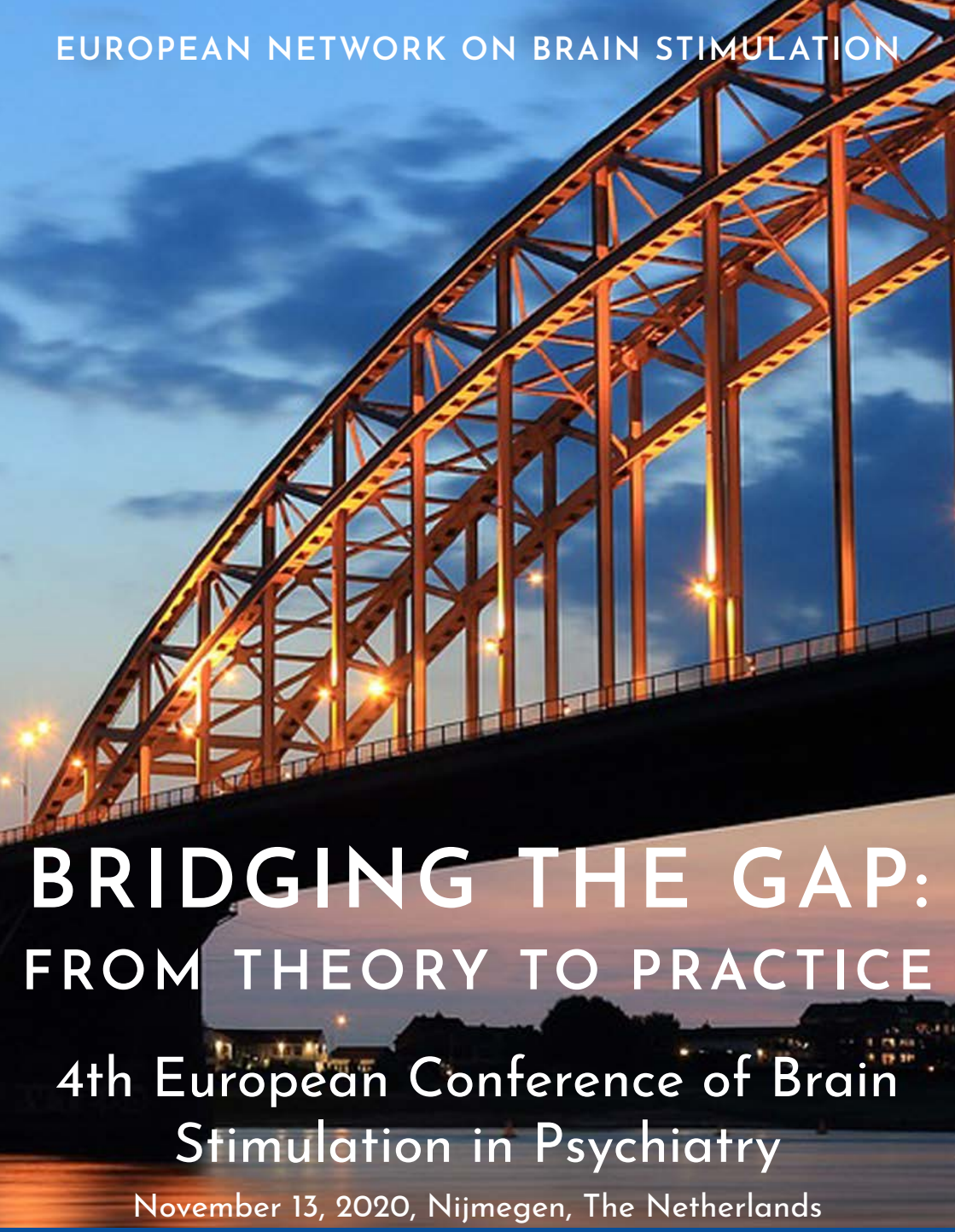
EUROPEAN NETWORK ON BRAIN STIMULATION



BRIDGING THE GAP:
FROM THEORY TO PRACTICE

4th European Conference of Brain Stimulation in Psychiatry

November 13, 2020, Nijmegen, The Netherlands

PROGRAM AND ABSTRACTS

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4th European Conference of Brain Stimulation in Psychiatry

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TRACK 1

08:45-09:00 **Opening and Welcome**

09:00-09:30 **Keynote 1** ***Dennis Schutter*** Cerebellar neuromodulation in the treatment of depression and anxiety.

09:30-10:30 **A** **What can we learn from ECT: Insights from the GEMRIC consortium.**
Chairs: ***Indira Tendolkar & Philip van Eijndhoven***

1 Using electric field modeling to inform ECT dosing and device development, *Zhi-De Deng*
2 Current connections: brain patterns in electroconvulsive therapy, *Peter Mulders*
3 Global collaboration to study brain changes after ECT - current findings and future prospects, *Leif Oltedal*
4 Efficacy of rTMS vs ECT for treatment resistant depression, *Philip van Eijndhoven*

10:30-10:45 Break

10:45-11:45 **C** **Transcranial Direct Current Stimulation and Psychological Interventions in Psychiatry: State of the Art and Promising Perspectives.**
Chair: ***Marie-Anne Vanderhasselt***

1 tDCS-augmented virtual reality exposure for PTSD: Possibility for Individualized Treatment, *Mascha van 't Wout-Frank*
2 PsychotherapyPlus: Augmentation of Cognitive-Behavioral Therapy with Direct Current Stimulation, *Malek Bajbouj*
3 Perspectives on Combined tDCS and Psychological Interventions, *Josefien Dedoncker*

11:45-12:45 **D** **Individualization and Personalization of NIBS.**
Chairs: ***Noralie Krepel & Martijn Arns***

1 Concurrent TMS-EEG-fMRI to Visualize Brain-State Dependent iTBS Effects on Signal Propagation from the DLPFC, *Alexander Sack*
2 Neurodevelopmentally Inspired EEG Biomarker for Treatment Stratification Across Various Antidepressant Interventions, *Helena Voetterl*
3 Neuro-Cardiac-Guided TMS (NCG-TMS) to target the depression network: Possibilities for rTMS treatment stratification?, *Martijn Arns*

12:45-13:30 Lunch break

13:30-14:00 **Keynote 2** ***Antonio Mantovani*** How to unlock OCD by non-invasive brain stimulation: from pathophysiology to clinical applications.

