TECHNICAL COMMENTARY

Transcranial magnetic stimulation

NeuRA Discover. Conquer. Cure.
BIPOLAR DISORDERS LIBRARY

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method to stimulate nerve cells in superficial layers of the brain. Traditionally, studies assessing the effectiveness of rTMS have been limited by small samples, a range of stimulation parameters and most studies lack long-term follow up assessments. Control comparisons also differ - 'sham' rTMS may involve tilting the stimulation coil against the scalp by 45 or 90 degrees, thus reducing the degree of brain stimulation, or use of a "placebo" coil of identical appearance. These placebo methods usually involve a 'click' noise but no magnetic field and no twitching sensation on the scalp. Comparison groups may receive active rTMS applied to other brain regions. The effects of differing dosage and duration of concurrent medication on rTMS response is unclear.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or comprehensive review was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[1]. Reviews reporting less than 50% of items have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found four systematic reviews that met our inclusion criteria[3-6].

- Moderate quality evidence finds improved clinical response, particularly for depression following high-frequency rTMS over the left dorsolateral prefrontal cortex. There was no benefit for mania and little risk of switching to mania in people with bipolar depression.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Transcranial magnetic stimulation

- Moderate to low quality evidence finds improved cognition post-treatment with high-frequency rTMS (10 Hz) over the left dorsolateral prefrontal cortex, although the findings were not significantly different to the improvements in sham conditions.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

TECHNICAL COMMENTARY

NeuRA Discover. Conquer. Cure.

BIPOLAR DISORDERS LIBRARY

Transcranial magnetic stimulation

Allan CL, Herrmann LL, Ebmeier KP

Transcranial magnetic stimulation in the management of mood disorders

Neuropsychobiology 2011; 64: 163-9

View review abstract online

Comparison	**rTMS vs. sham control.** **The studies included patients with bipolar or unipolar depression.**
Summary of evidence	**Moderate to low quality evidence (large samples, inconsistent, some imprecision and indirectness) suggests improved depression symptoms following rTMS. Low quality evidence is unable to determine the benefits for mania or for after-treatment effects.**

Depression

A significant, medium-sized effect of improved depression symptoms following rTMS;

Depression scale scores: 31 studies, N = 1,531, g = 0.64, 95%CI 0.50 to 0.79, $p < 0.05$, I^2 = 43.5%, p = 0.005

Treatment response: 25 studies, N = 1,317, OR = 4.10, 95%CI 2.85 to 5.90, $p < 0.05$, I^2 = 41.7%, p = 0.01

This effect was maintained at follow-up, with no significant differences in depression scores at the end of treatment and follow-up (average = 4.33 weeks);

9 studies, N not reported, g = -0.02, 95%CI -0.22 to 0.18, $p > 0.05$

Moderator analyses revealed the effect size reduced as the number of stimulus sessions increased. There was greater efficacy of rTMS when patients entering the studies were previously treatment resistant. There were no effects of site, stimulus intensity, stimulus frequency, year of publication, diagnosis (bipolar depression vs. unipolar depression), mean age, treatment resistance or medication effects.

Authors report possible publication bias in the depression scale (not treatment response).

Mania

1 controlled study (N not reported) found significant improvements in mood ($p < 0.01$) for patients treated with right, but not left prefrontal rTMS at 20 Hz.

1 open-label study (N not reported) found significant improvements in mania symptoms in people with bipolar disorder using right high-frequency prefrontal stimulation.

1 controlled study (N not reported) found no differences between groups.

Consistency in results‡	Inconsistent

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Precision in results§	Precise for depression scale scores, imprecise for treatment response.
Directness of results‖	Direct comparison, indirect sample (not all patients had bipolar disorder).

Nguyen TD, Hieronymus F, Lorentzen R, McGirr A, Ostergaard SD

The efficacy of repetitive transcranial magnetic stimulation (rTMS) for bipolar depression: A systematic review and meta-analysis

Journal of Affective Disorders 2021; 279: 250-5

View review abstract online

Comparison	**rTMS for bipolar depression vs. sham control.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, consistent, imprecise, direct) finds improved depression symptoms following rTMS, particularly high-frequency rTMS over the left dorsolateral prefrontal cortex. There was little risk of switching to mania.**

Clinical response

A significant, medium-sized effect of better clinical response with rTMS (mixed applications);

14 studies, N = 274, OR = 2.72, 95%CI 1.44 to 5.14, $p = 0.002$, $I^2 = 0\%$

The subgroup analysis of high-frequency rTMS over the left dorsolateral prefrontal cortex showed it was significantly different to sham, while the subgroup analyses of bilateral stimulation or low-frequency rTMS over the right hemisphere was not significantly different to sham.

The crude response rates across all 20 studies included in the review were 50.3% for rTMS and 32.5% for sham-treatment.

