Journal of Affective Disorders 409 (2026) 121908

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Auditory mismatch-negativity predicts response to dorsomedial prefrontal intermittent theta-burst stimulation in major depressive disorder

Marcus Anderson [a,*,1], Robert Bodén [a,1], Caroline E. Wass [b,2], Hatice Zora [c,d,3,4], Johan Bengtsson [a,1], Jonas Persson [a,1]

[a] Clinical Psychiatry, Department of Medical Sciences, Uppsala University, Sweden
[b] Department for Affective Disorders, Department of Pharmacology, University of Gothenburg & Sahlgrenska University Hospital, Sweden
[c] Department of Linguistics, Stockholm University, Sweden
[d] Neurobiology of Language Department, Max Planck Institute for Psycholinguistics, the Netherlands

ARTICLE INFO

Keywords:
rTMS
iTBS
DMPFC
MDD
Event-related potential
Mismatch negativity

ABSTRACT

Background: Impaired plasticity has been implicated in major depressive disorder (MDD), which is reflected in impaired automatic sensory detection as measured using mismatch negativity (MMN). Intermittent theta-burst stimulation (iTBS) is used to treat MDD and its mechanism of action has been suggested to be plasticity dependent. Thus, we aimed at evaluating MMN as a MDD biomarker and predictor of antidepressant effect of iTBS.

Methods: This study comprised 46 patients with MDD and 64 healthy controls. The participants completed an auditory duration deviant MMN paradigm. In patients, MMN was recorded before and after a two-week intervention of twice-daily stimulation with a prolonged iTBS protocol, or sham, over the dorsomedial prefrontal cortex (DMPFC). Depressive symptoms were assessed with the affective subscale of the Brief Psychiatric Rating Scale (BPRS-affective) and through the self-report version of the Montgomery-Åsberg Depression Rating Scale (MADRS-S).

Results: There were no differences in MMN amplitude at baseline between patients and controls, nor any correlations between depressive symptoms and MMN amplitude. MMN amplitude did not change after iTBS. However, in the active iTBS group a larger baseline MMN amplitude correlated significantly with greater reductions of depressive symptoms following iTBS, Δ-MADRS-S ($r = 0.48$, $p = 0.021$) and Δ-BPRS-affective ($r = 0.46$, $p = 0.026$). No correlation between baseline MMN amplitude and change of depressive symptoms was observed in the sham group.

Conclusion: Larger MMN amplitudes at baseline were associated with greater improvement in depressive symptoms only after active iTBS over the DMPFC. Indicating potential predictive properties of MMN in DMPFC iTBS in MDD, warranting replication in larger samples.

1. Introduction

Major depressive disorder (MDD) is a common mental disorder characterised by anhedonia, decreased mood and cognitive deficits, including pre-attentive sensory processing. MDD can be understood under the umbrella of the predictive coding framework, which is a model to describe the brain's ability to perceive discrepancy between expected outcomes and deviant novel outcomes (i.e., "prediction error"), which in turn serves to update the knowledge base for future predictions (Gilbert et al., 2022). The neuronal processes underlying the integration of a prediction error into an updated knowledge of future predictions, likely rely on synaptic plasticity (Fitzgerald and Todd, 2020), in line with reported deficits of plasticity in depression measured by paired associative stimulation (Noda et al., 2018).

* Corresponding author.
E-mail address: Marcus.anderson@uu.se (M. Anderson).
[1] Address: Clinical Psychiatry, Department of Medical Sciences, Akademiska Sjukhuset, Ingång 10, plan 3, 751 85, Uppsala, Sweden.
[2] Address: Department of Pharmacology, Institute of Neuroscience and Physiology, Göteborgs Universitet, Box 431, 405 30 Göteborg Gothenburg, Sweden.
[3] Address: Institutionen för lingvistik, 106 91, Stockholm, Sweden.
[4] Address: Wundtlaan 1, 6525 XD, Nijmegen, The Netherlands (present address).

https://doi.org/10.1016/j.jad.2026.121908
Received 10 October 2025; Received in revised form 29 April 2026; Accepted 1 May 2026
Available online 3 May 2026
0165-0327/© 2026 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

In recent decades, repetitive transcranial magnetic stimulation (rTMS) has emerged as an effective treatment option for patients that have not responded to at least two antidepressant pharmacotherapies. Response rates to high frequency rTMS for depression varies between 30 and 50% (Ekman et al., 2023). However, predictive biomarkers of rTMS treatment response are lacking (Fitzsimmons et al., 2024; Kim et al., 2021). A TMS pulse activates cortical neurons by electromagnetic induction, through repetition of pulses rTMS alter cortical excitability and functional connectivity (Iwabuchi et al., 2017). Time efficient rTMS protocols delivering three 50 Hz bursts at 5 Hz intervals, so called intermittent theta burst stimulation (iTBS), over the medial prefrontal cortex (DMPFC) have proven to be effective in treating depression (Bakker et al., 2015; Blumberger et al., 2018). The exact mechanism of action is unknown, changes in plasticity are thought to underly the effect of iTBS in depression (Huang et al., 2007; Noda et al., 2018).

In depression, insufficient reward error prediction may contribute to negative bias and anhedonia (Gilbert et al., 2022). A surrogate measure of prediction error is Mismatch Negativity (MMN), a neurophysiological, pre-attentive measure of pattern deviation detection (Harms et al., 2021). Specifically, MMN is an event-related potential (ERP) in response to an infrequent deviant stimulus, e.g., a deviant auditory signal in a sequence of otherwise identical stimuli (Duncan et al., 2009; Näätänen et al., 1978). A recent meta-analysis concluded that MMN amplitude and latency following duration deviants differed between patients with MDD and healthy controls, but that depressive symptom burden did not correlate to MMN responses (Tseng et al., 2021). More precisely, using 50 ms as standard and 100 ms as deviant duration (Chen et al., 2015) or 50 ms as standard and 150 ms as deviant duration (Qiao et al., 2015) has been shown to differentiate between patients with MDD and healthy controls. A narrative review suggested that there is a pattern of attenuated amplitude in duration MMN but increased amplitude of frequency MMN in patients with MDD (Kangas et al., 2022). The knowledge of rTMS effects on MMN are still in its infancy. No study on the effects of high frequency rTMS over the DMPFC cortex on MMN has been conducted. However, one study of patients with MDD and comorbid somatic pain randomized to treatment with either Sertraline or Sertraline combined with left dorsolateral prefrontal cortex (DLPFC) iTBS and right DLPFC 1 Hz rTMS treatment, found significantly lower MMN latencies in a secondary analysis in the rTMS group at six week follow-up (Sun et al., 2023), thus indicating that rTMS targeted at prefrontal areas may modulate MMN.