14:00-14:30 **Keynote 3** ***Linda Carpenter*** Insights and Inspirations from the first Decade of TMS Therapy in Psychiatry: A TMS Clinician's Perspective.

14:30-15:30 **F** **Updated TMS Guidelines, Implications for Psychiatry.**
Chairs: ***André Aleman & Chris Baeken***

1 Efficacy of non-invasive brain stimulation on cognitive functioning in brain disorders: a meta-analysis, *Marieke Begemann*
2 rTMS for depressive disorders: current knowledge and future directions, *Chris Baeken*
3 NIBS for treatment of schizophrenia: hallucinations and negative symptoms, *André Aleman*

15:30-16:00 Break

KEYNOTE DEBATE: TO BIOTYPE OR NOT TO BIOTYPE

16:00-16:30 **Keynote 5** ***TBA*** ...

16:30-17:00 **Keynote 6** ***André Marquand*** Fractionating psychiatric cohorts using machine learning and big data.

17:00-17:30 **Keynote 7** ***Amit Etkin*** Grounding Psychiatry in Scalable Brain-Based Biomarkers.

17:30-18:00 **DISCUSSION: HOW TO FOSTER A FUTURE OF ROBUST BIOMARKER STUDIES IN NIBS?**

Closing Remarks and End

09:30-10:30

B **New Methods in Non-Invasive Brain Stimulation.**
Chairs: ***John Rothwell & Walter Paulus***

1 Updates on theta burst transcranial magnetic stimulation, *Ying-Zu Huang*
2 Practicalities and Possibilities of Transcranial Ultrasound Stimulation, *Lennart Verhagen*
3 Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields, *Nir Grossman*
4 New Applications for Transcranial Alternating Current Stimulation, *Ivan Alekseichuk*

11:45-12:45

E **Non-Invasive Brain Stimulation in Multiple Sclerosis.**
Chair: ***Ulrich Palm***

1 Fatigue and Affective Manifestations in Multiple Sclerosis, *Samar Ayache*
2 Cognitive Deficits in Multiple Sclerosis: Current knowledge and Perspectives, *Moussa A. Chalah*
3 tDCS and Fatigue in Multiple Sclerosis, *Ulrich Palm*
4 tDCS and Cognitive Symptoms in Multiple Sclerosis, *Christina Grigorescu*

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Dear Colleagues,

It is our great pleasure and privilege to announce that the 4th European Conference of Brain Stimulation in Psychiatry will take place on Friday, November 13th in form of a digital hybrid conference with on-site speakers in Nijmegen, NL and a worldwide audience joining us live online. In these unusual times, we decided to join forces with the 7th International Conference on Non-Invasive Brain Stimulation (November 10-14, aka the Baden-Baden meeting), allowing us to provide and critically expand our scientific and clinical program addressing all relevant themes in the field of brain stimulation.

These are exciting times. Brain Stimulation and Neurotechnology are among the most dynamically developing areas of research and considerable progress has been made. Yet, there is still so much work ahead of us and it becomes increasingly evident that we need to further increase our efforts in a true interdisciplinary and transdisciplinary research cooperation with regard to both, our fundamental understanding of the basic mechanisms of action of brain stimulation as well as with regard to the clinical applications for treating various neuropsychiatric brain disorders. To this end, the level and scale of brain stimulation research need to span all the way from in-vitro investigations on molecular or cell level, to in-vivo human studies on brain network dynamics and state-dependency. Combining brain stimulation with brain imaging, individualizing stimulation protocols, predicting reactivity and treatment response, identifying biomarkers and stratifying patient populations; these are all buzz words representing important and thriving developments currently worked on in many labs worldwide and we are glad to be able to present some of the most recent findings with regard to these developments during our 4th European Conference of Brain Stimulation in Psychiatry 2020.

The Dutch-Flemish Brain Stimulation Foundation (www.hersenstimulatie.com) is the official host of the 4th European Conference of Brain Stimulation in Psychiatry and we are proud to be one of the founding members of the biannual Conferences of Brain Stimulation in Psychiatry, together with our friends and colleagues from the German Society for Brain Stimulation in Psychiatry (https://www.dghp-online.de) and the French Society for Brain Stimulation. We cordially invite other EU countries to join our efforts, establish similar societies in their country and join the umbrella organization of the European Society of Brain Stimulation.

We are looking forward to welcoming you to our digital hybrid conference.

Best regards,

Prof. Dr. Alexander Sack (President of Dutch-Flemish Brain Stimulation Foundation; Professor of Brain Stimulation, Maastricht University)

Prof. Dr. Chris Baeken (Vice-President of Dutch-Flemish Brain Stimulation Foundation; Professor of Psychiatry, Ghent University)

KEYNOTE 1

Cerebellar neuromodulation in the treatment of depression and anxiety

Presented by *Dennis Schutter*
Affiliation(s) *Utrecht University*

Keywords *Cerebellum, Mood, Non-invasive brain stimulation*

Abstract

Background: Non-invasive brain stimulation (NBS) to the prefrontal cortex is an evidenced-based method to treat major depressive disorder. Despite its efficacy, individual differences in therapeutic responsivity are observed. To further optimize efficacy, targeting other brain areas with NBS may be a viable option. The cerebellum with its close reciprocal connections to the forebrain may be such an alternative candidate region in the treatment of mood disorders.

Methods: In search of a functional neuroanatomic basis for cerebellar neuromodulation in emotions and mood disorders the empirical evidence of the effects of cerebellar NBS on physiological and psychological indices of anxiety and depression and mood improvement will be reviewed.

Results: Findings provide evidence for cerebellar involvement in anxiety and depression, and demonstrate the feasibility of cerebellar NBS to influence mood states through the modulation of the posterior and midline regions of the cerebellum.

Discussion/conclusion: NBS to the cerebellum is proposed to have therapeutic potential. Randomized controlled trials are needed to explore the therapeutic range of cerebellar neuromodulation in mood disorders.

