# ABSTRACTS

## LIMITING AND OPTIMISABLE CONDITIONS IN rTMS OF DEPRESSION AND OTHER MENTAL DISEASES

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Repetitive transcranial magnetic stimulation (rTMS) is one of the brain stimulation methods which may help to overcome the stuttering development of the treatment of psychiatric disorders as can be seen in pharmacotherapy. After the first clinical trials in the 90's scientific based evidence shows the efficacy of rTMS in depression and other mental diseases. It is now the time to work on further developments to increase efficacy of rTMS by identifying limiting conditions and by optimizing available protocols. In the present symposium we will show how or if medication, gender, age, personality and similar aspects has influence on the efficacy of rTMS on the example of depression (Martin Schecklmann, Chis Baeken). We will also highlight the clinical perspectives of deep TMS (Maud Rotharmel) and the combination of different neurostimulation techniques (Virginie Moulier). The findings presented in this symposium may help to pave the way for future applications of rTMS in psychiatry.

## INFLUENCE OF TMS, CLINICAL AND DEMOGRAPHIC PARAMETERS ON THE EFFICACY OF rTMS IN DEPRESSION

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Repetitive transcranial magnetic stimulation (rTMS) was shown to be effective in the treatment of depression. A amelioration of symptoms for over 50% or full remission takes place in 30-40% of the treated patients. The number needed to treat is about 4-5 against placebo treatment. Up to now limited evidence is available which patient will benefit from rTMS. In a retrospective analysis of a cohort of 505 patients with depression treated in a naturalistic clinical setting the Hamilton depression rating scale was used as treatment outcome. Parameters such as age, gender, motor threshold, stimulation intensity, type of depression, medication were analysed. The overall cohort shows an effect size of about 0.9 according to Cohen's d. Preliminary analyses show significant influence of gender, antipsychotic medications and benzodiazepines. In conclusion, treatment in normal care fits to the positive controlled clinical trials. Data from large scaled data bases may help developing individual probability signatures for treatment response.

## BRAIN PERFUSION PATTERNS AS CLINICAL (NON) PREDICTOR TO aiTBS TREATMENT IN MEDICATION-RESISTANT DEPRESSION

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Accelerated intermittent Theta Burst Stimulation (aiTBS) has been put forward as an effective treatment to alleviate depressive symptoms. In this arterial spin labeling (ASL) brain imaging study 50

medication-resistant depressed patients received twenty sessions (5 per day) of neuronavigated left DLPFC aiTBS in an accelerated sham-controlled crossover fashion, where all stimulation sessions were spread over four days (Trial registration: http://clinicaltrials.gov/show/NCT01832805). Active aiTBS, in contrast to sham, resulted in prompt perfusion increases in functionally connected brain regions such as the ventromedial prefrontal cortex, the left (para)hippocampus, and the right posterior cerebellum. Stronger individual baseline interregional covariance perfusion connectivity patterns between the subgenual Anterior cingulate cortex and the individual left dorsolateral prefrontal cortical (DLPFC) targets predicted response and/or remission. Furthermore, responders and remitters with higher Behavioural Inhibition (BIS) scores displayed stronger baseline interregional perfusion connections. Our perfusion findings indicate that active aiTBS treatment promptly affects brain regions functionally and structurally connected to the stimulated area and known to be part of deregulated brain circuits when clinically depressed. However, targeting the left DLPFC with aiTBS based on personal structural imaging data only may not be the most optimal method to enhance meaningful antidepressant responses. Additional therapies dealing with behavioural inhibition may be warranted.

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## BEYOND CLINICAL SYNDROMES: UNDERSTANDING MECHANISMS OF NEUROMODULATION FORM A DIMENSIONAL PERSPECTIVE

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Clinical syndromes in Psychiatry include great heterogeneity, biological and also phenomenological. Dimensional approaches to psychophathology, pathophysiology, biomarker discovery and treatment development have prompted a paradigm shift in neuropsychiatry. That said, this framework is still relatively uncommon to study and optimize treatment development with device neuromodulation technologies. This symposium will present early work introducing dimensional analyses (beyond syndromal clinical severity) of device neuromodulation therapies for depression. We will highlight how this framework allows a more direct identification of structural and functional circuit dynamics characterizing maladaptive pathophysiological processes with translational implications. We will explore these questions across neuromodulation methods, including transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT) and magnetic seizure therapy (MST).

Dr. Kristen Ellard will discuss the impact of TMS on emotional regulation in major depressive disorder, the role of executive function in mediating these effects, and the circuit-level mechanisms of action.

Dr. Tracy Barbour will present on the effects of TMS and ECT on positive valence processes, including affective (anhedonia) and behavioral (approach/avoidance) components, and dissect the convergence and differences of these 2 treatment modalities.

Dr. Benjamin Ward will outline recent work using machine learning to predict dimensional changes in depressive symptoms in response to ECT and serial ketamine infusion using neuroimaging data.

Dr. Zhi Deng will present a secondary data analysis comparing the efficacy of ultrabrief pulse, right unilateral ECT and MST, using an exploratory factor analysis with the 24-item HAMD (primary outcome of the study) to define clinical dimensions and assess longitudinal response trajectories and predictors of response.

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# CEREBELLAR-THALAMO-CORTICAL CIRCUITRY IN TREATMENT-RESISTANT OBSESSIVE-COMPULSIVE DISORDER: A NEUROPHYSIOLOGICAL STUDY PROTOCOL

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**Introduction:** Obsessive-compulsive disorder (OCD) is a chronic condition with a high rate of poor response to conventional treatments. Recent neurophysiological studies involving OCD patients reported dysfunction of the cerebellar-thalamo-cortical network. Transcranial magnetic stimulation (TMS) is a brain stimulation technique that can be used to non invasively assess cerebellar functions in humans, by paired stimulation of the cerebellum and the primary motor cortex (M1). Transcranial magnetic pulses in the inion region reduced the excitability of corticospinal outputs from the M1 contralateral to the site of cerebellar stimulation if tested 5-6 ms later (Ugawa et al. 1991). This is called cerebellar inhibition of the motor cortex (CBI). Stimulation of cerebellum was also found to interact with other local circuits in M1 that were involved in short interval intracortical inhibition (SICI), long interval intracortical inhibition (LICI) and intracortical facilitation (ICF) (Daskalakis et al. 2004).

This study has two aims:

- to correlate OCD symptoms severity with CBI;
- to compare the CBI of treatment-resistant and non-treatment-resistant OCD patients.

**Methods:** We will recruit 30 treatment-resistant OCD patients and 30 non-treatment-resistant OCD patients. Treatment response is defined as an absence of significant reduction in YBOCS scores (>35%) after at least two trials with SSRIs and one trial with clomipramine. We will measure the CBI for each patient of both groups.

**Discussion:** There is little literature regarding the correlation between OCD and the neurophysiological measures of cerebellar function. This is the first study aiming at correlating the CBI dysfunction with OCD symptoms severity and treatment response. Our results will hopefully shed light on the putative neurophysiological features underpinning the treatment response of OCD patients.

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# CEREBELLAR TRANSCRANIAL DIRECT CURRENT STIMULATION FOR SCHIZOPHRENIA: A CURRENT MODELLING STUDY

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**Background:** Schizophrenia is a severe and chronic mental disorder affecting millions of people worldwide. Given that the cerebellum is involved in the pathophysiology of schizophrenia, it constitutes a promising target for transcranial direct current stimulation (tDCS) interventions. However, illness progression and aging have been associated with cerebellar volume loss which might hinder the efficacy of tDCS. Therefore, we aim to conduct a proof-of-concept study on the effect of tDCS in the cerebellum and for that, we will 1) simulate the electric field (EF) of four right cerebellar tDCS (ctDCS) montages, and 2) investigate if age and sex can significantly predict EF strength.

**Methods:** Open access T1-w scans from the Collaborative Informatics and Neuroimaging Suite Data Exchange tool1 of 69 individuals diagnosed with schizophrenia were preprocessed with SimNIBS2. After segmentation, we excluded 24 participants (due to MRI processing persistent errors) and 45 participants were included in the analysis (M=35.4 years, SD=12.7; 22.2% female). We tested three standard ctDCS montages and one novel montage (Figure 1, panels A, B, C, and D respectively). The mean EF of the best performing montage was extracted and entered into a multiple linear regression analysis with age and sex as predictors.

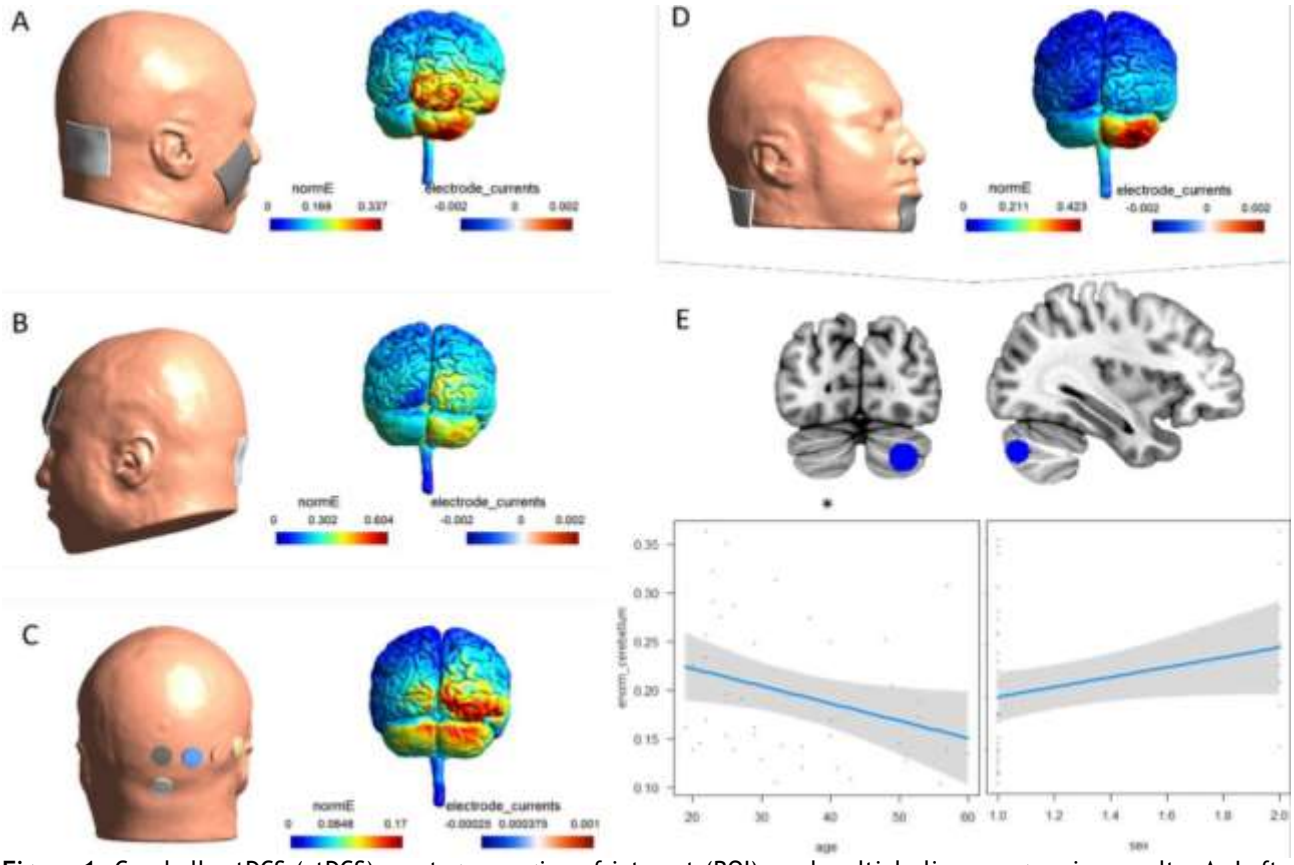


**Figure 1.** Cerebellar tDCS (ctDCS) montages, region of interest (ROI), and multiple linear regression results. A. Left: Anode over the right cerebellum (1 cm below and 3 cm lateral to Iz, 10/10 EEG system); cathode over the right buccinator muscle. Right: Electric field (EF) simulation on gray matter (electrode current: 2mA, peak EF strength [normE]: 0.337 V/m). B. Left: Anode over the right cerebellum (1 cm below and 3 cm lateral to Iz); cathode over the contralateral supraorbital area (FP1). Right: EF simulation on gray matter (electrode current: 2mA, peak EF strength [normE]: 0.604 V/m). C. Left: High-Definition ctDCS montage. Anode (3.14 $cm^2$) over the right cerebellum (Iz), and four 3.14 $cm^2$ cathodes over Oz, O2, P8, and PO8. Right: EF simulation on grey matter (total electrode current: 1mA, peak EF strength [normE]: 0.170 V/m). D. Left: Anode over the right cerebellum (PO10); cathode over the chin. Right: EF simulation on gray matter (electrode current: 2mA, peak EF strength [normE]: 0.423V/m). E. Top: Spherical ROI of the cerebellum (xyz: 28, -78, -40) over MNI template in blue. Bottom: Multiple linear regression plots. Dependent variable: mean EF strength of the cerebellar ROI for montage D; Predictors: age (*p<0.05), and sex (not significant)

**Results:** The EF maps showed spillover stimulation effects to neighboring regions in montages A-C. Montage D presented the most focal and highest current in the target region. The regression model explained 15.5% of the variance, and only age was a significant predictor of EF strength (β=-0.0017, p<0.05).

**Conclusions:** We show that the tDCS montage with the anode over the right cerebellum (PO10) and the cathode over the chin might be the preferred setup to stimulate the right cerebellum in schizophrenia. Also, the EF strength decreases with age. Future studies should consider individually-optimized tDCS montages to account for age.

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# MODULATION OF BRAIN-BODY INTERACTIONS USING NON-INVASIVE BRAIN STIMULATION

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The past decade there has been emerging evidence for the role of aberrant brain-body bidirectional communication in several stress-related affective and somatic health issues. Crucially, non-invasive brain stimulation (NIBS) techniques, such as transcutaneous vagus nerve stimulation (tVNS) and transcranial direct current stimulation (tDCS), can be used to enhance brain-body interactions in both healthy and clinical samples.

In this symposium, researchers from the Universities of Ghent (Belgium), Guglielmo Marconi University (Italy) and German sport University of Cologne (Germany), will present up-to-date research on the use of NIBS to modulate brain-body interactions with the aim to improve cognitive and emotional functioning and related clinical phenomena. Moreover, novel perspectives regarding the use of different types of NIBS interventions to modulate brain-body interactions for research and clinic purposes will be presented.

In the first presentation, Marie-Anne Vanderhasselt (University of Ghent, Belgium) will present state of-the-art bottom-up and top-down interventions to increase vagus nerve activity and stress resilience.

In the second presentation, Maximilian Schmaußer (German sport University Cologne, Germany) will discuss meta-analytical evidence for the modulation of autonomic nervous activity, including vagally-mediated heart rate variability, using different NIBS techniques.

In the third presentation, Stefanie De Smet (University of Ghent, Belgium) will the effects of transcutaneous vagus nerve stimulation (taVNS) on psychophysiological correlates of perseverative cognition following psychosocial stress.

In the fourth presentation, Giuseppe Salvo (Guglielmo Marconi University, Italy), will present his work on the effects of tDCS on disgust, moral rigidity and heart rate variability, and its implications for interventions in patients suffering from obsessive-compulsive disorder.

Finally, Marie-Anne Vanderhasselt (University of Ghent, Belgium) will serve as discussant of the symposium. All speakers will give their views on future research directions on the use of NIBS to modulate brain-body interactions.

***Key words:*** *brain-body interactions - vagus nerve – psychophysiology - transcutaneuous vagus nerve stimulation (tVNS) - transcranial direct current stimulation (tDCS) - repetitive transcranial magnetic stimulation (rTMS)*

# COMBINING ELECTRICAL STIMULATION AND LIFESTYLE INTERVENTIONS TARGETING THE VAGUS NERVE TO INCREASE RESILIENCE

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Chronic stress has dramatically increased over the last years and is one of the major health concerns of the 21st century. Crucially, bodily functions have received little attention to increase mental health, despite increasing evidence on the impact of mind-body interactions on resilience. An exemplary model is constituted by accumulating empirical support on the longest cranial nerve, the vagus nerve, which enables two-way communication between heart and brain, enabling the ability to engage in an adaptive stress response in a context-appropriate manner. Yet, research on such bidirectional communication so far is mainly correlational. I propose to consider resonant breathing, physical exercise, or transcutaneous vagus nerve stimulation (tVNS) (bottom-up approach, heart > brain), and prefrontal neuromodulation (top-down approach, brain > heart) as evidence-based ways to increase vagal nerve inhibitory control and hence increase flexibility and stress resilience. These promising, likely cost-effective and easily employable techniques can be used alone or in combination, harnessing neurobiological scientific advances to select treatment options with the greatest likelihood of success.

***Key words:*** *resilience - vagus nerve - heart rate variability - resonance breathing - non-invasive brain modulation*

# THE EFFECTS OF NONINVASIVE BRAIN STIMULATION ON HEART RATE AND HEART RATE VARIABILITY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Noninvasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are widely used to test the involvement of specific cortical regions in cognitive, affective and (sensori-)motor processing. Despite NIBS being capable of testing causal directions, current models on cortical regulation of autonomic nervous system (ANS) functions such as heart rate (HR) and heart rate variability (HRV) rely primarily on brain imaging studies or animal models. In a systematic review and meta-analysis, we explored whether NIBS represents an effective method for modulating HR and HRV and to examine whether the ANS is modulated by cortical mechanisms that can be targeted by NIBS. In a series of four meta-analyses, 131 effect sizes from 35 sham-controlled trials were analyzed using meta-regression models. Robust variance estimation (RVE) was employed to account for dependencies between multiple outcomes from individual studies. NIBS was found to effectively modulate HR and HRV with small to medium effect sizes. Moderator analyses yielded significant differences in effects between stimulation of distinct cortical areas, particularly for HRV. In primarily vagally mediated HRV measures, stimulation of the dorsolateral prefrontal cortex (dlPFC) produced higher effect sizes than stimulation of temporal/insular areas. Although the motor cortex is rarely if ever mentioned in current models of cortical ANS regulation, stimulation of the motor cortex resulted in effect sizes comparable to stimulation of the dlPFC. Our results show that NIBS is a promising tool to investigate the cortical regulation of ANS, whereby future research is needed to identify further factors modulating the size of effects. To advance research in this area, we recommend the use of high methodological standards (e.g., use of neuronavigation), the use of newly developed TMS and tDCS devices that allow more focal or deeper stimulation, as well as the combined use of NIBS and neuroimaging.

