Effects of right prefrontal theta-burst transcranial magnetic stimulation or transcranial direct current stimulation on apathy in patients with schizophrenia: A multicenter RCT

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tDCS. rTMS is a non-invasive technique that makes use of a pulsed magnetic field to focally target neural circuits and alter their activity. rTMS has emerged as a promising treatment for apathy and negative symptoms (Aleman et al., 2017). In recent years, noninvasive brain stimulation has shown promise in the treatment of schizophrenia but has not been tested specifically for apathy. We conducted a randomized controlled trial of intermittent theta-burst (iTBS) transcranial magnetic stimulation and transcranial direct current stimulation (tDCS) targeted at the right dorsolateral prefrontal cortex (DLPFC) in patients diagnosed with a psychotic disorder suffering from apathy. The study was a multicenter, randomized, placebo-controlled, and rater-blinded trial. Patients (N = 88) were randomized into active iTBS, active tDCS, sham iTBS or sham tDCS treatment, daily for two weeks (excluding weekends). Effects were measured post-treatment and at four week and ten week follow-up. Primary outcome was apathy severity (Apathy Evaluation Scale, clinician-rated). Additional measures included assessment of negative symptoms, depression, anhedonia and quality of life.

No significant difference in improvement of apathy or negative symptoms was observed for real versus sham treatment with either iTBS or tDCS, though all groups improved to a small extent. We conclude that two weeks of brain stimulation over the right DLPFC with either iTBS or tDCS is not effective for improving apathy or negative symptoms. Longer and more intensive protocols may yield different results.

1. Introduction

Apathy can be described as a reduction in self-initiated goal-directed behavior, that is associated with diminished motivation for longer periods of time. It is part of the negative symptom cluster which describes absence or diminished presence of behaviors that are usually seen within healthy populations (Andreasen, 1982). Negative symptoms include anhedonia, asociality, alopecia, blunted affect, and apathy (i.e. avolition). Of these, apathy is most frequently present, namely in 50 % to 75 % of schizophrenia patients (Fervaha et al., 2015; Mulin et al., 2011). Furthermore, it is the strongest predictor of poor functional outcome, poor psychosocial functioning, lower medication compliance, and higher caregiver burden (Fervaha et al., 2013, 2015; Foussias et al., 2015; Konstantakopoulos et al., 2011). Moreover, patients can experience high levels of distress to this particular aspect of their illness (Selten et al., 2000). It is therefore of utmost importance to investigate possible treatments for apathy and negative symptoms.

Pharmaceutical treatments appear to be insufficient in treating negative symptoms (Aleman et al., 2017). In recent years, neuro-stimulation has emerged as a promising treatment for apathy and negative symptoms. This mainly concerns repetitive transcranial magnetic stimulation (rTMS) and transcranial direct-current stimulation (tDCS). rTMS is a non-invasive technique that makes use of a pulsed magnetic field to focally target neural circuits and alter their activity (Barker et al., 1985). High frequency rTMS (10–20 Hz) can increase cortical excitability and may help activate the frontal cortex in people...
with negative symptoms. tDCS, on the other hand, selectively and non-invasively modulates cortical excitability using much weaker fields than rTMS (Been et al., 2007; Miranda et al., 2006). Thus far, meta-analyses and systematic reviews have described positive (small–to-moderate) effects for active over sham rTMS and tDCS in treating negative symptoms (Aleman et al., 2018; Diabac-de Lange et al., 2010; Yokoi et al., 2017). For rTMS, it should be noted that there are only a few small studies as yet. Reasonably powered (e.g., N > 50) randomized controlled trials investigating its effectiveness are lacking, and are also scarce for rTMS. Furthermore, newer rTMS protocols using higher frequency stimulation, i.e. intermittent theta burst stimulation (iTBS), are becoming increasingly used in preclinical and clinical research because of its potential stronger and more prolonged effect compared to conventional rTMS (Bor et al., 2009; Eberle et al., 2010; Huang et al., 2005; Poulet et al., 2010). By repetitive treatments, neurostimulation is thought to bring about changes in neuroplasticity and yield neuroprotective effects (Cheryyakov et al., 2015) that could translate into amelioration of symptoms.

