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Research paper

Dorsomedial prefrontal theta burst stimulation to treat anhedonia, avolition, and blunted affect in schizophrenia or depression – a randomized controlled trial

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ABSTRACT

Background: Intermittent theta burst stimulation (iTBS) over the dorsomedial prefrontal cortex (DMPFC) has shown promise in open-label trials of depression.
Methods: In this randomized, double-blind, sham controlled trial we evaluate iTBS over the DMPFC for anhedonia, avolition, and blunted affect in patients with schizophrenia or depression. Active iTBS was delivered over the DMPFC with 1200 pulses per session, twice daily over ten weekdays at target intensity with an angled figure-of eight coil. Sham condition comprised the magnetically shielded side of the coil and simultaneous transcutaneous electrical nerve stimulation. Primary outcome was change on the Clinical Assessment Interview for Negative Symptoms (CAINS).
Results: Twenty-eight patients were randomized to active iTBS and 28 to sham. Mean (standard deviation) change in CAINS score from baseline to the day after last treatment was -5.3 (8.1) in active iTBS and -2.1 (7.1) in sham. A linear model showed no significant effect of treatment, accounting for baseline scores p=.088. Sub analyses per diagnostic group showed a significant effect in patients with depression, p=.038, but not in the schizophrenia group, p=.850. However, overall depressive symptoms did not change significantly in patients with depression. There were three serious adverse events, all in the sham group.
Limitations: Possibly too short treatment course and few patients with schizophrenia.
Conclusion: In this first transdiagnostic randomized controlled trial of iTBS over DMPFC for anhedonia, avolition, and blunted affect it can be concluded that it was generally tolerable and safe but only more effective than sham in the subgroup of patients with depression.

1. Introduction

Anhedonia, avolition and blunted affect are disabling deficit symptoms within the emotional and motivational realm. These symptoms are often difficult to treat and presenting over categorical diagnostic boundaries (Winograd-Gurvich et al., 2006). In schizophrenia, these symptoms are reported to be persisting in 40% of patients (Haro et al., 2018). Similarly, residual anhedonia alone has been noted in 20-25% of patients with remitted or euthymic uni- and bipolar depression (Di Nicola et al., 2013; Nierenberg et al., 1999). The Clinical Assessment Interview for Negative Symptoms (CAINS) is an instrument that was developed for use in treatment trials and has been extensively validated, mainly in patients with schizophrenia (Kring et al., 2013), but also in patients with depression (Richter et al., 2019).

While repetitive transcranial magnetic stimulation (rTMS) is an effective alternative for decreasing total symptom burden in treatment resistant depression (Trevizol and Blumberger, 2019), anhedonia specifically has repeatedly been associated with poor response to conventional rTMS protocols over the dorsolateral prefrontal cortex (DLPFC) in patients with depression (Krepel et al., 2020; Rostami et al., 2017). Although there were early reports in patients with schizophrenia of beneficial effect of high-frequency rTMS over the left DLPFC on anhedonia, as well as on avolition and blunted affect (Prikryl et al., 2013), the largest rTMS trial thus far noted no significant effect (Wobrock et al., 2015).

In search of the underlying neurobiology of anhedonia and avolition, these symptoms have been linked to a deficient reward system, including the dorsomedial prefrontal cortex (DMPFC). Indeed, it has

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been demonstrated in rodent models that neuromodulation of medial prefrontal structures affects striatal dopaminergic signaling, with subsequent changes in reward-seeking behavior (Ferenczi et al., 2016). Along the same line, in several human psychiatric transdiagnostic samples, anhedonia and avolition have been linked to aberrant DMPFC function in patients with schizophrenia, as well as uni- and bipolar depression (Bersani et al., 2014; Chai et al., 2011; Kinou et al., 2013; Salomons et al., 2014; Zhang et al., 2016).

The DMPFC has recently been suggested as a possible rTMS treatment target as it is now possible to reach with angled coils that have deeper penetration (Downar and Daskalakis, 2013). An open-label study of DMPFC rTMS for total depressive symptoms reported similar effectiveness as with conventional coil and stimulation site, while being safe and tolerable (Bakker et al., 2015; Downar et al., 2014). However, this preliminary positive finding could not be confirmed in a recent placebo controlled trial of high-frequency rTMS over the DMPFC (Dunlop et al., 2020). In patients with schizophrenia, the DMPFC has to our knowledge not yet been evaluated as a treatment target for anhedonia, avolition, and blunted affect.