To summarise, MDD has been associated with impaired plasticity with aberrant MMN, which may in part be related to deviant reward error prediction which in turn may contribute to the depressive state. The effects of iTBS on depressive symptoms may partially be partially dependent on plasticity, which might be possible to assess using MMN as a proxy.

The aim of this study was therefore threefold; *1*) to investigate whether baseline depressive symptomatology would correlate with measures of MMN; *2*) whether a treatment course of DMPFC iTBS would alter MMN and; *3*) whether baseline MMN could predict treatment response of iTBS.

2. Materials and methods

2.1. Study design and ethical considerations

This is a sub-analysis of data from a randomized double blinded sham-controlled study on DMPFC iTBS previously conducted (Bodén et al., 2021) at the brain stimulation unit at Uppsala University Hospital, Sweden. The trial was pre-registered at clinicaltrials.gov, ID: NCT02905604. Inclusion criteria: being 18 years or older, current MDD episode, unaltered pharmacotherapy the past month and written informed consent. Exclusion criteria: Established contraindications for TMS, continuous benzodiazepine treatment, bipolar depression, substance use disorder, pregnancy, significant intellectual disability impairing comprehension of informed consent. Pharmacotherapy remained unaltered until the second follow-up. No patients participated in psychotherapy during the trial period. All participants underwent pregnancy and illicit drug screening by urinary analysis.

2.2. Participants

Forty-six patients, ages 18–54, with primary or recurrent unipolar MDD were recruited between 2015 and 2020. Patients were referred by their out-patient psychiatrist and consecutively approached regarding research participation. Sixty-four healthy controls, ages 18–58, were enrolled via digital and physical adverts. Healthy controls only underwent baseline testing. Patients first underwent baseline testing and thereafter randomization to receive either active or sham iTBS. All patients initially randomized to sham iTBS were offered open-label active treatment after follow-up testing.

2.3. Procedures

2.3.1. Assessments

Baseline testing was performed by a psychiatrist and comprised of a physical, neurological and psychiatric evaluation and interview including Mini International Neuropsychiatric Interview (M.I.N.I.) Swedish translation of version 6.0.0 (Sheehan, 1998) and Brief Psychiatric Rating Scale (BPRS) Swedish translation of version 4.0 (Shafer et al., 2017; Zanello et al., 2013). Current medication was confirmed. Participants self-reported data utilizing the Swedish version of the Alcohol Use Disorders Identification Test (AUDIT) (H Berman et al., 2022), the Drug Use Disorders Identification Test (DUDIT) (H Berman et al., 2022), the EuroQol-5D visual analogue scale (EQ-5D VAS) (Brazier et al., 2014) and the Montgomery-Åsberg Depression Rating Scale-Self Assessment (MADRS-S) (Svanborg and Åsberg, 2001). The BPRS-affective subscale was calculated from the sum of the four *Affect Factor* items Anxiety, Depression, Suicidality, and Guilt (Bengtsson et al., 2022; Shafer et al., 2017).

2.3.2. Mismatch negativity

The MMN task was conducted with headphones to present 1200 volume-normalized auditory stimuli of 1000 Hz to the participants of which 1020 (85%) were standard tones with a duration of 25 ms and 180 (15%) deviant tones with a duration of 50 ms. Interstimulus interval was 300 ms. Participants watched a black and white movie as a visual distraction. One EEG electrode was attached frontomedially midway between Fz and Cz, with a reference electrode on the nose, and an earth electrode medially just above the eye brows. EEG was recorded using the Nexus-10 MKII and the Biotrace+ software from Mindmedia (Murphy et al., 2013; Näätänen, 2008). This approach was chosen after consideration of practical clinical feasibility, the methodology and results provided on main outcome-lead data from Murphy et al. (Murphy et al., 2013) and given the well-established predominantly frontal distribution of the MMN component (Näätänen, 2008, 2001). The auditory signal was split between the headphones and a trigger box which generated a trigger signal at the onset of each auditory stimulus. The trigger signal was recorded by the Nexus-10MKII to enable temporal synchronization.

2.3.3. iTBS intervention

The magnetic stimulator Magventure Magpro X100 with Magoption with Cool-DB80 A/P, a combined active/sham coil with two identical sides, was used for the iTBS intervention. The shielded sham coil prevented approximately 95% of the magnetic field from affecting patients (Opitz et al., 2015). Resting motor threshold was determined by single pulse TMS over the primary motor cortex of extensor hallucis longus. The DMPFC treatment target for the first nine patients was defined as 25% of the nasion-inion distance in the middle-line of the scalp. Due to participation in an add-on neuroimaging study (Persson et al., 2020), an MRI-based neuronavigational system (TMS Navigator, Localite, Bonn,

Germany) with the Montreal Neurological Institution (MNI) coordinates x = 0, y = 30, z = 30 (Mir-Moghtadaei et al., 2016) was utilized to locate the DMPFC in the remaining 37 patients.

Intervention was given five days a week for two weeks and detailed procedures have previously been described in the main study by Bodén et al. (Bodén et al., 2021). In short, the iTBS intervention was given at 90% of the resting motor threshold and consisted of two treatment sessions per day, amassing a total of 2400 pulses per day. Sham intervention consisted of an identical protocol; however, the sham coil was angled at the patient and transcutaneous electrical nerve stimulation (TENS) electrodes delivered a current synchronized to the magnetic pulses to induce the sensation of active stimulation. Follow-up testing mirrored baseline testing and was performed four weeks after baseline.

2.3.4. Pre-processing of mismatch negativity data

Data were pre-processed with EEG-lab (Delorme and Makeig, 2004) in MATLAB. After removing DC offset from continuous data and high-pass filtering with a cut-off frequency of 1 Hz, mains noise was removed using the Clean Line toolbox. Data were then low-pass filtered with a cut-off frequency of 30 Hz and epochs were extracted between −50 ms and 500 ms relative to stimulus onset and baseline corrected, while rejecting epochs exceeding +/− 100 μV. The sorted averaging approach (Murphy et al., 2013) was applied to standard and deviant epochs separately to discard epochs not contributing to increased signal-to-noise ratio. Remaining epochs were averaged per condition and standard responses were subtracted from deviants to obtain event related potentials representing the mismatch negativity. The mismatch negativity was then defined as the peak negative response between 80 and 130 ms post stimulus onset (Duncan et al., 2009; Murphy et al., 2013; Näätänen et al., 1978).

2.4. Outcomes

The analyses were made with three different outcomes:

Outcome I

Differences in MMN amplitude between healthy controls and patients with MDD at baseline. Correlation of baseline MMN and baseline symptom, rated by MADRS-S and BPRS-affective.

Outcome II

Change in MMN amplitude between baseline and follow-up testing in the active, compared to sham, group.