How to unlock OCD by non-invasive brain stimulation: from pathophysiology to clinical applications

Presented by *Antonio Mantovani*
Affiliation(s) *Siena University Brain Investigation and Neuromodulation Lab, CUNY School of Medicine*
Coauthors *Simone Rossi, Sarah H. Lisanby, Helen B. Simpson, Giordano D'Urso, Emiliano Santarnecchi*
Keywords *obsessive compulsive disorder; rTMS; supplementary motor area*

Abstract

Background: Intrusive thoughts and compulsive behaviors that characterize obsessive compulsive disorder (OCD) are associated to aberrant resting state functional connectivity (rsFC) within the cortico-striatal-thalamo-cortical (CSTC) circuits and to deficit in intracortical inhibition. Because a high percentage of OCD patients do not respond to pharmacological treatments or psychotherapy, circuitry guided interventions have been tested . In those patients, non-invasive repetitive transcranial magnetic stimulation (rTMS) to the Supplementary Motor Area (SMA) has resulted in significant clinical benefits.

Methods: We have applied MRI-guided single and double-daily sessions of rTMS treatment (1-Hz; 110% of resting Motor Threshold; 36,000-72,000 pulse protocols), to bilateral SMA in OCD patients. We have tested its (i) feasibility-safety, (ii) clinical efficacy , (iii) neurophysiological effects and (iv) rsFC related changes.

Results: Patients reported no side effects during and after rTMS. Personalized rTMS treatment led to a significant improvement of OCD symptoms. Clinical improvement correlates with increased motor threshold in the right hemisphere and normalization of intracortical excitability. rsFC analysis revealed a significant reduction of connectivity patterns between bilateral SMA and subcortical regions, specifically in the basal ganglia and thalamus. Additional analysis showed that the persistence of some symptoms after treatment correlates with a higher connectivity pattern between bilateral SMA and subcortical regions.

Discussion/conclusion: rTMS delivered in single and double-daily sessions is safe, feasible and effective in OCD. The clinical outcomes, consistent in the open-label and randomized controlled trials, are linked to a normalization of cortical excitability and decreased connectivity between SMA and subcortical brain areas implicated in control over obsessions and maladaptive compulsive behaviors.

Insights and Inspirations from the first Decade of TMS Therapy in Psychiatry: A TMS Clinician's Perspective

Presented by *Linda Carpenter, MD*
Affiliation(s) *Brown University Department of Psychiatry*

Keywords *Transcranial Magnetic Stimulation; Depression; Neuromodulation*

Abstract

Background: It is estimated that over 20 million TMS treatment sessions have been delivered to depressed patients since the US regulatory agencies approved the first commercial TMS device to treat patients with Major Depressive Disorder in late 2008. Exciting findings have arisen from innovative research with regard to effects of high frequency TMS on functional connectivity, and effects of different pulse frequencies and patterns on cortical excitability. Clinicians still struggle with critical questions such as, what is the best brain target for stimulation and the best method to find it? Do different stimulation frequencies and protocols impact overall clinical outcomes? How quickly can we get depressed patients better with TMS and how do we keep them better over time with TMS?

Methods: This presentation will review some of the decade's most promising research findings relevant to clinical application of TMS for depression and their insights and limitations with regard to personalizing therapy. Pressing questions that clinicians face in the everyday practice of TMS therapy will be raised with the aim to stimulate future research directions in clinical TMS research to improve patient outcomes.

Results: There are numerous ways to identify a DLPFC location for stimulation and no real evidence that any one is better than the other, a reality that does not currently support the time and cost of MRI-guided neuronavigation to a target which is either anatomically or functionally defined; indeed, data are lacking to guide clinicians with regard to which brain region or hemisphere should be stimulated. Translations of the most promising neuroimaging and EEG findings to clinical practice are lacking, which may prompt clinicians to introduce even more variance into TMS treatment protocols and stray from evidence-based care.

Fractionating psychiatric cohorts using machine learning and big data

Presented by *Andre F. Marquand*
Affiliation(s) *Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands*
Coauthors *Richard Dinga, Mariam Zabihi, Seyed Mostafa Kia, Christian Beckmann, Lianne Schmaal*
Keywords *Stratification, Machine Learning, Big Data*

Abstract

Background: Psychiatric disorders are all highly heterogeneous at the level of clinical presentation and underlying biology, which poses major challenges to understanding their underlying mechanisms and developing better treatments. In this talk I will review work from our group that approaches the stratification problem from multiple complimentary perspectives, highlighting this discussion via applications in autism, depression and schizophrenia.

Methods: I will first adopt a historical perspective showing subtyping is not new in psychiatry. I will then present work that aims to replicate some high-profile findings before presenting some recent methodological innovations that provide a new perspective on the stratification problem.

Results: I will show that despite decades of effort, the classical approach has still not converged on a set of subtypes that challenge the diagnostic labels for any disorder. I will propose theoretically grounded reasons for this, and highlight methodological issues that are underappreciated, yet prevalent in such studies. Finally, I will introduce alternative perspectives on the stratification problem using normative modelling and latent variable models.

Discussion/conclusion: Stratification remains an important challenge in psychiatry. I argue that methodological innovation and careful validation is crucial to capitalize on the wealth of biological, clinical and behavioural measures that are routinely acquired in 'big data' cohorts. In particular approaches that provide statistical inferences at the individual level and allow multiple overlapping fingerprints to overlap in the same individual are crucial to precisely dissect the heterogeneity underlying mental disorders. Ultimately, the hope is that this will pave the route towards precision psychiatry.

KEYNOTE 7

Grounding Psychiatry in Scalable Brain-Based Biomarkers

Presented by *Amit Etkin, MD PhD*
Affiliation(s) *CEO, Alto Neuroscience. Professor, Stanford University, USA*

Keywords *Machine learning, biomarker, depression*

Abstract
Over the past two decades, brain imaging studies have defined a set of distributed brain systems that contribute to cognition, emotion, mood and other mental processes. Perturbations in these circuits have been identified in different ways across psychiatric disorders. Yet, these insights have not translated to the development and deployment of treatments in psychiatry. I will discuss work on neural circuit signatures that either define specific biologically-discrete forms of psychopathology, or predict treatment outcome, doing so at the individual patient level through a range of new machine learning-based analyses of electroencephalography (EEG) data. Together, these data suggest that we are now on the brink of scalable and clinically-applied innovations in circuit-based diagnostics and treatments for mental illness, thereby taking us beyond dependence on symptom checklists for diagnosis, and having only one-size-fits-all treatments.