The emerging use of patterned protocols such as intermittent theta burst stimulation (iTBS) has enabled a more intensive stimulation during a much shorter time span, which renders clinically feasible treatment protocols (Trevizol and Blumberger, 2019). Several studies have concluded that iTBS is a safe, feasible treatment for depression, and not less effective than standard high-frequency protocols (Bakker et al., 2015; Blumberger et al., 2018; Li et al., 2018; Plewnia et al., 2014). There are only a few available pilot studies of iTBS for negative symptoms in schizophrenia, none of them targeting the DMPFC (Demirtas-Tatlidede et al., 2010; Wang et al., 2020; Zhao et al., 2014). Another way to shorten time to response and possibly increase effectiveness is to administer several treatments per day in so-called accelerated protocols. This is an emerging, but yet inconclusive, field (Cole et al., 2020; Duprat et al., 2016; Tse et al., 2018).

In this randomized controlled trial, our aim was to evaluate the effectiveness of an accelerated iTBS protocol over the DMPFC for anhedonia, avolition, and blunted affect, in patients with schizophrenia or depression.

2. Material and methods

2.1. Trial design and ethical standards

This is a randomized parallel double-blind sham controlled trial, with a 1:1 allocation ratio. The trial was pre-registered at clinicaltrials.gov, with ID: NCT02905604. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Participants

The trial was conducted at Uppsala university hospital in Sweden. Inclusion criteria comprised: being 18-59 years old, having a schizophrenia spectrum disorder or uni- or bipolar depression diagnosis verified through Mini International Neuropsychiatric Interview (M.I.N.I.) Swedish translation of version 6.0.0 (Sheehan et al., 1998), ≤40 points on The Motivation and Pleasure Scale-Self-Report (MAP-SR) (Llerena et al., 2013), unchanged pharmacotherapy the past month, and written informed consent. The pharmacotherapy was kept constant until the second follow-up, four weeks after baseline. None of the participants were in psychotherapy during the trial. Exclusion criteria comprised: epilepsy, conductive ferromagnetic or other magnetic sensitive metals implanted in the head or within 30 cm of the treatment coil (such as cochlear implants, implanted electrodes/stimulators, aneurysm clips/coils, stents, and bullet fragments). Further exclusion criteria were implanted devices activated or controlled by physiological signals such as pacemakers, implantable cardioverter-defibrillators (ICD's), vagus nerve stimulators, wearable cardioverter-defibrillators, implanted medication pumps, present or removed intracardiac lines, any condition that seriously increases the risk of non-compliance or loss of follow-up, active substance use disorder (except for nicotine and caffeine), benzodiazepine use, and pregnancy. The Drug Use Disorders Identification Test (DUDIT) (Berman et al., 2005), and urine screening test for illicit drugs, benzodiazepines, and pregnancy were performed at the screening visit.

2.3. Procedures

A magnetic stimulator Magpro X100 with Magoption with a Cool-DB80 A/P, and a combined active/placebo coil with two identical sides, was used to deliver the interventions. The sham side of the coil is insulated preventing approximately 95% of the magnetic field from reaching the participant (Opitz et al., 2015). A randomization code was entered in the stimulator research software by the operator. Through a position sensor in the coil the research software then directed the operator as to which side of the coil should be angled towards the participant. The DMPFC treatment target for the first 14 patients was defined as 25% of the nasion-inion distance in the middle-line of the scalp. For the remaining 42 patients, who also participated in an add-on brain imaging study (Persson et al., 2020), the DMPFC was located with an MRI-based neuronavigational system (TMS Navigator, Localite, Bonn, Germany), with the following Montreal Neurological Institution (MNI) coordinates x=0, y=30, z=30 in (Mir-Moghtadaei et al., 2016). The coil was positioned tangentially to the scalp and with the handle pointing towards the right side of the patient.

The active intervention was delivered with the unshielded side of the coil, comprising a modified version of previously described iTBS protocols (Bakker et al., 2015; Chistyakov et al., 2010). The magnetic stimulation was applied at 90% of resting motor threshold, with 20 trains of stimulation with right-left stimulation and 20 trains with left-right stimulation. Each train consisted of two seconds stimulation, eight seconds off. The stimulation comprised ten bursts at five Hz and within each burst three biphasic pulses at 50 Hz, giving a total of 1200 pulses/session. To accelerate the treatment, and promoting plasticity to occur, a second identical treatment session was undertaken after a 15 minutes break (Duprat et al., 2016; Tse et al., 2018).

The sham treatment delivered an identical stimulation protocol but with the shielded side of the coil towards the participant. Moreover, two transcutaneous electrical nerve stimulation (TENS) electrodes were placed medially on the forehead under the coil of all patients. In the sham group only, a current of maximum four mA, scaled to the magnetic stimulator output intensity, was delivered synchronous with the magnetic pulses to mimic the sensation of magnetic stimulation. To evaluate blinding, patients were asked to guess the treatment allocation following the first, fifth, and last treatment day.

