Non-Pharmaceutical Treatment - Repetitive Transcranial Magnetic Stimulation (rTMS)

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.

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. As part of a wider search for all topics included in the Library, reviews on rTMS for schizophrenia 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. The decision to include or exclude reviews was conducted in duplicate by two reviewers with any disagreements settled by discussion. All quality assessments and data extraction have been completed in duplicate by two independent reviewers who were not masked to review authors.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (formerly the QUOROM statement) which describes a preferred way to present a meta-analysis. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. For instance, a low possibility of bias would be assigned to reviews checking over 66% of items, a medium possibility between 33 and 66% and a high possibility would be given to reviews checking less than 33%. Reviews rated as having a high possibility of reporting bias 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.
Non-Pharmaceutical Treatment - Repetitive Transcranial Magnetic Stimulation (rTMS)

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 randomized controlled trials (RCT) may be downgraded to moderate, low or very low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[5]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of the Schizophrenia Research Institute.

Results

See table below for a detailed summary of the available evidence pertaining to the use of rTMS for symptoms of schizophrenia. We found eleven systematic reviews that met our inclusion criteria [2, 3, 6-14]. Eight reviews were excluded [15-22], all were not systematic reviews.

All trials assess whether rTMS is being tested as an additional treatment to antipsychotics rather than as an alternative treatment and participants vary in their degree of response to antipsychotic treatment. Note that primary studies are included in multiple reviews.

See PRISMA Checklists for assessment of reporting quality.

Conclusions

• For auditory hallucinations, there is high quality evidence showing that low frequency rTMS applied via continuous stimulation to the left temporo-parietal cortex can reduce the severity of auditory hallucinations in the short term (immediately after treatment). Low quality evidence is uncertain as to the benefits over the longer term (1 month post-treatment).

• For negative symptoms, high quality evidence indicates some benefit of high frequency rTMS (10 Hz) applied to the left dorsolateral prefrontal cortex in the short term.

• For other positive symptoms in general, there is high quality evidence indicating no benefit of low frequency rTMS applied to the left temporoparietal cortex in the short term.

• Low quality evidence is uncertain as to the effects of high frequency rTMS applied to the left or dominant dorsolateral prefrontal cortex on general cognitive state, executive functioning, working memory or psychomotor speed.

• Mild headache, scalp and facial discomfort may be reported.
Aleman, A., Sommer I.E., and R.S. Kahn

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


View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>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 or placebo. Varying treatment duration and application (continuous stimulation or stimulation with multiple pauses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence 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. Adverse and long term effects not reported</td>
</tr>
</tbody>
</table>

**Auditory hallucinations**

Measured by the AHRS, HCS, LS, PSYRATS (hallucination subscale), RHSRS, SAH

†Meta-analysis results reported for immediately post treatment only. Some individual studies reported longer term follow up, not reported here

All studies at end of treatment

Medium to large effect size favouring rTMS

N = 212, 9 RCT, 1 observational study

\[ d = 0.76, \text{95\%CI}\ 0.36\ to\ 1.17,\ p = 0.0001 \]

\[ Q = 21.4, p = 0.01, I^2 = 58\% \]

Random effects model

Subgroup analysis to investigate heterogeneity - continuous stimulation studies only

Large effect size favouring rTMS

N = 196, 8 RCT, 1 observational study

\[ d = 0.88, \text{95\%CI}\ 0.52\ to\ 1.23,\ p = 0.0001 \]

\[ Q = 12.2, p = 0.14, I^2 = 34\% \]
Random effects model

**Subgroup analysis to investigate differences in the number of stimulation sessions**

Not dose dependent

4 RCT, mean # sessions = 4.25
\[ d = 0.79, 95\% CI -0.01 \text{ to } 1.60, \text{ no } N, Q \text{ or } p \text{ values reported} \]

6 RCT, mean # sessions = 9.83
\[ d = 0.80, 95\% CI 0.21 \text{ to } 1.40, \text{ no } N, Q \text{ or } p \text{ values reported} \]