Outcome III

Correlation of baseline MMN and treatment outcome measured by Δ-BPRS-affective, and Δ-MADRS-S.

2.5. Statistical methods

Normally distributed data are presented with standard deviations (SD) and parametric tests used. Non-normally distributed data are presented using interquartile range (IQR) and non-parametric tests used. A p-value of ≤ 0.05 was considered statistically significant and two-sided p-values presented. Post hoc power calculations used the same sample size of each outcome, respectively, at $\alpha = 0.05$ (two-sided). Analyses were performed using JASP version 0.19 (JASP Team, 2024) and post hoc power calculations using G*power version 3.1.9.7 (Faul et al., 2009).

Outcome I:

A Student's t-test was applied to examine differences in MMN amplitude between patients and healthy controls. Additionally, a Pearson's r correlation analysis was used to assess whether MMN amplitude correlated with MADRS-S and BPRS-affective among patients at baseline.

Outcome II:

A linear mixed model was used to evaluate treatment-dependent changes in MMN amplitude, with treatment (active or sham), time-point (baseline or follow-up) and their interaction as fixed effects, and a random intercept per subject. The Satterhwaite test method was used and sum as factor contrast.

Outcome III:

A Pearson's r correlation analysis was used to assess whether baseline MMN amplitude correlated with Δ-MADRS-S and Δ-BPRS-affective. Δ-scores were calculated by subtracting baseline value from follow-up value. A Fisher r-to-z transformation was used to test for a significant difference between each condition's respective correlations coefficients.

3. Results

This sub-analysis study consists of 46 patients with MDD and 64 healthy controls. Baseline characteristics of patients and healthy controls are presented in Table 1. Baseline data, co-morbidities and current pharmacotherapy of patients in the active and sham groups showed no significant differences, except for a higher prevalence of ADHD/ADD in the sham group presented in Table 2.

Two patients allocated to the active group were excluded from statistical analysis of *Outcome II* and *Outcome III*. One was unblinded after four sessions and one declined follow-up testing. One patient allocated to the sham group was excluded from the statistical analysis of *Outcome II* and *Outcome III* after the patient was unblinded after eight sessions. The median time to follow-up testing after the last iTBS session was 15.5 (IQR = 8.5) days.

In the patient group, the mean number of MMN epoch trials accepted at baseline were n = 521 standard and n = 92 deviant tones, and at follow-up n = 510 standard and n = 88 deviant tones. Mean MMN amplitude were at baseline −2.459 μV (SD = 1.628) and at follow-up −2.876 μV (SD = 1.779). In healthy controls the mean number of

Table 1
Demographics.
Baseline data of all participants. Normally distributed data are reported as means (m) and standard deviations (SD). Rank scores are reported in medians (Mdn) and interquartile ranges (IQR).

	Patients	Healthy controls
Total n	46	64
Male/Female	19/27	28/36

		Patients		Helthy controls	
Age	m (SD)	29.6	(9.3)	30.8	(10.3)
AUDIT[1,a]	Mdn (IQR)	4.0	(5.0)	4.0	(3.3)
BPRS[b]	m (SD)	49.5	(7.2)	26.5	(2.7)
BPRS-affective[c]	m (SD)	17.3	(4.4)	4.0	(1.2)
DUDIT[2,d]	Mdn (IQR)	0.0	(0.0)	0.0	(0.0)
EQ-5D-VAS[3,e]	Mdn (IQR)	30	(23.8)	85	(10.0)
MADRS-S[f]	m (SD)	29.8	(7.7)	3.5	(3.2)

1. Data missing from 1 patient. 2. Data missing from 7 patients. 3. Data missing from 10 healthy controls.
a. Alcohol Use Disorders Identification Test (AUDIT) b. Brief Psychiatric Rating Scale (BPRS) c. Brief Psychiatric Rating Scale Affective Subscale (BPRS-affective) d. Drug Use Disorders Identification Test (DUDIT) e. EuroQol-5D-Visual Analog Scale (EQ-5D-VAS) f. Montgomery Åsberg Depression Rating Scale – Self rating (MADRS-S).

Table 2
Baseline data of patients, comparing active and sham groups. Normally distributed data are reported as means (m) and standard deviations (SD). Rank scores are reported in medians (Mdn) and interquartile ranges (IQR).

	Active	Sham
Total n	25	21
Male/Female	9/16	10/11

		Active		Sham	
Age	m (SD)	30.2	(10.0)	28.8	(8.6)
AUDIT[1,a]	Mdn (IQR)	3.0	(3.0)	4.0	(5.3)
BPRS[b]	m (SD)	48.4	(8.8)	51.0	(4.5)
BPRS-affective[c]	m (SD)	17.3	(4.7)	17.2	(4.0)
DUDIT[2,d]	Mdn (IQR)	0.0	(0.0)	0.0	(0.0)
EQ.5D-VAS[e]	Mdn (IQR)	30	(25.0)	30	(20.0)
MADRS-S[f]	m (SD)	29.5	(8.5)	30.2	(6.9)
Maudsley staging method[3]	Mdn (IQR)	10.0	(2.0)	10.5	(2.5)

	Active	Sham
Co-morbidities		
No other diagnosis	15/25	12/21
One anxiety disorder	8/25	9/21
Two anxiety disorders	3/25	4/21
Three anxiety disorders	0/25	3/21
Borderline personality disorder	2/25	1/21
Unspecified personality disorder	0/25	1/21
Autism spectrum disorder	4/25	1/21
ADHD[g]	2/25	7/21
Pharmacotherapy		
Antidepressants		
Any antidepressant	22/25	17/21
SSRI[h]	7/25	5/21
SNRI[i]	7/25	9/21
NaSSA[j]	6/25	7/21
NDRI[k]	4/25	1/21
TCA[l]	5/25	2/21
Combination	7/25	7/21
Mood stabilizers		
Lithium	3/25	3/21
Lamotrigine	2/25	1/21
Antipsychotics[4]	4/25	5/21

1. Data missing from $n = 1$ in sham group. 2. Data missing from $n = 4$ in active group and n = 2 in sham group. 3. Data missing from n = 1 in sham group. 4. Mean Olanzapine dose equivalent for all patients was 4.3 mg (SD = 2.6).
a. Alcohol Use Disorders Identification Test (AUDIT) b. Brief Psychiatric Rating Scale (BPRS) c. Brief Psychiatric Rating Scale affective subscale (BPRS-affective) d. Drug Use Disorders Identification Test (DUDIT) e. EuroQol-5D-Visual Analog Scale (EQ-5D-VAS) f. Montgomery Åsberg Depression Rating Scale – Self rating (MADRS-S) g. Attention Deficit Hyperactivity Disorder (ADHD) h. Selective Serotonin Reuptake Inhibitors (SSRI) i. Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) j. Noradrenaline and Specific Serotonergic Antidepressants (NaSSA) k. Norepinephrine and Dopamine Reuptake Inhibitors (NDRI) l. Tricyclic Antidepressants (TCA).

MMN epoch trials accepted were $n = 533$ standard and n = 92 deviant tones, the mean MMN amplitude were − 2.664 μV (SD = 2.057). Plotted grand mean waveforms are presented in Fig. 1.

Outcome I:

No significant difference in MMN amplitude was found between patients and healthy controls (t (108) = 0.56, $p = 0.575$, d = 0.11, SE d = 0.19) at baseline, as presented in Fig. 2. Post hoc sensitivity calculation of the baseline comparison indicated a power of 82% to detect differences between the groups. No correlations were detected between MMN amplitude and MADRS-S ($r = -0.22$, $p = 0.133$) and BPRS-affective ($r = -0.08$, $p = 0.593$) at baseline, see Table S1. Post hoc power analyses indicated power to detect effect of the observed magnitude at 31% and 8%, respectively.

Outcome II:

No significant Treatment x Time interaction for MMN amplitude (F (1,41) = 1.62, B = 0.211, SE = 0.17, $t = 1.28$, $p = 0.210$) was revealed, indicating that changes in MMN amplitude over time did not differ between the active and sham treatment groups, presented in Fig. 3. Post hoc power estimation for the Treatment x Time interaction was 53%.

Outcome III:

In the active treatment group ($n = 23$), baseline MMN amplitude correlated significantly with Δ-MADRS-S ($r = 0.48$, $p = 0.021$) and Δ-BPRS-affective ($r = 0.46$, $p = 0.026$). No significant correlations were detected in the sham group ($n = 20$), presented in Fig. 4 and Table 3. Post hoc power analyses indicated power to detect effect of the observed magnitude at 67% (Δ-MADRS-S) and 63% (Δ-BPRS-affective) in the active group, and 5% (Δ-MADRS-S) and 9% (Δ-BPRS-affective) in the sham group. Comparison of correlations coefficients between the treatment conditions showed no significant difference for MADRS-S (z = 1.69, $p = 0.091$) and BPRS-affective (z = 1.94, $p = 0.052$). To correct for significant baseline differences between the conditions, an ancillary analysis which excluded all patients with ADHD or ADD was performed. The results of Outcome III remained robust, and the data are presented in Table S3.

4. Discussion

This study is the first to report that a greater MMN amplitude in patients with MDD before treatment with active iTBS over the DMPFC correlates significantly with a subsequent reduction in depressive symptoms. No such correlation was observed in those receiving sham iTBS. However, this study cannot ascertain a statistically significant difference between the active and sham correlations. No differences were observed in MMN amplitude between healthy controls and patients with MDD, no correlation between MMN amplitude and depressive symptoms at baseline were observed and iTBS did not induce significant changes in MMN amplitude in patients.

To our knowledge, the present study constitutes one of the larger reports to date comparing MMN amplitude between healthy controls and patients with MDD. Previous studies comparing MMN amplitude, induced by duration deviants, between patients with MDD and healthy controls have reported conflicting results (Kangas et al., 2022; Tseng et al., 2021). The present study, where no difference in MMN amplitude was observed, used 25 ms as the standard stimuli and 50 ms as the deviant stimuli. This constitutes one methodological difference compared with studies of similar participant samples that have reported significant differences in MMN amplitude between patients with MDD and healthy controls. For example, Chen et al. (Chen et al., 2015) used 50 ms as standard and 100 ms as deviant duration, while Qiao et al. (Qiao et al., 2015) used 50 ms as standard and 150 ms as deviant duration. The lack of replication of previous results in the present study may therefore be attributed to different stimulus durations. We postulate two possible implications: to differentiate patients with MDD from healthy controls, either the duration of the standard stimuli should exceed 25 ms or the difference between the standard and deviant stimulus should exceed 25 ms.

The present study did not detect any change of MMN amplitude induced by iTBS, when compared to sham iTBS. We are not aware of any previous studies reporting how MMN amplitude, induced by a duration deviant stimulus, is affected by iTBS over the DMPFC in patients with MDD. Sun et al. reports a significant decrease of MMN latency induced by pitch deviants in patients receiving a combination of iTBS and 1 Hz rTMS. However, the treatment target was the DLPFC, intervention was

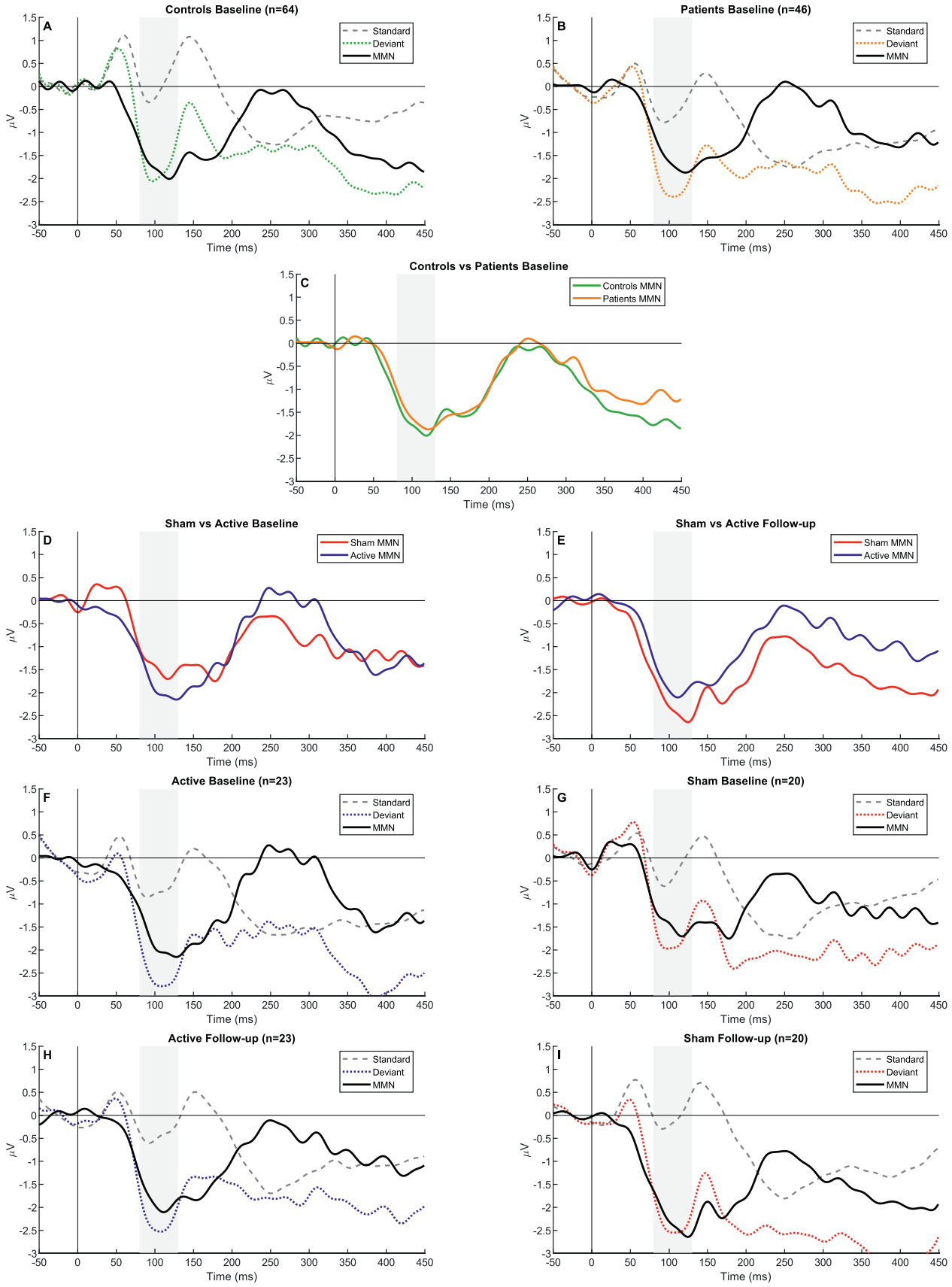

Fig. 1. Average grand means of MMN for each constellation of conditions and groups. Greyed out area depicted between x = 80–130 ms is the MMN window. Y-axis = μV, X-axis = time in ms, x = 0 represent stimulus onset.

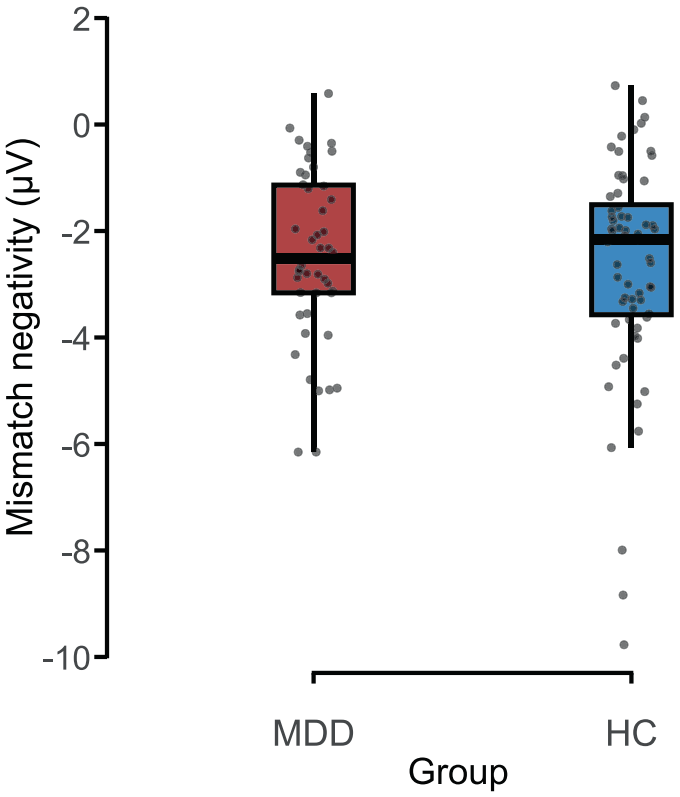

Fig. 2. Outcome I. Symptom comparison at baseline.
Scatter- and boxplot descripting mismatch negativity amplitude in millivolts (μV) of patients with major depressive disorder (MDD) and healthy controls (HC) at baseline.

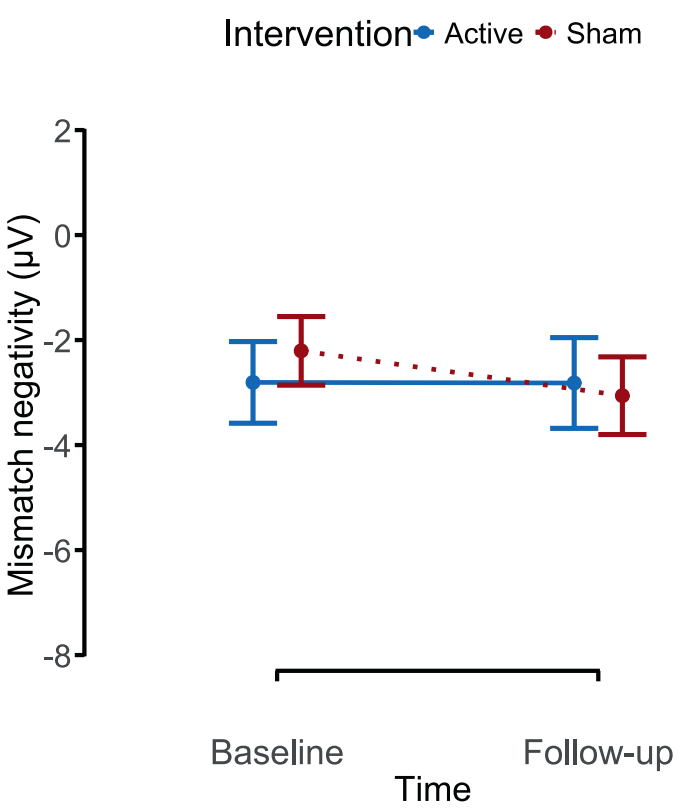

Fig. 3. Outcome II. Treatment related change of MMN.
Mismatch negativity amplitude in millivolts (μV) at baseline and follow-up for sham and active conditions, CI 95%.

given bilaterally using a figure-of-eight coil, a different type of stimulus to induce MMN was used and the change of MMN amplitude was not presented (Sun et al., 2023). Thus, limiting comparability with our results. Furthermore, the sample size of the present study does not yield power enough to rule out the possibility of a type-II error affecting *Outcome II*. Thus, no certain conclusions can be drawn from *Outcome II*.

The main findings from the present study are the results presented in *Outcome III*. For the first time, we report a significant correlation between a greater baseline MMN amplitude (larger negativity) and a greater reduction of MDD symptoms following a two-week course of active iTBS over the DMPFC. The absence of a correlation between MMN amplitude and symptom reduction in the sham group further suggests MMN amplitude as a potential predictor of treatment response to iTBS. Notably, the correlation coefficients were not statistically different between active and sham treatment for any of the symptom ratings, although the comparison exhibited tendencies towards significance. Symptoms of MDD were assessed using self-report (MADRS-S) and clinician-rated measures (BPRS-affective), both reflecting similar constructs, thereby increasing the internal reliability of our findings.