The resting motor threshold was determined by delivery of single-pulse TMS over the medial primary motor cortex of extensor hallucis longus, which was localized according to a standardized procedure (Bakker et al., 2015). The lowest intensity needed to elicit a visually observable muscle contraction in the foot in 50% of the trials, was defined as the resting motor threshold, and this was determined using an automated maximum likelihood strategy (Ah Sen et al., 2017).

During the initial treatments the intensity was ramped up to minimize discomfort by letting the patients gradually getting used to the sensation. Interventions was given daily aiming at 10 weekdays twice-daily treatments with at least 50% of the trains reaching the predetermined target intensity. If a treatment day did not meet these criteria the treatment course was prolonged with one extra day at a time, adding up to a maximum of 15 days for the whole treatment course.

At the baseline visit, patients were assessed by a trained physician (RB, JB, & ET) with two semi-structured interviews, the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013), and the Brief Psychiatric Rating Scale– extended (BPRS-E)

(Zanello et al., 2013), a rating with the Clinical Global Impression – Severity (CGI-S) (Guy, 1976), and a medical and neurological examination. The patients with depression were also assessed with the Maudsley Staging Method for treatment resistance in depression (MSM) (Fekadu et al., 2009). The following self-reports were filled out by the patients: (MADRS-S (Svanborg and Åsberg, 2001), Insight Scale for Psychosis (ISP) (Birchwood et al., 1994), EQ-5D (Burström et al., 2014), Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), Subjective memory item from the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al., 1978), Sheehan disability scale (Sheehan et al., 1996), sociodemographics, coffee-, nicotine consumption, and The Alcohol Use Disorders Identification Test (AUDIT) (Bohn et al., 1995).

Daily ratings of side effects were made on a 4-point scale (no, mild, moderate, or severe symptoms). The patients also rated the pain intensity of the intervention on a numerical rating scale ranging from 1, no pain, to 10, intolerable pain. The day after the last treatment (first follow-up) and four weeks after baseline (second follow-up), all pre-treatment examinations were repeated.

2.4. Outcomes

The primary outcome was reduction in CAINS score from baseline to the end of treatment, i.e. the first follow-up. Secondary outcomes included reduction in CAINS score from baseline to the four week follow-up (second follow-up), reduction from baseline to first and second follow-up for the following scales: the CAINS subscales (motivation, pleasure, and expression), clinical improvement defined as a >25% decrease on CAINS total score, CGI, BPRS total score, MADRS-S, PSQI, and EQ-VAS. For patients with schizophrenia spectrum disorder, changes in BPRS-positive symptoms and ISP from baseline to end of treatment, and at four week follow-up were also analyzed.

2.5. Sample size

Similar studies at the time of planning the trial had shown that clinical response for patients with schizophrenia was 9% for sham and 54% for active TBS (Zhao et al., 2014), and in depression the response rate was 17% for sham and 52% with active TBS (Li et al., 2014). Therefore we assumed that 20% would respond to sham and 54% to active TBS (alpha = 0.05 and a power of 80%). Based on this we would need approximately 60 patients (half sham and half active) to have a reasonable chance to detect a clinically relevant treatment effect (defined as response above). When assuming an attrition of 20%, we would then need to enroll 80 patients.

2.6. Randomization and blinding

The magnetic stimulator operating nurse received a randomization code, in an envelope prepared by a separate contract research organization. The code was entered in the stimulator's research software, which then guided the operator which side of the coil to place towards the participant. The research software automatically activated the TENS stimulation if the patient was allocated to the sham group. The symptom raters were not allowed to enter the treatment room during treatment sessions. Patients were instructed not to talk about the sensation of the treatment with the symptom raters.

2.7. Statistical methods

In the primary analysis, group differences in delta-values of CAINS baseline to the day after last treatment were assessed with a general linear model taking into account the baseline level and diagnosis. As a follow-up to this analysis additionally incorporating the four weeks from baseline follow-up assessments, a general linear mixed model analysis was performed, modeling the interaction between group and follow-up time point, with random intercept by subject to account for repeated measures. This analysis was repeated for the two diagnostic groups (depression and schizophrenia) separately.

Group differences in the secondary outcomes were assessed at each time point, comparing delta scores (follow-up minus baseline) using Student's t-test for continuous outcomes and summed scores, Wilcoxon rank-sum test for ordinal data, or chi-square test for categorical variables. The ISP scale was considered separately for the schizophrenia group.

To assess any treatment dependent side effects, daily ratings for each symptom were first plotted to make a visual judgement on the distribution of rating scores. For many symptoms, the majority of ratings reported an absence of symptoms, with few or no ratings on the highest scores. For these symptoms, the ratings were dichotomized to reflect presence or absence of symptoms. For dichotomized outcomes, data were entered into mixed effects logistic regression models, while ordinal outcomes were entered into proportional odds mixed effect models. For each model, the treatment*day interaction was specified, with baseline (prior to first treatment session) ratings and diagnostic category as fixed effects covariates and random intercepts at the subject level.

