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Motor cortex excitability in schizophrenia or depression and its modulation with prefrontal intermittent theta-burst stimulation

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ABSTRACT

Altered cortical excitability is reported in schizophrenia and depression, but findings are inconsistent. Prefrontal repetitive transcranial magnetic stimulation (TMS) induces short-term motor cortex excitability changes in healthy individuals, but its effect in schizophrenia and depression remains unexplored. Prefrontal intermittent theta burst stimulation (iTBS) improves negative symptoms in depression. Cortical excitability is a suggested biomarker for prefrontal iTBS response. We investigated if prefrontal iTBS affects motor cortex excitability in schizophrenia or depression. Secondary aims were to examine motor cortex excitability as a predictor of iTBS effect on negative symptoms in depression and to compare excitability between groups with schizophrenia, depression and healthy controls. TMS indices of cortical excitability – resting motor threshold, short-interval intracortical inhibition, intracortical facilitation and long-interval intracortical inhibition (LICI) – were pooled from previous studies, including an RCT evaluating iTBS for negative symptoms. The dataset comprised 44 patients with schizophrenia, 52 with depression, and 62 healthy controls. Regression models indicated no effect of active versus sham iTBS on any TMS index (all $p \geq .61$). No baseline TMS index predicted negative symptom changes after iTBS in depression (all $p \geq .44$). Patients with schizophrenia exhibited more pronounced LICI inhibition than the other groups (Mann-Whitney $U = 1670$, $p < .001$). LICI correlated with antipsychotic dose (Spearman's $\rho = -0.28$, $p = .04$). Prefrontal iTBS does not modify cortical excitability in schizophrenia or depression, nor does cortical excitability predict prefrontal iTBS effects on negative symptoms. The more pronounced LICI inhibition in schizophrenia may be related to the illness or medication.

1. Introduction

Intermittent theta burst stimulation (iTBS), a patterned form of repetitive transcranial magnetic stimulation (rTMS), is an established treatment for depression while remaining an investigational treatment in schizophrenia (Brandt et al., 2021; Lefaucheur et al., 2020).

Both disorders are characterized by negative symptoms such as anhedonia and avolition, suggesting a disruption in the reward system of the brain (Winograd-Gurvich et al., 2006). While early pilot studies of high frequency rTMS targeting the left dlPFC showed promising results ameliorating negative symptoms in schizophrenia (Shi et al., 2014), these results could not be replicated in a subsequent sufficiently powered clinical trial (Wobrock et al., 2015). Reward system impairments in both depression and schizophrenia potentially share dysfunctional activation of the medial prefrontal cortex and its network connections (Liang et al., 2022; Zhang et al., 2016). However, while iTBS targeting the dorsomedial prefrontal cortex (dmPFC) improves negative symptoms in depression, it does not seem to have the same effect in schizophrenia (Bodén et al., 2021). This raises questions about the underlying neurophysiological mechanisms of iTBS and its different effects on psychiatric conditions.

It has been proposed that rTMS modulates cortical excitability through effects on neural synaptic plasticity and intrinsic excitability (Dufor et al., 2023). It has been further proposed that the effect of rTMS in psychiatric conditions is mediated by altering cortical excitability in nodes of functional neural networks regulating mood and cognition (Idlett-Ali et al., 2023). An rTMS protocol with net excitatory effects in the directly stimulated area, like iTBS (Kanig et al., 2023), has both excitatory and inhibitory effects on different neurons in multiple cortical circuits (Dufor et al., 2023), and could therefore induce either inhibitory or excitatory effects in other areas within the functional network. Possible effects of prefrontal rTMS stimulation on motor cortex

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excitability are often examined with paired-pulse transcranial magnetic stimulation (ppTMS) coupled with electromyography (EMG) (Nordmann et al., 2015). In healthy subjects, previous studies report that prefrontal rTMS has short-term effects on motor cortex excitability (Cao et al., 2018; Furukawa et al., 2010), but no long-term effects (Bajbouj et al., 2005). It is unknown whether similar effects can be seen in patients with depression or schizophrenia.

Understanding more of the neurophysiology of rTMS might also allow for better treatment selection for the individual patient. There are reports of motor cortex excitability assessed with ppTMS as a possible predictor for antidepressive effect of a subsequent 10 Hz-rTMS treatment course over the dorsolateral prefrontal cortex (Hinchman et al., 2022; Oliveira-Maia et al., 2017). However, whether baseline motor cortex excitability can predict the treatment effect of iTBS targeting dmPFC has not yet been investigated.

Motor cortex excitability measured with ppTMS may be influenced by a multitude of factors (Pellegrini et al., 2020), including pharmacological effects (Minzenberg and Leuchter, 2019) and state effects of psychiatric disorders such as depression and schizophrenia (Mehta et al., 2021). Impaired cortical inhibition has been reported in both schizophrenia and depression along with increased cortical excitability in depression (Kinjo et al., 2021; Miyazawa et al., 2022), although the literature is still inconclusive.

Accordingly, this report includes three aims: the primary aim was to compare how active versus sham iTBS treatment targeting dmPFC affects motor cortex excitability as measured with ppTMS in a cohort of participants with either schizophrenia or depression.

