NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcranial magnetic stimulation for auditory hallucinations

Auditory hallucinations are when you hear sounds that do not exist (such as hearing voices). In this procedure, a device containing an electromagnet is held against the scalp. This produces pulses of magnetic energy that stimulate specific areas in the brain through the skull (transcranial). Treatment involves daily or twice daily sessions lasting about 20 minutes. The aim is to stop or reduce the auditory hallucinations.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2019 and updated in June 2020.

Procedure name

- Transcranial magnetic stimulation for auditory hallucinations

Professional societies

- Royal College of Psychiatrists
- The British Psychological Society.

Description of the procedure

Indications and current treatment

Auditory hallucinations are when you hear sounds that do not exist (such as hearing voices). They are often symptoms of mental health problems such as schizophrenia, bipolar disorder, major depression and post-traumatic stress disorder. However, they may also be symptoms of temporal lobe epilepsy, dementia, neurological infections and brain tumours. And they are sometimes caused by lack of sleep, extreme hunger, or the use of recreational or prescribed drugs.

The treatment options for auditory hallucinations depend on the underlying cause. For example, antipsychotic medication may help with hallucinations for people living with schizophrenia. Some people find strategies such as learning to understand their voices, taking control and keeping busy are helpful in managing the condition.

What the procedure involves

Transcranial magnetic stimulation is typically done with the patient awake and sitting in a chair. The operator places an electromagnetic coil against the scalp, over a specific region of the brain, usually the left temporoparietal area. Pulses of electrical current in the coil generate rapidly pulsating magnetic fields that pass through the skull and meninges and into the brain. The magnetic field produced is relatively powerful but short lived (milliseconds). The precise mechanism of action is unclear but it produces both excitatory and inhibitory effects on cortical neurons. The amount of stimulation and the target area is adjusted for each patient. Treatment usually comprises daily or twice daily sessions lasting up to about 20 minutes. The number of sessions varies, but it could be up to 30. The aim is to stop or reduce the auditory hallucinations.

Stimulation can be repetitive, with pulses of magnetic energy delivered at various frequencies or stimulus intensities. In the standard repetitive technique, individual pulses are repeated at a pre-set interval (repetition of pulses). In the theta-burst technique, short bursts of pulses are repeated at a pre-set interval (repetition of bursts). In the deep repetitive technique, deeper and broader brain regions are stimulated than in the standard technique.

Outcome measures

Auditory Hallucinations Rating Scale

The Auditory Hallucinations Rating Scale (AHRS) gives a composite score by summing the following 7 dimensions: hallucination frequency, reality, loudness, number of different voices, length of hallucinations (single words, phrases, sentences, or extended discourse), attentional salience (how demanding of attention the voice is) and distress level. The total score ranges from 2 to 41, with higher scores indicating more severe symptoms.

Psychotic Symptom Rating Scale

The Psychotic Symptom Rating Scale (PSYRATS) is comprised of 17 items on specific dimensions of hallucinations and delusions, with each item being rated from 0 (absent) to 4 (severe). The PSYRATS has 2 subscales: the auditory hallucinations subscale (AHS) consisting of 11 items, and the delusions subscale (DS) consisting of 6 items. The AHS items are frequency, duration, location, loudness, origin, negativity (amount and degree), distress (amount and intensity), disruption, and controllability.

Hallucination Change Scale

The Hallucination Change Scale (HCS) is a visual-analogue scale personalised for each participant following a narrative description of auditory hallucinations at the beginning of the study. The baseline is set at 10, possible choices start at 0 (no hallucinations) to 20 (increased auditory hallucinations).

Positive and Negative Syndrome Scale

The positive and negative syndrome scale (PANSS) assesses positive, negative, and general psychopathology associated with schizophrenia. It uses a standardised clinical interview that rates the presence and severity of positive and negative symptoms, as well as general psychopathology for people with schizophrenia within the past week. Of the 30 items, 7 are positive symptoms (including hallucinatory behaviour), 7 are negative symptoms, and 16 are general psychopathology symptoms. Symptom severity for each item is rated on a 7-point scale (1=absent, 7=extreme).

Efficacy summary

Reduction in auditory hallucinations

In a systematic review of 768 patients, with auditory hallucination data for 578 patients, there was a statistically significant reduction in auditory hallucinations, as measured by a composite score derived from the AHRS and PANSS auditory hallucination subscale, for patients who had repetitive magnetic stimulation (rTMS) compared with sham (Hedges' g=−0.51, p=0.0001; I^2=59%, 14 studies).[1]

In a randomised controlled trial (RCT) of 74 patients who had active high frequency rTMS or sham, there was no statistically significant difference in the proportion of patients with a decrease of more than 30% in the AHRS frequency item at 2 successive ratings (50% compared with 49%). At day 30, the percentage of responders was 27% for patients who had active rTMS compared with 18% for those who had sham (p=0.421).[2]

In an RCT of 51 patients who had low frequency left rTMS, bilateral rTMS or sham, there were no statistically significant differences between the groups in self-reported hallucination scores, as measured with the AHRS and the Positive and Negative Affect Scale (PANAS) at 3-month follow up. The proportion of patients with an improvement of 1 point or more on the PANSS Hallucination item was 50% (8/16) in the left rTMS group, 33% (5/15) in the bilateral rTMS group and 25% (4/16) in the sham group. For an improvement of 3 points or more on the AHRS frequency item, the proportions were 31% (5/16), 7% (1/15) and 19% (3/16) respectively.[3]

In an RCT of 71 patients who had theta burst rTMS or sham (also included in the systematic review), there was a similar decrease in hallucination severity in both groups. The proportion of patients with a decrease of 25% or more in severity measured by AHRS was 13% (4/32) for patients who had active theta burst rTMS and 13% (4/32) for those who had sham (p=1.00). The proportion of patients with a decrease of 25% or more in severity measured by PSYRATS was 9% (3/32) for patients who had active theta burst rTMS and 3% (1/32) for those who had sham (p=0.61).[4]

In an RCT of 83 patients who had active rTMS to 2 different sites or sham rTMS (also included in the systematic review), there was no statistically significant difference in the Hallucination Change Scale (HCS) at the end of treatment (6.38 in the active rTMS group compared with 7.78 in the sham group, p=0.09). There was a statistically significant greater improvement for hallucination frequency (effect size 0.65, 95% confidence interval [CI] 0.19 to 1.11, p=0.005) and Clinical Global Improvement score (effect size 0.47, 95% CI 0.01 to 0.93, p=0.045) for patients who had active rTMS compared with sham. When the analysis was restricted to patients for whom the motor threshold could be consistently detected, the difference in HCS was statistically significant at the end of treatment (6.55 in the active rTMS group and 8.37 in the sham group, p=0.04).[5]