Statistical calculation was performed with Matlab 2020a using the Statistics and Machine Learning toolbox and R version 3.6.3 using the ordinal and lme4 packages.

3. Results

3.1. Participant flow

Out of 85 eligible patients, 56 were finally randomized. Please see flowchart in Fig. 1. Two patients in the sham group discontinued the intervention due to adverse events and one withdrew consent. Two patients in the active group discontinued due to adverse events (one fainted and one experienced temporary cognitive slowness after one stimulation), one withdrew consent, and one discontinued due to technical problems with the coil.

3.2. Recruitment

The first patient was enrolled in October 2016 and the last patient out was in January 2020. The study was ended because the planned study time had elapsed and the inclusion rate of patients with schizophrenia was too low.

3.3. Baseline data

The two treatment groups were similar regarding baseline sociodemographic and clinical baseline data, except that fewer patients in the sham group were studying or in current employment (Table 1).

3.4. Outcome data

The CAINS scores for the drop-outs, three patients in the sham group and four in the active group, were imputed by last observation carried forward in the primary intention to treat analysis.

The primary analysis showed no significant effect of treatment on change in total CAINS score between baseline and the first follow-up, i.e., the day after the last treatment, controlling for baseline scores and diagnostic group, (beta=-3.46, 95% CI=-7.45 – .53, p=.088). Similarly, there was no effect of treatment for the motivation and pleasure subscale (beta=-2.45, 95% CI=-5.3 – .4, p=.092) or the expression subscale (beta=-1.14, 95% CI=-2.7 – .41, p=.146). This was followed up with a linear mixed model, incorporating both follow-up assessments and modeling the treatment*time-point interaction to assess any delayed effect of treatment, with random intercepts per subject to account for repeated measures. No main effect of treatment was observed (beta=-3.49, 95% CI=-7.54 – .55, p=.090), but a main effect of time point (beta=-2.39, 95% CI=-4.28 – -.51, p=.013), and a treatment*time-point

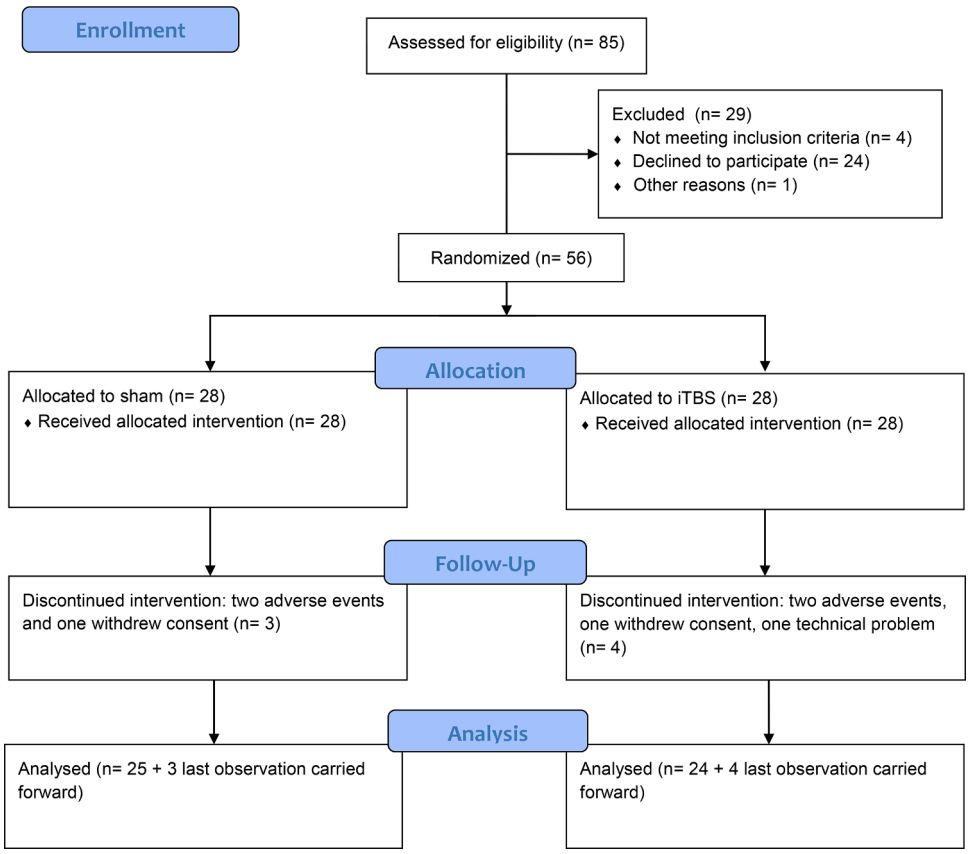

Fig. 1. CONSORT Flow Diagram of the study.

interaction (beta=2.71, 95% CI=.05 – 5.38, p=.046), reflecting a convergence of CAINS scores between the treatment arms at the second follow-up, see Fig. 2.