The second aim was to examine if motor cortex excitability at baseline predicts clinical outcome of iTBS on negative symptoms in depression. The third was to compare motor cortex excitability between participants with schizophrenia, depression, and healthy controls.

2. Materials and methods

2.1. Participants

This report includes pooled data from four previous studies: a randomized controlled clinical trial (RCT) on dmPFC iTBS in schizophrenia and depression (Bodén et al., 2021), its add-on study (Struckmann et al., 2022) and two observational studies only including participants with schizophrenia (Bengtsson et al., 2022; Bodén et al., 2017). Inclusion criteria relevant for the current report were: age 18–59 years, schizophrenia spectrum disorder or ongoing major depressive episode (uni- or bipolar) verified with the Mini International Neuropsychiatric Interview version 6.0.0 (Sheehan et al., 1998) for patients, or negative screening for healthy controls, unchanged medication since at least one month, and for the RCT on dmPFC iTBS also $\leq$40 points on the Motivation and Pleasure Scale – Self-Report (MAP-SR) (Llerena et al., 2013). Exclusion criteria included epilepsy, intracranial ferromagnetic material, pregnancy, and active substance use disorder (except nicotine and caffeine). One of the included studies required two months stable medication with clozapine, olanzapine or quetiapine for inclusion, non-smoking status for healthy controls, and allowed benzodiazepine use, which was an exclusion criterion in the other three studies (Bodén et al., 2017). The participants with benzodiazepines were only included in the third analysis of the current report.

All included studies were approved by the regional ethical board of Uppsala, Sweden (registration numbers 2017/073, 2014/286, 2015/362 and 2018/018) and performed in accordance with the ethical standards of local and national institutional committees on human research ethics, as well as with the Helsinki Declaration of 1964, as revised 2013. All participants gave written informed consent before inclusion, after obtaining written information followed by individual meeting with investigators for complementary information and assessment of capacity for informed consent.

2.2. Cortical excitability assessment with TMS-EMG

TMS measurements were performed similarly in all four pooled studies, using. a Cool D-B80 coil (MagVenture) and a X100 Stimulator (MagVenture, Farum, Denmark) (Bengtsson et al., 2022; Bodén et al., 2017, 2021; Struckmann et al., 2022). The coil was held with the handle rotated 45° to the midsagittal line during stimulation. The resting motor threshold (rMT) "hotspot" (motor area of musculus interosseus dorsalis I) was located by finding the point of stimulation eliciting the largest MEP response in a 1 × 1 cm square grid starting 1 cm anterior and 5 cm left from the skull vertex. Individual rMT, defined as the percentage of maximum stimulator output required for a MEP response of 0.1 mV, was determined using the freeware TMS Motor Threshold Assessment Tool (MTAT 2.0) (Awiszus, 2003; Awiszus, Friedemann and Borckardt, Jeffrey J, n.d.). Electromyography motor-evoked potentials (MEP) (Dual Bio Amp, ADInstruments, Sydney, Australia) were recorded and digitized with LabChart 8 (ADInstruments, Sydney, Australia). EMG filter bandwidth was 4–1000 Hz, and sampling rate was 4 k/s. Due to a high level of EMG noise in some recordings, the rMT threshold was set at 0.1 mV rather than the more common 0.05 mV threshold, to optimize the signal-to-noise ratio.

The four cortical excitability TMS indices measured were rMT and three ppTMS parameters: short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), and long-interval intracortical inhibition (LICI). RMT serves as a measure of net corticospinal excitability, and is considered largely dependent on the excitability of glutamate-activated non-N-methyl-D-aspartate receptors and voltage-gated sodium channels, (Paulus et al., 2008), together with inputs from inhibitory and excitatory interneurons (Kobayashi and Pascual-Leone, 2007). SICI is thought to reflect $GABA_A$-receptor activity, with some variability at different interstimulus intervals (ISI), whereas ICF is mediated mainly by glutamatergic signaling, and LICI by $GABA_B$-receptor activity (Rossini et al., 2015).

For the three ppTMS parameters, conditioning pulse intensity (% of rMT) was 80% for SICI, 80% for ICF, and 120% for LICI. Test pulse intensity was 120% of rMT for all three parameters. ISIs were 3 ms for SICI, 12 ms for ICF, and 100 ms for LICI. Unconditioned motor evoked potential (ucMEP) was averaged from twenty trials, and the motor evoked potential (MEP) of the other three indices were averaged from ten trials in each protocol. Mean SICI, ICF and LICI was then defined as the percentage of the mean ucMEP amplitude (Patuzzo et al., 2003). The TMS-EMG indices were measured consecutively in the order ucMEP-SICI-ICF-LICI with no pauses between the measurements.

