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APPLICATION OF TRANSCRANIAL DIRECT CURRENT STIMULATION COMBINED WITH COGNITIVE-BEHAVIORAL THERAPY FOR COMMUNICATION AND PRAGMATIC SKILLS' IMPROVEMENT IN AUTISM SPECTRUM DISORDER

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BACKGROUND: Pragmatic skills' impairment and communication difficulties are common in Autism Spectrum Disorder (ASD), regardless of symptoms severity [1]. The social-reciprocity deficit was considered an important risk factor for social isolation [2]. Recently, it has been assumed that the hypo-activation of Broca's area has a pivotal role in atypical communication [3]. In this context, non-invasive brain stimulation **methods**, including transcranial direct current stimulation (tDCS), have been examined as promising therapeutic options to modify aberrant neuroplasticity involved in neuropsychiatric disorders, including ASD [4].

OBJECTIVES: The aim of the study is to assess the effect of anodal tDCS application combined with a cognitive-behavioral therapy (CBT) for the improvement of pragmatic skills, the increase of spontaneous speech and the enhancement of social interaction quality within a group of individuals with ASD.

METHODS: 8 young males diagnosed with ASD were enrolled (age range 18-22 years) so far.

At the baseline (T0) each patient performed a neuropsychiatric assessment of: cognitive abilities (Wechsler Adult Intelligence Scale – Revised), adaptive skills (Adaptive Behavior Assessment System–Second Edition), autistic symptoms (Autism Diagnostic Observation Schedule–Second Edition) and communication abilities (Assessment Battery for Communication-ABaCo). The evaluation of communication abilities was repeated at the end of each conditions (T1,T2).

After the baseline, each patient underwent a treatment with both anodal real tDCS (20 minutes, 1mA) and sham tDCS (30 seconds, 1 mA) on the left Broca's area (F5). Each condition was delivered for 5 consecutive days, for a total of 10 sessions, interspersed with a 14-day break. The order of the conditions was blindly randomized. In each conditions the cathod was located on the contralateral orbitofrontal cortex and the CBT was delivered simultaneously with tDCS.

RESULTS: Preliminary results on 5 males (age M±DS 20.4±2.1) reported no significant differences in clinical profiles at the baseline in terms of cognitive (M±DS 87.7±17.4), adaptive skills (M±DS 82±9.5), autistic symptoms (M±DS 6.75±1.2) and communication abilities (M±DS 63.2±10.5).

Paired t test analyses revealed statistically significant improvement of global communication abilities measured through the Global Index of ABaCo battery after 5 consecutive sessions of anodal real tDCS associated with CBT ($t_{(4)}= 3.01$; $p = 0.03$), in comparison to sham condition associated with CBT ($t_{(4)}= 0.04$; $p = 0.70$). Interestingly, the comparison between real tDCS and sham condition revealed an increasing also in paralinguistic comprehension after real tDCS sessions ($t_{(4)}= 2.75$; $p = 0.05$). Even if not significant, ($t_{(4)}= 0.47$; $p = 0.07$) we found an enhancement of the communication behaviours' appropriateness after real tDCS condition (M±DS100±0), in comparison to sham (M±DS 70±27).

CONCLUSIONS: Preliminary results show that the application of anodal tDCS stimulation of left Broca's area (F5) associated with CBT focused on communication and pragmatic skills, significantly improved global conversational abilities in young adults with ASD. Surprisingly, the improvement of paralinguistic comprehension abilities suggests the involvement of Broca's area not only in verbal and non-verbal production, but also in comprehension.Aware that CBT is the first line intervention for ASD, its association with tDCS may represent a promising approach to improve rehabilitation's outcomes.

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TRANSCRANIAL RANDOM NOISE STIMULATION AND HEART RATE VARIABILITY

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Introduction: Transcranial random noise stimulation (tRNS) is a transcranial electric stimulation (tES) method, in which an electrical current alternates randomly between two stimulation electrodes in direction and amplitude, within a given range [1]. High frequency alteration of the current has been shown to induce increase or decrease in sustained levels of cortical excitability in the motor cortex, depending on the intensity of the current [2]. Transcranial direct current stimulation (tDCS), another tES method, has been associated with alterations in autonomic nervous system (ANS) activity as measured through heart rate variability (HRV) in different settings [3, 4].

