Targeting Cognition in Schizophrenia Trough Transcranial Direct Current Stimulation: A Systematic Review and Perspective

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Tables: 2

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Abstract

Cognitive deficits are a fundamental feature of schizophrenia for which currently no effective treatments exist. This paper examines the possibility to use transcranial direct current stimulation (tDCS) to target cognitive deficits in schizophrenia as evidence from studies in healthy participants suggests that tDCS may improve cognitive functions and associated neural processes.

We carried out a systematic review with the following search terms: 'tDCS', 'electric brain stimulation', 'schizophrenia', 'cognitive', 'cognition' until March 2019. 659 records were identified initially, 612 of which were excluded after abstract screening. The remaining 47 articles were assessed for eligibility based on our criteria and 25 studies were excluded. In addition, we compared several variables, such as online vs. offline-stimulation protocols, stimulation type and intensity on mediating positive vs. negative study outcomes.

The majority of studies (n = 21) identified significant behavioural and neural effects on a range of cognitive functions (versus n = 11 with null results), including working memory, attention and social cognition. However, we could not identify any single parameter (electrode montage, stimulation protocol, type and intensity) that clearly mediated effects on cognitive deficits.

There is preliminary evidence for the possibility that tDCS may improve cognitive deficits in schizophrenia. We discuss the rationale and strength of evidence for using tDCS for targeting cognitive deficits in schizophrenia as well as methodological issues and potential mechanisms of action.

Introduction

Schizophrenia (ScZ) is a severe mental disorder characterized by psychotic experiences and disorganized and negative symptoms. In addition, the disorder involves profound deficits in a range of cognitive processes of up to 2 standard deviations (SD) compared to healthy controls (Heinrichs, 2005). These impairments involve both basic sensory processes as well as impairments in higher cognitive functions, such as working memory (WM) and executive control (Javitt, 2009, Ursu et al., 2011). Cognitive deficits are present before the onset of psychosis and persist following the remission of symptoms, leading to the conceptualization of ScZ as a cognitive illness (Kahn and Keefe, 2013).

Importantly, no effective treatments for cognitive impairments in ScZ currently exist. Antipsychotic medication has only small effects on cognitive deficits (Hill et al., 2010) with even some evidence for a negative impact (Ballesteros et al., 2018). More recently, efforts have been made to develop psychological interventions, such as cognitive remediation therapy (CRT). However, while CRT confers significant benefits on cognition in ScZ, effect sizes are small to moderate (Wykes et al., 2011). Accordingly, the identification of novel treatment approaches for targeting cognitive deficits remains an important objective.

One possibility to target cognitive deficits in ScZ is through non-invasive brain stimulation (NIBS), which can influence neural activity and cognitive processes via delivery of magnetic or electrical fields. While transcranial magnetic stimulation (TMS) has been extensively applied in ScZ (Dougall et al., 2015), in particular for the treatment of auditory hallucinations, the potential of transcranial direct current stimulation (tDCS) has only been explored more recently.

Although the mechanisms through which tDCS can affect neural processes remain to be fully elucidated, tDCS has been shown to have potential for influencing brain activity and

behavioural performance in many cognitive domains (Jacobson et al., 2012a, Vosskuhl et al., 2018). However, more recent data have also provided negative findings on the efficacy of tDCS in modulating cognition, including failures to replicate existing positive findings (Learmonth et al., 2017, Heroux et al., 2017).

Unlike TMS, the application of a continuous electric field with tDCS does not directly induce action potentials (i.e. neural firing) but, generally speaking, can up- or down-regulate spontaneous neuronal activity (i.e. proneness to firing) by modulating membrane potentials and in turn modulate the excitability of cortical areas underneath the stimulation electrodes (Jacobson et al., 2012a). An important distinction is between anodal and cathodal stimulation in this context. It is generally assumed that anodal tDCS increases neuronal excitability whereas cathodal tDCS decreases the firing threshold of neuronal populations (Paulus, 2011). However, there is emerging evidence that many factors contribute to tDCS stimulation effects in a non-linear manner (Jacobson et al., 2012b).

Several studies have examined the mechanisms underlying the changes in excitability following tDCS. Specifically, anodal tDCS has been shown to reduce γ-aminobutyric acid (GABA) concentrations (Stagg et al., 2011). In contrast, glutamate and glutamine concentrations (Glx) are increased (Hunter et al., 2015) which may be mediated by N-methyl-D-aspartate (NMDA) receptors as tDCS-effects are not observed after administration of an NMDA receptor antagonist (Nitsche et al., 2003). Cathodal tDCS has also been associated with changes in glutamate and GABA-levels (for a review see (Stagg et al., 2018).