Random effects model

**Other positive psychotic symptoms**

Measured by the PANSS (positive subscale) and the SAPS

*All studies at end of treatment*

No significant treatment effect

N = 134, 5 RCT, 1 observational study
\[ d = 0.21, 95\% CI -0.29 \text{ to } 0.72, p = 0.20 \]

Random effects model

<table>
<thead>
<tr>
<th>Risks</th>
<th>Not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consistency in results†</strong></td>
<td>Consistent for continuous stimulation trials only, no significant heterogeneity in results. Heterogeneity not reported for other positive psychotic symptoms outcome</td>
</tr>
<tr>
<td><strong>Precision in results§</strong></td>
<td>Precise for auditory hallucinations outcome. Imprecise for frequency of stimulation subgroup analysis. Imprecise for other positive psychotic symptoms outcome</td>
</tr>
<tr>
<td><strong>Directness of results‖</strong></td>
<td>Direct comparison for people with schizophrenia and auditory hallucinations</td>
</tr>
</tbody>
</table>

*Cordes J., Arends M., Mobascher A., Brinkmeyer J., Kornischka J., Eichhammer P., Klimke A., Winterer G., Agelink MW.*

**Potential Clinical Targets of Repetitive Transcranial Magnetic Stimulation Treatment in Schizophrenia**

*Neuropsychobiology, 2006. 54(2): p. 87-99*
## TECHNICAL COMMENTARY

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<table>
<thead>
<tr>
<th>Comparison 1</th>
<th>Low frequency rTMS (1Hz) applied to various regions of the temporal lobe vs sham or placebo or no control. Varying treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (inconsistent), authors conclude there might be a benefit</td>
</tr>
</tbody>
</table>

### Auditory hallucinations
**Measured by the AHRS, CGI, HCS, LS, SAPS, TVRS**

- Results reported for immediately post treatment only
- No meta-analysis
- N = 263, 11 RCT, 1 observational study

**Risks**
10% of participants reported mild transient headache

**Consistency in results**
Inconsistent – heterogeneity measure not reported

**Precision in results**
No confidence intervals reported

**Directness of results**
Direct comparison for people with schizophrenia and auditory hallucinations

### Comparison 2
High frequency (>1 Hz), rTMS applied to various regions of the frontal lobe vs sham or placebo or no control. Varying treatment duration

### Summary of evidence
Moderate quality evidence (inconsistent), authors conclude there might be a benefit

### Negative symptoms
**Measured by the BPRS, HDRS, PANSS (negative subscale), SANS**

- Results reported for immediately post treatment only
  - No meta-analysis, no results reported
  - N = 153, 6 RCT, 5 observational studies

**Risks**
10% of participants reported mild transient headache

**Consistency in results**
Heterogeneity measure not reported

**Precision in results**
No confidence intervals reported
Non-Pharmaceutical Treatment - Repetitive Transcranial Magnetic Stimulation (rTMS)

<table>
<thead>
<tr>
<th>Directness of results</th>
<th>Direct comparison for people with schizophrenia and negative symptoms</th>
</tr>
</thead>
</table>

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:e15–e16

View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Low frequency (1 Hz) rTMS applied to unspecified brain regions vs. sham for auditory hallucinations. Varying treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence indicates a medium benefit of rTMS over sham treatment for improving auditory hallucinations</td>
</tr>
</tbody>
</table>

**Auditory hallucinations**

Various measures

Meta-analysis results reported for immediately post treatment only

9 RCT (N not reported), $g = 0.42$, 95%CI 0.13 to 0.70, $p = 0.004$

$I^2 = 17.1\%$ (not significant)

Random effects model

<table>
<thead>
<tr>
<th>Risks</th>
<th>Not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency in results</td>
<td>Consistent</td>
</tr>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>
Dlabac-de Lange JJ, Knegtering R, Aleman A.

