of these findings.

Conclusions: Despite the lack of a significant influence of sample and treatment characteristics, we validated the efficacy of rTMS for depression across three different sets of clinically relevant outcomes. Our results, based on the largest set of studies to date, support the use of rTMS as a non-invasive and effective treatment option for depression.

Keywords: rTMS, Depression, Meta-analysis, Meta-regression

P3.008

A RAT MODEL TO UNDERSTAND TDCS MECHANISTIC UNDERPINNINGS

Luuk van Boekholdt, Silke Kerstens, Boateng Asamoah, Ahmad Khatoun, Myles Mc Laughlin. KU Leuven, Leuven, Belgium

Abstract

Transcranial direct current stimulation (tDCS) is a widely used non-invasive neuromodulation method. It is under investigation as a clinical therapy for a range of neurological and psychiatric disorders. Additionally, consumer tDCS devices are marketed as a means to boost motor function, learning and memory. In spite of this widespread use, the basic neurophysiological mechanisms underpinning tDCS effects are poorly understood. One question that has recently been sparking debate, is whether co-activation of peripheral nerves could contribute to observed effects in conventional tDCS montages. To investigate this, we developed a tDCS model in the awake rat in which activation of peripheral nerves can be separated from a true transcranial mode of action. True transcranial stimulation was achieved by implanting stimulation electrodes on the skull over the auditory cortices and cerebellum, while avoiding co-stimulation of peripheral nerves. Isolated peripheral nerve stimulation was accomplished by placing stimulation electrodes on the neck of the rat, over the occipital nerve. By stimulating either transcranially or peripherally, effects of these two tDCS stimulatory pathways can be separated. Neurophysiological effects were assessed by implanting EEG electrodes on the skull. Preliminary results show that DCS of both pathways paired with high frequency tone presentation, can enhance auditory evoked potentials of the presented tone. To further understand the mechanistic basis of tDCS-induced changes at a molecular and behavioral level, we are performing molecular analyses and memory tasks in this rat model. Initial results indicate that activation of both transcranial and peripheral pathways of tDCS can improve memory, as assessed by a passive fear conditioning paradigm. An effective rat model has been developed in which the peripheral and transcranial pathways of tDCS can be distinctly stimulated. In the future, this model can be further utilized to gain insights in the mechanisms of action and advance clinical implementation.

Keywords: Rat model, tDCS, Peripheral nerves, Evoked potentials

P3.009

CAN PALLIDAL DEEP BRAIN STIMULATION GENERATE HIGH-FREQUENCY OSCILLATIONS IN BASAL GANGLIA IN DYSTONIA? A CASE REPORT

Jessica Vidmark¹, Estefania Hernandez-Martin¹, Terence Sanger^{1,2}. ¹University of California, Irvine, Irvine, CA, USA; ²Children's Health Orange County, Orange, CA, USA

Abstract

Deep brain stimulation (DBS) is a common treatment of movement disorders, including dystonia and Parkinson's disease. Despite the clinical success of DBS, its mechanisms of action remain largely unexplained; however, recent studies have detected high-frequency oscillations within the subthalamic nucleus (STN) and globus pallidus (GP) as a response to DBS. While having previously been recorded only in Parkinsonian patients during stimulation in STN, we here present novel sightings of these high-frequency basal ganglia (BG) oscillations during pallidal stimulation in a patient with pediatric generalized dystonia.

Data were recorded from externalized DBS electrodes implanted in the thalamus and BG. Bilateral pallidal 150-Hz stimulation, applied in 100-ms bursts separated by 100 ms without stimulation, generated high-