A disturbance in the balance between excitation and inhibition (E/I-balance) is considered a possible mechanism for impaired cognition in ScZ (Uhlhaas and Singer, 2012). Specifically, there is evidence for increased Glx-levels as assessed through Magnetic Resonance Spectroscopy (MRS) (Merritt et al., 2016) while the direction of effects for GABA-levels is less consistent (Egerton et al., 2017). Post-mortem data, however, have consistently shown

abnormal expression of GABAergic interneurons (Lewis et al., 2012) that are likely to represent a fundamental aspect of the pathophysiology of the disorder.

The current systematic review will examine the evidence for the role of tDCS in improving cognition in ScZ. While there is evidence for the efficacy of tDCS to reduce the severity of hallucinations (Pondé et al., 2017) and for other brain stimulation approaches, such as TMS, to improve cognitive functions in ScZ (Hasan et al., 2016), the efficacy of tDCS to enhance cognitive functions in ScZ is currently unclear. Accordingly, we identified n = 32 studies that examined the effects of tDCS on measures of cognition in ScZ, alone or in combination with electrophysiological or neuroimaging approaches. We computed effect sizes and compared studies that identified positive effects of tDCS on cognition vs. those with negative findings in an attempt to identify the most promising experimental design, such as anodal vs. cathodal tDCS or other TES parameters.

Method

PubMed and Google Scholar were searched for publications with the following search terms: ‘tDCS’, ‘electric brain stimulation’, ‘schizophrenia’, ‘cognitive’, ‘cognition’ until March 2019. Moreover, the reference lists of relevant articles were searched for studies matching our search criteria. Results from all search terms were combined and PMIDs (unique identifier number used in PubMed) were used to exclude duplicates. The titles and abstracts of each publication were carefully inspected and studies which did not include ScZ-patients, cognitive functions and tDCS were excluded. Reviews, meta-analysis, case studies and case reports were also excluded from the sample.

Inclusion criteria for papers were as follows: 1) employed tDCS, 2) a sample size of 10 or more patients with ScZ, and 3) measurement of at least one aspect of cognition. Finally, the following information was retrieved from each study: primary and secondary cognitive measures, number of participants in the study, patient type (first-episode vs. chronic ScZ), age and sex of participants, tDCS protocol, timing of stimulation (during cognitive assessment – online, vs. before or following stimulation), electrode positions, current intensity, current density, experimental design, duration of stimulation and number of sessions, and main cognitive results. Effect sizes are provided where available.

In an attempt to provide information on the most effective tDCS parameters, we contrasted studies that reported positive versus null/negative effects on cognition in regards to the following parameters: tDCS polarity (anodal vs. cathodal), electrode positions (frontal vs. non-frontal tDCS), current intensity, current density, duration of stimulation, number of sessions, and experimental design parameters (n participants, blinding, within/between-participant design) (see Table 2).

Data extraction

The data for each study was extracted by RK, and supervised by RC, GT, and PU. When effect sizes were missing from published articles, the corresponding authors were contacted for the relevant data.

Statistical analysis

T-tests and chi-squared tests were performed to identify variables associated with studies that reported significant effects of tDCS vs. no effects (Table 2). Hedge's g values were computed as a measure for effect sizes for studies where information was available (n =19). R was used to plot the standardised mean differences with 95% confidence intervals.

Publication bias was tested visually using a funnel plot and with a Egger's regression test performed in R (Team R, 2013, Sterne and Egger, 2001, Schwarzer, 2007). Moreover, risk of bias and quality of studies were assessed following Cochrane risk of bias guidelines (Higgins and Green, 2011).

Results

Study selection

659 records were identified initially by searching for the key terms in databases, 612 of which were excluded after abstract screening. The remaining 47 articles were assessed for eligibility based on our criteria and 26 studies were excluded. Of these 26 studies, 16 studies had a sample smaller than 10 participants, and 9 did not include cognitive measures. One study that applied tDCS during sleep was also excluded (Göder et al., 2013). During the preparation of the manuscript, 11 more studies meeting our inclusion criteria were included due to being published after the initial selection (see Figure 1) bringing the final total to 32 included articles.