Aims: To determine whether tRNS modulates ANS basal state activity or ANS activity after cognitive tests assessing risk-taking and impulsivity, as assessed with HRV.

Methods: All participants (n=52) received tRNS and sham in two successive sessions, in random order. All stimulation interventions were double-blinded. The participants received tRNS over the F3 and the F4, through conductive rubber electrodes, placed in two saline-soaked sponges. The stimulation time was 20 minutes, and the current 2 mA. The interventions were conducted using NeuroConn DC-STIMULATOR PLUS. The electrocardiogram (ECG) was measured continuously throughout both study visits using a Faros ECG sensor. The sensor was attached to participant's chest using disposable Ambu BlueSensor wet-paste electrodes. The heart rate data was analyzed with the Kubios program in eight 5-minute time blocks: at baseline, right before stimulation, on 4 blocks during stimulation, immediately after stimulation, and in the end after post-stimulation cognitive testing. Statistical analyses consisted of paired samples T-tests and one-way repeated measures analysis of variance (ANOVA). Analyses were performed using IBM SPSS Statistics 27 software.

Results: A paired samples T-test revealed no statistically significant differences between tRNS and sham conditions over the examined eight blocks, when they were compared individually. One-way repeated measures ANOVA showed a significant effect for time in all the measured HRV parameters; average heartbeat interval duration (Wilks' Lambda = .165, F (7, 45) = 32.44, $p < .001$, multivariate partial eta squared = .835), standard deviation of the heartbeat intervals (Wilks' Lambda = .352, F (7, 45) = 11.83, $p < .001$, multivariate partial eta squared = .648), beat-to-beat variance (Wilks' Lambda = .493, F (7, 45) = 6.62, $p < .001$, multivariate partial eta squared = .507), and the randomness in HRV time series (Wilks' Lambda = .317, F (7, 45) = 13.82, $p < .001$, multivariate partial eta squared = .683). There was no significant stimulation effect in any of the measured HRV parameters, in any of the utilized eight blocks, in the ANOVA, either.

Conclusions: Transcranial random-noise stimulation did not modulate the autonomic nervous system basal state activity or the activity following cognitive tests, as measured by HRV. Our findings supplement previous research on transcranial electric stimulation safety [5] by introducing tRNS as a potential tES method that does not induce autonomic cardiac effects.

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ELECTROCONVULSIVE THERAPY – CHARGE AND FREQUENCY RELATE TO THERAPEUTIC OUTCOME

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Introduction: Electroconvulsive therapy (ECT) is a well-known treatment option despite the obscure mechanism of action. We aimed to explore the effect of key variables in ECT on the therapeutic response in acute psychiatric patients with major depressive disorder, bipolar disorder, schizophrenia, and schizoaffective disorder. We hypothesized that the clinical outcome of ECT is influenced by not only the seizure duration but also, the temporal properties of the treatment, specifically the frequency and charge.

Methods: We included ECT recordings of 62 patients and 1,011 ECT sessions from September 6, 2017 to August 13, 2021. The patients' Clinical Global Impressions (CGI) scores, indicating clinical outcomes, were assessed based on ECT session recordings and hospital records. The charge of ECT pulses were calculated using parameters from ECT recordings. We examined the relationship between CGI score improvement and ECT parameters on linear regression model. CGI scores were treated as ordinal values (1-4), and a cumulative link function was used. We created two models, one with ECT pulse charge as the predictor and another with ECT frequency. Co-variates included the choice of anesthetics, placement of electrodes, age, gender, diagnosis, and symptoms. Anesthetics were coded as a bivariate variable for contrast within the group. The models were compared using the Akaike Information Criterion (AIC) to predict CGI scores.

Results: The frequency model, with a lower AIC value of 2058.379 compared to the charge model (2069.839), provided a better fit to the data. This finding was supported by a confirmatory analysis using type 2 ANOVA, which demonstrated a significant difference ($p < .001$) and lower Chisq for the frequency model.

