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Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults (Review)

Li H, Wang J, Li C, Xiao Z

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Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults.
Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD009083.
DOI: 10.1002/14651858.CD009083.pub2.

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[Intervention Review]

Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults

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Editorial group: Cochrane Common Mental Disorders Group.
Publication status and date: New, published in Issue 9, 2014.

Citation: Li H, Wang J, Li C, Xiao Z. Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 9. Art. No.: CD009083. DOI: 10.1002/14651858.CD009083.pub2.

ABSTRACT

Background

Panic disorder (PD) is a common type of anxiety disorder, characterized by unexpected and repeated panic attacks or fear of future panic attacks, or both. Individuals with PD are often resistant to pharmacological or psychological treatments and this can lead to the disorder becoming a chronic and disabling illness. Repetitive transcranial magnetic stimulation (rTMS) can deliver sustained and spatially selective current to suppress or induce cortical excitability, and its therapeutic effect on pathological neuronal activity in people with PD has already been examined in case studies and clinical trials. However, a systematic review is necessary to assess the efficacy and safety of rTMS for PD.

Objectives

To assess the effects of repetitive transcranial magnetic stimulation (rTMS) for panic disorder (PD) in adults aged 18 to 65 years, either as a monotherapy or as an augmentation strategy.

Search methods

An electronic search of the Cochrane Depression, Anxiety and Neurosis Review Group Controlled Trials Register (CCDANCTR) was conducted to 19 February 2014. The CCDANCTR includes reports of relevant randomised controlled trials (RCTs) from MEDLINE (1950 to date), EMBASE (1974 to date), PsycINFO (1967 to date) and the Cochrane Central Register of Controlled Trials (CENTRAL) (all years). Additional searches were conducted in Psyndex and the main Chinese medical databases.

Selection criteria

RCTs or quasi-randomised trials evaluating rTMS for PD in people aged between 18 and 65 years, either as a monotherapy or as an augmentation strategy.

Data collection and analysis

Two review authors independently selected studies and extracted data and verified the data by cross-checking. Disagreements were resolved by discussion. For binary data, we calculated fixed-effect model risk ratio (RR) and its 95% confidence interval (CI). For continuous data, we calculated fixed-effect model standardized mean difference (SMD) and its 95% CI.

Main results

Two RCTs (n = 40) were included in this review. The included trials compared rTMS with sham rTMS; no trials comparing rTMS with active treatments (electroconvulsive therapy (ECT), pharmacotherapy, psychotherapy) met our inclusion criteria. Both included studies used 1 Hz rTMS over the right dorso-lateral prefrontal cortex (DLPFC) for two or four weeks as an augmentation treatment for PD. However, in both studies the data for the primary outcome, panic symptoms as measured by the Panic Disorder Severity Scale (PDSS), were skewed and could not be pooled for a quantitative analysis. For this primary outcome one trial with 25 participants reported a superior effect of rTMS in reducing panic symptoms compared with sham rTMS ($t = 3.04$, $df = 16.57$, $P = 0.007$), but this trial had a 16% dropout rate and so was deemed as having a high risk of attrition bias. The other trial found that all 15 participants exhibited a reduction in panic symptoms but there was no significant difference between rTMS and sham rTMS (Mann Whitney U test, $P > 0.05$). Regarding the acceptability of rTMS, no significant difference was found between rTMS and sham rTMS in dropout rates or in reports of side effects. The quality of evidence contributing to this review was assessed as very low. Assessments of the risk of bias for the two studies were hampered by the lack of information provided in the reports, especially on methods of sequence generation and whether allocation concealment had been applied. Of the remaining sources of bias, we considered one of the studies to have been at risk of attrition bias.

Authors' conclusions

Only two RCTs of rTMS were available and their sample sizes were small. The available data were insufficient for us to draw any conclusions about the efficacy of rTMS for PD. Further trials with large sample sizes and adequate methodology are needed to confirm the effectiveness of rTMS for PD.

PLAIN LANGUAGE SUMMARY

Repetitive transcranial magnetic stimulation (rTMS) for panic disorder

Why is this review important?

Panic disorder is a common mental disorder and its lifetime prevalence is 5.1%. The major characteristic of panic disorder is the occurrence of unexpected panic attacks with consequent anxiety about experiencing another attack. Despite major advances in the treatment, many people with panic disorder do not respond well to either medication or psychological therapy. In recent years, an association was found between panic symptoms and increased activity in the right frontal region of the brain. Repetitive transcranial magnetic stimulation (rTMS) is a new technique for the stimulation of the central nervous system. It works through placing an electromagnetic coil against the scalp, which generates a rapidly changing magnetic field to induce localised electrical currents. Low frequency rTMS can reduce this increased activity in the brain and so rTMS is emerging as a new way to treat people with panic disorder. Some studies have investigated the effect of rTMS on patients with PD and observed a reduction in anxiety levels. The aim of this review was to combine the results of all the randomised controlled trials of rTMS for panic disorder to investigate the effectiveness and safety of this treatment.

Who will be interested in this review?

People affected by panic disorder.

General practitioners (GPs).

Professionals working in adult mental health services.

Families and friends of people who suffer from major depression.

What questions does this review aim to answer?

Is rTMS effective in treating adults with panic disorder, either on its own or in combination with other treatments?

Which studies were included in the review?

We searched for all the relevant studies on rTMS for panic disorder in people aged 18 to 65 years. Our search found only two studies which met our inclusion criteria and they were included in this review. Information about the way that the studies were conducted were not very well detailed and for one study there was a large proportion of people whose data were not incorporated in to the analysis.

The two studies involved a total of 40 people with panic disorder and reported the effect of rTMS on panic symptoms after two or four weeks of rTMS. Both studies used low-frequency rTMS which lasted 30 minutes and was applied to a region of the brain called the right prefrontal site. Most participants were also taking antidepressant drugs or receiving psychological therapy. No studies compared the differences between rTMS and any other therapy, such as medication, psychological therapy and electroconvulsive therapy (ECT).

What does the evidence from the review tell us?

One study found that all patients improved during the study period, but the treatment effect did not differ between the group who received rTMS and the group who received sham rTMS. The other study administered more sessions and reported higher levels of improvement of panic symptoms in those people who received rTMS compared to those who received sham rTMS.

Although neither trial reported any serious side effects, they provided only very low quality evidence for adverse event outcomes. On the basis of the limited quality of the evidence available we were unable to determine how safe rTMS is.

The limited information available from these two studies is insufficient to conclude whether rTMS is effective in reducing the severity of panic disorder symptoms. The main limitation of this review was that the number of people with panic disorder who were involved was too small.

What should happen next?

To find out more about rTMS for panic disorder, there is a need for more studies to be carried out which involve larger numbers of people and compare sham rTMS with real rTMS.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy for panic disorder

rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy for panic disorder

Patient or population: participants with panic disorder
Settings: outpatients
Intervention: rTMS + pharmacotherapy

Comparison：sham rTMS + pharmacotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	sham rTMS + pharmacotherapy	rTMS + pharmacotherapy				
Reduction of panic symptoms: Panic Disorder Severity Scale (PDSS) (high=poor, data skewed) PDSS, Scale from: 0 to 28)	No data available	No data available				Because of large standard deviations, data were skewed
Acceptability: dropouts for any reason number of dropouts Follow-up: mean 2 weeks	**155 per 1000**	**41 per 1000** (5 to 347)	**RD** -0.09 (-0.29 to 0.11)	40 (2 studies)	⊕⊖⊖⊖ very low [1, 2, 3]	Risks were calculated from pooled risk differences
Acceptability: dropouts for adverse effects number of dropouts Follow-up: mean 2 weeks	**0 per 1000**	**0 per 1000** (0 to 0)	**RD** 0.00 (-0.14 to 0.14)	40 (2 studies)	⊕⊖⊖⊖ very low [1, 2, 3]	Risks were calculated from pooled risk differences
Improvment of social function: Self-reported social adaptation scale (SASS) (low=poor), acute effect SASS. Scale from: 0 to 60.	The improvement of social function in the control groups was 38.6	The improvement of social function in the intervention groups was 2.30 higher (5.33 lower to 9.93 higher)		21 (1 study)	⊕⊖⊖⊖ very low[3,4,5]	Outcome measure favours rTMS intervention over sham rTMS, although not to a significant extent

Quality of life (such as the SF-36 Health Survey (Ware 1992)	No data available	No data available		No study reported the data of related life quality
Safety of rTMS: Frequency of rTMS side effects (values are percentages) self-reported questionnaire			Not estimable	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RD:** Risk difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1 One of the included studies had high risk of attrition bias.
2 Total number of events is 21.
3 Very small sample size.
4 The included study had a high risk of attrition bias.
5 Imprecision: rated 'serious' as 95% confidence intervals crossed line of no effect.

BACKGROUND

Description of the condition

Panic disorder (PD) is a common type of anxiety disorder, typified by frequent uncued panic attacks or fear of future panic attacks, or both. The condition is characterized by cognitive arousal accompanied by bodily sensations due to activation of the peripheral nervous system, with subsequent autonomic and sympathetic responses (for instance, hyperventilation, dizziness, tachycardia, increased blood pressure, gastrointestinal symptoms) (Pallanti 2009). It is subdivided into PD with and without agoraphobia, as in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (APA 1994), depending on whether there is any secondary phobic avoidance (Hollander 2007). The 2001 to 2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) revealed the one-year and lifetime prevalence of PD as 2.1% and 5.1%, respectively (Grant 2006). PD frequently co-occurs with other anxiety disorders, depression or substance abuse. Some basic research has indicated that people with PD have abnormalities in neuroimaging, genetic susceptibility and neurobiological or psychopathological processes(Roy-Byrne 2006). Increasing evidence has found associations between PD and abnormalities in some brain structures, such as the prefrontal cortex, amygdale, parahippocampal, the anterior cingulate cortex and brainstem structures (De Carvalho 2010).

Despite major advances in the study and treatment of PD, participants often do not respond to, or experience only a partial remission with, treatments. The most common reasons for treatment failure in PD are side effects and major depression comorbidity (Heldt 2003). PD can result in considerable functional impairment and distress (Sherbourne 2010), and quality of life among participants is much poorer than nonclinical controls (Kinley 2009).

Description of the intervention

Treatment options for PD are diverse and include psychological therapies (such as cognitive behavioral therapy), pharmacological interventions, or a combination. Pharmacological interventions which have been shown to be effective in the treatment of PD include benzodiazepines, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs) and the more recently developed second-generation antipsychotics (Depping 2010; Holt 2007). However, several studies have suggested that PD patients often do not get adequate treatment or even receive no treatment at all (McHugh 2009). It might also be worth noting that whilst some drug types are effective, they might have side effects in this population (for example TCAs). Because of these issues, alternative treatments for PD have been developed. In 1985, Anthony Barker developed a compact machine for transcranial magnetic stimulation (TMS) that permits non-invasive stimulation of the cerebral cortex (Barker 1985). TMS uses powerful but extremely brief magnetic fields which induce a current in the brain. It has been applied for evaluation of the motor system (Edwards 2008), functional research of cerebral regions, and pathophysiological mechanisms of mental disorders (Haraldsson 2004).

TMS has also developed as an intervention tool, which is administered in a rhythmic and repetitive form and is thus referred to as repetitive transcranial magnetic stimulation (rTMS) (Pallanti 2009). In rTMS, trains of magnetic pulses temporarily summate to cause greater changes in neural activity than a single pulse, which can modulate cortical excitability. While high-frequency rTMS is considered to increase the cortical excitability in certain regions, low-frequency rTMS is postulated to inhibit the cortical excitability of stimulated areas (Pal 2005; Rossi 2009). However, the effects of rTMS are not limited to the areas of the brain under the stimulating coil and remote brain areas connected to the stimulated site can also be affected (Li 2004). The cortical inhibition or excitation elicited by rTMS can last for up to several hours beyond the time of stimulation (Di Lazzaro 2005; Pal 2005).

How the intervention might work

In PD the activation of the peripheral nervous system might reflect a central increase in cortical excitability in different regions of the brain, including the prefrontal cortex, anterior cingulate cortex, insula and limbic areas (hippocampus and amygdala), etc. (De Carvalho 2010). Among these brain regions, the dorso-lateral prefrontal cortex (DLPFC) has received much attention from researchers. Indeed, state or trait measures of anxiety have been associated with relative electroencephalogram (EEG) right-frontal hyperactivity (Crost 2008; Davidson 2000).

Functional abnormalities in the prefrontal cortex (PFC) provide a rationale for the potential therapeutic effect of rTMS in anxiety. The anxiolytic potential of rTMS has been investigated and a reduction in self-rated anxiety levels after low-frequency rTMS to the right DLPFC was reported among healthy volunteers by Schutter 2001; D'Alfonso 2000 examined the effects of slow rTMS at the PFC among healthy female participants and found that right PFC rTMS resulted in selective attention towards angry faces. In addition, Kanno 2003 reported that a three-day series of rTMS significantly improved anxiety-related behavior in Wistar rats using the elevated plus-maze test.

Lateral asymmetries of more activation (right more than the left) in the DLPFC have also been reported in individuals with PD using functional magnetic resonance imaging (Van den Heuvel 2005). These functional asymmetries were reduced after the individuals were treated with cognitive behavioral therapy or antidepressants (Prasko 2004). The role of the PFC in regulating emotions is through its inhibition of activation in the subcortical limbic regions, such as the amygdala (Berkowitz 2007). Therefore, the prefrontal rTMS could be hypothesized to have anxiolytic effects.

In clinical research, rTMS has also showed potential value in the treatment of PD. Both Garcia-Toro 2002 and Zwanzger 2002 provide case reports which describe the first evidence of effectiveness of low-frequency rTMS over PFC in PD. In addition, the rTMS intervention model is not limited to slow frequency or to the PFC. For instance, Dresler 2009 reported the potential of high-frequency rTMS in PD with comorbid depression, and Guaiana 2005 reported a case using primary motor cortex stimulation.

Why it is important to do this review

Patients with PD are often resistant to pharmacological or psychological interventions (Holt 2007), which can lead to the disorder becoming a chronic and disabling illness. There are published Cochrane systematic reviews analysing the effectiveness of the different therapies for PD, such as combined

psychotherapy plus antidepressants (Furukawa 2007), combined psychotherapy plus benzodiazepines (Watanabe 2009), and second-generation antipsychotics (Depping 2010). There are also Cochrane systematic reviews in progress on benzodiazepines versus placebo, antidepressants versus placebo, and azapirones versus placebo for PD (Guaiana 2013a; Guaiana 2013b; Guaiana 2013c), respectively, as well as a multiple-treatment meta-analysis in progress on psychological therapies for PD (Pompoli 2014) and a protocol in progress for a review on psychological therapies versus pharmacological interventions for PD (Imai 2014). Whether PD patients could benefit from an rTMS intervention is an important issue to be addressed in clinical practice. Beside case reports (Sakkas 2006), there are already clinical trials examining the effect of rTMS for PD (for instance, Mantovani 2007; Prasko 2007). In order to assess the efficacy and safety of rTMS for PD, a systematic review was necessary. The review can provide valuable information as to how rTMS could be integrated into the clinical management of PD.

OBJECTIVES

To assess the effects of repetitive transcranial magnetic stimulation (rTMS) for panic disorder (PD) in adults aged 18 to 65 years, either as a monotherapy or as an augmentation strategy.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised control trials (RCTs) of rTMS in the treatment of PD. Quasi-randomised studies, such as those allocating participants by using alternate days of the week, were also eligible for inclusion but would be subject to a sensitivity analysis. Where the method of randomisation was unclear in a double blind trial, the trial would have been included and then subjected to a separate sensitivity analysis. Cluster-randomised trials and cross-over trials were eligible for inclusion. We included trial reports in all languages.

Types of participants

Populations with PD diagnosed by the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (APA 1994), the International Classification of Disease (ICD-10) (WHO 1992), validated diagnostic instruments, or other self-rated or clinician-rated validated instruments that assessed the level of anxiety disorder symptoms, irrespective of gender, race or nationality.

We excluded studies in which anxiety was a secondary symptom of a different disorder (for example, depression or other psychiatric diagnoses).

We excluded participants suffering panic attacks due to general medical conditions (for instance, hyperthyroidism, hypothyroidism, cardiac disease, etc) or due to substance abuse (for instance, alcohol, amphetamine, heroin, etc).

We excluded participants diagnosed with schizophrenia, schizo-affective disorder or mood disorder with a comorbid PD.

The age range of participants had to be 18 to 65 years.

In order to be as inclusive as possible, there were no limitations on the setting of trials.

Types of interventions

Interventions

rTMS of high (stimulus rates of more than 1 Hz) or low frequency (stimulus rates of 1 Hz or less) (Rossi 2009). The stimulating coil could be placed over the right or left dorso-lateral prefrontal cortex (DLPFC). The rTMS could be administered in combination with other interventions (for instance, pharmacotherapy, psychotherapy, etc). We compared these variations (see below). We excluded single-pulse TMS intervention, or rTMS intervention over a period of less than one week.

Comparators

1. Sham rTMS
2. Electroconvulsive therapy (ECT)
3. Pharmacotherapy (for example, antidepressants, benzodiazepines, anticonvulsants, azapirones, antipsychotic drugs)
4. Psychotherapy (for example, behavioral therapies, cognitive therapies, cognitive behavioral therapies, humanistic therapies, psychodynamic therapies, integrative therapies)
5. Variations of rTMS

Different methods of application of rTMS

1. High frequency versus low frequency
2. Right DLPFC versus left DLPFC

Types of outcome measures

Primary outcomes

1. Effectiveness: symptom severity, determined from the Panic Disorder Severity Scale (PDSS) (Shear 1997)

2. Acceptability: (1) dropouts for any reason as a proxy measure of total acceptability; (2) dropouts for adverse effects

Secondary outcomes

3. Treatment response (responders versus non-responders) determined from the Clinical Global Impressions scale - Improvement item (CGI-I) (or closely-related measure), a widely used global outcome measure (Guy 1976). Responders are defined on the CGI-I as those with a score of 1 = 'very much' or 2 = 'much' improved

4. Scores on symptom rating scales for disorders other than the primary anxiety disorder, including: (1) depression symptom severity scales, such as the Hamilton Depression scale (HAM-D) (Hamilton 1960) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery 1979); (2) anxiety symptom severity scales, such as the Hamilton Anxiety scale (HAM-A) (Hamilton1959)

5. Cognitive functioning: change of cognitive functioning as defined by individual studies

6. Functional disability, such as the Sheehan Disability Scale (SDS), which includes subscales to assess work, social and family-related impairment (Sheehan 1996)

7. Quality of life, such as the Short Form (SF)-36 Health Survey (Ware 1992)

8. Safety of rTMS: difference of any adverse events between the treatment and control groups

Search methods for identification of studies

Electronic searches

1. CCDAN Controlled Trial Registers (CCDANCTR)
The Cochrane Depression, Anxiety and Neurosis Group (CCDAN) maintain two clinical trials registers at their editorial base in Bristol, UK, a references register and a studies-based register. The CCDANCTR-References Register contains over 33,000 reports of RCTs in depression, anxiety and neurosis. Approximately 60% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual. Please contact the CCDAN Trials Search Co-ordinator for further details.

Reports of trials for inclusion in the Group's registers are collated from routine (weekly) generic searches of MEDLINE (1950-), EMBASE (1974-) and PsycINFO (1967-); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); and review specific searches of additional databases. Reports of trials are also sourced from international trials registers c/o the World Health Organization's trials portal (ICTRP) and ClinicalTrials.gov; drug companies; the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses.

Details of CCDAN's generic search strategies can be found on the Group's website.

CCDAN's Trials Search Co-ordinator (TSC) searched the CCDAN Registers (to 19 February 2014) using the following search terms.

CCDANCTR-Studies Register
Diagnosis=(panic)
and
Intervention= ("transcranial magnetic stimulation")

CCDANCTR-References Register
The references register was searched using a more sensitive set of free-text terms to identify additional untagged or uncoded reports of RCTs:
Free-text= (panic and (((magnet* or transcrani*) and stimulat*) or TMS or rTMS))

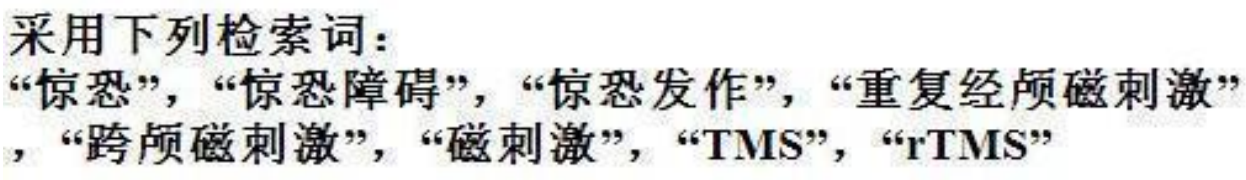
We carried out complementary searches in CENTRAL, the Web of Science, PSYNDEX and the WHO ICTRP trials portal (available at: http://apps.who.int/trialsearch/) (all years to 19 February 2014).

No restriction on date, language or publication status was applied to the searches.

2. Chinese medical databases

For details of search terms in Chinese see Figure 1.
2.1. Chongqing VIP Database (VIP) (1989-)
2.2. Wan Fang Database (1980-)
2.3. Chinese Hospital Knowledge Database (CHKD) (1985-)
2.4. Chinese Biomedical Database (CBM-disc) (1979-)
2.5. China National Knowledge Infrastructure (CNKI) (1994-)

Figure 1. Chinese search terms



Searching other resources

1. Reference searching

We sought additional RCTs in reference lists of the retrieved articles.

2. Personal contact

We contacted the first author or corresponding author of each included study for information regarding other published and unpublished trials.

We also contacted manufacturers of TMS equipment (Brainsway, MagStim, Neotonus, Nueronetics, Medtronic, Nexstim) for information on published and unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (ZX and CL) independently assessed all RCTs identified from the search for inclusion, based on the information included in the abstract or method section of the trial report. We also independently collated the data listed under Data extraction and management from RCTs that we regarded as satisfying the specified inclusion criteria in Criteria for considering studies for this review. We listed studies that required additional information to determine their suitability for inclusion in the review in the 'Studies awaiting assessment' table in the Review Manager (RevMan) software pending the availability of this information. We resolved any disagreements in the independent trial assessment and data collation procedures by discussion with a third author (JW).

Data extraction and management

Review authors ZX and CL independently extracted data on the participants, methods, interventions and outcomes using a data extraction form. We discussed any disagreement, documented and reported the decisions and contacted authors of studies for clarification.