Enter Figure 1 about here

Study Characteristics

From the 32 studies (Table 1), 29 were randomised and sham-controlled trials, 4 of which included a group of healthy controls who also received stimulation. Three studies did not include a sham condition, comparing only baseline to stimulation (Narita et al., 2017, Subramaniam et al., 2015, Moon et al., 2019). 17 studies used a multi-session tDCS design (Dunn et al., 2016, Gomes et al., 2015, Mondino et al., 2015, Narita et al., 2017, Nienow et al., 2016, Palm et al., 2016, Smith et al., 2015, Subramaniam et al., 2015, Rassovsky et al., 2018, Orlov et al., 2017a, Orlov et al., 2017b, Mellin et al., 2018, Koops et al., 2018, Jeon et al., 2018, Moon et al., 2019, Lindenmayer et al., 2019, Chang et al., 2019), whereas 15 implemented single sessions of tDCS (Dunn et al., 2017, Gögler et al., 2017, Hoy et al., 2014, Hoy et al.,

2015, Impey et al., 2017, Rassovsky et al., 2015, Reinhart et al., 2015, Ribolsi et al., 2012, Vercammen et al., 2011, Hoy et al., 2016, Reinhart et al., 2018, Papazova et al., 2018, Schülke and Straube, 2018, Schwippel et al., 2018).

Cognitive tasks were administered concurrently with tDCS in 7 studies (Hoy et al., 2016, Orlov et al., 2017a, Vercammen et al., 2011, Orlov et al., 2017b, Papazova et al., 2018, Schwippel et al., 2018, Schülke and Straube, 2018). An offline stimulation protocol with pre/post tDCS measurements was used in 29 studies.

tDCS protocols

Twenty studies applied anodal tDCS over the left dlPFC with return electrode over either contralateral supraorbital area (n = 13), left temporo-parietal junction (TPJ, n = 5), or right deltoid muscle (n = 2). One study applied a cathodal electrode over the left dlPFC and an anodal electrode over the right dlPFC. Six studies applied an anodal electrode between FP1 and F3 with a cathode between P3 and T3. In addition, 5 studies compared the effects of anodal and cathodal tDCS over bilateral frontal or central areas with varying montages (Dunn et al., 2017, Dunn et al., 2016, Rassovsky et al., 2015, Rassovsky et al., 2018, Schülke and Straube, 2018). Twenty-four studies employed a current intensity of 2 mA, while n = 9 used 1 mA and n = 3 used 1.5 mA. In addition, the majority of studies employed large rubber electrodes, resulting in electrode surface area of 25 cm^2 or 35 cm^2, which in combination with 1-2 mA stimulation can lead to any of the following current densities: 0.028 mA/cm^2, 0.057 mA/cm^2, 0.08 mA/cm^2. Four studies used smaller electrodes which achieved higher current densities (Smith et al., 2015, Reinhart et al., 2018, Reinhart et al., 2015).

N = 27 studies applied tDCS for 20 min, while the remaining studies applied stimulation for 30 min (n =1), 21 min (n = 2), and 10 min (n = 2) respectively.

Risk of bias within and across studies

Of the reviewed studies (n = 32), 19 reported double-blinding and randomization, 9 reported single-blinding and randomization and 2 reported randomization without information on blinding (Ribolsi et al., 2012, Schülke and Straube, 2018). Three studies had only a ScZ-group in which performance was compared before and after stimulation, with no sham-control (Narita et al., 2017, Subramaniam et al., 2015, Moon et al., 2019). (See Supplementary Material Table 2 for quality assessment).

Risk of Publication Bias

Egger's regression test was not significant (t = -1.4006, df = 18, p = 0.1783), suggesting no publication bias.

Cognitive Measures

WM was explored in 14 studies, 8 of which used an N-back task (Hoy et al., 2014, Hoy et al., 2015, Hoy et al., 2016, Orlov et al., 2017a, Papazova et al., 2018, Schwippel et al., 2018, Nienow et al., 2016, Impey et al., 2017). In addition, 4 studies examined learning with a feedback-based learning task (Reinhart et al., 2015), source monitoring (Mondino et al., 2015), probabilistic category learning (Vercammen et al., 2011), and the California verbal learning test – CVLT (Moon et al., 2019).