Repeating the same analyses for patients with depression separately yielded a significant main effect of treatment (beta=-5.5, 95% CI=-10.6 – -.3, p=.038) reflecting a significant difference in CAINS score between sham and active at follow-up, a main effect of time (beta=-3.1, 95% CI=-5.5 – -.6, p=.014) but no time*treatment interaction (beta=3.0, 95% CI=-.5 – 6.6, p=.088), see Fig. 2. Conversely, considering MADRS-S scores, there was no main effect of treatment (beta=-2.8, 95% CI=-7.0 – 1.4, p=.189) or time (beta=-1.0, 95% CI=-2.7 – .6, p=.211) and no time*treatment interaction (beta=1.5, 95% CI=-.9 – 3.9, p=.211).

In the schizophrenia subsample, there was no main effect of treatment (beta=.5, 95% CI=-5.3 – 6.4, p=.850) or time (beta=-.4, 95% CI=-2.7 – 1.9, p=.706) and no time*treatment interaction (beta=1.4, 95% CI=-1.6 – 4.5, p=.349) on the CAINS scores, see Fig. 2.

3.5. Ancillary analyses

Results from the secondary outcome measures are summarized in Table 2. None showed an effect of treatment at either time point. Median (IQR) treatment days in the active group was 10 (3.5) and 10 (.5) in the sham group, Z= 1.67, (p=.096). ISP change scores were considered separately for the schizophrenia group and did not differ between the two treatment arms at first (median and IQR for active: 0±.5, and sham: 1±1, p=.143) or second (median and IQR for active: 0±2, and sham: 0±.75, p=.726) follow-up. Further analyses of the schizophrenia group showed that there was no worsening of BPRS and no difference between active or sham in any of the psychosis subscales: activation, disorganization, or reality distortion (data not shown).

To assess any difference in treatment effectiveness due to targeting method (25% nasion-inion versus neuronavigation) the primary analysis was rerun while adding targeting method*treatment interaction to the model. There was no main effect of targeting method (beta=.3, 95% CI=-6.2 – 6.8, p=.923) or targeting*treatment interaction (beta=-4.4, 95% CI=-13.9 – 5.0, p=.352), while the main effect of treatment approached the significance threshold (beta=4.5, CI=-.04 – 9.0, p=.052).

After the first treatment day, 17 out of 26 patients (65%, 2 missing values) who received sham treatment correctly guessed the treatment allocation, while patients who received active treatment correctly guessed allocation in 18 out of 25 cases (72%, 3 missing values). A binomial test showed that participants were more likely than chance to correctly guess treatment allocation (p=.011), however this did not differ as a function of treatment (χ^2=.26, p=.611). After the fifth treatment day, 19 out of 26 patients (73%, 2 missing values) in the sham group correctly guessed the treatment allocation. In the active group, 13 out of 25 patients (52%, 3 missing values) correctly guessed treatment allocation. A binomial test showed that participants no longer guessed above chance level (p=.092), and this did not differ as a function of treatment (χ^2=2.42, p=.120).

After the last treatment day, 17 out of 22 patients (77%, 6 missing values) in the sham group correctly guessed the treatment allocation. In the active group, 9 out of 23 patients (39%, 5 missing values) correctly guessed treatment allocation. A binomial test did not show that participants guessed above chance level (p=.371), however at this time, the rate of correctly guessed allocation did differ as a function of treatment (χ^2=6.71, p=.010).

3.6. Harms

There were three serious adverse events, all in the sham group: one severe migraine with emergency room referral, one suicide attempt, and one hospitalization due to intensified suicidal ideation. Daily ratings of

Table 1
Sociodemographic and clinical baseline data.