***Key words:*** *transcranial magnetic stimulation (TMS) - transcranial direct current stimulation (tDCS) - autonomic nervous system - heart rate variability - meta-analysis*

# EFFECTS OF TRANSCUTANEOUS AURICULAR VAGUS NERVE STIMULATION (taVNS) ON AUTONOMIC AND COGNITIVE RIGIDITY DURING PERSEVERATIVE COGNITION

**Stefanie De Smet[1,2], Cristina Ottaviani[3,4] , Bart Verkuil[5,6], Chris Baekena[2,7,8,9] & Marie-Anne Vanderhasselt[1,2]**

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Perseverative cognitions can provoke psychophysiological stress in the absence of an actual stressor and are considered important transdiagnostic vulnerability factors for several (mental) health issues. These stress-related cognitive processes are reflected by both cognitive and autonomic inflexibility (assessed by heart rate variability; HRV), with a key role attributed to the vagus nerve. Interestingly, modulation of vagal activity can be achieved with transcutaneous auricular vagus nerve stimulation (taVNS), a non-invasive technique that employs a low-intensity electrical current applied to the ear. In a sample of healthy subjects, we investigated the effects of taVNS of the left concha, compared to sham (earlobe) stimulation, on the cognitive and autonomic correlates of perseverative cognition following a

psychosocial stress task. Interestingly, taVNS significantly reduced cognitive rigidity, reflected by reduced subjective perseverative thinking after psychosocial stress. Although there were no direct effects on autonomic correlates of perseverative cognition, stimulation intensity significantly moderated the effects of taVNS on HRV, with higher taVNS intensities being associated with higher levels of HRV. Contrarily, the results indicated that individuals who engaged more in perseverative thinking showed more autonomic flexibility during stress recovery following taVNS, suggesting a possible dissociation between the physiological and psychological changes following taVNS. Again, this effect was moderated by stimulation intensity. Overall, the study findings endorse the causal link between perseverative cognitions and the vagus nerve and, although replication is pivotal, hint towards a linear relationship between taVNS intensity and HRV.

***Key words:*** *transcutaneous auricular vagus nerve stimulation (taVNS) - perseverative cognition - heart rate variability - cognitive rigidity - psychosocial stress*

## REDUCING DISGUST AND MORAL RIGIDITY THROUGH TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS): CLINICAL IMPLICATIONS FOR OBSESSIVE-COMPULSIVE DISORDER

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The experience of deontological guilt has been found to selectively activate the brain region of the insula, a well-known structure implicated in the processing of disgust. Moreover, previous studies showed a hyperactivity of the insula in persons with obsessive-compulsive disorder (OCD), in which deontological guilt and disgust play a pivotal role in pathogenesis and maintenance of symptoms. The present study tested the hypothesis that indirect inhibition of the insula via cathodal transcranial direct current stimulation (tDCS) would decrease disgust and moral rigidity. By using a randomized, sham-controlled, within-subject design, 36 healthy individuals (18 women) underwent 15-min anodal, cathodal, and sham tDCS over T3 in three different days. Levels of OC tendencies as well as pre and post-stimulation momentary emotional states were assessed. Subjects' heart rate (HR) was recorded to derive measures of parasympathetic nervous system activity (Heart Rate Variability, HRV). After the first 10 minutes of tDCS stimulation, participants were asked to complete a computerized moral task and a word-stem completion task with either disgust-related words or neutral alternatives. Compared to sham condition, anodal and cathodal stimulation of T3 respectively enhanced and decreased self-reported disgust, severity of moral judgements in the deontological domain, and HRV. A positive correlation emerged in the anodal condition between scores on the Obsessive-Compulsive Inventory-Revised (OCI-R) and self-reported disgust, between deontological guilt and the Fear-of-Sin (FoS) subscale of the Pennsylvania Inventory of Scrupolosity (PIOS), and between deontological guilt and the washing and obsessing subscales of the OCI-R; in the cathodal condition, disgust inversely correlated with the FoS and the washing and obsessing subscales of the OCI-R. To conclude, results showed a decrease in self-reported and physiological disgust, and deontological moral rigidity following cathodal tDCS on T3, with stronger effects in individuals with higher levels of OC traits, thereby suggesting potential implications for OCD treatment.

***Key words:*** *transcranial direct current stimulation (tDCS) – disgust - moral rigidity - heart rate variability - obsessive-compulsive disorder (OCD)*

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## DOUBLE-DOSED NON-INVASIVE BRAIN STIMULATION: IS MORE BETTER?

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Since the FDA-approved once-daily intermittent theta-burst stimulation (iTBS) treatment for depression rapidly extends to six weeks, patients and caregivers face a considerable logistic burden. Therefore, twice-daily stimulation has gained popularity as a therapeutic tool for stress-related psychiatric disorders. However, the neuro-endocrinological effect of one or two (double-dosed) iTBS sessions remains unclear. Considering that the most frequently stimulated target of non-invasive brain stimulation in psychiatry, the dorsolateral prefrontal cortex (DLPFC), is involved in regulating the hypothalamic-pituitary-adrenal (HPA) system, stress regulation responses, such as cortisol secretion, are of interest. Using a two-period cross-over design, this study looked at the effect of double-dosed iTBS over the left DLPFC on salivary cortisol in 38 healthy volunteers after being stressed with the Trier Social Stress Test (TSST). After the first active iTBS session, no differential effects on salivary output were observed as contrasted to sham. However, after the second active session, there was a significantly smaller decrease in salivary cortisol concentrations in the active iTBS condition than in the sham condition. Our results suggest that double-dosed iTBS after being stressed might affect stress recovery differently than a single session of iTBS.

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## BRAIN DERIVED NEUROTROPHIC FACTOR NEGATIVELY RESPONDED TO TRANSCRANIAL DIRECT CURRENT STIMULATION: RANDOMIZED CONTROLLED TRIAL

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**Background:** Brain-derived neurotrophic factor (BDNF) levels could objectively indicate the synaptic plasticity; it has also been suggested that modulation of the (BDNF) might be a part of the mechanisms involved in transcranial direct current stimulation tDCS effects on synaptic connectivity. The aim of this study is to investigate associated change within BDNF level in response to brain stimulation in subacute stroke patients. The trial registration in the clinical trial ID is NCT04770363.

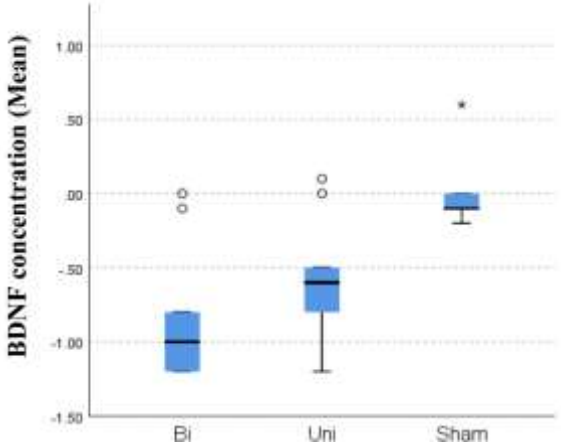


**Figure 1.** Mean negative change in BDNF concentration between unihemispheric, bihemispheric, and sham groups, as represented in the Box-plot of the Kruskal-Wallis rank-sum test

**Methods:** 36 sub-acute ischemic stroke survivors participated in the study, randomly assigned to one of three groups receiving (tDCS), bihemispheric (Anodal over affected M1, and cathodal over healthy M1) or unihemispheric (Anodal over affected M1, and cathodal stimulation over the supraorbital bone of the healthy side) or sham (No current). ActivaDose tDCS (USA) used, consisted of 20 minutes of 2 mA intensity; in each session for 12 sessions three sessions per week. A 3ml blood sample was withdrawn from one of the arm veins. The first sample was withdrawn in the first session and the second sample after the end of the tDCS sessions after four weeks of the treatment. Serum levels of BDNF were determined using commercially available ELISA kits (SunRed Biotechnology Company).

**Results:** There was a statistically significant difference (Negative change) within the groups for bihemispheric (P-value = 0.011), and unihemispheric stimulation (P-value = 0.003). For the sham group, no significant difference (P-value = 0.492) as presented in figure 1. There was significant difference between groups (P-value = 0.005). Running post-hoc test by pairwise revealed both bihemispheric and unihemispheric stimulation significantly decreased BDNF levels more than sham (P=0.001), (P=0.021), respectively and with no significant difference between both experimental groups (P=0.217).

**Conclusion:** BDNF has showed significant decrease after tDCS application in ischemic stroke patients, even the motor measures have been positively improved.

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## LONG-TERM HOME-BASED FRONTO-CEREBELLAR TRANSCRANIAL DIRECT CURRENT STIMULATION FOR AUTISM SPECTRUM DISORDER: A CASE SERIES

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**Introduction:** In a previous study, we reported that right cerebellar/left frontal transcranial direct current stimulation (tDCS) is feasible, safe and potentially effective for improving Autism Spectrum Disorder (ASD) symptoms among children (D'Urso 2021).

Considering the cumulative neurophysiological effect of repeated sessions of tDCS and the potential decay of the obtained clinical improvements after discontinuation, longer-term treatments show great promise to increase the clinical outcomes. Home-based tDCS is a suitable option for ensuring a long-lasting compliance to the treatment, especially in ASD patients, who are very susceptible to routine changes and environmental stressors.

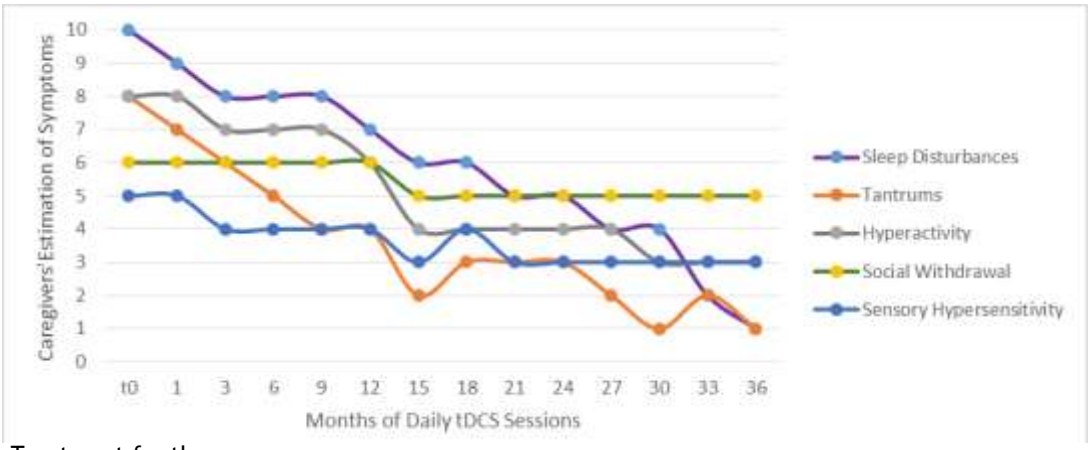


**Figure 1.** Treatment for three years

**Methods:**

- 6 patients (4M, 2F) with ASD, aged 7 to 37 years (mean 15.2);
- Continuous daily 20-minute tDCS sessions with current intensity ranging from 1 to 2 mA;
- The anode was placed over the dorsolateral prefrontal cortex (DLPFC) and the cathode over the right cerebellum;

- Treatment was carried out at home by caregivers, after training;
- During the treatment no changes were made to the ongoing therapies;
- A 10 point VAS was administered to the caregivers to assess the most disturbing and disabling behavioral problems at baseline, after 1 month of treatment and every three months afterwards.

**Results:**

- One patient has been treated uninterruptedly for three years (Figure 1), two patients for one year, and one for three months.
- One patient stopped the treatment after 43 sessions due to lack of clinical improvement.
- The five patients who are continuing the treatment showed a significant improvement during the first few months, which has been maintained over time.
- The only patient who did not show any improvement suffers from a comorbid rare genetic syndrome.
- No adverse effects were reported, besides mild skin irritation.

**Conclusion:** Our findings suggest that fronto-cerebellar tDCS is feasible, safe and easy to administer to ASD patients even at home and for long periods of time, provided that the patients' caregivers are appropriately trained. Long-term therapy ensures the persistence of the previously obtained clinical improvement without additional side effects.

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## A 20-YEAR JOURNEY IN TRANSCRANIAL ULTRASOUND STIMULATION – LESSONS LEARNED

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**Introduction:** Transcranial Ultrasound Stimulation (TUS) is an innovative technique allowing for the first time non-invasive deep brain neuromodulation with a millimetric precision. But since the proof of concept of ultrasonic neuromodulation with the skull bone removed, in 1958, many challenges remained to be overcome: (i) the development of technologies enabling to focus ultrasound beams through the human skull, (ii) the identification of stimulation parameters allowing sustained neuromodulation effects and (iii) the definition of safety limits for clinical application. Over the last 20 years our laboratory has gained an internationally recognized track record in addressing each of these three key issues. In this presentation, we review 20 years of research in our laboratory that paved the way to the translation of TUS in medicine.

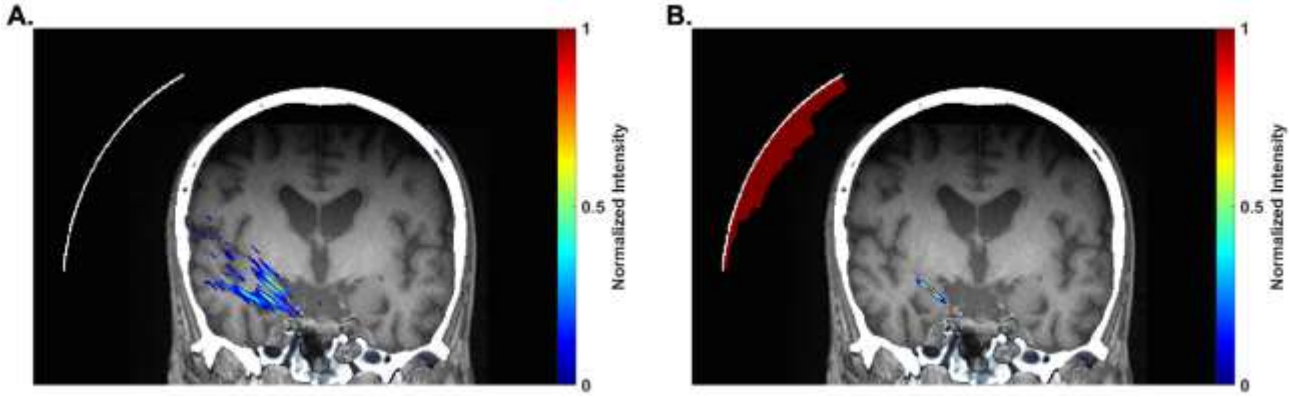


**Figure 1.** Acoustic intensity map when targeting the right amygdala without (A.) and with (B.) the use of a 3D printed acoustic lens (in dark red) covering a single-element ultrasonic transducer (in white). Sagittal planes are represented. The thickness of the lens was calculated based on a CT scan of the skull

**Methods:** Ultrasonic neuromodulation has been demonstrated in rodents, non-human primates and healthy volunteers. We will first review the pioneering studies on transcranial ultrasonic neuromodulation. Transient effects (lasting less than 1s) were initially induced. The acoustical stimulation parameters were further optimized to extend the duration of the neuromodulation to more than an hour (Verhagen et al. 2019), in line with potential clinical applications. Nevertheless, the first proofs of concept on healthy volunteers were limited to cortical stimulations because of the defocusing effect of the human skull. To counteract this, transcranial focusing was initially achieved by using multi-element arrays made of hundreds of ultrasound transducers. But a disruptive approach was introduced recently: it consists in the use of a single-element transducer covered with a 3D printed acoustic lens (Maimbourg et al. 2018) (Figure 1). The acoustic lens also enables non-invasive simultaneous multisite deep brain stimulation.

**Conclusions:** Altogether, the demonstration of sustained ultrasonic neuromodulation and the development of precise, low cost and mobile prototypes for noninvasive deep brain ultrasound focusing indicate that Transcranial Ultrasound Stimulation is now ready for clinical translation.

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# COMBINING APP-BASED PSYCHOLOGICAL INTERVENTION WITH HOME-BASED TRANSCRANIAL DIRECT STIMULATION FOR THE TREATMENT OF DEPRESSIVE AND ANXIETY SYMPTOMS: A CASE SERIES

**Mónica Sobral[1,2], Raquel Guiomar[1], Vera Martins[2,3] & Ana Ganho-Ávila[1]**

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Evidence indicates high heterogeneity in tDCS efficacy as a stand-alone treatment. Combining tDCS with psychological interventions may yield promising results to increase its therapeutic effects (Dedoncker et al. 2021). The current case series details the effects of 6 weeks of self-administered tDCS paired with behavioral therapy smartphone app (using Flow™), on depressive and anxiety symptoms, in seven patients (26-51y; 5 female) presenting distinctive neuropsychiatric disorders. The stimulation protocols consisted of 30min daily sessions, for 10 working days (two weeks from Monday-to-Friday; Protocol 1) or 15 consecutive workdays (three weeks from Monday-to-Friday; Protocol 2), followed by twice-weekly sessions for 2 or 3 weeks, respectively (18 or 21 sessions in total). Flow™ uses a current intensity of 2mA, targeting the bilateral dorsolateral prefrontal cortex. The app offers virtually guided sessions of behavioral therapy to be completed during stimulation which are not mandatory. At baseline and week 6 of treatment, we assessed depressive symptoms using MADRS-s and BDI-II, anxious symptoms using STAI-Trait, acceptability using ACCEPT-ETCC, and side effects using the Portuguese translation of the Thair et al. questionnaire (Thair et al. 2017). According to the Reliable Change Index (RCI), clinically reliable changes were found in symptoms of depression in 4 patients using MADRS-s (out of 7; RCI: -1.44 to -4.82; 90% CI) and in 3 patients using BDI-II (out of 4; RCI: -3.61 to -6.18; 90% CI). For anxiety symptoms, we found clinically reliable improvement in 4 patients (out of 5; RCI: -1.79 to -8.64; 90% CI). Stimulation was well tolerated and accepted (M=87.71, SD=4.92), with mild tingling sensation and scalp discomfort being the most common side effects. This case series highlights the applicability, acceptance, and promising results of combined home-based tDCS and app-based psychological interventions for the treatment of depression and anxiety symptoms.

**References:**

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# MODELLING NON-INVASIVE BRAIN STIMULATION OF DEEP BRAIN STRUCTURES FOR PSYCHIATRIC APPLICATIONS

**Emilė Radytė[1], Karen Wendt[2,3], Majid Memarian Sorkhabi[2], Jacinta O'Shea[1] & Timothy Denison[2,3]**

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*[3]Department of Engineering Science, University of Oxford, Oxford, UK*

**Introduction:** Recent neuropathological and neuroimaging work has identified the lateral habenula as a critical deep brain structure that likely contributes to the neuro-pathophysiology of prevalent psychiatric illnesses. The ability to modulate deep psychiatric targets will become critical to the development of novel treatment protocols and modalities. This is a computational modelling study to explore two common (transcranial alternating current stimulation (tACS) and transcranial magnetic stimulation (TMS)) and one novel (temporally interfering electric fields (TI EFs)) non-invasive brain stimulation (NIBS) methods in their ability to reach and modulate deep brain targets, and anticipate relevant local effects.