The majority of rTMS and tDCS trials that have been performed so far, have targeted the dorsolateral prefrontal cortex (DLPFC). The rationale behind this is that there is diminished involvement (hypo-functioning) of the DLPFC in negative symptoms. Indeed, associations between altered neuronal activation in this region (Siever and Davis, 2004; Tan et al., 2007), lower blood perfusion (Gonul et al., 2003; Lahti et al., 2001), and lower connectivity with striatal and parietal brain regions (Sanfilipo et al., 2002) and higher negative symptoms (including apathy) have been reported. It has been suggested that especially the right DLPFC is involved in apathy, as it is an essential ‘node in the network’ of brain regions underlying goal-directed behavior (Levy and Dubois, 2006). Studies using brain stimulation in healthy participants have reported evidence of right DLPFC involvement in decision-making (van ’t Wout et al., 2005; Bogdanov et al., 2017), an important component of goal-directed behavior. Notably, apathy has been associated with compromised functioning of specifically the right DLPFC in several patient populations, including stroke patients (Okada et al., 1997), frontotemporal dementia (Zamboni et al., 2008) and schizophrenia (Lahti et al., 2001). A PET study of glucose metabolism showed that patients with schizophrenia and negative symptoms had a lower glucose metabolic rate in the right hemisphere (frontal and temporal cortex), compared to patients without negative symptoms and healthy control subjects (Potkin et al., 2002). Using positron emission tomography with \(^{15}\text{O}\)H\(_2\)O, Lahti et al. (2001) reported reduced activation of the right middle frontal cortex in schizophrenia patients with predominantly negative symptoms, as compared to other patients. Resting state fMRI in patients with schizophrenia showed that severity of negative symptoms was inversely correlated with functional connectivity of the right DLPFC with the default mode network (Brady et al., 2019).

Our objective was to test whether noninvasive brain stimulation in the form of either iTBS (strong magnetic stimulation) or tDCS (weak electrical stimulation) over the right prefrontal cortex would improve apathy in patients with schizophrenia or schizoaffective disorder. Our first interest was iTBS, which we expected to improve apathy. We also wanted to know whether mild brain stimulation with tDCS would be able to achieve similar effects, as it is less costly and may be conducted outside a medical environment. To our knowledge, this is the first study that focuses on apathy as primary outcome. Furthermore, effectiveness of rTMS/iTBS and tDCS has not been investigated yet as in a single design. Our design could be seen as two parallel RCTs: one comparing iTBS active and sham and one comparing tDCS active and sham. However, it was registered as one study. Indeed, the primary aim was to investigate the effects of non-invasive brain stimulation on apathy and in all four arms, the right DLPFC was targeted and the same measures were used at baseline and at follow-up. Studying novel interventions is of great importance because apathy is one of the most disabling symptoms that hampers patients’ quality of life.

2. Methods

2.1. Participants

Patients were recruited from inpatient and outpatient facilities of six mental healthcare institutions in the Netherlands (see Supplement). A total of 88 patients participated in the study. Six patients dropped out during the treatment phase and were not available for further measurements, thus data for comparing post- and pre-treatment was available for 82 patients: 32 patients in the active iTBS group (of whom 13 received Behavioral Activation Therapy after the iTBS phase), 16 patients (sham) iTBS, 17 patients in the active tDCS group and 17 in the sham tDCS group. Patients with apathy, or negative symptoms in general, were forwarded by their clinicians, responded to advertisements within mental health care institutions, or signed up via the study website. In order to be included, patients needed to obtain a minimum score of 27 on the shortened version of the (clinician rated) Apathy Evaluation Scale (Faerden et al., 2008) (pAES-C), indicative for heightened levels of apathy. This 12-item shortened version of the AES represents the apathy subscale and was used because of its conciseness and good psychometric properties (Faerden et al., 2018). All patients met the DSM-IV diagnostic criteria for schizophrenia or schizoaffective disorder, which was confirmed by a trained interviewer using the relevant subscales of the Mini International Neuropsychiatric Interview-plus (van Vliet and de Beurs, 2007). Furthermore, all patients were above 18 years old and were stable on medication for at least four weeks prior to inclusion. Patients were asked to remain on their regular medication for the complete duration of the study. Patients were excluded if they (i) had received rTMS or tDCS treatment within the past year, (ii) had comorbidities of severe mood or neurological disorders, (iii) had current alcohol or substance dependence disorder or (iv) insufficient Dutch language abilities to perform interviews and tests in a valid way. Due to the use of rTMS and tDCS treatment, but also MRI (only performed in the rTMS-group), contraindications for these procedures were additional exclusion criteria (including metal implants, claustrophobia, and a diagnosis of epilepsy in patients or their first-degree relatives). Patients’ demographic characteristics can be found in Table 1. All

Table 1 Baseline characteristics of the participants in the Active and Sham groups.