We included continuous data from rating scales only if the measuring instrument has been described in a peer-reviewed journal (Marshall 2000) and the instrument was either self-report or completed by an independent rater (not the rTMS therapist). We included clinician-rated scale data if the clinician was blind to the intervention group.

Main comparisons

1. rTMS (± pharmacotherapy) versus sham rTMS (± pharmacotherapy)
2. rTMS (± psychotherapy) versus sham rTMS (± psychotherapy)
3. rTMS versus pharmacotherapy
4. rTMS versus ECT
5. rTMS versus psychotherapy

Assessment of risk of bias in included studies

Again working independently, ZX and CL assessed the risk of bias using the tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This tool encourages consideration of how the sequence was generated, how allocation was concealed, the integrity of blinding at outcome assessment, the completeness of outcome data, selective reporting, and other biases. We resolved differences in ratings on the risk of bias instrument by discussion with a third author (JW).

Measures of treatment effect

1. Binary data

For binary outcomes we calculated a standard estimation of the fixed-effect model risk ratio (RR) and its 95% confidence interval (CI). However, if the results were very heterogeneous (according to Assessment of heterogeneity) we also would have considered the random-effects model estimation. For statistically significant results we used the odds ratio to calculate the number needed to treat to benefit or to harm statistic (NNTb or NNTh) and its 95% confidence interval (CI) using Visual Rx (http://www.nntonline.net/), taking account of the event rate in the control group. When there were no events in either group, we calculated the risk difference (RD).

2. Continuous data

2.1 Summary statistic

For continuous outcomes, anticipating different measures across studies we pooled data by calculating the standardized mean difference (SMD) using a fixed-effect model with the 95% CI. However, if the results were very heterogeneous (according to Assessment of heterogeneity) we used the random-effects model estimation.

2.2 Endpoint versus change data

Certain information required to use change scores (that is, the standard deviation of the change score) is often not provided, and change scores are also not suitable for use with SMDs. Therefore, we preferred to use scale endpoint data, which typically cannot have negative values. If endpoint data were unavailable, we would have used change data.

2.3 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to all data before inclusion: (a) standard deviations and means are reported in the paper or obtainable from the authors; (b) when a scale starts from the finite number zero, the standard deviation when multiplied by two is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution) (Altman 1996); (c) if a scale starts from a positive value (such as the Zung Self-Rating Anxiety Scale which can have values from 20 to 80) the calculation described above will be modified to take the scale starting point into account. In these cases skew is present if 2SD > (S - S min), where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and endpoint and these rules can be applied. When continuous data are presented on a scale which includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We would enter skewed data from studies of fewer than 200 participants in additional tables rather than in an analysis (that is, we will exclude small studies with skew (continuous) data from the analysis). Skewed data pose less of a problem when looking at means if the sample size is large, and in such instances such data would have been entered into the syntheses (Higgins 2008). The reason for selecting 200 as the cut-off for using non-normal data is that large samples usually mean at least 100 in each randomised group in clinical trials (Schulz 2002a; Schulz 2002b; Schulz 2006).

Unit of analysis issues

1. Cluster-randomised trials

Studies increasingly employ 'cluster randomisations' (such as randomisations by clinician or practice), but analysis and pooling of clustered data pose problems. Firstly, authors often fail to account for intraclass correlation in clustered studies leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, CIs unduly narrow, and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering was not accounted for in primary studies, we would have presented the data in a table with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain the intraclass correlation co-efficient of their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster randomised study but adjust for the clustering effect.

If cluster studies have been appropriately analysed, taking into account the intraclass correlation co-efficient and the relevant data documented in the report, synthesis with other studies may be possible using the generic inverse variance technique.

2. Studies with multiple treatment groups

Where a study involved more than two treatment arms, we would have included the arm receiving low-frequency rTMS on the right DLPFC in the main analysis (it being the standard rTMS intervention for anxiety disorders) in the comparison of rTMS versus sham rTMS. We presented the additional relevant treatment arms in comparisons although the control would be used once again in a particular meta-analysis. Where the additional treatment arms were not relevant, we did not reproduce these data.

3. Cross-over trials

PD can be a chronic condition but not necessarily a stable one and thus it is inappropriate to use data from both periods of cross-over trials (Higgins 2011). Therefore, we considered data from the first period of the cross-over trials for analysis. However, because taking data from the first period only may have bias implications, we would have performed a sensitivity analysis to investigate the impact of including such study designs.

Dealing with missing data

1. Overall loss of credibility

In terms of loss to follow-up, should more than 40% of data be unaccounted for by 12 weeks or longer we included these data or used them within analyses. The reason for choosing 40% as the cut-off for an acceptable amount of missing data was based on the findings from one survey (Xia 2009). We also considered the comparison of loss rates between the two groups.

1. Binary data

In the case where attrition for a binary outcome was between 0% and 40% and the outcomes of these people were described, we included these data as reported. Where these data were not clearly described, we would have assumed the worst case for all dropouts using the rationale that this represents a more conservative approach.

2. Continuous data

In the case where attrition for a continuous outcome was between 0% and 40% and completer-only data were reported, we included data from these studies for analysis.

Assessment of heterogeneity

1. Clinical heterogeneity

We planned to use the baseline data (before rTMS intervention) of all included studies to judge clinical heterogeneity.

2. Statistical

2.1 Visual inspection

We visually inspected graphs to investigate the possibility of statistical heterogeneity.

2.2 Employing the I^2 statistic

The I^2 statistic provides an estimate of the percentage of inconsistency thought to be due to chance. An I^2 value equal to or greater than 50% was interpreted as evidence of high levels of heterogeneity (Higgins 2011), where a random-effects model should be applied.

If sufficient studies had been found, and the data were clearly heterogenous, we would have first checked that the data were correctly extracted and entered and that we had made no unit of analysis errors. If the high levels of heterogeneity remained (for example, I^2 = 75% to 100%), the meta-analysis would not been undertaken at that point as if there is considerable variation in results, and particularly if there is inconsistency in the direction of effect, it might be misleading to quote an average value for the intervention effect (Higgins 2011). We did not pre-specified characteristics of studies that might be associated with heterogeneity except risk of bias. However, should the heterogeneity have been substantially unaffected by the use of random-effects model meta-analysis and no other reasons for heterogeneity were clear, we presented the final data in narrative form without a meta-analysis.

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of the results. These are described in section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases. Should sufficient studies be included in future updates of this review, we will create funnel plots for outcomes where there are more than 10 studies, or where all studies were of similar sizes, and seek statistical advice for their interpretation.

Data synthesis

We conducted a fixed-effect model meta-analysis in the first instance. Where heterogeneity was identified (I^2 = 50% to 75%), potential reasons for this would have been explored through subgroup analysis as described below. Where this heterogeneity between studies could not be explained, we would have undertaken a random-effects model meta-analysis. As a random-effects model meta-analysis awards relatively more weight to smaller studies than a fixed-effect model meta-analysis, sensitivity analyses were planned to to investigate whether the results of smaller studies were systematically different from the results of larger ones. Where we identified high levels of heterogeneity (I^2 = 75% to 100%), we would not have undertaken a meta-analysis and instead would have presented the data in narrative form. Where the number of included studies was very small, we conducted a fixed-effect model meta-analysis.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses involve dividing all the participant data into subgroups, often so as to make comparisons between them. Subgroup analyses were planned to be done for subsets of participants or for subsets of studies. Subgroup analyses were a means of investigating heterogeneous results, or to answer specific questions about particular patient groups (Higgins 2011).

We planned to undertake subgroup analyses in order to assess the degree to which methodological differences between trials might have systematically influenced differences observed in the primary treatment outcomes. In consideration of the possibility of differential effects of rTMS for different conditions, we planned to stratify all comparisons by:

1. the specific PD (participants with agoraphobia, and participants without agoraphobia);

2. whether participants had co-occurring depression; and
3. the level of past treatment (i.e. treatment-resistant PD).

We proposed to summarise all data together but to present these subgroups separately for the primary outcomes.

Sensitivity analysis

We planned to perform the following sensitivity analyses.

1. Exclude cross-over trials from the analysis.
2. Exclude trials described as 'double blind' that were quasi-randomised or had unclear randomisation.
3. Small study effects and potential publication bias examined using funnel plots.
4. Where it was deemed appropriate to use a random-effects model meta-analysis, we would compare the findings from fixed-effect and random-effects model meta-analyses to investigate the effects of small studies on the pooled estimate.

Summary of findings tables

The GRADE profiler was used to import data from RevMan 5 (RevMan 2012) and to create a 'Summary of findings' table (www.ims.cochrane.org/revman/gradepro). This table records outcome specific information on all important outcomes for clinical practice and further research, including overall quality of the evidence from all included studies and the magnitude of effect of the interventions examined.

We planned to select the following main outcomes for inclusion in the summary of findings table.

1. Clinical response in terms of panic symptoms.

2. Acceptability, assessed by the dropouts for any reason or because of adverse effects.

3. Global state.

4. Quality of life.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The electronic searches identified six references in CCDANCTR-References, nine references in CENTRAL or the international trial registers (six duplicates of references in the CCDANCTR; three unique references), and 351 references in the Chinese medical databases. After de-duplication, we had 310 references. We screened them by their titles and abstracts and identified seven candidate studies. Six were read as the full text. Of these, four studies did not fully meet our inclusion criteria. The Prasko 2009 reference was a secondary report of Prasko 2007 with no additional information, so all data for the qualitative findings, bias and other analyses in this review were from Prasko 2007. For one of the seven candidate studies, only the abstract from an academic conference was acquired and the authors have not responded to requests to provide further information, so we classified this study as awaiting classification (Deppermann 2013). Finally only two studies were included in the review (Prasko 2007; Mantovani 2013).

See Figure 2 for a PRISMA flow diagram illustrating the study selection process.

Figure 2. PRISMA study flow diagram.

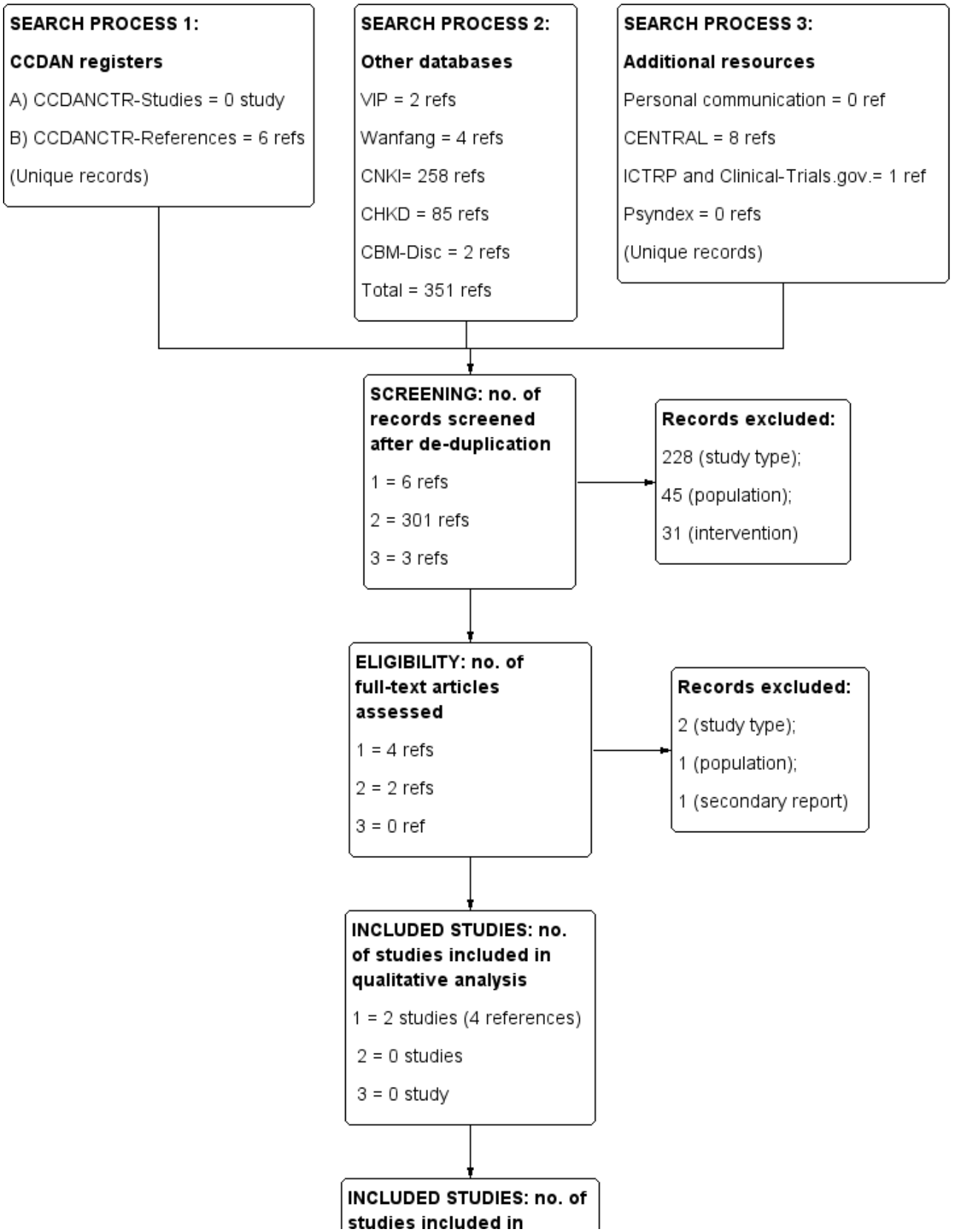
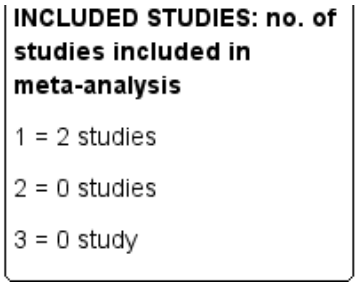


Figure 2. (Continued)



We contacted the authors of these included studies to enquire about potential trials of rTMS for PD, but received no response. We contacted manufacturers of TMS equipment (Brain-sway, Magstim, Neotonus, Nueronetics, Medtronic, Nexstim) for information on published and unpublished trials and received a reply from all manufactures except Neotonus, but no additional studies were found.

Included studies

We included two studies (Prasko 2007; Mantovani 2013) with data from 40 participants (19 in the treatment group and 21 in the sham group) (see Characteristics of included studies). Attempts to contact the first authors of these studies to obtain detailed information and other possible data were unsuccessful.

Design

Both studies had used a controlled trial design, though neither adequately described the method of randomisation. Prasko 2007 performed a double blind, randomised, sham stimulation parallel designed study. The trial of Mantovani 2013 consisted of two phases: four weeks double blind and four weeks open label, and only the data from the four-week double blind phase were included in this review. Both trials used rTMS as an augmentation treatment for PD.

Sample sizes

The sample sizes of both trials were small: 15 participants in Prasko 2007 and 25 participants in Mantovani 2013.

Participants

Both trials involved participants with a primary diagnosis of PD and most of them were taking medications while they participated. Prasko 2007 recruited PD participants according to the ICD-10 research diagnostic criteria. The participants in Mantovani 2013 had a primary diagnoses of PD and major depression disorder (MDD) according to a structured clinical interview using the DSM-Ⅳ.

Setting

Both trials included only outpatients. The trial of Prasko 2007 was conducted in a psychiatric centre in Italy. The study of Mantovani 2013 was administered at two clinics in the United States between January 2008 and December 2010.

Interventions

rTMS Intervention

All included studies used a similar protocol: 1 Hz rTMS to stimulate the right DLPFC, 110% resting motor threshold (RMT), 1800 pulses (lasting for 30 minutes) in each session, and one session per day. While Prasko 2007 administered 10 sessions of rTMS over two weeks, Mantovani 2013 administered 20 sessions in four weeks.

Sham rTMS Intervention

The control group received sham rTMS stimulation. Most of the parameters of the sham stimulation (frequency, pulses, stimulation site and intensity) were the same as for active stimulation. Prasko 2007 administered sham stimulation with a coil diverted by 90 ° over the right DLPFC. Mantovani 2013 used a Magstim Sham coil, which was specially designed to deliver less than 3% magnetic fields to the cortex.

Outcomes

The primary outcome for the efficacy of rTMS on panic symptoms, measured by the PDSS, was reported in both trials (Prasko 2007, Mantovani 2013). Dropouts due to any reason or due to adverse effects of rTMS were reported in both studies.

The effect of rTMS on general anxious symptoms was assessed using the severity of illness scale of the CGI (CGI-SI), HAM-A (or HARS), Beck Anxiety Inventory (BAI) (or Zung Self-Rating Anxiety Scale (ZUNG-SAS)), Screening, Assessment and Support Services (SASS) and Patient Global Impression (PGI). Mantovani 2013 assessed the effect of rTMS on depressive symptoms using the Hamilton Rating Scale for Depression (HDRS-24) and Beck Depression Inventory (BDI). Both trials paid attention to the effect of rTMS on cognitive function, and Mantovani 2013 used a structured form to interview participants before and after each rTMS session.

Both trials only studied the short-term effect of rTMS for PD, for two weeks or four weeks. Whilst in Mantovani 2013 the four-week RCT was then switched to an open trial, in Prasko 2007 a follow-up assessment was performed at an interval of two weeks after the rTMS intervention.

Excluded studies

We identified seven potentially relevant studies from our searches. After assessing the full-text papers, we excluded four of these studies. The reasons for exclusion were: one lacked a randomised control group (Mantovani 2007), Hao 2011 was excluded because some participants were not diagnosed with PD, Prasko 2009 was a secondary report of Prasko 2007, and Wang 2013 did not use sham rTMS stimulation as a control condition.

See: Characteristics of excluded studies.

Ongoing studies

We didn't identify any ongoing studies.

Studies awaiting classification

Only the abstract for Deppermann 2013 was acquired (from an academic conference) so we sent the screening checklist to the corresponding author of this study. The author replied saying their study met all inclusion criteria and will be published online this year. However, we received no further response when we asked for the data so this study is awaiting classification until the study is published.

Risk of bias in included studies

See Figure 3 and Figure 4 for graphical summaries of the methodological quality of the two included studies.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

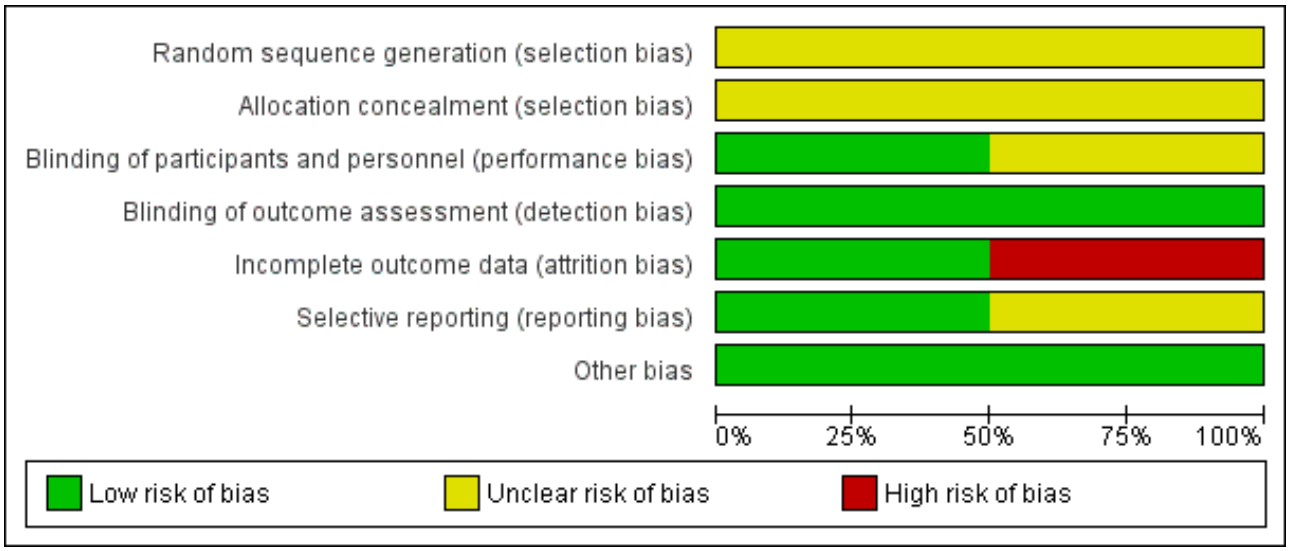
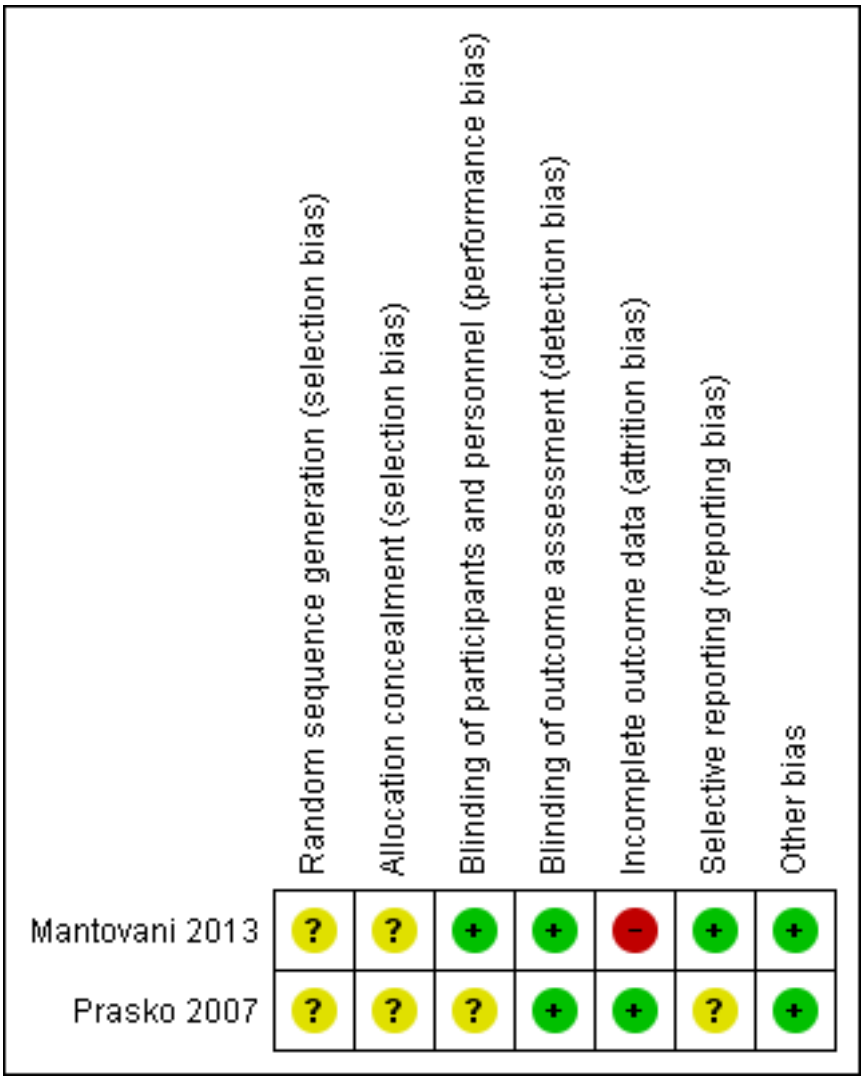


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Allocation was simply described as "randomly assigned to the two treatment groups" (Mantovani 2013) and "patients were randomly assigned in a 1:1 ratio to either rTMS or sham" (Prasko 2007). Neither described the methods of how the randomisation sequence was generated. Allocation concealment was also poorly reported. We received no response when we made personal contact with the first author asking for this information. Therefore, bias relating to allocation was unclear.

Blinding

Both included trials were designed as double blind. The allocation was blind to the participants and the response raters. Information on the blinding method was introduced by Mantovani 2013 but not by Prasko 2007. Regarding the sham coil, Mantovani 2013 used a Magstim Sham coil which contained a mu-metal shield that diverts the majority of magnetic flux. An insignificant difference in the "best guess questionnaire" about the blinding was reported between the two TMS groups at the end of phase one. Prasko 2007 only applied sham stimulation with a coil diverted by 90 ° over the same area as that of TMS. Therefore, bias relating to blinding was rated as unclear in Prasko 2007 and rated as low in Mantovani 2013.

Incomplete outcome data

No dropouts were reported by Prasko 2007, and attrition bias was rated as low. In the trial of Mantovani 2013 four participants (one from the group receiving rTMS and three from the sham group) dropped out within the first week because they felt it too demanding to attend rTMS treatment on a daily basis. The percentage of dropouts in the rTMS and sham groups were 1/12 (8.3%) and 3/13 (23%) respectively, therefore attrition bias was rated as high.

Selective reporting

The study protocol was not available for the trial of Prasko 2007 so we couldn't compare the published outcomes with what was measured during the conduct of the trial. The trial of Mantovani 2013 had been registered in www.ClinicalTrials.gov [NCT00521352]; we compared the registered information with the full text of the published article and found that all the pre-specified outcomes had been reported. Therefore, the risk of bias for selective reporting in

Mantovani 2013 was rated as low, and the risk of reporting bias for Prasko 2007 was rated as unclear.

Other potential sources of bias

No information associated with other potential sources of bias was found in Prasko 2007 or in Mantovani 2013, but we noted that one of the participants in Mantovani 2013 was not on medication during the trial because of intolerance, which may potentially have resulted in a bias.

Effects of interventions

See: **Summary of findings for the main comparison** rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy for panic disorder

All participants in Prasko 2007 were resistant to treatment with serotonin reuptake inhibitors (SSRIs), while the participants in Mantovani 2013 had not fully responded to conventional pharmacotherapy; so both studies investigated the effect of rTMS as an augmentation therapy for panic disorder (PD). Neither of them compared rTMS with active treatments (ECT, pharmacotherapy, psychotherapy). The main comparison was: rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy.

The two included studies used the same rTMS protocol of 1 Hz rTMS on the right DLPFC.

Comparison: rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy

See: Summary of findings for the main comparison.

Primary outcomes

1.1 Effectiveness: reduction of panic symptoms at two or four weeks and follow-up

In the study by Prasko 2007, at the end of 10 sessions of rTMS the panic symptom severity measured by the PDSS was 10.75 (SD 6.43) for the sham group (n = 8) and 14.57 (SD 4.43) for the rTMS group (n = 7) with no difference between groups. In the trial of Mantovani 2013, at the end of 20 sessions of rTMS the rTMS group showed a 44% reduction in PDSS, while the sham group showed a 5% reduction, and the group difference was statistically significant (t = 3.04, df = 16.57, P = 0.007). At four weeks the PDSS was 10.4 (SD 6.5) for the rTMS group (n = 11) and 16.7 (SD 4.2) for the sham group (n = 10). The data from both studies were skewed however. Therefore, these data were not eligible for a meta-analysis and were only described in a table (Analysis 1.1, Analysis 1.2).

In the trial of Mantovani 2013, a full response had been defined as a reduction of more 40% in PDSS. Six participants in the rTMS group (50%, n = 12) and one patient in the sham group (8%, n = 13) showed a reduction of more than 40% in the PDSS. There was a group difference between real versus sham rTMS (Fisher's Exact Test, P = 0.005).

Prasko 2007 made a follow-up assessment of the effect of rTMS on PDSS after two weeks, reporting no group difference between the two rTMS groups.

1.2a Acceptability: dropouts for any reason

There were no dropouts in Prasko 2007. There were four dropouts in the study by Mantovani 2013. Total attrition was 10% and there was no significant difference between the rTMS and sham groups for dropouts for any reason (RD -0.09, 95% CI -0.29 to 0.11). See Analysis 1.3.

1.2b Acceptability: dropouts for adverse effects

None of the participants dropped out from the studies due to side effects of rTMS. The reason for the dropouts from Mantovani 2013 was that participants felt it too demanding to attend the rTMS treatment sessions on a daily basis.

Secondary outcomes

1.3 Treatment response: global state at two or four weeks and follow-up

Neither study reported data on the CGI-I. Mantovani 2013 defined responders as those with a reduction of 40% on the PDSS and 50% on the HDRS-24 at four weeks, but found that the difference in the rate of responses between the rTMS and sham groups was only significant in the case of panic symptoms.

1.4a Anxiety symptoms as measured by BAI, Zung-SAS, HARS or HAMA at two or four weeks and follow-up

Acute effects

There was no significant difference between groups (2 RCTs, SMD 0.08, 95% CI 0.44 to 0.60).

Prasko 2007 reported the changes in anxiety symptoms rated by the BAI and HAMA. In the Mantovani 2013 trial these symptoms were evaluated using the Zung-SAS and HARS scales.

At the end of rTMS, with regard to self-reported changes the data for the BAI at the end of rTMS were skewed in Prasko 2007 and reported in 'other data' (Analysis 1.6). No significant difference in the Zung-SAS was reported between the real and sham groups in Mantovani 2013 (SMD -0.19, 95% CI -1.05 to 0.67).

At the end of rTMS, with regard to changes reported by raters in both studies (Prasko 2007; Mantovani 2013), the data for the HAM-A and HARS (they refer to the same scale) were pooled and there was no significant difference between the real and sham groups (2 RCTs, SMD 0.24, 95% CI -0.42 to 0.90).

See: Analysis 1.5 and Analysis 1.6.

Maintaining effects at two-weeks follow-up

There was no significant difference between groups in the acute effects (1 RCT, SMD 1.07, 95% CI 0.29 to 1.86).

Prasko 2007 also evaluated the maintenance effect of rTMS two weeks later, and reported an insignificant difference between the two groups in terms of the BAI (SMD 1.05, 95% CI -0.06 to 2.15) or in terms of the HAM-A (SMD 1.10, 95% CI -0.01 to 2.21).

See: Analysis 1.7.

1.4b. Depression symptoms as measured by HAM-D and BDI-Ⅱ at four weeks

Only Mantovani 2013 rated depression symptoms using the HDRS and BDI. At the end of rTMS, no significant difference in depression symptom reduction was noted between rTMS and sham rTMS (HDRS: MD -1.50, 95% CI -9.89 to 6.89; BDI-Ⅱ: MD -9.50, 95% CI -19.90 to 0.90). He defined a response as a reduction of more than

50% in HDRS. Three participants in the rTMS group (25%, n = 12) and one patient in the sham group (8%, n = 13) showed a reduction of more than 50% in HDRS, and the group difference was not significant.

See: Analysis 1.8 and Analysis 1.9.

1.5 Cognitive functioning at two or four weeks and follow-up

The effect of rTMS on cognitive function was noted in both trials as 'no cognitive difficulties, or no subjective complaints about memory or concentration impairment'. However, no detailed information was provided in Prasko 2007. Mantovani 2013 used a structured form to ask participants before and after each rTMS session and reported the percentages of 'yes' answers. See Analysis 1.10.

1.6 Functional disability at four weeks

Functional disability was measured only in Mantovani 2013 by self-reported social adaptation (SASS). No significant difference was observed between the real and sham groups after four weeks of rTMS (MD 2.30, 95% CI -5.33 to 9.93).

1.7 Quality of life

No study reported data on health-related quality of life.

1.8 Safety of rTMS

No severe effects, such as seizures, were reported (Prasko 2007; Mantovani 2013). With regard to common adverse effects, such as headache, neck pain, scalp pain and hearing impairment, Mantovani 2013 used a structured form to ask participants before and after each rTMS session and reported the percentages of 'yes' answers. The percentages of each side effect are described in Analysis 1.12 and there was no statistical difference between the rTMS group and the sham group. There were four dropouts in Mantovani 2013, but none of them were due to side effects. Therefore, rTMS was well tolerated.

Subgroup analysis

We planed to carried out subgroup analysis in participants with and without comorbid major depression. The participants were diagnosed as PD without co-occurring depression symptom in Prasko 2007, while in Mantovani 2013 all had PD with comorbid depression. As there were only two studies available for the comparison, we did not conduct the pre-planned subgroup analyses.

Sensitivity analysis

The sensitivity analyses were not performed because both included trials were RCTs.

DISCUSSION

Summary of main results

Two trials involving 40 participants were included in this review (Prasko 2007; Mantovani 2013). Both trials compared rTMS with sham rTMS in PD participants who were receiving medications or psychotherapy. Both used the same stimulation parameters (1800 pulses/day, 1 Hz, at 110% RMT, right DLPFC). However, the duration of treatment was different, 10 sessions in Prasko 2007 and 20 sessions in Mantovani 2013. After the end of trial, Prasko 2007 observed the maintenance effect of rTMS two weeks later and Mantovani 2013 administered an open trial of rTMS for all participants. Neither of these trials used a navigation system to locate the optimal site for coil placement. Both studies used the PDSS to evaluate whether rTMS was effective in reducing panic symptoms. Both studies had relatively small sample sizes, 15 in Prasko 2007 and 25 in Mantovani 2013.

At the end of the rTMS intervention, the data on reductions in PDSS scores from both trials were skewed and could not be pooled for quantitative analysis. Mantovani 2013 reported that rTMS was superior to sham in reducing participants' PDSS, and there was also a significant difference in the number of responders in terms of panic symptoms between real versus sham rTMS. The PD participants of Mantovani 2013 had a comorbidity of major depressive disorder (MDD), but there was no difference in depressive symptoms or in the number of responders between the two rTMS groups. Both trials reported no difference in the occurrence of side effects between the two rTMS groups and that rTMS was well tolerated.

At an interval of two weeks after rTMS, Prasko 2007 also found no difference between the two rTMS groups in the efficacy.

After the RCT phase, Mantovani 2013 administered rTMS to all participants, lasting four weeks. They also performed a naturalistic six-month follow-up for responders and reported that, on average, responders on the PDSS showed an 81% reduction at the one- and three-month visits, and 80% improvement at six months.

Overall completeness and applicability of evidence

After a thorough search of the databases and contacting the manufactures of rTMS and authors of included trials, we only included two trials (Prasko 2007; Mantovani 2013). The study of Hao 2011, which included subgroups of participants with generalized anxiety disorder (GAD) and PD, was excluded because the authors could not provide the data for the PD subgroup when contacted. We contacted the authors of the two included studies but got no response from either. Therefore, data extraction and analyses were only based on the published data. The sample sizes of both trials are small. Although all participants had a primary diagnosis of PD the participants in the trial of Mantovani 2013 also had a diagnosis of MDD, which added a confounding effect of rTMS on depression. The rTMS intervention was investigated only as an augmentation to ongoing therapy rather than as a monotherapy. The studied rTMS intervention was limited to low-frequency stimulation on the right DLPFC, therefore the effect of other rTMS protocols (for instance, high-frequency stimulation, or to stimulate the left DLPFC) are totally unknown.

Although the two included trials reported all their pre-specified outcomes, the most important data on PDSS scores were skewed. This meant that we could not do further analyses of the efficacy of rTMS for panic symptoms. Considering the safety of rTMS, both trials reported the reasons for dropouts and the adverse effects of the rTMS intervention. Therefore, the overall completeness of data on rTMS for PD is quite low. The conclusions of this review should be applied with caution due to the small number of studies identified, the small sample size and the skewed data.

Quality of the evidence

Overall, the quality of evidence in this review is very low.

1. Risk of bias

Both included trials were RCTs and were very similar in the parameters of rTMS that they used. Mantovani 2013 and Prasko 2007 clearly stated that their studies were randomised, sham rTMS controlled trials. However, neither described the methods of sequence generation and whether allocation concealment had been applied. Therefore, the selection bias is unclear in each trial.

Allocation was blinded to the participants and symptom raters in both studies. Detailed information on blinding was not provided in Prasko 2007, however in the trial of Mantovani 2013 it was revealed that a sham coil was used and the allocation was also blinded to the rTMS physicians. At the end of the randomised phase participants were asked to guess which form of rTMS they thought they had received, and no difference was found between the two rTMS groups. The implementation of sham stimulation in a rTMS trial is a complex technique, and some participants randomised to sham might become unblinded during the trial. Therefore, the bias of blinding was unclear in the trial of Prasko 2007 but low in the trial of Mantovani 2013.

2. Inconsistency

The heterogeneity of results was low, and there was no serious inconsistency.

3. Indirectness

Both trials compared the effectiveness and safety of rTMS to sham rTMS in PD with similar rTMS parameters, and both of them reported on the side effects, primary outcome (panic symptoms) and dropouts. So we consider that the evidence is direct.

4. Imprecision

Only two trials with 40 participants (less than 400) were included in the review, and for panic symptoms rated by PDSS the imprecision was rated as 'very serious', with large standard deviations (SDs), and the data were skewed. For other results, the imprecision was rated as 'serious'; the 95% confidence intervals crossed the line of no effect.

5. Publication bias

Both trials (Prasko 2007; Mantovani 2013) reported all the pre-specified, expected results, and no other evidence of publication bias was found, so publication bias was rated as 'unlikely'.

Potential biases in the review process

We applied an extensive search strategy to find all potential studies and only identified two trials for inclusion, both of which are published studies. The number of participants in each trial was small. We did not identify any ongoing trial meeting our inclusion criteria for this review. However, there might be some studies that were published in journals not indexed in the databases we searched. We hope to include any missed trials in updates of this review when we identify them in the future.

The participants in Prasko 2007 were on serotonin reuptake inhibitor (SRI) medication, while the participants in Mantovani 2013 were treated with adequate but different types of medications; one of the participants in Mantovani 2013 was on no medication during the trial because of intolerance to the side effects. The two conditions were sources of potential bias when we combined the two trials.

Agreements and disagreements with other studies or reviews

After an extensive search, we did identify seven literature reviews of rTMS treatment for anxiety disorders (Pigot 2008; George 2009; Pallanti 2009; Zwanzger 2009; Xu 2010; Paes 2011; Machado 2012). One systematic review was found (Vennewald 2013) which addressed the efficacy of rTMS in anxiety disorder but this review included randomised controlled studies, open studies and case reports. Most of the authors stated that rTMS studies of PD were hampered by small sample sizes, and there were few placebo-controlled designs. These reviews do not conflict with the content of the present Cochrane review and we agreed with these viewpoints. High quality trials of rTMS for PD are required before any conclusions can be drawn about its effectiveness.

AUTHORS' CONCLUSIONS

Implications for practice

Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a potential treatment for various neurologic and psychiatric disorders, and rTMS for major depressive disorder was approved by the Food and Drug Administration (FDA) in 2008 (Fitzgerald 2012; George 2012). Several studies have already examined the effect of rTMS for panic disorder (for instance, Sakkas 2006; Mantovani 2007; Prasko 2007), but to date no systematic review has been undertaken. So this review is intended to update the academic or practising psychiatrist on the efficacy and safety of rTMS in panic disorder and to clarify the optimal stimulation characteristics. However, only two studies were eligible for this review; they compared rTMS (as an adjunct to pharmacotherapy) with sham rTMS. Both trials were of small sample size and one was at risk of bias from attrition (Mantovani 2013). Neither of them compared the differences between rTMS and other interventions. Data from both trials on our primary outcome, reduction of symptom severity determined using the Panic Disorder Severity Scale (PDSS), were skewed and could not be pooled for meta-analyses. Therefore, there is insufficient evidence for us to draw any conclusions about the efficacy of rTMS for panic disorder. Neither trial reported any serious side effects, however the evidence is very limited and of low quality and so we are unable to determine how safe rTMS is.

Implications for research

The sample size of RCTs of rTMS for panic disorder (PD) needs to be greatly increased. PD is not a scarce disorder, with a lifetime prevalence of 5.1% (Grant 2006). We suggest that future studies of rTMS for PD include much larger sample sizes in each arm. In order to avoid the interaction of rTMS with medications or other therapies, and to better address the efficacy of rTMS, trials should be designed to compare rTMS monotherapy among PD populations, that is, to compare rTMS with sham rTMS among unmedicated participants.

In trials of rTMS it is difficult to implement the sham stimulation. It should be noted, however, that there is no guarantee nowadays that a true sham rTMS condition is available (Rossi 2009). The method of delivering a coil by a shift of 45 ° or 90 ° over the stimulated site will be not blind to the administer. Mantovani 2013

used a sham coil which contains a mu-metal shield, looks and sounds like a coil, but does not generate a strong tapping sensation on the scalp. The RCT-oriented sham coils, which could induce the same cutaneous sensations as those induced by rTMS, are already available and should be applied in future trials.

Information on the generation of a random sequence and the method of allocation concealment should be clearly reported in future trials of rTMS for PD.

While Prasko 2007 used participants without significant depressive symptoms, Mantovani 2013 used participants with a comorbidity of MDD. Because of the effect of rTMS on depression, we suggest that future trials should use participants with PD without a comorbidity of MDD.

With regard to the outcomes of rTMS on PD, the medium- and long-term effects also need to be investigated. Mantovani 2013 conducted a naturalistic follow-up only for rTMS responders for six months. Follow-up should be performed for all participants.

Further suggestions to improve future RCTs for panic disorder are summarised in Table 1.

ACKNOWLEDGEMENTS

The authors would like to thank the staff and editors of the Cochrane Depression, Anxiety and Neurosis Group (CCDAN) for advice and assistance. We would also like to thank Stephanie Sampson for her language assistance.

CRG Funding Acknowledgement:

The National Institute for Health Research (NIHR) is the largest single funder of CCDAN.

Disclaimer:

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Mantovani 2013

Methods	**Allocation**: The study consisted of two phases: phase 1, 4-week randomised control-sham; phase 2, 4-week open-label rTMS (not used in this review)

Mantovani 2013 *(Continued)*

	Blinding: double blind, no further description the style of blinding
Participants	**Diagnosis**: panic disorder with comorbid major depression (DSM-Ⅳ–TR) **N** = 25 **Age**: 18 to 65 years **Sex**: male = 12, female = 13 **Group**: **rTMS group**: 12 participants, 8 females and 4 males **sham group**: 13 participants, 5 females and 8 males **Inclusion criteria**: (1) Current episode duration is at least a month (2) The panic and depression symptoms were residual (PDSS score ≥15, and HDRS-24 score ≥20) after adequate medication treatment (at least 6 to 8 weeks, at recommended dosage) or psychotherapy treatment or couldn't tolerate the side effects of medication (3) Participants on medication must have been in stable treatment for at least 4 weeks before initiation and throughout the study; participating in psychotherapy, should be in stable treatment for at least 3 months prior to entry into the study **Exclusion criteria**: (1) Acute suicide risk (2) A history of bipolar disorder, any psychotic disorder, substance abuse or dependence (3) Implanted devices, metal in the brain (4) Unstable medical conditions (5) Pregnancy, or breast-feeding (6) Prior rTMS treatment **Dropout**: One patient dropped out from the rTMS group; three participants dropped out from the sham group
Interventions	1 Hz, stimulated the right DLPFC **1. rTMS therapy + pharmacological or psychotherapy therapy:** Used the Magstim Super Rapid stimulator device and vacuum cooled 70 mm figure-8 coil, each patient was administered 5 daily sessions of rTMS for 2 consecutive weeks (1800 pulses/day, 1 Hz, 110% RMT) DLPFC was defined 5 cm anterior to the RMT site **2. Sham rTMS therapy + pharmacological or psychotherapy therapy:** Sham coil was over the same area without producing a magnetic field
Outcomes	**The outcomes include:** Total endpoint score of PDSS, PDSS-SR, HDRS-24, BDI-Ⅱ, HARS, ZUNG-SAS, CGI-SI, SASS and PGI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Mantovani 2013 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	The randomisation method was not provided, just described: "were randomly assigned in a 1:1 ratio either rTMS or sham"
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants were naive to rTMS and both participants and rTMS treating physician were blinded to the stimulation condition
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The clinical raters were blind to the treatment condition and had a separation to the rTMS treating physician, who was not in the lab while the TMS lab manager, not involved in rTMS treatment session, set up the real or sham coil
Incomplete outcome data (attrition bias) All outcomes	High risk	One patient dropped out of the rTMS group, and three participants dropped out of the sham group. The dropout rate was 16%
Selective reporting (reporting bias)	Low risk	All the pre-specified expected outcomes were reported in this article
Other bias	Low risk	Funded by a NARSAD Young Investigator Award

Prasko 2007

Methods	**Allocation**: Parallel randomised control-placebo, no further description **Blinding**: Double blind **Duration**: 2 weeks treatment + 2 weeks follow-up post-treatment
Participants	**Diagnosis**: PD or PD with agoraphobia (ICD-10) **N** = 15 **Age**: 18–45 years **Sex**: male = 4, female = 11 **duration of illness**: 9.5 years (SD=6.5) **Inclusion criteria:** Non-responders on SRIs (at least 6 weeks treatment) **Exclusion criteria:** (1) Major depressive disorder, organic psychiatric disorder, psychotic disorder, abuses of alcohol or other drugs, risk of suicidality (2) 17-item HAM-D scores more than 16 (3) Serious somatic disease (4) Non-prescribed medication (5) Gravidity or lactation (6) Epilepsy or pathological EEG (7) Implants or pacemakers
Interventions	**1. rTMS therapy +SSRI pharmacological therapy:** Coil position over the right dorso-lateral prefrontal cortex, Magstim Super Rapid stimulator, figure-eight 70-mm coil,1 Hz, 1800pulses/session,110% of MT, 10 sessions Equivalent of paroxetine dose = (22.0±1.6) mg **2. Sham rTMS therapy + SSRI pharmacological therapy:**