Using electric field modeling to inform ECT dosing and device development

Presented by *Zhi-De Deng*
Affiliation(s) *National Institute of Mental Health, National Institutes of Health, USA*
Coauthors *Egill Axfjord Fridgeirsson, Damiaan Denys, Jeroen A. van Waarde, Guido A. van Wingen*
Keywords *Electroconvulsive therapy; modeling; device*

Abstract

Background: Electroconvulsive therapy (ECT) electrode placement and current amplitude are crucial determinants of its efficacy. A recent GEMRIC study found that right unilateral (RUL) ECT induces electric field that causes volumetric changes in the amygdala and hippocampus. In this current study, we extended the sample with bilateral (BL) ECT patients, and test whether these electric field distributions were associated with ECT outcome.

Methods: Patients participated in a prospective observational ECT study at Rijnstate Hospital in Arnhem, Netherlands. Depression severity was scored using the Montgomery–Åsberg Depression Rating Scale (MADRS). Patients received RUL ECT at 6x seizure threshold and/or BL ECT at 2.5x seizure threshold, using a Thymatron System IV (900 mA). Baseline T1-weighted MRI was used to construct the head model and simulate the electric field using SimNIBS.

Results: In BL ECT patients, we found three major clusters where the electric field strengths were significantly correlated with MADRS. The first cluster ($p=0.0422$) was in the left temporal lobe (peak at MNI: -57, 7, -11). The second cluster ($p=0.0432$) was situated in the right superior temporal gyrus (MNI: 41, -26, -23). The third cluster ($p=0.0468$) was in the left middle temporal gyrus (MNI: -71, -17, -16).

Conclusion: Using a computer model derived from individual MRI data, we showed that less optimal ECT outcome was associated with higher electric field strength in the temporal lobes. We will discuss strategies for new ECT device design to optimize targeting and dosing.

Current Connections: Brain patterns in electroconvulsive therapy

Presented by *Peter C.R. Mulders*
Affiliation(s) *Radboudumc, Donders Center for Cognitive Neuroimaging, Nijmegen, The Netherlands*

Keywords *ECT, depression, network*

Abstract

Background: Electroconvulsive therapy (ECT) is the most effective treatment for depression but its underlying mechanisms remain poorly understood. While structural changes in the brain through ECT have been consistently identified, these have mainly focused on specific subcortical regions such as the hippocampus and a link to clinical improvement has not been clearly established. If and how structural volumetric changes relate to clinical effects remains elusive, but important to determine for current and future antidepressant research.

Methods: We used recursive feature elimination and linear discriminant analysis using the Global ECT-MRI consortium sample (n=192) to determine whether a multivariate pattern of structural changes induced by ECT could discriminate responders from non-responders.

Results: A pattern of structural changes in cortical midline, striatal and lateral prefrontal areas discriminates responders from non-responders (75% accuracy, $p<0.001$) while left-sided mediotemporal changes discriminate unilateral from bilateral electrode placement (81% accuracy, $p<0.001$).

Discussion/conclusion: The identification of a multivariate discriminative pattern shows that structural change is relevant for clinical response to ECT, but this pattern does not include mediotemporal regions that have been the focus of electroconvulsive therapy research so far.

Global collaboration to study brain changes after ECT - current findings and future prospects

Presented by *Leif Oltedal*
Affiliation(s) *Department of Clinical Medicine, University of Bergen, Bergen, Norway. Mohn Medical Imaging and Visualization Centre, Department of Radiology, Haukeland University Hospital, Bergen, Norway.*

Keywords *gray matter, global collaboration, ECT*

Abstract

Background: Over the last couple of decades Magnetic Resonance Imaging (MRI) has been increasingly utilized for the study of the neurobiological underpinnings of electroconvulsive therapy (ECT). Among the best documented effects is an increase in the volume of brain gray matter following ECT. However, results of individual studies vary, and most investigations have not found a clear link between changes seen on MRI and clinical outcome. Hence, we do not know whether the volumetric changes can be therapeutic or not.

Methods: The Global ECT-MRI Research Collaboration (GEMRIC) was established in June 2015. Today 22 groups around the world has joined and share data and conduct analyses together. The current database includes more than 700 subjects. Through a centralized server, members can process data and perform analyses remotely.

Results: The large sample improves statistical power and allows characterization of structural and functional brain changes following ECT in more detail compared to individual studies. So far, GEMRIC has documented that the gray mater volumetric increases seen after ECT are not specific to depression circuitry, but broadly distributed. Although effect sizes are large; both for volume increases and changes in depression scores – a clear link between imaging findings and therapeutic outcome is missing. However, we have documented how the length of treatment, electrode position and the electrical field distribution relates to volumetric brain changes.

Discussion/conclusion: Through collaboration, we have gained knew knowledge about the effects of ECT on the human brain. Ongoing efforts and future prospects will be discussed.

Efficacy of rTMS vs ECT for treatment resistant depression

Presented by *Philip van Eijndhoven, MD, PhD*
Affiliation(s) *Department of Psychiatry, Radboudumc Nijmegen, The Netherlands. Donders Institute of Brain, Cognition and behaviour, Nijmegen, The Netherlands*
Coauthors *Indira Tendolkar, Iris Dalhuisen*
Keywords *ECT, rTMS, TRD*

Abstract
In recent years rTMS has emerged as a new treatment strategy for treatment resistant depression (TRD). The question arises how rTMS relates to the gold standard treatment for TRD: ECT. In this talk I will give a comprehensive overview of the literature of studies on the comparative efficacy of rTMS and ECT. Metaregression and recent network-analyses that make indirect comparisons between the treatment options will be included and the limitations of these approaches will be discussed. Next, differences in side effects, patient preference and cost-effectiveness of rTMS and ECT will be addressed. Finally, the predictors of treatment response and neurobiological changes after treatment will be discussed, to give a balanced perspective on the place of rTMS and ECT in the treatment of TRD.

Updates on theta burst transcranial magnetic stimulation

Presented by *Ying-Zu Huang*
Affiliation(s) *Department of Chang Gung Memorial Hospital and Chang Gung University College of Medicine*

Keywords *TBS, dose, variability*

Abstract

Background: Theta burst stimulation (TBS) has been introduced to the world for 15 years, and is still the most effective form of rTMS in the world. Like other non-invasive brain stimulation (NIBS) protocols, the variability and fragility of its after-effects have been questioned. Moreover, more profound and longer-lasting effects are demanded.

