EEG brain states occurring before the stimulation impact response to TMS. Our results show that specific brain states, with a motor network spatial and spectral signature, feature larger Motor Evoked Potential amplitude. These findings enable brain-state-dependent TMS based on real-time excitability and connectivity information, a critical step towards individualized therapeutic brain stimulation.

Research Category and Technology and Methods

Translational Research: 7. Responsive (Closed-Loop) Stimulation

Keywords: EEG-TMS, Hidden Markov model, Brain-state-dependent TMS, Motor cortex

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Abstract key: PL- Plenary talks; S- Regular symposia oral; FS- Fast-Track symposia oral; OS- On-demand symposia oral; P- Posters

S2a.4

ENHANCING THE CONNECTIVITY IN A 2-NODE MOTOR NETWORK USING REINFORCEMENT LEARNING-BASED CLOSED-LOOP RTMS

Dania Humaidan. *Eberhard Karls University Tübingen, Germany*

Abstract

TMS has been extensively used to investigate the physiology of the central nervous system in health and disease. However, there is a strong need for a personalized, multi-locus, real-time stimulation procedure, which can be adaptively fine-tuned based on case-specific feedback. Here, we modulate the effective connectivity of the 2-node brain network from supplementary motor area (SMA) to primary motor cortex (M1) by closed-loop stimulation, optimized by application of an online reinforcement learning algorithm. This algorithm learns to identify the individually optimal phase of the ongoing μ-rhythm to be targeted by paired SMA-M1 TMS for maximized long-term enhancement of facilitatory effective connectivity between SMA and M1. This is one of the first demonstrations of true closed-loop stimulation, a crucially important step towards individualized highly-effective brain stimulation for therapeutic modulation of dysfunctional brain networks, e.g., the deficient SMA-M1 connection in motor stroke.

Research Category and Technology and Methods

Translational Research: 7. Responsive (Closed-Loop) Stimulation

Keywords: EEG-TMS, Machine Learning, Closed-loop stimulation, Motor cortex

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Abstract key: PL- Plenary talks; S- Regular symposia oral; FS- Fast-Track symposia oral; OS- On-demand symposia oral; P- Posters

S2b.1

EFFECTS OF REPEATED TDCS ON FEAR EXTINCTION IN MICE

Andries Van Schuerbeek [1], Marie-Anne Vanderhasselt [2], Chris Baeken [2,1], Anouk Pierre [1], Ilse Smolders [1], Vincent Van Waes [3], Dimitri De Bundel [1]. [1] *Vrije Universiteit Brussel, Belgium;* [2] *Universiteit Gent, Belgium;* [3] *Université Bourgogne Franche-Comté, France*

Symposium title: Brain stimulation in fear and anxiety disorders

Symposium description: Anxiety disorders, together with depression, are the most common mental health disorders in the world. Although evidence-based treatments for anxiety disorders exist, more than half of treated individuals do not show sufficient improvement in clinical symptoms after therapy or show a relapse after successful therapy. Therefore there is a continuing need to develop novel and effective treatments for anxiety. The use of non-invasive brain stimulation represents a promising approach to complement current evidence-based treatments as therapeutic tools. This symposium takes a bench-to-bedside approach covering both basic and clinical studies using the two most common non-invasive brain stimulation techniques, transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), in the context of fear and anxiety disorders. First, Dimitri de Bundel will demonstrate in an animal model that tDCS is capable of modulating fear extinction in mice. Next, Mascha van 't Wout-Frank will cover the use of tDCS to modulate fear extinction and anxious habituation during exposure in individuals with posttraumatic stress disorder (PTSD). This will be followed by Martin Herrmann who will present a clinical study investigating whether rTMS can be used to improve exposure therapy in phobic patients. The symposium will conclude with a lecture by Sara Borgomaneri who will demonstrate that rTMS can be used to disrupt the consolidationand reconsolidation of fear memory, providing a novel option for the treatment of anxiety disorders.

Abstract

Exposure-based psychotherapy is a first line treatment for fear-related disorders. Not all patients achieve long-term remission but adjunctive non-invasive neuromodulation may be a promising strategy to enhance the efficacy of exposure therapy. In a proof of concept study, we explored whether tDCS over the prefrontal cortex (PFC) could enhance fear extinction in mice. While this preclinical model of exposure therapy is appealing for in-depth exploration of mechanisms of action, it comes with technical challenges that may hamper direct comparisons of online with offline tDSC effects and the translation towards applications in humans. Nevertheless, we found that repeated offline anodal tDCS (0.2 mA, 20 min, twice daily for five consecutive days) over the PFC resulted in enhanced fear extinction when extinction training followed one day after the last stimulation session. We found that tDCS was most effective in experimental conditions corresponding to high fear expression. Our data provide a rationale to further explore anodal tDCS over the PFC as potential support for exposure-based psychotherapy.

