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

Marco Manzo[1], Luigi Franzese[1], Mattia Vittorio Pomes[1], Hekla Lamberti[1], Manganelli Fiore[2], Andrea De Bartolomeis[1], Raffaele Dubbioso[2] & Giordano D'Urso[1]

[1]Department of Neurosciences and Reproductive and Dental Sciences, Division of Psychiatry, Università degli Studi di Napoli Federico II, Naples, Italy
[2]Department of Neurosciences and Reproductive and Dental Sciences, Division of Neurology, Università degli Studi di Napoli Federico II, Naples, Italy

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

Raquel Guiomar[1], Beatriz Catoira[2,3], Mónica Sobral[1], Paula Castilho[1], Chris Baeken[2,3] & Ana Ganho-Ávila[1]

[1]University of Coimbra (Portugal), Center for Research in Neuropsychology and Cognitive and Behavioral Intervention (CINEICC), Faculty of Psychology and Educational Sciences, Coimbra, Portugal
[2]Department of Head and Skin (UZGent), Ghent Experimental Psychiatry (GHEP) Lab, Ghent University, Ghent, Belgium
[3]Department of Psychiatry (UZBrussel), Free University Brussels, Brussel, Belgium

Background: Schizophrenia is a severe and chronic mental disorder affecting millions of people world-wide. 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.

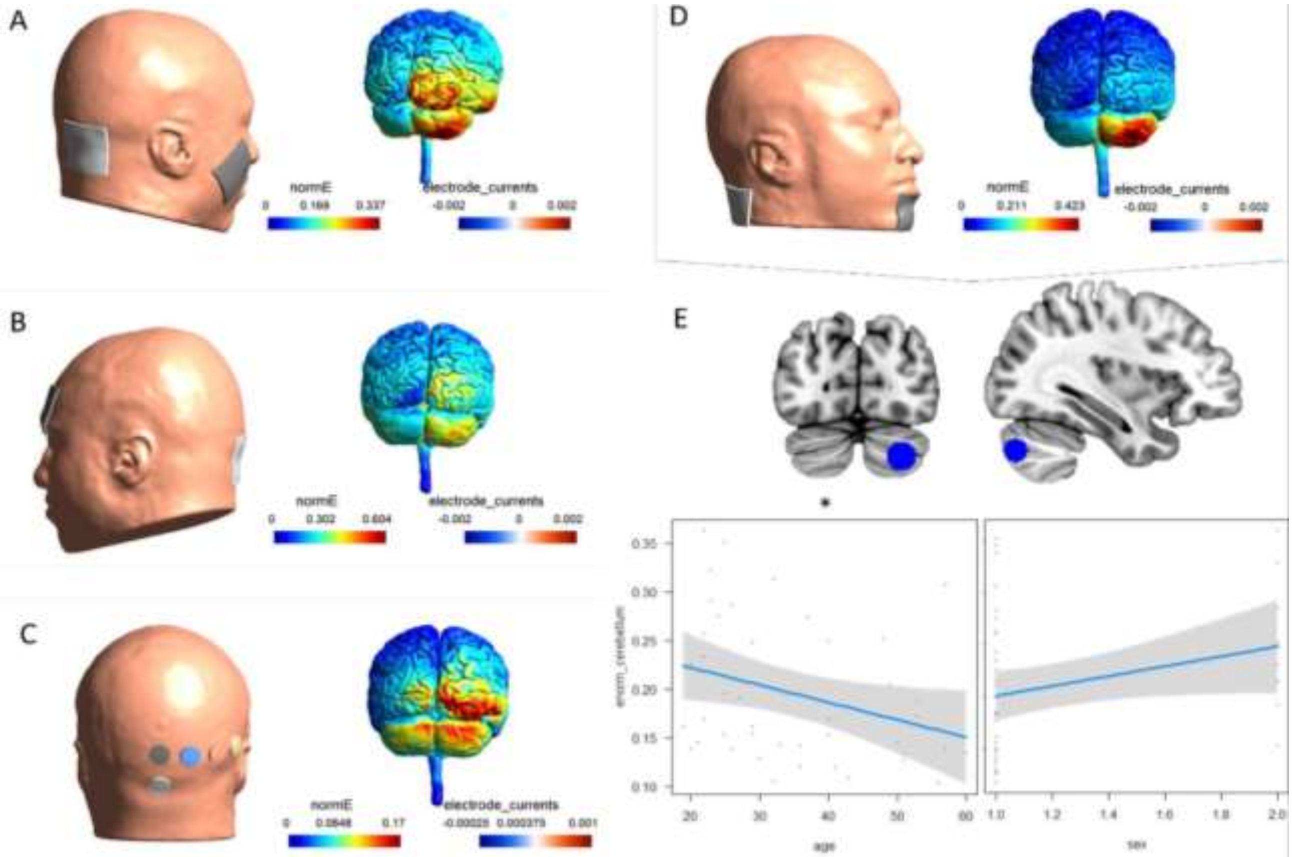

Figure 1. Cerebellar tDCS (ctDCS) montages, region of interest (ROI), and multiple linear regression results. A. Left: Anode over the right cerebellum (1 cm below and 3 cm lateral to Iz, 10/10 EEG system); cathode over the right buccinator muscle. Right: Electric field (EF) simulation on gray matter (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 (ß=-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

Stefanie De Smet & Marie-Anne Vanderhasselt

Department of Head and Skin, Ghent University, Ghent, Belgium
Ghent Experimental Psychiatry (GHEP) Lab, Ghent, Belgium

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

Marie-Anne Vanderhasselt

Department of Head and Skin, Ghent University, Ghent, Belgium
Ghent Experimental Psychiatry (GHEP) Lab, Ghent University, Ghent, Belgium

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*