Risks	There was one case of hypomania and one case of mania with active rTMS, although the latter occurred 10 days after rTMS and with cessation of medication.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Sciortino D, Pigoni A, Delvecchio G, Maggioni E, Schiena G, Brambilla P

Role of rTMS in the treatment of cognitive impairments in Bipolar Disorder

and Schizophrenia: a review of Randomized Controlled Trials **Journal of Affective Disorders 2021; Part A. 280: 148-55** View review abstract online	
Comparison	**rTMS for cognition in bipolar disorder vs. sham control.**
Summary of evidence	**Moderate to low quality evidence (small samples, appears inconsistent, direct) finds improved cognition post-treatment with high-frequency rTMS (10 Hz) over the left dorsolateral prefrontal cortex, although the findings were no different to sham conditions.**
Cognition	
1 study (N = 50) assessed two weeks of high-frequency rTMS (10 Hz) over the left dorsolateral prefrontal cortex and found working memory and processing speed significantly improved post-treatment. 1 study (N = 43) assessed 4 weeks of high-frequency rTMS (18 Hz) over the left dorsolateral prefrontal cortex vs. sham rTMS and found active stimulation was superior to sham at week 4 but not at week 8. All cognitive domains improved over time in both groups. 1 study (N = 35) assessed four weeks of high-frequency rTMS (10 Hz) over the left dorsolateral prefrontal cortex vs. low-frequency rTMS (1 Hz) over the right dorsolateral prefrontal cortex vs. sham rTMS (coil vertical to the scalp for 20 sessions) and found no differences between groups in the Wisconsin Card Sorting Test, the Stroop Test, and Trail-Making Test.	
Risks	Not reported
Consistency in results	Appears inconsistent
Precision in results	Unable to assess; no CIs are reported
Directness of results	Direct

Tee MMK, Au CH **A Systematic Review and Meta-Analysis of Randomized Sham-Controlled Trials of Repetitive Transcranial Magnetic Stimulation for Bipolar Disorder** **Psychiatric Quarterly 2020; 91: 1225-47** View review abstract online	
Comparison	**rTMS for bipolar disorder vs. sham control.** **Most studies investigated rTMS as add-on therapy.**

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Transcranial magnetic stimulation

Summary of evidence	**Moderate quality evidence (small to medium-sized samples, some inconsistency and imprecision, direct) finds improved depression symptoms following rTMS, with no benefits for mania symptoms.**
Symptoms, remission, and response	
A significant, small effect of improved depression symptoms with rTMS (mixed applications); 8 studies, N = 257, SMD = 0.302, 95%CI 0.005 to 0.548, *p* = 0.016, I^2 = 0% *There were no significant differences in mania symptoms;* 3 studies, N = 86, SMD = 0.298, 95%CI -0.773 to 1.369, *p* = 0.585, I^2 = 82% *There were higher rates of remission with rTMS;* 7 studies, N not reported, RD = 0.104, 95%CI 0.018 to 0.190, *p* = 0.18, I^2 = 0% *A trend effect of greater response rate with rTMS;* 7 studies, N not reported, RD = 0.074, 95%CI -0.003 to 0.151, *p* = 0.06, I^2 = 0%	
Risks	Authors report no serious adverse events, and the risk of treatment-emergent mania was low.
Consistency in results	Consistent, apart from mania symptoms.
Precision in results	Precise for depression symptoms, imprecise for mania, unable to assess RDs.
Directness of results	Direct

Explanation of acronyms

g = Hedges' *g* = standardized mean differences, Hz = hertz, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, RD = risk difference, rTMS = repetitive transcranial magnetic stimulation, vs. = versus

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[7].

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[7].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[8]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the

number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) which is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[9].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was comparethat which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Allan CL, Herrmann LL, Ebmeier KP (2011): Transcranial magnetic stimulation in the management of mood disorders. *Neuropsychobiology* 64: 163-9.
4. Nguyen TD, Hieronymus F, Lorentzen R, McGirr A, Ostergaard SD (2021): The efficacy of repetitive transcranial magnetic stimulation (rTMS) for bipolar depression: A systematic review and meta-analysis. *Journal of Affective Disorders* 279: 250-5.
5. Sciortino D, Pigoni A, Delvecchio G, Maggioni E, Schiena G, Brambilla P (2021): Role of rTMS in the treatment of cognitive impairments in Bipolar Disorder and Schizophrenia: a review of Randomized Controlled Trials. *Journal of Affective Disorders* Part A. 280: 148-55.
6. Tee MMK, Au CH (2020): A Systematic Review and Meta-Analysis of Randomized Sham-Controlled Trials of Repetitive Transcranial Magnetic Stimulation for Bipolar Disorder. *Psychiatric Quarterly* 91: 1225-47.
7. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
8. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
9. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*