	Sham (28)	Active (28)
Sex, N (female/male)	12/16	12/16
Age, mean (SD)	31.5 (10.4)	31.3 (9.7)
Level of education		
Less than 10 years	7	2
10-12 years	17	17
Higher education	4	9
In current employment or studying	9	17
Sheltered housing	3	1
Baseline symptoms		
CAINS total	29.8 (8.0)	27.9 (7.7)
Motivation and pleasure scale	20.9 (6.0)	21.0 (6.1)
Expression scale	8.9 (4.2)	6.9 (3.1)
MAP-SR	19.6 (8.4)	20.0 (10.1)
Clinical Global Impression	4.9 (.8)	4.6 (.6)
BPRS total	50.1 (6.5)	46.6 (7.9)
Sheehan disability scale	16.2 (6.4)	14.9 (7.6)
EQ-VAS	39.4 (19.3)	42.1 (22.3)
PSQI		
Sleeping time*	7.4 (2.3)	8.1 (2.4)
Sleep quality	1.7 (1.0)	1.5 (.9)
Subjective memory item from CPRS	2.6 (1.5)	3.1 (1.3)
Primary diagnosis		
Major depressive disorder†	21	19
Schizophrenia spectrum disorder††	7	9
Pharmacotherapy		
Antidepressant	17	20
Antidepressant combination	7	7
Antipsychotics	12	13
Lithium	3	4
Nicotine user	4	5
AUDIT	3.9 (3.9)	4.8 (5.3)
Left-handed**	1	4
Resting motor threshold‡	51.3 (10.7)	54.3 (9.7)

SD=Standard deviation, CAINS= Clinical Assessment Interview for Negative Symptoms, MAP-SR=Motivation and Pleasure Scale-Self-Report, BPRS= Brief Psychopathological rating scale 24-item version, CPRS= Comprehensive Psychopathological Rating Scale, AUDIT= Alcohol Use Disorders Identification Test

* Three missing values

** One missing value

† Of which four were diagnosed bipolar depression

†† Of which four were diagnosed schizoaffective disorder

‡ Visual inspection of twitch in musculus extensor Hallucis Longus

side effects are illustrated graphically in supplementary figure S1, and results from statistical inference testing reported in supplementary table S1. Additionally, one patient in the active condition reported the presence of mild disorganization symptoms which were constant throughout treatment. Two syncopes were reported in the sham group. There were no epileptic seizures.

4. Discussion

4.1. Key results

This is the first RCT of a transdiagnostic intervention with iTBS over DMPFC for anhedonia, avolition, and blunted affect and we observe that iTBS was safe and tolerable but only significantly more effective than sham in patients with depression. There was virtually no symptom improvement in patients with schizophrenia.

4.2. Limitations

One limitation with this study is that we encountered difficulties enrolling sufficient number of patients with schizophrenia spectrum disorder. We ended up with a smaller number than required in our sample size calculation (56 instead of 80). However, we had assumed a 20% attrition, but we only had a few drop-outs, thus we still nearly reached the required sample size. Another possible limitation is that we might have been using a partly active comparator, an issue that has been raised by the authors of a recent RCT using the same sham condition (Dunlop et al., 2020). The combination of residual magnetic stimulation from the shielded side of the coil and the prefrontal TENS might constitute a partly active intervention through trigeminal nerve modulation. Another possible reason for our lack of treatment effect in the schizophrenia group, and a potential limitation, is that the treatment course was too short. Even though an open-label study of DMPFC rTMS indicated that accelerating the treatment by giving several treatments per day might be as effective (Schulze et al., 2017), the more recent RCT by Dunlop et al could not show superiority over sham of accelerated twice daily DMPFC rTMS over three weeks (Dunlop et al., 2020). Further we applied 90% of resting foot motor threshold instead of 120%, which might have been too little. However, earlier studies of motor cortex plasticity support using the lower intensity (Nettekoven et al., 2014), and 90% also seems to have been sufficient in a recent trial of accelerated iTBS, although over the DLPFC (Cole et al., 2020). We also used two different ways of targeting in the study, but this is not likely to co-vary with treatment allocation and the effect of targeting method on treatment outcome was negligible.

Regarding blinding integrity, about two thirds of the patients in both groups correctly guessed treatment allocation after the first treatment day. We regard this as an acceptable level of blinding, yet not fully blinded even though there were no difference between active or sham. After the last treatment day however, about four fifths in the sham group and two fifths in the active group correctly guessed treatment allocation, i.e. more patients in the active group now guessed that they had received sham stimulation. Our interpretation of this is that the lack of a treatment effect made patients in the active group guess that they had received sham stimulation, and that more patients in the sham group correctly guessed their treatment allocation for the same reason.

4.3. Interpretation

Our overall findings are in line with the recently published first blinded RCT of rTMS over the DMPFC, which could not demonstrate a significant effect on overall depressive symptoms (Dunlop et al., 2020), as opposed to what was noted in an early open-label study (Bakker et al., 2015). Further comparison is however hampered by our study differing in delivering iTBS instead of conventional high- or low-frequency rTMS and by specifically targeting anhedonia, avolition, and blunted affect, and also including patients with schizophrenia. We used an arbitrarily chosen cut-off on the MAP-SR as an inclusion criterion being one-third of the maximum rating of the subjective negative symptoms. The sample of patients that we included had a mean CAINS total points just under 30, and in a recent study of persistent negative symptoms a cut-off of 25 has been proposed for moderate severity of negative symptoms (Li et al., 2018). Thus, we have probably captured a sample of patients with moderate to severe levels of anhedonia, avolition, and blunted affect.