Research Category and Technology and Methods

Basic Research: 9. Transcranial Direct Current Stimulation (tDCS)

Keywords: Fear extinction, mice, tDCS

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S2b.2

UTILIZING TDCS TO AUGMENT THE FORMATION OF SAFETY SIGNALS FOR FEAR INHIBITION IN POSTTRAUMATIC STRESS DISORDER

Mascha van 't Wout-Frank [1,2,3], Sydney Brigido [2], Julia Cole [3], Noah Philip [4,1]. [1] *Warren Alpert Medical School of Brown University, USA;* [2] *VA Providence Healthcare System, USA;* [3] *COBRE Center for Neuromodulation, Butler Hospital, USA;* [4] *VA Providence Healthcare System, USA*

Abstract

Posttraumatic stress disorder (PTSD) can be understood as a disorder in the processing of traumatic fear memories due to hyperactivity in amygdala-based threat reactivity, exacerbated by a failure to down-regulate this threat responding attributed to hypoactivity in ventromedial prefrontal cortex (VMPFC) and hippocampal aberrations. Here we test whether transcranial direct current stimulation (tDCS) targeting the VMPFC can augment the inhibition of fear responses in the context of extinction learning and recall as well as exposure to trauma cues in individuals with PTSD. In all experiments, tDCS involved 2 mA intensity with the anode placed around EEG locations Fp1/AF3 and the cathode over EEG location P08, and we assessed skin conductance reactivity (SCR) as a biologically relevant measure of emotional arousal. First, we demonstrate that the modulation of extinction learning and memory by tDCS may depend on the timing of stimulation, such that when applied during synaptic consolidation immediately following extinction learning of conditioned fear tDCS may prevent the return of fear during extinction recall. Yet we also observed a possible generalization of the fear response because of tDCS. Next, we demonstrate that the repeated application of tDCS during exposure to virtual reality trauma cues may bolster anxious habituation in individuals with warzone PTSD. Yet again we appear to observe a seemingly initial increase in emotional arousal before a more rapid reduction of emotional arousal and subsequent reduction of PTSD symptom severity. Taken together this research highlights the importance of the application of tDCS in context, including the timing of stimulation in relation to safety learning and memory processing and the importance of repeated sessions for clinical benefit.

Research Category and Technology and Methods
Clinical Research: 9. Transcranial Direct Current Stimulation (tDCS)
Keywords: Fear, tDCS, Extinction, PTSD

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Abstract key: PL- Plenary talks; S- Regular symposia oral; FS- Fast-Track symposia oral; OS- On-demand symposia oral; P- Posters

S2b.3

THE EFFECTS OF LEFT FRONTAL INTERMITTENT THETA BURST STIMULATION ON THE EFFICACY OF EXPOSURE-BASED THERAPY IN ACROPHOBIA

Martin Herrmann [1], Lisa Cybinski [1], Dominik Gall [1], Daniel Gromer [1], Tommi Raij [2,3], Florian Gundelach [1], Stefan Unterecker [1], Angelika Erhardt-Lehmann [1,4], Andreas Mühlberger [5], Thomas Polak [1], Paul Pauli [1]. [1] *University Hospital of Wuerzburg, Germany;* [2] *Massachusetts General Hospital, USA;* [3] *Harvard Medical School, USA;* [4] *Max Planck Institute of Psychiatry, Germany;* [5] *University of Regensburg, Germany*

Abstract
Evidence-based treatments for anxiety disorders, as cognitive behavioral and pharmacological therapy achieves good therapeutic results. However, studies have shown that the therapy can be further optimized. Transcranial magnetic stimulation (TMS) may be useful as an adjunct to exposure-based therapy for anxiety disorders, as laboratory studies in healthy subjects have shown (Raij et al., 2018) that extinction learning, as an underlying mechanism in exposure therapy, can be improved using rTMS. The aim of this double-blind, randomized, placebo-controlled clinical trial with 76 patients with acrophobia is to verify whether the stimulation localization (left frontal cortex), shown to be benefical in healthy subjects, can be effectively used to enhance exposure therapy. For this purpose, patients underwent neuronavigational stimulation over the individually defined stimulation localization using the activating intermittent theta burst stimulation (iTBS) protocol before exposure therapy in virtual reality. Clinical symptoms were evaluated via questionnaires and two behavioral approach tests before, after, and for follow-up after 6 months. Furthermore, process variables during the exposure sessions, such as duration of exposure, and maximal anxiety depending on the stimulation groups were investigated.
Research Category and Technology and Methods
Clinical Research: 10. Transcranial Magnetic Stimulation (TMS)
Keywords: rTMS, Anxiety disorders, Psychotherapy