In an RCT of 62 patients who had low frequency functional MRI-guided rTMS, rTMS directed at the left temporoparietal region, or sham (also included in the systematic review), there was no statistically significant difference between the 3 groups in the proportion of patients with more than 20% reduction on the total AHRS score (p=0.734).[6]

Safety summary

Aggravation of sensory symptoms

Aggravation of sensory symptoms was reported in 2% (28/1,815) of patients who had rTMS for pathological positive sensory phenomena in a systematic review of 1,815 patients. In patients with auditory hallucinations, the crude risk for high frequency rTMS was 0% (0/21) and the crude risk for low frequency rTMS was 1% (4/373); 95% CI 0.03 to 2.11%. A case report described a single patient who had an increase in auditory hallucinations for 1 month, described as ‘tolerable’ after the final low frequency rTMS session to the left temporoparietal cortex.[7]

Psychiatric symptom exacerbation

Psychiatric symptom exacerbation was reported in 2% (6/393) of patients in the systematic review of 1,815 patients.[7]

Headache

Headache was statistically significantly more common in the active treatment group compared with sham in the systematic review of 768 patients (odds ratio 3.15, 95% CI 1.65 to 5.99, p=0.0005).[1]

Headache was reported after 14% of active rTMS sessions and 7% of sham sessions in an RCT of 74 patients (p value not significant).[2] Mild transient headache after at least 1 stimulation session was reported in 29% (9/31) of patients who had active rTMS and 13% (2/16) of patients who had sham rTMS in an RCT of 51 patients.[3]

Pain

Local pain was reported after 11% of active rTMS sessions and 4% of sham sessions in an RCT of 74 patients (p<0.05). The mean visual analogue scale score for pain was 2.8 in the active group and 1.4 in the sham group (p<0.05).[2] Scalp discomfort and cervical pain were each reported in 1 patient who had functional MRI-guided rTMS in an RCT of 62 patients. Abdominal pain was reported by 9% (2/22) of patients who had rTMS directed at the left temporoparietal area in the same study.[6]

Clenched jaw or squeezing

Clenched jaw was reported after 29% of active rTMS sessions and 2% of sham sessions in an RCT of 74 patients (p<0.0001). Hemi-facial pain and squeezing were reported after 12% of active rTMS sessions and 8% of sham sessions in the same study (p value not significant). Squeezing alone was reported after 12% and 2% of session respectively (p<0.01).[2]

Twitching facial muscles

Blepharospasm was reported after 14% of active rTMS sessions and 1% of sham sessions in an RCT of 74 patients (p<0.001).[2] Twitching facial muscles was reported in 32% (10/31) of patients who had active rTMS in the RCT of 51 patients.[3] Facial muscle twitching was reported in 35% (7/20) of patients who had functional MRI-guided rTMS and 1 patient who had sham rTMS in an RCT of 62 patients.[6]

Dizziness

Dizziness was reported in 1 patient who had rTMS directed at the left temporoparietal area and 1 patient who had sham rTMS in the RCT of 62 patients.[6] Light-headedness was reported in 1 patient who had active rTMS in the RCT of 51 patients.[3]

Concentration or memory difficulty

Concentration difficulty and memory difficulty were each reported in 1% (3/393 and 4/393 respectively) of patients who had rTMS for auditory hallucinations in the systematic review of 1,1815 patients.[7]

Other

Earache and a tingling sensation in the arm were each reported in 1 patient who had active rTMS in the RCT of 51 patients.[3] Nausea was reported in 1 patient who had functional MRI-guided rTMS and fatigue was reported in 1 patient who had rTMS directed at the left temporoparietal area in the RCT of 62 patients.[6] Hearing problems were reported in 1% (2/393) of patients who had rTMS for auditory hallucinations in the systematic review of 1,815 patients.[7]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts described the following anecdotal adverse event: tiredness and fatigue. They considered that the following were theoretical adverse events: TMS induced psychosis, anxiety, insomnia and suicidal ideations.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transcranial magnetic stimulation for auditory hallucinations. The following databases were searched, covering the period from their start to 12 February 2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with auditory hallucinations
Intervention/test	Transcranial magnetic stimulation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on about 900 patients from 1 systematic review, 5 randomised controlled trials (3 of which are also included in the systematic review) and 1 review of safety events (including some of the same studies that are included in the systematic review).[1–7]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on transcranial magnetic stimulation for auditory hallucinations

Study 1 Kennedy N (2018)

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported for individual studies
Recruitment period	Search date: February 2017
Study population and number	**n=768 (30 RCTs); 578 (340 active rTMS, 238 sham) for auditory hallucinations** Patients with schizophrenia and related psychoses
Age and sex	Mean 38 years
Patient selection criteria	Study selection criteria: peer-reviewed original studies of patients with schizophrenia and related psychoses diagnosed according to standardised criteria; double-blind randomised sham controlled design; symptom ratings using the Auditory Hallucinations Rating Scale (AHRS) or the Positive and Negative Syndrome Scale (PANSS); sufficient data to calculate effect size using Hedges' g; information about study dropouts and withdrawals. Based on the criteria set out by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group, the studies selected would be rated as 4 (highest rating). Conference abstracts, open label trials, case reports and case series were not included.
Technique	The most common treatment sites were the temporoparietal junction (TPJ) and dorsolateral prefrontal cortex (DLPFC). Studies varied in pulse frequency (1 to 50 Hz), number of sessions (4 to 30) and trial duration (2 days to 4 weeks).
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported for individual studies. The authors of the systematic review declared no competing interests.

Analysis

Study design issues: Systematic review was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria. Only double-blind randomised sham-controlled studies were included. For auditory hallucinations, the main outcome was a reduction in auditory hallucinations as measured by a composite score derived from the AHRS and the PANSS auditory hallucination subscale. The review also included studies on transcranial direct current stimulation, but the results from these have not been included because they are outside the remit of this overview.

Study population issues: The study samples comprised patients with persistent symptoms despite adequate antipsychotic treatment. Data on auditory hallucinations were analysed from 14 of the 30 studies using rTMS for schizophrenia (18 datasets).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **578 (340 active rTMS, 238 sham) for auditory hallucinations**

For auditory hallucinations, there was a statistically significant effect of treatment (Hedges' g=−0.51, p=0.0001) with evidence of moderate heterogeneity (I^2=58.8%; 14 studies; n=578).

Older age was associated with a small reduction in response to the active (coefficient=0.08, p=0.03) and the sham condition (coefficient=0.14, p<0.0001).

Higher antipsychotic dose was associated with a small but statistically significant reduction in response in the active condition (coefficient=0.003, p=0.03).

The effect of other patient-related variables was not statistically significant.

Reductions in the composite hallucinations scores was associated with short trial duration (less than 3 weeks) (Hedges' g=−6.03, p=0.001).

Summary of the results of meta-analyses of the efficacy of rTMS in the treatment of auditory hallucinations, positive, negative and overall symptoms in patients with schizophrenia

Outcome	Hedges' g effect size	p value	I^2	Number of datasets	Number of patients in the active treatment group	Number of patients in the sham group
Composite hallucination	-0.51	0.0001	58.81	18	340	238
PANSS Positive	0.28	0.13	87.87	27	585	414
PANSS Negative	-0.49	0.01	86.60	21	496	373
PANSS Total	-0.29	0.06	78.63	21	467	350

Safety

Dropouts

- Active rTMS=16.5% (56/340)
- Sham=18.5% (44/238)

In the active group, reasons for dropout included unreliable attendance, deterioration in cognitive tests, light-headedness, paranoia, headache, inability to tolerate, exacerbation of psychotic symptoms, facial muscle twitching, and deterioration in symptoms.

In the sham group, reasons for dropout included unreliable attendance, intolerance to procedure, deterioration of mental state, deterioration in cognitive tests, paranoia, worsening psychosis, dizziness or tremor, fatigue, and headache.

Side effects

- Active rTMS=72.1% (245/340)
- Sham=60.9% (145/238)

Odds ratio (OR)=1.6, 95% confidence interval (CI) 1.28 to 2.11, p=0.0001

The most common adverse event was headache, which was statistically significantly more common in the active treatment group (OR=3.15, 95% CI 1.65 to 5.99, p=0.0005).

Abbreviations used: AHRS, Auditory Hallucinations Rating Scale; CI, confidence interval; OR, odds ratio; PANSS, Positive and Negative Syndrome Scale; rTMS, repetitive transcranial magnetic stimulation

Study 2 Dollfus S (2018)

Details

Study type	**Randomised controlled trial (NCT01022489)**
Country	France (7 centres)
Recruitment period	2009 to 2015
Study population and number	**n=74 (35 active rTMS, 39 sham)** Patients with schizophrenia or schizoaffective disorders
Age and sex	• Active rTMS: mean age 35 years; 65% male • Sham rTMS: mean age 40 years; 45% male
Patient selection criteria	Inclusion criteria: diagnosis of schizophrenia or schizoaffective disorder (DSM-IV R) assessed with the Mini International Neuropsychiatric Interview, age between 16 and 65 years, severity score of hallucinations on the AHRS higher than 10, and clinically stable disease defined by the absence of antipsychotic treatment modifications within the last 2 months. Exclusion criteria: pregnancy or active breastfeeding, brain tumour, history of epilepsy, previous rTMS treatment, and metal objects in the body.
Technique	**High frequency rTMS (20 Hz) over a specific site on the left superior temporal sulcus, guided by neuronavigation** Devices: Magstim rapid (the Magstim Company Limited, UK) and the MagPro X-100 (MagVenture, Denmark) with a figure-8 coil. Treatment protocol consisted of 13 trains with a duration of 10 seconds and 200 pulses in each train. The intertrain interval was 50 seconds, resulting in 2,600 total pulses and a total duration of 13 minutes. Four sessions were done, with 2 sessions per day. The stimulation intensity was set at 80% of the resting motor threshold. For the control group, sham coils that delivered a very slight magnetic field were used. They had the same appearance and sound and provided the same tactile sensations as the active coils.
Follow-up	**4 weeks**
Conflict of interest/source of funding	The financial grant was supported by the French Health Ministry and the Regional Council of Basse-Normandie. Three authors are experts or consultants for companies including Astra Zeneca, Gedeon Richter, Roche, Takeda, Fabre, Janssen, Lilley, ONO Pharma, JNJ, Sanofi, Servier, Lundbeck, Otsuka. Six authors have received honoraria, travel grants or have other relationships with companies including DA pharma, Ethypharm, Lundbeck, Janssen, Lilly, Otsuka, Astra Zeneca, F Hoffmann-La Roche ltd, Sanofi, Servier and Pierre Fabre. The remaining 23 authors have no conflicts of interest.

Analysis

Follow-up issues: Of the 74 randomised patients, 15 (20%) dropped out, 6 from the sham group and 9 from the active group. Of these 15 patients, 12 did not have all 4 sessions of rTMS because of cerebral anatomical abnormalities (n=4), technical issues with the rTMS (n=4), withdrawal of consent (n=3) and improvement of AHRS (n=1). There was 1 protocol violation related to a violation of inclusion criteria and 2 patients were lost before the beginning of rTMS treatment. Patients were assessed at 6 visits over 4 weeks (immediately preceding the first treatment session [day 1], after the last session [day 2], and at days 7, 14, 21 and 30).

Study design issues: Randomised double-blind placebo-controlled multicentre trial. The primary outcome was defined as the percentage of patients who had a decrease of more than 30% in the AHRS frequency item at 2 successive evaluations, spaced 1 week apart. Open-ended questions and a visual analogue scale were used to assess adverse effects and the overall painfulness of the procedure after each treatment session. A sample size of 72 patients was calculated for a power of 90% and an alpha risk of 0.05. The high dropout rate reduced the power of the study to 77%.

Study population issues: There were no statistically significant differences between the groups in age, gender, age of onset, duration of illness, marital status, employment status, severity of hallucinations, severity of illness, antipsychotic doses, or diagnosis. Patients in the sham group had been hospitalised more often (7.6 admissions compared with 4.6 in the active group, p=0.059), had a longer duration of illness (15.2 years compared with 11.0 years, p=0.079), and had fewer years of education than the active group (11.0 years compared with 12.5 years, p=0.058).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **59 (26 active rTMS, 33 sham)**

Percentage of patients with a decrease of more than 30% in the AHRS frequency item at 2 successive ratings (primary outcome)

- Active rTMS=50%
- Sham rTMS=48.5% (p=not significant)

Percentage of responders (decrease of more than 30% in total AHRS score) by follow up

Follow up	Active rTMS, n=26	Sham rTMS, n=33	p
Day 2	19.2	21.2	0.851
Day 7	30.8	21.2	0.403
Day 14	34.6	9.1	0.016
Day 21	26.9	18.2	0.421
Day 30	26.9	18.2	0.421

Variation in AHRS total score was statistically significant (p<0.001) but not different between the active and sham groups (p=0.978), and time x group interaction was statistically significant (p<0.001).