**Methods:** Firstly, the relative strengths of electric fields on- and off-target, a novel target of the lateral habenula in humans, are modelled and compared using simulations based on human neuroimaging data with SimNIBS. Secondly, local effects of these field strengths are modelled on single-compartment neuronal models. Finally, potential side effects such as conduction blocks are investigated using simple single-compartment neuronal models to assess the diverse potential impact of field strength on neuronal activity on- and off-target in the brain.

**Results:** Across the studied NIBS modalities, the ratio of maximum electric field strength off-target to that at the target remains high, especially for figure-8 coil TMS. Investigation of local effects suggests that the field strengths of all the studied NIBS modalities engage off-target regions of the brain while barely modulating activity at the target when constrained to safe currents for tACS and TI EFs in particular. Finally, it is suggested that electric fields off-target could generate conduction blocks, which can lead to a lack of neuronal response to additional inputs.

**Discussion:** This exploratory study demonstrates some of the challenges –such as off-target conduction blocks – to be considered if NIBS methods were applied for deep brain structure targeting when treating neuropsychiatric conditions in the future.

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## UNDERSTANDING CIRCUIT MECHANISMS OF ELECTROCONVULSIVE THERAPY USING MULTIMODAL MRI

**Joan A. Camprodon[1], Tracy Barbour[1], Benjamin Ward[2], Carles Soriano-Mas[3] & Marta Cano[4]**

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*[4]Univestitat Autonoma de Barcelona, Barcelona, Spain*

Electroconvulsive therapy (ECT) remains the most effective treatment in psychiatry, and among the most effective in medicine. While our clinical understanding of ECT is significant, it contrasts with how little we know about its neurobiological mechanisms of action. Given how diffuse the induced electric fields are and the fact that ECT leads to a generalized seizure, ECT has been traditionally considered a non-specific neuromodulation treatment. However, neuroimaging research is challenging this notion and suggesting ECT is more focal than previously considered. In this symposium, we will present data from groups working in the Global ECT-MRI Research Collaboration (GEMRIC) using structural and functional MRI to understand predictors and mechanisms of action of ECT at the circuit level.

Dr. Wade will discuss results using functional connectivity MRI to compare the mechanisms of action of ECT to other rapidly acting treatments (serial ketamine infusion and total sleep deprivation), identifying modality-specific mechanisms and treatment-response biomarkers.

Dr. Soriano-Mas will present data from GEMRIC aiming to understand the anatomical antidepressant mechanisms of action of ECT using structural covariance. Changes in structural covariance of the hippocampus and the anterior insula are associated with antidepressant efficacy, highlighting the importance of a circuit-based approach to understanding pathophysiology and the and mechanisms of treatment response.

Dr. Cano will present data from GEMRIC analyzing 148 patients with treatment resistant depression, assessing structural changes (volume, area and thickness) associated with the antisuicidal properties on ECT, and highlighting the role of the anterior cingulate.

Dr. Camprodon will discuss results assessing patterns of functional connectivity that both predict and explain the antisuicidal efficacy of ECT at the circuit level. This study illustrates the use ECT as a systems neuroscience translational tool to identify treatment targets and inform subsequent treatment development research for suicide, using other neuromodulation interventions such as TMS.

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## POTENTIAL OF ELECTRIC FIELD SIMULATIONS IN CLINICAL PRACTICE

**Chris Baeken[1], Martin Tik[2], Oula Puonti[3], Debby Klooster[1], Alex Opitz[4] & Maria Vasileiadi[5]**

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*[2]Brain Stimulation Lab, Psychiatry and Behavioral Sciences, Stanford, CA, USA*
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*[4]University of Minnesota, Minneapolis, MN, USA*
*[5]Medical University of Vienna, Vienna, Austria*

Brain stimulation induced electric field simulations can identify how brain regions are affected depending on the individual's gyral folding pattern. The information about the distribution and strength of the electric fields can be used to derive personalized stimulation parameters or be considered retrospectively in statistical analyses. In this symposium,

First, Oula Puonti (Danish Research Center for Magnetic Resonance) will give an introduction on electric field simulations in practice. Furthermore, he will talk about the link between field modeling and personalized stimulation protocols and present results on the validation of the simulations using invasive and non-invasive approaches identifying crucial aspects for accurate electric field estimates.

Debby Klooster (Ghent University) will demonstrate how electric field simulations could be used in clinical practice to derive the optimal coil position. Current clinical routines assume highest stimulation effects under the center of the coil. This model falls short in explaining the real induced currents. Using data from the HCP, she shows the added value of electric field simulations over simple projection methods.

Alexander Opitz (University of Minnesota) will talk about combining electric field modeling with traditional meta-analysis to simulate effects of tDCS. Due to differences in electrode montages and stimulation intensities across studies, results are difficult to aggregate for meta-analytic inferences. A novel meta-analytic method relating behavioral effect sizes to electric field strength was developed to identify brain regions underlying the largest tDCS-induced working-memory improvement.

Maria Vasileiadi (Medical University Vienna) will talk about the application of electric field simulations in pre-surgical language mapping. TMS mapping has been shown to be clinically useful and safe but standard approaches are lacking the accuracy of direct cortical stimulation. She will propose a procedure including fMRI, causal mapping using TMS and improved estimation of effective stimulation targets by combining electric field modeling with high-precision neuronavigation.

## INTRODUCTION TO ELECTRIC FIELD MODELING: HOW, WHY, AND WHAT IS STILL MISSING?

**Oula Puonti**

*Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Amager and Hvidovre, Copenhagen, Denmark*

The electric field induced in the brain by non-invasive brain stimulation approaches, such as transcranial magnetic or electric stimulation (TMS/TES), often has a complex spatial distribution shaped by the individual anatomy of a subject (Saturnino et al. 2019, Puonti et al. 2020). Using electric field simulations we can study the magnitude and direction of the induced field in the brain and link its properties to stimulation outcomes, or to plan the stimulation protocol so that the direction and magnitude of the field in a given target is matched for all subjects in a study. In this talk, I will give a basic introduction to electric field modeling: how the simulations are done in practice, why they are useful, and what we are currently still missing. I will cover the different steps in a simulation pipeline, starting from an MRI scan all the way to the electric field estimates, and how the output from such pipeline should be interpreted. To demonstrate how simulations can be exploited, I will present specific examples of how to analyze data that has already been acquired and how to use the simulations in the planning of new studies. In relation to prospective planning, I will also talk about the link between field modeling and personalized stimulation protocols. I will then present results on the validation of the simulations using invasive and non-invasive approaches, and discuss which aspects of the modeling are most crucial for getting accurate electric field estimates. Finally, I will conclude with an outlook for the future developments that are needed to fill the gap between simulation and stimulation.

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## DO ELECTRIC FIELD SIMULATIONS HAVE ADDED VALUE FOR DETERMINATING TMS COIL POSITIONS AT THE SCALP FOR OPTIMAL TARGETING?

**Debby C.W. Klooster[1,2], G. Vanhollebeke[1] & Chris Baeken[1,2]**

*[1]Ghent Experimental Psychiatry Laboratory, Ghent University, Ghent, Belgium*
*[2]Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands*

Transcranial magnetic stimulation has shown promising results in treatment of depression. Personalized stimulation parameters to improve the clinical efficacy of stimulation is a hot topic. Personalized cortical stimulation targets have been proposed, for example based on the functional connections with the deeper subgenual anterior cingulate cortex. In clinical practice, the coil position is a simple projection above this predefined cortical stimulation target. However, individual gyral folding patterns shape the distribution of the TMS induced electric fields within the brain and hence the projection method might not be optimal to determine the coil position. In line, it has been suggested that electric field simulations can provide added value in determination of the ideal TMS coil position at the scalp (Klooster et al. 2021). However, this has not been investigated in detail.

In this study, we will investigate if the use of electric field simulations can lead to more accurate TMS targeting using data from the human connectome project. A priori knowledge will be used to define the cortical target (MNI - 38, 44, 26 (Fox et al. 2021) mapped to the individual T1-w MRI files). The coil position on the scalp is determined using the projection method. Subsequently, the TMS induced electric field distributions were computed using SimNIBS (Thielscher et al. 2015).

The region of the brain assumed to be affected by the stimulation was defined as the brain areas in which the electric field strength exceeded a threshold. This threshold varies between zero and the maximum induced electric field strength. At the conference, we will show an overview of percentage of subjects in which the predefined cortical target area falls within the stimulated region as a function of threshold derived from the electric field strengths, when the projection method is used for coil positioning. If these percentages are small, electric field simulations might be beneficial.

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3. *Thielscher A, Antunes A, Saturnino GB: In IEEE Engineering Medical Biology Society 2015; pp. 2-5*

## META-ANALYTIC ELECTRIC FIELD MODELING

**Alexander Opitz**

*University of Minnesota, Minneapolis, MN, USA*

In this presentation, I will talk about our efforts in combining electric field modeling with traditional meta-analysis on the effects of tDCS on working memory. Due to differences in electrode montages and stimulation intensities across different studies, results are difficult to aggregate for meta-analytic inferences. To overcome these limitations, we have developed a novel meta-analytic method relating behavioral effect sizes to electric field strength, to identify brain regions underlying the largest tDCS-induced WM improvement. Simulations on 69 studies targeting left prefrontal cortex showed that tDCS electric field strength in lower dorsolateral prefrontal cortex (Brodmann area 45/47) relates most strongly to improved WM performance. This brain region could be a target area for future tDCS studies. Our metanalytic framework can be applied to other stimulation modalities and behavioral measures.

## HIGH-PRECISION LANGUAGE MAPPING THROUGH MULTIMODAL fMRI, TMS AND E-FIELD MODELLING

**Maria Vasileiadi[1], A.L. Schuler[1,2], Martin Tik[1,3], M. Woletz[1], D. Linhardt[1] & C. Windischberger[1]**

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*[2]Laboratory of Clinical Imaging and Stimulation, San Camillo Istituto di Ricovero e Cura a Carattere Scientifico, Venice, Italy*
*[3]Stanford University Department of Psychiatry and Behavioral Sciences, Palo Alto, CA, USA*

**Introduction:** Neurosurgery requires careful planning to minimize damage to eloquent brain areas. Combining Transcranial Magnetic Stimulation (TMS) with frameless stereotactic neuronavigation and MR imaging allows for image-guided stimulation with high precision. While TMS is increasingly used for preoperative mapping of language areas, standard TMS mapping approaches lack the accuracy of direct cortical stimulation. We propose an optimised procedure for language mapping bringing together fMRI, TMS and improved estimation of effective stimulation targets by combining electrical field (E-field) modelling with precision neuronavigation.

**Methods:** We evaluated our newly developed multimodal precision mapping in a sample of healthy subjects. An fMRI task was administered to functionally localize language eloquent areas in the brain. For each subject, the fMRI data was used to define a language 'hotspot' in the superior temporal gyrus (STG). TMS-bursts of 10 Hz were applied to a circular grid around this hotspot while subjects performed an object naming task. Images were displayed on a screen and TMS bursts were administered after image onset. The E-fields of coil positions that effectively interfered with speech, i.e. resulted in a speech arrest, were calculated using SIMNIBS.

**Results:** For all subjects, language fMRI resulted in activity in the STG. TMS around the language hotspot-grid evoked speech arrests in all subjects. Mean effective E-fields and fMRI activation maps were found overlapping. The overlap indicates the causal area leading to speech arrests and thus highlights the most important language eloquent area.

**Conclusion:** We herein demonstrate that TMS may be used as a mapping approach for functional localisation studies. The approach presented in this study used E-field simulation of TMS fields to generate maps of the E-fields effective for function disruption. This method allowed for verification of causally involved speech eloquent areas. Presurgical planning may benefit greatly from the proposed multimodal mapping procedure.

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## NEW TOOLS TO MONITOR AND OPTIMIZE TMS TARGET ENGAGEMENT

**Christian Windischberger[1], Debby Klooster[2], Martin Tik[3], Shanice Janssens[4], Hanneke van Dijk[5] & Jord Vink[6]**

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Recent advances in neuroscience-informed brain stimulation therapy have shown the great potential of patient-specific measures acquired before treatment (Cole et al. 2021, Weigand et al. 2018). Techniques for demonstrating brain stimulation target engagement are among the most promising developments in order to ensure treatment suiting the individual patient's needs. This symposium highlights different techniques to monitor the acute effects of stimulation as they happen.

Martin Tik (Stanford University) will demonstrate that recent innovations in concurrent TMS/fMRI enable continuous image data acquisition during effective clinical stimulation protocols. This allows for direct insights into the therapeutic effects in an individual patient's brain.

Shanice Janssens (Maastricht University) uses a pioneering simultaneous TMS-EEG-fMRI setup to investigate how the individual oscillatory brain state impacts on signal propagation of TMS within targeted brain networks. This is a promising approach for improving individualized TMS depression protocols.

Hanneke van Dijk (Brainclinics Foundation) developed a deep learning (DL) model using a large subset of the TD-BRAIN+ dataset, consisting of EEG recordings from adults in a ground-truth scenario – sex classification. In a subsequent transfer learning scenario, the model enabled predicting MDD treatment outcomes with accuracies up to 78% based on individual EEG recordings. Methods of model interpretation and future applications of DL predictive models will be presented and discussed.

Jord Vink (University Medical Center Utrecht) will focus on the direct effect of single TMS pulses delivered to the left DLPFC in healthy participants using concurrent TMS/fMRI to learn more about the mechanism of action and a potential connection with the subgenual anterior cingulate cortex. Moreover, a novel method for TMS target engagement in the treatment of depression will be discussed.

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# FUNCTIONAL CONNECTIVITY- AND E-FIELD-OPTIMIZED TMS TARGETING: A PILOT TMS-FMRI VALIDATION AT THE SINGLE-SUBJECT LEVEL

**Maximilian Lueckel[1,2], Angela Radetz[2], Kenneth Yuen[1,2], Florian Mueller-Dahlhaus[3], Raffael Kalisch[1,2] & Til Ole Bergmann[1,2]**

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Effectiveness of personalized, functional connectivity (FC)-guided TMS treatments (Cole et al. 2021) can profit from optimizing coil position and orientation based on E-field simulations. However, existing optimization routines (e.g., SimNIBS; (Saturnino et al. 2019)) typically only consider the E-field in a small patch surrounding a single target coordinate, thus ignoring whole-brain topography of both subject-specific FC map and E-field. To increase target specificity of FC-guided TMS, we developed an optimization approach that takes into account the available spatial information and tested its validity in a single-subject TMS-fMRI experiment, indirectly targeting ventromedial prefrontal cortex (vmPFC) via its FC with left dorsolateral prefrontal cortex (LdlPFC).

Using SimNIBS, we simulated TMS-induced E-fields for multiple coil positions and orientations surrounding an individualized, vmPFC-anticorrelated LdlPFC coordinate (Figure 1B+C). Within our approach, the optimal combination of coil position and orientation simultaneously maximized (Cole et al. 2021) overlap between E-field and negative FC cluster in LdlPFC and (Saturnino et al. 2019) E-field strength in the target cluster, while minimizing overlap with non-target (e.g., positive FC) areas (Figure 1C). For concurrent TMS-fMRI, we used two TMS-compatible 7-channel RF surface coil arrays and a MR-compatible TMS coil that was neuronavigated to the optimized position and orientation (Figure 1A). TMS pulses were applied during gaps between volumes at suprathreshold intensity.

Our optimization approach resulted in a very good overlap between subject-specific vmPFC-based FC map and simulated E-field, with minimal off-target coverage. Concurrent TMS-fMRI revealed specific TMS-induced BOLD modulations in both the directly stimulated LdlPFC target area and the indirectly targeted bilateral vmPFC (Figure 1D).

Preliminary TMS-fMRI data indicates that our FC- and E-field-based TMS optimization approach ensures precision and specificity of stimulation-induced brain activation in both directly targeted and functionally connected regions. We will further validate this approach in a larger sample, yet concentrating on single-subject level evaluations. We hope that this approach will further increase specificity and effectiveness of personalized TMS.

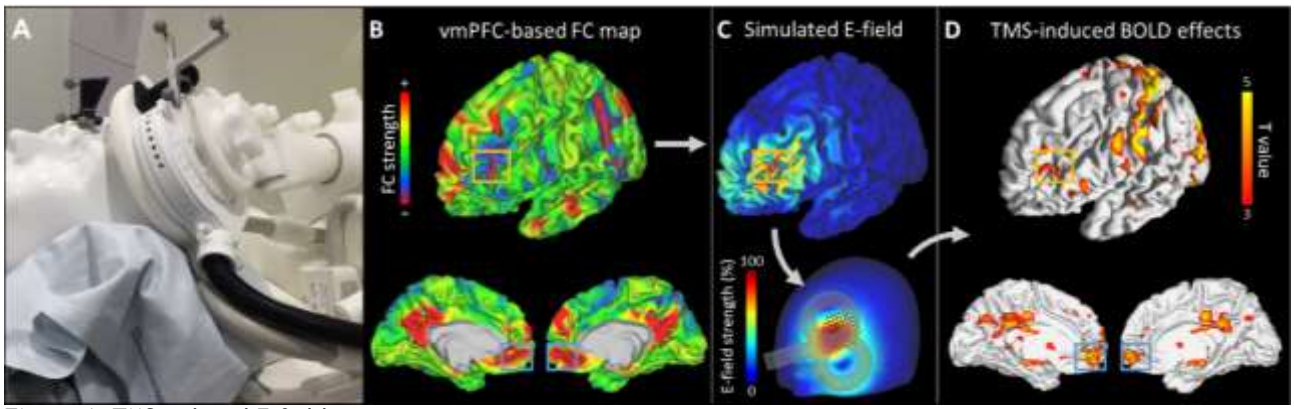


**Figure 1.** TMS-induced E-fields

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# EMOTION PROCESSING TASK AS A NEW STRATEGY FOR LOCATING INDIVIDUALIZED TMS TARGETS

**Maria Vasileiadi[1], Martin Tik[1,2], G. Kranz[3,4], M. Rütgen[5], M. Princic[1], T. Vanicek[3], D.M. Pfabigan[6], A. Hahn[3], R. Sladky[5], R. Lanzenberger[3], C. Lamm[5] & C. Windischberger[1]**

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**Introduction:** Dysfunctions in emotion processing and regulation are common in subjects suffering from MDD, paradigms involving emotion processing and regulation might be ideal for revealing the corresponding neurocircuitry. Functional MRI localisers using emotion processing paradigms reveal individual dorsolateral prefrontal cortex (DLPFC) activation clusters. This method could be advantageous as these regions may then be used as targets for TMS treatment. In this study, we compared targets derived from individual functional localisers to targets commonly used in TMS for MDD.

**Methods:** Twenty-eight patients diagnosed with acute MDD (16f/12m, mean age: 28.7±7.1) participated in the study and performed a facial emotion discrimination task (EDT). Data acquisition was performed on an ultra-high 7 Tesla whole-body MR scanner (Siemens Magnetom 7T). The Euclidean distances to seven commonly used DLPFC targets were calculated for each patients EDT activation peak within the group-level DLPFC activation cluster.