2.3. Treatment with iTBS

In the iTBS treatment trial, participants received two daily sessions of 50 Hz-iTBS treatment sessions over dmPFC over 10 consecutive weekdays (1200 pulses/session, with reversed current direction after 600 pulses in order to stimulate both sides of the dmPFC). The coil used was Cool D-B80 A/P coil (MagVenture), with two identical sides, active and sham. The sham side was magnetically shielded, with transcutaneous electric nerve stimulation (TENS) applied simultaneously as the sham stimulation. All participants had TENS electrodes applied to their foreheads, directly under the rTMS coil. Both participants and iTBS operators were blinded to treatment allocation. Target stimulus intensity was 90% of rMT, which in turn was defined as the lowest stimulation intensity needed to elicit a visually observed motor contraction in the foot in 50% of stimulus trials.

Baseline TMS assessments were performed one or two days before the first treatment day, and at the last treatment day. Participants randomized to sham treatment were offered active treatment after unblinding, including an additional TMS assessment on the last day of open treatment phase. Please refer to the previously published report for more details on the iTBS treatment (Bodén et al., 2021).

2.4. Negative symptom assessment

To examine the relationship between baseline TMS indices and clinical effect of iTBS, clinical effect was defined as reduction in the total score on The Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013). Participants in the iTBS RCT were assessed with CAINS at baseline, and four weeks after the first day of treatment. As previously reported, only the subgroup with depression showed a significant change in total CAINS score (Bodén et al., 2021). Therefore, the analysis of possible predictive value of TMS indices on change in CAINS score was only performed in the subgroup with depression.

2.5. Medication

Medication was noted upon inclusion. Antipsychotics dose was transformed to olanzapine equivalents using Gardner international consensus of 2010 (Gardner et al., 2010), as this covered the most antipsychotics used among study participants. Five participants (all in the schizophrenia group) had long-acting injection antipsychotics (one olanzapine, four paliperidone), which were not included in the Gardner consensus paper. Two other participants, also in the schizophrenia group, had long-acting injection antipsychotics with a different interval than in the consensus (one with haloperidol decanoate and one with perphenazine enanthate). For these seven participants, we calculated the daily dose in milligrams by dividing the injection dose by the number of days between injections and using the equivalency ratio of the corresponding oral antipsychotic to reach an estimated olanzapine equivalence.

2.6. Statistical methods

The effect of active versus sham iTBS treatment on changes in each of the four TMS indices was compared using regression analyses. Each TMS index was treated as a separate dependent variable, with time (before or after iTBS), treatment (sham or active), and 'time × treatment' as fixed effects. RMT was included in a linear mixed model using maximum likelihood estimation to allow for model comparison and study ID as a random intercept. SICI, ICF, and LICI did not yield normally distributed residuals in linear mixed models. These three indices were instead entered into generalized estimated equations with the same fixed and random effects as above using gamma log link as the scale response and null values recoded to 0.00001. In each regression model, a second analysis was performed with diagnosis (depression or schizophrenia) and 'time × treatment × diagnosis' added as fixed effects.

The predictive effect of baseline TMS indices on CAINS at pre- and postassessments was explored with a separate linear mixed model for each TMS index (rMT, SICI, ICF and LICI). CAINS score was entered as the dependent variable, with time (before or after iTBS), one baseline TMS-index, and 'time × baseline TMS-index' as fixed effects. Maximum likelihood estimation was used for model comparison and study ID entered as random intercept.

Baseline TMS indices were compared with Kruskal-Wallis across patients with schizophrenia, depression and healthy controls. This was followed by Mann-Whitney *U* test if significant differences were found.

Statistical calculations were performed in SPSS Statistics version 28.0.1.0 (IBM Corporation and others).

3. Results

3.1. Analysis 1. comparing motor cortex excitability change after active versus sham iTBS

Data on TMS assessments before and after an active or sham iTBS treatment were available for 63 patients. Participant age, sex, diagnosis and medication are shown in Table 1, along with the duration between the last iTBS treatment and follow-up TMS-EMG assessments. The ppTMS indices are shown in Fig. 1. There was no significant effect of time (all $p \geq .17$, data not shown) or 'time × treatment' interaction (as shown in Table 2) on any TMS index. Adding diagnosis as a fixed variable showed no effect of 'time × treatment × diagnosis' on any TMS index (all $p \geq .24$, data not shown). In conclusion, there was no significant change in any TMS index after iTBS. Active iTBS did not affect motor cortex excitability measures differently than sham, and there was no difference between participants with schizophrenia and depression.

Table 1
Analysis 1 participant descriptives.

	Active ($n = 32$)	Sham ($n = 31$)
Schizophrenia/depression, *n*	7/25	5/26
Women, *n*	15	15
Median age, years (Q_1,Q_3)	29 (23,36)	27 (22,36)
Days from last iTBS to follow-up, mean (SD)	10 (5)	12 (3)
Psychotropic drugs		
Antidepressants, *n*	24	20
Antiepileptics, *n*	6	4
Lithium, *n*	4	4
Nicotine users, *n*	10	11
Stimulants, *n*	0	7
Antipsychotics, *n*	11	11
Median antipsychotics dose[a], mg (Q_1,Q_3)	9 (6,13)	5 (3,17)

[a] Daily olanzapine equivalents.

