Psychiatry Research 317 (2022) 114908

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Stimulating learning: A functional MRI and behavioral investigation of the effects of transcranial direct current stimulation on stochastic learning in schizophrenia

Natasza D. Orlov [a,b,c,1,*], Syed Ali Muqtadir [a,d,1], Hooman Oroojeni [e], Bruno Averbeck [f], John Rothwell [g], Sukhi S. Shergill [a,h]

[a] Cognition Schizophrenia Imaging Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
[b] Liu Lab, Athinoula A. Martinos Center for Biomedical Imaging Center, Massachusetts General Hospital, Charlestown, MA, USA
[c] Lab of Precision Brain Imaging, Department of Neuroscience, Medical University of South Carolina, Charleston, SC, USA
[d] Lahore University of Management and Sciences, Lon, Lahore, Pakistan
[e] Department of Computing, Goldsmiths College, London, United Kingdom
[f] Laboratory for Neuropsychology Section on Learning and Decision Making, National Institute of Mental Health Research, Bethesda, MD, United States
[g] Institute of Neurology, University College London, London, United Kingdom
[h] Kent and Medway Medical School, Canterbury, United Kingdom

ARTICLE INFO

Keywords:
Imaging
Schizophrenia
tDCS
Stochastic learning
Neuromodulation
Cognition
Cognitive deficits

ABSTRACT

Transcranial direct current stimulation (tDCS) of the medial prefrontal cortex (mPFC) is under clinical investigation as a treatment for cognitive deficits. We investigate the effects of tDCS over the mPFC on performance SSLT in individuals with schizophrenia, and the underlying neurophysiological effect in regions associated with learning values and stimulus-outcome relationships. In this parallel-design double-blind pilot study, 49 individuals with schizophrenia, of whom 28 completed a fMRI, were randomized into active or sham tDCS stimulation groups. Subjects participated in 4 days of SSLT training (days 1, 2, 14, 56) with tDCS applied at day-1, and during a concurrent MRI scan at day-14. The SSLT demonstrated a significant mean difference in performance in the tDCS treatment group: at day-2 and at day-56. Active tDCS was associated with increased insular activity, and reduced amygdala activation. tDCS may offer an important novel approach to modulating brain networks to ameliorate cognitive deficits in schizophrenia, with this study being the first to show a longer-term effect on SSLT.

1. Introduction

Schizophrenia is a complex psychotic disorder characterized by prominent positive (hallucinations and delusions), negative (social withdrawal and low motivation) symptoms, and cognitive (impaired attention and learning) deficits (Weickert et al., 2000). Over time it has become increasingly apparent that cognitive deficits are the most influential predictor of functional and clinical outcomes of individuals with schizophrenia (Addington and Addington, 2000; Green, 1996; Heaton et al., 2001). Cognitive deficits (CDs) have been linked to impairments in psychosocial interactions, problem-solving, and independent living skills (Green et al., 2000; McGurk et al., 2007). CDs in schizophrenia span multiple domains, including executive function, decision-making, and learning from feedback (Averbeck et al., 2011a; Dickinson and Harvey, 2009). Extant literature has established Working Memory (WM) as a central feature of schizophrenia and linked the dysfunction of areas like the medial Prefrontal Cortex (mPFC) and the left Dorsolateral Prefrontal Cortex (DLPFC) to WM impairments (Lett et al., 2014; Tripathi et al., 2018). Recent evidence suggests that the use of pharmacologic agents like 5-HT1A agonists (Wang et al., 2019) and more recently GlyT1 inhibitors (Fleishhacker et al., 2021) may show modest improvements in cognitive performance in patients with

* Corresponding author at: Cognition Schizophrenia Imaging Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom.
E-mail address: natasza.orlov@kcl.ac.uk (N.D. Orlov).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.psychres.2022.114908
Received 12 August 2021; Received in revised form 19 April 2022; Accepted 13 October 2022
Available online 14 October 2022

schizophrenia, however, at present, there are no approved pharmacological treatments for CDs. Even cognitive training - the most effective behavioral treatment - yields only small to medium range effect size improvements in CDs (Keshavan et al., 2014). Nonetheless, many people are unable to make use of these techniques.

With the suboptimal performance of pharmacological interventions for CDs, non-invasive brain stimulation (NIBS) has been put forth as a promising intervention, with the advantages of being relatively easy application and high patient acceptability due to benign side effects, along with low cost (Mondino et al., 2016; Papazova et al., 2018; Rushby et al., 2011). Additionally, some NIBS techniques, such as transcranial direct current stimulation (tDCS) allow for the application of stimulation during cognitive training; thus, permitting exploration of adjunct effects to the most effective treatment. tDCS represents a brain stimulation method whereby low current is applied through electrodes placed over the scalp; although the mechanisms of action are not fully understood, they are likely depending on endogenous synaptic plasticity, whereby the neurophysiological induction of long term potentiation and long term depression is mediated by GABAergic inhibition, modulation of glutamatergic NMDA receptors and glutamatergic neurotransmission (Kronberg et al., 2017; Nitsche and Paulus, 2011; Yavari et al., 2018).

There have been investigations of the use of tDCS to improve working memory and decision-making tasks (Minzenberg and Carter, 2012), and the positive results suggest that modulating the function of the mPFC offers a promising target for tDCS application in working memory and probabilistic learning performance. The mPFC has also been targeted to benefit individuals with schizophrenia on the n-back and weather prediction task (Nienow et al., 2016; Orlov et al., 2017a; Vercammen et al., 2011). However, more complex organized behavior is often dependent on sequential learning and learning from feedback – processes that require the integration of information from other cognitive processes (Averbeck et al., 2012), including working memory and decision making and hypothesis testing (Paulus et al., 2002). This learning is compromised in schizophrenia; with individuals performing significantly worse on decision making as compared to healthy controls, during a stochastic sequence-learning task (SSLT) (Averbeck et al., 2011a). Specifically, individuals with schizophrenia learned fewer correct button presses in the sequence than healthy controls, when they had to integrate stochastic feedback to determine the correct response.

Here, we proposed to examine the effects of tDCS on sequential learning, using the SSLT, which involves sensory-motor integration, decision-making, and learning from feedback.

Non-invasive stimulation including tDCS and TMS have been used to good effect as an intervention intending to remediate cognitive deficits across numerous brain disorders (Begemann et al., 2020). More recently, a meta-analysis by Narita et al. (2020) has shown a significant beneficial effect of prefrontal tDCS on working memory with a medium effect size. WM accuracy in particular has been shown to susceptible to modulation through prefrontal tDCS across a number of studies (Papazova et al., 2018; Schwippel et al., 2018; Meiron et al., 2021).