**Results:** DLPFC activation maxima were successfully derived in all subjects. Group-averaged distances of the different targeting approaches to the EDT maxima ranged from 16 mm to 40.5 mm. Targeting approaches that are generally considered less effective (e.g. 5 cm method and EEG-F3 targeting) showed the highest spatial distances to individual functional activation peaks. The spatial reproducibility of the EDT was stable for most subjects, however, in some subjects the spatial variability was quite high (Figure 1). The variability could be improved by performing multiple runs to achieve reliable DLPFC localisation (Geissberger et al. 2020).

**Conclusion:** We conclude that the EDT may be used to obtain single-subject activation clusters within the DLPFC in a clinical sample. Based on this, individually localized DLPFC with fMRI show considerable inter-subject variability and therefore using the same target for all subjects is suboptimal. We therefore suggest future usage of functional localisers for determining stimulation targets as we showed they can be reliable and reproducible in patients.

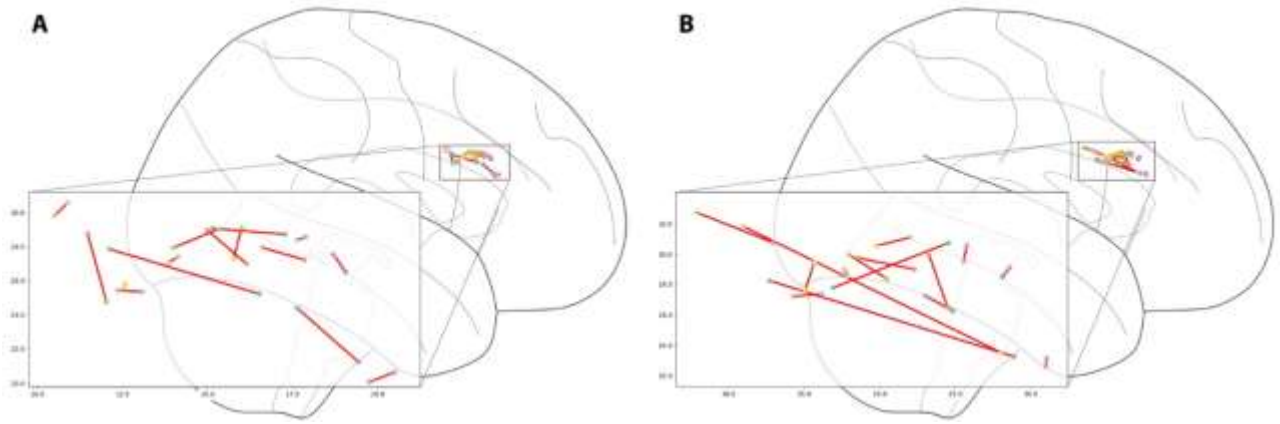


**Figure 1.** (a) Intra-session distances of single-subject activation maxima in l-DLPFC cluster between two runs. Dots are marking runs, while red lines represent each subject. (b) Inter-session distances of single-subject activation maxima in l-DLPFC cluster. Dots are marking sessions, while red lines represent each subject. Data is represented in a lateral view of the right hemisphere glass brain

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## NO EVIDENCE FOR CHANGES IN PREFRONTAL AND TEMPORO-PARIETAL AREAS BY tDCS TREATMENT OF AUDITORY HALLUCINATIONS

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According to a prominent theory, transcranial direct current stimulation (tDCS) reduces auditory hallucinations in individuals with schizophrenia by inhibiting neural activity in hyperactive language areas in the temporo-parietal cortex (TPC), while simultaneously boosting neural activity in hypoactive attentional control areas in the dorsolateral prefrontal cortex (DLPFC). In a series of studies, we tested the effects of tDCS over TPC and DLPFC regions in healthy participants but also a small sample of patients with medication resistant, auditory-verbal hallucinations that received tDCS treatment. Anatomical, neurotransmitter, brain activity, and network connectivity changes in both patients and healthy individuals were examined.

The results revealed a small reduction of auditory hallucinations in patients as compared to sham with d=0.14 to 0.47, consistent with previous findings. However, tDCS did not lead to measurable effects in the neuroimaging data of the patients. In healthy participants, single session tDCS did not lead to robust changes in GABA, glutamate or in functional activity measures in the TPC or DLPFC. In line with previous reports, modelling of the tDCS electrical currents suggested that with the DLPFC/TPC montage that is used in most tDCS treatment studies, the activation is strongest in Broca's area, not the DLPFC or the TPC itself.

In conclusion, our findings call into question the currently leading theory behind tDCS treatment of AVH. New avenues, including Broca's area will be discussed.

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## ACCELERATED ITBS rTMS PROTOCOL IN A CLINICAL ROUTINE SETTING: ONE YEAR EXPERIENCE

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**Background:** Williams reported results of Stanford Accelerated intelligent Neuromodulation Therapy: they found striking 78/90% remission rates from depression in severely treatment-resistant patients in a short 5-days duration of treatment (depending on the open label or sham-controlled, double blinded clinical trials). Neverthless, high-dose, accelerated and spaced protocol is challenging for implementation in clinical routine setting.

**Method:** We report here one year experience of 10 daily neuronavigated spaced rTMS sessions regimen (intermittent theta burst protocol of 1800 pulses at 90% motor threshold) for 5 consecutive days, MRI individually targeting of L-DLPFC (using Broadmann area 46) with 75 patients suffering from treatment-resistant depression, in our neuromodulation unit. Clinical screening included BDI, QIDS, SHAPS, STAI A, Pichot fatigue, EPWORTH, WEMWBS, PDQ-D and automated neurocognitive battery (CogniFit).

**Results:** no serious adverse effect were reported and all but 3 patients completed the protocol. Response and remission rate was of only 18/14% on QIDS-SR16 and 23/15% on BDI-SF 13 items.

We present the socio-demographic, big Five personality traits and clinical comorbidity profiles of our entire population along with individual Talairach coordinates and MRI results.

During an exploratory phase with the twenty first patients, we found a 94% improvement on cognitive flexibility score: we implement a more detailed neuropsychological testing for the 40 next ones, including Corsi test, facial emotions recognition task (TREF), switch task, N back task, sustain attention to response task (SART) and Trail Making Test A and B.

**Conclusion:** such a protocol is feasible and safe in a clinical routine setting. Cognitive improvement was more systematically present than symptoms reduction in a highly comorbid treatment-resistant cohort, especially for facial emotion recognition.

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# A CASE SERIES EXPLORING THE EFFECTS OF HIGH-FREQUENCY TRANSCRANIAL RANDOM NOISE STIMULATION IN PATIENTS WITH SCHIZOPHRENIA

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**Background:** One out of three patients with schizophrenia experiences symptoms which are refractory to conventional antipsychotic treatments. In such cases, transcranial direct current stimulation, a non-invasive brain stimulation technique, has been proposed as a novel therapeutic approach and has showed promising beneficial effects for reducing symptoms of schizophrenia, namely auditory hallucinations and negative symptoms. However, the high variability observed in clinical response leaves much room for optimizing stimulation parameters and strengthen its benefits. We propose to investigate the effects of high frequency transcranial random noise stimulation (hf-tRNS), which is supposed to induced larger effects than conventional direct current stimulation. Here, we present an initial case series of patients with schizophrenia who underwent hf-tRNS with the anode placed over the left dorsolateral prefrontal cortex and the cathode over the left temporoparietal junction.

**Methods:** Seven patients with schizophrenia according to DSM5 criteria (4 females, 3 males) presenting persistent symptoms received 10 sessions (2 sessions per day over 5 consecutive days) of 20 minutes hf-tRNS (2 mA, 100-500 Hz, 1 mA offset). Each patient underwent assessments of schizophrenia symptoms with the Positive and Negative Syndrome Scale (PANSS) and auditory hallucinations with the Auditory Hallucination Rating Scale (AHRS) at baseline and within 3 days after the final hf-tRNS session.

**Results:** Patients showed a significant mean reduction of total PANSS scores (-16 ± standard deviation 18%, p=0.039), mainly driven by a reduction in positive symptoms (-12±5%, p=0.002). Furthermore, they showed a significant reduction of auditory hallucinations (-33±24%, p=0.019).

**Conclusions:** The current case series suggests that hf-tRNS merits further investigation in the treatment of schizophrenia symptoms. However, additional work should investigate how some participant characteristics may affect outcome and therefore explain the observed variability in clinical response.

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# CONCURRENT TMS-fMRI – SYSTEMATIC REVIEW OF METHODOLOGICAL DIFFERENCES AND SOURCES OF BIAS

**Yuki Mizutani-Tiebel[1,2], Kai-Yen Chang[1,2], Martin Tik[3], Aldo Soldini[1,4], Lucia Bulubas[1,2,4], Esther Dechantsreiter[1], Christian Windischberger[3], Daniel Keeser[1,2,5] & Frank Padberg[1]**

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**Introduction:** Concurrent TMS-fMRI is a method which TMS pulses, bursts, or trains are interleaved with fMRI. Using this technique, the immediate effects of TMS can be measured while the subjects are being scanned with fMRI. To describe the methodological strengths and limitations across research, we conducted a systematic review on previously published concurrent TMS-fMRI studies.

**Method:** On April 16, 2021, literature was systematically collected from PubMED, Ovid Medline, and Embase. After deduplication, 4911 articles were included in a PRISMA screening and eligibility check was completed by two raters independently. 77 interleaved TMS-fMRI papers were identified. Out of those, 63 articles with at least 5 human subjects were examined in detail.

**Results:** A synopsis of studies may be downloaded from the link on the poster. Only four of the 63 publications were pre-registered, and only twelve were conducted with patients. Motor cortex research accounted for over half of the papers (28). There were three potential causes of bias that we discovered:

- different motor threshold (MT) measurements (31 with resting MT, 21 with MT in MR environment, 6 with electromyography),
- different motion control (35 stabilized the head with cushions or straps, 48 reported motion removal from fMRI image (i.e. removal of datasets with excessive motion, insertion of motion as covariate, denoising during preprocessing),
- lack or variation of control conditions (7 studies with sham TMS, 7 with low intensity, 7 with control location).

**Discussion:** To date, only 23 institutes in seven countries have published all of these studies. The majority investigated the motor cortex function in healthy subjects. Researchers are encouraged to collaborate not only to share their knowledge of the complex technological setting, but also to minimize the source of bias.

*This study was supported by the Federal Ministry of Education and Research (BMBF): ERA-NET NEURON, FKZ: 01EW1903.*

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# EFFICACY OF TRANSCRANIAL DIRECT CURRENT STIMULATION TO IMPROVE INSIGHT IN PATIENTS WITH SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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**Importance:** Lack of insight in schizophrenia, i.e. the unawareness of illness and its consequences, is associated with poor outcomes and usual treatments do not appear to convincingly improve it. While transcranial direct current stimulation (tDCS) may represent a potentially useful treatment strategy to relieve various symptoms of schizophrenia, its impact on insight remains unclear.

**Objective:** To investigate the association between repeated sessions of tDCS and insight improvement in patients with schizophrenia.

**Methods:** PubMed and ScienceDirect databases were systematically searched up until March 2021. Eligible randomized sham-controlled trials were those comparing active *versus* sham tDCS, including at least 10 sessions, in patients with schizophrenia. Only studies measuring insight with the PANSS #G12 item were selected. Of 116 studies identified, 17 studies were selected and 13 were included. Effect sizes were calculated for all studies and pooled using a random-effects model. Meta-regression and subgroup analyses were conducted. The primary outcome established prior data collection was the change of insight score, assessed by PANSS #G12 item, following active tDCS sessions compared to sham stimulation.

**Results:** Thirteen studies including 587 patients with schizophrenia were included (297 receiving active stimulation and 290 receiving sham stimulation). A significant pooled effect size of -0.46 (95% CI [-0.62; -0.30]) was observed, suggesting that 10 sessions of active treatment was associated with a greater improvement in insight compared to sham treatment. Age and G12 score at baseline were identified as significant moderators.

**Conclusions:** This study suggests that patients with schizophrenia showing poor insight may benefit from treatment with tDCS with the anode over the dorsolateral prefrontal cortex, using either bifrontal or frontotemporal montage. This effect could contribute to beneficial outcomes observed following stimulation.

**Acknowledgments:** Andre R. Brunoni, MD, PhD; Hsin-An Chang, MD; July S. Gomes, PhD; Daniel C. Javitt, MD, PhD; Do-Un Jung, MD, PhD; Joshua T. Kantrowitz, MD; Sanne Koops, PhD; Jean-Pierre Lindenmayer, MD; Ulrich Palm, MD, PhD; Robert C. Smith, MD, PhD; Iris E. Sommer, MD, PhD; Leandro Do Costa Lane Valiengo, MD, PhD; Thomas W. Weickert, PhD.

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# THE ROLE OF THE CEREBELLUM ON SOCIAL SEQUENCES: PRELIMINARY FINDINGS OF A CONCURRENT tDCS-fMRI STUDY

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The cerebellum is a brain structure traditionally known for its role in motor sequences. However in the last decades the posterior cerebellum has shown to be involved in understanding social sequences as well (Heleven et al. 2019). In order to understand these social sequences humans use complex cognitive processes such as mentalizing. Mentalizing is the ability to attribute mental states such as desires, intentions and beliefs to other people. This ability helps us to predict future behaviour by generating social sequences. The ability to mentalize seems to be impaired in some clinical populations such as the autism spectrum (Olivito et al. 2018), thus the possibility of using brain stimulation in order to enhance it sounds enticing.

In order to prove the causal role of the cerebellum in social sequences we conducted an experiment that included a pictorial sequencing task in order to compare false belief sequences (which require mentalizing) with other types of social and non-social sequences. A within-subjects sham-controlled design

was used. Healthy participants completed two sessions (sham and stimulation) in a randomised order. We applied a novel tDCS montage in order to maximise the focality of the anodal stimulation over the right posterior cerebellum while concurrently measuring brain activity using fMRI (Figure 1).

Preliminary results showed differences due to stimulation mostly in temporal areas, suggesting that remote effects were more prominent than local effects. These differences in brain activation did not affect all conditions equally, having the smallest effects in the non-social conditions.

Further, a more exhaustive analysis (including simulations of the induced electric field, resting state connectivity and scores in autism questionnaires) will be performed in order to further unravel the specifics of this interaction between stimulation and different types of sequences.

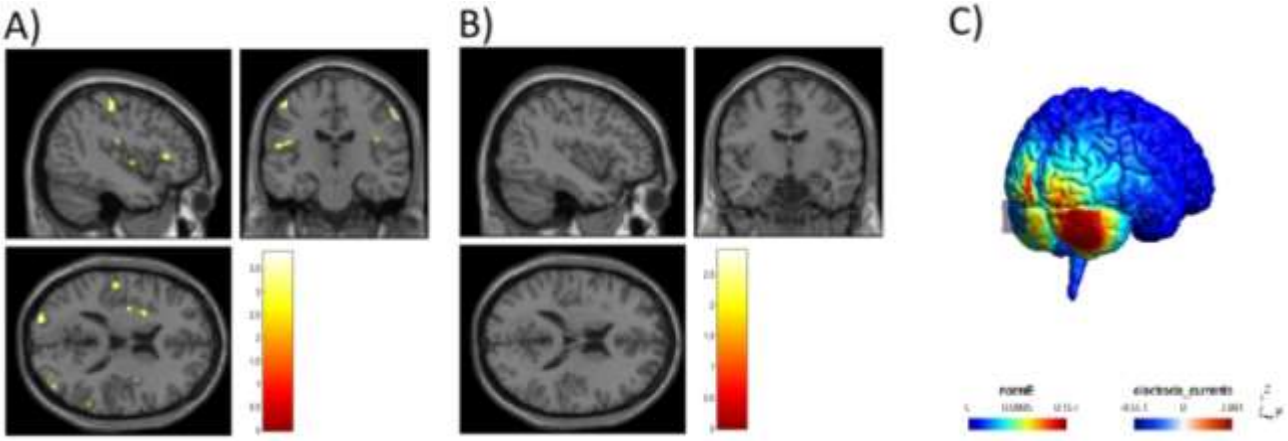


**Figure 1.** A) t-test of all social conditions averaged stimulation<sham. B) t-test of social conditions averaged sham<stimulation. C) simulation of the electrode montage

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# TRANSCRANIAL DIRECT CURRENT (tDCS) NEUROSTIMULATION FOR OLD AGE PEOPLE WITH DEPRESSION LIVING IN RESIDENTIAL CARE HOME: THE LIMONADE PROJECT

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In France, the prevalence of depression in the elderly living at home varies from 3.1 to 13.4%. In institutions, it increases considerably, from 22% in residential care home to 40% in long-term care units. Indeed, institutionalization is an important risk factor for APD, as is female gender, social isolation, bereavement, sleep disorders, disability, somatic illness or a history of depression.

Late-life depression is associated with a major functional impact, an alteration in quality of life and a significant risk of suicide. Often not identified, it can be insufficiently treated when it is diagnosed.

The reference treatments are essentially based on psychological and drug treatments, in cases of moderate to severe intensity. However, they are often poorly tolerated and iatrogenic. Neurostimulation treatments such as electroconvulsive therapy are reserved for resistant or very severe forms, with a vital risk (suicidal or somatic).

tDCS is a particularly suitable treatment for the geriatric population because of its excellent tolerance, even at a very advanced age in patients with high multimorbidity, compared with psychotropic drugs. The response rate increases in elderly patients with a higher current intensity (2 mA) and a greater number of tDCS sessions (30 treatments over 6 weeks). Therefore, the application of higher stimulation doses and a greater number of treatments may be important for the efficacy of tDCS in the elderly depressed patient. Thus, these potential antidepressant effects and cognitive improvement and the absence of major side effects make tDCS a promising treatment option for depression in geriatric populations.

The LIMONADE project aims to evaluate the feasibility of using tDCS in patients with depression living in residential care home. Indeed, it is a real strategy of care offer with: diagnosis, deployment of treatment by tDCS at the patient's bed, evaluation/coordination by a psychiatry team and articulation of care with geriatrics.

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## EFFECT OF GENOTYPE ON RESPONSE TO tDCS-INDUCED BEHAVIOURAL PLASTICITY

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**Introduction:** A common single nucleotide polymorphism (Val66Met) in the gene that codes for brain derived neurotrophic factor (BDNF) is associated with reduced motor learning, retention, and plastic response to tDCS. Since one third of Caucasians carry the met allele, this may be a significant source of variability in response to tDCS. We have previously observed that anodal tDCS enhanced retention of prism adaption, a form of motor learning used in stroke therapy, but only in individuals with the dominant val66val allele. Here we aimed to replicate this val/val effect and determine the met allele effect in an adequately powered sample.

**Method:** Twenty participants were recruited, informed by a power calculation. To avoid the known variability in motor learning and brain chemistry associated with the menstrual cycle, only men were recruited. We used a double-blind, repeated measures design, in which participants performed prism adaptation combined with motor cortex tDCS (anodal versus sham, counterbalanced order). Subsequent retention of the prism after effect was measured 10 minutes and 24 hours later. Participants provided saliva samples for genotyping.

