Repellent Transcranial Magnetic Stimulation in the Treatment of Bipolar Disorder

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Abstract: Bipolar disorder (BD) is a debilitating mood disorder marked by manic, hypomanic and/or mixed or depressive episodes. It affects approximately 1–2% of the population and is linked to high rates of suicide, functional impairment and poorer quality of life. Presently, treatment options for BD are limited. There is a strong evidence base for pharmacological (e.g., lithium) and psychological (e.g., psychoeducation) treatments; however, both of these pose challenges for treatment outcomes (e.g., non-response, side-effects, limited access). Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, is a recommended treatment for unipolar depression, but it is unclear whether rTMS is an effective, safe and well tolerated treatment in people with BD. This article reviews the extant literature on the use of rTMS to treat BD across different mood states. We found 34 studies in total (N = 611 patients), with most assessing bipolar depression (n = 26), versus bipolar mania (n = 5), mixed state bipolar (n = 2) or those not in a current affective episode (n = 1). Across all studies, there appears to be a detectable signal of efficacy for rTMS treatment, as most studies report that rTMS treatment reduced bipolar symptoms. Importantly, within the randomised controlled trial (RCT) study designs, most reported that rTMS was not superior to sham in the treatment of bipolar depression. However, these RCTs are based on small samples (NBD = 52). Reported side effects of rTMS in BD include headache, dizziness and sleep problems. Ten studies (N = 14 patients) reported cases of affective switching; however, no clear pattern of potential risk factors for affective switching emerged. Future adequately powered, sham-controlled trials are needed to establish the ideal rTMS treatment parameters to help better determine the efficacy of rTMS for the treatment of BD.

Keywords: bipolar disorder, depression, mania, repetitive transcranial magnetic stimulation, rTMS, treatment

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Introduction

Bipolar disorder (BD) is a chronic mood disorder often characterised by fluctuations in mood, energy, activity levels and functioning. Those affected suffer from debilitating, recurrent episodes of depression and (hypo)mania, with some people experiencing both mood episodes at the same time (referred to as mixed states).1–3 BD affects approximately 1–2% of the population and is associated with significant functional impairment as well as high suicide and relapse rates.4–8 Pharmacological interventions, including mood stabilisers (e.g., lithium) and atypical antipsychotics (e.g., quetiapine) are the recommended first-line treatments for BD.9 However, these medications pose challenges for treatment, as they are associated with side effects (e.g., weight gain, metabolic dysregulation, sedation) and high levels (approximately 50%) of nonadherence.10–13 Further, the use of traditional antidepressants (e.g., selective serotonin reuptake inhibitors) to treat BD depression remains a contentious issue, given the strong clinical concerns that antidepressants cause affective switching into (hypo)mania—now referred to as treatment emergent affective switch (TEAS).14–16 Generally, the evidence supporting the use of antidepressants in BD is weak and conflicting.17–20 Although there is growing evidence for the use of
psychological therapies (e.g., cognitive behavioural therapy, psychoeducation, family interventions) alongside medication, many BD patients fail to respond to these treatments, emphasising the need for novel treatment approaches to be developed and tested.

A form of non-invasive brain stimulation, called repetitive transcranial magnetic stimulation (rTMS), has emerged as a potential line of investigation for the treatment of BD. In rTMS, an electromagnetic coil is placed over the patient’s scalp, usually targeting the dorsolateral prefrontal cortex (DLPFC) region—an area that has been implicated in the regulation of mood and depression. The coil delivers magnetic pulses that serve to alter neural circuits in the brain by non-invasively depolarising neurons. Different forms of TMS exist (e.g., single-pulse); however, it is the repetitive nature of these pulses, across short intervals, that distinguishes rTMS from other forms. The repetitive pulses are known to provoke long-lasting changes to the brain, with high-frequency rTMS (>1 Hz) thought to have an excitatory effect, compared with low-frequency rTMS (≤1 Hz), which is thought to have an inhibitory effect on the cerebral cortex. These frequencies can be applied alone or sequentially, either unilaterally or bilaterally. A newer form of rTMS has also emerged, called theta-burst stimulation (TBS). This differs from standard rTMS in that pulses are applied in a pattern known as theta bursts, delivering more stimulation within a shorter time-frame.

rTMS is an effective and well-tolerated intervention in the treatment of unipolar depression [i.e., major depressive disorder (MDD)] in adults, and there is a developing, yet promising, evidence-base for its use in adolescent depression. For unipolar depression, it appears that both high-frequency rTMS applied to the left DLPFC (L-DLPFC) and low-frequency rTMS applied to the right DLPFC (R-DLPFC) are the protocols adopted most widely. However, meta-analyses report that high-frequency rTMS applied to the L-DLPFC is the protocol most associated with antidepressant properties (standardised mean difference = −0.73, p<0.00001). However, it still remains unclear whether: (1) rTMS is an effective treatment for BD; (2) whether it is safe; and (3) especially, whether there is a risk of affective switching.

A previous review on the effectiveness of rTMS in BD concluded that rTMS targeting the R-DLPFC, was effective at reducing symptoms of bipolar depression compared with sham. In that work, the risk of TEAS was observed to be low, suggesting that rTMS is a safe and well-tolerated treatment for bipolar depression. A more recent review by Gold et al, evaluated outcomes of rTMS in BD across different mood episodes (e.g, depressive and manic). The authors searched the literature through to October 2018, investigating a variety of TMS procedures including rTMS, as well as deep TMS and conclude that TMS appears to be effective at reducing depressive symptoms.

In this review, we will extend the work by Gold et al. by focusing specifically on the use of rTMS in BD to provide an in-depth summary and critical analysis of the evidence to date. Address two key research questions: (1) what is the effectiveness of rTMS in reducing depressive, mixed and manic episodes of BD; and (2) what is the safety profile of rTMS in the treatment of BD? We also discuss areas for future research and clinical practice implications.