Our previous research suggests that anodal tDCS to the left mPFC can improve working memory performance, however, the improvements in cognitive performance are not always evident during online stimulation or immediately after (Orlov et al., 2017b), but enhanced after a consolidation period of 24 h. Furthermore, the data suggests that the modulatory effects of tDCS can also be observed within distal regions within the wider task-related networks, rather than being limited to the stimulation site (Keeser et al., 2011; Orlov et al., 2017b). Based on our previous findings, we hypothesized that active tDCS will improve learning rates on the SSLT, but only after a consolidation period.

Given what we know of the network involved in learning and the connectivity of the mPFC one would predict that the insula would be involved in learning from feedback and be involved during the SSLT (Averbeck et al., 2011b); specifically associated with learning values and stimulus-outcome relationships (Averbeck et al., 2011b). The mPFC has also been demonstrated to exert inhibitory effects on the orbitofrontal cortex (OFC)-amygdala pathway via feed-forward inhibition and is involved in stimulus-outcome learning (Chang and Ho, 2017), and mPFC tDCS has been shown to reduce amygdala reactivity in healthy controls with trait anxiety (Ironside et al., 2019). Schizophrenia is associated with reduced mPFC and insular activity (Uddin, 2015), and with increased reactivity of the amygdala, even to neutral stimuli (Potvin et al., 2016). Thus, at a network level, we anticipated active tDCS to increase brain activation underneath the stimulation site (F3 - mPFC), and also in the insula (Averbeck et al., 2011b) and consequently reduced activation of the amygdala (Ironside et al., 2019).

2. Methods

2.1. Participants

We recruited 49 right-handed individuals who met the criteria for the DSM-IV diagnosis of schizophrenia or schizoaffective disorder (American Psychiatric Association. and American Psychiatric Association. Task Force on DSM-IV., 1994) from the South London and Maudsley and the Oxleas NHS Trust, London United Kingdom; 28 participants were eligible and consented to undergo a functional MRI scan during the tDCS stimulation. All participants were on stable antipsychotic doses, defined as no more than 50% change in dosage in the last three months. Participants with a history of neurological disorder, head injury with a loss of consciousness, use of hypnotics, and alcohol/-substance abuse were excluded. All participants provided written consent. This study was approved by the Stanmore National Research Ethics Committee (REC number 11/LO/0248) and conducted in accordance with the Declaration of Helsinki.

2.2. Experiment design

Participants attended study visits on five separate days (Supp. Methods and Fig. 1); a baseline assessment followed by four days of cognitive training (Days 1, 2, 14, and 56). Clinical and neuropsychological assessments were completed during the baseline assessment using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and Cogstate Neurocognitive Battery. The Wechsler Abbreviated Scale of Intelligence (Matrix reasoning and vocabulary) (Wechsler, 1999) was used to assess participants' IQ (Supp. Figs. 1 and 1).

Illustration of the study protocol. A baseline assessment (B) was followed by four cognitive training days (days 1, 2, 14, and 56). Eight training sessions occurred (blue numbers 1–8), two on each of the days. tDCS was applied during training sessions 2 and 6, with neuroimaging occurring during the sixth session. Neuropsychological assessment was tested via Cogstate at the baseline and on Day 14 after the sixth session. The gray cylinder beside training session 6 represents fMRI scanning; the red 'lightning bolts' beside training sessions 2 and 6 represent tDCS application.

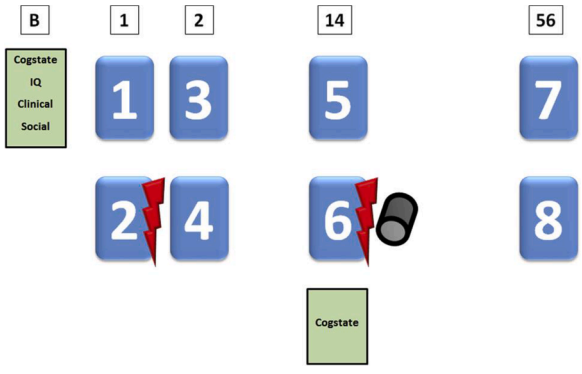

Fig. 1. Study protocol.

2.3. Randomization

Participants were randomly assigned to cognitive training and either active (n = 24) tDCS or sham (n = 25) stimulation using a 2:2 ratio randomization procedure stratified for smoking status and sex using STATA 12.1. Concealment of randomization assignment was done through the stimulator's study mode software.

2.4. Blinding

The tDCS was well tolerated and the most common side-effect observed was itching or tingling underneath the electrodes. This tolerability was also evidenced in insignificant differences in participants' accuracy in identifying their treatment group post tDCS ($\chi 2$=0.3; p = 0.85; $\chi 2$=0.42; p = 0.52)

2.5. Study design

During each study visit, participants completed two cognitive training sessions separated by 45 min. Thus, each participant completed 8 cognitive training sessions in total. During sessions 2 and 6 participants received concomitant active or sham tDCS, and those who were eligible and willing underwent an fMRI scan during session 6. Following session 6 participants completed a CogState assessment after a 45 min break. tDCS was applied during the second session of training days 1 and 14. This allowed us to obtain baseline task performance and ensure that tDCS was applied when the task was familiar to the participants, thus reducing any novelty effect and initial attentional variability in task performance. Additionally, pairing the stimulation with the second session allowed for the assessment of learning retention after a short overnight period, and longer periods, independent of stimulation itself.

2.6. Cognitive training

The cognitive training sessions were comprised of the SSLT, a working memory task (n-back), and an implicit learning task (language learning). The latter two have been reported elsewhere (Orlov et al., 2017a, 2017b).

For the SSLT task, the participants were asked to learn a sequence of 4 button presses, using their left and right index fingers to press the left and right arrow keyboard buttons. Each trial consisted of one of six possible sequences with an equal number of L and R button presses namely LLRR, RRLL, RLRL, LRLR, LRRL, and RLLR. The participants were not informed about the order of presses in any of the sequences.

At the start of each trial, participants were presented with an outline of a circle with a number as a cue to perform a button press. For each press, the participants were given feedback in the form of the circle outline being filled green if the button press was correct, or red if it was incorrect. Following the feedback, the circle outline was presented again to cue the next response. This was repeated four times to make up a trial of 4 button presses (Fig. 2). Stochastic feedback was provided after each button press and was erroneous in 15% of cases, i.e., the circle outline was filled with red for correct responses and green for incorrect responses. Participants were informed about the misleading feedback.

During each training session, participants learned a set of 6 sequences (blocks) of 4 button presses. Participants were informed when the blocks changed, and a new sequence needed to be learned. In order to successfully move on to the next block, the participants needed to execute the correct order of button presses four times with at least two being consecutive. If the participant failed to learn the sequence by 18 trials, they were moved onto the next block.

2.7. fMRI acquisition

Functional magnetic resonance images were acquired on a Discovery MR750 3T scanner (Supp. Methods).