<table>
<thead>
<tr>
<th></th>
<th>Active iTBS</th>
<th>Sham iTBS</th>
<th>Active tDCS</th>
<th>Sham tDCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>32</td>
<td>16</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>n (%) female</td>
<td>8 (25 %)</td>
<td>4 (25 %)</td>
<td>1 (5.9 %)</td>
<td>4 (23.5 %)</td>
</tr>
<tr>
<td>Median age (Q,R)</td>
<td>33.0</td>
<td>34.0</td>
<td>41.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Mean/median years of education, (sd/IQR)</td>
<td>17.1 (2.9)</td>
<td>16.0 (2.8)</td>
<td>16.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Median age of onset (Q,R)</td>
<td>23.0</td>
<td>22.5</td>
<td>26.0</td>
<td>26.0</td>
</tr>
<tr>
<td>Median illness duration in years (Q,R)</td>
<td>7.0</td>
<td>5.5</td>
<td>10.0</td>
<td>7.0</td>
</tr>
<tr>
<td>PANS total, mean (sd)</td>
<td>66.3 (14.9)</td>
<td>59.7 (12.9)</td>
<td>57.8 (13.5)</td>
<td>69.5 (15.1)</td>
</tr>
<tr>
<td>CDSS, median (Q,R)</td>
<td>4.0 (1.0-8.5)</td>
<td>2.5 (1.0-5.75)</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>TEPS, mean (sd)</td>
<td>60.1 (15.0)</td>
<td>61.2 (10.0)</td>
<td>63.8 (10.4)</td>
<td>58.7 (14.6)</td>
</tr>
<tr>
<td>MANSA, mean (sd)</td>
<td>51.9 (14.5)</td>
<td>52.6 (9.3)</td>
<td>54.0 (9.0)</td>
<td>46.8 (11.8)</td>
</tr>
</tbody>
</table>

PANS= Positive and Negative Syndrome Scale; TEPS= Temporal Experience of Pleasure Scale; CDSS= Calgary Depression Scale for Schizophrenia; MANSA= Manchester Short Assessment of Quality of Life.

Means and SD are given for approximately normally distributed variables. Median and IQR (Weighted average) are given in case of skewness (skewness <1 or skewness>1) in one or both condition groups. Note that this can vary across the two RCTs (i.e. iTBS vs. Sham and tDCS vs. Sham).
patients provided oral and written informed consent after full oral and written explanation of the study. The study was executed in accordance with the procedures described in the Declaration of Helsinki (‘World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects,’ 2013), was approved by the local medical ethical committee and registered in the Dutch Trial Register (www.onzoeektmetmensen.nl) with number NTR3805.

2.2. Study design

The study was a multi-center, randomized, placebo-controlled, and rater-blinded trial. The nurse or researcher who provided the stimulation was also blind to the condition of the participant. Patients were randomized into active rTMS or active tDCS treatment, sham rTMS or sham tDCS treatment, or active rTMS treatment followed by Behavioral Activation Therapy (rTMS+BAT). To this end, a randomized block design (with a fixed block size of six) was used to assure equal balance in treatment arms. Patients were randomized within centers to ensure that active and sham condition participants were from the same patient population (two centers only participated in the tDCS trial, cf. Supplement). Randomization was performed by the Trial Coordination Center of the University Medical Center Groningen. Patients, raters, and medical staff performing neurostimulative treatment were all blind to the condition of the patient. Measurements included a pretreatment measurement session, two weeks of neurostimulative treatment, a post-treatment measurement, and follow-up measurements four and ten weeks after neurostimulative treatment. In case a patient was randomized into the rTMS+BAT condition, ten BAT sessions were provided after neurostimulative treatment (one session per week).

2.3. Interventions

2.3.1. Repetitive transcranial magnetic stimulation (rTMS): iTBS protocol

Intermittent theta burst stimulation (iTBS) was provided using one of three Medtronic MagPro machines (one X100 and two R30 machines) that were equipped with a dynamically liquid-cooled figure-of-eight active/placebo coil of 75 mm diameter (MagVenture Ltd.). Entering a stimulation code onto the apparatus determined which side of the coil had to be placed on the head of the participant, i.e. whether stimulation was provided to the scalp or not. Stimulation was provided to the right DLPFC, which was localized using an EEG cap with the F4 location of the international 10/20 system. The stimulation paradigm that was used involved iTBS in order to increase excitability of the right DLPFC (Holzer and Padberg, 2010; Wu et al., 2012). It consisted of 33 trains of 2 s including bursts of 3 magnetic pulses at 30 Hz that were repeated every 200 ms. We decided on the use of 30 Hz because of a putatively lower risk of overheating the coil and/or epileptic seizure. Wu et al. (2012) showed that 30 Hz TBS induced similar neurophysiologic effects over M1 as conventional 50 Hz TBS. The trains were repeated every 10 s (thus with an intertrain interval of 8 s), for a total of 330 s (990 pulses). Stimulation was provided at 80% of the resting motor threshold, which was defined as the minimum required intensity to provoke a visible movement in the dominant hand in five out of ten magnetic pulses administered at the primary motor cortex (Schutter and van Honk, 2006). The motor threshold was determined for all participants (i.e. both in the active and placebo conditions). In three cases where it took too long to determine the motor threshold, stimulation was provided at 45% of the output of the apparatus.