Methods
We searched both PubMed and PsycINFO databases up to June 2020, using the terms ‘bipolar disorder’ or ‘mania’ or ‘depression’ AND ‘repetitive transcranial magnetic stimulation’ or ‘rTMS’ or ‘TMS’ [see Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram]. We also searched ClinicalTrials.gov to identify any current ongoing trial studies or completed but unpublished trials. We included any English language, peer-reviewed study [e.g., pre–post intervention, randomised controlled trials (RCTs), naturalistic studies, case series, case reports] that assessed the effects of rTMS in adult BD clinical samples. Case reports/series studies were included to help extract more detailed patient information (e.g., medication history) that may be associated with increased risk of affective switching. Where studies included a mixed sample (e.g., bipolar and unipolar depression), we only included those studies which assessed outcomes for bipolar and unipolar separately. We excluded studies that employed a non rTMS protocol (e.g., deep TMS) (for a summary of these studies see Gold et al.). Following the searches, title and abstracts of all returned studies were screened to determine eligibility. Potential eligible studies then underwent full-text review.
**Results**

**Summary of included studies**
The search revealed 34 studies in total, and most were assessing rTMS for bipolar depression ($n = 26$; Table 1), but evidence on bipolar mania ($n = 5$; Table 2), bipolar mixed states ($n = 2$; Table 3) and no active current episode ($n = 1$) was also available. The overall mean age range across all studies was 29.76–62.00 years. The most common measure used to assess depressive symptoms was the Hamilton Depression Rating Scale (HAM-D) ($n = 16$), followed by the Montgomery-Åsberg Depression Rating Scale (MADRS) ($n = 5$), the Beck Depression Inventory (BDI) ($n = 3$) and the Quick Inventory of Depressive Symptomology (QIDS) ($n = 2$).36–39

The Young Mania Rating Scale (YMRS) was most often employed to assess manic symptoms ($n = 4$).40

In the bipolar depression studies, a total of 470 bipolar patients received rTMS (mean age range = 27.40–60.00 years). This literature included case reports ($n = 8$), naturalistic studies ($n = 3$), open-label trials/follow-up studies ($n = 3$), RCTs comparing active treatments ($n = 3$) and sham-controlled RCTs ($n = 9$). rTMS protocols varied (see Table 1), with most studies employing standard rTMS using high-frequency only ($n = 9$), followed by low-frequency only ($n = 4$), sequential rTMS (low + high-frequency) ($n = 4$), low versus high-frequency ($n = 3$), TBS ($n = 3$) and low versus sequential rTMS ($n = 2$). One study failed to state the rTMS protocol.58

Across these studies, there was a total of 32 different active rTMS treatment protocols being investigated with: 12 of these targeting the L-DLPFC alone (similar to the unipolar depression literature), 11 targeting the R-DLPFC, 6 targeting both the R- and L-DLPFC sequentially. Three studies failed to report the target location for stimulation.

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**Figure 1.** Systematic review process: PRISMA diagram.

PRISMA, preferred reporting items for systematic reviews and meta-analyses; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation.
Table 1. Summary of bipolar depression studies (n = 26).

| Study                          | Sample size (n) | rTMS sessions (n) | rTMS location                  | rTMS motor threshold (%) | rTMS frequency (Hz) | rTMS protocol                                                                 | Depression symptom outcomes                                                                                   |
|--------------------------------|-----------------|-------------------|--------------------------------|--------------------------|---------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| **Case report/series (n = 8)** |                 |                   |                                |                          |                     |                                                                              |                                                                                                               |
| Garcia-Toro                    | 1               | 10                | Unknown                        | 90%                      | High [20 Hz]         | 30 trains, 2 s duration with a 30 s interval                                    | Symptoms reduced throughout treatment                                                                        |
| Dolberg et al.                 | 2               | 20                | Unknown                        | High [10 Hz]             | 20 trains, duration 6 s, with 30 s between each                                 | Not reported                                                                                                  |
| Hausmann et al.                | 1               | 7                 | L-DLPFC + R-DLPFC              | 100% + 120%              | High [20 Hz] + Low [1 Hz] + Low [1 Hz]                                         | 10 trains of 10 s + 20 min of low                                                                             | Symptoms reduced throughout treatment                                                                        |
| Li et al.                      | 1               | 40                | L-DLPFC                        | 120%                     | High [10 Hz]          | 5 s train and 10 s interval                                                    | Symptoms reduced throughout treatment                                                                        |
| Zendjidjian et al.             | 1               | 40                | L-DLPFC                        | 120%                     | High [10 Hz]          | 5 s train, 25 s interval                                                       | Symptoms reduced throughout treatment                                                                        |
| Brunelin et al.                | 1               | 20                | L-DLPFC                        | 110%                     | High [5 Hz]           | 8 s on and 22 s off, repeated every 30 s                                       | Symptoms reduced after 15 sessions                                                                         |
| Huang et al.                   | 1               | 3                 | L-DLPFC                        | 100%                     | High [5 Hz]           | 8 s train, 40 trains per day                                                   | Symptoms reduced with three rTMS sessions                                                                    |
| Kaster et al.                  | 1               | 12                | L-DLPFC                        | 120%                     | Theta-burst [50 Hz]          | 2 s on and 8 s off for a total of 600 pulses                                   | Symptoms reduced throughout treatment—up to session 10                                                      |
| **Naturalistic studies (n = 3)** |                 |                   |                                |                          |                     |                                                                              |                                                                                                               |
| Cohen et al.                   | 56              | >30               | L-DLPFC                        | <100%                    | High [20 Hz]          | Unclear                                                                      | rTMS treatment improved symptoms                                                                           |
| Carnell et al.                 | 50              | 18–20             | R-DLPFC + L-DLPFC              | 110%                     | Low [1 Hz]          | 15 min                                                                        | rTMS treatment improved symptoms                                                                           |
| Philips et al.                 | 17              | 30                | L-DLPFC                        | 120%                     | High [10 Hz]          | 3000 pulses per session                                                        | rTMS treatment improved symptoms                                                                           |