2.8. tDCS protocol

The tDCS was administered offline, due to a pseudo-randomization of cognitive training during session 2 and session 6, whereby the working memory and language learning tasks were trained online (Orlov et al., 2017a, 2017b), and the probabilistic task was trained offline. Such a design allowed for assessing the effects of tDCS without introducing the additional confound of differential online/offline effects on task performance. tDCS stimulation was provided using an Eldith

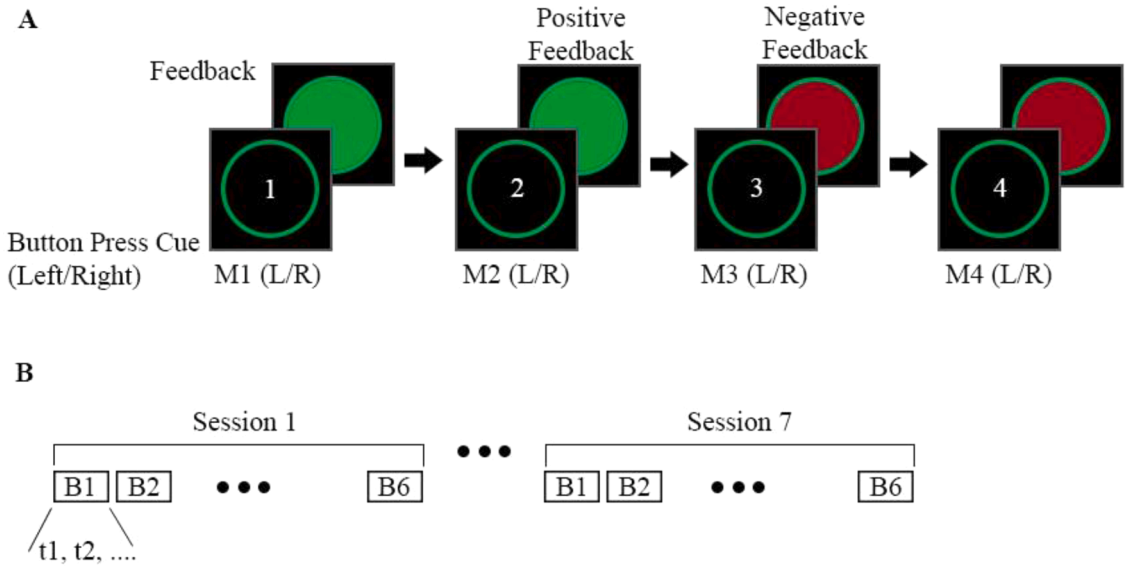

Fig. 2. Sequential stochastic learning task
(A) Participants executed a sequence of four button presses (M1, M2, M3, and M4) using combinations of left and right button presses. At the start of each trial, participants were presented with an outline circle with a number as a cue to perform a button press. After each button press, they were given feedback about whether or not they were correct and were informed that 15% of the feedback will be misleading **(B)** Participants completed six sequences during each session (B1, B2, …, B6) within which they responded to each trial (t1, t2, …). Participants had to learn and then execute the sequence correctly four times, at least two consecutive, before advancing to the next sequence in the set.

DC-Stimulator (NeuroConn GmbH, Germany). The anode (35cm2) was placed over the left mPFC (F3) and the cathode (35cm2) over the right supraorbital area under the 10–20 international system for EEG electrode placement. The stimulation was provided for 30 min at 2 mA with 30 s of ramping up and down of current at the start and end of stimulation. Only 30 s of stimulation was applied for the sham condition with the same ramping conditions.

The tDCS protocol during the MRI phase was identical except for the use of magnetic field compatible electrodes pre-gelled with EEG paste.

The same tDCS protocol was utilized for the functional MRI phase of the study including duration, strength, and electrode placement with the exception being the use of magnetic field compatible electrodes pre-gelled with EEG paste.

2.9. Task data analysis

Due to the inherent task difficulty, the analysis was based on changes in the average learning rate during each session. The learning rate for each sequence was calculated by subtracting the number of correct responses between the last trial and first trial where feedback was available (2nd trial of each sequence). This assessed the learning from feedback for each sequence, including not fully learned sequences. The mean of all sequences for each session was calculated and the data analysis was carried out using a maximum likelihood-random effect multilevel model (MLREM). The framework for model fitting and testing was adopted from Singer and Willett (Singer and Willett, 2003) (Supp. Methods). The final model included task-relevant outcomes, learning rate, during tDCS application (session 2), short-term retention following tDCS application (session 3), and long-term retention (session 7), controlled for baseline performance (session 1), with fixed categorical effects for group (1=active tDCS, 0=sham tDCS) and time (1–4) and an interaction of time and group (exploratory analysis of the impact of working memory task performance on the SSLT performance Supp. Material).

CogState results have been reported previously thus we refer the reader to Orlov et al. (2017b).

Stata (StataCorp, 2015) was used to conduct the analyses. T-tests and chi-squared tests were used to investigate group differences in the baseline demographic data (see Table 1).

2.10. Functional MRI analysis

All data were pre-processed and analyzed using Statistical Parametric Mapping 12 (SPM12) (www.fil.ion.ucl.ac.uk/spm) in MATLAB R2017a (https://uk.mathworks.com/). Functional data were spatially realigned to the mean image from the series, then resliced. Spatial normalization into Montreal Neurological Institute (MNI) stereotactic space was carried out by diffeomorphic anatomical registration using exponential lie algebra (DARTEL) using a study-specific template generated from all participants' structural images (Ashburner, 2007)

The subject-specific model included regressors encoding the predicted blood oxygen-dependent (BOLD) signal for two separate conditions, experimental and control; the fixation cross was left unmodeled. Participants' head movements were modeled as six nuisance regressors. The contrast parameters estimated for the condition of interest (experimental > control) was taken forward to a region of interest (ROI) analysis, with a two-sample test (active/sham tDCS). The ROI analysis was based on the insula and the amygdala, as both regions are involved in choice behavior and sequential decision making with stochastic feedback (Averbeck et al., 2011b; Yizhar and Klavir, 2018). The mask was created in Pickatlas (Wake Forest University, 2020) within SPM for the left hemisphere only, consistent with anodal tDCS application. Results were considered significant if they had a p-value of <0.05 following peak-level family-wise error correction (FWE). To investigate the effects of anodal tDCS at the stimulation site, we used the same mPFC as in our previous study, which was also created in Pickatlas (Supp. Fig. 3a and b) (Orlov et al., 2017a).

Table 1
Demographic and clinical information of behavioral study participants.