Greater MMN amplitude have been suggested to be linked to NMDA-R plasticity (Garrido et al., 2009; Kangas et al., 2022) and modulation of NMDA-R plasticity has been suggested to be a central mechanism of iTBS in MDD (Huang et al., 2007; Wang et al., 2019). iTBS has been suggested to depend on pre-existing NMDA-R plasticity to perform effectively, a notion also suggested by previous research (Cole et al., 2021; Wrightson et al., 2023). Specifically, when the partial NMDA-R agonist D-Cycloserine (DCS) was administered as an adjunct to iTBS in healthy individuals, motor response increased (Wrightson et al., 2023), and in patients with MDD impaired motor plasticity was recovered (Cole et al., 2021). Furthermore, patients with MDD treated with iTBS show drastically improved antidepressant outcomes when given adjunctive DCS (Cole et al., 2022). The present study raises the thought that MMN could be a potential predictor of iTBS response in MDD. However, this remains speculative and further research is needed to validate this theory. We propose MMN as a possible focus of further research aiming to identify predictors of outcome in iTBS treatment of MDD.

4.1. Limitations

We recognize several limitations of the current study. This is a subanalysis of a larger RCT previously conducted (Bodén et al., 2021) and is thus underpowered in regards of *Outcome II* and *Outcome III*. The lack of power is most apparent in Outcome *III*, where the trend towards significance suggests the possibility to ascertain a significant effect in larger samples. The use of a one channel EEG to capture ERPs could potentially decrease the reliability of the calculated MMN due to increased sensitivity to operator placement error of EEG-electrodes and interference, potentially affecting results of *Outcome II* and *Outcome III* in any direction. Participants did not discontinue or alter any current pharmacotherapy during the trial, though we did not consider the time since the patient was started on their current pharmacotherapy. The result of *Outcome III* could thus have been affected by a pharmacologically induced plasticity from a drug prescribed close in time to entering the study. The variance in follow-up times and the approach to targeting the DMPFC during iTBS was not the same for all participants, which introduced additional variability of the results in *Outcome II* and *Outcome III*. Furthermore, no individualization of treatment target was performed, which could have optimized the effect of iTBS (Ji et al., 2026) and reduced variability of our results. Given the limited statistical power for *Outcome II* and *Outcome III*, the possibility to conduct ancillary testing using the follow-up time and targeting approaches as co-variates was restricted.

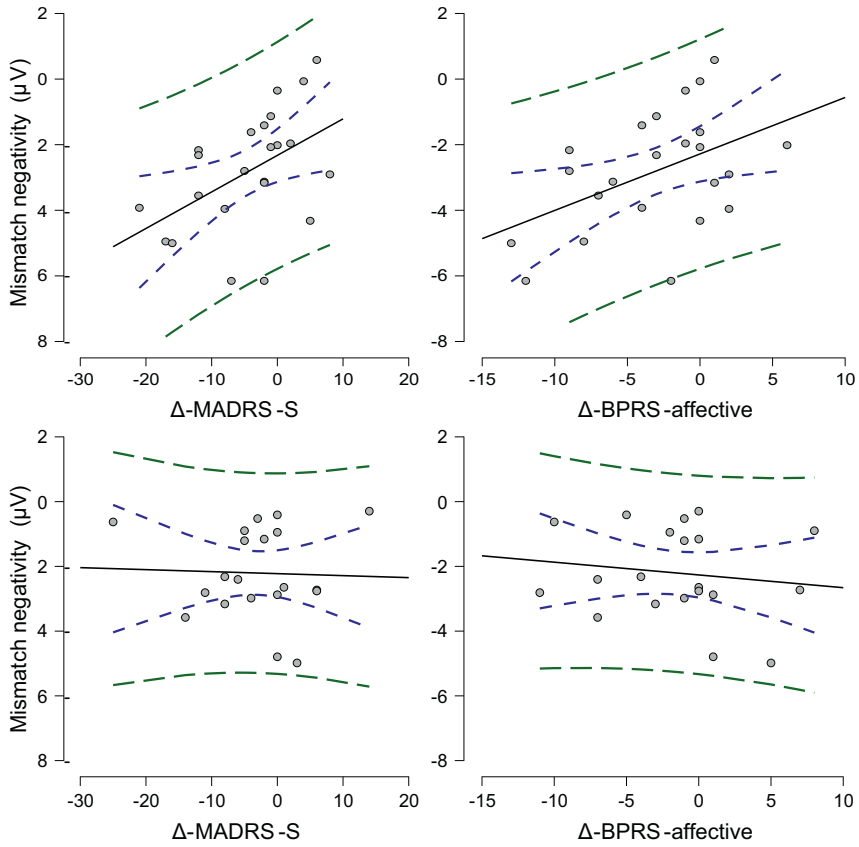

Fig. 4. Outcome III. Correlation of baseline MMN and treatment outcome.
Scatterplot of change (Follow up – Baseline) in Montgomery Åsberg Depression Rating Scale – Self rating (MADRS-S) and Brief Psychiatric Rating Scale Affective Subscale (BPRS-affective) respectively in relation to baseline mismatch negativity amplitude in millivolts (μV).

Table 3
Outcome III. Correlation of baseline MMN and treatment outcome.
Pearson's correlations (r) between baseline MMN and symptom rating change in the blinded phase, as a function of treatment arm. Effect size calculated using Fisher's z.

	Δ-MADRS-S[a]					Δ-BPRS-affective[b]				
	r	95% CI	*p*	z	(SE)	r	95% CI	*p*	z	(SE)
Active (n = 23)[1]	0.48	[0.08–0.74]	*0.021*	0.52	(0.22)	0.46	[0.06–0.73]	*0.026*	0.50	(0.22)
Sham (n = 20)[2]	−0.03	[−0.47–0.41]	*0.879*	−0.14	(0.24)	−0.14	[−0.55–0.32]	*0.555*	−0.04	(0,24)
All (*n* = 43)	0.27	[−0.03–0.53]	*0.080*	0.28	(0.16)	0.24	[−0.07–0.50]	*0.126*	0.24	(0.16)

1. Two patients excluded. 2. One patient excluded. a. Montgomery Åsberg Depression Rating Scale – Self rating (MADRS-S) b. Brief Psychiatric Rating Scale Affective Subscale (BPRS-affective).

4.2. Conclusion

In conclusion, we observed no differences in MMN between patients with MDD and healthy controls, and our data do not allow us to determine whether iTBS modulates MMN. Although MMN showed some indication of a relationship with treatment response, the absence of statistically significant differences between active and sham correlation coefficients limits the strength of this finding. Accordingly, any potential role of MMN as a neurophysiological marker of iTBS response in MDD should be interpreted with caution. Further studies are required to evaluate whether MMN has utility as a biomarker of rTMS efficacy. We suggest that future clinical trials incorporate MMN assessments at baseline and follow-up to permit more robust analyses. In addition, systematic comparisons of different standard and deviant stimulus durations may help identify the most informative approach to MMN quantification in relation to treatment outcomes.