(Continued)
| Study         | Sample size (n) | rTMS sessions (n) | rTMS location       | rTMS motor threshold (%) | rTMS frequency (Hz) | rTMS protocol | Depression symptom outcomes |
|--------------|----------------|------------------|---------------------|--------------------------|---------------------|---------------|----------------------------|
| Dell'Osso et al.\(^54,53\) | 11 | 15 | R-DLPFC | 110% | Low [1 Hz] | 300 stimuli per day | Reduction in depression scores from baseline to post treatment |
| Kazemi et al.\(^54\) | 20 | 10 | R-DLPFC + LDLPFC | 120% + 100% | Low [1 Hz] + High [10 Hz] | 10 s train, 2 s interval and 150 pulse trains + 5 s, 10 s interval and 75 pulse trains | Reduction in depression scores from baseline to post treatment |
| Fitzgerald et al.\(^53\) | 25 | 10–20 | R-DLPFC | 110% | Low [1 Hz] | 15 min, 900 pulses | Significant effect of time on depression scores. 12 patients receiving 2 Hz and 5 patients receiving 1 Hz achieved a clinical response |
| Dell’Osso et al.\(^54\) | 19 | 20 | 1. R-DLPFC | 110% | Low [1 Hz] | Seven trains of 60 s, interspersed by 1 min pause | Significant reduction in HAM-D scores across all diagnostic groups |
| 2. R-DLPFC | 110% | Low [1 Hz] | Continuous 15 min of treatment |
| 3. L-DLPFC | 80% | High [10 Hz] | 15 trains of 5 s, 25 s interval |
| Kazemi et al.\(^57\) | 30 | 20 | 1. R-DLPFC | 120% | Low [1 Hz] | 10 s, 2 s interval, 250 trains | Both groups demonstrated a reduction in depression symptoms from pre to post. No significant between group differences. |
| 2. R-DLPFC + L-DLPFC | 100% | Low [1 Hz] + High [10 Hz] | 10 s, 2 s interval, 150 trains + 5 s, 10 s interval, 75 trains |
| Sham-controlled RCTs (n = 9) | Dolberg et al.\(^58\) | 20 | 20 | Not stated | Not stated | Not stated | Not stated | rTMS group demonstrated significant improvement in depression symptoms |
| Nahas et al.\(^59\) | 23 | 10 | L-DLPFC | 110% | High [5 Hz] | 8 s on, 22 s off, over 20 min | No significant differences between groups for depression symptoms |

(Continued)
**Table 1.** (Continued)

| Study                | Sample size (n) | rTMS sessions (n) | rTMS location | rTMS motor threshold (%) | rTMS frequency (Hz) | rTMS protocol | Depression symptom outcomes |
|----------------------|-----------------|-------------------|---------------|--------------------------|--------------------|---------------|-----------------------------|
| Fitzgerald et al.    | 8               | 10+               | R-DLPFC + L-DLPFC | 110% + 100% | Low [1 Hz] + High [10 Hz] | Three trains, 140 s, 30 s interval, + 15 trains, 5 s duration, 25 s interval | Some evidence that rTMS had an effect: 2/4 patients in the sequential rTMS group showed improvements, compared with 1/4 in the sham group |
| Tamas et al.         | 5               | 8                 | R-DLPFC       | 95%          | Low [1 Hz]            | 100 consecutive stimuli | rTMS group showed greater symptom improvement compared with sham, but there was no significant group differences in depression scores throughout the first 4-weeks of treatment |
| Beynel et al.        | 12              | 10+               | L-DLPFC       | 80%          | Theta-burst [50 Hz]   | Applied twice a day, 5 days a week for 1–3 weeks. 2 s train of bursts, 3 pulses at 50 Hz was repeated at 200 ms every 10 s | A reduction in symptoms noted in both groups, but no difference between sham or TBS group post-treatment |
| Hu et al.            | 38              | 20                | 1. L-DLPFC    | 80%          | High [10 Hz]          | 30 trains, 4 s stimulation, 12 s off | No significant difference in depression scores over the trial, across the three groups |
|                      |                 |                   | 2. R-DLPFC    | 80%          | Low [1 Hz]            | 120 trains, 10 s stimulation, 2 s off | |
| Fitzgerald et al.    | 49              | 20                | R-DLPFC + L-DLPFC | 110% + 110% | Low [1 Hz] + High [10 Hz] | 1000 pulses + 20 trains, 5 s duration with 25 s interval | Results showed that both groups reported a significant reduction in depression symptoms over time. However, there were no significant between group differences in depression scores found |
| Yang et al.          | 52              | 10                | L-DLPFC       | 110%         | High [10 Hz]          | 5 s, 30 s intervals | No significant improvement in symptoms were found for the active rTMS versus sham |
| Bulteau et al.       | 26              | 30                | L-DLPFC       | 80%          | TBS [50 Hz]           | iTBS applied twice daily with a 3-h interval. 990 pulses per session, 3 s train containing 3 pulses at 50 Hz | Both groups demonstrated a reduction in symptoms over time, but no significant differences in depression scores or the number of patients who achieved remission, were found between active TBS and sham |

iTBS, intermittent theta-burst stimulation; L-DLPFC, left dorsolateral prefrontal cortex; R-DLPFC, dorsolateral prefrontal cortex; TBS, theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation.
For bipolar mania, five studies were found (see Table 2), which included a total of 93 bipolar patients (mean age range = 29.76–62.00 years). These studies included open-label trials (n = 2), RCTs comparing active treatments (n = 1) and sham-controlled RCTs (n = 2). All studies investigated high-frequency rTMS (10–20 Hz) and, unlike the results for bipolar depression, more of the mania studies targeted the R-DLPPFC (R-DLPFC only n = 2; both L- and R-DLPFC separately n = 1; L-DLPFC only n = 2). No studies investigated sequential rTMS.

For bipolar mixed states, two studies (N = 42; mean age range 44.90–52.00 years) were found (see Table 3). The case report investigated high-frequency rTMS applied to the L-DLPFC, whereas the open-label trial investigated low-frequency rTMS applied to the R-DLPFC.

Finally, one case series study by Li et al. investigated whether rTMS could be used as a maintenance treatment in BD. Here, seven patients who had responded to rTMS, received weekly rTMS sessions for more than 1 year (thus, at the time of treatment they were not currently in an active depressive or manic episode). This study applied high-frequency rTMS to the L-DLPFC.

**Evidence for the use of rTMS for treating bipolar depression**

**Case reports/series**

Most case reports/series investigated the effects of high-frequency rTMS, with all but one reporting that rTMS helped to reduce patients’ depression symptoms. Some (n = 2)
of these studies highlight the risk of affective switching in bipolar patients (for a detailed outline see the results section ‘What is the safety profile of rTMS in BD?’). Only one case report investigated sequential rTMS, reporting a reduction in depression symptoms after seven sessions of rTMS, but also a manic switch. More recently, Kaster et al. reported the beneficial effects of TBS at reducing depression symptoms following 10 sessions in one patient, but again there was a reported manic switch.