Safety

There were no major adverse effects.

Adverse effects

	Active rTMS, n=104	Sham rTMS, n=132	p
Local signs			
Tingling	9.6%	3.8%	-
Squeezing	11.5%	2.3%	<0.01
Pain	10.6%	3.8%	<0.05
Regional signs			
Hemi-facial pain and squeezing	11.5%	8.3%	-
Clenched jaw	28.8%	1.5%	<0.0001
Blepharospasm	14.4%	0.8%	<0.001
General signs			
Headache	13.5%	6.8%	-
Asthenia	1.0%	1.5%	-
Other complaints			
Noise	6.7%	12.9%	-
Uncomfortable body position	0%	5.3%	<0.05
Motor threshold	1.9%	2.3%	-
Other	4.8%	6.8%	-
No complaints	32.7%	56.1%	<0.0001
Treatment painfulness			
VAS score (mean of 4 sessions)	2.8±1.6 (n=21)	1.4±1.7 (n=28)	<0.05

Abbreviations used: AHRS, Auditory Hallucinations Rating Scale; rTMS, repetitive transcranial magnetic stimulation; VAS, visual analogue scale

Study 3 Bais L (2014)

Details

Study type	**Randomised controlled trial**
Country	The Netherlands
Recruitment period	2006 to 2012
Study population and number	**n=51 (18 left rTMS, 17 bilateral rTMS, 16 sham)** Patients with schizophrenia and frequent, medication resistant auditory verbal hallucinations
Age and sex	• Left rTMS: mean 37 years; 56% (9/16) male • Bilateral rTMS: mean 34 years; 53% (8/15) male • Sham: mean 37 years; 62.5% (10/16) male
Patient selection criteria	All patients met DSM-IV criteria for schizophrenia; diagnoses were confirmed using Schedules for Clinical Assessment in Neuropsychiatry. Only patients reporting frequent (at least daily) medication resistant auditory verbal hallucinations were included. Medication resistance was defined as daily occurring auditory verbal hallucinations despite at least 2 adequate trials of antipsychotic medication for at least 4 weeks before study inclusion. Exclusion criteria: personal or family history of epileptic seizures, history of severe head trauma or neurological disorder, the presence of intra-cerebral or pacemaker implants, inner ear prosthesis or other metal prosthetics or implants, severe behavioural disorder, current substance abuse, and pregnancy.
Technique	Low frequency rTMS over the temporoparietal cortex. Device: Magstim Rapid System (Magstim Company Ltd., UK) with a 70 mm figure-of-8 coil. Sham stimulation was administered using a coil that produced the same clicking sound, without delivering a measurable magnetic field. Motor threshold was only determined in patients who had active rTMS treatment. Treatment was done over 6 consecutive days (except during the weekends), twice daily, for 20 minutes at 1 Hz on 90% of resting motor threshold (total 14,400 pulses). There was always a minimum period of 5 hours between 2 treatment sessions. During the trial, patients were either admitted to an inpatient care unit, a day hospital, or visited the hospital twice a day. Medication dose remained unchanged throughout the study.
Follow-up	**3 months**
Conflict of interest/source of funding	The project was supported by the University of Groningen, which had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Analysis

Follow-up issues: Of the 51 randomised patients, 4 did not have the allocated intervention (2 in the left rTMS group and 2 in the bilateral rTMS group). The reasons were exacerbation of psychotic symptoms during treatment (n=1), lack of motivation (n=1), illness (n=1) and back pain (n=1). Seven patients did not send their questionnaires back and were lost to follow up (2 in the left rTMS group, 3 in the bilateral rTMS group and 2 in the sham group).

Study design issues: Randomised sham-controlled double blind trial. A researcher drew tokens for 1 of the 3 treatment groups and placed them into envelopes with patient ID numbers on. The envelopes were sealed and opened by a researcher before each patient's treatment started. Only the people who administered the TMS (either the researchers or a nurse) were aware of the treatment group. All other people involved (patients, clinical raters and clinicians) were kept blind. Outcome measures included the PANSS, the AHRS and the Positive and Negative Affect Scale (PANAS) adapted for hallucinations.

Study population issues: There were no statistically significant differences between the groups in demographic characteristics or baseline hallucination severity as measured by the AHRS. Baseline scores on hallucination item P3 of the PANSS were not equal between the 3 groups but post-hoc testing revealed no statistically significant differences.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **47 (16 left rTMS, 15 bilateral rTMS, 16 sham)**

PANSS P3 item and subscales – short term efficacy, mean (SD)

Outcome measure	Baseline			End of treatment		
	Left n=16	Bilateral n=15	Sham n=16	Left n=16	Bilateral n=15	Sham n=16
PANSS Item P3	5.19 (0.66)	4.60 (0.63)	4.69 (0.70)	4.44 (1.21)	4.33 (0.90)	4.69 (0.70)
PANSS Positive	16.31 (4.76)	15.80 (3.88)	16.69 (4.60)	15.06 (5.64)	15.21 (4.14)	16.56 (3.88)
PANSS Negative	15.12 (4.70)	13.67 (4.67)	16.63 (5.57)	14.50 (4.40)	14.00 (4.95)	16.81 (5.04)
PANSS General	30.12 (8.85)	27.67 (6.20)	32.50 (9.41)	28.38 (9.04)	26.71 (5.81)	31.56 (7.50)

There was no statistically significant main effect of group on the PANSS hallucination item P3; F(2,44.0)=1.034, p=0.364. The main effect of time was significant, F(1,44.0)=5.942, p=0.019. The interaction between time and treatment group showed a trend for significance, F(2,44.0)=2.545, p=0.09.

AHRS – short and long term efficacy, mean (SD)

Follow up period	AHRS – frequency item			AHRS total		
	Left n=16	Bilateral n=15	Sham n=16	Left n=16	Bilateral n=15	Sham n=16
Baseline	6.88 (2.83)	5.87 (2.70)	5.88 (2.96)	28.31 (5.67)	25.60 (6.73)	24.75 (5.97)
End of treatment	5.50 (3.06)	5.13 (3.07)	4.75 (3.00)	26.13 (5.55)	23.27 (7.09)	21.63 (9.95)
4 weeks	5.07 (3.13) n=14	5.83 (3.19) n=12	4.14 (2.91) n=14	24.79 (8.76) n=14	22.50 (8.10) n=12	20.00 (10.41) n=14
3 months	5.14 (3.18) n=14	5.42 (3.23) n=12	4.14 (2.83) n=14	24.29 (9.43) n=12	23.92 (7.10) n=14	21.79 (9.41) n=14

There was a statistically significant main effect of time for the frequency scores, F(3,41.6)=4.92, p=0.005. There was no main effect of treatment, or interaction between time and treatment. Total AHRS scores decreased with time, F(3,40.9)=2.89, p=0.047. The main effects of treatment and the interaction between treatment and time were not statistically significant.