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


View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Varying treatment duration and application – mostly high frequency rTMS (10 to 20Hz) over the left dorsolateral prefrontal cortex.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence (consistent, precise, direct) indicates medium benefit of high frequency rTMS applied to the left dorsolateral prefrontal cortex for improving negative symptoms of schizophrenia. Adverse and long term effects not reported</td>
</tr>
</tbody>
</table>

### Negative symptoms

**Measured by the PANSS (negative subscale), SANS**

Meta-analysis results reported for immediately post treatment only

*All studies at end of treatment*

Medium effect size favouring rTMS

N = 213, 9 RCT

\[ d = 0.43, 95\% CI 0.05 to 0.80, p = 0.03 \]

\[ Q = 16.69, p = 0.05, I^2 = 46\% \]

Random effects model

After excluding one small study with drug-naïve sample:

\[ d = 0.34, 95\% CI 0.01 to 0.67, p = \text{not reported, but authors state significance and consistency} \]

**Subgroup analysis to investigate effect of variations in frequency across studies (Hz)**

Medium effect size favouring rTMS applied at 10 Hz

N = not reported, 7 RCT

\[ d = 0.63, 95\% CI 0.11 to 1.15, p = 0.02 \]

\[ Q = 12.96, p = 0.04, I^2 = 54\% \]

Random effects model

After excluding one small study with drug-naïve sample:

\[ d = 0.50, 95\% CI 0.03 to 0.96, p = \text{not reported, but authors state significance and consistency} \]
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Subgroup analysis to investigate effect of variations in treatment duration across studies

- **< 3 weeks, N = not reported, 6 RCT, d = 0.32, 95%CI -0.03 to 0.95, p = not reported**
- **> 3 weeks, N = not reported, 3 RCT, d = 0.58, 95%CI 0.19 to 0.97, p = not reported**
- Q = not reported

Subgroup analysis to investigate effect of variations in rating scales across studies

- **PANSS, N = 172, 8 RCT, d = 0.35, 95%CI -0.12 to 0.82, p = not reported**
- **SANS, N = 93, 3 RCT, d = 0.73, 95%CI 0.26 to 1.19, p = not reported**
- Q = not reported

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks</td>
<td>Not reported</td>
</tr>
<tr>
<td>Consistency in results</td>
<td>Consistent for overall analysis and frequency of application (less one study)</td>
</tr>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct comparison for people with schizophrenia with negative symptoms</td>
</tr>
</tbody>
</table>

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


View review abstract online

Comparison 1

- Low frequency rTMS (1Hz) over the left temporoparietal cortex (80 to 100% motor threshold) vs sham or placebo or no control. Varying treatment duration

Summary of evidence

- Moderate quality evidence (inconsistent) 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. Adverse effects not reported

Auditory hallucinations

- Measured by the AHRS, HCS, SAH
Non-Pharmaceutical Treatment - Repetitive Transcranial Magnetic Stimulation (rTMS)

Meta-analysis results reported for immediately post treatment only

All studies at end of treatment
Large effect size favouring rTMS in pre-post treatment comparison (no control)
N = 122, 7 RCT, 2 observational studies
\[ d = 1.35, 95\% CI 1.11 \text{ to } 1.58, p = 0.001 \]
\[ Q = 19.5, p = 0.012, I^2 = 59\% \]
Fixed effects model

Subgroup analysis to investigate effect of study quality - RCT only
Large effect size favouring rTMS over placebo
N = 160, 7 RCT
\[ d = 0.96, 95\% CI 0.65 \text{ to } 1.27, p = 0.001 \]
\[ Q = 26.85, p = 0.001 \]
Fixed effects model

Risks
Not reported

Consistency in results
Inconsistent – heterogeneity reported but not explored (see Aleman for possible explanation)

Precision in results
Precise

Directness of results
Direct comparison for people with schizophrenia and auditory hallucinations

Comparison 2
Low frequency rTMS (1Hz) over the left temporoparietal cortex (80 to 100\% motor threshold) vs sham or placebo or no control. Varying treatment duration

Summary of evidence
High quality evidence from RCT indicates no benefit of low frequency rTMS applied to the left temporoparietal cortex for positive symptoms. Adverse and long term effects not reported