Naturalistic studies
Cohen et al. investigated pred. Authors report that age, refractoriness, baseline depression severity and number of prior depressive episodes were all associated with a need for a longer duration of rTMS treatment.

Using data (N= 240, BD = 50) from an Australian private rTMS clinic comparing treatment responses by diagnostic group, Carnell et al. examined an rTMS treatment response among a mixed sample of unipolar and bipolar depression. Participants received one of three rTMS protocols (see Table 1), each employing the ‘5 cm rule’ to target the prefrontal cortex. All patients completed 18–20 treatment sessions over 4–6 weeks (for specific details of the methods used for this data see Galletly et al.). Results showed that all patients demonstrated an improvement in depression symptoms (HAM-D) from baseline to post treatment [bipolar sample baseline mean (M) = 20.26, standard deviation (SD) = 5.97 versus post treatment M = 12.38, SD = 7.31]. Further, 17/50 bipolar patients met treatment response criteria (>50% reduction in HAM-D) and 13/50 met remission criteria (post-treatment HAM-D score of ≤7).

A second naturalistic study conducted by Philips et al. analysed patient records of those who had been treated with rTMS (>30 sessions) for either treatment-resistant unipolar (n = 54) or bipolar (n = 17) depression. The main outcome here was the QIDS, which was assessed at baseline and after every five treatment sessions and post intervention. Both unipolar and bipolar patients demonstrated an equal response (>50% reduction in QIDS scores) over the 30 treatment sessions, with 11/17 (65%) of bipolar patients specifically. Remission (QIDS score ≤5) was also achieved equally in both groups, with 6/17 (35%) bipolar patients. Overall, bipolar patients’ mean depression scores significantly reduced from baseline to post treatment.

Open-label trials
One 3-week open-label trial examined the effectiveness of low-frequency rTMS. This was also the first open-label rTMS trial to adopt the use of neuro-navigation techniques [magnetic resonance imaging (MRI)] to target the R-DLPFC, as earlier RCT trials had adopted the ‘5 cm rule’ for example Fitzgerald et al. and Nahas et al. Depression measures included the HAM-D and MADRS, which were assessed at baseline and after each week of treatment (time 1, 2, 3). All patients (N=11) completed the trial. Results showed a significant reduction in HAM-D scores from baseline to time 2 (mean difference = −6.9) and in MADRS scores from baseline to time 3.

### Table 3. Study of bipolar mixed states (n = 2).

| Study | Sample size (n) | rTMS sessions (n) | rTMS location | rTMS motor threshold (%) | rTMS frequency (Hz) | rTMS protocol | Depression and/or manic symptom outcomes |
|-------|-----------------|------------------|---------------|--------------------------|---------------------|---------------|------------------------------------------|
| Case reports/series (n = 1) | | | | | | | |
| Zeeuws et al. | 1 | 20 | L-DLPFC | 120% | High (20 Hz) | Unknown | Symptoms reduced throughout treatment |
| Open-label trials (n = 1) | | | | | | | |
| Pallanti et al. | 40 | 15 | R-DLPFC | 110% intensity | Low [1 Hz] | 140 s trains, 30 s interval | Both depression and mania symptoms reduced throughout treatment |

L-DLPFC, left dorsolateral prefrontal cortex; R-DLPFC, dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation.
Dell’Osso group achieved remission. This randomised 4-week trial used rTMS applied to both the R- and L-DLPFC, high-frequency stimulation was explored by Kazemi et al. unilateral rTMS versus The effects of bilateral protocol or diagnostic group. Depression symptoms significantly reduced for all patients over 4 weeks, irrespective of rTMS treatment. Authors found a significant reduction in depression scores from pre (M = 30.15, SD = 10.05) to post (M = 15.25, SD = 8.37) treatment, p < 0.0001.

RCTs comparing active treatments

One study explored two different forms of low-frequency rTMS (1 Hz versus 2 Hz) in a mixed sample (MDD n = 105, BD n = 52). Patients were also offered an additional 2 weeks of treatment (10 sessions) if they demonstrated a treatment response following the first 10 sessions (defined as >20% reduction in HAM-D scores). After 4 weeks of treatment, 12/13 BD patients in the 2 Hz group and 5/12 patients in the 1 Hz group achieved remission.

Dell’Osso et al. were the first to examine the effectiveness of both low versus high-frequency rTMS applied to both the R- and L-DLPFC, respectively. This randomised 4-week trial used a mixed sample of unipolar (n = 14) and bipolar (n = 19) patients, who were assigned randomly to receive one of three rTMS protocols (see Table 1). Depression symptoms significantly reduced for all patients over 4 weeks, irrespective of rTMS protocol or diagnostic group.

The effects of bilateral versus unilateral rTMS stimulation was explored by Kazemi et al. They investigated the use of beta wave activity [via electroencephalography (EEG)] to understand whether it correlated with depression symptoms throughout rTMS treatment. Results showed a significant difference in treatment responses (BDI > 50% reduction from baseline) between the bilateral (12/15 patients) and the unilateral (7/15 patients), p < 0.005, but no differences in remission (BDI < 8 post-treatment) or response were found (bilateral = 6/15 versus unilateral 6/15, p > 1.00). Lastly, changes in BDI scores were compared at baseline and post treatment for both groups; however, no significant differences were found.

**Sham-controlled RCTs**

Dolberg et al. conducted the first RCT (double-blind) with an exclusive sample of bipolar patients experiencing a depressive episode (N = 20). This study found that patients in the active rTMS group had significantly lower depression scores at treatment end (M = 15.7, SD = 4.80), compared with the sham (M = 21.3, SD = 5.3) (p < 0.05). However, the type of rTMS or sham condition is not described and sample size was small.

Following this work, Nahas et al. conducted a separate RCT focusing on high-frequency (5 Hz) rTMS. Although the rTMS treatment appeared to be well tolerated by patients (i.e. no withdrawals or reported adverse cognitive effects), the authors found no significant differences in the number of treatment responders between groups (4/11 in the active rTMS group and 4/12 in the sham). The mean percentage change for HAM-D scores from baseline to treatment end did not differ significantly between groups (p = 0.83).