Both the charge and frequency of ECT were significantly associated with CGI scores. The direct effect of charge on CGI was significant (standardized estimate = -0.190, $p < 0.001$, Cohen's d = 0.96 [large]), as was the direct effect of frequency (standardized estimate = -0.085, $p < 0.001$, Cohen's d = 0.97 [large]). Seizure duration was 19.8 +/- 8.09 sec. The mediation analysis did not reveal a significant indirect interaction through seizure duration for either the charge model (Beta = -0.0005, p = 0.95) or the frequency model (Beta = -0.0004, p = 0.9). The small effect sizes (Cohen's d effect size = 0.002 for the charge model and 0.021 for the frequency model) further supported the absence of significant indirect effects mediated by seizure duration.

Conclusion: Both the charge and frequency of ECT were found to have a direct effect on CGI scores, independent of seizure duration. Notably, the frequency of ECT pulses emerged as a stronger predictor of clinical improvement compared to the total energy delivered by ECT. These results contribute to our understanding of ECT mechanisms and suggest the potential for personalized treatment approaches based on individual subjects' frequency spectra. Targeting a seizure duration around 20 sec by optimizing frequency and charge may have implications for further research in this area to enhance the efficacy of ECT interventions.

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DISASSOCIATING TASK FMRI ACTIVATION AND RESTING-STATE FUNCTIONAL CONNECTIVITY TO NEGATIVE EMOTION IN COMMON MENTAL DISORDERS IN UK BIOBANK

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Introduction: Alcohol misuse, depression, and anxiety are among the most common mental disorders, and can lead to disabilities and financial loss to the family and society. Non-invasive brain stimulation interventions for these common mental disorders have been shown effective while developments are emerging in using resting-state fMRI functional connectivity (FC) to guide individualized stimulation targets [1].

Aim: First, with the population-based dataset the UK Biobank, the present study aims to identify the brain function abnormalities that are related to these three dimensions in 21,000 participants' negative emotion face task fMRI data. Second, using more than 35,000 participants' resting-state fMRI data and 1400 participants' repeated scans, we evaluate FC individual differences and reproducibility in guiding individualized brain stimulation targets on the dorsolateral prefrontal cortex (DLPFC) for clinical interventions.

Methods: In the task fMRI analysis, we related participants' brain activation to the disease severity scores at voxel-wise (threshold at Gaussian Random Field correction voxel $p < 0.01$ and cluster $p < 0.05$). The resultant deep brain structures were used as region-of-interest (ROI) to conduct seed-based FC analyses for each dimension. In the FC analysis, we identified group mean FC peak and individual peak on DLPFC to calculate the Euclidean distance between these peaks (the individual difference). With repeated resting fMRI, we identified each participant's Euclidean distance between the FC peak from each scan (the reproducibility).

Results: With task fMRI, we identified that more alcohol use related to hyperactivity in the amygdala whereas higher depression scores related to hyperactivity in the striatum (including nucleus accumbens, putamen, and caudate), hypothalamus, and extending to subcallosal cortex. High depression or anxiety scores related to hypo-activity in the bilateral DLPFC with no subcortical findings with anxiety severity. When using these hyperactive deep structures as seed ROIs to conduct FC analyses, extensive negative FC can be seen on DLPFC. The individual negative peak FC had large individual differences, a large mean Euclidean distance, with the group mean FC peak: in all analyses, the distance between the individual peak and group mean FC peak was larger than 10mm, e.g. in the smallest distance occasion in depression dimension, mean = 11.78mm and SD = 4.60 and in this case, 61% of the participants had a distance larger than 10mm to the group mean FC peak. These results indicate that if use classical brain stimulation techniques and targets, at least 61% of the participants missed out on the most effective stimulation areas for depression treatment. Despite both alcohol misuse and depression showing connectivity to DLPFC from subcortical regions which were identified in the task fMRI, the connected areas are not overlapping with each other, indicating different functional networks behind the two dimensions.

Conclusion: Our findings of dissociable activation patterns to negative faces, together with their DLPFC connectivity patterns, have important implications for negative emotional theories underlying addiction, depression, and anxiety mechanisms. These findings are clinically relevant as the FC individual differences and reproducibility results can potentially guide neuromodulation techniques and targets for alcohol misuse and depressive symptoms.

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Conflict of interest: