TECHNICAL COMMENTARY

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Transcranial Magnetic Stimulation

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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 for the treatment of schizophrenia have reported mixed results. They 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. Further, the effects of differing dosage and duration of concurrent medication on rTMS response is unclear. All these factors impact on study results and may hinder interpretation.

In the last 10 years, more studies have been conducted which has allowed the synthesis of their results in meta-analyses, which helps clarify rTMS's usefulness. Based on findings that the left temporoparietal cortex is involved in speech perception and is active during auditory hallucinations, some studies have assessed whether the application of low frequency rTMS (1 Hz) reduces the severity of hallucinations by suppressing brain activity in that region. Studies have assessed whether slow rTMS applied to the temporal lobe also relieves other positive symptoms such as delusions and whether the application of high frequency rTMS (≥5 Hz) to the frontal lobe increases brain activity, relieving negative symptoms. Systematic reviews have concentrated on combining results from these studies to give more power to detect differences in symptom severity.

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 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. 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, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version 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

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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 18 systematic reviews that met our inclusion criteria[3-20].

- For positive symptoms, there is moderate to high quality evidence showing low frequency rTMS applied via continuous stimulation to the left temporo-parietal cortex can reduce the severity of auditory hallucinations in the short term (medium-sized effect). Lower quality evidence is uncertain as to the benefits over the longer term (>1-month post-treatment), and there was no clear benefit for other positive symptoms. Mild headache, scalp and facial discomfort may be reported.
- For negative symptoms, there is moderate to high quality evidence showing small to medium-sized improvements with rTMS applied to the dorsolateral prefrontal cortex (mostly left side).
- General psychopathology and negative symptoms were most improved in studies with a pulse frequency of 20 to 50Hz, in those with motor threshold intensity of 110%, in those with a trial duration over 3 weeks, and in those with the treatment site over the prefrontal cortex. However, positive symptoms were worsened in studies using these parameters.
- Moderate to high quality evidence finds a small placebo effect of improved auditory hallucinations with sham rTMS; either non-active sham, or active sham with 45° or 90° tilt away from the stimulation site.
- Moderate to high quality evidence indicates a small benefit of rTMS applied to the left DLPFC for <30,000 pulses for improving working memory, with no improvements in other cognitive domains. This effect may last for up to 3 months.
- Moderate to low quality evidence finds no benefit of rTMS for symptoms in people who are resistant to clozapine, although this analysis consisted of a very small sample.

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Aleman A, Sommer IE, Kahn RS

Efficacy of Slow Repetitive Transcranial Magnetic Stimulation in the Treatment of Resistant Auditory Hallucinations in Schizophrenia: A Meta-Analysis

Journal of Clinical Psychiatry 2007; 68(3): 416-21

View review abstract online

Comparison	**Low frequency rTMS (1Hz) over the left temporoparietal cortex (9 studies) or left superior temporal gyrus and Broca's area (1 study) at 80 to 100% motor threshold vs. sham/placebo.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized samples, consistent, precise, direct) shows a large effect of low frequency rTMS applied via continuous stimulation to the left temporoparietal cortex for reducing the severity of auditory hallucinations in the short term.** **Moderate quality evidence (imprecise) indicates no benefit of low frequency rTMS applied to the left temporoparietal cortex for other psychotic symptoms.**
Auditory hallucinations **Measured with the AHRS, HCS, LS, PSYRATS (hallucination subscale), RHSRS, SAH**	
A significant, medium to large effect of reduced hallucination severity and frequency at the end of treatment with rTMS compared to sham/placebo; 10 studies, N = 212, *d* = 0.76, 95%CI 0.36 to 1.17, *p* = 0.0001, I^2 = 58%, *p* = 0.01 *Subgroup analysis of studies using continuous stimulation only (not intermittent stimulation) showed a large effect of reduced hallucination severity and frequency for rTMS compared to sham/placebo at the end of treatment;* 9 studies, N = 196, *d* = 0.88, 95%CI 0.52 to 1.23, *p* = 0.0001, I^2 = 34%, *p* = 0.14	
Overall positive psychotic symptoms **Measured with the PANSS positive subscale and the SAPS**	
No significant differences between rTMS and sham/placebo at the end of treatment; 6 studies, N = 134, *d* = 0.21, 95%CI -0.29 to 0.72, *p* = 0.20, I^2 not reported	
Consistency in results‡	Consistent for continuous stimulation trials only.
Precision in results§	Precise for auditory hallucinations outcome. Imprecise for frequency of stimulation subgroup analysis. Imprecise for other positive psychotic

	symptoms outcome
Directness of results‖	Direct

Aleman A, Enriquez-Geppert S, Knegtering H, Dlabac-de Lange JJ

Moderate effects of noninvasive brain stimulation of the frontal cortex for improving negative symptoms in schizophrenia: Meta-analysis of controlled trials

Neuroscience and Biobehavioral Reviews 2018; 89: 111-8

View review abstract online

Comparison	**Effectiveness of rTMS over the DLPFC (varying applications) vs. sham.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a small effect of improved negative symptoms with rTMS. Authors conclude that protocols with high frequency stimulation containing more than 7,500 stimuli per week at an intensity of >100% motor threshold may be more effective than other protocols, and treatment may be more effective in younger patients with a shorter duration of illness.**

Negative symptoms

Measured with the SANS or PANSS negative subscale

A significant, medium-sized effect of greater improvement in negative symptoms with rTMS;

20 samples, N = 825, d = 0.64, 95%CI 0.32 to 0.96, $p < 0.0001$, I^2 = 79%, $p < 0.00001$

Removing two outliers reduced the effect size and the heterogeneity;

18 samples, N = 722, d = 0.31, 95%CI 0.12 to 0.50, $p < 0.05$, I^2 = 30%, p = 0.11

Moderator analyses without the outliers showed small to medium-sized effects in studies using 10Hz (d = 0.43, $p < 0.05$), in those with >30,000 stimuli (d = 0.42, $p \leq 0.05$), in those applying stimuli to the left prefrontal regions (d = 0.36, $p < 0.05$), in those using a motor threshold >100% (d = 0.45, $p < 0.05$), and in those with duration of treatment over 2 weeks (d = 0.40, $p < 0.05$).

Studies that applied equal or more than 7,500 stimuli per week had a small to medium-sized effect (d = 0.41, $p < 0.05$), while those with less than 7,500 stimuli per week found a small effect (d = 0.25, $p < 0.05$). Studies with younger patients (< mean 39.1 years) found a small to medium-sized effect (d = 0.46, $p < 0.05$), while studies with older patients found a small effect (d = 0.26, $p < 0.05$). Studies with patients who had a shorter duration of illness (<3 years) found a medium-sized effect (d = 0.56, $p < 0.05$), while studies with patients who had a longer duration of illness found a small

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effect (d = 0.29, p < 0.05). Studies with more than 65% males found a small to medium-sized effect (d = 0.41, p < 0.05), while studies with less than 65% male participants found a small effect (d = 0.33, p < 0.05). Authors report the sham condition also improved negative symptoms pre to post-treatment (d = 0.31, p < 0.05), with low heterogeneity (I^2 = 0%).	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Demeulemeester M, Amad A, Bubrovszky M, Pins D, Thomas P, Jardri R

What Is the Real Effect of 1-Hz Repetitive Transcranial Magnetic Stimulation on Hallucinations? Controlling for Publication Bias in Neuromodulation Trials

Biological Psychiatry 2012; 71: 15-16

View review abstract online

Comparison	**Low frequency (1 Hz) rTMS applied to unspecified brain regions vs. sham.**
Summary of evidence	**Moderate to high quality evidence (unclear sample size, consistent, precise, direct) indicates a medium benefit of rTMS over sham treatment for improving auditory hallucinations.**
Auditory hallucinations	
A significant, medium-sized effect of improved auditory hallucinations with rTMS compared to sham immediately after treatment; 9 RCTs, (N not reported), g = 0.42, 95%CI 0.13 to 0.70, p = 0.004, I^2 = 17.1%, p > 0.05	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Dlabac-de Lange JJ, Knegtering R, Aleman A

Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: review and meta-analysis

Journal of Clinical Psychiatry 2010; 71(4): 411-418

View review abstract online

Comparison	**High frequency rTMS (10 to 20Hz) mostly over the left dorsolateral prefrontal cortex vs. sham.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, unable to assess consistency, precise, direct) indicates a medium benefit of high frequency rTMS applied to the left dorsolateral prefrontal cortex for improving negative symptoms as rated by the SANS.**

Negative symptoms

Measured with the PANSS (negative subscale) or SANS

A significant, medium-sized effect of improved negative symptoms at the end of treatment with rTMS compared to sham;

9 RCTs, N = 213, d = 0.43, 95%CI 0.05 to 0.80, p = 0.03, I^2 = 46%, p = 0.05

Authors state that after excluding one small study with a drug-naïve sample, results were similar and data were consistent.

Subgroup analysis showed a significant effect for symptoms rated on the SANS only;

PANSS, 8 RCTs, N = 172, d = 0.35, 95%CI -0.12 to 0.82, $p > 0.05$

SANS, 3 RCTs, N = 93, d = 0.73, 95%CI 0.26 to 1.19, $p < 0.05$

A medium-sized effect was reported in the subgroup analysis of studies that applied 10Hz stimulation;

7 RCTs, N not reported, d = 0.63, 95%CI 0.11 to 1.15, p = 0.02, I^2 = 54%, p = 0.04

After excluding one small study with drug-naïve sample results were similar and data were consistent.

Subgroup analysis showed a larger effect size for treatment duration over 3 weeks than under 3 weeks;

< 3 weeks, 6 RCTs, N not reported, d = 0.32, 95%CI -0.03 to 0.95, $p > 0.05$

> 3 weeks, 3 RCTs, N not reported, d = 0.58, 95%CI 0.19 to 0.97, $p < 0.05$

Consistency in results	Consistent for overall analysis and frequency of application (less one study), unable to assess subgroup analyses.
Precision in results	Precise
Directness of results	Direct

Dollfus S, Lecardeur L, Morello R, Etard O

Placebo Response in Repetitive Transcranial Magnetic Stimulation Trials of Treatment of Auditory Hallucinations in Schizophrenia: A Meta-Analysis

Schizophrenia Bulletin 2016; 42(2): 301-8

View review abstract online

Comparison	**Changes in auditory hallucinations pre-post sham rTMS.** **Sham rTMS involves; a non-active coil or an active coil administered to the same brain location as active rTMS but tilted away from the head in either a 45° or 90° position to reduce brain stimulation, or an active coil administered to another site unrelated to auditory hallucinations.**
Summary of evidence	**Moderate to high quality evidence (large sample size, inconsistent, precise, direct) suggests a small placebo effect of improved auditory hallucinations with sham rTMS.**

Auditory hallucinations

A significant, small effect of improved auditory hallucinations after sham rTMS;

21 RCTs, N = 303, g = 0.287, 95%CI 0.128 to 0.446, $p < 0.0001$, I^2 = 79%

When studies were assessed separately according to design (parallel vs. crossover), only parallel studies revealed a significant effect (13 parallel studies, g = 0.44, $p < 0.0001$, 8 crossover studies, g = 0.06, $p > 0.05$).

Further analysis on the 13 parallel studies showed that the use of 45° coil position showed the largest pre-post effect size (g = 0.65, p = 0.01), although 90° coil position (g = 0.25, p = 0.005), and non-active coil (g = 0.36, p = 0.002) also showed significant pre-post effect sizes. Application to an unrelated brain location showed no significant effects (stats not reported).

A significant placebo effect was observed in the 16 studies for which there was no significant effect of active rTMS over sham rTMS, whereas the placebo effect was not significant in the 5 studies that reported a significant superiority of active rTMS treatment over sham rTMS.

There was no effect of the number of pulses applied.

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Dougall N, Maayan N, Soares-Weiser K, McDermott LM, McIntosh A

Transcranial magnetic stimulation (TMS) for schizophrenia (Review)

Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD006081.

View review abstract online

Comparison 1	**Temporoparietal rTMS (5 to 12 sessions, mostly left side and low frequency, continuous or intermittent stimulation, various motor thresholds) vs. sham.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, some inconsistency, imprecise, direct) suggests global state, mental state, and positive symptoms, but not negative symptoms, may be improved with temporoparietal rTMS stimulation compared to sham.**
Global state **Measured with the CGI score**	
Significant greater improvement in global state for patients receiving rTMS than sham; 7 RCTs, N = 224, MD -0.50, 95%CI -0.76 to -0.23, p = 0.00030, I^2 = 44%, p = 0.10	
Mental state **Measured with the PANSS total scale**	
Significant greater improvement in mental state for patients receiving rTMS than sham; 5 RCTs, N = 127, MD -6.09, 95%CI -10.95 to -1.22, p = 0.014, I^2 = 0%, p = 0.89	
Positive symptoms **Measured with the PANSS positive scale**	
Significant greater improvement in positive symptoms for patients receiving rTMS than sham; 11 RCTs, N = 333, MD -2.14, 95%CI -3.15 to -1.14, p = 0.000028, I^2 = 0%, p = 0.66	
Hallucinations **Various scales**	
A trend effect of greater improvement in hallucinations for patients receiving rTMS compared to sham; 9 RCTs, N = 327, MD -2.11, 95%CI -4.38 to 0.16, p = 0.068, I^2 = 62%, p = 0.01	
Negative symptoms **Measured with the PANSS negative scale**	

No significant differences between groups; 7 RCTs, N = 162, MD -0.31, 95%CI -1.87 to 1.25, $p = 0.70$, $I^2 = 0\%$, $p = 0.93$	
Risks	Significant, medium sized effect of increased risk of headache for patients receiving rTMS compared with sham: 10 RCT, N = 392, RR 2.65, 95%CI 1.56 to 4.50, $p = 0.00030$, I^2 0%, $p = 0.88$. No differences in; leaving the study early; lightheaded/dizziness; tinnitus; memory; concentration; movement problems; facial contraction; quality of life.
Consistency in results	Consistent for global state, mental state, positive symptoms, negative symptoms, headaches, inconsistent for hallucinations.
Precision in results	Authors report that data were precise for global state only.
Directness of results	Direct
Comparison 2	**Temporoparietal rTMS (5 to 12 sessions, mostly left side and low frequency, continuous or intermittent stimulation, various motor thresholds) vs. antipsychotic medication.**
Summary of evidence	**Moderate to low quality evidence (small sample, imprecise, direct) suggests no benefit of temporoparietal rTMS over antipsychotic medication for global state.**
Global state **Measured with the CGI score**	
No significant differences in global state between rTMS and sham; 1 RCT, N = 100, RR 1.19, 95%CI 0.91 to 1.57, $p > 0.05$	
Risks	No significant differences in the number of patients leaving the study early: 2 RCTs, N = 140, RR 0.33, 95%CI 0.08 to 1.46, $p = 0.14$.
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise
Directness of results	Direct
Comparison 3	**Prefrontal or dorsolateral prefrontal rTMS (mostly left side, 10Hz, 15Hz, or 20Hz) varying durations and motor thresholds vs. sham.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, imprecise, direct) suggests greater improvements in negative symptoms as measured by the SANS, but not the PANSS, with left dorsolateral prefrontal rTMS compared to sham, with an increased risk of headache. There were no differences in**

	positive symptoms.
Negative symptoms **Measured with the PANSS negative**	
Significant greater improvement in negative symptoms for patients receiving rTMS than sham measured by the SANS, but not the PANSS; SANS: 3 RCTs, N = 71, MD -12.68, 95%CI -18.60 to -6.77, $p = 0.000027$, $I^2 = 14\%$, $p = 0.31$ PANSS: 12 RCTs, N = 341, MD -1.59, 95%CI -4.68 to 1.50, $p = 0.31$, $I^2 = 89\%$, $p < 0.00001$	
Positive symptoms **Measured with the PANSS positive scale**	
No significant differences in positive symptoms; 10 RCTs, N = 279, MD -0.33, 95%CI -0.99 to 0.33, $p = 0.33$, $I^2 = 24\%$, $p = 0.22$	
Risks	Significant, medium sized effect of increased risk of headache for patients receiving rTMS compared with sham: 6 RCTs, N = 164, RR 2.77, 95% CI 1.22 to 6.26, $p = 0.015$, $I^2 = 0\%$, $p = 0.70$. No differences in; leaving the study early; cognitive difficulties; movement problems; facial twitching; discomfort/pain.
Consistency in results	Consistent for SANS negative symptoms and PANSS positive symptoms, inconsistent for PANSS negative symptoms.
Precision in results	Imprecise
Directness of results	Direct
Comparison 4	**Prefrontal theta burst rTMS (50Hz applied in bursts) vs. sham.**
Summary of evidence	**Moderate quality evidence (small sample, consistent, imprecise, direct) suggests greater improvements in mental state and negative symptoms with theta burst rTMS compared to sham.**
Mental state **Measured with the PANSS total or general scales**	
Significant greater improvement in mental state for patients receiving theta burst rTMS than sham; PANSS total: 3 RCTs, N = 108, MD -5.71, 95%CI -9.32 to -2.10, $p = 0.0020$, $I^2 = 0\%$, $p = 0.93$ PANSS general: 3 RCTs, N = 108, MD -2.47, 95%CI -4.21 to -0.73, $p = 0.0055$, $I^2 = 0\%$, $p = 0.84$	
Negative symptoms **Measured with the PANSS negative symptom scale**	

Significant greater improvement in negative symptoms for patients receiving theta burst rTMS than sham; 3 RCTs, N = 108, MD -2.67, 95%CI -4.25 to -1.09, p = 0.00095, I^2 = 0%, p = 0.68	
Positive symptoms **Measured with the PANSS positive symptom scale**	
No differences in positive symptoms; 3 RCTs, N = 108, MD -0.42, 95%CI -1.64 to -0.80, p = 0.50, I^2 = 0%, p = 0.90	
Risks	No differences in leaving the study early, cognitive difficulties, sleep problems, headache.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Freitas C, Fregni F, Pascual-Leone A

Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia

Schizophrenia Research 2009; 108(1-3): 11-24

View review abstract online

Comparison 1	**Low frequency rTMS (1Hz) over the left temporoparietal cortex (80 to 100% motor threshold) pre-treatment vs. post-treatment. Varying treatment duration.**
Summary of evidence	**Moderate quality evidence (small samples inconsistent, precise, direct) indicates a large effect of low frequency rTMS applied to the left temporoparietal cortex for reducing the severity of auditory hallucinations in the short term. Authors state some studies reported benefit of treatment for up to 13 weeks.**
Auditory hallucinations **Measured with the AHRS, HCS, SAH**	

A significant, large effect of improved auditory hallucinations for rTMS after treatment compared to before treatment; 7 RCTs + 2 observational studies, N = 122, *d* = 1.35, 95%CI 1.11 to 1.58, *p* = 0.001, I² = 59%, *p* = 0.012 *Results were similar in the subgroup analysis of RCTs only;* 7 RCTs, N = 160, *d* = 0.96, 95%CI 0.65 to 1.27, *p* = 0.001, Q = 26.85, *p* = 0.001	
Risks	Not reported
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Low frequency rTMS (1Hz) over the left temporoparietal cortex (80 to 100% motor threshold) pre-treatment vs. post-treatment. Varying treatment duration.**
Summary of evidence	**Moderate to high quality evidence from RCT (small to medium sized samples, consistent, precise, direct) indicates no benefit of low frequency rTMS applied to the left temporoparietal cortex for positive symptoms.**
Positive symptoms **Measured with the PANSS (positive subscale), SAPS**	
A significant, medium-sized effect favouring rTMS in pre-post treatment comparison; 10 RCTs + 2 observational studies, N = 149, *d* = 0.50, 95%CI 0.31 to 0.68, *p* = 0.001, I² = 26%, *p* = 0.186 *This was not significant in the subgroup analysis of RCTs only;* 10 RCTs, N = 204, *d* = 0.17, 95%CI -0.05 to 0.39, *p* = 0.129, I² = 0%, *p* = 0.966	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct
Comparison 3	**High frequency rTMS (10 to 20Hz) over the left dorsolateral prefrontal cortex (80 to 110% motor threshold) pre-treatment vs. post-treatment. Varying treatment duration.**
Summary of evidence	**Moderate quality evidence from RCT (small samples, consistent, precise, direct) indicates no benefit of high frequency rTMS applied to the left dorsolateral prefrontal cortex for negative**

	symptoms.
Negative symptoms **Measured with the PANSS (negative subscale), SANS**	
A significant, medium-sized effect favouring rTMS in pre-post treatment comparison; 5 RCTs + 3 observational studies, N = 63, *d* = 0.49, 95%CI 0.17 to 0.82, *p* = 0.003, I^2 = 45%, *p* = 0.081 *However, this was not significant in the subgroup analysis of RCTs only;* 5 RCTs, N = 87, *d* = 0.21, 95%CI -0.23 to 0.64, *p* = 0.351, I^2 = 54%, *p* = 0.07	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

He H, Lu J, Yang L, Zheng J, Gao F, Zhai Y, Feng J, Fan Y, Ma X

Repetitive transcranial magnetic stimulation for treating the symptoms of schizophrenia: A PRISMA compliant meta-analysis

Clinical Neurophysiology 2017; 128: 716-24

View review abstract online

Comparison	**Effectiveness of rTMS (3-20 sessions of 1Hz over the temporal lobe for auditory hallucinations, 10-20 sessions of 10Hz over the left DLPFC for negative symptoms) vs. sham.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, inconsistent, precise, direct) finds a small improvement in auditory hallucinations with rTMS, but no benefit for negative symptoms.**
Negative symptoms **Measured with various scales**	
No significant differences between groups; 7 studies, N = 412, *d* = -0.41, 95%CI -1.16 to 0.35, *p* > 0.05, Q-test *p* < 0.0001 Cumulative analyses by publication date and sample size did not show any stable trends.	

Auditory hallucinations Measured with various scales	
A significant, small effect of greater improvement in auditory hallucinations with rTMS; 13 RCTs, N = 354, *d* = -0.29, 95%CI -0.57 to -0.01, *p* < 0.05, Q-test *p* = 0.06 Authors report this effect was driven by 6 studies and removing any of these studies gave non-significant results. The effect increased gradually and became positive as small-sample studies were added to the analysis. There was evidence of potential publication bias. There were no effects of publication year, study design, total stimulation, type of coil, and percentage of the individual motor threshold.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Jiang Y, Guo Z, Xing G, He L, Peng H, Du F, McClure MA, Mu Q

Effects of high-frequency transcranial magnetic stimulation for cognitive deficit in schizophrenia: A meta-analysis

Frontiers in Psychiatry 2019; 10: 135

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Comparison	**10-20 sessions of high frequency (10 Hz) rTMS applied to left or bilateral DLPFC for cognitive symptoms vs. sham.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) indicates a small benefit of rTMS applied to the left DLPFC for <30,000 pulses for improving working memory, with no improvements in other cognitive domains. This effect may last for up to 3 months.**
Cognition	
A small, significant improvement in working memory with rTMS; 7 RCTs, N = 250, SMD = 0.34, 95%CI 0.08 to 0.59, *p* = 0.009, I^2 = 0% Subgroup analysis showed rTMS was most effective when applied to the left DLPFC and the total pulses < 30,000. The effects remained for up to 3 months.	

There were no significant differences in executive function, attention, processing speed, and language. The effect for language became significant in follow-up analysis (up to 3 months).	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Kennedy NI, Lee WH, Frangou S

Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: A meta-analysis of randomized controlled trials

European Psychiatry 2018; 49: 69-77

View review abstract online

Comparison	**Effectiveness of rTMS over the DLPFC (varying applications) vs. sham.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) finds medium-sized effects of greater improvement in negative symptoms and auditory hallucinations with rTMS, with no effect on positive symptoms or overall symptoms.** **General psychopathology and negative symptoms improved the most in studies with a pulse frequency of 20 to 50Hz, in those with motor threshold intensity of 110%, in those with a trial duration over 3 weeks, and in those with the treatment site over the prefrontal cortex. Conversely, positive symptoms worsened in studies using these parameters.**

Overall symptoms

Measured with the PANSS (total score)

No significant differences between groups;

18 RCTs, N = 817, g = -0.29, 95%CI not reported, p = 0.6, I^2 = 79%

Subgroup analyses showed significant improvements in general psychopathology in studies with a pulse frequency of 20 to 50Hz (g = -0.97, p = 0.002), in those with motor threshold intensity of 110% (g = -0.53, p = 0.02), in those with a trial duration over 3 weeks (g = -0.50, p = 0.01), and in those

Negative symptoms **Measured with the PANSS (negative subscale)**	
A significant medium-sized effect of greater improvement in negative symptoms with rTMS; 19 RCTs, N = 869, *g* = -0.49, 95%CI not reported, *p* = 0.01, I^2 = 87% Subgroup analyses showed improvements in negative symptoms in studies using pulse frequency of 20 to 50 Hz (*g* = -0.93, *p* = 0.03), in those with motor threshold intensity of 110% (*g* = -1.07, *p* = 0.0005), in those with a trial duration over 3 weeks (*g* = -0.90, *p* = 0.001), and in those with the treatment site over the left prefrontal cortex (*g* = -0.72, *p* = 0.007). Older age was associated with greater symptom improvement, while male sex was associated with less symptom improvement.	
Positive symptoms **Measured with the PANSS (positive subscale)**	
No significant differences between groups; 22 RCTs, N = 999, *g* = 0.28, 95%CI not reported, *p* = 0.13, I^2 = 89% Older age was associated with greater symptom improvement. Subgroup analyses showed worsening of positive symptoms in studies with stimulation over 20Hz (*g* = 0.64, *p* = 0.0008), in those with 110% motor threshold intensity (*g* = 1.13, *p* = 0.001), in trials lasting over 3 weeks (*g* = 0.70, *p* = 0.01) and in treatment site over the prefrontal cortex (*g* = 0.84, *p* = 0.006).	
Auditory hallucinations **Measured with the AHRS and PANSS**	
A significant, medium-sized effect of greater improvement in auditory hallucinations with rTMS; 14 RCTs, N = 578, *g* = -0.51, 95%CI not reported, *p* = 0.0001, I^2 = 59% The efficacy of active rTMS increased significantly with higher antipsychotic dose and decreased with older age.	
Risks	A medium-sized effect of more headache with active rTMS; OR = 3.15, 95%CI 1.65 to 5.99, *p* = 0.0005
Consistency in results	Inconsistent
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Osoegawa C, Gomes JS, Grigolon RB, Brietzke E, Gadelha A, Lacerda ALT, Dias

AM, Cordeiro Q, Laranjeira R, de Jesus D, Daskalakis ZJ, Brunelin J, Cordes J, Trevizol AP

Non-invasive brain stimulation for negative symptoms in schizophrenia: An updated systematic review and meta-analysis

Schizophrenia Research 2018; 197: 34-44.

View review abstract online

Comparison	**Effectiveness of rTMS (varying applications) vs. sham.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) finds a small effect of greater improvement in negative symptoms with rTMS, regardless of treatment protocol.**
Negative symptoms **Measured with the PANSS (negative subscale), BPRS and SANS**	
A significant, small effect of greater improvement in negative symptoms with rTMS; 24 RCTs, N = 1,103, SMD = 0.19, 95%CI 0.07 to 0.32, $p < 0.05$, $I^2 = 0\%$, $p = 0.75$ Authors report no significant differences in results with one study removed or in the subgroup analyses of different treatment protocols.	
Risks	There were no differences in dropout rates.
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Shi C, Yu X, Cheung EFC, Shum DHK, Chan RCK

Revisiting the therapeutic effect of rTMS on negative symptoms in schizophrenia: A meta-analysis

Psychiatry Research 2014; 215: 505-513

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Comparison 1	**Pre-treatment vs. post-treatment rTMS and sham rTMS applied to the dorsolateral or left dorsolateral prefrontal cortex at 10-**

	20Hz, and 80-100% motor threshold over 5-20 sessions.
Summary of evidence	**Moderate quality evidence (medium-sized samples, some inconsistency, precise, direct) suggests rTMS and sham both improve negative symptoms.**
Negative symptoms	
A significant medium-sized effect of reduced negative symptoms with rTMS, and a small placebo effect for sham rTMS; rTMS: 10 RCTs + 3 open-label studies, N = 342, *d* = 0.625, 95%CI 0.228 to 1.021, *p* = 0.002, I^2 = 70%, *p* < 0.001 Sham rTMS: 10 RCTs, N = 322, *d* = 0.396, 95%CI 0.158 to 0.677, *p* = 0.002, I^2 = 32%, *p* = 0.17	
Consistency in results	Consistent for sham only.
Precision in results	Precise
Directness of results	Direct
Comparison 2	**rTMS vs. sham rTMS applied to various regions, at 1-20Hz, and 80-110% motor threshold, over 10-20 sessions.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, inconsistent, precise, direct) suggests rTMS may be beneficial for negative symptoms when compared to sham, particularly in patients with symptom duration under 8 years, more severe negative symptoms at baseline, treatments for 3 weeks or more with stimulation at the left dorsolateral prefrontal cortex, at 10HZ, and 110% motor threshold.**
Negative symptoms	
Significant medium-sized effect of reduced negative symptoms with rTMS compared to sham; 10 RCTs, N = 322, *d* = 0.532, 95%CI 0.191 to 0.874, *p* = 0.002, I^2 = 51%, *p* = 0.017 *Subgroup analyses* Shorter duration of negative symptoms (< 8 years), higher baseline level of negative symptoms, longer duration of rTMS treatment (≥ 3 weeks), 10Hz frequency, stimulation of the left DLPFC, and a 110% motor threshold all showed the largest effect sizes.	
Consistency in results	Inconsistent
Precision in results	Precise

Directness of results	Direct

Siskind D, Honarparvar F, Hasan A, Wagner E, Sinha S, Orr S, Kisely S

rTMS for clozapine refractory schizophrenia - A systematic review and pairwise meta-analysis

Schizophrenia Research 2019; 211: 113-4

View review abstract online

Comparison	**High or low frequency rTMS applied to the left temporoparietal or left dorsolateral prefrontal cortex in people with schizophrenia who are clozapine-resistant vs. sham.**
Summary of evidence	**Moderate to low quality evidence (small samples, consistent, imprecise, indirect) suggests no benefit of rTMS for people who are resistant to clozapine.**
Symptoms	
No significant differences between groups; Total symptoms: 3 RCTs, N = 54, SMD = -0.33, 95%CI -0.89 to 0.23, p = 0.25, I^2 = 0% Positive symptoms: 3 RCTs, N = 54, SMD = -0.05, 95%CI -0.61 to 0.51, p = 0.86, I^2 = 0% Negative symptoms: 3 RCTs, N = 54, SMD = -0.26, 95%CI -0.82 to 0.30, p = 0.36, I^2 = 0%	
Risks	15% of people receiving rTMS reported headache vs. 0% in the sham condition.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Indirect; mixed treatments and sham conditions.

Slotema CW, Dirk Blom J, Hoek HW, Sommer I

Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of

the efficacy of rTMS in psychiatric disorders **Journal of Clinical Psychiatry 2010; 71 (7): 873-884** View review abstract online	
Comparison 1	**Low frequency rTMS (1 Hz) to the left or right temporoparietal cortex vs. sham, 4 - 10 sessions.**
Summary of evidence	**Moderate quality evidence (small to medium-sized sample, direct, consistent, unable to assess precision) suggests rTMS may reduce auditory verbal hallucinations compared to sham.**
Auditory verbal hallucinations	
Significant medium-sized effect of reduced auditory verbal hallucinations with rTMS compared to sham; 7 RCTs, N = 189, *g* = 0.54, 95%CI not reported, *p* < 0.001, I^2 = 0%, *p* = 0.61	
Risks	Headaches (5.7% of treatment group vs. 1.9% of comparison group), dizziness (1.9% vs. 0.9%) and amnesia (0.9% vs. 0%).
Consistency in results	Consistent
Precision in results	Unable to assess
Directness of results	Direct
Comparison 2	**High frequency rTMS (10Hz) applied to the dorsolateral prefrontal cortex (5 studies applied 10Hz to left hemisphere, 1 study applied 1 Hz to right hemisphere, and one study applied 10Hz bilaterally) vs. sham, 10 - 15 sessions. Most studies applied rTMS to the left dorsolateral prefrontal cortex.**
Summary of evidence	**Moderate to low quality evidence (small sample, direct, inconsistent, unable to assess precision) is unsure of the benefits of high frequency rTMS compared to sham for negative symptoms.**
Negative symptoms	
Trend towards a small to medium effect of improved negative symptoms for those who received rTMS compared to sham treatment; 7 RCTs, N = 148, *g* = 0.39, 95%CI not reported, *p* = 0.11, I^2 = 56%, *p* = 0.03	

Risks	Headache (12.5% of treatment group vs.1.4% of comparison group), scalp discomfort (8.6% vs. 1.4%), facial twitching (25% vs. 0), increased akathisia (6.3% vs. 0%) and increased comorbid obsessive-compulsive disorder (6.3% vs. 0%).
Consistency in results	Inconsistent
Precision in results	Unable to assess
Directness of results	Direct

Slotema CW, Aleman A, Daskalakis ZJ, Sommer I

Meta-analysis of repetitive transcranial magnetic stimulation in the treatment of auditory verbal hallucinations: Update and effects after one month

Schizophrenia Research 2012; 142(1-3): 40-45

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Comparison 1	**Low frequency rTMS to the left temporo-parietal region (1 Hz) vs. sham, 3 to 20 sessions.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, consistent, precise, direct) indicates low frequency rTMS applied to the left temporoparietal region reduces auditory verbal hallucinations in the short-term (immediately after treatment).** **Low quality evidence (small sample, imprecise, inconsistent, direct) suggests no differences one month after treatment.**

Auditory verbal hallucinations

Measured with the AHRS, HCS

A significant medium-sized effect of reduced auditory verbal hallucinations with rTMS compared to sham;

15 RCTs, N = 337, g = 0.44, 95%CI 0.19 to 0.68, $p < 0.001$, $I^2 = 35.7\%$

A similar effect was reported after excluding crossover design RCTs (parallel design RCTs only);

10 RCTs, N = 265, g = 0.40, 95%CI 0.10 to 0.70, $p < 0.05$, $I^2 = 35.6\%$

A similar effect was reported in studies using different rTMS-foci;

17 studies, N = 459, *g* = 0.33, 95% CI 0.17 to 0.50, *p* < 0.05, I^2 = 12.9% *No significant differences between active and sham groups one month after the end of treatment;* 5 studies, N = 127, *g* = 0.40, 95%CI −0.23 to 1.02, *p* = 0.215, I^2 = 63.6% Authors report no differences in effect sizes between different duration/number of treatments, different percentages of motor threshold for stimulation, different measures (interview-based clinician rated vs. self-report), and different samples (therapy-resistant auditory verbal hallucinations and non-therapy-resistant auditory verbal hallucinations).
Severity of psychosis **Measured with the PANSS - positive**
Significant small effect of reduced severity of psychosis in people with schizophrenia who received rTMS compared to sham; Number of studies/N unclear: *g* = 0.28, 95% CI 0.04 to 0.52, *p* < 0.05, I^2 = 0

Risks	Headaches (12.7% of treatment group vs. 0.03% of comparison group), dizziness (1.8% vs. 1.4%) and twitching (8.2% vs. 0.68%).
Consistency in results	Consistent, apart from long-term effects.
Precision in results	Precise, apart from long-term effects.
Directness of results	Direct

Slotema CW, Blom JD, van Lutterveld R, Hoek HW, Sommer IEC

Review of the Efficacy of Transcranial Magnetic Stimulation for Auditory Verbal Hallucinations

Biological Psychiatry 2014; 76: 101-110

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Comparison	**Any rTMS vs. sham - 3 to 20 sessions.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) indicates rTMS reduces auditory verbal hallucinations when compared to sham, particularly low frequency stimulation applied to the left temporoparietal region, with no differences between groups in overall severity of psychotic symptoms.**
Auditory verbal hallucinations	

Measured with the AHRS, HCS, PSYRATS, or the Severity of Hallucinations scale	
A significant medium-sized effect of reduced auditory verbal hallucinations with rTMS compared to sham; 19 RCTs, N = 548, g = 0.44, 95%CI not reported, $p < 0.001$, I^2 = 27%, p = 0.10 *Subgroup analyses* The effect size for rTMS was larger (g = 0.63) in 15 studies applying low frequency (1Hz) rTMS to the left temporoparietal region and was similar (g = 0.45) in 10 studies of antipsychotic-resistant patients. No significant differences were found in 3 studies applying rTMS to the right temporoparietal regions (g = 0.25), or in 3 studies comparing low to high frequency rTMS (g = 0.19). No significant correlations were found between effect sizes and the number of pulses, duration of treatment, motor threshold levels, type of coil used, or the focus of treatment.	
Severity of psychosis **Measured** with **the PANSS – positive, or the SANS**	
No significant differences between groups; 14 RCTs, N = 353, g = 0.21, 95%CI not reported, p = 0.11, I^2 = 23%, p = 0.19	
Consistency in results	Consistent
Precision in results	Forest plots indicate data are precise.
Directness of results	Direct

Tranulis C, Sepehry AA, Galinowski A, Stip E

Should We Treat Auditory Hallucinations With Repetitive Transcranial Magnetic Stimulation? A Meta-analysis

Canadian Journal of Psychiatry 2008; 53(9): 577-586

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Comparison	**Low frequency rTMS (1Hz) applied to the left temporoparietal cortex (80 to 100% MT) vs. sham or placebo. Varying treatment duration.**

Summary of evidence	**Moderate to high quality evidence (small to medium-sized sample, consistent, precise, direct) indicates a medium-sized effect of low frequency rTMS applied to the left temporoparietal cortex for reducing the severity of auditory hallucinations in the short term. Authors state that some studies reported benefit of treatment for up to 15 weeks.** **Moderate to low quality evidence (unclear sample size, unable to assess consistency or precision, direct) suggests little benefit of left temporoparietal stimulation for other psychotic symptoms.**
Auditory hallucinations **Measured with the AHRS, HCS, PANSS (auditory hallucination subscale), PSYRATS (hallucination subscale), SAH**	
A significant, medium-sized effect of improved auditory hallucinations for rTMS compared to control immediately after treatment; 10 RCTs, N = 232, g = 0.514, 95%CI 0.225 to 0.804, p = 0.001, I^2 = 23%, p = 0.162	
Other positive psychotic symptoms **Measured with the PANSS (positive, general and total scales), SAPS**	
No significant treatment effect at end of treatment; 6 RCT, effect sizes not reported.	
Risks	Approximately 10% of participants reported mild headache.
Consistency in results	Consistent for auditory hallucinations, heterogeneity not reported for other positive psychotic symptoms.
Precision in results	Precise for auditory hallucinations, not reported for other positive psychotic symptoms.
Directness of results	Direct

Wang J, Zhou Y, Gan H, Pang J, Li H, Wang J, Li C

Efficacy towards negative symptoms and safety of repetitive transcranial magnetic stimulation treatment for patients with schizophrenia: A systematic review

Shanghai Archives of Psychiatry 2017; 29: 61-76.

View review abstract online

Comparison	**Efficacy of rTMS (most studies used high frequency stimulation of the left DLPFC) vs. sham.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds a small to medium-sized effect of greater improvement of negative symptoms with active rTMS.**
Negative symptoms **Measured with the PANSS (negative subscale) and SANS**	
A small to medium-sized effect of greater improvement in negative symptoms with rTMS; 29 RCTs, N = 1,440, SMD = -0.40, 95%CI -0.62 to -0.18, $p = 0.0004$, $I^2 = 73\%$, $p < 0.00001$ Meta-regression showed increased baseline severity of negative symptoms was associated with increased effect sizes. There were no moderating effects of treatment protocol, age, or illness stage.	
Risks	There were more mild adverse effects with rTMS; RR = 2.20, 95%CI 1.53 to 3.18, $p < 0.05$
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

AHRS = Auditory Hallucination Rating Scale, AVH = Auditory Verbal Hallucination, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression Scale, CI = Confidence Interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardized mean differences (see below for interpretation of effect size), DLPFC = dorsolateral prefrontal cortex, HCS = Hallucination Change Scale, HDRS = Hamilton Depression Rating Scale, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), LS = 10-point Likert scale of hallucination intensity, MD = mean difference, MT = motor threshold, N = number of participants, OCD = obsessive compulsive disorder, PANSS = Positive and Negative Syndrome Scale, PSYRATS = Psychotic Symptom Rating Scales, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity, RCT = randomized controlled trial/s, RHSRS = Revised Haddock Self-Rating Scale, rTMS = repetitive transcranial magnetic stimulation, SAH = Scale for Auditory Hallucinations, SANS = Scale of assessment of negative symptoms, SAPS = Scale for the Assessment of Positive Symptoms, SMD = standardised mean difference, TVRS = Topography of Voices Rating Scale, vs. = versus

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[21].

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† 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[21].

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[22]. 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

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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[23].

‖ 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.

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