Fitzgerald et al. conducted an RCT, whereby a mixed sample of unipolar depression (n = 42) and bipolar patients (n = 8) were recruited. Clinical response was defined as a 50% reduction in MADRS scores and, for the bipolar sample, there was some evidence that the rTMS treatment had a beneficial effect at reducing depression scores, as 2/4 rTMS patient’s versus 1/4 sham patients demonstrated a treatment response.

Adopting a slightly different rTMS protocol, Tamas et al. assigned participants to receive either low intensity (1 Hz) rTMS applied to the R-DLPFC (n = 4) or sham rTMS (n = 1), with treatments scheduled twice a week for 4 weeks. Outcomes were assessed via the HAM-D and the YMRS. Compared with sham, at the end of treatment, those who received active rTMS demonstrated significantly fewer depression symptoms. Notably, contrary to Dolberg et al., improvement in depression symptoms was found only at 2 weeks post treatment.

Beynel et al. investigated TBS in a 3-week pilot study and randomly assigned patients to either intermittent TBS (iTBS) (n = 5) or sham (n = 7). Here, following treatment, 4/5 patients from the active rTMS group versus 4/7 from the sham met...
clinical response criteria (>50% reduction in MADRS scores). However, analysis of post-treatment MADRS between groups showed no significant difference \((p=0.92)\), nor was there any significant difference in the improvement of MADRS scores between groups (active rTMS improvement score \(M=60.00, SD=18.00\) versus sham improvement score \(M=56.00, SD=29.00\), \(p=0.81\).

Hu et al. examined the effectiveness of rTMS in bipolar patients who were also taking quetiapine medication.\(^63\) This 4-week trial examined the clinical efficacy of rTMS (i.e., on reducing depression symptoms) as well as the cognitive functioning of patients following treatment. The authors found that active rTMS (both low and high-frequency) alongside quetiapine was no more effective at reducing depression symptoms compared with the quetiapine sham stimulation condition. Further, there were no statistically significant differences in cognitive outcomes across the three groups, either before or after rTMS treatment.

In an RCT (\(N=49\)), Fitzgerald et al. investigated sequential rTMS (low and high-frequency stimulation) versus sham and found that both groups reported a significant reduction in depression symptoms over time \((F=15.00, p<0.001)\), with no differences in scores by treatment group.\(^64\) Further, there were no significant differences in the mean reduction of HAM-D scores between the active \((M=21.30, SD=30.0\%)\) versus sham \((M=15.00, SD=21.70\%)\) groups, \(p>0.005\), and neither was there any significant difference in the number of patients meeting response/remission criteria \((p's>0.05)\).

Yang et al. have conducted the largest (published) bipolar depression rTMS trial to date.\(^65\) This RCT recruited BD patients who had at least 3 months of clinical remission before randomisation. The main outcome measures were cognitive functioning, as measured via the MATRICS Consensus Cognitive Battery (MCCB), and clinical symptoms (e.g. depression/mania) measured via a modified version of the HAM-D (24-item) and the YMRS. These were assessed at baseline and at follow up (2 weeks after the last rTMS treatment). There were no significant differences in HAM-D or YMRS scores between groups at follow up \((p>0.42)\). However, the data did show that rTMS improved cognitive functioning, specifically the Spatial Span and Category Fluency items on the MCCB.

Another recent TBS study was conducted by Bulteau et al.\(^66\) This 3-week trial investigated the efficacy of intermittent TBS (iTBS) \((n=12)\) versus sham \((n=14)\), with the number of patients entering remission (BDI score <10) at treatment end as the primary outcome. Patients from both the active iTBS treatment group \((n=7/12)\) and the sham \((n=5/14)\) achieved remission response post intervention, with no significant difference between treatment groups found \((p=0.43)\).

Evidence for the use of rTMS for treating bipolar mania

Open-label trials

The two open-label trials found both investigated high-frequency rTMS. Michael and Erfurth’s 4-week trial reported that manic symptoms – assessed via the Bech-Rafaelsen Mania Scale – significantly reduced post treatment \((M=6.90, SD=6.81)\), compared with baseline \((M=22.22, SD=5.90)\). Most \((8/9)\) patients were also taking psychotropic medication.\(^67\) Similarly, Saba et al. found that manic symptoms improved from baseline \((M=23.25, SD=6.67)\) to treatment end \((M=11.00, SD=4.7), p=0.02 (10 sessions)\). In this study, all patients were taking psychotropic medication during rTMS treatment.

RCTs comparing active treatments

Grisaru et al. were the first to investigate rTMS for manic symptoms in BD.\(^66\) After 2 weeks of treatment, patients who had rTMS applied to the L-DLPFC, versus R-DLPFC, demonstrated a significant improvement in manic symptoms from baseline to post treatment.

Sham-controlled RCTs

The first sham-controlled RCT for rTMS in the treatment of mania showed that both the active rTMS and sham groups reported significant improvements in manic symptoms over time.\(^70\) However, no significant main effect for treatment group, or time \(\times\) treatment interaction effect was found \((Fs<0.8, p values>0.5)\). The authors propose that this could be due to the illness severity of patients in this sample (noted to be more severe compared with the results of Grisaru et al.) or that a more intensive (e.g. greater duration) treatment is possibly required to target symptoms of mania.\(^69\)

The largest study to date to assess rTMS for the treatment of manic symptoms was conducted by
Results revealed a significant treatment $\times$ time interaction effect ($F=12.95$, $p<0.001$, eta squared = 0.25), demonstrating significant differences between groups at post treatment (day 10), with lower manic symptoms in the active rTMS group ($M=5.76$, $SD=3.26$) versus the sham ($M=11.05$, $SD=6.86$).

**Evidence for the use of rTMS for treating mixed state bipolar**

**Case reports/series**

Zeeuws et al. report a 52-year old woman who had previously tried, and been resistant to, electroconvulsive therapy (ECT). She was treated with 20 sessions high-frequency rTMS and demonstrated a significant decreased in depression symptoms from baseline to post treatment (i.e. 50% reduction in HAM-D scores).

**Open-label trials**

Pallanti et al. conducted a 4-week trial whereby low-frequency rTMS was applied to the R-DLPFC to all patients. Analysis of both HAM-D and YMRS showed a significant main effect of time, with significant differences found between baseline and after 10 ($p'\text{s}<0.05$) and 15 stimulations ($p'\text{s}<0.01$).