Prasko 2007 *(Continued)*

	Sham stimulation by distortion of the coil 90 degrees over the same area Equivalent of paroxetine dose = (22.5±17.5) mg
Outcomes	Total endpoint score of CGI-SI, HAMA, PDSS and BAI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	''...randomly assigned...'' No further information
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The rater was blinded to the rTMS therapy
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patient dropped out
Selective reporting (reporting bias)	Unclear risk	The protocol of this study is not available, therefore it is not clear if all pre-specified outcomes have been reported
Other bias	Low risk	Grant funded research. No other obvious bias was identified

BDI-Ⅱ - Beck depression inventory-Ⅱ
BAI - Beck Anxiety Inventory
CGI-SI - Clinical Global Impression-Severity of Illness
DLPFC - dorso-lateral prefrontal cortex
HAM-A - Hamilton Rating Scale for Anxiety
HARS - Hamilton anxiety rating scale
HDRS - Hamilton depression rating scale
ICD-10 - International Classification of Diseases, tenth Edition
MT - motor threshold
PD - panic disorder
PDSS - Panic Disorder Severity Scale
PDSS-SR - Panic Disorder Severity Scale self-report
PGI - Patient Global Impression
rTMS - repetitive transcranial magnetic stimulation
RMT - resting motor threshold
SSRI - selective serotonin reuptake inhibitor
SASS - self-reported social adaptation scale
ZUNG-SAS - Zung self-administered scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Hao 2011	Population: the participants were PD or GAD, and the author couldn't offer the data for PD
Mantovani 2007	Study type: not a RCT; lack of a randomised control group. All the included participants received rTMS stimulation
Wang 2013	Study type: not combined sham rTMS stimulation as a control condition

PD - panic disorder
rTMS - repetitive transcranial magnetic stimulation
GAD - generalized anxiety disorder

Characteristics of studies awaiting assessment *[ordered by study ID]*

Deppermann 2013

Methods	**Allocation**: randomised control-placebo, no further information **Blinding**: no related information **Duration**: 2 weeks treatment + 2 weeks follow-up post-treatment
Participants	The only description of participants was "forty PD patients"
Interventions	The comparison was: rTMS therapy + cognitive behavioral therapy (CBT) versus sham rTMS therapy + CBT The parameters of rTMS were not described
Outcomes	Prefrontal activation while performing emotional paradigms as well as a cognitive task
Notes	All the information came from the abstract of this study and the response of the author

DATA AND ANALYSES

Comparison 1. rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction of panic symptoms: 1. acute effect			Other data	No numeric data
1.3 Panic Disorder Severity Scale (PDSS, high=poor, data skewed)			Other data	No numeric data
1.4 PDASS self report (PDSS-SR, high=poor, data skewed)			Other data	No numeric data
2 Reduction of panic symptoms: 2. maintaining effect: Panic Disorder Severity Scale (PDSS, high=poor, data skewed),			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Acceptability: 1. dropouts for any reason	2	40	Risk Difference (M-H, Fixed, 95% CI)	-0.09 [-0.29, 0.11]
4 Acceptability: 2. dropouts for adverse effects	2	40	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.14, 0.14]
5 Anxiety symptoms: 1. acute effect	2	57	Std. Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.44, 0.60]
5.1 Zung-self administered scale for Anxiety (Zung-SAS, high=poor)	1	21	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-1.05, 0.67]
5.2 Hamilton rating scale for anxiety (HAMA or HARS, high=poor)	2	36	Std. Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.42, 0.90]
6 Anxiety symptoms: 2. acute effect: Beck Anxiety Inventory (BAI, high=poor, data skewed)			Other data	No numeric data
7 Anxiety symptoms: 3. Maintaining effect	1	30	Std. Mean Difference (IV, Fixed, 95% CI)	1.07 [0.29, 1.86]
7.1 Beck Anxiety Inventory (BAI, high=poor), 4 weeks follow-up	1	15	Std. Mean Difference (IV, Fixed, 95% CI)	1.05 [-0.06, 2.15]
7.2 Hamilton Rating Scale for Anxiety (HAMA, high=poor), 4 weeks follow-up	1	15	Std. Mean Difference (IV, Fixed, 95% CI)	1.10 [-0.01, 2.21]
8 Depression symptoms: acute effect: Hamilton depression rating scale-24 (HDRS-24, high=poor)	1	21	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-9.89, 6.89]
9 Depression symptoms: acute effect: Beck depression inventory-Ⅱ (BDI-Ⅱ, high=poor)	1	21	Mean Difference (IV, Fixed, 95% CI)	-9.5 [-19.90, 0.90]
10 Cognitive functioning: Frequency of rTMS impaired cognitive function(Values are percentages)			Other data	No numeric data
11 Social function: Self-reported social adaptation scale (SASS, low=poor), acute effect	1	21	Mean Difference (IV, Fixed, 95% CI)	2.30 [-5.33, 9.93]
12 Safety of rTMS: Frequency of rTMS side effects (Values are percentages)			Other data	No numeric data

Analysis 1.1. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 1 Reduction of panic symptoms: 1. acute effect.

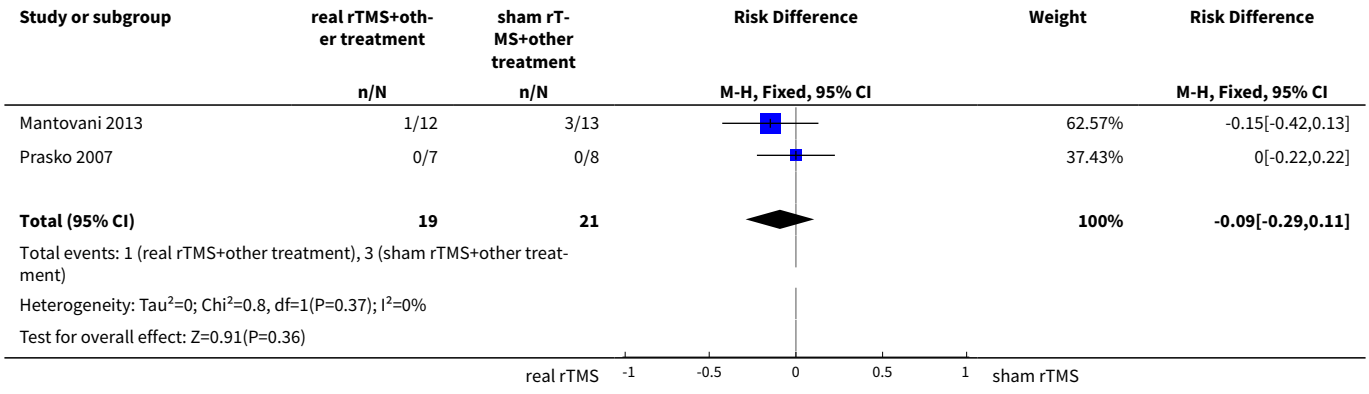
		Reduction of panic symptoms: 1. acute effect			
Study	Intervention	Mean	SD	N	Note
Panic Disorder Severity Scale (PDSS, high=poor, data skewed)					
Mantovani 2013	real rTMS+other treatment group	10.4	6.5	11	

Reduction of panic symptoms: 1. acute effect					
Study	**Intervention**	**Mean**	**SD**	**N**	**Note**
Mantovani 2013	sham group+other treatment group	16.7	4.2	10	
Prasko 2007	real rTMS+other treatment group	14.57	4.429	7	
Prasko 2007	sham rTMS+other treatment group	10.75	6.431	8	
PDASS self report (PDSS-SR, high=poor, data skewed)					
Mantovani 2013	real rTMS+other treatment group	10.4	5.5	11	
Mantovani 2013	sham group+other treatment group	15.5	5.1	10	

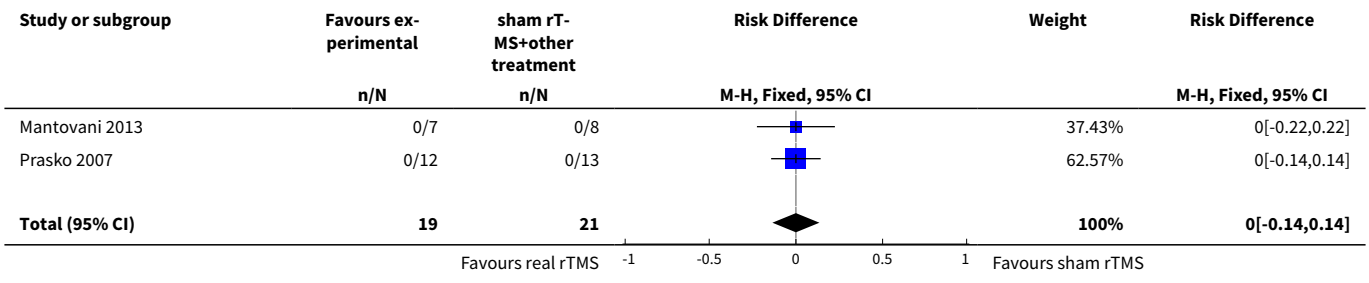
Analysis 1.2. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 2 Reduction of panic symptoms: 2. maintaining effect: Panic Disorder Severity Scale (PDSS, high=poor, data skewed),.

Reduction of panic symptoms: 2. maintaining effect: Panic Disorder Severity Scale (PDSS, high=poor, data skewed),					
Study	**Intervention**	**Mean**	**SD**	**N**	**Note**
Prasko 2007	real rTMS+other treatment group	11.71	4,071	7	
Prasko 2007	sham rTMS+other treatment group	8.25	4.95	8	

Analysis 1.3. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 3 Acceptability: 1. dropouts for any reason.



Analysis 1.4. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 4 Acceptability: 2. dropouts for adverse effects.



Study or subgroup	Favours experimental	sham rTMS+other treatment	Risk Difference	Weight	Risk Difference
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Total events: 0 (Favours experimental), 0 (sham rTMS+other treatment)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%					
Test for overall effect: Not applicable					

Favours real rTMS -1 -0.5 0 0.5 1 Favours sham rTMS

Analysis 1.5. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 5 Anxiety symptoms: 1. acute effect.