Excluding the patients with schizophrenia from the analysis, however, yielded a significant effect of active treatment on anhedonia, avolition, and blunted affect. The effect was specific to this group of symptoms, with no significant treatment effect on overall depressive symptoms, which is in line with the reported role of DMPFC in reward and motivational functions (Ferenczi et al., 2016; Zhang et al., 2016). On the other hand, a recent circuit-based symptom-clustering analysis has proposed the DMPFC as a suitable anti-anxiety neuromodulation target (Siddiqi et al., 2020). Another possibility is that the observed specific effect on anhedonia, avolition, and blunted affect in our study was mediated through an effect on anxiety. At least anhedonia has been suggested to partly be a consequence of anxiety (Winer et al., 2017).

The reason that we do not find a treatment effect in patients with schizophrenia might be that this patient group is treatment resistant to a larger extent (Haro et al., 2018; He et al., 2017) and might have required a longer treatment duration to alleviate the persisting symptoms (Aleman et al., 2018). Further, the etiology of the negative

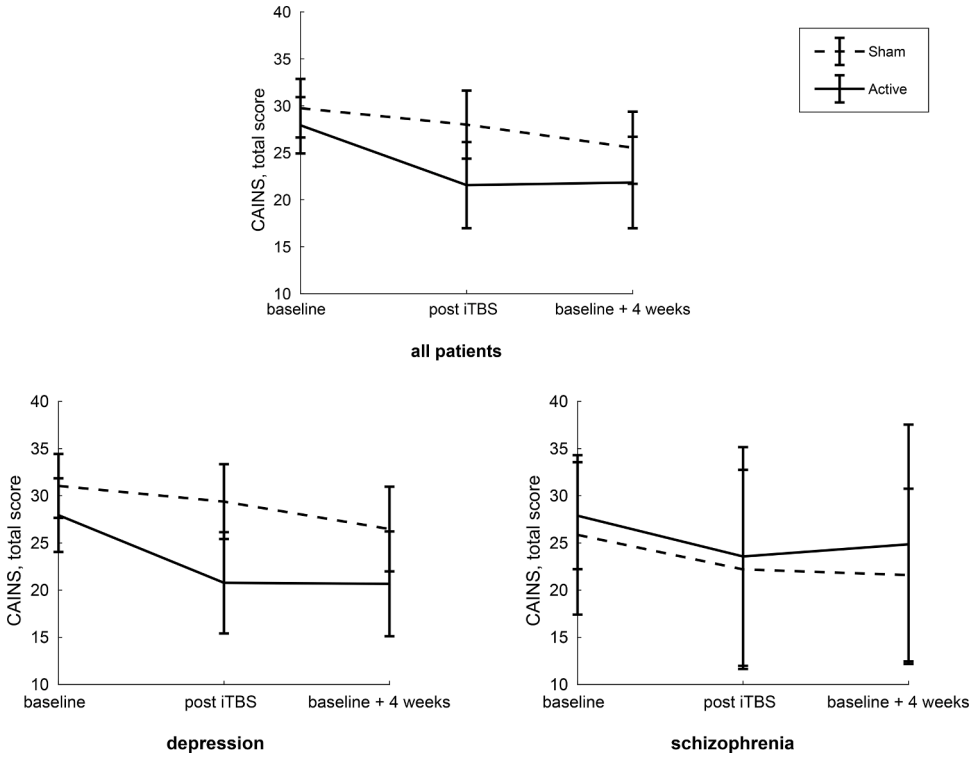

Fig. 2. Changes of scores on the Clinical Assessment Interview for Negative Symptoms (CAINS) assessment from baseline to end of treatment (post iTBS) and at the follow-up four weeks from baseline in the active iTBS and sham group respectively. On top displays data on all patients and below divided into the two subgroups depression and schizophrenia.

Table 2
Comparison between sham and active conditions at the two follow up assessments, for each of the secondary outcome measures. Delta scores (follow-up minus baseline) are reported as means (m) and standard deviations (sd), unless data represents rank scores from single items, in which case medians (Mdn) and interquartile ranges (IQR) are reported instead. Results from significance tests with Student's t-test (t-values), Wilcoxon rank-sum tests (z-values), and Chi-square tests (χ^2) are reported.