CRediT authorship contribution statement

Marcus Anderson: Writing – original draft, Visualization, Formal analysis, Data curation. **Robert Bodén:** Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Caroline E. Wass:** Writing – review & editing, Writing – original draft. **Hatice Zora:** Methodology. **Johan Bengtsson:** Investigation, Conceptualization. **Jonas Persson:** Writing – original draft, Supervision, Methodology, Funding acquisition.

Financial support

This research was supported by unrestricted grants from the Swedish Research Council (Grant number 2016-02362), the Swedish Society of Medicine, Märta and Nicke Nasvell Foundation, JP was supported by a postdoctoral grant from the Swedish Brain Foundation. CW was

supported by Petrus & Augusta Hedlunds Foundation (M-2024-2287).

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

We thank MagVenture for lending the sham coil.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2026.121908.

References

Bakker, N., Shahab, S., Giacobbe, P., Blumberger, D.M., Daskalakis, Z.J., Kennedy, S.H., Downar, J., 2015. rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. Brain Stimul. 8, 208–215. https://doi.org/10.1016/j.brs.2014.11.002.

Bengtsson, J., Bodén, R., Neider, D., Cernvall, M., 2022. A blinded validation of the Swedish version of the Clinical Assessment Interview for Negative Symptoms (CAINS). Nord. J. Psychiatry 76, 44–51. https://doi.org/10.1080/08039488.2021.1933174.

H Berman, A., Wennberg, P., Källmén, H., 2022. AUDIT & DUDIT Identifiera problem med alkohol och droger, 3rd ed. Gothia Kompetens, Stockholm.

Blumberger, D.M., Vila-Rodriguez, F., Thorpe, K.E., Feffer, K., Noda, Y., Giacobbe, P., Knyahnytska, Y., Kennedy, S.H., Lam, R.W., Daskalakis, Z.J., Downar, J., 2018. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet 391, 1683–1692. https://doi.org/10.1016/S0140-6736(18)30295-2.

Bodén, R., Bengtsson, J., Thörnblom, E., Struckmann, W., Persson, J., 2021. Dorsomedial prefrontal theta burst stimulation to treat anhedonia, avolition, and blunted affect in schizophrenia or depression - a randomized controlled trial. J. Affect. Disord. 290, 308–315. https://doi.org/10.1016/j.jad.2021.04.053.

Brazier, J., Connell, J., Papaioannou, D., Mukuria, C., Mulhern, B., Peasgood, T., Lloyd Jones, M., Paisley, S., O'Cathain, A., Barkham, M., Knapp, M., Byford, S., Gilbody, S., Parry, G., 2014. A systematic review, psychometric analysis and qualitative assessment of generic preference-based measures of health in mental health populations and the estimation of mapping functions from widely used specific measures. Health Technol. Assess. 18. https://doi.org/10.3310/hta18340.

Chen, J., Zhang, Y., Wei, D., Wu, X., Fu, Q., Xu, F., Wang, H., Ye, M., Ma, W., Yang, L., Zhang, Z., 2015. Neurophysiological handover from MMN to P3a in first-episode and recurrent major depression. J. Affect. Disord. 174, 173–179. https://doi.org/10.1016/j.jad.2014.11.049.

Cole, J., Selby, B., Ismail, Z., McGirr, A., 2021. D-cycloserine normalizes long-term motor plasticity after transcranial magnetic intermittent theta-burst stimulation in major depressive disorder. Clin. Neurophysiol. 132, 1770–1776. https://doi.org/10.1016/j.clinph.2021.04.002.

Cole, J., Sohn, M.N., Harris, A.D., Bray, S.L., Patten, S.B., McGirr, A., 2022. Efficacy of adjunctive D-cycloserine to intermittent theta-burst stimulation for major depressive disorder: a randomized clinical trial. JAMA Psychiatry 79, 1153. https://doi.org/10.1001/jamapsychiatry.2022.3255.

Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J. Neurosci. Methods 134, 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009.

Duncan, C.C., Barry, R.J., Connolly, J.F., Fischer, C., Michie, P.T., Näätänen, R., Polich, J., Reinvang, I., Van Petten, C., 2009. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. Clin. Neurophysiol. 120, 1883–1908. https://doi.org/10.1016/j.clinph.2009.07.045.

Ekman, C.J., Popiolek, K., Bodén, R., Nordenskjöld, A., Lundberg, J., 2023. Outcome of transcranial magnetic intermittent theta-burst stimulation in the treatment of depression - a Swedish register-based study. J. Affect. Disord. 329, 50–54. https://doi.org/10.1016/j.jad.2023.02.098.

Faul, F., Erdfelder, E., Buchner, A., Lang, A.-G., 2009. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav. Res. Methods 41, 1149–1160. https://doi.org/10.3758/BRM.41.4.1149.

Fitzgerald, K., Todd, J., 2020. Making sense of mismatch negativity. Front. Psych. 11. https://doi.org/10.3389/fpsyt.2020.00468.

Fitzsimmons, S.M.D.D., Oostra, E., Postma, T.S., Van Der Werf, Y.D., Van Den Heuvel, O. A., 2024. Repetitive transcranial magnetic stimulation–induced neuroplasticity and the treatment of psychiatric disorders: state of the evidence and future opportunities. Biol. Psychiatry 95, 592–600. https://doi.org/10.1016/j.biopsych.2023.11.016.

Garrido, M.I., Kilner, J.M., Stephan, K.E., Friston, K.J., 2009. The mismatch negativity: a review of underlying mechanisms. Clin. Neurophysiol. 120, 453–463. https://doi.org/10.1016/j.clinph.2008.11.029.

Gilbert, J.R., Wusinich, C., Zarate, C.A., 2022. A predictive coding framework for understanding major depression. Front. Hum. Neurosci. 16, 787495. https://doi.org/10.3389/fnhum.2022.787495.

Harms, L., Parras, G.G., Michie, P.T., Malmierca, M.S., 2021. The role of glutamate neurotransmission in mismatch negativity (MMN), a measure of auditory synaptic plasticity and change-detection. Neuroscience 456, 106–113. https://doi.org/10.1016/j.neuroscience.2020.01.046.

Huang, Y.-Z., Chen, R.-S., Rothwell, J.C., Wen, H.-Y., 2007. The after-effect of human theta burst stimulation is NMDA receptor dependent. Clin. Neurophysiol. 118, 1028–1032. https://doi.org/10.1016/j.clinph.2007.01.021.