Methods: Thanks to studies over the past decade, the mechanisms, variability, influence of physical and mental activities of TBS is better known. Moreover, the efficiency of TBS makes it the most suitable protocol for dose titration and after-effect consolidation.

Results: The results of the studies give the clues for minimising variability of the effects. On the other hand, the after-effects of TBS could be enhanced or modulated to the wanted direction to, for example, improve the therapeutic benefits by manipulating some factors. Furthermore, the dose effect of TBS is now better known, and the benefit of dose titration has begun to be demonstrated in the clinical practice.

Discussion/conclusion: By understanding the factors causing the variability or modulating the after-effects of TBS, people can easier control for predict effects or even manipulate TBS for a specific purpose. The knowledge of factors for dose titration will be helpful for developing a more powerful and efficient therapeutic protocol using TBS.

Practicalities and Possibilities of Transcranial Ultrasound Stimulation

Presented by *Lennart Verhagen*
Affiliation(s) *Donders Institute, Radboud University, Nijmegen, The Netherlands*
Coauthors *Davide Folloni, Nima Khalighinejad, Alessandro Bongioanni, Jean-Francois Aubry, Jerome Sallet, Matthew Rushworth*
Keywords *focused ultrasound, non-invasive, neuromodulation*

Abstract

Background: It has long been a dream in medicine and neuroscience to be able to non-invasively stimulate deep in the brain. This would open up completely new horizons for research and treatment of brain disorders such as Parkinson's disease, epilepsy, and depression. Recent discoveries now suggest that this promise can be met by ultrasonic neuromodulation. Low-intensity focused ultrasound provide a means to deliver energy – safely and remotely – to virtually any region of the brain with millimetre precision. There, the sound waves can tune neural activity.

Methods: In this introductory overview, I will discuss how we can use low-intensity ultrasound to safely stimulate the brain with high specificity, even deep in the brain. I will review the history of this approach, our current understanding of the biophysical mechanisms and physiology, its impact on both local and circuit activity, its modulation of behavioural performance, and an outlook on current trends and future applications.

Results: In particular, I will describe pioneering non-human primate work, showing how a novel repetitive protocol can induce hour-long plastic changes. Whole-brain fMRI allowed us to track how ultrasound impacted both local and remote circuits. Behavioural measurements revealed the specific consequences of a focal neural perturbation on cognitive computations. I will discuss work on the causal roles of the anterior cingulate cortex, amygdala, basal forebrain, and medial prefrontal cortex in decision-making and learning.

Discussion/conclusion: Non-invasive high-precision deep brain stimulation now seems within grasp with ultrasonic neuromodulation. Yet, the field is young and many foundational questions are still to be answered.

Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields

Presented by *Nir Grossman*
Affiliation(s) *Department of Brain Sciences, Imperial College London, UK. Dementia Research Institute, Media Lab and McGovern Institute for Brain Research, Massachusetts Institute of Technology, USA*
Coauthors *Bono, D., Dedic, N., Kodandaramaiah, S.B., Rudenko, A., Suk, H.J., Cassara, A.M., Neufeld, E., Kuster, N., Tsai, L.H., Pascual-Leone A., Boyden S.E*
Keywords *temporal interference, non-invasive, deep brain stimulation*

Abstract

Background: Electrical brain stimulation is a key technique in research and clinical neuroscience studies, and also is in increasingly widespread use from a therapeutic standpoint. However, to date all methods of electrical stimulation of the brain either require surgery to implant an electrode at a defined site, or involve the application of non-focal electric fields to large fractions of the brain.

Methods: By delivering to the brain multiple electric fields at frequencies too high to recruit neural firing, but which differ by a frequency within the dynamic range of neural firing, we can electrically stimulate neurons throughout a region where interference between the multiple fields results in a prominent electric field envelope modulated at the difference frequency.

Results: We validated this temporal interference (TI) concept via modeling and physics experiments and verified that neurons in the living mouse brain could follow the electric field envelope. We demonstrate the utility of TI stimulation by stimulating neurons in the hippocampus of living mice without recruiting neurons of the overlying cortex. Finally, we show that by altering the currents delivered to a set of immobile electrodes, we can steerably evoke different motor patterns in living mice.

Discussion/conclusion: We report a noninvasive strategy for electrically stimulating neurons at depth using well-known electrical fields and without the need for chemical or genetic manipulation of the brain tissue.

New applications for transcranial alternating current stimulation

Presented by *Ivan Alekseichuk*
Affiliation(s) *Dept of Biomedical Engineering, University of Minnesota, Minneapolis, Minnesota, USA*

Keywords *tACS, NIBS*

Abstract

Background: Transcranial alternating current stimulation (tACS) is a non-invasive neuromodulatory method hypothesized to entrain neural spiking timing and local field potentials in the frequency- and phase-dependent manner. Despite the great promise of manipulating complex, intrinsic brain activity, prevailing applications take limited advantage of knowledge regarding the inherent organization and connectivity in the brain oscillations.

Methods: Recent studies using non-invasive and invasive electrophysiological recordings in awake humans and non-human primates illuminate the mechanism of actions and potential of tACS in informed manipulation of neural connectivity in the brain.

Results: Here, I will first present the advances regarding the mechanistic understanding of tACS in the brain on the cellular level. I will then discuss new promising approaches for targeting neural communication mechanisms such as cross-frequency coupling and neocortical traveling waves. The talk will highlight the recent use cases as well as possible future directions.

Discussion/conclusion: Neural communications are inherently complex and multi-dimensional and include various forms of coordinations on different scales. Thanks to the frequency-specific effects, tACS is in the unique position to selectively manipulate phase-based connectivity. Systematic research and pursuit of informed stimulation of cross-frequency coupling and traveling waves in the neocortex can amplify the intervention's effectiveness both in research and clinical applications.

tDCS-augmented virtual reality exposure for PTSD: possibility for individualized treatment

Presented by *Prof. Mascha van 't Wout-Frank*
Affiliation(s) *Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, USA*

Keywords *transcranial direct current stimulation, virtual reality, posttraumatic stress disorder*

Abstract

Background: At its core, posttraumatic stress disorder (PTSD) involves the presence of persistent maladaptive fear responses seemingly due to inadequate down-regulation mediated by the ventromedial prefrontal cortex (VMPFC). Here we piloted whether transcranial direct current stimulation (tDCS), aimed to facilitate endogenous VMPFC activity, during presentation to standardized warzone-related virtual reality (VR) scenes reduces psychophysiological arousal and symptoms in veterans with PTSD. Additionally, we explored feasibility to standardize tDCS intensity based on individual neuroanatomy using electrical field modeling.