Twelve studies evaluated cognitive control/attention processing which included a STROOP task (Orlov et al., 2017a, Koops et al., 2018), a trail-making test (Palm et al., 2016, Koops et

al., 2018, Papazova et al., 2018, Moon et al., 2019, Chang et al., 2019), a d2 test (Papazova et al., 2018), a visual attention task (Gögler et al., 2017), line and number bisection (Ribolsi et al., 2012), a go/no-go task (Reinhart et al., 2015), a tone discrimination (Dunn et al., 2017) an antisaccade task (Subramaniam et al., 2015), and a visual search task (Reinhart et al., 2018). Rassovsky et al. (2015), Rassovsky et al. (2018) and Schülke and Straube (2018) examined the effects of tDCS on social cognition.

The MATRICS Consensus Cognitive Battery (MCCB) was used in 6 studies (Smith et al., 2015, Rassovsky et al., 2015, Gomes et al., 2015, Rassovsky et al., 2018, Jeon et al., 2018, Lindenmayer et al., 2019). In addition, two studies (Narita et al., 2017, Mellin et al., 2018) employed the Brief Assessment for Cognition in Schizophrenia battery (BACS), and Narita et al. (2017) used the UCSD Performance-based Skills Assessment (UPSA-B).

Concurrent Neuroimaging/Electrophysiology

One study used tDCS concurrently with fMRI (Orlov et al., 2017a) and Palm et al. (2016) examined functional connectivity in fMRI-data following stimulation with tDCS. Event-related potentials (ERPs) were examined in 7 studies. ERP measures included Mismatch negativity (MMN) (Dunn et al., 2016, Impey et al., 2017, Dunn et al., 2017, Rassovsky et al., 2018), error-related negativity (ERN) examined during a learning task (Reinhart et al., 2015), the flanker task (Moon et al., 2019), and the posterior-contralateral N2 (N2pc) and anterior P1 examined during a visual search task (Reinhart et al., 2018). Finally, the effects of tDCS on neural oscillations were measured by Reinhart et al. (2015) and Hoy et al. (2015).

tDCS in ScZ: Memory

Twelve out of 18 tDCS studies revealed a significant effect on memory. Ten studies on memory used anodal stimulation over the left dlPFC with a cathode over the right supraorbital area. Eight studies implemented multiple-session designs (ranging from 10 to 40 sessions per condition).

Behavioural effects were found for different stimulation parameters. Four studies (Hoy et al., 2014, Hoy et al., 2015, Impey et al., 2017, Schwippel et al., 2018) found behavioural effects (accuracy) of 2 mA tDCS that were not observed for 1 mA stimulation. The opposite effect was reported by Papazova et al. (2018) and Orlov et al. (2017a) who found improvement on the WM n-back task (accuracy but no reaction times) only 24-hours post-stimulation with 2 mA but not immediately after treatment (see also findings by (Hoy et al., 2016, Rassovsky et al., 2018)). Moreover, Rassovsky et al. (2018) compared cathodal with anodal stimulation over the dlPFC in a working memory task and surprisingly found improvement in accuracy in the sham condition compared to both other treatments.

Two studies that examined the effects of tDCS on other aspects of memory reported mixed effects. tDCS failed to improve spatial WM after 10 sessions of left dlPFC anodal stimulation (Moon et al., 2019), while tDCS reduced source-monitoring errors after 10 sessions (Mondino et al., 2015).

tDCS in ScZ: Learning

The effects of tDCS on learning have yielded conflicting results. Vercammen et al. (2011) assessed probabilistic category learning while ScZ-patients were stimulated with 2 mA anodal tDCS over the left dlPFC. There was no significant difference between anodal tDCS and sham stimulation. Feedback-based learning was assessed by Reinhart et al. (2015) who applied stimulation over the medial frontal cortex at 1.5 mA anodal tDCS. Both ScZ-patients and

controls became more accurate and had faster RTs after one session of active stimulation compared to sham. Significant improvement of verbal learning was found after 10 sessions of 2-mA tDCS (Moon et al., 2019).

tDCS in ScZ: Cognitive Control and Attention

Eight studies examined the effects of tDCS on attention with 5 studies reporting significant effects. Two out of five reports with significant results employed anodal stimulation over the left dlPFC. The remaining n = 3 studies which found an effect used anodal tDCS over the right posterior parietal cortex (PPC), the medial frontal cortex, and cathodal tDCS over the bilateral temporal cortex.