**Evidence for the use of rTMS for treating bipolar (no current mood episode)**

**Case reports/series**

Only one study investigated the effectiveness of rTMS as a maintenance treatment in BD patients not currently in a mood episode. Responders ($n=7$) from a previous trial were offered maintenance rTMS for up to 1 year. Out of seven patients, three completed a full 1 year of weekly rTMS treatment and demonstrated an average HAM-D score of 13 ($SD=5.9$).

**Current ongoing trials**

A search of ClinicalTrials.gov revealed 16 registered trials, of which 9 were excluded as they were either terminated, not relevant to this review or the trial status was unknown; this left 7 trials ($n=6$ completed trials and $n=1$ ongoing trial).

From the completed trials ($n=6$), only one was published and already included in this review and the rest appeared to be completed, but unpublished, studies. Two completed studies – both open-label trials – reported results: one looked at the effectiveness of low-frequency (1Hz) rTMS applied to the R-DLPFC in treatment resistant bipolar depression ($N=28$). The results suggest that the rTMS reduced depressive symptoms in this sample [ClinicalTrials.gov identifier: NCT00186485]. Another open-label trial investigated a 3-week intervention of high-frequency rTMS for bipolar depression ($N=15$), with results suggesting that rTMS reduced depressive symptoms [ClinicalTrials.gov identifier: NCT00699218]. Other completed studies included a randomised study comparing bilateral high-frequency rTMS versus unilateral low-frequency rTMS [ClinicalTrials.gov identifier: NCT01932749] and two RCTs: (1) investigating theta-burst stimulation versus sham in bipolar depression [ClinicalTrials.gov identifier: NCT00186758] and (2) investigating rTMS versus sham on depression, mania and cognitive functioning outcomes [ClinicalTrials.gov identifier: NCT03207048].

The search revealed one ongoing study that relevant to this review [ClinicalTrials.gov identifier: NCT02749006] that is being conducted in Canada. This randomised double-blind study plans to investigate the effects of TBS versus sham on depressive symptoms in an acute bipolar sample ($N=100$). Primary outcome measure is depressive symptoms as measured via the MADRS, and secondary outcomes include manic symptoms, cognitive functioning and quality of life ratings.

**What is the safety profile of rTMS in BD?**

Table 4 outlines the reported side effects and risk of induced mania found from the included studies. A total of 19 studies reported that patients experienced no side effects. However, from the studies that did report side effects, these included: headache, scalp pain, sleep problems (e.g. insomnia), dizziness, nausea, fatigue and anxiety. Notably, induced seizure from rTMS treatment was not reported in any of these studies. In studies that utilised one active rTMS treatment arm, it is clear that headache and scalp pain are two side effects reported across different all rTMS protocols (i.e. both high and low-frequency applied to L- and R-DLPFC. Interestingly, the two TBS trial studies both reported no side effects.

A total of 10 studies ($n=5$ case series/reports, $n=5$ trial studies) reported instances of affective switching (see Tables 4 and 5). Focusing on these 10 studies, we extracted information on
Table 4. Summary of reported side effects across all studies (N=34).

| Study             | Headache | Scalp pain | Nausea | Fatigue | Sleep problems | Dizziness | Anxiety | Patients reported none of these side effects | Side effects not reported | Frequency of sample whom reported side effects | Did active rTMS induce affective switching in any of the sample? (yes/no/not reported) |
|-------------------|----------|------------|--------|---------|----------------|-----------|---------|-----------------------------------------------|---------------------------|------------------------------------------------|---------------------------------------------------------------------------------|
| Grisaru et al.49  | ✓        |            | N/A    |         |                |           |         | N/A                                           | N/A                       | No                                             | No                                                                              |
| Garcia-Toro41     | ✓        |            | N/A    |         |                |           |         | N/A                                           | Yes                       | Yes                                            | Yes                                                                              |
| Dolberg et al.58  | ✓        |            | N/A    |         |                |           |         | N/A                                           | Not reported              | Yes                                            | No                                                                              |
| Dolberg et al.62  | ✓        |            | N/A    |         |                |           |         | 1/2 [50%]                                    |                           | Yes                                            | Yes                                                                              |
| Nahas et al.59    | ✓        |            | N/A    |         |                |           |         | N/A                                           |                           | Yes                                            | Yes                                                                              |
|第三届等46         | ✓        |            | N/A    |         |                |           |         | 1/19 [5.26%]                                 |                           | No                                             | No                                                                              |
| Michael and Erufurth57 | ✓       |            | N/A    |         |                |           |         | Unclear. Article reports there were 'little subjective side effects' |                           | No                                             | No                                                                              |
| Saba et al.68     | ✓        |            | N/A    |         |                |           |         | No                                            |                           | No                                             | No                                                                              |
| Hausmann et al.63 | ✓        |            | N/A    |         |                |           |         | N/A                                           | Yes                       | Yes                                            | Yes                                                                              |
| Li et al.76       | ✓        |            | N/A    |         |                |           |         | N/A                                           |                           | No                                             | No                                                                              |
| Fitzgerald et al.75 | ✓        |            | N/A    |         |                |           |         | Unclear. Article reports there were ‘no significant adverse events’ |                           | Yes                                            | Yes                                                                              |
| Fitzgerald et al.80 | ✓      | ✓          | N/A    |         |                |           |         | 8/25 [active group] however, it is unclear whether these were BD patients or unipolar |                           | No                                             | No                                                                              |
| Tamas et al.41    | ✓        |            | ✓      | ✓       |                | ✓         |         | Frequency information not reported            |                           | No                                             | No                                                                              |
| Praharaj et al.71 | ✓        |            | ✓      | ✓       |                | ✓         |         | Frequency information not reported            |                           | Yes                                            | Yes                                                                              |
| Dell’Osso et al.52,53 | ✓   |            | ✓      | ✓       |                | ✓         |         | 3/11 [27.27%]                                 |                           | No                                             | No                                                                              |
| Brunelin et al.46 | ✓        |            | N/A    |         |                |           |         | N/A                                           |                           | No                                             | No                                                                              |
| Cohen et al.49    | ✓        |            | ✓      |         |                |           |         | 11/56 [19.64%]                                |                           | Yes                                            | Yes                                                                              |
| Zeeuws et al.72   | ✓        |            | N/A    |         |                |           |         | N/A                                           |                           | No                                             | No                                                                              |