Furthermore, weak electrical stimulation was provided to a region on the scalp close to the coil. This was done to provide tactile stimulation and make it harder to distinguish the placebo condition from the active condition.

2.3.2. Transcranial direct-current stimulation (tDCS)

tDCS was applied using the Eldith DC stimulator (www.neuroconn.de/dc-stimulator_plus_en/). Entering a stimulation code onto the device determined whether active or placebo treatment was given. Active stimulation implied the delivery of a weak direct current (DC) of 2 mA via 2 electrodes (7 × 5 cm, 35 cm²), with two sponge electrodes soaked in a saline solution (0.9% NaCl). The electrodes were placed based on the international 10–20 electrode placement system using an EEG-cap. A strap covered the electrodes to keep them in place and in contact with the skull. The active electrode (i.e. anode) was placed on F4, which corresponds to the right DLPFC, and the reference electrode (i.e. cathode) was placed on the contralateral orbit. The reason for not using F3 cathodal was to avoid reducing the excitability of the left DLPFC, therefore a different region was chosen. Choosing the contralateral orbit is a common method in tDCS studies. Stimulation was provided for 20 min per day, five days per week, for two weeks. During placebo treatment, first 40 s of real stimulation was provided, where after small current pulses (110 µA) were delivered every 550 ms for the remaining duration of the treatment (only for impedance checks, stimulation did not exceed 2 µA, which does not have therapeutic effects).

2.4. Clinical measures

Apathy was considered as our primary outcome, and was assessed with the Apathy Evaluation Scale, clinician rated (AES-C) (Marin et al., 1991). For reference purposes, the AES informant rated was also included (AES-I). This questionnaire was filled in by a family member of the participant, friend or involved practitioner. Furthermore, negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1989), and positive, negative and generalized psychopathology with the Positive and Negative Syndrome Scale (PANSS). Furthermore, depression was evaluated using the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1990, 1992), anhedonia using the Temporal Experience of Pleasure Scale (TEPS; Bard et al., 2006), and quality of life using the Manchester Short Assessment of Quality of Life (MANS; Prieb et al., 1999). Lastly, by means of a self-constructed questionnaire, participants were asked to evaluate the treatment, possible side effects, and how they experienced participating in the study.

A number of additional measurements were done, that will not be discussed in this paper, but will be published elsewhere (cf. Supplement).

2.5. Statistical analyses

2.5.1. Descriptive statistics

Baseline descriptive information was given by the mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for non-normally distributed continuous variables, and by frequencies and percentages for discrete variables. No baseline statistical comparisons were conducted as no systematic differences were expected due to randomization.

2.5.2. Longitudinal data analyses

Both the effect of treatment on the primary outcome (apathy measurements with the AES) as on negative symptoms in general (SANS and PANSS negative) were evaluated. For both types of treatment (iTBS and tDCS), longitudinal data analyses of mean response profiles were conducted to investigate the effect of treatment on each outcome of interest. Here, an unstructured covariance structure was estimated to account for dependency of repeated measurements within persons. Using this approach, subjects with one or more missing measurements could also be included in the model estimation. In each model, the continuous outcome was modeled as a function of the independent variables: treatment condition (0-placebo; 1-intervention), categorical time (Dummy 1: post-treatment−0/1; Dummy 2: 4-week follow-up−0/1, Dummy 3: 10-week follow-up−0/1; baseline = reference), and the interactions between each of the time-dummy variables and treatment condition. To adjust for effects of potential baseline differences in the
outcome variable, a constrained longitudinal data analytical (cLDA) approach was used. This approach entails that the main effects for the time dummies and the fixed interaction effects between the time-dummies and condition are included in the model, but no main effect for condition is included. Using the above-described variable coding, this approach allows for an estimation of the treatment-effect (i.e. the time-dummy by condition interactions), assuming no baseline difference on the outcome between conditions, which is applicable in the setting of an RCT. The interaction terms between time dummies and treatment condition were evaluated as estimates of the treatment effects.

All analyses were run using SPSS (v. 28.0.1.1) using the MIXED command with restricted maximum likelihood estimation and Sattherthwaite approximation of the denominator degrees of freedom (default settings). For each analysis, assumptions of approximate conditional normality and homoscedasticity were checked by inspection of Q-Q plots and residual plots. In case of non-normality, the outcome was transformed (e.g., natural log, power, square root), analyses were rerun and assumptions were checked again. Because multiple statistical tests were run, findings were only considered to be statistically significant after surviving adjustment for multiple testing for secondary outcomes (all measures other than the AES), using the Holm-Bonferroni method. We originally did not plan to compare tDCS to iTBS, the trial aimed to investigate whether either or both of the neurostimulation methods would improve apathy. Given the design, with some centers only participating with the tDCS intervention, a direct comparison would have been problematic.

3. Results

For all analyses, the iTBS (N = 19) and iTBS+BAT group (n = 13) were combined because the iTBS+BAT group was too small to include on its own, and both groups received active iTBS justifying analyzing them as one group for the current purpose (of comparing with sham iTBS). Moreover, the primary outcome measure (AES post-treatment) was taken before the BAT started.

3.1. Demographic and clinical characteristics

Table 1 presents the baseline characteristics for the included participants and baseline clinical outcomes. Tables 2a and 2b provide the mean scores over time on the AES and also indexes mean/median scores on the SANS (total) and PANSS negative subscale, for all measurements over time. The scores show a small decline in severity over time, for all groups.

3.2. Differences between the active and sham groups

On the AES, for both iTBS and tDCS, there were no significant Condition * time-dummy interaction effects, indicating that the active treatment was not superior to sham in reducing AES scores (cf. Fig. 1 and Tables 3a and 3b). Analyses for measures of negative symptoms (SANS and PANSS negative) also did not reveal differences between active and sham groups (cf. supplementary Tables). Exploratory analyses of the subscales of the AES and SANS did not reveal significant differences either (cf. supplementary Tables). Only for the comparison of tDCS active versus sham a marginally significant difference was initially observed post-treatment ($B = -2.57; 95\%$ confidence interval: $-4.11$ to $-1.04, p = 0.002$) and at 4-week follow-up ($B = -3.00; 95\%$ confidence interval: $-5.37$ to $-0.63, p = 0.015$) on the SANS-apahty subscale. However, neither of these effects were significant anymore after correction for multiple comparisons.

As an exploratory analysis, we compared the active iTBS only group to the iTBS + BAT group, after 4 and 10 weeks. Repeated measures ANOVA showed no significant Group difference on the AES, F(1, 27) = 0.46 (p = 0.50). Antipsychotic dose equivalents (based on D2 receptor occupancy, Lako et al. 2013) were not significantly correlated with AES change in the active iTBS group ($r = -0.33$), but did show a correlation with AES change in the active tDCS group ($r = 0.61$).

3.3. Tolerability and blinding

No serious adverse event was reported. Asked after the treatment (with our questionnaire), 18 patients reported to have experienced side effects, the proportion did not differ significantly between groups. That is, 63 participants filled in the questionnaire, and for tDCS 4/16 reported side effects (mostly headache) in the placebo group, compared to 5/17 in the experimental group. For the iTBS groups this was 3/13 in the placebo group and 6/25 in the experimental group. In general, the treatment was well tolerated. Three patients in the iTBS discontinued after a few treatment sessions because of side effects. Of the other participants, across the different groups, 24 reported mild side effects, mostly headache up to a few hours after stimulation (N = 13) and muscle contractions during stimulation (N = 4), for a list of side effects see the Supplementary Information. In two patients (both in the iTBS group) a slight increase in psychotic symptoms was noted during treatment, though not confirmed with the PANSS, which their treating clinician ascribed as an increase in activity and being more talkative.

With regard to blinding, 27 % in the sham tDCS condition guessed their condition correctly, compared to 33 % in the active group. The majority of participants indicated “I don’t know”. For the iTBS, 50 % in the sham condition guessed their condition correctly, compared to 53 % in the active condition. For the iTBS+BAT condition, there was no placebo condition as this condition was meant to see whether addition of BAT would yield better results than iTBS only.

Table 2a

Descriptive statistics of scores over time on outcome scales in Active and Sham groups of iTBS.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>4-week FU</th>
<th>10-week FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES, mean (SD)</td>
<td>Active</td>
<td>47.5 (7.3)</td>
<td>44.1 (7.8)</td>
<td>43.2 (7.2)</td>
<td>42.7 (8.0)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>46.4 (6.6)</td>
<td>43.6 (6.8)</td>
<td>42.2 (8.0)</td>
<td>41.2 (9.3)</td>
</tr>
<tr>
<td>AES Apathy factor, mean (SD)</td>
<td>Active</td>
<td>27.8 (5.1)</td>
<td>25.5 (5.3)</td>
<td>25.2 (4.9)</td>
<td>24.9 (5.2)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>26.4 (4.3)</td>
<td>24.4 (3.8)</td>
<td>24.1 (5.1)</td>
<td>23.1 (5.7)</td>
</tr>
<tr>
<td>AES Disinterest factor, mean (SD)</td>
<td>Active</td>
<td>12.1 (2.1)</td>
<td>11.8 (2.2)</td>
<td>11.2 (2.6)</td>
<td>11.5 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>12.1 (2.1)</td>
<td>11.8 (2.2)</td>
<td>11.2 (2.7)</td>
<td>11.5 (2.7)</td>
</tr>
<tr>
<td>AES Social Withdrawal factor, mean (SD)</td>
<td>Active</td>
<td>7.6 (1.8)</td>
<td>7.2 (1.9)</td>
<td>7.2 (1.8)</td>
<td>6.8 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>7.9 (2.1)</td>
<td>7.5 (2.4)</td>
<td>6.9 (2.2)</td>
<td>6.6 (2.3)</td>
</tr>
<tr>
<td>SANS total, mean (SD)</td>
<td>Active</td>
<td>54.4 (12.9)</td>
<td>49.1 (15.8)</td>
<td>49.3 (18.8)</td>
<td>49.5 (18.8)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>54.3 (12.4)</td>
<td>48.4 (13.8)</td>
<td>47.1 (17.9)</td>
<td>47.4 (19.0)</td>
</tr>
<tr>
<td>PANSS negative, mean (SD)</td>
<td>Active</td>
<td>18.4 (4.1)</td>
<td>16.8 (4.6)</td>
<td>17.7 (5.0)</td>
<td>17.4 (4.9)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>17.9 (4.0)</td>
<td>16.5 (4.5)</td>
<td>16.8 (4.7)</td>
<td>16.6 (5.3)</td>
</tr>
</tbody>
</table>

AES= Apathy Evaluation Scale; SANS= Scale for the Assessment of Negative Symptoms; PANSS= Positive and Negative Syndrome Scale.

For (approximately) normally distributed variables at most time points, means and SD are given. For variables that have skewed distributions at most time points ($\geq$ skewness $>1$), median and interquartile range (IQR) are given.
the effects on the SANS), our main results concur with the trial of left 10 Hz rTMS (over three weeks) for negative symptoms reported by Wobrock et al. (2015). In contrast, in a previous trial from our research group (Dlabac-de Lange et al., 2010), we did find improvement of negative symptoms, after bilateral DLPFC stimulation (two sessions a day, for three weeks). We will first discuss our results in relation to these two previous studies and then discuss a number of methodological issues that are of relevance, considering the wider literature. We will then discuss our tDCS results in relation to previous studies. We will conclude by highlighting methodological issues that should be taken into account in future research.

It should be noted that meta-analyses of neurostimulation trials for negative symptoms in schizophrenia do report a treatment effect of active above sham conditions (Aleman et al., 2018; Lorentzen et al., 2022; Tseng et al., 2022). This begs the question whether moderator variables could explain the inconsistencies between studies. With regard to rTMS (be 10 Hz or iTBS protocols), an important variable may be the total number of pulses that are delivered to the brain within the entire treatment. For our current iTBS study this number was 9900 pulses. For the study by Wobrock et al. (2015) this number was 15,000. For our earlier study with bilateral 10 Hz stimulation (Dlabac-de Lange et al., 2010), the total number of pulses was 60,000. There may be other variables of interest, though, as identified in our meta-analysis (Aleman et al., 2018), such as age (stronger effect in younger patients) and duration of illness (stronger effect with lower duration of illness). Another factor that has been suggested to be of relevance is the scalp-to-cortex distance (SCD). This refers to the distance, measured on an MRI scan at the targeted area, from the outer rim of the scalp to where the cortex starts. Nathou et al. found a relationship between SCD and hallucinations in schizophrenia (Nathou et al., 2015). They therefore

4. Discussion

Treatment with either iTBS or tDCS was not superior to the respective sham conditions with respect to improving apathy or negative symptoms. A small reduction in apathy (and negative symptoms more in general) was observed for all groups. Besides a placebo effect, this may be due to the behavioral activation induced by participating in the trial and/or social-emotional support for study participants by the research team. To the best of our knowledge, this is the first neurostimulation trial targeted at apathy specifically. However, considering that apathy is a core symptom of negative symptoms (and indeed taking into account the effects on the SANS), our main results concur with the trial of left 10 Hz rTMS (over three weeks) for negative symptoms reported by Wobrock et al. (2015). In contrast, in a previous trial from our research group (Dlabac-de Lange et al., 2010), we did find improvement of negative symptoms, after bilateral DLPFC stimulation (two sessions a day, for three weeks). We will first discuss our results in relation to these two previous studies and then discuss a number of methodological issues that are of relevance, considering the wider literature. We will then discuss our tDCS results in relation to previous studies. We will conclude by highlighting methodological issues that should be taken into account in future research.