PANAS – short and long term efficacy, mean (SD)

Follow up period	PANAS - Positive			PANAS - Negative		
	Left	Bilateral	Sham	Left	Bilateral	Sham
Baseline	28.79 (10.6) n=14	25.67 (10.1) n=15	21.08 (6.97) n=14	21.50 (7.98) n=14	23.40 (10.5) n=15	29.43 (10.3) n=13
End of treatment	24.47 (9.67) n=15	19.93 (8.08) n=15	19.14 (7.16) n=14	20.13 (8.40) n=15	21.80 (11.2) n=15	25.43 (10.6) n=14
4 weeks	24.33 (10.3) n=15	21.53 (7.92) n=15	17.69 (6.86) n=13	18.27 (6.72) n=15	19.40 (9.42) n=15	24.92 (11.9) n=13
3 months	24.19 (10.1) n=16	22.13 (7.99) n=15	17.62 (6.20) n=13	18.94 (8.44) n=15	19.53 (9.14) n=15	26.46 (13.0) n=13

Safety

There were no serious adverse effects.

Side effects reported in the active rTMS groups were:

- Twitching facial muscles, n=10
- Light headedness, n=1
- Earache, n=1
- Tingling sensation in the arm on the contralateral side of rTMS stimulation and minor pain in the left arm, n=1

These side effects were confined to the actual stimulation session and disappeared immediately after stimulation.

Mild transient headache after at least 1 stimulation session:

- Active=29.0% (9/31)
- Sham=12.5% (2/16)

Other side effects reported in the sham group:

- Tingling sensation near the ear, n=1
- Blunted affect during the stimulation session, n=1
- Concentration problems during the treatment period, n=1

Both positive and negative affect scores showed statistically significant decreases with time, F(3,38.0)=5.69, p=0.003 and F(3,40.5)=6.29, p<0.001, respectively. There were no main effects for treatment or interaction effects on either PANAS positive or negative scores.

Pairwise comparisons between baseline and follow-up measurements – mean difference

	AHRS frequency	AHRS total	PANAS positive	PANAS negative
End of treatment-baseline	1.08**	2.55	4.57**	1.85
4 weeks follow-up-baseline	1.26**	3.35*	4.77**	3.63**
3 months follow-up-baseline	1.31**	3.03*	4.04**	3.61**

** significant at p≤0.05, * trend for significance 0.01<p<0.05

Responder analysis

Improvement of 1 point or more on the PANSS Hallucination item P3

- Left rTMS=50.0% (8/16)
- Bilateral rTMS=33.3% (5/15)
- Sham=25.0% (4/16)

Improvement of 3 points or more on the AHRS frequency item

- Left rTMS=31.3% (5/16)
- Bilateral rTMS=6.7% (1/15)
- Sham=18.8% (3/16)

Blinding

Of the 16 patients in the left rTMS group, 10 (62.5%) thought they had active treatment. In the bilateral group, 75% (9/12) of patients thought they had active treatment. In the sham group, 62.5% (10/16) thought they had sham rTMS.

Abbreviations used: AHRS, Auditory Hallucinations Rating Scale; PANAS, Positive and Negative Affect Scale; PANSS, Positive and Negative Syndrome Scale; rTMS, repetitive transcranial magnetic stimulation

Study 4 Koops S (2016)

Details

Study type	**Randomised controlled trial**
Country	The Netherlands
Recruitment period	2012 to 2014
Study population and number	**n=71 (37 theta burst rTMS, 34 sham)** Patients with schizophrenia and auditory verbal hallucinations
Age and sex	• Theta burst rTMS: mean age 38 years; 65% (24/37) male • Sham: mean age 42 years; 47% (16/34) male
Patient selection criteria	Inclusion criteria: diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder or psychosis not otherwise specified; frequent auditory verbal hallucinations (at least 5 times per hour); a stable dose of antipsychotic medication for more than 2 weeks. Exclusion criteria: age under 18 years; nonremovable metal objects in or around the head; history of seizures; increased intracranial pressure because of infarcts or trauma; professional metal workers or a history of eye trauma with a metal object; coercive treatment at a psychiatric ward (based on a judicial ruling); representation by a legal ward or under legal custody; pregnancy.
Technique	Theta burst rTMS over the left temporoparietal cortex. Device: MagStim Rapid2 stimulator (Magstim Company Ltd.) with a 70 mm air-cooled figure-of-eight coil. Stimulation parameters: 60 second stimulation train with a 3 pulse burst at 50 Hz repeated every 200 milliseconds. Stimulation was at 80% of the individual motor threshold, or at the highest intensity the stimulator could apply for the protocol (51% of the maximal stimulator output). In 8 out of 32 patients, stimulation was at 64% to 78% of the individual motor threshold. The sham device looked identical and produced identical sounds but no magnetic pulses. Patients had 10 treatment sessions over 5 consecutive days, with a 30 minute break between sessions.
Follow-up	**1 month**
Conflict of interest/source of funding	Work was supported by a fellowship and a grant from the Netherlands Organization for Health Research and Development. One author has shares in Brain Science Tools BV and acts as its managing CEO. All other authors declared no conflict of interest.

Analysis

Follow-up issues: Participation entailed 6 study visits and a follow-up measurement by phone. Of the 71 randomised patients, 7 (10%) of patients dropped out before study completion (5 in the active group and 2 in the sham group). Reasons for dropping out: exacerbation of symptoms (n=2), no longer willing to participate (n=2), fear of treatment (n=1), travelling too tiring (n=1) and relocation to closed inpatient setting in another clinic (n=1).

Study design issues: Randomised placebo-controlled double blind trial. Computer generated randomisation was used to allocate patients to each group. Patients, study staff and clinical staff were blinded to treatment allocation. Only rTMS administrators had access to the randomisation list; they had minimal contact with the patients and no role in assessing auditory verbal hallucinations. The primary outcome measure was auditory verbal hallucination change after treatment and at follow-up, as measured by the AHRS and Psychotic Symptom Rating Scale (PSYRATS). All dropouts were excluded from the analysis.