Positive symptoms
Measured by the PANSS (positive subscale), SAPS

Meta-analysis results reported for immediately post treatment only

All studies at end of treatment
Medium effect size favouring rTMS in pre-post treatment comparison (no control)
N = 149, 10 RCT, 2 observational studies
\[ d = 0.50, 95\% CI 0.31 \text{ to } 0.68, p = 0.001 \]
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<table>
<thead>
<tr>
<th>Q = 14.92, ( p = 0.186 ), ( I^2 = 26% )</th>
<th>Fixed effects model</th>
</tr>
</thead>
</table>

**Subgroup analysis to investigate effect of study quality - RCT only**

No significant treatment effect

- **N = 204, 10 RCT**
- \( d = 0.17, 95\% CI -0.05 \) to 0.39 , \( p = 0.129 \)
- \( Q = 2.96, p = 0.966, I^2 = 0\% \)
  
  Fixed effects model

<table>
<thead>
<tr>
<th>Risks</th>
<th>Not reported</th>
</tr>
</thead>
</table>

**Consistency in results** Consistent, no significant heterogeneity in results

**Precision in results** Precise

**Directness of results** Direct comparison for people with schizophrenia and auditory hallucinations

**Comparison 3** Varying treatment duration. High frequency rTMS (10 to 20Hz) over the left dorsolateral prefrontal cortex (80 to 110% motor threshold) vs sham or placebo or no control

**Summary of evidence** High quality evidence from RCT indicates no benefit of high frequency rTMS applied to the left dorsolateral prefrontal cortex for negative symptoms. Adverse and long term effects not reported

**Negative symptoms**

**Measured by the PANSS (negative subscale), SANS**

Meta-analysis results reported for immediately post treatment only

*All studies at end of treatment*

Medium effect size favouring rTMS in pre-post treatment comparison (no control)

- **N = 63, 5 RCT, 3 observational studies**
- \( d = 0.49, 95\% CI 0.17 \) to 0.82 , \( p = 0.003 \)
- \( Q = 12.64, p = 0.081, I^2 = 45\% \)
  
  Fixed effects model

**Subgroup analysis to investigate effect of study quality - RCT only**

No significant treatment effect

- **N = 87, 5 RCT**
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\[ d = 0.21, \, 95\% \text{CI} -0.23 \text{ to } 0.64, \, p = 0.351 \]
\[ Q = 8.65, \, p = 0.07, \, I^2 = 54\% \]

### Fixed effects model

#### Risks
Not reported

#### Consistency in results
Consistent, no significant heterogeneity in results

#### Precision in results
Precise

#### Directness of results
Direct comparison for people with schizophrenia and negative symptoms

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**Guse, B., Falkai, P., Wobrock, T.**

**Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review**

*Journal of Neural Transmission, 2009. 117:105–122*

[View review abstract online](#)

### Comparison 1
High frequency rTMS (20Hz): 10 sessions over 2 weeks of real rTMS plus 10 sessions over 2 weeks of sham rTMS applied to left dorsolateral prefrontal cortex. No control group

### Summary of evidence
Low quality evidence (1 small study, no control group) is uncertain as to the effects of high frequency rTMS applied to left dorsolateral prefrontal cortex on psychomotor speed

#### Psychomotor speed
No improvement – no statistics reported

1 study, \( N = 12 \)

#### Risks
Not reported

#### Consistency in results
N/A – 1 study

#### Precision in results
No confidence intervals reported

#### Directness of results
Direct
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### Comparison 2
High frequency rTMS applied to dominant dorsolateral prefrontal cortex. No control group

### Summary of evidence
Low quality evidence (1 small study, no control group) is uncertain as to the effects of high frequency rTMS applied to dominant dorsolateral prefrontal cortex on psychomotor speed

**Psychomotor speed**

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Low quality evidence (1 small study, no control group) is uncertain as to the effects of high frequency rTMS applied to dominant dorsolateral prefrontal cortex on psychomotor speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>Improvement in women, no improvement in men – no statistics reported</td>
</tr>
<tr>
<td>Men</td>
<td>1 study, N = 12</td>
</tr>
</tbody>
</table>

| Risks | Not reported |
| Consistency in results | N/A – 1 study |
| Precision in results | No confidence intervals reported |
| Directness of results | Direct |