3.2. Analysis 2. predictive effects of baseline motor cortex excitability on clinical outcome of iTBS for negative symptoms in depression

This analysis included 46 patients with depression who received active iTBS in either the blinded or open phase of the RCT. Group characteristics are shown in Table 3. The depression group in the table includes six patients who were lost to follow up and thus excluded from analysis 2, but included in analysis 3. There was no significant effect of 'time × baseline TMS index' on CAINS score for any of the included TMS indices, as shown in Table 4, implying that motor cortex excitability at baseline did not predict the effect of active iTBS on negative symptoms in depression.

3.3. Analysis 3. group comparison of motor cortex excitability in patients with schizophrenia, depression and healthy controls

Group characteristics are shown in Table 3. Comparisons of the four baseline TMS indices between participants with schizophrenia, depression, and healthy controls are shown in Fig. 2. The group with schizophrenia had lower median LICI MEPs (2.5% of ucMEP) than both the group with depression and healthy, which both had median LICI MEPs of 38% of ucMEP (both groups: Mann-Whitney $U = 1670$, $p < .001$). The other three TMS indices did not differ between the three groups (all $p > .17$, data not shown).

3.4. Post-hoc analyses

In analysis 1, the time interval from the last iTBS treatment to the follow up TMS-EMG assessment was considered a potential confounder. A *t*-test comparing the mean time intervals between the active and sham groups showed that the active group had a shorter mean time interval from the last iTBS to follow-up ($p = 0.03$). Therefore, in a post-hoc analysis, time interval was entered as an added fixed effect in the four regression models. However, the effects of time and 'time × treatment' on the respective TMS-EMG indices were minimally affected by this addition (all $p \geq .15$, data not shown).

All participants with schizophrenia were on antipsychotics ($n = 44$) but only one-fifth of the participants with depression ($n = 11$), and the group with schizophrenia had higher antipsychotic doses and included 20 individuals with clozapine, as shown in Table 3. Therefore, we