It should be noted that meta-analyses of neurostimulation trials for negative symptoms in schizophrenia do report a treatment effect of active above sham conditions (Aleman et al., 2018; Lorentzen et al., 2022; Tseng et al., 2022). This begs the question whether moderator variables could explain the inconsistencies between studies. With regard to rTMS (be 10 Hz or iTBS protocols), an important variable may be the total number of pulses that are delivered to the brain within the entire treatment. For our current iTBS study this number was 9900 pulses. For the study by Wobrock et al. (2015) this number was 15,000. For our earlier study with bilateral 10 Hz stimulation (Dlabac-de Lange et al., 2010), the total number of pulses was 60,000. There may be other variables of interest, though, as identified in our meta-analysis (Aleman et al., 2018), such as age (stronger effect in younger patients) and duration of illness (stronger effect with lower duration of illness). Another factor that has been suggested to be of relevance is the scalp-to-cortex distance (SCD). This refers to the distance, measured on an MRI scan at the targeted area, from the outer rim of the scalp to where the cortex starts. Nathou et al. found a relationship between SCD and treatment efficacy of rTMS over the temporoparietal cortex for auditory hallucinations in schizophrenia (Nathou et al., 2015). They therefore

![Fig. 1. Violin plots for the four conditions at the different time points. Pre = before treatment, post = immediately after treatment, 4WF = 4 week follow-up, 10WF = 10 week follow-up.](image-url)

### Table 3a

Analyses of treatment-by-time interaction effects to assess differences in change over time on the total AES score between active iTBS treatment and sham iTBS.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Model fixed effects&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Estimates</th>
<th>B</th>
<th>95 %CI</th>
<th>df</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES</td>
<td>Intercept</td>
<td></td>
<td>47.15</td>
<td>45.10–49.20</td>
<td>47.00</td>
<td>46.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Post (0/1)</td>
<td>–3.00</td>
<td>–5.55–0.45</td>
<td>40.81</td>
<td>–2.37</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-week (0/1)</td>
<td>–4.57</td>
<td>–7.36–1.77</td>
<td>41.00</td>
<td>–3.30</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-week (0/1)</td>
<td>–5.35</td>
<td>–8.58–2.12</td>
<td>37.40</td>
<td>–3.35</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post (0/1)*Active treatment (0/1)</td>
<td>–0.51</td>
<td>–3.61–2.59</td>
<td>39.00</td>
<td>–0.33</td>
<td>0.741</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-week (0/1)*Active treatment (0/1)</td>
<td>0.81</td>
<td>–2.59–4.21</td>
<td>39.31</td>
<td>0.48</td>
<td>0.633</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-week (0/1)*Active treatment (0/1)</td>
<td>1.53</td>
<td>–2.49–5.54</td>
<td>37.45</td>
<td>0.77</td>
<td>0.446</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> Interaction-effects of interest are printed in **bold** font.

<sup>2</sup> The model does not include a main effect for condition in line with the constrained longitudinal data analysis (cLDA) approach.
A very recent study randomized 50 patients with schizophrenia to active sessions a week for three weeks. The authors report a large effect size for the orbitofrontal region (Lisoni et al., 2022). The treatment included five 10-week (0/1) active treatments with a total of 1200 pulses at 110% of motor threshold over 10 days of treatment. Stimulation of the target area, which may differ between people. In the current study, SCD was not taken into account when determining the strength of the pulses.

Another possible explanation for the lack of a treatment effect of iTBS could be the hemisphere targeted: we stimulated the right DLPFC, whereas most previous studies targeted the left DLPFC. For example, in one recent study (Barton et al., 2021) 22 patients with schizophrenia and treatment-resistant negative symptoms received 20 sessions of either active or sham iTBS (twice a day on 10 consecutive working days) over the left DLPFC. A significant improvement on the SANS was reported for the active versus sham group. Another recent trial (Kumar et al., 2020) also targeted the left DLPFC, involving 100 patients with schizophrenia and predominantly negative symptoms, who received 20 sessions of rTMS at 20 Hz frequency and 100% motor threshold (randomized to either active or sham coil conditions), over 4 weeks. A significant improvement of SANS scores was observed in the active group over the sham group. Indeed, there is evidence from neuroimaging studies to suggest that the left DLPFC is involved in negative symptoms of schizophrenia (Fuentes-Claramonte et al., 2022; Liu et al., 2002).