### Comparison 3
High frequency rTMS (15Hz) over 4 weeks applied to the left dorsolateral prefrontal cortex. No control group

### Summary of evidence
Low quality evidence (1 small study, no control group) is uncertain as to the effects of high frequency rTMS applied to the left dorsolateral prefrontal cortex on general cognitive state, executive functioning, working memory or psychomotor speed

**General cognitive state, executive functioning, working memory or psychomotor speed**

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Low quality evidence (1 small study, no control group) is uncertain as to the effects of high frequency rTMS applied to the left dorsolateral prefrontal cortex on general cognitive state, executive functioning, working memory or psychomotor speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>No improvement</td>
<td>No improvement – no statistics reported</td>
</tr>
<tr>
<td>Men</td>
<td>1 study, N = 4</td>
</tr>
</tbody>
</table>

| Risks | Not reported |
| Consistency in results | N/A – 1 study |
| Precision in results | No confidence intervals reported |
| Directness of results | Direct |

Machii K, Cohen D, Ramos-Estebanez C, Pascual-Leone A.
# TECHNICAL COMMENTARY

## Non-Pharmaceutical Treatment - Repetitive Transcranial Magnetic Stimulation (rTMS)

### Safety of rTMS to non-motor cortical areas in healthy participants and patients

**Clinical Neurophysiology 2006; 117(2):455-471**

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<table>
<thead>
<tr>
<th>Comparison 1</th>
<th>rTMS applied to prefrontal or temporal lobes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of evidence</strong></td>
<td>Low quality evidence (mostly observational studies, small samples), authors conclude headache most commonly reported</td>
</tr>
</tbody>
</table>

**Adverse effects**

- No meta-analysis
- N = 61, 1 RCT, 3 observational studies

Results reported for patients with schizophrenia immediately post treatment

- Number of participants reporting;
  - Headache 11/49 (22%)
  - Light-headedness 4/21 (19%)
  - Facial muscle twitches 3/16 (19%)
  - Memory difficulties 3/21 (14%)
  - Increased auditory hallucinations 3/21 (14%)
  - Concentration difficulties 3/21 (14%)
  - Worsening of pre-existing akathesia (inability to sit still) 2/16 (12.5%)
  - Worsening of pre-existing obsessive compulsive symptoms 2/16 (12.5%)
  - Visual hallucinations 1/9 (11%)
  - Racing thoughts 1/12 (.08%)
  - Shoulder pain 1/12 (.08%)

**Risks**

Not applicable

**Consistency in results**

Not reported

**Precision in results**

No confidence intervals reported

**Directness of results**

Not reported

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*McNamara B, Ray JL, Arthurs OJ, Boniface S*

*Transcranial magnetic stimulation for depression and other psychiatric*
Non-Pharmaceutical Treatment - Repetitive Transcranial Magnetic Stimulation (rTMS)

disorders

Psychological Medicine, 2001. 31(7): p. 1141-6

View review abstract online

<table>
<thead>
<tr>
<th>Comparison 1</th>
<th>Comparison details not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Low quality evidence (1 RCT, small sample), authors conclude not enough evidence available</td>
</tr>
<tr>
<td>Positive and negative symptoms</td>
<td>Measured by the BPRS, PANSS</td>
</tr>
<tr>
<td>Results reported for immediately post treatment only</td>
<td>No meta-analysis</td>
</tr>
<tr>
<td>N = 16, 1 RCT</td>
<td></td>
</tr>
</tbody>
</table>

Risks

Not reported

Consistency in results

Not reported

Precision in results

No confidence intervals reported

Directness of results

Not reported

Slotema CW. Dirk Blom J. Hoek HW. and 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

<table>
<thead>
<tr>
<th>Comparison 1</th>
<th>Low frequency rTMS to the temporoparietal cortex (1 Hz): 10 sessions (1 study - 4 sessions) vs. sham: 10 sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (large sample, direct, consistent, appears imprecise) suggests that rTMS may reduce Auditory Verbal Hallucinations (AVH) compared to sham</td>
</tr>
</tbody>
</table>
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### Auditory Verbal Hallucinations (AVH)