	Real		Sham			
N	21		18			
	Mean	**SD**	**Mean**	**SD**	***t*-value**	***p*-value**
Age (Years)	34.5	9.5	38.4	9.2	1.3	0.20
Duration of Illness (Years)	11.5	7.6	16.7	8.4	1.4	0.17
WASI[a]	98	16.7	92	17.8	−0.98	0.33
PANSS Positive Scale[b]	13.5	4.1	12.4	3.5	−0.93	0.36
PANSS Negative Scale	13.4	4.8	14.7	5.2	0.78	0.44
PANSS General Scale	27.4	5.8	27.4	7.6	0.04	0.97
PANSS Total	53.6	12.6	53.9	11.1	0.06	0.95
Chlo_Equiv[c]	559	300.6	545.6	297	−0.14	0.89
Gender	3 (F)[d]		4 (F)			0.52
1st Gen Antipsychotic	2		2			0.96
2nd Gen Antipsychotic	18		17			

[a] Wechsler Abbreviated Scale of Intelligence.
[b] Positive and Negative Syndrome Scale.
[c] Chlorpromazine Equivalent Units.
[d] Female.

3. Results

Behavioral data for 39 and neuroimaging data from 25 subjects was analyzed.

3.1. Sequential stochastic learning task

Data from ten participants were excluded, three participants' data were excluded as they failed to attend to the task, responding in a perseverative pattern throughout all task assessments; seven participants' data were excluded due to technical problems leading to missing data for at least four assessments points. Analysis of the SSLT demonstrated no differences in learning rate at baseline (session 1: $b = -0.29$, 95% CI −0.65 - 0.07; $p = 0.112$) and during the acute stimulation (session 2: $b = 0.20$, 95% CI −0.26 – 0.65; $p = 0.405$). The interaction of group and time were found to be significant for next day retention (session 3: $b = 0.47$, 95% CI 0.01 - 0 0.93; $p = 0.046$) and for longer-term retention (session 7: $b = 0.50$, 95% CI 0.02 - 0.97; $p = 0.040$), with the active tDCS group performing better than the sham tDCS group (Fig. 3).

Average performance on the SSLT during study assessments. S-session, higher value indicates better performance. Error bars represent standard errors. # - significant difference

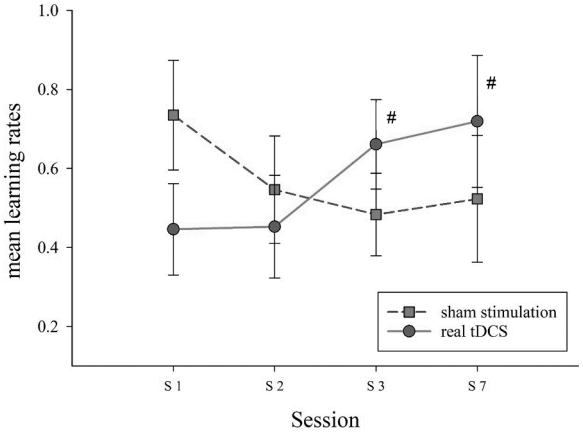

Fig. 3. Learning rates on sequential stochastic learning task.

3.2. Functional MRI analysis

28 went through fMRI scanning procedures. Data from three participants were excluded, one marked atrophy, two due to technical problems with incomplete imaging acquisition thus leaving 14 participants in the active and 11 in the sham stimulation group for analysis (Table 2).

The SSLT task was associated with brain activation in bilateral inferior frontal gyri, insula, superior temporal gyri, and occipital cortex, in addition to bilateral thalamus and midbrain. (Supp. Fig. 2, Supp. Table 1).

We found significantly higher activation in the active tDCS group, relative to sham tDCS, in the insula x, y, $z = -34, 6, 8$; [$t(1,23) = 2.81$ ($t_{peak} = 4.23$); $K_E = 356$, $P_{FWE} = 0.039$, z-score$_{peak} = 3.60$ FWE]; and significantly lower activation in the amygdala x, y, $z = -22, -4, 24$; [$t(1,23) = 2.81$ ($t_{peak} = 4.22$); $K_E = 14$, $P_{FWE} = 0.040$, z-score$_{peak} = 3.59$ FWE]. There were no significant differences in brain activity underneath the site of the anodal tDCS electrode.

4. Discussion

This is the first study to combine behavioral and fMRI methods to understand the effect of tDCS on probabilistic learning in individuals with schizophrenia. In line with our hypothesis, we found that active tDCS was associated with improved performance on the SSLT task, however, this was evident after a consolidation phase 24 h after the tDCS administration. Improved performance was maintained at the follow-up visit, suggesting a sustained effect on learning. NIBS application was associated with increased brain activation in the insula, and reduced activation in the amygdala in the active tDCS group. Contrary to our hypothesis there was no significant effect of tDCS on the cortex underneath the anode.

Our data demonstrates that improvement in probabilistic learning requires a consolidation period. These results are consistent with previous findings which have shown that despite a neurophysiological effect of anodal tDCS (Orlov et al., 2017b), the behavioral effects benefit from the presence of a consolidation period (Orlov et al., 2017b), especially in tasks involving holding and manipulation of feedback information. Pharmacological studies demonstrate that anodal tDCS effects are at least partially mediated by NMDA receptors. NMDA receptors affect neuroplasticity and learning by promoting long-term potentiation of neuronal networks and changing synaptic strength (Malenka and Bear, 2004). Rodent studies have demonstrated how anodal tDCS can recruit LTP mechanisms when hippocampal synapses are stimulated and can stimulate α1 adrenergic receptors on astrocytes to increase intracellular calcium ion concentrations while in humans increased intracellular Ca ion concentrations resulting from tDCS implicate astrocytes in LTP action (Yamada and Sumiyoshi, 2021).

Longer-term effects of tDCS have been demonstrated by our group (Orlov et al., 2017b) and others (Cohen-Kadosh et al., 2010; Reis et al., 2009) impacting working memory, motor, and numerical skill acquisition. However, other studies have found no effect beyond stimulation (Ditye et al., 2012). The different results may be related to differences in key variables including stimulation time, site of anodal and cathodal electrode placement, and clinical features of the samples under study.

We observed changes in activation during tDCS within a task-related network – with regions including the insula and amygdala. If one assumes that the BOLD response indexes local field potential change reflecting synaptic activity (Attwell and Iadecola, 2002), then tDCS might increase the probability that a synaptic input will generate a response in an output neuron. Since most energy is consumed synaptically, rather than by action potentials (Attwell and Iadecola, 2002), it is likely that tDCS simply reduces the threshold for some of the output neurons and increases the effectiveness of processing—rendering the underlying neuronal populations more likely to respond in line with task-related demands.

This is supported by data from our group and others demonstrating that anodal tDCS effects are observable in task-relevant functionally connected regions within the stimulated hemisphere (Orlov et al., 2017a). However, we did not find an effect underneath the anode. We have observed a direct effect during a working memory task (n-back) but not during inhibitory control assessment (Stroop) (Orlov et al., 2017b). This lack of activation underneath the anode might be explained by differential network recruitment associated with task execution, or by the fact that the SSLT task was administered offline. However, a recent offline tDCS fMRI study suggests, that in healthy participants, neurophysiological effects of offline tDCS are observed both underneath the anode as well as in a task-related network (Sallard et al., 2018). Thus, it is possible that tDCS effects on pathological brain/neuronal networks are evident across wider-task relevant neuronal networks, while not being necessarily evident underneath the active electrode, and might be affected by online/offline delivery (Orlov et al., 2017a). Yamada and Sumiyoshi (2021) provides further evidence for this in their review, positing the extension of tDCS effects beyond the stimulation site may occur through the action of monoamine transmitters like dopamine while modulation of the glutamate/GABA balance by anodal tDCS may alter functional connectivity between disparate brain regions.