Anodal stimulation over the left dlPFC led to the reduction of antisaccade errors (Subramaniam et al., 2015) and improved RTs during the incongruent condition of the Stroop task (Orlov et al., 2017a). Three studies using similar stimulation protocols could not confirm effects on visual attention (Gögler et al., 2017), Stroop task (Koops et al., 2018) or the trail-making test (Chang et al., 2019).

Ribolsi et al. (2012) found a reduction of the leftward bias on a line bisection task after right posterior parietal cortex stimulation, while Reinhart et al. (2018) found that 2 mA anodal tDCS over the medial frontal cortex during a visual search task improved accuracy and RTs. Finally, Dunn et al. (2017) applied 1 mA anodal, cathodal or sham tDCS bilaterally over the temporal cortices. Cathodal tDCS, but not anodal tDCS, significantly improved performance on the tone-matching task compared to sham.

tDCS in ScZ: Social cognition

Measures of social cognition improved in 2 out of 3 studies with tDCS including anodal tDCS over bilateral dlPFC (Rassovsky et al., 2015) and cathodal tDCS over the left dlPFC (Schülke and Straube, 2018).

Rassovsky et al. (2015) tested bilateral anodal, bilateral cathodal or sham stimulation over the dlPFC on emotion recognition. Anodal stimulation over the dlPFC, but not cathodal or sham, improved facial emotion identification on one of four social cognitive tasks. The same group (Rassovsky et al., 2018) did not find an effect of tDCS on social nor non-social cognitive measures with anode or cathode over F3. Moreover, there was a significant improvement on WM after sham stimulation.

Schülke and Straube (2018) examined the effects of anodal, cathodal or sham stimulation over frontal, parietal or frontoparietal areas on gesture matching and semantic speech in ScZ-patients and healthy controls. Cathodal stimulation of 1.5 mA over the left dlPFC significantly improved the discrimination between related and unrelated gestures in the ScZ group.

tDCS in ScZ: Neuroimaging/Neurophysiology

Eleven studies examined the effects of tDCS on neuroimaging measures with 7 studies reporting significant effects. Hoy et al. (2015) investigated EEG-activity over frontal electrodes during a WM-task. Event-related gamma synchronization (ERS) and WM-performance was increased at 40 min post-stimulation with 2 mA tDCS compared to sham, while no effect was found with 1 mA stimulation. Reinhart et al. (2015) found increased intertrial phase coherence of theta oscillations and improved performance on a go/no-go task after anodal stimulation (FCz electrode), but not after sham. Reinhart et al. (2015) also showed that anodal tDCS over the medial frontal cortex (FCz) can lead to significantly larger ERN in ScZ-patients which

correlated with improved feedback-based learning. In addition, frontal anodal tDCS led to improved performance on a visual search task and decline of the contralateral delay activity (CDA) waveform and increase in P1 in ScZ-patients (Reinhart et al., 2018). However, multiple sessions of frontal anodal tDCS did not show change in peak amplitude or latencies of ERN and CRN (Moon et al., 2019).

Four studies examined MMN after tDCS. Dunn et al. (2016) found a decrease of MMN-amplitude after anodal stimulation of the bilateral dlPFC (d = 0.95), but not after cathodal or sham. The same group used anodal and cathodal tDCS bilaterally over the auditory cortex and did not find a significant effect on MMN (Dunn et al., 2017). Similarly, Impey et al. (2017) did not observe a significant effect of 2 mA anodal dlPFC stimulation on MMN. Finally, Rassovsky et al. (2018) found no effect of 2 mA anodal tDCS over dlPFC in 37 ScZ patients on MMN, P300 and N170.

Orlov et al. (2017a) applied tDCS concurrently with fMRI while measuring WM and Stroop task performance. Anodal tDCS was associated with increased BOLD-activation during the Stroop task in a network related to inhibitory control. Moreover, during WM-performance, medial frontal cortex was characterized by increased activation compared to sham. Palm et al. (2016) examined the effects of tDCS on functional connectivity in 16 ScZ-patients. The exploratory fcMRI analysis showed changes in subgenual cortex and dlPFC connectivity within fronto-thalamic-temporo-parietal networks following one session of active tDCS stimulation, although there were no significant effects on WM and executive function.

tDCS in ScZ: Neuropsychological tests

Narita et al. (2017) showed that frontal tDCS was able to significantly improve verbal memory (d = 0.55), while small to medium effect sizes for motor/speed (d = 0.44), verbal fluency (d =

0.36), and composite scores (d = 0.49) on the BACS. No significant improvement was found on WM, attention/information processing, and executive function, however. Mellin et al. (2018) compared the effects of tACS, tDCS and sham stimulation on cognitive deficits as assessed by the BACS-battery. There was no significant effect of stimulation type on the total BACS-score nor on specific tasks. Effect size analysis showed, however, that tDCS was associated with a large-effect sizes (d = 1.50) on BACS-scores compared to sham (d = 0.57) and tACS (d = 0.26).