Methods: Twelve veterans with PTSD underwent six VR exposure sessions while receiving either 25 minutes of 2mA tDCS or sham; anode over EEG-coordinate AF3, cathode over PO8. Outcome measures were changes in skin conductance-based arousal and self-reported PTSD symptom severity. In a separate cohort of 24 patients with PTSD we extracted electrical field variability of this tDCS montage in neural targets associated with "fear" and "extinction".

Results: A significant interaction indicated a greater decrease in psychophysiological arousal in the tDCS+VR versus tDCS+sham group across sessions ($p=.03$). Individualized e-field modeling resulted in a 0.12 - 0.34 V/m range in obtained electrical field values across both neural targets. In order to obtain the average electrical field, reverse-calculations suggest tDCS intensities should range between 1.36 - 3.04 mA.

Discussion/conclusion: The application of tDCS during VR is feasible, with small sample preliminary data suggesting reduction in psychophysiological arousal. The wide range in obtained electrical field values and subsequent reverse-calculated tDCS intensities validates the need for prospective, individualized electrical field modeling in clinical trials of tDCS.

PsychotherapyPlus: Augmentation of cognitive-behavioral therapy with direct current stimulation

Presented by *Prof. Malek Bajbouj*
Affiliation(s) *Center for Affective Neuroscience at Department of Psychiatry Charité, Germany*
Coauthors *Prof. Frank Padberg, Dr. Sabine Aust*

Abstract

Background: Both cognitive interventions and non-invasive brain stimulation have been proven to be effective in the treatment of affective disorders. The simultaneous application of both interventions holds promise to act synergistically if combined in a neurobiologically informed fashion.

Methods: A total of 150 patients have been treated in the PsychotherapyPlus study, a prospective, randomized study, in which patients have been allocated either to a combined cognitive psychotherapy-tDCS arm, a CBT-placebo arm, or a psychotherapy alone arm. CBT was administed in a group setting with 12 sessions within 6 weeks. Extensive neuropsychological testing as well as neuroimaging was performed before and after the end of the intervention.

Results: First results with respect of the interventions on neurocognitive (and clinical) domains are intended to be presented.

Discussion/conclusion: The combination of behavioral and neuromodulatory interventions might be an approach to improve the treatment of patients with affective disorders.

Perspectives on combined tDCS and psychological interventions

Presented by *Dr. Josefien Dedoncker*
Affiliation(s) *Ghent Experimental Psychiatry Lab, Ghent University, Belgium*
Keywords *endophenotypes; psychological interventions; transcranial direct current stimulation*

Abstract

Background: As the reported efficacy of transcranial direct current stimulation (tDCS) as a standalone psychiatric treatment shows great heterogeneity, tDCS is increasingly being combined with psychological interventions aiming to increase its efficacy. However, it is not yet clear to what extent a combination of both treatments leads to synergistic clinical effects.

Methods: We conducted a state-of-the art review of sham-controlled studies in which both tDCS and a psychological intervention are administered (i.e., dual active treatments).

Results: Our state-of-the-art review of such dual active treatments indicates that they do not usually appear to produce synergistic clinical effects. Therefore, we explored more basic mechanisms related to the dependency of tDCS effects on the brain state. Based on our state-of-the art review, the efficacy of dual active treatments appears to depend on whether individual patients exhibit endophenotypes involved in the development and maintenance of psychopathology, such as prefrontal-mediated cognitive dysfunction.

Discussion/conclusion: We discuss how, by adhering to the Research Domain Criteria (RDoC) framework, future studies can contribute to the development of personalized dual active treatments. Mechanistic clinical research based on the RDoC principles can reveal alternative neural circuits that need to be functionally targeted by both tDCS and psychological interventions, with promising potential for clinical psychological science and practice. Lastly, we discuss basic mechanistic questions that need to be investigated more thoroughly.

Concurrent TMS-EEG-fMRI to visualize brain-state dependent iTBS effects on signal propagation from the DLPFC

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Keywords *Simultaneous TMS-EEG-fMRI, Multimodal Brain Stimulation, Depression*

Abstract

Background: Repetitive Transcranial Magnetic Stimulation (rTMS) has great therapeutic potential in a range of clinical applications, particularly in the treatment of Major Depressive Disorder (MDD). The main treatment target is the left dorsal-lateral prefrontal cortex (DLPFC), which is stimulated using either high frequency rTMS or intermittent Theta Burst Stimulation (iTBS). The DLPFC is thought to be a node through which rTMS activates deeper cortical structures, however there is little evidence that stimulation effects are able to propagate within these networks.

Methods: Using a novel concurrent TMS-EEG-fMRI setup, we investigated whether the efficacy of signal propagation through these nodes is brain state dependent. In a fully within-subject design, we stimulated healthy participants with either active or sham iTBS. During fMRI acquisition, we gave single TMS pulses to DLPFC to probe the network, using BOLD signal to visualize local and remote brain activation changes. We used EEG to detect whether these pulses are more effective when given at certain phases of ongoing alpha oscillations.

Results: Using this concurrent TMS-EEG-fMRI setup, we were able to visualize the cortico-subcortical signal propagation and brain-state dependency of iTBS stimulation to DLPFC in frontostriatal brain networks known to be involved in MDD.

Discussion/conclusion: Stimulating the depression network at specific predefined oscillatory states determines the direction and strengths of TMS signal propagation through the depression network. Whether this state-dependent network effects also relate to increased clinical efficacy will need to be investigated in future studies on MDD patients.

Neurodevelopmentally Inspired EEG Biomarker for Treatment Stratification Across Various Antidepressant Interventions

Presented by *Helena Voetterl*
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Coauthors *Hanneke van Dijk, Martijn Arns*
Keywords *Individual alpha peak frequency, clinical biomarker, EEG processing*

Abstract

Background: Different treatments for depression and ADHD show limited efficacy on the group level, thus being able to predict treatment response would aid in informing treatment prescription. The individual alpha peak frequency (iAPF) recorded during resting-state EEG shows promise in predicting outcome to various treatments for depression and ADHD but different ways to analyze EEGs can hinder replication of findings and thereby implementation in clinical practice.