Probabilistic learning occurs as a result of a combinatorial effect of more than one cognitive process including but not limited to working memory, attention, and sensory-motor integration (Averbeck et al., 2011b; Paulus et al., 2002). Prior research demonstrates that deficits in probabilistic learning in patients with schizophrenia are associated with aberrant insula and amygdala activity (White et al., 2010), regions associated with salience processing. The orbito- and medial prefrontal cortex have both afferent and efferent connections with the insula and amygdala (Augustine, 1996). The mechanisms through which tDCS influences activation are similar to that of long-term potentiation, both being facilitated by NMDA receptor function (Liebetanz, 2002). The left insula has extensive structural connections (via the major association pathways i.e. the arcuate and uncinate fasciculus, as well as short u-shaped fibers) with the orbito-frontal and mPFC through which it is thought to be involved in higher-order cognitive processes, supporting attention and executive function (Mufson et al., 1981; Nomi et al., 2018). Increased activation of the insula in the active tDCS group is likely to arise as a consequence of these connections between the insula and the mPFC (Cauda et al., 2012).

Research in rodents shows that both pharmacological (NMDA administration) and electrical stimulation of the mPFC exerted inhibitory modulation of the left OFC on the amygdala via a feed-forward pathway (Chang and Ho, 2017). Conversely, activation lOFC exerts an

Table 2
Demographic and clinical information of scanned participants.

	Real		Sham			
N	14		11			
	Mean	SD	Mean	SD	*t*-value	*p*-value
Age (Years)	33.3	10.1	36.7	9.7	0.86	0.40
Education (Years)	12.8	2.4	13.2	2.6	0.29	0.77
Duration of Illness (Years)	10.6	7.3	14	9.5	1.00	0.32
WASI[a]	103	12.5	103	11.0	−0.28	0.78
PANSS Positive Scale[b]	14.7	3.9	13.5	3.5	−0.83	0.41
PANSS Negative Scale	15.2	4.5	15.7	4.4	0.29	0.78
PANSS General Scale	28.4	4.7	26.7	6.6	−0.76	0.46
PANSS Total	58.6	10.3	55.9	11.1	−0.57	0.57
Chlo_Equiv[c]	416	299	331	151	−0.85	0.40
Gender	3 (F)[d]		4 (F)			0.41
1st Gen Antipsychotic	1		2			0.40
2nd Gen Antipsychotic	13		9			

[a] Wechsler Abbreviated Scale of Intelligence,.
[b] Positive and Negative Syndrome Scale,.
[c] Chlorpromazine Equivalent Units,.
[d] Female.

inhibitory modulatory effect on the mPFC and amygdala. Since we have applied tDCS to the mPFC, such inhibitory processes could be potentially induced by heterosynaptic plasticity, or via multi-synaptic connections between the mPFC and OFC (Chang and Ho, 2017). In line with this, our data suggests that tDCS reduced the threshold for some neuron populations and potentially increased the effectiveness of processing in more distant task-relevant brain regions.

The insula activation is particularly interesting as the insula and the (lateral) prefrontal cortex are co-activated during cognitive control tasks, indexing attention, and response selection. More specifically, the insula has been found to be involved in the conscious perception of error (Cauda et al., 2012, 2011; Klein et al., 2013; Vercelli et al., 2016; Wylie and Tregellas, 2010) and a number of brain imaging studies across several task domains have suggested that the insula is activated whenever an exogenous sensory stimulus is considered as salient or an endogenous perceptual task is challenging and may require the individual to change his/her behavior in an adaptive way (Sterzer and Kleinschmidt, 2010). This is supported by data from the oddball paradigm suggesting that it plays a role in the detection of novel salient stimuli, and is correlated with subjective salience influenced by cognitive factors (Uddin, 2015). Prior findings suggest that cognitive dysfunction in schizophrenia is associated with a failure of effective integration in multi-modal structures, including the insula and mPFC (Palaniyappan et al., 2013). A recent meta-analysis of neuroimaging studies demonstrated substantial dysconnectivity in the schizophrenia brain including the insula (Goodkind et al., 2015). Reduced connectivity between the cognitive networks and the insula, as well as impaired insula functional connectivity was associated with inter-individual variation in cognitive deficits. It has been suggested that during SSLT, the insula facilitates task-related processing by updating feedback-based probability information (Averbeck et al., 2011b). Thus, in our study, the increased activation of the insula during tDCS provides a link between working memory- and attention-related problems solving and salience systems (Clos et al., 2014; Nelson et al., 2010), optimizing probabilistic learning by initiating appropriate transient control signals focusing attention on relevant external stimuli (Menon and Uddin, 2010).

The amygdala, along with the prefrontal cortex, has been implicated in reward-associated learning, goal-directed behavior, and decision making (Hampton et al., 2007). Both structures couple exteroceptive sensory information with interceptive information of conditioned or learned cues (Bechara et al., 2006). Abnormal amygdala activity has been associated with deficits in executive functioning. In schizophrenia, bidirectional information sharing between the medial frontal cortex (MFC) and the amygdala is significantly reduced (Palaniyappan et al., 2013).

Research in primates suggests that lesions to the amygdala produce increased MFC and decreased OFC processing, as well as a decrease in sensitivity to errors (Averbeck and Costa, 2017). Specifically, amygdala lesioned animals were consistently impaired in the degree to which they tended to learn from negative feedback to guide subsequent choices. In humans, lesions in the amygdala altered reward processing in the ventral mPFC and OFC during the learning and reversal of stimulus-reward associations (Hampton et al., 2007). This suggests that amygdala dysfunction alters the evaluation and encoding of stimuli, rather than the reward, and has an impact on choice behavior. A potential mechanism may relate to the inability to update prefrontal-stimulus-outcome associations. Certainly, there is evidence that the amygdala plays a role in prediction error and value expectancy. In schizophrenia, amygdala reactivity is a well-established phenomenon, including to neutral stimuli (Potvin et al., 2016). The prefrontal amygdala pathway may be thus critical to the integration of stimulus-specific outcomes with more sophisticated goal-directed actions (Hampton et al., 2007). In individuals with schizophrenia, anodal tDCS to the medial frontal cortex normalized event-related negativity, a putative electrophysiological signature of the prediction error signal in the brain, during a go/no go task (Reinhart et al., 2015). Increased amygdala and orbitofrontal activity has been associated with increased sensitivity to reward, associated with deficient prediction error signal, and suggested to be an endophenotype in another psychotic disorder, namely Bipolar I disorder (Linke et al., 2012). Thus our findings of the decreased amygdala activity might represent top-down regulation of feedback processing via the OFC (Chang and Ho, 2017), resulting in improved learning in the active-tDCS group.