Contrasting TES-Studies with Positive vs. Negative Findings

To identify potential sources of variability for cognitive effects of TES in ScZ, we systematically compared studies who reported positive findings (n = 22 studies) vs. those that did not (n = 11 studies) (see Table 2). Studies were compared based on differences in stimulation, stimulation intensity, design, number of participants and sessions. Overall, studies which reported significant, positive effects of TES did not differ on any of the tested parameters from studies that reported negative findings.

Contrasting Single vs Multiple Sessions

It has been suggested that multi-session designs could be superior to single-session ones, expecially for learning and memory (Au et al., 2017). Of the 15 studies which used multiple-session desings, 7 studies found no effect of tDCS on cognition. In contrast, 15 out of 17 studies with single-session tDCS found a significant effect on at least one cognitive function.

Moreover, beneficial effects seem to depend on spacing between sessions. Multiple sessions per day did yield more beneficial effectscompared to designs with more than 24 hours between sessions.

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Conclusions

This is the first systematic review to investigate the impact of tDCS on cognitive dysfunctions in ScZ. Following a standardized literature search, we identified n = 32 studies that examined the effects of tDCS on performance in different cognitive domains, including WM, executive functions, social cognition and learning. The large majority of these studies applied tDCS using anodal stimulation of frontal sites (n = 28). Overall, n = 21 studies reported significant effects of tDCS on behavioural and cognitive outcome measures with a mean medium effect size (g = 0.49). In addition, n = 7 out of n = 11 studies indicated that tDCS improved neural correlates of cognitive dysfunctions in ScZ as assessed by EEG or fMRI. Overall, we could not establish a reporting bias.

While these initial results appear to indicate the potential efficacy of tDCS in improving cognitive deficits in ScZ, several important issues need to be considered in the evaluation of these findings. Firstly, a substantial number of studies (n = 11) reported no effect of tDCS on cognition in ScZ-patients, which includes studies that failed to replicate positive findings with a comparable design and stimulation-protocol (n = 3).

The studies reviewed differed considerably in the experimental design and stimulation protocols. To address the potential role of these factors in mediating positive vs. negative study outcomes, we compared several variables, such as online vs. offline-stimulation protocols, stimulation type and intensity. One of the important conclusions of this review is that we could not identify any single parameter that clearly mediated differences in cognitive outcome. One possibility is therefore that other factors, such as state-dependent variables, anatomical differences and possibly also clinical variables (illness-stage, medication) may contribute towards the effects of tDCS on cognition in ScZ.

The majority of studies utilized anodal tDCS over frontal areas (n = 28). The current results, however, do not support that frontal montages are more effective than other stimulation sites. While deficits in frontal cortex are a well-established feature of ScZ (Berman et al., 1988), cognitive deficits in processes such as WM are not confined to frontal regions but also involve impairments in sensory areas, for example (Tan et al., 2013). Accordingly, it is conceivable that the selection of the most promising stimulation site may vary between patients and cognitive tasks.

Similarly, the rationale for predominatly employing anodal tDCS in ScZ may also deserve further scrutiny. Anodal tDCS increases the excitability of neuronal populations by reducing the firing threshold of neurons (Stagg et al., 2018). In ScZ, dysfunctional neural circuits involve a E/I dysbalance (Uhlhaas and Singer, 2012) which, however, may be differentially expressed according to illness stages. Thus, there is evidence to suggest that early-stage ScZ may be characterised by increased excitability of brain networks in contrast to chronic ScZ (Anticevic et al., 2015, Grent-'t-Jong et al., 2018). Accordingly, this finding would suggest that different tDCS protocols may have different effects on patients at different illness stages and the choice of anodal vs. cathodal stimulation may be crucial in determining the efficacy of tDCS.