Methods: The present study aims to optimize determination of the biologically most plausible iAPF by utilizing the well-studied effect of iAPF indexing maturation during childhood. IAPFs determined with various EEG processing parameter combinations are correlated with age in a large number of children and adolescents. The combinations that reflect the maturation effect best are selected to replicate previous treatment prediction across multiple datasets.

Results: We identify EEG processing parameters most suitable to determine iAPF in a large, heterogeneous dataset and use these to improve treatment prediction with iAPF. We, furthermore, implement these analysis parameters to examine the predictive potential of the iAPF for depression and ADHD interventions for which this relationship has not been studied before.

Discussion/conclusion: Optimizing EEG analysis is crucial to prevent false negative results and to develop reliable biomarkers such as the iAPF that will promote informed treatment choice.

Neuro-Cardiac-Guided TMS (NCG-TMS) to target the depression network: Possibilities for rTMS treatment stratification?

Presented by *Martijn Arns*
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Keywords *rTMS, depression, heart-brain*

Abstract
In depression (MDD) treatment there is a clear need for novel treatments, biomarkers and individualized treatment approaches. This presentation will focus on repetitive Transcranial Magnetic Stimulation (rTMS) treatment in MDD on EEG and clinical predictors (Krepel et al., 2018; 2019). The efficacy of rTMS is thought to be mediated through a frontal-vagal pathway, including structures such as the DLPFC and sgACC. A new method called Neuro-Cardiac-Guided TMS (NCG TMS), exploits the network connectivity in this frontal vagal pathway, as a target engagement approach (Iseger et al., 2019). In addition, co-activation of these structures (e.g. using psychotherapy) enhance clinical response to rTMS (Donse et al., 2017). Stimulation of pre-frontal areas using TMS results in downstream activation of the vagal nerve, with subsequent heart-rate deceleration, only for specific and individualized locations (Iseger et al., 2017; 2019). Preliminary results on its potential for individualizing rTMS stimulation locations and possible better clinical outcomes will be presented. Finally, clinical implications and implementations will be discussed from a 'treatment stratification' perspective, which might be a more realistic goal relative to 'personalized medicine' perspective.

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Fatigue and affective manifestations in multiple sclerosis

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Keywords *fatigue, anxiety, depression*

Abstract
Since the report of Charcot, the famous French Neurologist, multiple sclerosis (MS) continues to be a worrisome neurological disease. It is responsible for a plethora of symptoms with variable degrees of severity and potential disability. Some of them are "silent", often go unnoticed, and could importantly alter the professional performance of MS patients and their social and familial relationships. Under the umbrella of what could be considered as silent symptoms, fatigue and affective manifestations stand among the ones that have aroused the curiosity of scientists over the last two decades [1].
Up to 90 % of MS patients could suffer from fatigue and usually perceive this complaint as the most invalidating one [1]. In addition to fatigue, a growing body of literature has documented the existence of psychiatric manifestations in MS, with anxiety and depression being the most frequent ones, affecting 41-50% of patients, respectively [2].
Common underlying pathophysiological mechanisms and close interaction exist between fatigue and affective manifestations, to the point that they have been recently perceived as a cluster of symptoms [1]. It is now widely accepted that this cluster is difficult-to-manage, its treatment is challenging and far from meeting the patients expectations. Therefore, special medical awareness and development of new pharmacological and non-pharmacological interventions (e.g., physical exercise, cognitive behavioral therapies, noninvasive brain stimulation, or their combinations) are highly needed in this domain in order to ameliorate the patients quality of life [1,3].

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Cognitive Deficits in Multiple Sclerosis: Current knowledge and Perspectives

Presented by *Moussa A. Chalah, MD, PhD*
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Keywords *Cognitive deficits; general cognition; social cognition*

Abstract
Even since their description in 1877, cognitive impairments (CI) are still sometimes overlooked in patients with multiple sclerosis (PwMS) and could halt patients' quality of life. CI are reported by up to 65% of PwMS; the prevalence might depend on methodological differences (e.g., cohorts' characteristics, CI definitions, assessment tools). CI involve general and social domains, among which information processing speed and episodic memory seem to be the most commonly impacted. Different CI patterns were described with regard to clinical data (e.g., disease phenotypes, duration or progression). From a mechanistic point of view, widespread alteration of neural networks has been suggested at the basis of this symptomatology. Among the suggested pathophysiological mechanisms stand the 'multiple disconnection syndrome', regional gray matter pathology, and insufficient compensatory processes. It is important to consider CI as part of a global routine evaluation. This could help quantifying disease evolution and monitoring treatment response. Brief batteries allow assessing cognitive function in clinical settings. In addition, the Symbol Digit Modalities Test - considered the sentinel test to evaluate cognition in PwMS- could be of help at baseline, during annual follow-up or when justified (e.g., suspecting a cognitive relapse, evaluating interventions). Regarding pharmacotherapeutics, small-to-medium effects were observed with disease-modifying therapies. To date, there is no enough evidence on the efficacy of drugs targeting CI in PwMS. Cognitive rehabilitation and physical exercise emerged as promising interventions, and transcranial brain stimulation recently attracted the researchers' attention. Future trials combining several approaches might help overcoming the current therapeutic limitations and optimize patients' management.

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tDCS and Fatigue in Multiple Sclerosis

Presented by *Ulrich Palm*
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Keywords *non-invasive brain stimulation, MS, fatigue*

Abstract

Background: Fatigue is a frequent and debilitating symptom in patients with central nervous system diseases. Up to 90% of patients with multiple sclerosis (MS) suffer from fatigue that drastically affects the quality of life. MS patients also complain of anxiety and depressive symptoms and these three manifestations tend to cluster together in this clinical population. Recent studies point out the potential of transcranial direct current stimulation (tDCS) over prefrontal areas to modulate fatigue symptoms.

Methods: Eleven fatigued MS patients randomly received two blocks (active and sham tDCS) of five consecutive daily sessions of bifrontal tDCS (anode/cathode over the left/right prefrontal cortices, respectively) in a crossover design, separated by a 3-week washout interval. Evaluation took place at day 1, day 5 (right after each block) and 1 week later.