<table>
<thead>
<tr>
<th><strong>Significant medium effect of reduced AVH in people with schizophrenia who received rTMS compared to sham</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>7 RCT, N = 189, applied rTMS to the left temporoparietal cortex and one study applied rTMS to the right temporoparietal cortex</td>
</tr>
<tr>
<td>( g = 0.54, \ p &lt; 0.001 )</td>
</tr>
<tr>
<td>( I^2 = 0%, \ p = 0.61 )</td>
</tr>
</tbody>
</table>

### 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
- CIs not stated

### Directness of results
- Direct

### Comparison 2
- High frequency rTMS (10Hz): 10 sessions (2 studies – 15 sessions) vs. sham: most applied to the left dorsolateral prefrontal cortex

### Summary of evidence
- Low quality evidence (direct, inconsistent, appears imprecise) is unsure of the benefits of high frequency rTMS compared to sham for negative symptoms

### Negative symptoms

<table>
<thead>
<tr>
<th><strong>Trend towards a small to medium effect of improved negative symptoms for those who received rTMS compared to sham treatment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>7 RCT, N = 148, applied rTMS 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.</td>
</tr>
<tr>
<td>( g = 0.39, \ p = 0.11 )</td>
</tr>
<tr>
<td>( I^2 = 56%, \ p = 0.03 )</td>
</tr>
</tbody>
</table>

### 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
### TECHNICAL COMMENTARY

**Non-Pharmaceutical Treatment - Repetitive Transcranial Magnetic Stimulation (rTMS)**

<table>
<thead>
<tr>
<th>Precision in results</th>
<th>Unable to assess, no CI reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**Slotema CW, Aleman, A., Daskalakis, Z.J. and Sommer I.**

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


View review abstract online

<table>
<thead>
<tr>
<th>Comparison 1</th>
<th>Low frequency rTMS to the left temporoparietal region (1 Hz) vs. sham - 3 to 20 sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence indicates that low frequency rTMS applied to the left temporoparietal region reduces auditory verbal hallucinations in the short-term (immediately after treatment). Low quality evidence (imprecise, inconsistent) is unsure of the benefits over the longer term</td>
</tr>
</tbody>
</table>

**Auditory Verbal Hallucinations (AVH)**

*Measured by the AHRS, HCS*

**Overall, there was a significant medium effect of reduced AVH in people with schizophrenia who received rTMS compared to sham**

15 RCT, N = 337, g = 0.44, 95% CI 0.19 to 0.68, p < 0.001, I² = 35.7%

A similar effect was reported in a separate analysis including only parallel design RCT (not crossover design)

10 RCT, N = 265, g = 0.40, 95% CI 0.10 to 0.70, p not reported, I² = 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, I² = 12.9%

No significant differences were reported between active and sham groups one month after the end
Non-Pharmaceutical Treatment - Repetitive Transcranial Magnetic Stimulation (rTMS)

of treatment
5 studies, N = 127, g = 0.40, 95% CI −0.23 to 1.02, p = 0.215, I² = 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 AVH and non-therapy-resistant AVH)

Severity of psychosis
Measured by 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, I² = 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

Tranulis C, Sepehry AA, Galinowski A, Stip E
Should We Treat Auditory Hallucinations With Repetitive Transcranial Magnetic Stimulation? A Meta-analysis

View review abstract online

Comparison 1
Low frequency rTMS (1Hz) applied to the left temporoparietal cortex (80 to 100% MT) vs sham or placebo. Varying treatment duration
## Non-Pharmaceutical Treatment - Repetitive Transcranial Magnetic Stimulation (rTMS)

### Summary of evidence

High quality evidence indicates a medium size effect of low frequency rTMS applied to the left temporoparietal cortex for varying sessions 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 quality evidence suggests little benefit of left temporoparietal stimulation for other psychotic symptoms. Unable to fully assess quality of evidence – insufficient data reported.