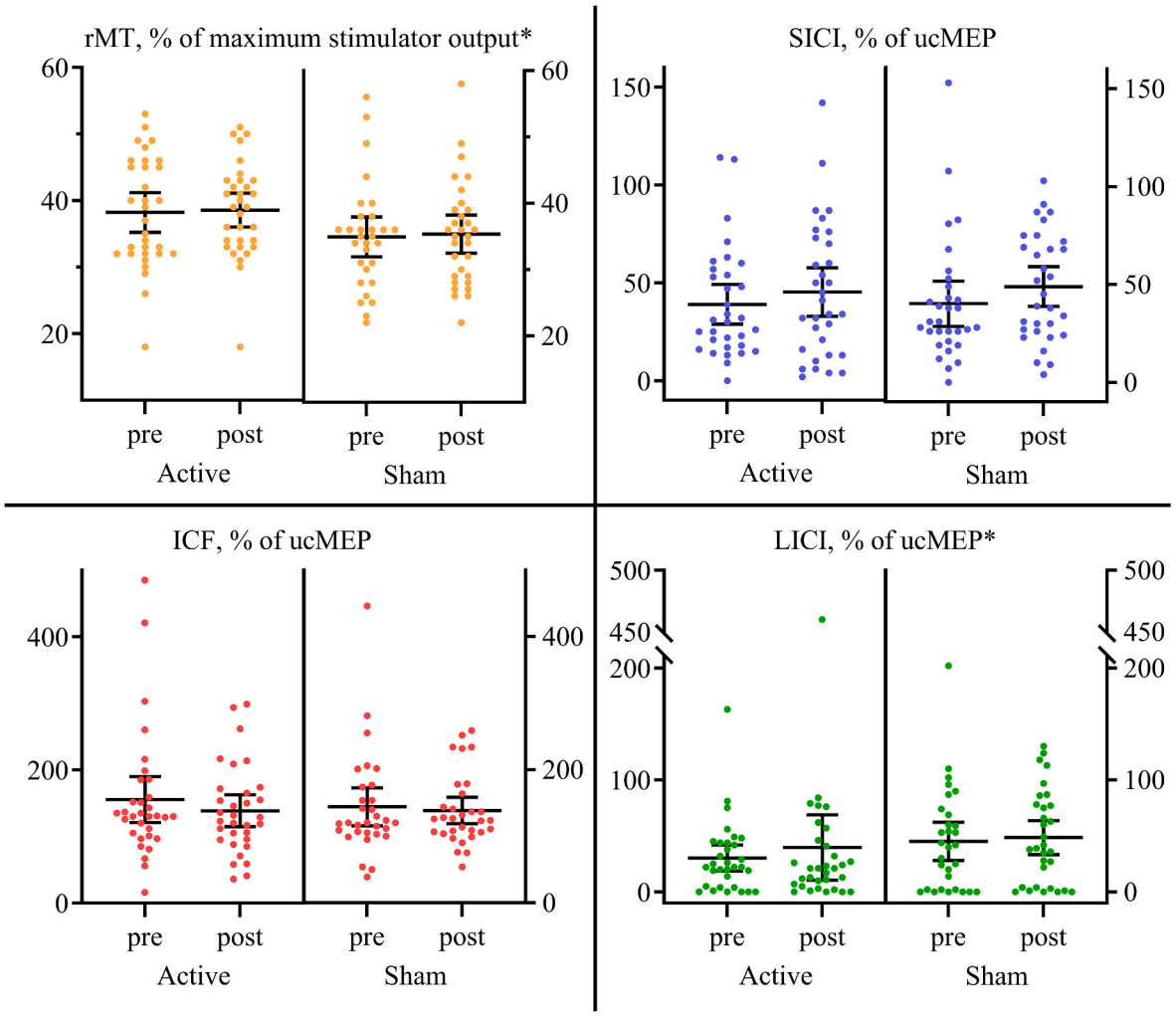

Fig. 1. Scatterplots of resting motor threshold (rMT), short-interval intracortical inhibition (SICI), intracortical facilitation (ICF) and long-interval intracortical inhibition (LICI) before and after two weeks twice daily active or sham intermittent theta burst stimulation treatment. Mean value and 95% confidence interval indicated. *Missing data: 1 rMT and 1 LICI in sham group.

Table 2
Effect of active/sham intermittent theta burst stimulation (iTBS) on paired pulse transcranial magnetic stimulation (ppTMS) indices, $n = 63$.

Dependent variable	β	95% CI	p
Resting motor threshold[a]	0.29	−1.82–2.39	0.79
Short-interval intracortical inhibition	0.05	−0.25–0.34	0.75
Intracortical facilitation	0.08	−0.22–0.37	0.61
Long-interval intracortical inhibition[a]	−0.20	−1.01–0.61	0.63

Each ppTMS index entered as dependent variable in four separate regression models with time (before or after iTBS), treatment (active or sham), and time × treatment as fixed effects. Linear mixed model was used for resting motor threshold, generalized estimation equations for the others. Results shown only for effect of time × treatment in each analysis.

[a] n = 62 (2 separate participants, both in depression/sham group).

considered antipsychotic dose and clozapine as possible confounders of the group differences observed in LICI. In a post-hoc correlation analysis of antipsychotic dose versus LICI MEP amplitude in the 54 participants with antipsychotics, daily antipsychotic dose (in olanzapine equivalents) correlated negatively with LICI MEP amplitude (Spearman's $\rho = -0.28$, $p = .04$). When comparing the 20 participants with clozapine with the 35 participants with other antipsychotics, LICI MEP amplitude was lower and antipsychotics doses higher in the group with clozapine (Mann-Whitney U 163 and 578, respectively, both $p < .001$). The correlation of antipsychotics dose and LICI is illustrated in Fig. 3.

In a final post-hoc analysis we explored possible effects of nicotine use on the results. The literature on nicotine effects on cortical excitability is inconsistent and mainly investigated during abstinence in nicotine users, but suggest possible effects on motor cortex plasticity and the GABA-dependent TMS-EMG indices SICI and LICI (Grundey et al., 2013; Lavender et al., 2019; Strube et al., 2015). Participants in our study were instructed to use nicotine according to their usual habit before TMS-EMG measurements, and were therefore not abstinent at the assessments. We considered it unlikely that nicotine use affected the negative results of analysis 1, as the ratio of nicotine users were similar in the active versus sham comparison. To examine if nicotine use could have affected the baseline group comparison in analysis 3, we compared the four TMS-EMG indices in nicotine users and non-nicotine users with Mann Whitney U. Nicotine users had more pronounced SICI ($U = 1972$, $p = 0.02$), but the other three indices did not differ between groups (all $p \geq 0.25$, data not shown). Baseline SICI was then compared across the diagnostic groups separately in nicotine users and non-nicotine users, according to analysis 3. No group differences were found among nicotine users. However, among non-nicotine users, participants with depression had lower SICI than participants with schizophrenia, which was confirmed by a subsequent Mann-Whitney U test ($U = 306$, $p = 0.03$).

Table 3
Analysis 2 and 3 participant descriptives and paired pulse transcranial magnetic stimulation (ppTMS) indices.

	Schizophrenia (n = 44)	Depression (n = 52)	Healthy (n = 62)
Women/men, n	12/32	28/24	35/27
Median age, years (Q_1,Q_3)	40 (31,47)	27 (22,35)	27 (23,39)
Psychotropic drugs			
Antidepressants, n	16	41	0
Antiepileptics, n	11	6	1
Lithium, n	3	7	0
Nicotine users, n	17	17	13
Stimulants, n	0	7	0
Antipsychotics, n[a]	44	11	0
Median antipsychotic dose[b], mg (Q_1,Q_3)	14 (8,25)	3 (2,7)	–
PpTMS indices, median (Q_1,Q_3)			
Resting motor threshold	37 (34,44)[c]	35 (31,40)[d]	36 (33,41)
Short-interval intracortical inhibition	44 (21,76)	30 (20,49)	36 (20,54)
Intracortical facilitation	139 (102,172)	129 (108,186)	153 (110,193)
Long-interval intracortical inhibition	3 (0,24)	38 (14,59)[d]	38 (3,70)

[a] Clozapine: 20 in schizophrenia group, 0 in depression group.
[b] Daily olanzapine equivalents.
[c] n = 43.
[d] n = 51.