Study population issues: There were no statistically significant differences between the 2 groups in age, gender, and baseline clinical scores. Type of medication differed between the groups on trend level (p=0.06). The mean AHRS score was 24 at baseline in both groups and the mean PSYRATS score was 28.

Other issues: Study is included in systematic review by Kennedy N et al. (2018). At the end of the study, patients in the sham group were offered active treatment and all but 1 patient chose to have it.

IP overview: transcranial magnetic stimulation for auditory hallucinations

Key efficacy and safety findings

Efficacy

Number of patients analysed: 64 (32 active, 32 sham)

Hallucination severity

Rating scale scores per group, mean (SD)

	Active theta burst rTMS (n=32)			Sham group (n=32)		
	T1	T2	T3	T1	T2	T3
PANSS positive	19 (7)	18 (6)	-	19 (5)	18 (5)	-
AHRS	24 (5)	22 (6)	22 (6)	24 (5)	22 (6)	22 (7)
PSYRATS	28 (6)	26 (6)	25 (6)	28 (5)	27 (5)	27 (5)

T1=baseline, T2=after last treatment, T3=1-month follow-up

The AHRS scores statistically significantly decreased over time in both groups (p<0.001).
The PSYRATS scores statistically significantly decreased over time in both groups (p=0.002).
There was no statistically significant interaction effect with treatment group for both the AHRS and the PSYRATS. Thus, the decrease in hallucination severity was the same in the active treatment group and in the sham group.
Scores on the positive PANSS scale decreased statistically significantly over time but there were no statistically significant time by group interactions.

Responders (decrease of 25% of more on severity score)
AHRS

- Active theta burst rTMS=12.5% (4/32)
- Sham=12.5% (4/32), p=1.00

PSYRATS

- Active theta burst rTMS=9.4% (3/32)
- Sham=3.1% (1/32), p=0.61

Study blinding
56.3% (36/64) of patients correctly guessed their treatment allocation, 40.6% (26/64) guessed incorrectly and 2 patients refused to guess because they had no idea what treatment they had.
In the active treatment group, 50% (16/32) of patients correctly guessed they had active treatment, 46.9% (15/32) incorrectly guessed they had sham treatment and 1 patient refused to guess.
In the sham group, 62.5% (20/32) of patients correctly guessed they had sham treatment, 34.4% (11/32) incorrectly guessed they had active treatment and 1 patient refused to guess.
There was no statistically significant effect of allocated treatment group on blinding (p=0.30).

Safety

Frequency of adverse events as measured by the Global Index of Safety

Adverse event	Active theta burst rTMS	Sham
Agitation	7	5
Speech disorder	5	1
Amblyopia	2	1
Anxiety	8	10
Apathy	4	8
Ataxy	3	1
Confusion	10	7
Convulsions	1	0
Pain	17	15
Euphoria	5	5
Incoordination	2	1
Insomnia	4	6
Malaise	5	5
Dizziness	14	9
Myoclonia	4	6
Nausea	9	6
Nervousness	6	12
Palpitation	3	2
Paraesthesia	3	6
Syncope	2	0
Twitching	4	8
Vertigo	4	3
Blurred vision	5	1
Vomiting	3	0

There were no statistically significant differences between the 2 groups in number or severity of adverse events.

None of the adverse events needed medical attention.

Abbreviations used: AHRS, Auditory Hallucinations Rating Scale; PANSS, Positive and Negative Syndrome Scale; PSYRATS, Psychotic Symptom Rating Scale; rTMS, repetitive transcranial magnetic stimulation

Study 5 Hoffman R (2013)

Details

Study type	**Randomised controlled trial**
Country	US
Recruitment period	2006 to 2011
Study population and number	**n=83 (55 active rTMS, 28 sham)** Patients with schizophrenia and auditory verbal hallucinations
Age and sex	• Active rTMS: mean 37 years; 47% (26/55) male • Sham rTMS: mean 34 years; 46% (13/28) male
Patient selection criteria	Inclusion criteria: diagnosis of schizophrenia or schizoaffective disorder per the Structured Clinical Interview for DSM-IV Version 2.0, with auditory verbal hallucinations experienced on average 5 or more times per day; age 18 to 55 years; estimated intelligence quotient >85; ability to clearly differentiate auditory verbal hallucinations from spontaneous verbal thoughts. Exclusion criteria included: previous rTMS, history of drug or alcohol dependence, seizures not caused by medication or medication withdrawal, unstable medical condition.
Technique	1 Hz rTMS of Wernicke's site (W) and a site in the right homologous region (rW). Device: Magstim Rapid-2 system (Magstim Ltd, UK) with air-cooled figure-8 coil. Sham stimulation was administered at the same location and strength angling the coil 45° off the head using a single-wing tilt. This reproduces sound and somatic sensation resembling active stimulation, with intracerebral voltages about 1/3 that of active TMS. Stimulation strength was 90% motor threshold with upward adjustments if scalp to cortex distance for the target site was greater than that for the ipsilateral motor cortex. Patients had 16 minutes (960 pulses) of stimulation per session for 5 sessions at 1 site and then 5 sessions at the other site. A third block of 5 stimulation sessions was delivered to the site associated with greater percent improvement in auditory visual hallucinations per the Hallucination Change Score (HCS). After completion of the third block of sessions, patients randomised to active rTMS were offered 5 more sessions and patients randomised to the sham group were offered unmasked rTMS following the same schedule. Five weekday sessions per week were offered. Before the procedure, patients had a high resolution structural MRI scan that was downloaded to a BrainLab Neuronavigation system (Brainlab AG, Germany). The scalp was then marked overlying the 2 target sites. Patients remained on their psychotropic medication at steady dosages for at least 4 weeks before and during the trial.
Follow-up	**End of treatment for all patients; up to 24 weeks for some patients**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Clinical assessments were done at baseline and after each 5-session block of stimulations. Telephone contact was maintained with patients after the trial to determine duration of rTMS effects. Of the 83 patients included in the trial, 3 patients in the sham group were removed from the trial or ended participation early because of worsening paranoia or non-response. Two patients in the active group dropped out because of early remission of auditory verbal hallucinations. Two patients were removed from the trial during the fourth 5-session block of rTMS. The first had a large drop in the Hopkins Verbal Memory task and the second had concentration difficulties for about 1 week. Follow-up data were provided by 72 patients.