Study or subgroup	real rTMS+other treatment		sham rTMS+other treatment		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
1.5.1 Zung-self administered scale for Anxiety (Zung-SAS, high=poor)							
Mantovani 2013	11	46 (10.8)	10	47.7 (5.6)		37.23%	-0.19[-1.05,0.67]
Subtotal ***	**11**		**10**			**37.23%**	**-0.19[-1.05,0.67]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.43(P=0.67)							
1.5.2 Hamilton rating scale for anxiety (HAMA or HARS, high=poor)							
Mantovani 2013	11	21 (9.2)	10	20.8 (7.1)		37.42%	0.02[-0.83,0.88]
Prasko 2007	7	18.4 (11.4)	8	13.1 (6.2)		25.35%	0.56[-0.48,1.6]
Subtotal ***	**18**		**18**			**62.77%**	**0.24[-0.42,0.9]**
Heterogeneity: Tau²=0; Chi²=0.6, df=1(P=0.44); I²=0%							
Test for overall effect: Z=0.71(P=0.48)							
Total ***	**29**		**28**			**100%**	**0.08[-0.44,0.6]**
Heterogeneity: Tau²=0; Chi²=1.19, df=2(P=0.55); I²=0%							
Test for overall effect: Z=0.3(P=0.76)							
Test for subgroup differences: Chi²=0.59, df=1 (P=0.44), I²=0%							

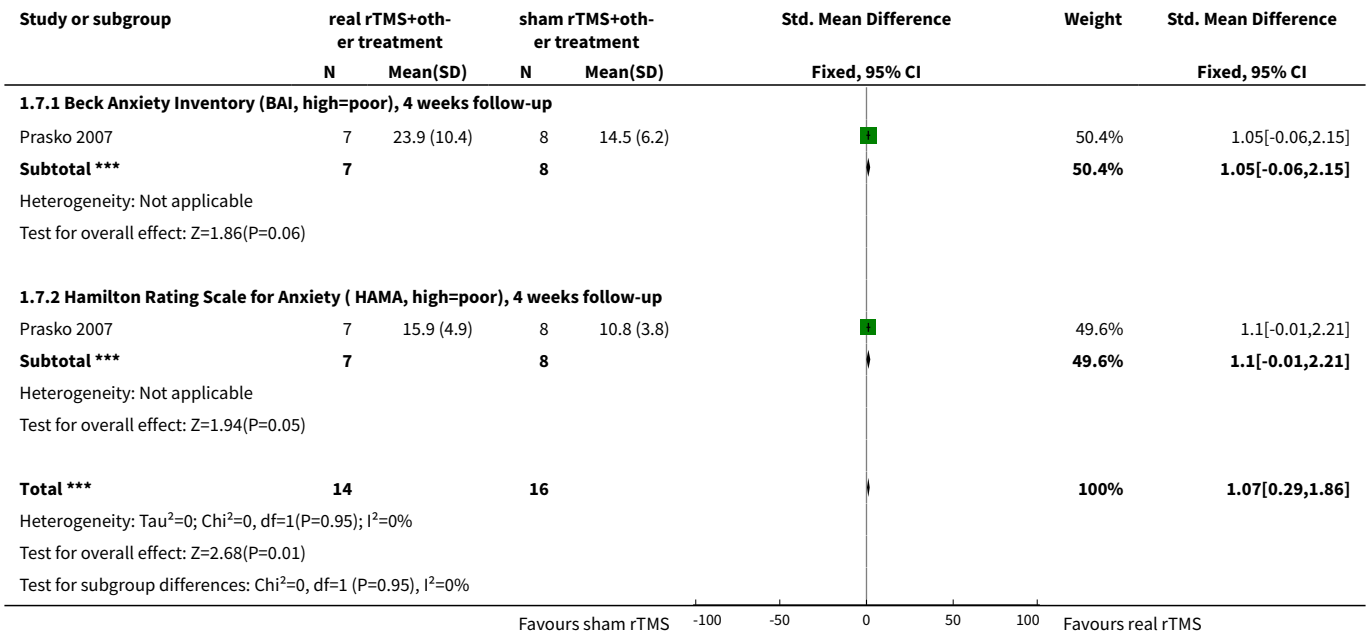
Favours sham rTMS -100 -50 0 50 100 Favours real rTMS

Analysis 1.6. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 6 Anxiety symptoms: 2. acute effect: Beck Anxiety Inventory (BAI, high=poor, data skewed).

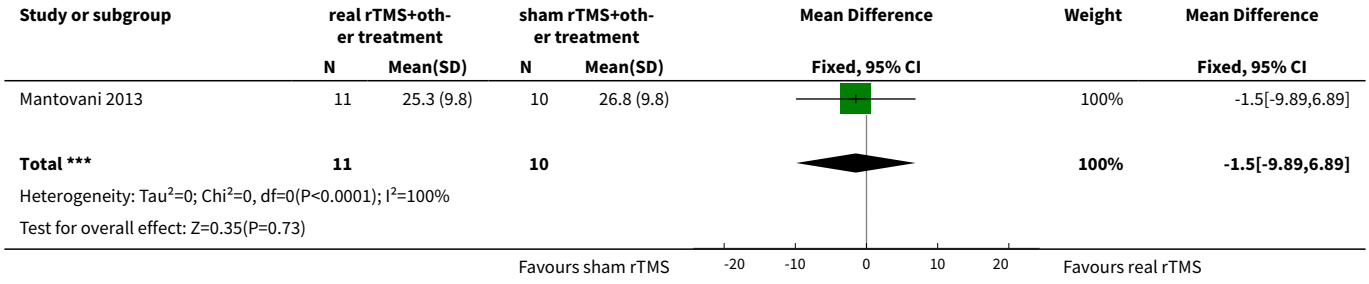
Anxiety symptoms: 2. acute effect: Beck Anxiety Inventory (BAI, high=poor, data skewed)

Study	Intervention	Mean	SD	N	Note
Prasko 2007	real rTMS+other treatment group	24.14	11.57	7	
Prasko 2007	sham rTMS+other treatment group	15.63	7.891	8	

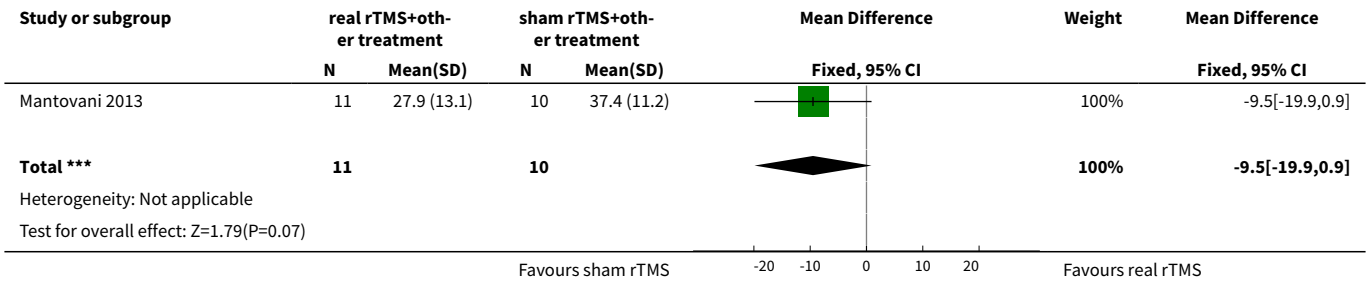
Analysis 1.7. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 7 Anxiety symptoms: 3. Maintaining effect.



Analysis 1.8. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 8 Depression symptoms: acute effect: Hamilton depression rating scale-24 (HDRS-24, high=poor).



Analysis 1.9. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 9 Depression symptoms: acute effect: Beck depression inventory- II (BDI- II , high=poor).

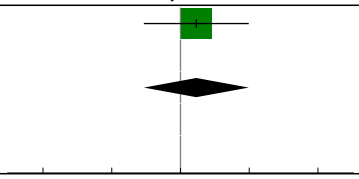


Analysis 1.10. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 10 Cognitive functioning: Frequency of rTMS impaired cognitive function(Values are percentages).

Cognitive functioning: Frequency of rTMS impaired cognitive function(Values are percentages)				
Study	**cognitive impairment**	**real rTMS+other treatment**	**sham rTMS+other treatment**	**N**
Mantovani 2013	Impared cognition	6	4	21
Mantovani 2013	Trouble concentrating	12	10	21
Mantovani 2013	Memory impairment	4.5	5.5	21

Analysis 1.11. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 11 Social function: Self-reported social adaptation scale (SASS, low=poor), acute effect.

Study or subgroup	real rTMS+other treatment		sham rTMS+other treatment		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Mantovani 2013	11	28.2 (10.4)	10	25.9 (7.3)		100%	2.3[-5.33,9.93]
Total ***	**11**		**10**			**100%**	**2.3[-5.33,9.93]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.59(P=0.55)							



Analysis 1.12. Comparison 1 rTMS + pharmacotherapy versus sham rTMS + pharmacotherapy, Outcome 12 Safety of rTMS: Frequency of rTMS side effects (Values are percentages).

Safety of rTMS: Frequency of rTMS side effects (Values are percentages)			
Study	**rTMS side effects**	**real rTMS+other treatment**	**sham rTMS+other treatment**
Mantovani 2013	Headache	15.5	22.5
Mantovani 2013	Neck pain	15	17.4
Mantovani 2013	Scalp pain	9.5	11.8
Mantovani 2013	Seizure	0	0
Mantovani 2013	Scalp burns	0	0
Mantovani 2013	Hearing impairment	0	0.5

ADDITIONAL TABLES

Table 1. Suggested design for future study

Methods	**Participants**	Interventions	Outcomes
1. Allocation: randomised and concealment fully explicit description 2. Double blinding 3. Duration: 4-8 weeks treatment, and then the follow-up of 1 and 6 months for all participants	1.Diagnosis: unmedicated panic disorders with or without agoraphobia (ICD-10); without a comorbidity of MDD 2. Age: adults 3. Sex: both 4. Sample size: much larger	1. rTMS versus sham rTMS 2. Sham rTMS is administered by RCT-oriented sham coils	1. Measures of panic and anxiety - continuous scales (PDSS, HAM-A, SAS, BAI, etc.) 2. Acceptability - dropouts for any reason, dropouts for adverse effects 3. Global state - no clinically important response (CGI) 4. Cognitive function 5. Quality of life measures (ADL)

Table 1. Suggested design for future study *(Continued)*

	6. Compliance with treatment 7. Economic outcomes

BAI - Beck Anxiety Inventory
CGI - Clinical Global Impression
HAM-A - Hamilton Rating Scale for Anxiety
ICD-10 - International Classification of Diseases, 10th Edition
PDSS - Panic Disorder Severity Scale
rTMS - repetitive transcranial magnetic stimulation
MDD - major depression disorder

CONTRIBUTIONS OF AUTHORS

ZX and HL contacted manufacturers of rTMS and the authors of included trials for potential trials of rTMS for PD. ZX and CL assessed all the papers, extracted data and provided statistical input. JW provided statistical advice. HL and JW drafted the manuscript. All authors participated in reviewing the manuscript.

DECLARATIONS OF INTEREST

HL: none known

JW: none known

CL: none known

ZX: none known

SOURCES OF SUPPORT

Internal sources

- Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, China.

  Z. Xiao, C. Li, J. Wang, H. Li.

External sources

- National Natural Science Foundations of China (81171267, 61102020, 81261120410, 81071098), China.

  to J. Wang
- National Key Technology R&D Program(2009BAI77B05), China.

  to H Li
- National Key Clinical Disciplines at Shanghai Mental Health Center(Office of Medical Affairs, Ministry of Health, 2011-873; OMA-MH, 2011-873), China.

  to J. Wang
- Shanghai Science and Technology Committee (11410708800, 10411966400), China.

  to J. Wang
- Shanghai Key Laboratory of Psychotic Disorders (13dz2260500), China.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

When there were no events in either group, we calculated the risk difference (RD).

NOTES

None

INDEX TERMS

Medical Subject Headings (MeSH)

Panic Disorder [*therapy]; Patient Dropouts [statistics & numerical data]; Prefrontal Cortex; Randomized Controlled Trials as Topic; Transcranial Magnetic Stimulation [adverse effects] [*methods]

MeSH check words

Adult; Humans