Table 4
Effects of the interaction between baseline ppTMS indices and time (before and after iTBS) on CAINS score in patients with depression, n = 46.

Independent variable	β	95% CI	p
Time × Resting motor threshold	0.04	−0.26–0.33	0.81
Time × Short-interval intracortical inhibition	−3.13	−11.16–4.91	0.44
Time × Intracortical facilitation	0.44	−2.13–3.01	0.73
Time × Long-interval intracortical inhibition	1.31	−4.62–7.23	0.66

ppTMS: paired pulse transcranial magnetic stimulation, iTBS: intermittent theta burst stimulation, CAINS: The Clinical Assessment Interview for Negative Symptoms, iTBS: intermittent theta burst stimulation, CI: confidence interval.

4. Discussion

In this first study of the effect of a treatment course of prefrontal iTBS on cortical excitability, two weeks of twice daily iTBS targeting dmPFC did not change motor cortex excitability and there was no difference in change between active and sham iTBS. Motor cortex excitability at baseline did not predict clinical outcome on negative symptoms after dmPFC iTBS in depression.

Patients with schizophrenia had more pronounced cortical inhibition in the LICI paradigm than patients with depression and healthy controls, but the groups did not differ in MT, SICI, or ICF. Cortical inhibition in the LICI paradigm also correlated positively with higher antipsychotic doses.

4.1. Analysis 1. comparing motor cortex excitability change after active versus sham iTBS

To our knowledge, there are no previous studies on possible effects of a whole treatment course of iTBS targeting the dmPFC on motor cortex excitability. There are however some studies targeting the adjacent dorsolateral prefrontal cortex (dlPFC). In line with our negative result, a sham-controlled study of healthy participants that received a treatment course of five days twice-daily iTBS targeting dlPFC did not observe any effect on motor cortex excitability (Bouaziz et al., 2021). Even though an enduring effect of a whole treatment course of prefrontal iTBS on motor cortex excitability seems to be absent, there are indications in healthy participants of immediate effects of one single dlPFC iTBS train leading to an increased MEP amplitude (Cao et al., 2018), and increased

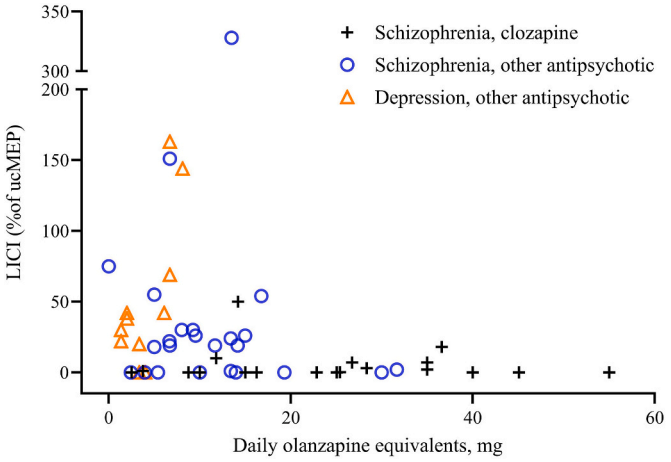

Fig. 3. Scatter plot of antipsychotic dose, converted to olanzapine equivalents, and long-interval intracortical inhibition (LICI). LICI presented as percentage of unconditioned motor evoked potential (ucMEP).

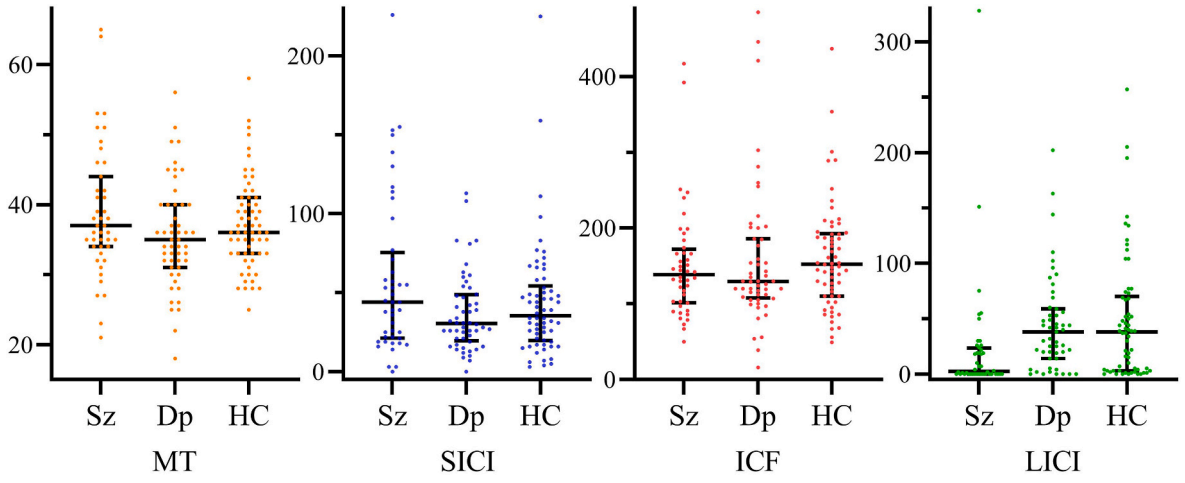

Fig. 2. Scatterplots with median and interquartile range of motor threshold (MT), short-interval intracortical inhibition (SICI), intracortical facilitation (ICF) and long-interval intracortical inhibition (LICI) in participants with schizophrenia (Sz), depression (Dp), and healthy controls (HC).

duration of the cortical silent period after a train of low-frequency rTMS targeting dmPFC with a circular coil (Furukawa et al., 2010).