Results: Active but not sham tDCS resulted in a significant improvement of fatigue at day 5 ($p < 0.05$), an effect that seems to last at least 1 week following the stimulation ($p = 0.05$). Active tDCS also significantly improved anxiety symptoms, but the effect emerged 1 week later ($p < 0.05$). No significant effects were obtained regarding depression ($p > 0.05$).

Discussion/conclusion: Bifrontal tDCS seems to modulate fatigue in MS patients. The observed anxiolytic effects could constitute delayed after effects of tDCS or might be mediated by fatigue improvement. These findings are in line with several other studies.

Cognitive Deficits in Multiple Sclerosis: Current knowledge and Perspectives

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Keywords *MS, cognition, tDCS*

Abstract

Background: Cognitive impairment is a frequent symptom of multiple sclerosis (MS), occurring in 40-60% of patients at one point in their lifetime. It can affect general cognition, e.g. working memory or attention but also social cognition, including the cognitive and affective Theory of Mind. Social cognition can have a high impact on someone's relationships as well as on the ability of coping with everyday life difficulties. Cognitive skills in general are omnipresent in daily life and have a high impact on quality of life and activities of daily living. Recently, non-invasive brain stimulation, namely transcranial direct current stimulation (tDCS), has gained attention in the treatment of MS symptoms in the last years. It has shown promising results on MS-related symptoms such as fatigue. The effect on cognitive symptoms is still sparsely investigated and positive effects have only been suggested by few trials so far.

Methods: Eleven right-handed MS patients received two blocks (bifrontal tDCS and sham) of five daily stimulations separated with a three-week washout interval. Working memory and attention was measured by N-Back and Symbol Digit Modalities Test while social cognition was evaluated using the Faux Pas and Eyes Test.

Results: Accuracy of 1-Back Test showed improvement after sham and not active tDCS. No significant effect of tDCS could be seen on social cognition.

Discussion/conclusion: Bifrontal tDCS could impair working memory in MS patients. Due to the small patient sample size this study should be considered a pilot study and further work is needed to help confirming the current results.

Efficacy of non-invasive brain stimulation on cognitive functioning in brain disorders: a meta-analysis

Presented by *Marieke Begemann*
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Keywords *rTMS, cognition, tDCS*

Abstract
Impaired neuropsychological function is common in psychiatric disorders, mainly affecting memory, attention and executive functioning. Non-invasive brain stimulation (NIBS) may have procognitive effects, with high tolerability. We present a meta-analysis evaluating the efficacy of two common techniques: transcranial magnetic stimulation (TMS) and transcranial Direct Current Stimulation (tDCS), in schizophrenia, depression, dementia, Parkinson's disease (PD), stroke, traumatic brain injury (TBI) and multiple sclerosis (MS). A PRISMA systematic search was conducted for randomized controlled trials. Hedges's g was used to quantify effect sizes (ES) for changes in cognition after TMS/tDCS versus sham. As different cognitive functions may have unequal susceptibility to TMS/tDCS, we separately evaluated effects on: attention/vigilance, working memory, executive functioning, processing speed, verbal fluency, verbal learning and social cognition. We included 83 studies (n=2800). For working memory, both TMS (ES=0.17,p=.015) and tDCS (ES=0.17, p=.021) showed small but significant effects. Age positively moderated the effect for TMS. tDCS was superior to sham for attention/vigilance (ES=0.19,p=.025). Effects were not different between disorders. Results were not significant for the other five cognitive domains. Our results revealed that both TMS and tDCS elicit a small trans-diagnostic effect on working memory, tDCS also improved attention/vigilance across diagnoses. Effects on the other domains were not significant. Observed ES were small. However, even slight cognitive improvements may facilitate daily functioning. As NIBS appear to be well-tolerated treatments, they can be considered for realistic indications (i.e. to induce a small improvement in working memory or attention).

rTMS for depressive disorders: current knowledge and future directions

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Keywords *rTMS, depression, future directions*

Abstract
Background: After more than 20 years of clinical rTMS research, major depression has proven to be the primary field of application, Nevertheless, there is still the need for improving clinical efficacy of existing rTMS protocols and promoting novel and more potent rTMS treatment approaches.

Methods: Review and expert opinions.

Results: Several promising new avenues have been proposed: novel stimulation patterns, targets, and coils; combinatory treatments and maintenance; personalization and stratification of rTMS parameters, treatment of subpopulations.

Discussion/conclusion: Although rTMS is an approved and acknowledged treatment for depression, the clinical field is rapidly evolving, aiming to optimize response and remission rates. New studies are emerging, evaluating novel stimulation parameters and fine-tuning individualized treatment protocols.

NIBS for treatment of schizophrenia: hallucinations and negative symptoms

Presented by *André Aleman*
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Keywords *rTMS, schizophrenia, hallucinations*

Abstract
Recent years have witnessed an increase of published studies regarding noninvasive brain stimulation (NIBS) using electromagnetic fields in psychiatric disorders. Such NIBS has been applied in patients with schizophrenia to alleviate both positive and negative symptoms, albeit at different locations and different frequencies of stimulation. The two forms of NIBS that have been studied in several trials are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). In this presentation, I take stock of recent findings. For positive symptoms, more specifically auditory hallucinations, studies have focused on 1Hz rTMS stimulation of the left temporal regions. Results have been mixed, although the most recent meta-analysis still shows an average stronger improvement in real rTMS conditions compared to sham stimulation. For negative symptoms, studies with rTMS have focused on the lateral prefrontal cortex, at 10 Hz or higher. The location of stimulation is based on theoretical models of the functional neuroanatomy of goal-directed behavior. These are discussed first as a starting point - indeed, results of trials will thus not only have clinical implications but will also inform neuroanatomical hypotheses. Meta-analyses suggest that treatment with noninvasive magnetic brain stimulation may ameliorate negative symptoms. Such stimulation has previously been shown to target circuits with dopaminergic innervation. We conducted a trial of prefrontal rTMS for negative symptoms and measured brain activation with fMRI before and after 3 weeks of treatment. Changes in activation of frontal regions were observed. In our most recent trial, we tested iTBS (intermittent theta-burst TMS) over the right DLPC for improving negative symptoms (especially apathy) in patients with schizophrenia. No significant improvement was observed for real versus sham treatment (both groups improved to a small extent). Taking all published findings together, the results of NIBS studies have clinical implications and may aid the development of novel treatment strategies.