4.1. Limitations

Firstly, tDCS was not administered with every training session; repeated administration might have yielded stronger effects. However, the study design was optimized to assess retention. It is possible that tDCS does not have the same impact on a probabilistic learning task training performed alone when compared to being part of a series of cognitive tasks (see Orlov et al. 2017a, 2017b). However, we minimized any systematic order effects by pseudo-randomizing the task order, and future studies could usefully scope one task at a time. Additionally, while this experimental medicine study used a multi-session design in its application of the tDCS intervention based on existing literature (Kostova et al., 2020), no recognized standard treatment regimen guidelines currently exist. A standardization effort would go a long way towards helping us better understand tDCS effects.

This study is also limited in the absence of any imaging data collected before tDCS application, which would have enhanced within-subject analysis of active tDCS. Nonetheless, we used a double-blind design and the blinding was robust as evidenced by participants not being able to discriminate reliably the active/sham group assignment.

Finally, this study is limited by its modest sample size but is one of the first studies that applied offline tDCS during fMRI in schizophrenia and found that tDCS can influence brain dynamics during probabilistic learning.

In conclusion, we have demonstrated that active tDCS of the left medial prefrontal cortex brings about a significant level of activation in the insula and a decrease of activation in the amygdala during a probabilistic learning task, as well as improvement in task performance following a consolidation period. Together with results from our previous study, the use of tDCS has resulted in improvement of attention, working memory, and probabilistic learning suggesting that tDCS has the potential to become part of existing interventions targeting cognitive deficits in schizophrenia.

Funding source

This study represents independent research part funded by the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

ClinicalTrials.gov Identifier

NCT04184830 (URL: https://clinicaltrials.gov/ct2/show/NCT04184830?term=NCT04184830&draw=2&rank=1);Title: Improving Cognition in Schizophrenia Using Non-invasive Brain Stimulation

CRediT authorship contribution statement

Natasza D. Orlov: Conceptualization, Methodology, Investigation, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Syed Ali Muqtadir:** Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Hooman Oroojeni:** Methodology, Formal analysis, Writing – review & editing. **Bruno Averbeck:** Methodology, Resources,

Formal analysis, Writing – review & editing, Project administration. **John Rothwell:** Methodology, Resources, Writing – review & editing, Project administration. **Sukhi S. Shergill:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors report no potential conflicts of interest, financial or otherwise.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2022.114908.

References

Addington, J., Addington, D., 2000. Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. Schizophr. Res. 44, 47–56. https://doi.org/10.1016/S0920-9964(99)00160-7.

American Psychiatric Association., American Psychiatric Association. Task Force on DSM-IV., 1994. Diagnostic and Statistical Manual of Mental Disorders : DSM-IV. American Psychiatric Association.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. Neuroimage 38, 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007.

Attwell, D., Iadecola, C., 2002. The neural basis of functional brain imaging signals. Trends Neurosci. 25, 621–625. https://doi.org/10.1016/S0166-2236(02)02264-6.

Augustine, J., 1996. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res. Rev. 22, 229–244. https://doi.org/10.1016/S0165-0173(96)00011-2.

Averbeck, B.B., Costa, V.D., 2017. Motivational neural circuits underlying reinforcement learning. Nat. Neurosci. 20, 505–512. https://doi.org/10.1038/nn.4506.

Averbeck, B.B., Evans, S., Chouhan, V., Bristow, E., Sukhwinder, S., 2012. Probabilistic learning and inference in schizophrenia 127, 115–122. 10.1016/j.schres.2010.08.009.Probabilistic.

Averbeck, B.B., Evans, S., Chouhan, V., Bristow, E., Sukhwinder, S., Shergill, S.S., Sukhwinder, S., 2011a. Probabilistic learning and inference in schizophrenia. Schizophr. Res. 127, 115–122. https://doi.org/10.1016/j.schres.2010.08.009.

Averbeck, B.B., Kilner, J., Frith, C.D., 2011b. Neural correlates of sequence learning with stochastic feedback. J. Cogn. Neurosci. 23, 1346–1357. https://doi.org/10.1162/jocn.2010.21436.

Bechara, A., Damasio, H., Damasio, A.R., 2006. Role of the amygdala in decision-making. Ann. N. Y. Acad. Sci. 985, 356–369. https://doi.org/10.1111/j.1749-6632.2003.tb07094.x.

Begemann, M.J., Brand, B.A., Ćurčić-Blake, B., Aleman, A., Sommer, I.E., 2020. Efficacy of non-invasive brain stimulation on cognitive functioning in brain disorders: a meta-analysis. Psychol. Med. 50 (15), 2465–2486.

Cauda, F., Costa, T., Torta, D.M.E., Sacco, K., D'Agata, F., Duca, S., Geminiani, G., Fox, P. T., Vercelli, A., 2012. Meta-analytic clustering of the insular cortex. Neuroimage 62, 343–355. https://doi.org/10.1016/j.neuroimage.2012.04.012.

Cauda, F., D'Agata, F., Sacco, K., Duca, S., Geminiani, G., Vercelli, A., 2011. Functional connectivity of the insula in the resting brain. Neuroimage 55, 8–23. https://doi.org/10.1016/j.neuroimage.2010.11.049.

Chang, C., Ho, T., 2017. Inhibitory modulation of medial prefrontal cortical activation on lateral orbitofrontal cortex-amygdala information flow. J. Physiol. 595, 6065–6076. https://doi.org/10.1113/JP274568.

Clos, M., Rottschy, C., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2014. Comparison of structural covariance with functional connectivity approaches exemplified by an investigation of the left anterior insula. Neuroimage 99, 269–280. https://doi.org/10.1016/J.NEUROIMAGE.2014.05.030.

Cohen Kadosh, R., Soskic, S., Iuculano, T., Kanai, R., Walsh, V., 2010. Modulating neuronal activity produces specific and long-lasting changes in numerical competence. Curr. Biol. 20, 2016–2020. https://doi.org/10.1016/j.cub.2010.10.007.

Dickinson, D., Harvey, P.D., 2009. Systemic hypotheses for generalized cognitive deficits in schizophrenia: a new take on an old problem. Schizophr. Bull. 35, 403–414. https://doi.org/10.1093/schbul/sbn097.

Ditye, T., Jacobson, L., Walsh, V., Lavidor, M., 2012. Modulating behavioral inhibition by tDCS combined with cognitive training. Exp. Brain Res. 219, 363–368. https://doi.org/10.1007/s00221-012-3098-4.

Fleischhacker, W.W., Podhorna, J., Gröschl, M., Hake, S., Zhao, Y., Huang, S., Pollentier, S., 2021. Efficacy and safety of the novel glycine transporter inhibitor BI 425809 once daily in patients with schizophrenia: a double-blind, randomised, placebo-controlled phase 2 study. Lancet Psychiatry 8 (3), 191–201.

Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., Ortega, B.N., Zaiko, Y.V., Roach, E.L., Korgaonkar, M.S., Grieve, S.M., Galatzer-Levy, I., Fox, P.T., Etkin, A., 2015. Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry 72, 305. https://doi.org/10.1001/jamapsychiatry.2014.2206.

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? [see comments] Am. J. Psychiatry 153, 321–330. https://doi.org/10.1111/j.1530-0277.2006.00335.x.

Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia : are we measuring the right stuff? : psychosocial treatment for schizophrenia. Schizophr. Bull. 26, 119–136.

Hampton, A.N., Adolphs, R., Tyszka, J.M., O'Doherty, J.P., 2007. Contributions of the amygdala to reward expectancy and choice signals in human prefrontal cortex. Neuron 55, 545–555. https://doi.org/10.1016/j.neuron.2007.07.022.

Heaton, R.K., Gladsjo, J.A., Palmer, B.W., Kuck, J., Marcotte, T.D., Jeste, D.V., 2001. Stability and course of neuropsychological deficits in schizophrenia 315. Arch. Gen. Psychiatry 58, 24–32.

Ironside, M., Browning, M., Ansari, T.L., Harvey, C.J., Sekyi-Djan, M.N., Bishop, S.J., Harmer, C.J., O'Shea, J., 2019. Effect of prefrontal cortex stimulation on regulation of amygdala response to threat in individuals with trait anxiety. JAMA Psychiatry 76, 71. https://doi.org/10.1001/jamapsychiatry.2018.2172.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.

Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., Brunelin, J., Moller, H.-J., Reiser, M., Padberg, F., 2011. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J. Neurosci. 31, 15284–15293. https://doi.org/10.1523/JNEUROSCI.0542-11.2011.

Keshavan, M.S., Vinogradov, S., Rumsey, J., Sherrill, J., Wagner, A., 2014. Cognitive training in mental disorders: update and future directions. Am. J. Psychiatry 171, 510–522. https://doi.org/10.1176/appi.ajp.2013.13081075.

Klein, T.A., Ullsperger, M., Danielmeier, C., 2013. Error awareness and the insula: links to neurological and psychiatric diseases. Front. Hum. Neurosci. 7, 1–14. https://doi.org/10.3389/fnhum.2013.00014.

Kostova, R., Cecere, R., Thut, G., Uhlhaas, P.J., 2020. Targeting cognition in schizophrenia through transcranial direct current stimulation: a systematic review and perspective. Schizophr. Res. 220, 300–310.

Kronberg, G., Bridi, M., Abel, T., Bikson, M., Parra, L.C., 2017. Direct current stimulation modulates LTP and LTD: activity dependence and dendritic effects. Brain Stimul. 10, 51–58. https://doi.org/10.1016/j.brs.2016.10.001.

Lett, T.A., Voineskos, A.N., Kennedy, J.L., Levine, B., Daskalakis, Z.J., 2014. Treating working memory deficits in schizophrenia: a review of the neurobiology. Biol. Psychiatry 75 (5), 361–370.

Liebetanz, D., 2002. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain 125, 2238–2247. https://doi.org/10.1093/brain/awf238.

Linke, J., King, A.V., Rietschel, M., Strohmaier, J., Hennerici, M., Gass, A., Meyer-Lindenberg, A., Wessa, M., 2012. Increased medial orbitofrontal and amygdala activation: evidence for a systems-level endophenotype of bipolar i disorder. Am. J. Psychiatry 169, 316–325. https://doi.org/10.1176/appi.ajp.2011.11050711.

Malenka, R.C., Bear, M.F., 2004. LTP and LTD: an Embarrassment of Riches. Neuron 44, 5–21. https://doi.org/10.1016/J.NEURON.2004.09.012.

McGurk, S.R., Twamley, E.W., Sitzer, D.I., McHugo, G.J., Mueser, K.T., 2007. A meta-analysis of cognitive remediation in schizophrenia. Am. J. Psychiatry 164 (12), 1791–1802. https://doi.org/10.1176/appi.ajp.2007.07060906.

Meiron, O., David, J., Yaniv, A., 2021. Left prefrontal transcranial direct-current stimulation reduces symptom-severity and acutely enhances working memory in schizophrenia. Neurosci. Lett. 755, 135912.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214, 655–667. https://doi.org/10.1007/s00429-010-0262-0.

Minzenberg, M.J., Carter, C.S., 2012. Developing treatments for impaired cognition in schizophrenia. Trends Cogn. Sci. 16, 35–42. https://doi.org/10.1016/j.tics.2011.11.017.

Mondino, M., Jardri, R., Suaud-Chagny, M.F., Saoud, M., Poulet, E., Brunelin, J., 2016. Effects of fronto-temporal transcranial direct current stimulation on auditory verbal hallucinations and resting-state functional connectivity of the left temporo-parietal junction in patients with schizophrenia. Schizophr. Bull. 42, 318–326. https://doi.org/10.1093/schbul/sbv114.

Mufson, E.J., Mesulam, M.-.M., Pandya, D.N., 1981. Insular interconnections with the amygdala in the rhesus monkey. Neuroscience 6, 1231–1248. https://doi.org/10.1016/0306-4522(81)90184-6.

Narita, Z., Stickley, A., DeVylder, J., Yokoi, Y., Inagawa, T., Yamada, Y., Sumiyoshi, T., 2020. Effect of multi-session prefrontal transcranial direct current stimulation on cognition in schizophrenia: a systematic review and meta-analysis. Schizophr. Res. 216, 367–373.

Nelson, S.M., Dosenbach, N.U.F., Cohen, A.L., Wheeler, M.E., Schlaggar, B.L., Petersen, S. E., 2010. Role of the anterior insula in task-level control and focal attention. Brain Struct. Funct. 214, 669–680. https://doi.org/10.1007/s00429-010-0260-2.

Nienow, T.M., MacDonald, A.W., Lim, K.O., 2016. TDCS produces incremental gain when combined with working memory training in patients with schizophrenia: a proof of concept pilot study. Schizophr. Res. 172, 218–219. https://doi.org/10.1016/j.schres.2016.01.053.

Nitsche, M.A., Paulus, W., 2011. Transcranial direct current stimulation - Update 2011. Restor. Neurol. Neurosci. 29, 463–492. https://doi.org/10.3233/RNN-2011-0618.

Nomi, J.S., Schettini, E., Broce, I., Dick, A.S., Uddin, L.Q., 2018. Structural connections of functionally defined human insular subdivisions. Cereb. Cortex 28, 3445–3456. https://doi.org/10.1093/cercor/bhx211.