4.2. Analysis 2. predictive effects of baseline motor cortex excitability on clinical outcome of iTBS for negative symptoms in depression

We found no predictive capacity of any baseline TMS index on the effect of iTBS on negative symptoms. This is in line with the only previous study that is somewhat comparable. This study observed that the degree of MEP facilitation after one session of 10 Hz rTMS predicted clinical effect of a subsequent 10 Hz rTMS treatment series for depression, whereas MEP facilitation after one session of iTBS did not (Hinchman et al., 2022).

4.3. Analysis 3. group comparison of motor cortex excitability in patients with schizophrenia, depression and healthy controls

In the group comparison, we found no difference in rMT between participants with schizophrenia, depression and healthy, which is similar to a previous large naturalistic group comparison (Mehta et al., 2021). This is also in line with most previous group comparisons of rMT in schizophrenia and healthy (Bagewadi et al., 2019; Daskalakis et al., 2002, 2008; Fitzgerald et al., 2002a; Liu et al., 2009; Mehta et al., 2014; Oxley et al., 2004; Pascual-Leone et al., 2002; Strube et al., 2014; Wobrock et al., 2008) although one well powered comparison found higher rMT in patients with schizophrenia (Soubasi et al., 2010). Previous studies comparing rMT in patients with depression and healthy are more inconsistent, reporting group differences in both directions, as reviewed by Bunse et al. (2014).

We did not observe any differences in SICI between patients with schizophrenia, depression, or healthy, which is in line with some previous reports (Bagewadi et al., 2019; Castricum et al., 2022; Daskalakis et al., 2008; Pascual-Leone et al., 2002; Strube et al., 2014). However, several other group comparisons with healthy participants report less SICI inhibition in schizophrenia (Bunse et al., 2014; Du et al., 2019) as well as in depression (Chen et al., 2023; Kinjo et al., 2021). Possible explanations for these conflicting findings could be different antipsychotic dose, group sizes, disease state of included participants, and ppTMS procedures. Our post-hoc finding of more pronounced SICI in the participants with depression versus participants with schizophrenia in the non-nicotine-using subgroup should be considered preliminary due to lower power and multiple comparisons, but may indicate that nicotine use normalizes SICI in schizophrenia, similar to reports of normalized cortical plasticity in schizophrenia (Strube et al., 2014).

In line with our findings, most group comparisons have found no difference in ICF in patients with schizophrenia (Daskalakis et al., 2002; Fitzgerald et al., 2002a, 2002b; Hasan et al., 2012; Liu et al., 2009; Strube et al., 2014; Wobrock et al., 2008), although less ICF is also reported (Bagewadi et al., 2019). In depression, increased ICF compared to healthy is the most common, albeit findings are yet again inconclusive (Chen et al., 2023; Kinjo et al., 2021).

We found more LICI inhibition in schizophrenia as compared to healthy and depressed. This differs from the results from a large group comparison that observed less LICI inhibition in patients with schizophrenia (Mehta et al., 2021). A possible explanation for the disparate results may be different study populations. All patients with schizophrenia in our study were on antipsychotic medication, and the dose correlated with LICI, which could imply that unmedicated schizophrenia entails less LICI inhibition while antipsychotic medication increase LICI inhibition. On the other hand, higher antipsychotics dose could reflect more pronounced symptomatology, which may in itself affect cortical excitability. Thus, we cannot ascertain whether the difference in LICI is caused by the antipsychotics, the schizophrenia disorder, or a combination.

We found no difference in LICI between depressed and healthy, contrariwise to previous reports (Chen et al., 2023; Jeng et al., 2020; Mehta et al., 2021). The patients with depression in our subgroup had several types of antidepressants and included both uni- and bipolar depressive episodes, which could potentially have increased the variability within the group. Further, our study only included depressed patients with a high degree of negative symptoms, which might reflect a separate neurophysiological subtype.

Another TMS method to study $GABA_B$-receptor dependent cortical inhibition is cortical silent period (CSP), which seems responsive to both $GABA_A$ and $GABA_B$ modulation (Rossini et al., 2015). Again, findings vary, but in a recent meta-analysis of schizophrenia, CSP is increased by clozapine, but not by other antipsychotics (Miyazawa et al., 2021) and CSP did not differ from healthy in drug naïve patients in early disease stages (Miyazawa et al., 2022). How cortical inhibition in later disease stages may be affected in schizophrenia may be even more difficult to disentangle from pharmacological effects.