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Abstract key: PL- Plenary talks; S- Regular symposia oral; FS- Fast-Track symposia oral; OS- On-demand symposia oral; P- Posters

S2b.4

'CUT THE ROOTS': RTMS REVEALS THE CRUCIAL ROLE OF PREFRONTAL CORTEX IN THREAT MEMORY CONSOLIDATION IN HUMANS

Sara Borgomaneri [1], Claudio Nazzi [2], Giuseppe di Pellegrino [1], Simone Battaglia [3]. [1] *University of Bologna, Italy;* [2] *Bologna, Italy;* [3] *University of Turin, Italy*

Abstract
It is unclear how the brain consolidates aversive memories and whether this process can be disrupted. We hypothesized that targeting the dorsolateral prefrontal cortex (dlPFC) within the consolidation time window by repetitive transcranial magnetic stimulation (rTMS) could block the encoding of a threat memory, disclosing the crucial involvement of this brain region in consolidation. To this aim, fifty-four healthy participants took part in a two-days threat conditioning paradigm. On the first day, participants underwent an acquisition phase. Immediately after, in different groups, an inhibitory rTMS protocol was applied to the dlPFC, or over an occipital control site or as sham. Subsequently, a threat memory recall was performed to test the effect of the rTMS on the consolidation of the previously acquired threat memory. The same procedure occurred after 1 hour to assess rTMS effect outside its inhibitory window, and 24 hours later to test the stability of the offline effects of the rTMS. The results suggested that all groups correctly acquired the threat conditioning, and no differences between groups were observed. The control groups showed memory recall across the three sessions after rTMS, while, critically, the dlPFC group did not recall threat responses in any of the three recall phases. We provide causal evidence that selectively targeting the dlPFC within the consolidation time window prevents the return of threat. Furthermore, memory disruption lasted longer than the inhibitory time window of the rTMS. This effect reveals that we have not only affected the dlPFC activations, but we have hampered the underlying time-locked consolidation process. Together with our previous findings targeting the reconsolidation process, the present results provide new evidence for future clinic applications aiming at interfering with the consolidation and the reconsolidation of traumatic memories.
Research Category and Technology and Methods
Basic Research: 10. Transcranial Magnetic Stimulation (TMS)
Keywords: Threat conditioning, Repetitive transcranial magnetic stimulation, Consolidation, Dorsolateral Prefrontal Cortex

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S3a.1

MODULATION OF STRIATAL ACTIVITY TO STUDY REINFORCEMENT LEARNING OF MOTOR SKILLS IN HUMANS

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Symposium title: Non-invasive deep brain stimulation via Temporal Interference (TI) of electric fields – New mechanistic insights and human translation
Symposium description: Cognitive functions, such as learning and memory, rely on neural processing in deep brain structures (e.g., basal ganglia or hippocampus). Their dysfunction is a critical pathophysiological hallmark of many neuropsychiatric disorders. It is not possible to neuromodulate the activity of these important deep brain regions directly with conventional non-invasive brain stimulation techniques, as the required stimulation intensities would exceed safety guidelines and result in strong co-activation of overlying brain regions. The promising technique of transcranial temporal interference electric brain stimulation (tTIS) provides a novel interventional opportunity for direct and non-invasive modulation of deep brain targets (Grossman 2017). It is a strategy for non-invasive steerable stimulation of neurons deep in the brain using multiple kHz-range electric fields with a difference frequency within the range of neural activity. The superposition of the fields leads to a slowly "beating" envelope oscillating at the difference (target) frequency. The peak amplitude of this envelope can be focused towards deep brain targets driving their neuronal activity. This session will briefly introduce the tTIS concept and present physics experiments, computational modeling, preclinical validation and new mechanistic insights. We will demonstrate the opportunities and challenges in non-invasively probing neural activities in deep brain structures, such as the hippocampus and striatum, using functional magnetic resonance imaging (fMRI) and behavioural paradigms. We will also demonstrate the ability to measure the direct electroencephalogram (EEG) response without confounding stimulation artefact. Based on these promising findings, we will discuss and present first approaches translating the tTIS technique towards investigational applications in healthy humans and patients. We aim to provide an up-to-date overview and strive to prime future work in this promising field in basic and clinical-translational neuroscience.

Abstract
The striatum is a crucial brain region for reinforcement learning. However, because of its deep localization in the brain, modulating striatal activity to understand its causal role has not been possible in healthy humans non-