(Continued)
| Study             | Headache | Scalp pain | Nausea | Fatigue | Sleep problems | Dizziness | Anxiety | Patients reported none of these side effects | Side effects not reported | Frequency of sample whom reported side effects | Did active rTMS induce affective switching in any of the sample? (yes/no/not reported) |
|-------------------|----------|------------|--------|---------|----------------|-----------|---------|-----------------------------------------------|----------------------------|------------------------------------------------|----------------------------------------------------------------------------------|
| Li et al.44       |          |            |        |         |                |           |         | Yes                                           |                            | N/A                                                                           | Not reported                                                               |
| Beynel et al.52   |          |            |        |         |                |           |         | Yes                                           | N/A                        | Not reported                                                               |
| Pallanti et al.73 | ✓        | ✓          |        |         |                | ✓         |         | 5/40 [12.5%]                                  | No                         | Yes                                                                           |
| Huang et al.47    |          |            |        |         |                |           |         | N/A                                           | Yes                        |                                                                                |
| Zendjidjian et al.55 |      |            |        |         |                |           |         | N/A                                           | No                         |                                                                                |
| Dell’Osso et al.56 | ✓        | ✓          |        |         |                | ✓         |         | 7/29 however, it is unclear whether these were BD patients or unipolar | Yes                        |                                                                                |
| Hu et al.63       | ✓        |            |        |         |                |           |         | Three patients [one from each protocol] withdrew from the study due to headaches | Yes                        |                                                                                |
| Fitzgerald et al.44 |      |            |        |         |                |           |         | N/A                                           | Not reported               |                                                                                |
| Carnell et al.50  | ✓        | ✓          |        |         |                | ✓         |         | Frequency information not reportedc            | No                         |                                                                                |
| Kazemi et al.37   |          |            |        |         |                |           |         | N/A                                           | No                         |                                                                                |
| Kazemi et al.34   |          |            |        |         |                |           |         | N/A                                           | Not reported               |                                                                                |
| Yang et al.65     | ✓        | ✓          |        |         |                | ✓         |         | 4/52 [7.69%]                                  | No                         |                                                                                |
| Bulteau et al.66  |          |            |        |         |                |           |         | N/A                                           | No                         |                                                                                |
| Philips et al.51  |          |            |        |         |                |           |         | Frequency information not reported            | Not reported               |                                                                                |
| Kaster et al.48   |          |            |        |         |                |           |         | 1/1 [100%]                                    | Yes                        |                                                                                |

aDefined as ‘sleep disturbances’. 
bDefined as insomnia. 
cReported side effects are documented in Galletly et al.76

BD, bipolar disorder; rTMS, repetitive transcranial magnetic stimulation.
Table 5. Themes for reported risk of induced switching (n = 10).

| Study               | % of sample reported to experience affective switching | Type of affective switching | rTMS frequency | Number of rTMS sessions before affective switch | Baseline depression severity information | Concurrent medication during rTMS treatment |
|---------------------|-------------------------------------------------------|-----------------------------|----------------|-----------------------------------------------|----------------------------------------|-------------------------------------------|
| Garcia-Toro⁴¹       | 100% [1/1]                                            | Manic                       | High [20 Hz]   | 1                                             | Baseline HAM-D: 31                     | ✗                                       |
| Dolberg et al.⁴²     | 100% [2/2]                                            | Manic                       | High [10 Hz]   | Patient 1: 15                                | Patient 1: 15-year history of BD       | ✗                                       |
|                     |                                                       |                             |                |                                               | Patient 2: 20                          |                                         |
|                      |                                                       |                             |                |                                               | Patient 2: one depressive episode      |                                         |
|                      |                                                       |                             |                |                                               | 15 years prior                         |                                         |
| Hausmann et al.⁴³    | 100% [1/1]                                            | Manic                       | High [20 Hz]   | 7                                             | Baseline HAM-D: 23                     | ✗                                       |
|                      |                                                       |                             | Low [1 Hz]     |                                               |                                       |                                         |
|                      |                                                       |                             |                |                                               |                                       |                                         |
| Fitzgerald et al.⁵⁵  | One patient a developed hypomanic episode soon after phase I (but doesn’t specify whether this was a BD or MDD patient) | Hypomanic                   | Unclear—either low 1 Hz versus 2 Hz            | 10                                            | Not stated                            | ✗                                       |
|                      |                                                       |                             |                |                                               |                                       |                                         |
|                      |                                                       |                             |                |                                               |                                       |                                         |
| Praharaj et al.⁷¹    | 1/41 [2.43%]                                          | Depression                   | High [20 Hz]   | 10                                           | Not stated                            | Patients in the trial were drug free for at least 2 months |
| Cohen et al.⁴⁹       | 4/56 [7.14%]                                          | Hypomanic                   | Unclear whether they received low [1 Hz] or high [20 Hz] | Not stated                        | Not stated                            | Not stated                        | Not stated                        | Not stated                        |
| Huang et al.⁴⁷       | 1/1 [100%]                                            | Manic                       | High [5 Hz]    | 3                                             | Baseline HAM-D: 22                     | ✗                                       |
| Dell’Osso et al.⁵⁶   | 1/19 [5.26%]                                          | Manic                       | Low [1 Hz]     | 10                                           | Not stated                            | Not stated                            | Not stated                        | Not stated                        | Not stated                        |
| Hu et al.⁶³          | 1/38 [2.63%]                                          | Manic                       | High [10 Hz]   | 15                                           |                                        | ✗                                       |
| Kaster et al.⁴⁸      | 1/1 [100%]                                            | Manic (with psychosis)      | Theta [50 Hz]  | 12                                           | Three prior episodes of mania with psychosis | ✗                                       |

*Unclear if the patient who experienced switching was on these medications during the treatment, but article reports that most patients were taking these alongside treatment. BD, bipolar disorder; HAM-D, Hamilton depression rating scale; MDD, major depressive disorder; rTMS, repetitive transcranial magnetic stimulation.
potential risk factors to affective switching across the studies (see Table 5). From this data, it is clear that affective switching was not only limited to patients whom were also taking antidepressants, as previously suggested,78 but it has also occurred in patients taking antipsychotic and anticonvulsant medication also. From the studies that report affective switching, most employed high-frequency rTMS protocols (including TBS) \( (n=6) \), versus low-frequency \( (n=2) \), sequential low versus high \( (n=1) \) and one where the protocol was unclear. Based on the limited available evidence, it appeared that the number of rTMS sessions conducted before evidence of affective switching emerged ranged from 1 to 15 (\( M=10.30, \ SD=5.70, \ median=10 \)) and those who did experience affective switching had a long history of depression and/or high current depressive symptoms.