Study design issues: Randomised sham-controlled double blind trial. Responses to stimulation targeting a Wernicke's site and a site in the right homologous region was compared. Stratified randomisation was used to allocate patients to

active or sham treatment. Random allocation software with random block sizes was used. Randomisation was concealed in sealed envelopes opened immediately before the first stimulation session. Patients, care-providers, assessors and all personnel other than the rTMS operators remained blind to allocation until unmasking after session 15. The primary outcome measure was the Hallucination Change Scale (HCS). This was anchored at 0 (corresponding to no auditory verbal hallucinations), 10 (no change in hallucination severity) and 20 (hallucinations twice as severe as baseline). A sample size of 90 was estimated to give statistical power of 0.80 to detect group differences in HCS for rTMS versus sham delivered to W for the first 5 sessions and at endpoint after stimulation to both sites.

Study population issues: There were no statistically significant differences in baseline characteristics between the 2 groups.

Other issues: Study is included in systematic review by Kennedy N et al. (2018).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **83 (55 active rTMS, 28 sham)**

Endpoint analyses of outcome variables after 15 sessions, mean (standard error)

Outcome variable	Active rTMS n=55	Sham rTMS n=28	p (group effect)	Estimated effect size (95% CI)
HCS (lower scores better)	6.38 (0.47)	7.78 (0.67)	0.09	0.40
Hallucination frequency difference (baseline-endpoint)	-1.32 (0.22)	-0.26 (0.31)	0.005	0.65 (0.19 to 1.11)
Total AHRS difference (baseline-endpoint)	-4.58 (0.85)	-2.78 (1.2)	0.22	0.28
CGI (lower scores better; range 1 to 7, with 4=no change)	2.70 (0.17)	3.33 (0.25)	0.045	0.47 (0.01 to 0.93)

Multiple imputations were used for missing data.

Endpoint analyses of outcome variables after 15 sessions, mean (standard error) – excluding patients for whom motor threshold could not be consistently detected

Outcome variable	Active rTMS n=48	Sham rTMS n=21	p (group effect)	Estimated effect size (95% CI)
HCS (lower scores better)	6.55 (0.48)	8.37 (0.76)	0.044	0.54 (0.02 to 1.06)
Hallucination frequency difference (baseline-endpoint)	-1.31 (0.24)	-0.06 (0.37)	0.005	0.74 (0.23 to 1.26)
Total AHRS difference (baseline-endpoint)	-4.11 (0.76)	-1.90 (1.16)	0.11	0.42
CGI (lower scores better; range 1 to 7, with 4=no change)	2.73 (0.18)	3.58 (0.29)	0.013	0.67 (0.14 to 1.18)

Multiple imputations were used for missing data.

Safety

No safety data were reported.

Site-specific HCS for low-salience hallucinators (salience is the degree to which hallucinations capture attention and alter ongoing thought and behaviour; defined as patients who, at most, were only briefly distracted by their auditory verbal hallucinations [score less than 4 for salience variable on AHRS at baseline])

	First 5-session block (week 1)	Second 5-session block (week 2)
Active to W*	6 (1.00), n=6	8.39 (1.02), n=9
Active to rW**	9 (0.81), n=9	4 (1.25), n=6
Sham to W	9.83 (1.41), n=3	9.2 (1.37), n=5
Sham to rW	9.1 (1.09), n=5	8.83 (1.77), n=3

* difference (post-hoc) between active and sham targeting W, week 1 p=0.035

** difference (post-hoc) between active and sham targeting rW, week 2 p=0.029, suggesting a site-order effect because rW in week 1 and W in week 2 did not produce a similar statistically significant difference

Site-specific HCS for high-salience hallucinators (defined as patients who mostly or always had to pay attention to their auditory verbal hallucinations [score 4 or more for salience variable on AHRS at baseline]) - excluding patients for whom motor threshold could not be consistently detected

	First 5-session block (week 1)	Second 5-session block (week 2)
Active to W	9.38 (0.57), n=17	6.71 (0.728), n=17
Active to rW*	6.91 (0.57), n=17	8.32 (0.728), n=17
Sham to W	8.36 (0.89), n=7	8.58 (1.20), n=6
Sham to rW	9.29 (0.89), n=7	7.07 (1.13), n=7

* difference (post-hoc) between active and sham targeting rW, week 1 p=0.029

Survivorship (defined as maintaining HCS<8)

For all patients who had rTMS (masked and unmasked) who provided follow-up data (n=72), mean survivorship was 17.5 weeks (standard deviation 19.3). 31.6% of patients retained survivorship at 24 weeks. For those patients who had an HCS score<8 after 15 sessions of rTMS, survivorship was 23.8 weeks (standard deviation 18.7).

Two patients with severe, treatment-resistant auditory verbal hallucinations that did not improve immediately after active rTMS went into full remission within 4 weeks of the trial with no change in medication.

Abbreviations used: AHRS, Auditory Hallucinations Rating Scale; CI, confidence interval; CGI, Clinical Global Improvement; HCS, hallucination change scale; rTMS, repetitive transcranial magnetic stimulation; rW. right homologous site; W, Wernicke's site

Study 6 Slotema C (2011)

Details

Study type	**Randomised controlled trial**
Country	The Netherlands
Recruitment period	2007 to 2009
Study population and number	**n=62 (20 MRI guided rTMS, 22 rTMS directed at left temporoparietal [TP] region, 20 sham)** Patients with medication-resistant auditory verbal hallucinations
Age and sex	• MRI guided rTMS: mean age 36 years; 50% (10/20) male • rTMS directed at left TP region: mean age 38 years; 73% (16/22) male • sham: mean age 41 years; 50% (10/20) male
Patient selection criteria	Inclusion criteria: auditory verbal hallucinations more frequent than 1 an hour; medication-resistant auditory verbal hallucinations (defined as insufficient response to at least 2 antipsychotic agents, administered at adequate dosages for at least 6 weeks; a stable dosage of antipsychotic medication for a month before trial inclusion; a functional MRI scan showing significant hallucinatory activity in at least 1 superficially located brain area (in the left or right temporal or parietal lobe). Exclusion criteria: history of epilepsy, unremovable metal objects inside or around the body, the use of cannabis or other drugs during the study or up to 1 month before participation, alcohol consumption of more than 3 units per day, and the use of benzodiazepines or antiepileptic agents.
Technique	**Low frequency rTMS** Device: Magstim Rapid 2 (Magstim Company, Wales) with an air-cooled 70 mm figure-of-8 coil. All patients had a functional MRI scan of the brain before randomisation. In the functional MRI guided group and the sham group, stereotactic navigation was used to mark the location of the scalp directly overlying the area of maximal hallucinatory activity. In the nonguided rTMS group, stimulation was directed at the left temporoparietal region. rTMS was administered for 20 minutes at 1 Hz and 90% of the personal motor threshold of the patient. Patients had daily treatments, except during weekends, for 3 consecutive weeks (15 sessions in total). For sham treatment, the coil was tilted away from the scalp at an angle of 90°.
Follow-up	**3 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Assessments were done at baseline, at the end of the first, second and last week or rTMS and 1, 2 and 3 months after treatment. In the MRI guided rTMS group, 2 patients dropped out because of facial muscle twitching (n=1) and increase of psychosis (n=1). In the standard treatment group, 3 patients dropped out because of inability to continue visiting the hospital (n=1), headache and lack of therapeutic effect (n=1) and an increase in psychotic symptoms (n=1). In the sham group, 6 patients discontinued the study because of an increase in psychotic symptoms (n=3), dizziness and tremor (n=1) and unknown reasons (n=2).