Only one previous study investigated sole stimulation of right DLPFC (Klein et al., 1999), whereas in a few studies both left and right DLPFC were stimulated (Barr et al., 2012; Dlabac-de Lange et al., 2015; Fitzgerald et al., 2008). The study by Klein et al. (1999) did not also find an improvement of rTMS over sham stimulation, but differed from our study by using low-frequency rTMS (at 1 Hz), with a total of 1200 pulses at 110% motor threshold over 10 days of treatment. Stimulation of both right and left DLPFC may yield better effect sizes, as shown in the studies by Dlabac-de Lange et al. (2015) and Fitzgerald et al. (2008) (with standardized mean effect sizes of 0.25 and 0.62, respectively), but the study by Barr et al. (2012) did not find improvement after real versus sham rTMS. Caution is needed, as all three studies were based on small samples (less than 20 participants per group). Thus, this is yet another parameter that deserves further research.

We also did not find an improvement of apathy after treatment with tDCS, as compared to sham tDCS. This is consistent with a recent meta-analysis of tDCS studies for improving negative symptoms in schizophrenia, in which 12 studies were pooled together and the mean weighted effect size across studies was non-significant. A sub-analysis of five studies that stimulated twice daily did show significant improvement, with a mean effect size of 0.31. Thus, a higher number of sessions per day may contribute to a stronger effect of tDCS. This deserves further investigation, as sample sizes have typically been very small for these studies (as is the case for the vast majority of rTMS and iTBS studies). A very recent study randomized 50 patients with schizophrenia to active or sham tDCS with anode over the left DLPFC and cathode over the right orbitofrontal region (Lisoni et al., 2022). The treatment included five sessions a week for three weeks. The authors report a large effect size (> d = 0.8) of active versus sham tDCS for improving the different negative symptoms measures that can be obtained from the PANSS. A major difference with our study is the placement of the anode over the left DLPFC, versus the right DLPFC in our study. Thus, stimulation of the left DLPFC might be more effective, but this needs to be confirmed in further investigations, preferably by contrasting left versus right stimulation directly in one study. It will also be of interest to investigate the possible modulatory effects of antipsychotic medication, given the correlation we observed between dose equivalents and change in AES score after iTBS. Because only 15 participants were in the active iTBS arm it would be premature to draw any conclusions at this point, but given that interactions of brain stimulation with dopaminergic neurotransmission are not unlikely, this deserves to be studied in more detail.

The limited sample size is also a limitation of the current study. Even though in total 82 patients with schizophrenia and negative symptoms participated, which constitutes a major effort, the total N was 48 patients for the iTBS sample and 34 for the tDCS sample. To detect moderate effect sizes with substantial power, one would need 60 patients per group. Our trial could be taken as a pilot study, and the results may imply that it is not encouraging to pursue this avenue further. This is not to say that iTBS (or other forms of high-frequency rTMS) don’t hold promise altogether. As indicated above, targeting the left or both hemispheres with multiple sessions a day and thus a significantly higher total number of pulses could already make a considerable difference (if replicated in future studies). Although apathy was the explicit focus of this trial, it could also be considered a limitation, as it may be regarded to be a narrow focus in the context of negative symptoms. Indeed, more comprehensive measures of negative symptoms have been developed in recent years, that also take into account an experiential component, e.g. CAINS (Kring et al., 2013) and BNNS (Kirkpatrick et al., 2011).

In conclusion, our RCT of iTBS and tDCS for improving apathy in patients with schizophrenia did not show superiority of active stimulation above sham stimulation. In the light of recent meta-analyses that do find some evidence for therapeutic effects of both rTMS and tDCS we suggest that this does not necessarily imply that noninvasive brain stimulation should be regarded to be ineffective in general. We do propose, however, that future studies should ensure sufficient intensity of treatment, i.e. a total number of rTMS pulses above a certain threshold (e.g. at least 60,000 pulses) or twice daily tDCS stimulation for at least three weeks. Accelerated protocols, such as the Stanford Neurostimulation Therapy (SNT) for depression (Cole et al., 2022), with ten sessions a day, may be promising also for targeting negative symptoms such as apathy in schizophrenia.

CRediT authorship contribution statement

Claire Kos: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft. Leonie Bais: Data curation,
Investigation, Project administration, Writing – review & editing. Nicky Klaassen: Data curation, Investigation, Methodology, Project administration, Writing – review & editing. Esther Opmeer: Methodology, Supervision, Writing – review & editing. Edith Liemburg: Methodology, Writing – review & editing. Klaas J. Wardenaar: Formal analysis, Methodology, Writing – review & editing. Marie-Jose van Tol: Methodology, Supervision, Writing – review & editing. Henderikus Knetgering: Conceptualization, Methodology, Supervision, Writing – review & editing. André Aleman: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare no interests in relationship to the work reported in this manuscript.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.115743.

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