**Results:** Data collection is currently in progress (n=15 complete to date, 5 more to complete). Results for the full sample will be reported at the conference. Analyses will test the following pre-registered predictions:

- Val/Val homozygotes will show greater retention of the prism adaptation after effect with anodal stimulation versus sham;
- Carriers of the Val66Met polymorphism will show smaller and/or more variable responses to tDCS, resulting in no significant difference in retention between anodal and sham tDCS.

**Discussion:** Given the prevalence of the Val66Met polymorphism, the implication of previous work is that this should account for significant variability in stimulation response. If confirmed, this would have significant implications for the use of tDCS both in basic research and clinical indications in neurology and psychiatry.

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# TRANSCRANIAL DIRECT CURRENT STIMULATION IN THE POSTPARTUM PERIOD: COMPUTATIONAL MODELLING OF ELECTRIC FIELD STRENGTH IN TWO STANDARD MONTAGES FOR DEPRESSION

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Transcranial direct current stimulation (tDCS) has been suggested to treat peripartum depression (PPD) using the F3 (Anode) - F4 (Cathode; 10:10 EEG international system) montage with 2mA electric current. However, the electric field (EF) strength varies with brain morphology and during the perinatal period structural changes seem to take place in brain grey matter, in regions associated with motherhood. To our knowledge, peripartum morphological specificities were never taken into account when choosing tDCS protocols for PPD. Therefore, we aim to contribute to the field by informing about the distinctiveness of the EF strength induced in postpartum brains when using two standard tDCS montages in major depression. T1 weighted scans and clinical assessments of 25 postpartum women (3-months postpartum; 19-33 years [M=26.6, SD=4.0]) from the open-access Postnatal Affective MRI Dataset1 were included. According to the Center for Epidemiologic Studies Depression Scale (CES-D), 12 women presented depressive symptoms (M=20.4). With SimNIBS2 , we simulated EF using the F3-F4, and the F5-F6 montages (10:10 EEG international system; 2mA current intensity). Mean EF strengths were calculated on the Anterior Cingulate Cortex -ACC, the left and right Dorsolateral Prefrontal Cortex -DLPFC, and the Dorsomedial Prefrontal Cortex -DMPFC). We performed two-way mixed ANOVAs to estimate the interaction between montage and presence of depressive symptoms on EF strength across regions. Although the interaction was not significant (Figure 1), we found a main effect of montage, with the F5-F6 montage presenting the peak mean EF strength in the ACC, the right DLPFC and the left DLPFC. The F3-F4 montage presented the peak strength in the DMPFC. Although both montages enable the modulation of the commonly targetted brain areas in PPD using tDCS the clinical decision between the F5-F6 and the F3-F4 should account for the target area of interest when treating PPD.

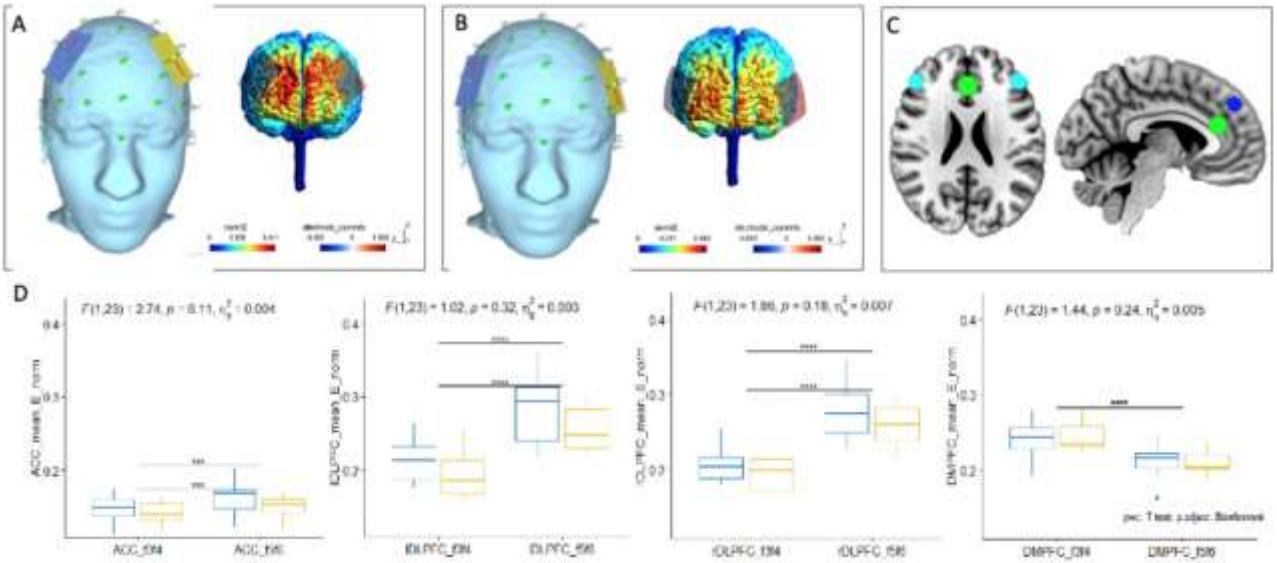


**Figure 1.** tDCS simulation montages, regions of interest (ROIs) and ANOVAs results. A. Left: tDCS montage F3 (Anode) - F4 (Cathode); 10:10 EEG International System. Right: Electric field (EF) simulation on gray matter (electrode current: 2mA, peak EF strength [normE]: 0.411 V/m). B. Left: tDCS montage F5 (Anode) - F6 (Cathode); Right: EF simulation on gray matter (electrode current: 2mA, peak EF strength [normE]: 0.483 V/m). C. Spherical ROIs over MNI template: anterior cingulate cortex (ACC; green), left and right dorsolateral prefrontal cortex (l and rDLPFC, light blue), dorsomedial prefrontal cortex (DMPFC, dark blue). D. ANOVA results: two-way mixed ANOVAs. Montage as within-group factor (F3-F4 vs. F5-F6) and presence of depressive symptoms (according to CES-D) as between-group factor. Left to right: results for mean EF strength in ACC, lDLPFC, rDLPFC, and DMPFC

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# THE INTERACTION OF TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) AND PACED BREATHING ON ACOUSTIC AND LEXICAL SPEECH FEATURES IN THE CONTEXT OF STRESS

**Mitchel Kappen, S. De Smet, J. Allaert, E. Schoonjans, J. Van der Donckt, S. Raeymakers & M.A. Vanderhasselt**

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Speech features are increasing in popularity as potential biomarkers for stress and have shown promising results in the context of psychosocial stressors (1). Speech is actively influenced by numerous bottom-up physiological processes, such as cardiac activity and breathing (2). Whereas slow-paced breathing quickly and directly affects the afferent vagus nerve, transcranial direct current stimulation (tDCS) has been shown to modulate stress regulatory processes. In this between-subjects study, we aim to investigate whether combining slow-paced breathing and tDCS stimulation could beneficially interact in modulating affective and stress processes. As such, we collected high-quality free speech recordings in 160 healthy subjects at (1) baseline, (2) after a controlled breathing baseline (slow/fast), (3) after a combination block where tDCS (active/sham) is added to the breathing condition (slow/fast), and (4) after subsequent stress induction (TSST; Trier Social Stress Test arithmetic task; Figure 1).

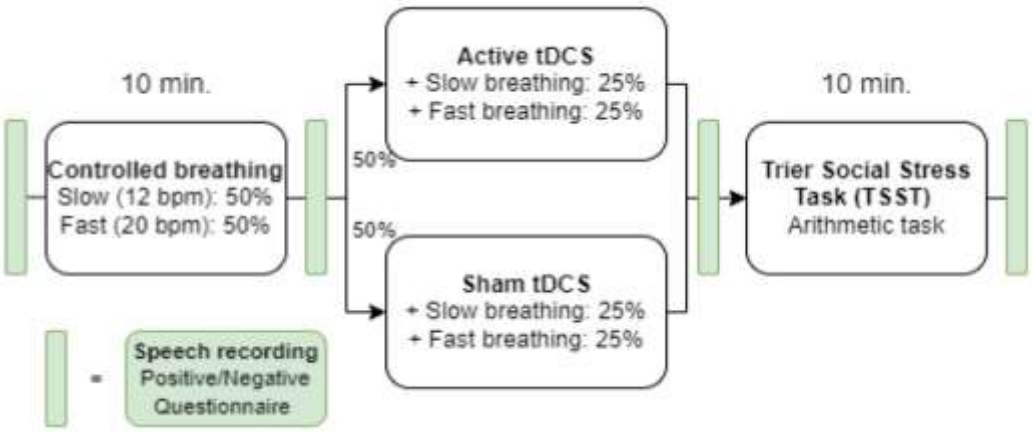


**Figure 1.** Study flow. Green blocks: speech and self-reported positive/negative affect collection. Participants were randomly assigned to one of four combined tDCS (active/sham) + controlled breathing (slow/fast) interventions; 4 groups. Abbreviations: bpm, breaths per minute; tDCS, transcranial direct current stimulation.

Interactive effects of controlled breathing and tDCS will be investigated on key acoustic features including F0, Jitter, and Shimmer, and lexical features including vocabulary size and use of personal pronouns. Specifically, we will compare the four groups in a 2 (active/sham tDCS) x 2 (slow/fast breathing) design using mixed models and ANOVA testing. These results will further unveil the complex dynamics of speech production and its relation to bottom-up (i.e., physiological activity) and top-down (i.e., tDCS) interventions. Moreover, due to the presence of a validated stressor post- manipulation, we can position these results in the context of stress and add to its potential as a novel biomarker for stress.

***Keywords:*** *paced breathing – tDCS – stress – speech - biomarker*

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# BI-FRONTAL tDCS CAN IMPROVE FACIAL EMOTION RECOGNITION IN MAJOR DEPRESSIVE DISORDER: AN EXPLORATORY PILOT STUDY

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The dorsolateral prefrontal cortex (DLPFC) plays a pivotal role in both depressive symptoms and emotional processing. Recently, transcranial Direct Current Stimulation (tDCS) applied over the DLPFC hold promises to alleviate clinical symptoms in patients with MDD. However, only a few studies investigated the effect of tDCS on emotional processing whereas antidepressant drugs are known to improve such deficits in patients with MDD. Here, we investigated the effect of DLPFC-tDCS a facial emotion recognition task (FER) in patients with MDD.

In a randomized sham-controlled study, 40 patients with treatment-resistant MDD received a single session (30 min) of either active (2 mA, n=18) or sham tDCS (n=17). The anode was placed over the left and the cathode over the right DLPFC, respectively. FER was assessed before and after the stimulation session.

After active tDCS, we observed an overall improvement in FER performance as compared with sham tDCS. The beneficial effect seemed mainly drive by an improved recognition of Sad faces. No significant effect of the sham stimulation was observed. The session was well tolerated.

Although exploratory, these results suggest that a single session of tDCS may improve social cognition in patients with MDD. Further studies are needed to replicate these results and investigate whether this acute improvement of FER in response to tDCS could translate into clinical benefits as observed with antidepressant drugs.

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# REAL WORLD TRANSCRANIAL MAGNETIC STIMULATION FOR MAJOR DEPRESSION IN FRANCE: A MULTISITE, NATURALISTIC, RETROSPECTIVE STUDY

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**Background:** Repetitive Transcranial Magnetic Stimulation (TMS) was approved in 2008 by the US FDA. Meta-analyses of randomized controlled trials have confirmed its efficacy in the treatment of depression. However, real-world outcomes of rTMS remain understudied. We aimed to study how TMS therapy used to treat depression is delivered in routine clinical practice in France, and to measure its effectiveness and potential moderators of this effectiveness.

**Methods:** Five French centers provided data on patients treated with TMS for resistant depression between January 2015 and December 2020. We included patients who were assessed by a hetero-questionnaire and had a baseline and immediate posttreatment assessment. We performed univariate analyses to investigate which factors were significantly associated with the efficacy of TMS. Next, we included age, sex, and significant factors in a multivariate model.

**Results:** 435 patients were included; 66% of individuals with depression were female and 26% had bipolar depression. Stimulation was delivered with four different stimulation parameters: 1Hz (7% of individuals), 10Hz (43%), 50Hz (38%), and 20Hz (12%). TMS resulted in a significant decrease in MADRS (Delta=9.47 (8.73, MW Stat. 150319.5, p<0.001) with a large effect size (CLES=0.79). The mean improvement was 33% (SD=31%). Response and remission rates were 31% and 23%, respectively. In multivariate analysis, improvement in depressive symptoms was associated with higher baseline symptoms.

**Conclusion:** TMS is effective in routine clinical practice. Response prediction and personalized targeting could improve its effectiveness.

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## BRAIN PERFUSION ALTERATIONS INDUCED BY STANDALONE AND COMBINED TRANSCRANIAL STIMULATION OVER THE PREFRONTAL CORTEX: A RANDOMIZED, PLACEBO-CONTROLLED STUDY, USING 99mTc SPECT

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**Background:** Non-invasive brain stimulation (NIBS) approaches have been increasingly used to target the prefrontal cortex (PFC), with mixed results in the fields of cognitive and behavioral neuroscience. Recent studies suggest that the combination of distinct NIBS techniques may maximize required changes in brain activity. However, it is unclear whether NIBS combinations could also enhance prefrontal cortical activity and its neurocircuitry.

To evaluate the application of standalone and combined protocols of transcranial direct current stimulation (tDCS) and intermittent theta-burst stimulation (iTBS) over the left dorsolateral PFC (DLPFC) of healthy volunteers through Single Photon Emission Computed Tomography (SPECT) neuroimaging.

**Methods:** A randomized, double-blind, sham-controlled, full-factorial design was conducted. Participants received four different stimulation protocols (tDCS, iTBS, Combined Interventions and Placebo), one per week, over the DLPFC located by structural neuronavigation. TDCS was applied with a current of 2mA for 20 minutes and iTBS with 1620 pulses for 9 minutes. A radiopharmaceutical (99mTc-ECD) was administered immediately after the start of the iTBS protocol. An adverse effects scale was applied after the end of the neurostimulation session and the SPECT was collected afterwards.

**Results:** Twenty-five adults with a mean age of 28.6 years (standard deviation (SD) = 7) were included. Of those, 23 underwent 4 sessions while 2 underwent only the first neurostimulation session. The first findings of the neuroimaging data analyses show that the combined intervention significantly modulated deeper regions from the PFC, such as the left anterior (*p=0.03*) and the right posterior cingulate cortex (*p=0.02*), while the tDCS protocol increased the blood flow of the orbitofrontal right (*p=0.04*) and left (*p=0.02*) cortices in comparison with the placebo protocol. iTBS alone did not show significant results compared to placebo. However, those are preliminary findings and will be further explored to be presented at the conference. Finally, all active protocols were similarly tolerable.

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# EFFECTS OF COGNITIVE TRAINING AND TRANSCRANIAL DIRECT CURRENT STIMULATION ON WORKING MEMORY OF PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA: A DOUBLE BLIND, RANDOMIZED, SHAM-CONTROLLED STUDY PROTOCOL

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**Background:** Working memory (WM) impairment is often found in patients with treatment-resistant (TR) schizophrenia and substantially affects their social functioning and quality of life (de Bartolomeis et al. 2013). Dorsolateral Prefrontal Cortex (DLPFC) embodies computational mechanisms for monitoring and manipulating items in WM. Transcranial direct current stimulation (t-DCS) is a noninvasive brain stimulation technique inducing small changes in membrane potentials that in turn influence the frequency of spike timing and modify net cortical excitability. Recent studies demonstrate that t-DCS on DLPFC in combination with Cognitive Training (CT) can improve working memory in healthy subjects and clinical population. Patients with TR schizophrenia have more robust cognitive impairment than non-TR subjects across several domains like selective attention, cognitive flexibility, processing speed, executive functions, verbal fluency (Frydecka et al. 2016).

**Methods:**

- Twenty patients with TR schizophrenia will be randomly assigned to receive one session of either active or sham tDCS (2 mA for 20 minutes, anode in F3, cathode in F4) in combination with cognitive training using the Sternberg's task. After two weeks, patients who received the active stimulation will undergo sham stimulation and the viceversa.
- All participants will be assessed with PANSS (Positive and Negative Syndrome Scale), MINI (Mini-International Neuropsychiatric Interview), and SCID-5 (Structured Clinical Interview for DSM V) at the beginning of the study.
- Before and after each stimulation, BACS (Brief Assessment Cognitive Schizophrenia), DSST (Digit Symbol Substitution Test), and N-BACK will be administered to evaluate WM functions.
- Patients with active implantable devices (e.g. pacemaker, intracranial electrodes, implantable defibrillator, cochlear implant), neurological disorders, and drug abuse in the previous six months will be excluded.
- Throughout the duration of the study, the pharmacological treatment will not be modified and will be the same of the previous two months.

**Conslusion:** This is the first study aiming to assess the potential role of combining t-DCS and CT for improving WM performance in patients with TR schizophrenia.

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## ETHNICITY-DEPENDENT RESPONSE TO dTMS TREATMENT

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**Background:** There are not many studies on ethnicity-dependent response to dTMS treatment. This study was conducted to identify whether there are differences in outcomes between deep Transcranial Magnetic Stimulation (dTMS) treatments for South Asians compared to Caucasians.

**Methods:** 16 age- and gender-matched patients (8 South Asian, 8 Caucasian) who completed a full treatment course (36 treatments), were compared using their self-reported baseline (1st treatment) and end (36th treatment) scores on the Patient Health Questionnaire-9 (PHQ-9), the Quick Inventory of Depressive Symptomatology (QIDS-SR-16), Generalized Anxiety Disorder Assessment (GAD-7), and Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF). All patients were treated within the past two years at a private TMS clinic in San Diego, California, USA.

**Results:** For Caucasians, the average difference for PHQ-9, QIDS-SR-16, GAD-7, and Q-LES-Q-SF between baseline and end scores was 11.25, 5.56, 8.88, and 13.88, respectively. In comparison, for South Asians, the average differences between baseline and end scales for PHQ-9, QIDS-SR-16, GAD-7, and Q-LES-Q-SF were 11, 10.20, 9.94, and 12.63, respectively. The average baseline scores for Caucasians were 19.75, 18.375 16.625, and 40.875 vs. average end scores of 8.5, 12.81, 7.75, and 54.75. For South Asians, the average baseline scores were 17.25, 17.57, 16.25, and 44.38 vs. average end scores of 6.25, 7.38, 6.31, and 57.

**Conclusions:** It is promising to see that interventional methods may be able to overcome differences in ethnicity-dependent variability in metabolism and response to psychopharmacologic treatments. For example, in comparison to Caucasians, South Asians had a larger clinical decrease in QIDS-SR-16 scores despite a greater baseline average. These results may help show that despite destigmatization efforts, interventional methods may provide care in minority groups, adjunctive to or in place of certain pharmacological options that are known to be less effective or provide greater side effects in some minority groups.

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## A SINGLE PSYCHOEDUCATIONAL SESSION INCREASES ACCEPTABILITY TOWARDS TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) IN TREATING ANXIETY DISORDERS

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**Objective:** In this study we sought to investigate the acceptability of transcranial direct current stimulation (tDCS) in treating anxiety disorders. We studied the impact of a psychoeducational session on acceptability as defined by a multidimensional framework employing a novel self-report questionnaire we developed, the ACCEPT-tDCS.