Discussion

Effectiveness of rTMS to treat BD

When reviewing the naturalistic studies, open-label trials and randomised studies, there appears to be a detectable signal of efficacy for rTMS treatment, as all of these studies report that rTMS treatment reduced symptoms of depression to varying extents. However, the extent to which evidence from RCTs support the efficacy of rTMS is unclear. Out of the nine sham-controlled RCTs investigating rTMS in bipolar depression, three reported that rTMS was superior to sham.58,60,61 However, all three studies are limited by their low sample sizes \( (n<20) \). Specifically, in Tamas et al. there was only one patient allocated to the sham condition and Dolberg et al. fail to report the type of rTMS treatment used.58,61 This is in contrast to the evidence of RCTs within unipolar depression literature,81,82 but the current review found no evidence for this in existing BD studies.

Safety profile of rTMS in bipolar disorder

Based on our included studies, the reported side effects found (not including affective switching) are similar to those documented in the rTMS unipolar depression studies.81 These are generally considered to be ‘mild’ and known to subside throughout treatment. Risk of seizure is a serious adverse effect documented in the unipolar depression literature,81,82 but the current review found no evidence for this in existing BD studies.

Based on the included studies, risk of affective mania switching was low, similar to previous reviews.34 However, detailed information on the cases who did switch was lacking, thus it remains unclear what the predictors of affective switching are. Early BD case reports were the first to document affective switching within rTMS treatment,42 and previous reviews have investigated this topic. For example, Xia et al. reported rates of affective switching among unipolar \( (n=455) \) versus bipolar depressed patients \( (n=65) \) and found risk to be higher among the bipolar (3.1%) versus the unipolar sample (0.34%).34 Another review conducted by Rachid searched the literature for published studies (from 1966 to 2015) documenting treatment-emergent mania during rTMS treatment78; 19 patients, diagnosed with either unipolar or bipolar depression, were found to have experienced treatment-emergent mania during rTMS treatment. The author concludes that rTMS in monotherapy, or alongside antidepressant medication, could possibly induce
(hypo)manic episodes, with both high- and low-frequency rTMS demonstrating and association with induced mania. They recommend that BD patients undergoing rTMS treatment also be prescribed a mood stabiliser to combat help combat the risk of induced mania.

In the current review, we note that patients who were taking other types of medication (e.g. antipsychotics/anticonvulsants) were also known to experience affective switching, suggesting that it is not just those who are also taking antidepressant medication who are at risk. Out of the 10 studies that reported affective switching (patients $N=14$), 50% (7/14) received high-frequency rTMS, 14.29% (2/14) received low-frequency rTMS, 7.14% (1/14) received both high and low-frequency (sequential) rTMS and in 28.57% (4/14) the exact rTMS protocol for those whom switched was unclear (either high 20 Hz or Low 1 Hz). Most of these switches were found among case series/report studies ($N=5$), followed by uncontrolled studies ($N=3$, e.g. randomised studies/naturalistic studies) and sham-controlled RCTs ($N=2$). However, due to the limited patient information available on those who experience affective switching, it is still unclear whether these variables pose significant risk factors. We do not fully understand the rate of affective switch, but it looks uncommon or rare. In order to design a trial to detect a very small difference between groups (rTMS versus treatment as usual or sham control), and allowing for the rate of baseline affective switch associated with mood disorders in general, it is likely to require a very large sample size within an RCT design. We would suggest more data are needed from observational (and controlled) studies to understand the affective switch rate, and what factors are associated with switch before an RCT could be designed to fully understand the risk of affective switch.

**Future research and clinical practice guidance**

Based on the reviewed evidence, we make several recommendations for future research. First, one limitation of the included studies is that they all have small samples ($<N=52$), thus, adequately powered, sham-controlled RCTs are necessary to determine the efficacy of rTMS in the treatment of BD. Given the current evidence, and therapeutic need, these RCTs should focus on the treatment of bipolar depression currently. Second, future work might also seek to employ more TBS protocols instead of standard rTMS, given its potential for greater treatment efficiency, reduction in participant burden and associated treatment costs. Third, we note many studies reported a lack of any side effects of the treatment. It is unclear whether these represent an omission to collect the data or some other form of bias, but it is unlikely that any effective treatment will not have any side effects, given the side effect burden in even placebo conditions. Fourth, research on the use of rTMS in the treatment of manic symptoms and those with mixed states BD, is still in its infancy. Future RCTs are necessary to understand how effective rTMS is, but also which protocols are best suited for this affective state; this remains unclear (e.g. low versus high-frequency, rTMS applied to the L versus R-DLPFC). Fifth, there is a strong clinical need to better understand those at risk of affective switching following rTMS treatment. Future research trials should offer detailed information on the patients who do experience induced mania from treatment. Specific details such as the types of medications currently prescribed, previous number of manic episodes and descriptions of depressive and/or manic symptoms are critical and would be an important step to help guide clinical decision making. Similarly, more information on patients who demonstrate a response (i.e. significant reduction in symptoms) from RCT trials would be important, especially in the context of an adequately powered RCT. For instance, in unipolar depression, predictors of rTMS treatment response cover a range of neurobiological (e.g. hormonal), neuroimaging (e.g. higher baseline metabolic activity) and treatment parameter (e.g. number of pulses) factors. Lastly, the mechanisms behind rTMS treatment remain largely unclear. A recent review of the potential mechanisms of rTMS unipolar depression has been conducted, but whether these apply to bipolar depression and mania is unknown and remains a future research priority.

**Conclusion**

There is growing interest in the use of rTMS as a treatment for BD, with studies separately investigating the effects of rTMS on both depressive and manic symptoms. Based on the literature to date, there appears to be a possible signal of efficacy for rTMS in treating bipolar depression and mania. However, when compared with sham treatments, most RCTs reported no significant differences in symptoms, but there is a lack of any adequately
powered trial. There is also a crucial need to establish the ideal rTMS treatment parameters to help better determine the efficacy of rTMS in the treatment of BD.

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