<table>
<thead>
<tr>
<th>Auditory hallucinations</th>
<th>Measured by the AHRS, HCS, PANSS (auditory hallucination subscale), PSYRATS (hallucination subscale), SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis results reported for immediately post treatment only</td>
<td></td>
</tr>
<tr>
<td>Low attrition</td>
<td></td>
</tr>
<tr>
<td>Medium effect size favouring rTMS</td>
<td></td>
</tr>
<tr>
<td>N = 232, 10 RCT</td>
<td></td>
</tr>
<tr>
<td>$g = 0.514$, 95%CI 0.225 to 0.804, $p = 0.001$</td>
<td></td>
</tr>
<tr>
<td>$Q = 13.022$, $p = 0.162$, $I^2 = 23%$</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other positive psychotic symptoms</th>
<th>Measured by the PANSS (positive, general and total scales), SAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies at end of treatment</td>
<td></td>
</tr>
<tr>
<td>No significant treatment effect</td>
<td></td>
</tr>
<tr>
<td>6 RCT</td>
<td></td>
</tr>
<tr>
<td>Effect sizes not reported</td>
<td></td>
</tr>
</tbody>
</table>

### Risks

Approximately 10% 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 comparison, with varying number of sessions, for people with...
Non-Pharmaceutical Treatment - Repetitive Transcranial Magnetic Stimulation (rTMS)

schizophrenia and auditory hallucinations

Explanation of acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHRS</td>
<td>Auditory Hallucination Rating Scale</td>
</tr>
<tr>
<td>AVH</td>
<td>Auditory Verbal Hallucination</td>
</tr>
<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
</tr>
<tr>
<td>CGI</td>
<td>Clinical Global Impression Scale</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>d</td>
<td>Cohen’s d</td>
</tr>
<tr>
<td>g</td>
<td>Hedges’ g</td>
</tr>
<tr>
<td>HCS</td>
<td>Hallucination Change Scale</td>
</tr>
<tr>
<td>HDRS</td>
<td>Hamilton Depression Rating Scale</td>
</tr>
<tr>
<td>I²</td>
<td>the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance)</td>
</tr>
<tr>
<td>LS</td>
<td>10-point Likert scale of hallucination intensity</td>
</tr>
<tr>
<td>MT</td>
<td>motor threshold</td>
</tr>
<tr>
<td>N</td>
<td>number of participants</td>
</tr>
<tr>
<td>OCD</td>
<td>obsessive compulsive disorder</td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
</tr>
<tr>
<td>PSYRATS</td>
<td>Psychotic Symptom Rating Scales</td>
</tr>
<tr>
<td>p</td>
<td>statistical probability of obtaining that result (p &lt; 0.05 generally regarded as significant)</td>
</tr>
<tr>
<td>Q</td>
<td>Q statistic (chi-square) for the test of heterogeneity</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial/s</td>
</tr>
<tr>
<td>RHSRS</td>
<td>Revised Haddock Self-Rating Scale</td>
</tr>
<tr>
<td>rTMS</td>
<td>repetitive transcranial magnetic stimulation</td>
</tr>
<tr>
<td>SAH</td>
<td>Scale for Auditory Hallucinations</td>
</tr>
<tr>
<td>SANS</td>
<td>Scale of assessment of negative symptoms</td>
</tr>
<tr>
<td>SAPS</td>
<td>Scale for the Assessment of Positive Symptoms</td>
</tr>
<tr>
<td>TVRS</td>
<td>Topography of Voices Rating Scale</td>
</tr>
<tr>
<td>vs</td>
<td>versus</td>
</tr>
</tbody>
</table>
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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 which 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[23].

† 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 randomized trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardized mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which 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 moderate effect, and 0.8 and over represents a large treatment effect[23].

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 large effect is considered if RR > 2 or < 0.5 and a very large effect if RR > 5 or < 0.2[24]. 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 unforeseen 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. Unstandardized (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. Standardized 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;

| Many thanks to Associate Professor Colleen Loo for reviewing the original version of this summary of evidence. |
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