**Method:** A cross-sectional study was conducted, aiming at observing the impact of a psychoeducational session on tDCS acceptability in treating anxiety disorders. Our sample was comprised of 536 participants.

**Results:** After a single psychoeducational session – administered via informative video – the acceptability of our sample towards the use of tDCS in treating anxiety disorders increased significantly. Also, the questionnaire we developed showed adequate psychometric properties.

**Conclusions:** This work has shown that a single psychoeducational session increased participants' acceptability towards tDCS, which highlights the importance of providing adequate knowledge about tDCS and other new and emerging interventions to promote a subsequent successful implementation of novel health interventions within health care provisioning systems. It has also shown that the ACCEPT-tDCS is an adequate tool to measure acceptability towards tDCS in anxiety disorders, and an added value both for clinical and research contexts.

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# FLUMAZENIL ADMINISTRATION DURING ELECTROCONVULSIVE THERAPY: A RETROSPECTIVE CHART REVIEW ON EEG DURATION, SIDE EFFECTS AND CLINICAL OUTCOME

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**Introduction:** Benzodiazepines are considered to negatively affect seizure quality and duration during electroconvulsive therapy (ECT). Several researchers have advocated the use of flumazenil, a competitive benzodiazepine receptor antagonist, for patients receiving benzodiazepines during ECT treatment. However, clinical evidence regarding flumazenil use in ECT remains sparse. The aim of this study is to describe the effects of flumazenil on EEG seizure duration, clinical outcome and adverse effects.

**Method:** Twenty-six depressive and/or catatonic patients with concomitant benzodiazepine use receiving flumazenil during ECT were identified through retrospective chart review. Effects of flumazenil on depressive symptoms, catatonia, EEG duration and postictal agitation were assessed by the Inventory of Depressive Symptomatology, the Bush-Francis Catatonia Rating Scale and seizure duration on EEG. Postictal agitation was ascertained by identifying patients who received sedatives immediately after ECT or who needed physical restraint. The study was approved by the ethics committee of Ghent University Hospital.

**Results:** In patients receiving flumazenil, response and remission rates after ECT were 66.7% and 41.7% for depression and 91.7% and 75% for catatonia. Flumazenil administration increased EEG seizure duration with 10.5 seconds on average in patients comparing ECT with or without flumazenil administration and 58.3% of patients had an adequate seizure (> 15s). We found no correlation between benzodiazepine dose and seizure duration in patients receiving flumazenil before ECT. Postictal agitation occurred in 34.6% of the patients. One case of prolonged seizure, successfully managed with diazepam administration, was noted.

**Conclusion:** Patients with depression and/or catatonia and concomitant benzodiazepine use show good clinical outcome and increased EEG seizure duration after flumazenil treatment before ECT. However, postictal agitation seems to be a frequent and important side-effect. Current strategies to mitigate agitation should be considered when administering flumazenil.

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# PSYCHIATRIC SYMPTOMS IN PARKINSON DISEASE PATIENTS BEFORE AND AFTER ONE YEAR OF SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION: ROLE OF LEAD POSITIONING AND TOTAL ELECTRICAL ENERGY DELIVERED

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**Introduction:** Most patients with Parkinson's disease (PD) experience psychiatric symptoms. Deep Brain Stimulation (DBS) is the most effective treatment for motor and non-motor symptoms of advanced Pd. However, several studies hypothesized a possible correlation between DBS and the occurrence of mood disorders such as apathy, depression, and suicidal ideation. Additionally, conflicting results have been reported on the correlation between psychiatric symptoms and lead placement and total electrical energy delivered.

**Methods:** The study was performed at the University Federico II of Naples from 2011 to 2020. Fourteen patients (7 females, and 7 males) underwent a comprehensive psychopathological examination at baseline and after one year of STN-DBS. We assessed PD motor symptoms, depression, anxiety, apathy, impulsivity, and suicidality using clinical rating scales and correlated the results to the leads' position using the Medtronic® Suretune™ software and to the total electrical energy delivered (TEED) according to the Koss formula.

**Table 1.** Outolook of the results of the psychiatric scales, lead positioning and TEED

| Case # | Δ total UPDRS (%) | Δ HAM-D (%) | Δ BDI (%) | Δ HAM-A (%) | Δ HAM-A (C) (%) | Δ HAM-A (P) (%) | Δ BAI (%) | Δ AES (%) | Δ BIS-11 (%) | Δ BIS-11 (A) (%) | Δ BIS-11 (M) (%) | Δ BIS-11 (NP) (%) | Δ SSI (%) | Δ RFL-48 (%) | Lead positioning left | Lead positioning right | TEED |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | -37.2 | -60 | +33.3 | -58.8 | -63.6 | -50.0 | -17.6 | +33.3 | +18.5 | +16.7 | +4.3 | +33.3 | / | +0.9 | PL | PL | 0.0301 |
| 2 | +6.1 | -50 | -73.3 | -56.25 | -54.5 | -60.0 | -30.0 | 18.2 | +18.6 | +33.3 | +13.6 | +16.0 | / | -14.5 | PL | PL | 0.0288 |
| 3 | -36.8 | +109.1 | -43.75 | -16.7 | +20.0 | -42.9 | +100 | +85.0 | -1.8 | -6.7 | -5.0 | +4.5 | / | -17.1 | M | C | 0.0298 |
| 4 | -48.9 | -46.1 | -50 | -26.7 | 0 | -57.1 | -64.7 | +10.0 | +9.1 | +37.5 | +11.8 | -13.6 | / | -5.7 | PL | PL | 0.0304 |
| 5 | -37.2 | -47.8 | +27.8 | -40.625 | -50.0 | -28.6 | -30.3 | +20.0 | +9.7 | +18.8 | +15.8 | 0 | / | -0.9 | PL | C | 0.0277 |
| 6 | -48.6 | +216.7 | +100 | +28.5 | +140 | -25.0 | +100.0 | +2.4 | -4.1 | -18.2 | +33.3 | -19.4 | / | -13.9 | M | M | 0.0286 |
| 7 | -51.6 | -57.1 | -36.4 | -10 | 0 | -33.3 | -90.0 | -33.3 | -1.6 | +7.1 | 0 | -7.4 | / | +3.1 | C | MA | 0.0284 |
| 8 | -38 | / | -50.0 | -37.5 | -33.3 | -50.0 | -57.1 | -12.5 | 0 | 0 | -9.5 | +9.1 | / | -8.9 | PL | PL | 0.0304 |
| 9 | -58.8 | +18.2 | +100 | 0 | 0 | 0 | -16.7 | -24.3 | +46.3 | +110 | +73.3 | +10.3 | / | -12.2 | L | CA | 0.0291 |
| 10 | -45.1 | +500 | +12.5 | +240 | +1000 | +50.0 | +45.5 | +27.0 | +45.3 | +40.0 | +23.8 | +76.5 | / | -16.6 | C | M | 0.0295 |
| 11 | -50.8 | -46.7 | -26.7 | -29.4 | -33.3 | -25.0 | -54.2 | -16.7 | +4.2 | +33.3 | +16.0 | -18.8 | / | -1.2 | CA | PL | 0.0285 |
| 12 | -59 | -41.2 | -12.5 | -62.5 | -61.5 | -66.7 | -56.3 | +19.2 | -16.4 | -21.1 | +41.2 | -23.3 | -100 | +13.3 | LA | LA | 0.0291 |
| 13 | -37.2 | -100 | -89.5 | -100 | -100 | -100 | -53.8 | -40.5 | +27.9 | +30.0 | +43.8 | +11.8 | / | +22.9 | PL | PL | 0.0279 |
| 14 | -16.1 | -16.7 | -25.0 | -52.9 | -50 | -57.1 | -53.8 | +22.7 | +3.6 | 0 | -30.4 | +47.4 | / | +10.2 | P | PL | 0.0306 |

Δ (delta): percentual difference between pre-operative and post-operative evaluation; PL: postero-lateral; M: medial; C: central; CA: central anterior; LA: lateral anterior; P: posterior; MA: medial anterior; TEED: total electical energy delivered

**Results:** DBS induced a statistically significant improvement in motor symptoms (-38.5%, according to the Unified Parkinson's Disease Rating Scale part III), in anxiety (-29% according to the Hamilton Anxiety Rating Scale), with the strongest reduction in the physiological anxiety subscore (-36.26%). A mild worsening of impulsivity was detected at the Barratt Impulsiveness scale (+9%) with the greatest increase in the attentional impulsiveness subscore (+13.60%). No significant differences were found for the other scales. While the positioning of the stimulating electrodes was shown to considerably influence the outcome, with more anterior and/or medial lead position in the STN negatively influencing psychiatric symptoms, no correlation was found between TEED and clinical scales score (Table 1).

**Conclusions:** STN-DBS reduced anxiety and slightly increased impulsivity in PD patients after one year of DBS targeting the STN. While TEED did not correlate with any clinical scale score, leads' placement significantly impacted on psychiatric symptoms.

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# THE EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON EPISODIC FUTURE THINKING FOLLOWING ACUTE PSYCHOSOCIAL STRESS

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**Introduction:** Research on stress-related disorders and brain imaging suggests that (acute) stress might impact the capacity to mentally simulate specific episodic future events (EFT) through the effects of cortisol on brain regions supporting this cognitive function, such as the prefrontal cortices. This study aims to examine the mechanisms underlying this link, using bifrontal transcranial Direct Current Stimulation (tDCS).

**Methods:** 60 healthy participants were subjected to the Montreal Imaging Stress Task (MIST), followed by either active or sham tDCS. After stimulation, the EFT task was administered. Salivary cortisol was measured throughout the protocol.

**Results:** Higher cortisol AUCi values were linked to less specific episodic future thoughts. Moreover, active tDCS enhanced EFT specificity irrespective of cortisol, especially in high trait ruminators. We did not observe an effect from active tDCS on cortisol AUCi, and equally there was no interaction effect between cortisol AUCi and stimulation condition predictive for EFT specificity.

**Conclusion:** Although we did not find evidence for the effects of tDCS on the HPA-system, our data reveal a crucial link between two critical predictors of mental health for the first time, and provide a solution to help rehabilitate EFT deficits.

***Keywords:*** *transcranial direct current stimulation - trait rumination – cortisol - Montreal Imaging Stress Task - episodic future thinking*

***Funding****: This work was supported by a grant from the Neuromodulation call from the UZGent. This work was also supported by the 'Fonds Wetenschappelijk Onderzoek' [grant number 11J7521N).*

***Acknowledgments****: We want to acknowledge the valuable contribution of MSc Elizabeth Se on conducting the testings, and Prof. Dr. Filip Raes and Dr. David Hallford for the procedure of the EFT task.*

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# OPTIMIZED RESTING-STATE fMRI ACQUISITION STRATEGY FOR RELIABLE DLPFC TARGETING

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**Introduction:** The sgACC resting-state network is highly relevant in clinical applications for determining brain stimulation targets in the left DLPFC. However, the effects of changes in resting-state fMRI acquisition parameters on the reliability and reproducibility of these functionally derived targets are largely unknown. Here, we quantify the effect of echo time choice and preprocessing strategies on the reliability of the resulting functional connectivity maps.

**Methods:** In a group of 15 healthy subjects, we performed single-session scanning at 3T acquiring six runs of rs-fMRI (three with TE=30 ms; three with TE=38 ms) each. Functional connectivity maps were calculated for each run, and correlations to a seed in the sgACC were computed. Smoothing kernel size (FWHM) was varied from 4 mm to 12 mm in steps of 2 mm. Intraclass Correlation Coefficients (ICC) were calculated for each run and for each smoothing kernel. Values below 0.5, between 0.5 and 0.75, 0.75 and 0.90, and greater than 0.90 are considered to indicate poor, moderate, good and excellent reliability, respectively.

**Results:** Overall, functional connectivity networks showed comparable distribution for both TE choices. However, connectivity maps acquired with TE=38 ms showed much higher ICC values within the DLPFC region. Specifically, the peak within the left DLPFC had a reliability value of 0.95 for TE=38 ms compared to 0.54 for TE=30 ms. Figure 1 shows the ICC reliability maps for both TEs using different smoothing kernels.

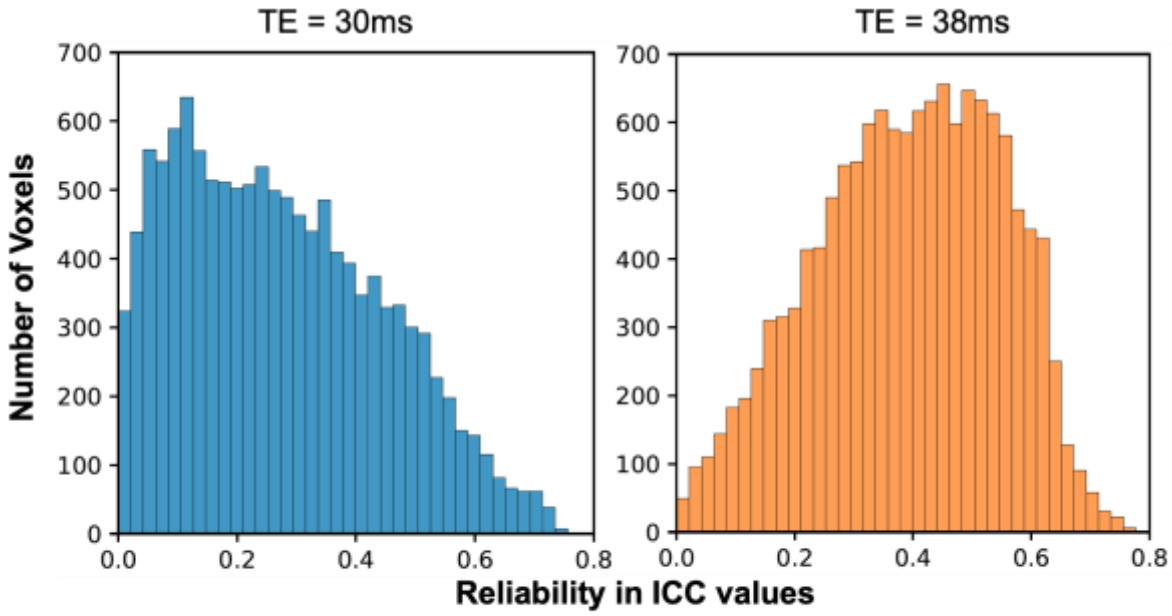


**Figure 1. Histogram of test-retest reliability of voxels within the left DLPFC for TE = 38ms and TE = 30ms.** On the y-axis the number of voxels for each bin is depicted. For TE = 30ms most voxels within the DLPFC have an ICC value below 0.5, which indicates poor reliability. For TE = 38ms, more voxels have an ICC value above 0.5, indicating moderate to good reliability.

**Discussion:** The choice of echo time has drastic effects on the reliability of the resulting functional connectivity maps. In addition, wider smoothing kernels could reduce the influence of local maxima within the correlation maps and increase the reproducibility. These findings highlight the value of exploring different acquisition and pre-processing strategies. Improved reliability of resting-state connectivity maps is important for improved outcome in clinical applications and for the optimization of data acquisition and multi-center data analysis in these resting-state networks.

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# SERT AVAILABILITY MODIFIED BY ACCELERATED HF-rTMS IN THE SUBGENUAL ANTERIOR CINGULATE CORTEX: A CANINE [$^{11}$C]-DASB POSITRON EMISSION TOMOGRAPHY STUDY

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**Background:** Repetitive transcranial magnetic stimulation (rTMS) has been proven to be a useful tool for the treatment of several neuropsychiatric disorders by partly exerting the antidepressant effect through the serotonergic system. Accelerated high-frequency rTMS (aHF-rTMS) may have the potential to result in a similar but faster clinical improvement compared to the classical daily rTMS protocols. Given that delayed clinical responses have been reported, the neurobiological effects of accelerated paradigms remain to be elucidated. More, the optimal stimulation parameters need to be refined.

**Hypothesis** We hypothesized that [$^{11}$C]-DASB binding alterations occurred in the regions with high SERT density. In line with antidepressant intake, we expected SERT decreases, more pronounced with the 20-sessions as compared to the 5-sessions protocol. No influences on any of the measurements following sham protocol were expected.

**Methods:** 10 dogs were allocated to the 5-sessions active group, 8 dogs were in the 20-sessions active group, 4 dogs were in the 20-sessions sham group. All dogs underwent four [$^{11}$C]-DASB PET scans: baseline, 24 hours, 1 month, and 3 months after the last TMS session. A binding index (BI) was calculated for each region of interest (ROI) at each time point with the cerebellum (excluding the vermis) as the reference region.

**Results:** 5-sessions active protocol did not result in significant SERT BI changes at any time point. For the 20-sessions active protocol, one month after stimulation the SERT BI attenuated in the subgenual Anterior Cingulate Cortex (sgACC). No significant SERT BI changes were found after the 20-sessions sham protocol.

**Conclusion:** Our results suggest delayed decreased SERT binding by aHF-rTMS in the sgACC, a key region involved in the therapeutic response of antidepressant therapy after 20 sessions and not after 5 sessions of aHF-rTMS. These preliminary findings suggest that an intensified aHF-rTMS protocol may be preferred and that a similar working mechanism compared to pharmacotherapy may be the base of its treatment utility. further research is needed to explore the exact pathways of the effects on the serotonergic system.

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# ACCELERATED dTMS IN THE ELDERLY DEPRESSED: PRELIMINARY INSIGHTS ON SAFETY, TOLERABILITY AND APPLICABILITY

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**Background:** Following encouraging results of our (Dardenne et al. 2018) pilot study with Accelerated High Frequency repetitive Transcranial Magnetic Stimulation (TMS) using a figure of eight coil in the elderly depressed, we started a more adapted randomized control trial (ClinicalTrials.gov) for this specific population with use of the H1 helmet coil for accelerated deep TMS (adTMS).

**Methods:** At time point T0 subjects are randomized (1:1) to either 20 sessions of real adTMS or sham. The sessions are spread over four succeeding days (5 sessions daily) with a stimulation intensity of 120% of the subject's resting MT, at a frequency of 18 Hz. Each dTMS repetition includes 2-sec. pulse trains separated by 20-sec inter-train intervals. Patients receive 55 trains, for a total of 1980 pulses per session. This makes 9900 pulses/day, and in total 39600 pulses per treatment. After each adTMS (real or sham) day, patients score a Visual Analogue Scale (VAS) about feeling any inconvenience. If such is the case, they can report any possible side-effect as well. Participants are also assessed for treatment-related adverse events (AE) by questionnaire on each time point.

**Results:** None of the first participants included (3 female, 1 male) dropped-out. For adTMS the VAS for discomfort values were never elevated above 50 mm, and AE questionnaires reported only (n=2) transient headache (rated as 'almost not' and 'sometimes').

**Conclusion:** Our preliminary observations indicate that adTMS was well tolerated and was safe to be used in elderly depressed patients.