Orlov, Natasza D, O'Daly, O., Tracy, D.K., Daniju, Y., Hodsoll, J., Valdearenas, L., Rothwell, J., Shergill, S.S., 2017a. Stimulating thought: a functional MRI study of

transcranial direct current stimulation in schizophrenia. Brain 140, 2490–2497. https://doi.org/10.1093/brain/awx170.
Orlov, Natasza D., Tracy, D.K., Joyce, D., Patel, S., Rodzinka-Pasko, J., Dolan, H., Hodsoll, J., Collier, T., Rothwell, J., Shergill, S.S., 2017b. Stimulating cognition in schizophrenia: a controlled pilot study of the effects of prefrontal transcranial direct current stimulation upon memory and learning. Brain Stimul. 10, 560–566. https://doi.org/10.1016/J.BRS.2016.12.013.
Palaniyappan, L., Simmonite, M., White, T.P., Liddle, E.B., Liddle, P.F., 2013. Neural primacy of the salience processing system in schizophrenia. Neuron 79, 814–828. https://doi.org/10.1016/j.neuron.2013.06.027.
Papazova, I., Strube, W., Becker, B., Henning, B., Schwippel, T., Fallgatter, A.J., Padberg, F., Palm, U., Falkai, P., Plewnia, C., Hasan, A., 2018. Improving working memory in schizophrenia: effects of 1 mA and 2 mA transcranial direct current stimulation to the left DLPFC. Schizophr. Res. 202, 203–209. https://doi.org/10.1016/j.schres.2018.06.032.
Paulus, M.P., Hozack, N.E., Zauscher, B.E., Frank, L., Brown, G.G., McDowell, J., Braff, D. L., 2002. Parietal dysfunction is associated with increased outcome-related decision-making in schizophrenia patients. Biol. Psychiatry 51 (12), 995–1004. https://doi.org/10.1016/S0006-3223(01)01358-0.
Potvin, S., Tikàsz, A., Mendrek, A., 2016. Emotionally neutral stimuli are not neutral in schizophrenia: a mini review of functional neuroimaging studies. Front. Psychiatry 7, 115. https://doi.org/10.3389/fpsyt.2016.00115.
Reinhart, R.M.G., Zhu, J., Park, S., Woodman, G.F., 2015. Synchronizing theta oscillations with direct-current stimulation strengthens adaptive control in the human brain. Proc. Natl. Acad. Sci. USA 112, 9448–9453. https://doi.org/10.1073/pnas.1504196112.
Reis, J., Schambra, H.M., Cohen, L.G., Buch, E.R., Fritsch, B., Zarahn, E., Celnik, P.A., Krakauer, J.W., 2009. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc. Natl. Acad. Sci. 106, 1590–1595. https://doi.org/10.1073/pnas.0805413106.
Rushby, J.A., Vercammen, A., Loo, C., Short, B., Weickert, C.S., Weickert, T.W., 2011. Frontal and parietal contributions to probabilistic association learning. Cereb. Cortex 21, 1879–1888. https://doi.org/10.1093/cercor/bhq255.
Sallard, E., Mouthon, M., De Pretto, M., Spierer, L., 2018. Modulation of inhibitory control by prefrontal anodal tDCS: a crossover double-blind sham-controlled fMRI study. PLoS ONE 13, e0194936. https://doi.org/10.1371/journal.pone.0194936.
Schwippel, T., Papazova, I., Strube, W., Fallgatter, A.J., Hasan, A., Plewnia, C., 2018. Beneficial effects of anodal transcranial direct current stimulation (tDCS) on spatial working memory in patients with schizophrenia. Eur. Neuropsychopharmacol. 28 (12), 1339–1350.
Singer, J.D., Willett, J.B., 2003. Applied Longitudinal Data analysis : Modeling Change and Event Occurrence. Oxford University Press.
Sterzer, P., Kleinschmidt, A., 2010. Anterior insula activations in perceptual paradigms: often observed but barely understood. Brain Struct. Funct. 214, 611–622. https://doi.org/10.1007/s00429-010-0252-2.
Tripathi, A., Kar, S.K., Shukla, R., 2018. Cognitive deficits in schizophrenia: understanding the biological correlates and remediation strategies. Clin. Psychopharmacol. Neurosci. 16 (1), 7.
Uddin, L.Q., 2015. Salience processing and insular cortical function and dysfunction. Nat. Rev. Neurosci. 16, 55–61. https://doi.org/10.1038/nrn3857.
Vercammen, A., Rushby, J.A., Loo, C., Short, B., Weickert, C.S., Weickert, T.W., 2011. Transcranial direct current stimulation influences probabilistic association learning in schizophrenia. Schizophr. Res. 131, 198–205. https://doi.org/10.1016/j.schres.2011.06.021.
Vercelli, U., Diano, M., Costa, T., Nani, A., Duca, S., Geminiani, G., Vercelli, A., Cauda, F., 2016. Node detection using high-dimensional fuzzy parcellation applied to the insular cortex. Neural Plast. https://doi.org/10.1155/2016/1938292, 2016.
Wake Forest University, 2020. WFU Pickatlas. Winston-Salem, NC, USA.
Wang, Y., Yang, X., Song, X., Zhao, L., Wei, J., Wang, J., Ma, X., 2019. Co-treatment of buspirone with atypical antipsychotic drugs (AAPDs) improved neurocognitive function in chronic schizophrenia. Schizophr. Res. 209, 135–140.
Wechsler, D., 1999. Wechsler abbreviated scale of intelligence. WASI. The Psychological Corporation, San Antonio, TX.
Weickert, T.W., Goldberg, T.E., Gold, J.M., Bigelow, L.B., Egan, M.F., Weinberger, D.R., 2000. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. Arch. Gen. Psychiatry 57, 907–913. https://doi.org/10.1001/archpsyc.57.9.907.
White, T.P., Joseph, V., Francis, S.T., Liddle, P.F., 2010. Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. Schizophr. Res. 123, 105–115. https://doi.org/10.1016/j.schres.2010.07.020.
Wylie, K.P., Tregellas, J.R., 2010. The role of the insula in schizophrenia. Schizophr. Res. 123, 93–104. https://doi.org/10.1016/j.schres.2010.08.027.
Yamada, Y., Sumiyoshi, T., 2021. Neurobiological mechanisms of transcranial direct current stimulation for psychiatric disorders; neurophysiological, chemical, and anatomical considerations. Front. Hum. Neurosci. 15, 21.
Yavari, F., Jamil, A., Mosayebi Samani, M., Vidor, L.P., Nitsche, M.A., 2018. Basic and functional effects of transcranial electrical stimulation (tES)—an introduction. Neurosci. Biobehav. Rev., 85, 81–92. https://doi.org/10.1016/j.neubiorev.2017.06.015. SI: 2016 IBNS Meeting.
Yizhar, O., Klavir, O., 2018. Reciprocal amygdala–prefrontal interactions in learning. Curr. Opin. Neurobiol. 52, 149–155. https://doi.org/10.1016/J.CONB.2018.06.006.