Interestingly, studies that examined the effects of tDCS on brain functioning with fMRI and EEG provided more consistent findings. These data could potentially indicate a novel way of probing circuit functions in ScZ. Current evidence suggests that the effects of tDCS on E/I-balance can outlast the stimulation protocol (Stagg et al., 2018). Abnormal E/I-balance has been implicated as a central circuit dysfunction in ScZ that underlies both cognitive deficits and certain symptoms of the disorder (Uhlhaas and Singer, 2012). Accordingly, targeted tDCS-protocols that address this imbalance could potentially prove important for the future treatment of cognition in ScZ.

In addition to tDCS, future studies may also consider the use of transcranial alternating current stimulation (tACS). In contrast to tDCS, tACS involves a continuous switching between the current polarity of two electrodes at a specified frequency. This type of TES, if applied in a frequency relevant to intrinsic brain oscillations, has the potential to interact with ongoing rhythms of the cortex (entrainment) and enhance communication between brain areas (Helfrich et al., 2014, Witkowski et al., 2016). This issue is potentially important for targeting cognitive dysfunctions in ScZ as current pathophysiological theories emphasize a failure of neuronal communication between and within brain regions that is potentially caused by impaired synchronization of neural activity (Uhlhaas and Singer, 2010). However, studies that used tACS to target cognitive deficits in ScZ reported inconsistent effects (Mellin et al., 2018, Hoy et al., 2016, Shanbhag et al., 2019). In addition, future studies may also consider to employ cross-frequency stimulation protocols to improve cognitive deficits in ScZ-patients (Alekseichuk et al., 2016).

Recommendation for Future tDCS-Research on Cognition in ScZ

Given the conflicting findings on the efficacy of tDCS for improving cognitive deficits in ScZ, we feel that several questions need to be considered for the design of future studies. We would like to note that the potential importance of this approach is considerable, given the absence of treatment significant advances in psychological and pharmacological treatments for cognitive dysfunctions in ScZ (Insel, 2010) and emerging evidence for the efficacy of tDCS in other psychiatric syndromes (Ironside et al., 2018).

It is likely that the considerable number of tDCS-studies with negative findings and replication failures are due to the fact that inter-individual differences in E/I-balance parameters, heterogeneity in the localization of circuit deficits and illness-stages have not been considered.

These factors likely constitute significant sources of variance across patients that are likely to impact on the effect sizes of tDCS. In addition, differences in anatomy, such as in the thickness and folding of the cortical surface, are likely to impact on the amount of current that reaches neuronal populations. As a result, futures studies employing tDCS in ScZ-patients but also in normal populations require potentially more complex designs in which individually-tailored stimulation protocols are employed that increase the chance of positive effects on cognition and behaviour.

Secondly, any intervention that targets cognitive deficits needs to establish that the effects are durable. Given that there is currently no follow-up data on the long-term effects of tDCS on cognitive impairments in ScZ, future studies need to establish how long-lasting acute effects of tDCS are. While immediate effects on behaviour and cognition, as well as the underlying circuit functions, are relevant for examining the plastic potential of circuit impairments in ScZ, remediation of cognitive deficits requires that the therapeutic effects are long-lasting and have a measurable effect on behaviour and functioning.

Finally, we believe that it is important to gain a mechanistic understanding of the effects of tDCS on cognition and circuit impairments in ScZ. One possibility is that tDCS has pro-cognitive effects in ScZ through modulating E/I-balance. This is because Magnetic resonance spectroscopy (MRS) studies have indicated that anodal tDCS reduces GABA-levels, whereas cathodal tDCS reduces excitatory glutamate levels (Stagg and Nitsche, 2011). Given that ScZ-patients altered Glutamate/GABA levels in MRS-data as well as profound alterations in GABAergic interneurons and NMDA-Rs, tDCScould potentially be used to modify E/I-balance non-invasively. MRS-measurements of GABA/Glutamate-levels accompanying tDCS-protocols could allow the testing of hypothesis regarding the underlying mechanisms of tDCS in ScZ.

In summary, this systematic review provides preliminary evidence for the efficacy of tDCS as a potential treatment approach for cognitive deficits in ScZ. Future studies needs to address a number of important questions, such individualized stimulation protocols a well as the duration of tDCS-induced effects. Given the lack of current therapeutic options for targeting cognitive impairments in ScZ, we believe, however, that tDCS could represent an important tool for efforts to improve cognitive and symptomatic aspects in patients with ScZ.

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