	Follow-up 1*				Follow-up 2**			
	Sham	Active	Statistic	p	Sham	Active	Statistic	p
CAINS total, m (sd)	-2.1 (7.1)	-5.3 (8.1)	t=1.54	.129	-4.5 (7.4)	-4.9 (8.6)	t=.20	.842
motivation and pleasure scale, m (sd)	-1.8 (5.5)	-4.3 (5.7)	t=1.67	.102	-3.5 (5.8)	-4.4 (6.5)	t=.54	.589
expression scale, m (sd)	-.3 (2.6)	-.9 (3.3)	t=.81	.421	-1.0 (2.5)	-.6 (3.1)	t=-.62	.536
Response, >25 % decrease	7/28	12/28	χ^2=1.99	.158	9/28	12/28	χ^2=.69	.408
MADRS-S total, m (sd)	-1.5 (4.1)	-3.6 (6.7)	t=1.42	.161	-2.7 (5.8)	-3.4 (7.2)	t=.37	.714
BPRS, m (sd)	-2.0 (5.9)	-3.3 (7.0)	t=.70	.488	-5.4 (7.3)	-4.0 (7.8)	t=.69	.494
PSQI								
Sleeping time, m (sd)	.2 (2.0)	-.4 (1.2)	t=1.35	.184	.1 (1.8)	-.3 (1.5)	t=.99	.325
Sleeping quality, Mdn (IQR)	0 (.5)	0 (.5)	z=1.59	.126	0 (.5)	0 (0)	z=1.24	.214
CGI, Mdn (IQR)	0 (1)	.5 (1)	z=1.18	.236	0 (2)	1 (2)	z=.38	.708
Sheehan disability scale, m (sd)	.5 (6.8)	-1.9 (6.5)	t=1.31	.196	.9 (7.1)	-1.4 (7.8)	t=1.13	.264
EQ-VAS, m (sd)	-3.2 (8.5)	-5.6 (23.1)	t=.51	.610	-6 (15.8)	-5.2 (24.6)	t=-.14	.887

* Day after last treatment
** Four weeks after baseline

symptoms in schizophrenia may be different. There is evidence of schizophrenia-specific prefrontal and temporo-limbic grey matter volume reductions that differ from patients with mood disorders (Koutsouleris et al., 2015). Thus, while a common transdiagnostical functional brain network dysfunction may underlie anhedonia and avolition, it would still be less amendable to change with neuromodulation in patients with schizophrenia if its origin is loss of brain tissue.

Another obvious reason for lack of a significant finding in patients with schizophrenia is that the transdiagnostic approach is flawed and that iTBS over the DMPFC might not be an effective treatment for anhedonia, avolition, and blunted affect in these patients. Findings supporting this stem from recent work identifying neurophysiological subtypes through analyses of combined symptom-clusters and resting-state connectivity patterns among mood-disorder patients that are not found in patients with schizophrenia (Drysdale et al., 2017). Maybe the DLPFC is a more suitable target for negative symptoms with higher frequency, given the promising results from the recent trials of four weeks 20-Hz rTMS on patients with schizophrenia (Kumar et al., 2020; Zhuo et al., 2019). Nevertheless, we can conclude that iTBS over the DMPFC was safe and tolerable, which is line with previous studies targeting DMPFC with conventional rTMS protocols (Bakker et al., 2015; Dunlop et al., 2020; Schulze et al., 2016).

4.4. Generalizability

We aimed to investigate a representative sample of patients seen in the every-day clinic to promote generalizability of the findings from our study, which we believe we succeeded with regarding the patients with depression. A caveat is that if we had managed to recruit more patients with schizophrenia spectrum disorder, the results might have been different, especially if more severely impaired patients would have participated. Thus our negative result is not enough evidence to rule out that there might be a possible treatment effect with DMPFC iTBS for anhedonia, avolition, and blunted affect in the schizophrenia group. The difficulties we faced with recruitment highlights the difficulties in conducting clinical trials in this patient population. Despite the overall negative results, our findings suggest that targeting the DMPFC may be beneficial in depression characterized by marked anhedonia.

4.5. Conclusion

In this first transdiagnostic randomized controlled trial of iTBS over DMPFC for anhedonia, avolition, and blunted affect, it can be concluded that the treatment was generally tolerable and safe but only more effective than sham in the subgroup of patients with depression and not in schizophrenia. Moreover, no significant effect was observed on overall self-rated depressive symptoms.

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Contributors

Robert Bodén: Conceptualization, Methodology, Validation, Investigation, Resources, Writing – Original draft, Supervision, Project administration, Funding acquisition. **Johan Bengtsson:** Conceptualization, Investigation. **Elin Thörnblom:** Investigation. **Wiebke Struckmann:** Methodology, Validation, Investigation. **Jonas Persson:** Methodology, Formal analysis, Data Curation, Writing – Original draft, Visualization, Supervision, Funding acquisition. All authors critically reviewed and revised the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.04.053.

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