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## TRANSLATING TMS-EEG METHODS INTO CLINICAL NEUROPSYCHIATRY: ILLUSTRATIVE CASE STUDIES

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Neuropsychiatric complaints are complex and varied, and often overlap across diagnostic entities. The underlying neurophysiologic signature of specific neuropsychiatric complaints can provide insights into the proximal substrate of a given patient's disability and suggest specific therapeutic targets and strategies. TMS-EEG provides a powerful approach to identify the neurophysiologic substrate of specific neuropsychiatric complaints and thus guide personalized therapeutics. I will show data from various clinical patients in whom TMS-EEG was used to identify bioelectrical features of their presenting and disabling complaints, and thus guide non-invasive brain stimulation treatment strategies. Single and paired pulse TMS, targeting DLPFC and M1 bilaterally, was used with concurrent EEG to map potential abnormalities in cortical excitability and inhibition balance, as well as TMS evoked response propagation patterns. These observations were used to inform and tailor noninvasive brain stimulation interventions for each patient. We report the clinical outcome of this approach and propose future directions to improve its clinical utility.

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## PLACEBO AND (UN)SPECIFIC EFFECTS OF TMS

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Placebo effect is an inescapable element of nearly all treatment interventions used in health care. Nonetheless, some health conditions as well as some treatment interventions are more susceptible to its effects. In that sense, it has been repeatedly argued that a large portion of responses to various interventions used for the treatment of depressive disorder can be attributed to placebo effects. However, these portions vary significantly as expectations, formed around more or less subtle cues about care setting, change. Transcranial magnetic stimulation (hereinafter TMS) has some unique and rather distinct features when compared with other usual treatment interventions (as psychoactive medication, that is, antidepressants). The placebogenic effect TMS has been widely discussed, both in research and clinical context, however still without any kind of firm conclusions.

Here we present a series of cases in which response to TMS was unusual and unexpected. We use these outlier cases to map out and disentangle possible specific and unspecific effects that total treatment setting in general and TMS in particular yielded. Further on, practical issues and challenges related to controlling the placebo effects in care settings are discussed.

As placebo is inevitable, and we might add critical, part of treatment interventions within the realm of mental health, in care settings it should be carefully harvested, so that it serves our patients and us for better and not for the worse.

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## PERSONALIZED rTMS BASED ON PREDICTION FACTORS

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Depression is a common mental disorder, globally is estimated that 5.0% of adults suffer from depression, with approximately 280 million people in the world have depression. rTMS has been approved as the treatment of depression and has been admitted in the clinical guidelines of many countries, accepted by the health insurance funds. Despite continuing advances in the development of antidepressant drugs, the condition of about 30% of patients remains refractory to drug treatment. Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (PFC) has been established as a new effective add-on therapy for depression. European recommendations mention the effectiveness of 30 to 64% of rTMS depression treatment. A combination of predictive factors of clinical response during care, such as a short duration of the current depressive episode, higher HDRS agitation item value, lower perceived sleepiness value and a higher number of previous rTMS treatments, were identified as predictors of the efficacy of rTMS.

Yet there are many other fields than Depression whereas rTMS shows high evidence and in the future new psychiatric indication will be available.

Catatonia is one of the most common severe motor syndromes, with an estimated prevalence among psychiatric inpatients of about 15%. Benzodiazepines and electroconvulsive therapy (ECT) are the most widely studied treatment methods and are recommended as first-line-therapy. Yet, recent studies show a successful utilization of rTMS in the treatment of catatonic symptoms by an inhibitory stimulation of the supplementary motor area (SMA). Few studies show that catatonia may be successfully treated with inhibitory rTMS.

Tinnitus treatment with rTMS have been examined in a large number of studies, whereas the uniform stimulation "1 Hz for all" didn`t prove to be effective. Still, there are many important predictors that should be taken into account as depressive mood, which means that patients with severe depression and tinnitus could be better responder compared with those having тinnitus without depression. Furthermore, there is a significant interaction between BDI and the response / non-response criterion indicating a higher decrease of depression symptoms in rTMS responders.

The artificial iintelligence using мmultimodal neuroimaging methods could provide the necessary insights into individual brain characteristics and can therefore be used to personalize rTMS. Further, the individual connectivity values of the identified neuroimaging biomarkers of long-term clinical response can also be used as features in the vector machine models defining and predicting the therapeutic response of patients with depression. Predictive and personalized approach of rTMS for patients with psychiatric diagnosis is ongoing process which will should be standardised as regular procedure.

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## CHALLENGES AND OPPORTUNITIES WITH TREATMENT OF MEDICATION-RESISTANT DEPRESSION IN SLOVENIA

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A review of health policies in the field of depression treatment in Slovenia has revealed certain deficiencies compared to the situation in the most developed countries. The national guidelines for the treatment of resistant depression have recently been updated. They define pathways and algorithms for the treatment of resistant depression, which include non-invasive methods of brain stimulation and drugs from new therapeutic groups. Newer forms of depression treatment are difficult to implement as publicly

funded health services in Slovenia, in part because it is difficult to objectively measure the success of treatment. Health authorities are aware of the importance of introducing new treatments, given the high social burden of depression. They expect us to introduce more systematic approaches to the treatment of depression in the near future, as well as more objective assessments of treatment success in individual patients and the impact of depression on their day-to-day functioning. We will present the planned approaches to these questions, which also have important consequences for the wider introduction of brain stimulation methods in the clinical practice of depression treatment in Slovenia.

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## ECT IN TREATMENT-RESISTANT SCHIZOPHRENIA: CURRENT PRACTICE AND FUTURE PERSPECTIVES

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Treatment resistance continues to represent the greatest unmet need in schizophrenia care, despite the ever growing number of antipsychotics. However, about one third of patients do not show sufficient improvement with antipsychotics. About half of those patients with treatment-resistant schizophrenia (TRS) have a poor response to clozapine. The pathophysiology of TRS is highly heterogeneous and includes dopaminergic, glutamatergic, and GABAergic dysfunction. Although electroconvulsive therapy (ECT) is primarily utilized to treat patients with severe depression, it can effectively reduce the symptoms of TRS, although some patients do not respond to this treatment. ECT produces changes in different brain regions/networks, that are supposed to correlate with the pathological findings in schizophrenia. In preclinical models, ECT had both acute and chronic effects on neurogenesis, while chronic ECT reduced neuroinflammation. However, the data on peripheral markers on inflammation and growth factors in patients are often heterogeneous, and studies were carried out mostly on patients with depression, while the data in schizophrenia are scarce. The mechanism of efficacy of ECT in TRS is not known. While preclinical trials suggest it may normalize dopamine supersensitivity state, clinical data are missing. Such effects may be important for patients who were not initially resistant. Other patients may be resistant from the illness onset, which could have unaltered dopamine synthesis capacity, but show NMDA receptor dysfunction on GABA interneurons. Chronic overactivation of the immune system can also be present from the illness onset.

Establishing clinical and biological markers of TRS, as well as predictors of response to ECT, is a priority. Such markers would distinguish patients who will benefit from ECT, and provide this treatment early in the disease course, which may improve the long-term outcome.

***Key words:*** *ECT - treatment-resistant schizophrenia - dopamine supersensitivity - neuroinflammation*

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## REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN TREATMENT OF PSYCHIATRIC DISORDERS AND COMORBIDITY

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Repetitive transcranial magnetic stimulation (rTMS) has emerged in recent decades as a noninvasive neuromodulatory intervention for treatment-resistant depression and obsessive-compulsive disorder. However, in the last decade, there is a growing body of literature on the potential beneficial effects of

rTMS treatment for diverse mental and neurological disorders. Therapeutic alternatives such as rTMS are urgently needed because treatment resistance is very common in psychiatric and neurological disorders. Based on neurophysiological findings, noninvasive brain stimulation methods offer an integrative treatment approach for many brain disorders. Therefore, this report presents an overview of the recent literature on the efficacy of rTMS and the treatment of various brain disorders, focusing on anxiety disorders, borderline personality disorder, eating disorders, and some neurological disorders such as multiple sclerosis and neuropathic pain. Overall, although the evidence base suggests that neuromodulation approaches are therapeutically promising, safe, and well-tolerated for many disorders, there are still gaps in the knowledge base. This report aims to present a practical guide for clinical application based on evidence from the literature and clinical experience in the field.

***Key words:*** *transcranial magnetic stimulation - psychiatric disorders - comorbidity*

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# ELECTROSTIMULATIVE THERAPY (EST) – TROUBLESHOOTING AND TIPS FOR CLINICAL PRACTICE – EXPERIENCE FROM PSYCHIATRIC CLINIC, CLINICAL HOSPITAL CENTRE OSIJEK (CROATIA)

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Often taken for granted and as an simple or even somewhat primitive tretment method, modern day EST represents a significant challenge for the clinician performing it. EST has evidence-based practice grounds which stand for a gold standard, but when giving EST the practicioner quickly confronts the clinical reality where evidence-base is limited and there are many areas where there is marked varitations in clinical practice. Given our, relatively short-lived clinical experience, the lightmotive is comprised in an imperative that EST practicioners have a sound understanding of evidence base that underpins EST but it is also important to have the capacity to integrate this knowledge into own clinical practice. This way, we ensure development of varied consumet-focused, practice-based which guide the delivery of EST treatment. As above mentioned, we will show and highlight the steps in performing EST among patients from different diagnostic categories, how to deal with public stigma, how to establish a team for the treatment, different ways in delivering treatment (with/without titration, electrode placement, preparation of electrodes and skin, which pulse and how to deliver, how to monitor/should we monitor etc.) what to do/react when some of these steps or treatment fails.

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# DIFFERENCES IN EFFICACY OF H1-COIL AND 8-COIL HR rTMS ON DIFFERENT DIMENSIONS OF MAJOR DEPRESSIVE DISORDER: POOLED SAMPLE FROM 2016-2022 STUDIES IN PSYCHIATRIC CLINIC SVETI IVAN

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**Objectives:** To compare the efficacy of HR rTMS with H1-coil and 8-coil on different dimension of major depressive disorder.

**Methods**: We conducted this analysis in intention-to-treat population of the pooled sample from two prospective cohort and two randomized controlled trials conducted in Psychiatric Clinic Sveti Ivan during 2016-2022. The outcome was Hamilton Depression Rating Scale-17 (HDRS-17). Allocation was concealed and outcome assessment was blinded. We conducted the analysis using adjusted within-between subject analysis of covariance. We controlled confounding effects of age, gender, diagnosis, duration of MDD and patients age at MDD onset. Using confirmatory factor analysis we tested the HDRS-17-part of the five-dimensions model derived by Uher (2012). We performed all interventions at 120% of the motor threshold, H1-coil with frequency of 18 Hz and 8-coil with 10 Hz, all in one session daily during 20 workdays (Figure 1).

**Table 1.** Characteristics of participants, ITT population

| | H1-coil (n=125) | 8-coil (n=107) |
|---|---|---|
| *Sociodemographic characteristics* | | |
| Age (years), median (IQR) | 54 (44; 60) | 52 (43; 61) |
| Gender, n (%) | | |
| men | 56 (44.8) | 52 (48.6) |
| women | 69 (55.2) | 55 (51.4) |
| *Clinical characteristics* | | |
| Diagnosis, n (%) | | |
| depressive episode (F32) | 35 (28.0) | 34 (31.8) |
| recurrent MDD (F33) | 90 (72.0) | 73 (68.2) |
| Duration of MDD (years), median (IQR) | 9 (4; 17) | 7 (3; 16) |
| Age at onset, median (IQR) | 41 (27; 50) | 42 (34; 51) |
| Psychiatric comorbidities, n (%) | 59 (52.2) | 73 (73.7) |
| Number of psychiatric comorbidities, mean (SD) | 1.9 (1.0) | 2.8 (1.2) |
| Neurotic, stress-related and somatoform disorders (F40-F48), n (%) | 33 (26.4) | 30 (28.0) |
| Disorders of adult personality and behaviour (F60-F69), n (%) | 22 (17.6) | 26 (24.3) |
| Organic mental disorders (F00-F09), n (%) | 6 (4.8) | 42 (39.3) |
| Mental and behavioural disorders due to psychoactive substance use (F10-F19), n (%) | 10 (8.0) | 10 (9.3) |
| Schizophrenia, schizotypal and delusional disorders (F20-F29), n (%) | 6 (4.8) | 2 (1.9) |
| Other psychiatric diagnosis*, n (%) | 5 (4.0) | 3 (2.8) |
| *Severity of MDD symptoms at baseline* | | |
| HDRS-17 at baseline, median (IQR) | 19 (15; 23) | 17 (13; 20) |
| HDRS-17 at baseline, n (%) | | |
| mild (≤13) | 27 (23.7) | 29 (29.0) |
| moderate (14-18) | 28 (24.6) | 34 (34.0) |
| severe (19-22) | 30 (26.3) | 20 (20.0) |
| very severe (≥ 23) | 29 (25.4) | 17 (17.0) |

Abbreviations: ITT - intention-to-treat; IQR - interquartile range; MDD - major depressive disorder; SD - standard deviation; HDRS-17 - Hamilton Depression Rating Scale-17

* Other psychiatric diagnosis: Behavioural syndromes associated with physiological disturbances and physical factors (F50-F59), Intentional self-harm by sharp object (X78), Other problems related to primary support group, including family circumstances (Z63), Problems related to employment and unemployment (Z56)

**Table 2.** Multivariable, adjusted analysis of efficacy of HR rTMS with H1-coil and 8-coil on different dimensions of major depressive disorder symptoms, ITT population

| | H1-coil (n = 125) | | | | 8-coil (n = 107) | | | | Interaction of time x arm | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | After intervention | $\Delta_{abs}$ | $\Delta_{\%}$ | Baseline | After intervention | $\Delta$ | $\Delta_{abs}$ | p | $\eta^2$ |
| Dimensions | | | | | | | | | | |
| Depressed mood | 6.5 (6.1; 7.0) | 2.7 (2.2; 3.2) | -3.8 (-4.4; -3.3) | -59 (-67; -51) | 6.0 (5.5; 6.5) | 3.0 (2.5; 3.6) | -3.0 (-3.6; -2.4) | -52 (-60; -44) | 0.046* | 0.02 |
| Anxiety | 4.5 (4.1; 4.9) | 1.9 (1.6; 2.2) | -2.6 (-3.0; -2.1) | -53 (-62; -44) | 4.3 (3.8; 4.8) | 1.7 (1.4; 2.1) | -2.5 (-3.0; -2.1) | -55 (-65; -45) | 0.880 | 0.00 |
| Pessimism | 1.7 (1.4; 2.0) | 0.6 (0.4; 0.8) | -1.1 (-1.3; -0.9) | -74 (-83; -65) | 1.6 (1.3; 1.9) | 7.0 (0.5; 0.9) | -0.9 (-1.2; -0.6) | -63 (-73; -53) | 0.270 | 0.01 |
| Sleep | 1.9 (1.6; 2.3) | 0.6 (0.4; 0.8) | -1.3 (-1.7; -1.0) | -71 (-81; -62) | 1.8 (1.5; 2.2) | 1.0 (0.7; 1.3) | -0.8 (-1.2; -0.5) | -59 (-70; -48) | 0.054 | 0.02 |
| Appetite | 0.7 (0.6; 0.9) | 0.3 (0.2; 0.5) | -0.4 (-0.6; -0.2) | -75 (-84; -66) | 0.6 (0.4; 0.8) | 0.2 (0.1; 0.4) | -0.4 (-0.6; -0.2) | -82 (-92; -72) | 0.282 | 0.001 |
| Factors (2nd order) | | | | | | | | | | |
| Observed mood | 11 (10; 12) | 5 (4; 5) | -6 (-7; -6) | -59 (-66; -52) | 10 (10; 11) | 5 (4; 6) | -6 (-6; -5) | -54 (-61; -47) | 0.826 | 0.00 |
| Cognitive | 4.3 (4.0; 4.7) | 1.8 (1.4; 2.1) | -2.6 (-3.0; -2.1) | -61 (-69; -53) | 4.1 (3.7; 4.5) | 2.0 (1.6; 2.4) | -2.2 (-2.6; -1.7) | -55 (-64; -46) | 0.497 | 0.00 |
| Neurovegetative | 4.3 (4.0; 4.7) | 1.8 (1.4; 2.1) | -2.6 (-3.0; -2.1) | -61 (-69; -53) | 4.1 (3.7; 4.5) | 2.0 (1.5; 2.4) | -2.2 (-2.6; -1.7) | -55 (-64; -46) | 0.500 | 0.00 |
| Complete HDRS-17 | 19 (17; 20) | 8 (7; 9) | -11 (-12; -10) | -59 (-65; -53) | 17 (16; 18) | 8 (7; 9) | -9 (-10; -7) | -52 (-59; -46) | 0.025* | 0.03 |

Data are presented as mean (standard deviation) in unadjusted and mean (95% confidence interval) in multivariable, adjusted analysis if not stated otherwise
Abbreviations: SD - standard deviation; $\Delta_{abs}$ - mean of absolute differences between the baseline and measurement after the treatment; CI - confidence interval; $\Delta_{\%}$ - mean of relative differences calculated as absolute difference divided by the baseline value; p - statistical significance of the difference from baseline to after the treatment within each of the two study groups, calculated using repeated measures analysis of covariance; $p_I$ - statistical significance of the interaction of study group and change during the treatment calculated using mixed, within-between analysis of covariance; $\eta^2$ - partial eta squared standardized effect size
Data are adjusted for age, gender, diagnosis (depressive episode or recurrent MDD), duration of MDD, and age at onset
* FDR < 5%

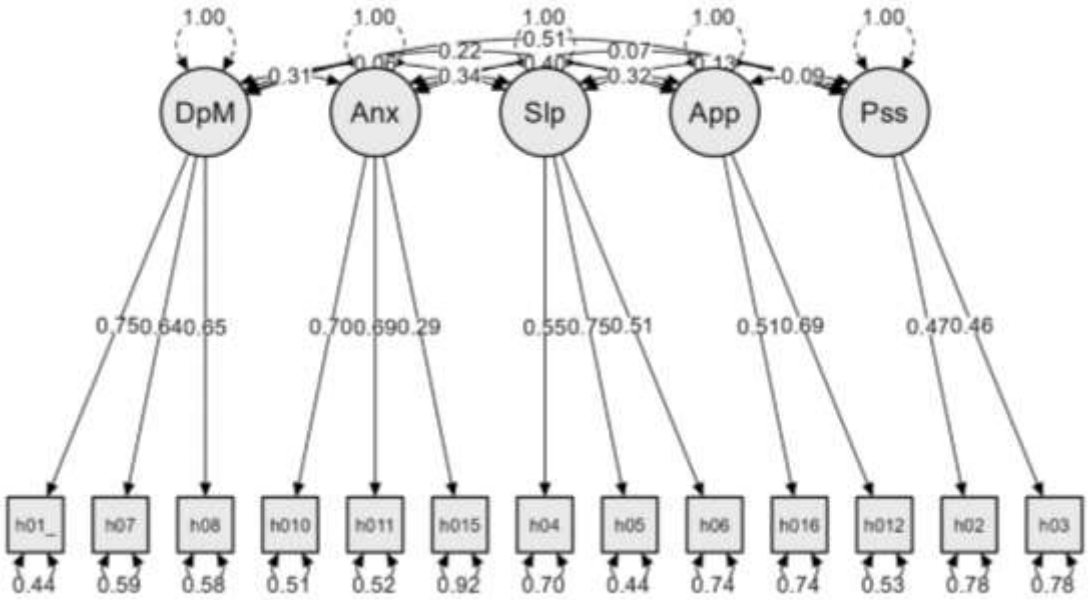


**Figure 1.** Hamilton depression rating scale confirmatory factor analysis model plot

**Results:** We analysed 125 patients treated with H1-coil, 55% women, and 107 patients treated with 8-coil, 51% women. Median (interquartile range; IQR) age was 54 (44-60) years in H1-coil arm and 52 (43-61) years in 8-coil arm. Two arms were well balanced in terms of diagnosis (depressive episode or recurrent MDD), duration and baseline severity of MDD. Patients in 8-coil arm more often had psychiatric comorbidity, primarily organic mental disorders. Five dimensions model of HDRS: depressed mood, anxiety, pessimism, sleep difficulties and changes in appetite fitted the empirical data very well ($X^2$=69.5, p=0.091; CFI = 0.96; TLI = 0.94; RMSEA = 0.035, 90% CI 0.000; 0.058), SRMR = 0.050).