Iwabuchi, S.J., Raschke, F., Auer, D.P., Liddle, P.F., Lankappa, S.T., Palaniyappan, L., 2017. Targeted transcranial theta-burst stimulation alters fronto-insular network and prefrontal GABA. NeuroImage 146, 395–403. https://doi.org/10.1016/j.neuroimage.2016.09.043.

JASP Team, 2024. JASP (Version 0.19) [Computer software] [WWW Document]. URL. https://jasp-stats.org/.

Ji, G.-J., Xu, W., Zhang, J., Li, Q., Yang, Y., He, K., Yu, F., Zhu, C., Jiang, X., Jing, L., Hu, P., Tian, Y., Wang, K., 2026. Distinct antidepressant therapies act on a common brain network. Nat. Commun. 17, 1176. https://doi.org/10.1038/s41467-025-67945-5.

Kangas, E.S., Vuoriainen, E., Lindeman, S., Astikainen, P., 2022. Auditory event-related potentials in separating patients with depressive disorders and non-depressed controls: a narrative review. Int. J. Psychophysiol. 179, 119–142. https://doi.org/10.1016/j.ijpsycho.2022.07.003.

Kim, H.K., Blumberger, D.M., Downar, J., Daskalakis, Z.J., 2021. Systematic review of biological markers of therapeutic repetitive transcranial magnetic stimulation in neurological and psychiatric disorders. Clin. Neurophysiol. 132, 429–448. https://doi.org/10.1016/j.clinph.2020.11.025.

Mir-Moghtadaei, A., Giacobbe, P., Daskalakis, Z.J., Blumberger, D.M., Downar, J., 2016. Validation of a 25% nasion–inion heuristic for locating the dorsomedial prefrontal cortex for repetitive transcranial magnetic stimulation. Brain Stimul. 9, 793–795. https://doi.org/10.1016/j.brs.2016.05.010.

Murphy, J.R., Rawdon, C., Kelleher, I., Twomey, D., Markey, P.S., Cannon, M., Roche, R. A., 2013. Reduced duration mismatch negativity in adolescents with psychotic symptoms: further evidence for mismatch negativity as a possible biomarker for vulnerability to psychosis. BMC Psychiatry 13, 45. https://doi.org/10.1186/1471-244X-13-45.

Näätänen, R., 2001. The perception of speech sounds by the human brain as reflected by the mismatch negativity (MMN) and its magnetic equivalent (MMNm). Psychophysiology 38, 1–21. https://doi.org/10.1111/1469-8986.3810001.

Näätänen, R., 2008. Mismatch negativity (MMN) as an index of central auditory system plasticity. Int. J. Audiol. 16–20. https://doi.org/10.1080/14992020802340116.

Näätänen, R., Gaillard, A.W.K., Mäntysalo, S., 1978. Early selective-attention effect on evoked potential reinterpreted. Acta Psychol. (Amst) 42, 313–329. https://doi.org/10.1016/0001-6918(78)90006-9.

Noda, Y., Zomorrodi, R., Vila-Rodriguez, F., Downar, J., Farzan, F., Cash, R.F.H., Rajji, T. K., Daskalakis, Z.J., Blumberger, D.M., 2018. Impaired neuroplasticity in the prefrontal cortex in depression indexed through paired associative stimulation. Depress. Anxiety 35, 448–456. https://doi.org/10.1002/da.22738.

Opitz, A., Legon, W., Mueller, J., Barbour, A., Paulus, W., Tyler, W.J., 2015. Is sham cTBS real cTBS? The effect on EEG dynamics. Front. Hum. Neurosci. 8. https://doi.org/10.3389/fnhum.2014.01043.

Persson, J., Struckmann, W., Gingnell, M., Fällmar, D., Bodén, R., 2020. Intermittent theta burst stimulation over the dorsomedial prefrontal cortex modulates resting-state connectivity in depressive patients: a sham-controlled study. Behav. Brain Res. 394, 112834. https://doi.org/10.1016/j.bbr.2020.112834.

Qiao, Z., Yang, A., Qiu, X., Yang, X., Zhang, C., Zhu, X., He, J., Wang, L., Bai, B., Sun, H., Zhao, L., Yang, Y., 2015. Gender effect on pre-attentive change detection in major depressive disorder patients revealed by auditory MMN. Psychiatry Res. Neuroimaging 234, 7–14. https://doi.org/10.1016/j.pscychresns.2015.05.011.

Shafer, A., Dazzi, F., Ventura, J., 2017. Factor structure of the Brief Psychiatric Rating Scale – Expanded (BPRS-E) in a large hospitalized sample. J. Psychiatr. Res. 93, 79–86. https://doi.org/10.1016/j.jpsychires.2017.05.011.

Sheehan, D.V., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 22–33.

Sun, Y., Lei, F., Zou, K., Zheng, Z., 2023. Rapid improvements and subsequent effects in major depressive disorder patients with somatic pain using rTMS combined with sertraline. Sci. Rep. 13, 17973. https://doi.org/10.1038/s41598-023-44887-w.

Svanborg, P., Åsberg, M., 2001. A comparison between the Beck Depression Inventory (BDI) and the self-rating version of the Montgomery Asberg Depression Rating Scale (MADRS). J. Affect. Disord. 2001, 203–216. https://doi.org/10.1016/s0165-0327(00)00242-1.

Tseng, Y.-J., Nouchi, R., Cheng, C.-H., 2021. Mismatch negativity in patients with major depressive disorder: a meta-analysis. Clin. Neurophysiol. 132, 2654–2665. https://doi.org/10.1016/j.clinph.2021.06.019.

Wang, X., Zhou, X., Bao, J., Chen, Z., Tang, J., Gong, X., Ni, J., Fang, Q., Liu, Y., Su, M., 2019. High-frequency repetitive transcranial magnetic stimulation mediates autophagy flux in human bone mesenchymal stromal cells via NMDA receptor–Ca^2

$^{+}$–extracellular signal-regulated kinase–mammalian target of rapamycin signaling. Front. Neurosci. 13. https://doi.org/10.3389/fnins.2019.01225.

Wrightson, J.G., Cole, J., Sohn, M.N., McGirr, A., 2023. The effects of D-cycloserine on corticospinal excitability after repeated spaced intermittent theta-burst transcranial magnetic stimulation: a randomized controlled trial in healthy individuals. Neuropsychopharmacology 48, 1217–1224. https://doi.org/10.1038/s41386-023-01575-7.

Zanello, A., Berthoud, L., Ventura, J., Merlo, M.C.G., 2013. The Brief Psychiatric Rating Scale (version 4.0) factorial structure and its sensitivity in the treatment of outpatients with unipolar depression. Psychiatry Res. 210, 626–633. https://doi.org/10.1016/j.psychres.2013.07.001.