In our study, LICI inhibition was most pronounced in patients with clozapine and antipsychotic dose correlated with LICI, which suggests that antipsychotics contributes to increased LICI inhibition in chronic schizophrenia, comparable to findings of CSP effects of antipsychotics. To our knowledge, there are no previous reports on increased LICI inhibition in schizophrenia with correlation to daily antipsychotic dose and clozapine use. Our results are in line with previous literature on CSP, insofar as LICI and CSP may be compared due to their shared sensitivity to $GABA_B$-active drugs.

4.4. Limitations

One important limitation of this report is that it is a pooled analysis across four studies that were conducted with separate primary aims and power analyses. Thus, investigations were not planned for the aims of this report, and the number of participants included may be insufficient to power the included analyses. On the other hand, TMS measurement methods were similar across the pooled studies, and performed by the same research staff. Although the number of participants were not calculated for these separate analyses, group sizes are still comparatively large compared to the previous literature, possibly lessening the risk of spurious false positive findings and false negatives.

Active TENS was only delivered in the sham paradigm and not in active iTBS treatment, which might have increased the difference between the two conditions. However, participant blinding seemed adequate at the end of the series, before follow-up TMS-EMG assessments (Bengtsson et al., 2023).

The negative result of analysis 1 could also be due to the delay between last iTBS and ppTMS assessment, where excitability might already have returned to baseline through homeostatic mechanisms.

Another limitation is including both patients with bipolar and unipolar disorders in the depression group. Some evidence suggests that motor cortex excitability measures may differ between uni- and bipolar depression (Bunse et al., 2014; Cotovio et al., 2022) in which case our group of patients with depression could have included a higher variability than if only uni-or bipolar depression had been included.

In the schizophrenia group, we had no patients without antipsychotic medication, which might have confounded the results. However, all included participants had symptom severity of a degree necessitating antipsychotic medication. Including participants with the same symptomatology without offering antipsychotic medication would have been ethically and clinically challenging.

From a TMS methodological perspective, there are potential limitations associated with the technique used in our study. The relatively longer ISI of 3 ms that we used in our studies for SICI measurements has been suggested to yield less pronounced inhibitory response than shorter ISI (Peurala et al., 2008). This could potentially lead to an underestimation of individual SICI due to contamination of short interval intracortical facilitation, which may occur in ISIs longer than 2 ms (Rossini et al., 2015). Thus, a potential difference in SICI might have gone undetected. Additionally, the baseline LICI MEP amplitudes in the group

comparison suffer from a floor effect, which probably also interferes with both the correlation analysis of antipsychotics dose and LICI as well as the comparison of LICI in participants with clozapine and other antipsychotics. Using a so-called adaptive stimulus ppTMS technique (Amandusson et al., 2017) could have mitigated the floor effect and allowed for more exact assessments.

4.5. Future directions

The heterogeneity and variability of TMS-EMG measures are a prevailing challenge to the field. Both TMS-EMG paradigms and excitability effects of iTBS has been found to be affected by baseline rMT, which could be controlled for in analyses to reduce variability (Corp et al., 2021, 2020). Mapping TMS-EMG responses over input/output curves rather than fixed ISIs, or developing alternative methods for stimulus intensities in the ppTMS protocols may provide further measurement reliability (Corp et al., 2021). At the same time, measurements must be reasonably framed to retain tolerability for research participants. Measuring how motor cortex excitability is affected by different challenges, such as specific tasks or activities, may provide more insights than comparisons of absolute TMS-EMG indices. Given the large inter-individual variability of TMS-EMG indices, repeated assessments over time may also reveal more information about how excitability regulation is affected by different states than direct comparisons between individuals, for example examining effects on TMS-EMG indices by medication changes. Repeated measures may also reveal how long such potential short-term excitability effects remain. Another possible way forward is comparison between medicated and drug naïve patients with similar conditions or increasing the specificity of diagnostic groups by examining the relation of TMS-EMG to definable symptoms and if changes correlate. Since small participant cohorts may be a cause of both type I and type II errors, increasing study power by multi-center collaborations with harmonized investigational procedures may yield more consistent findings in the future (Corp et al., 2021, 2020).

5. Conclusion

A treatment series of dmPFC iTBS did not affect motor cortex excitability in patients with schizophrenia or depression. Baseline motor cortex excitability could not predict the efficacy of iTBS over dmPFC treating avolition and anhedonia in depression. Going forward, it might be more informative to measure excitability effects directly in the stimulated area when investigating psychiatric iTBS.

Patients with schizophrenia had more pronounced LICI inhibition over the motor cortex compared to both patients with depression and healthy controls. However, we cannot discriminate between potential biological illness factors and pharmacological effects. Prospective and repeated measurements may be a possible method to further disentangle effects of medication and disease on cortical excitability in schizophrenia.

CRediT authorship contribution statement

Elin Thörnblom: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Linda Steinholtz:** Writing – review & editing, Methodology, Conceptualization. **Jonas Persson:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Hans Axelson:** Writing – review & editing, Supervision, Methodology. **Robert Bodén:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

None.

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