Lowering of total HDRS-17 score was significantly larger in H1-coil, than in 8-coil arm (59% and 52% respectively; p=0.025; $\eta^2$=0.03; FDR <5%). H1-coil had significantly better effect on depressed mood dimension (p=0.046; $\eta^2$=0.02; FDR <5%). In other dimensions and 2$^{nd}$ order factors (mood, cognitive, neurovegetative) we have not observed significant differences between the two coils (Table 1, 2).

**Conclusion:** This study indicated somewhat better effect of H1-coil on total HDRS-17 score and on depressed mood dimension, but not on any other dimension or the 2$^{nd}$ order factor.

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# THE USE OF TMS IN TREATMENT OF GAMBLING DISORDERS

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Gambling disorder is characterized by persistent and recurrent gambling behavior that can lead to devastating consequences for those with the disorder and their families. Disorders in the prefrontal activity of the brain are mentioned as the upcoming pathophysiological substrate in the development of gambling disorders (GD). A fundamental feature of this disorder is a craving that we define as an urgent and irresistible desire to indulge in addictive behavior, which usually results in a loss of control, and its biological correlates are dysfunctional dopamine cortical – subcortical pathways, particularly of the inhibitory control of the dorsolateral prefrontal cortex (DLPFC).

Repetitive transcranial magnetic stimulation (rTMS) is used to modulate local brain activity and thus modulating neurocircuitries involved in the pathophysiology of gambling disorders (GD) potentially resulting in therapeutic effects. Dopaminergic dysfunctions have been found to be critically involved in the development of GD, especially in presynaptic structures, in the reduced availability of dopamine transporters (DAT) in GD subjects. Stimulating the DLPFC with rTMS may restore a physiological basal dopaminergic activity and increase DAT levels, as well as modulate glutamatergic neurotransmission.

The aim of this review paper was to highlight possibilities for further research in determining efficacy of rTMS in the treatment of cravings in behavioral addiction, as well as recommendations for optimal stimulation settings and its clinical application.

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## TREATING DEPRESSION IN PATIENTS WITH NEUROPATHIC PAIN AND DEMYELINATING DISEASE OF THE CENTRAL NERVOUS SYSTEM

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Transcranial magnetic stimulation (TMS) is a technique for noninvasive stimulation of the human brain. Stimulation is produced by generating a brief, high-intensity magnetic field by passing a brief electric current through a magnetic coil. The field can excite or inhibit a small area of brain below the coil.

Repetitive TMS has a modulatory effect on cortical excitability, which outlasts the stimulation period and can be used in a variety of indications, delivered to either motor or nonmotor brain regions. The impact of rTMS can be observed at the site of stimulation and mostly at a distance, according to the nature of the activated neural circuits.

Functional or clinical effects outlast the period of stimulation for minutes or hours, likely due to long-term depression (LTD) of synaptic transmission for low-frequency rTMS and long-term potentiation (LTP) for high-frequency rTMS.

Therefore by modifying brain functions, with after-effects lasting beyond the time of stimulation, rTMS opens exciting perspectives for therapeutic applications, especially in the domain of depression and chronic pain syndromes.

Neuropathic pain is caused by a lesion or disease of the somatosensory system, including peripheral fibres (Aβ, Aδ and C fibres) and central neurons, and affects 7-10% of the general population. The somatosensory system allows for the perception of touch, pressure, pain, temperature, position, movement and vibration. Neuropathic pain is associated with increased drug prescriptions and visits to health care providers and can substantially impair quality of life as it often associates with other problems, such as loss of function, anxiety, depression, disturbed sleep and impaired cognition.

Progress in the understanding of the pathophysiology of neuropathic pain is spurring the development of new diagnostic procedures and personalized interventions, which emphasize the need for a multidisciplinary approach to the management of neuropathic pain. Repetitive sessions (5-10 sessions over 1-2 weeks) with high-frequency rTMS (5-20 Hz) have shown benefits in a mixture of central, peripheral and facial neuropathic pain states, with effects lasting >2 weeks after the stimulation. Contraindications of rTMS include a history of epilepsy and the presence of aneurysm clips, deep brain electrodes, cardiac pacemakers and cochlear implants.

Multiple sclerosis (MS) is a chronic inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms. Multiple sclerosis (MS) associated neuropsychiatric disorders include major depression (MD), obsessive-compulsive disorder (OCD-MS), bipolar affective disorder, euphoria, pseudobulbar affect, psychosis, and personality change. A point prevalence of 15% to 30% and a lifetime prevalence of 40-60% of MD have been reported in MS patients; this rate of depression is 3 to 10 times that of the general population. H-coil rTMS is safe and well tolerated in patients with MS. The observed sustained reduction in fatigue after subthreshold MC stimulation warrants further investigation.

Our experience in treating depression in patients with demyelinating disease of the central nervous system also showed promising results on mood disorder.

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# REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN TREATMENT OF TINNITUS: META-ANALYSIS OF RANDOMIZED SHAM-CONTROLLED TRIALS

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**Background:** Tinnitus etiology and clinical presentations are highly variable. There is no stringent and universally accepted definition of the disorder, and objective diagnostic biomarkers are missing. There is no gold treatment standard, and the results of studies on various treatment effects are inconsistent. Clinical practice guidelines from 2014 stated that rTMS may not be recommended for the routine treatment of tinnitus neither, because of methodological heterogeneity/weaknesses, and inconsistencies of results of rTMS randomized controlled trials. Since 2014, more studies of rTMS efficacy on tinnitus have been published, but the results are still highly heterogenous, poorly reported, with low reproducibility, and non-conclusive. To access the efficacy of rTMS on idiopathic, chronic tinnitus disorder.

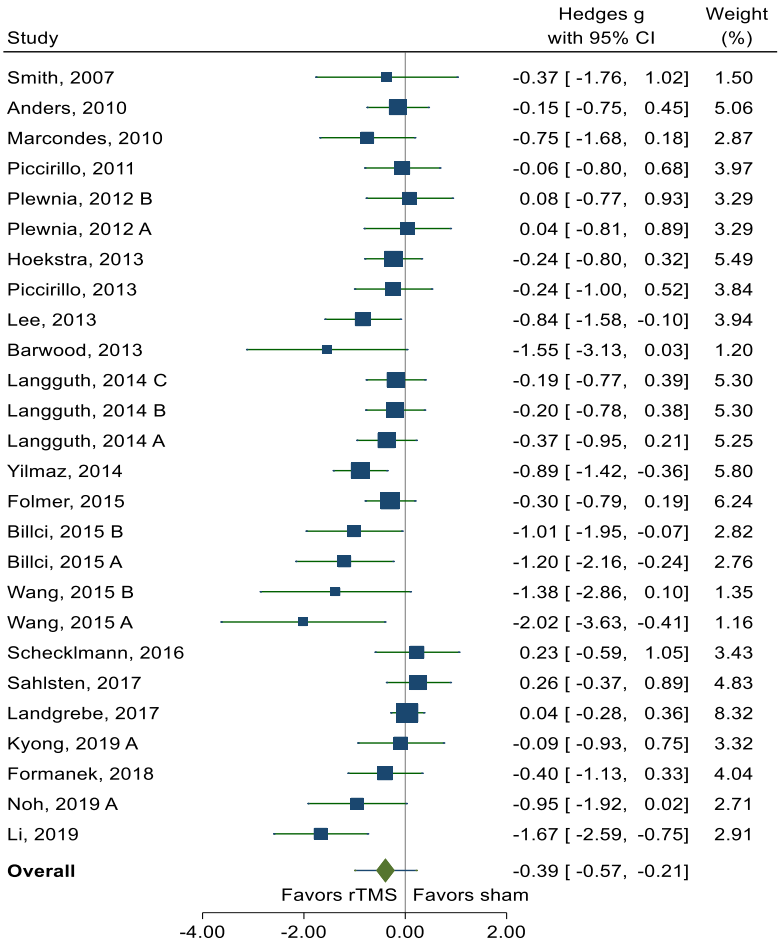


**Figure 1.** Forest plot of standardized mean differences (Hedges g) between active rTMS and passive sham coil in the effect on tinnitus severity measured immediately after the intervention; error lines in the summary measure represent 95% prediction interval (-1.00; 0.22); (n = 26 studies; 549 patients in active rTMS arms, 537 in passive sham arms); studies are sorted by the year of publishing of the first results in order starting with the oldest one

**Methods**: We conducted a meta-analysis of randomized sham-controlled, double-blind trials. Instead of a systematic search for the primary studies and new risk-of-bias assessment, we used 13 systematic reviews and meta-analyses that were published by February 25, 2022. We used a random-effects model, and analyzed the standardized effect sizes, and instead of only calculating the confidence intervals, as was done in literally all 13 meta-analyzes, we calculated the 95% prediction intervals to respect the uncertainty in estimating between-study variance.

**Results:** Total number of eligible studies was 42, of witch large number did not define the primary outcome. In the final analysis, we included 26 studies with 549 patients in active and 537 in passive sham arms. The overall effect of rTMS on severity of tinnitus was Hedges g= -0.39 (95% CI -0.57; -0.21; 95% prediction interval -1.00; 0.22) (Figure 1).

**Conclusion:** Too many randomized sham-controlled trials on the efficacy of rTMS on tinnitus and reporting of their results are of unsatisfactory quality. The whole body of literature is fragmented into small, too often poorly designed trials with exclusive/new protocols and presumably low reproducibility. The whole field would probably benefit from larger, better theoretically founded studies, replications of the most promising experiments, and the empirically founded patient-oriented approach that will respect the tinnitus phenotype heterogeneity and the existence of distinct patient subpopulations. In this area of research, the race for the ad-hoc discovery of the Holy Grail of rTMS *perfect* protocol should be stopped, and the traditional scientific paradigm of theoretically grounded gradual improvement on previous studies and theories should be adhered to.

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# EFFICACY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION WITH H7-COIL IN THE TREATMENT OF TINNITUS: PROTOCOL FOR PHASE IIA, PROOF OF CONCEPT, RANDOMIZED, SHAM-CONTROLLED, DOUBLE BLIND CLINICAL TRIAL

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**Background:** There is no gold standard for treating tinnitus. A relatively large number of studies of the efficacy of rTMS on tinnitus have been conducted. Generally, low-frequency (LF) stimulation of the auditory cortex in combination with high-frequency (HF) stimulation of the DLPFC, has shown efficacy in reducing symptoms (especially loudness and anxiety). A possible alternative target for HF rTMS of the DLPFC, is the medial prefrontal cortex (mPFC), using the H7 coil. There is no study of the acceptable quality on the effects of H7-coil in stimulating the auditory cortex and mPFC.

**Objectives:** To examine the efficacy of H7 coil LF/HF rTMS, with H7-coil applied in the treatment of idiopathic, chronic, tinnitus disorder with normoacusis.

**Hypothesis**: The LF rTMS (1Hz) placed over auditory cortex combined with HF (10Hz) H7-coil placed over mPFC, applied for 15 days, has superior efficacy on tinnitus symptoms measured by the overall Tinnitus Handicap Inventory (THI) score, than the SHAM passive coil.

**Study design**: We plan an industry-independent, single-center, prospective, randomized sham-controlled, two-arms, double-blind superiority clinical trial with concealed allocation and masked independent outcome assessment.

**Population:** Outpatients diagnosed for ≥ 12 months and ≤ 5 years with persistent, subjective, normoacoustic tinnitus disorder of at least moderate severity defined by the THI score ≥ 38, both unilateral and bilateral, both genders, and with no hearing loss, age 18-65 years, with the tinnitus treatment unchanged for at least one months. Exclusion criteria: organically caused tinnitus and organic brain lesion, objective

tinnitus, severe hearing loss or Menier's disease, middle ear disease, diagnosed mental disorder, suicidality, alcohol or drugs addictions, clinically relevant neurological disorder, and standard rTMS exclusion criteria.

**Sample size:** 52 in HR rTMS H7-coil arm, and 52 in sham control arm.

**Primary outcome:** Adjusted median of differences in total THI score. We will adjust the means for the distribution of age, gender, tinnitus severity, duration, and treatment.

**Secondary outcomes**: Change in TQ score, change in VAS score, the proportion of patients with clinically relevant lowering of total THI score ≥ 7 points, percentage of the awake time aware of tinnitus, percentage of awake time annoyed, distressed or irritated by tinnitus, change in BDI-II score, change in BAI score, change in PSQI score.

**Data analysis:** Within-between subjects ANCOVA or multivariable quantile regression of outcome measure score after the therapy to the treatment group, adjusted for baseline outcome measure score and all preplanned possible confounding variables in the intention-to-treat population.

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# INTERIM ANALYSIS OF EFFICACY AND SAFETY OF HIGH-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION WITH H7-COIL IN TREATMENT OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA SPECTRUM DISORDERS: A RANDOMIZED, SHAM-CONTROLLED TRIAL

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**Background:** At present, the main treatment for schizophrenia relies on antipsychotic medication. Antipsychotics, although relatively effective on positive symptoms, have no consistent, reliable, and satisfactory effect on negative and cognitive symptoms. High frequency repetitive transcranial magnetic stimulation (HF rTMS) with H7-coil represents a safe, non-invasive technique that has been hypothesized to improve negative symptoms in this population.

**Objectives:** The purpose of this randomized sham-controlled, two-arms, double-blind superiority clinical trial with concealed allocation and masked independent outcome assessment study is to examine the efficacy and safety of HF rTMS with H7-coil applied once daily during the twenty days, augmentative to the standard antipsychotic and other pharmacotherapy of negative symptoms in schizophrenia.

**Methods:** This is a report of the interim analysis after completing 50% of the planned sample size. The target population was outpatients diagnosed with SSD (ICD-10: F20-F29), both genders, age 18-55 years, with PANSS negative symptoms subscale score > 24, and PANSS positive symptoms subscale score < 20, stable during at least three months and with the antipsychotic therapy unchanged for at least three months. The primary outcome was adjusted mean of total score on The Scale for the Assessment of Negative Symptoms (SANS).

**Results:** We randomized 25 patients in active, H7-coil arm, 44% of them women, and 26 in inactive, sham-coil arm, 38% of them women. The median (interquartile range) of age was 38 (27-48) years in H7 and 34 (24-44) years in sham arm. During the intervention total SANS score was lowered in both study groups [-45% (95% CI -55; -35%) lowering of SANS score in H7, and -33% (95% CI -43; -23%) in sham arm]. Time x group interaction was significant p=0.035; $\eta^2$=0.11; false discovery rate <5%). We observed significant effects on blunting and alogia SANS subscales, and no significant effects on avolition/apathy, anhedonia, and attention subscales.

**Conclusion:** This interim analysis indicated a possible effect of HF rTMS with H7-coil on the overall severity of negative symptoms and acceptable safety and tolerability in the population of patients diagnosed with schizophrenia and pronounced negative symptoms.

***Key words:*** *transcranial magnetic stimulation - schizophrenia spectrum and other psychotic disorder - psychotic disorder - negative symptoms*

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## GENDER DIFFERENCES IN THE EFFICACY OF rTMS TREATMENT ON MAJOR DEPRESSIVE DISORDER

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Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that is effective in treatment of major depressive disorder (MDD). A probable association of short-term antidepressant properties of rTMS with gender has been observed.

Objective of our study was to investigate gender differences in the efficacy of 8-coil rTMS on major depressive disorder (MDD).

We performed an industry-independent, unicentric, randomized, controlled, single-blinded study in Psychiatric Hospital "Sveti Ivan" in Zagreb. Patients were randomized into two groups: experimental group treated with 8-coil rTMS (n=47) and standard pharmacotherapy and the control group (n=43) treated with the standard pharmacotherapy alone. The primary outcome was HAM-D17. Variables whose possible confounding effect we controlled by multivariable statistical analysis were: age, diagnosis, age at MDD onset, treatment with SSRIs, SNRIs and other antidepressants.

After the adjustment for all preplanned possible confounding variables, the lowering of HAM-D17 score after 4-weeks treatment was statistically significantly different between experimental and control group. In women, the lowering of HAM-D17 score was statistically significantly and clinically relevantly larger in the experimental group than in the control group. The interaction of the study group and gender on the change in HAM-D17 scores was not statistically significant after adjustment for confounding variables. It cannot be reasonably reliably claimed that there are differences in the effect of rTMS between men and women using the 8-coil, but the results indicate the need for further research.

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## BINGE-EATING DISORDER AND TRANSCRANIAL MAGNETIC STIMULATION – STATE OF KNOWLEDGE

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Binge-eating disorder (BED) is characterized by repetitive episodes of excessive food consumption in the absence of regular compensatory behaviors used to avoid weight gain. As the most common eating disorder, BED is an important public health problem, associated with obesity, life impairment, poor outcomes and significant psychopathology and comorbidity. Due to its complex multifactorial etiology, BED represents a challenge in terms of treatment strategies, with limited therapeutic options.

Neurostimulation strategies, such as Transcranial magnetic stimulation (TMS), modulate cortical or subcortical excitability producing therapeutic effects. There are several studies that suggest a possible positive effect of brain stimulation on the neural mechanisms underlying BED, especially on the increased neural activity in the orbitofrontal cortex and decreased regulatory influence in dorsolateral prefrontal cortex (DLPFC).

The objective of this poster is to describe the state of literature and to asses clinical and scientific findings of the use of TMS procedures for modulating food cravings and food consumption in treating BED.

With respect to BED, several TMS trials have been published and have yielded promising results. Furthermore, application of multi-session Non-invasive brain stimulation (NIBS), predominantly Repetitive transcranial magnetic stimulation (rTMS) to BED has also yielded promising, but ultimately inconclusive results. These results provide a rationale for further exploring TMS as a treatment option for BED as more clinical trials should be conducted in order for more definite conclusions to be made.

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