Study design issues: Randomised sham-controlled double blind trial. Randomisation was done by a psychologist who was not involved in the study. Patients were notified of their treatment group after the last follow-up assessment. A sample size of 20 patients per arm was calculated to give 80% power with an estimated effect size 0.50. The primary outcome measure was the severity of auditory hallucinations measured by the AHRS.

Study population issues: There were no statistically significant differences between the groups in demographic data and mean baseline values of the outcome measures.

Other issues: Study is included in systematic review by Kennedy N et al. (2018).

IP overview: transcranial magnetic stimulation for auditory hallucinations

Key efficacy and safety findings

Efficacy

Number of patients analysed: **62 (20 functional MRI guided rTMS, 22 rTMS directed at left TP area, 20 sham)**

Effects of rTMS treatment on specific features of auditory verbal hallucinations (AVH), mean (SD)

	MRI guided rTMS		rTMS directed at left TP area		Sham	
	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment
Frequency	5.8 (3.2)	4.5 (3.0)	5.5 (3.0)	4.5 (3.2)	5.4 (2.8)	4.6 (3.4)
Reality	3.8 (2.0)	3.3 (2.0)	3.9 (1.4)	3.5 (1.9)	4.0 (1.3)	3.7 (1.9)
Loudness	2.6 (1.1)	2.3 (1.1)	2.9 (1.2)	2.4 (1.3)	3.2 (1.4)	2.8 (1.3)
Number of voices	3.5 (1.9)	3.2 (2.1)	3.8 (2.0)	3.7 (2.0)	3.9 (2.0)	3.2 (2.1)
Length	3.4 (1.0)	3.0 (1.2)	3.3 (1.1)	2.9 (1.1)	3.2 (1.0)	3.0 (1.1)
Attentional salience	4.3 (1.5)	3.5 (1.6)	3.8 (1.6)	2.9 (1.3)	4.3 (1.3)	3.7 (1.6)
Distress	3.3 (1.5)	2.8 (1.4)	3.2 (1.1)	2.7 (0.9)	3.4 (1.3)	2.8 (1.3)
Sum AHRS	26.6 (6.3)	22.6 (7.4)	26 (6.6)	22.7 (6.4)	27.4 (6.9)	24.1 (8.1)
Positive items PANSS	15.5 (3.8)	14 (5.7)	16.4 (4.2)	15.5 (3.9)	18.7 (4.7)	15.9 (3.5)
AVH-related items of PSYRATS	26.2 (7.5)	21.8 (10.0)	27 (5.5)	25.1 (8.6)	28 (7.0)	25.4 (8.9)

There was no statistically significant difference between the 3 groups in the proportion of patients with >20% reduction on the total AHRS score (p=0.734).

Effect sizes between baseline and end of rTMS treatment for specific outcome parameters, standard differences in means (p value)

	MRI guided rTMS	rTMS directed at left TP area	Sham
Sum AHRS	0.524 (0.10)	0.508 (0.10)	0.439 (0.17)
Positive items of the PANSS	0.310 (0.33)	0.222 (0.46)	0.676 (0.04)
AVH-related items of PSYRATS	0.583 (0.07)	0.263 (0.39)	0.325 (0.31)

Proportion of patients who correctly guessed their treatment allocation

- MRI guided rTMS=76% (13/17)
- rTMS directed at left TP area=88% (14/16)
- Sham=13% (2/15), p<0.001

Safety

Side-effects

MRI guided rTMS

- Facial muscle twitching, n=7
- Headache, n=3
- Scalp discomfort, n=1
- Cervical pain, n=1
- Nausea, n=1

rTMS directed at left temporoparietal area

- Headache, n=5
- Dizziness, n=1
- Abdominal pain, n=2
- Fatigue, n=1

Sham

- Facial muscle twitching, n=1
- Dizziness, n=1

Abbreviations used: AHRS, Auditory Hallucinations Rating Scale; AVH, auditory verbal hallucinations; PANSS, Positive and Negative Syndrome Scale; PSYRATS, Psychotic Symptom Rating Scale; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; TP, temporoparietal

Study 7 Muller P (2012)

Details

Study type	**Review**
Country	Not reported for individual studies
Recruitment period	Search date: January 1985 to April 2011
Study population and number	**n=1,815 (106 publications); 38 publications (n=393) related to auditory hallucinations** Patients who had rTMS for pathological positive sensory phenomena
Age and sex	Not reported
Patient selection criteria	Studies that used rTMS for tinnitus, auditory and visual hallucinations, and pain syndromes were included. A separate search was done to specifically identify reports of seizures.
Technique	77 publications (n=1,202) used low frequency rTMS protocols, 39 (n=804) used a high frequency protocol and 3 (n=177) used combined low and high frequency rTMS. For auditory hallucinations, 35 publications (n=373) used low frequency and 4 studies (n=21) used high frequency rTMS.
Follow-up	**Not reported**
Conflict of interest/source of funding	One author serves on the scientific advisory board for Codman-Johnson & Johnson, Nexstim, Neuronix, Starlab, and Neosync, and holds intellectual property for various aspects of TMS technology and the combination of TMS with EEG and MRI. Another author holds intellectual property for TMS technology and the combination of TMS with EEG.

Analysis

Study design issues: The aim of the review was to describe the safety profile of rTMS. The search was done using PubMed, including English language studies only. Of 106 publications, 67 studies included sham rTMS as part of either a crossover or a group comparison design. The review included 27 case reports, of which 8 described unwanted side effects. The incidence of adverse events was reported in 65 studies. In 8 studies, adverse events were described but not quantified in terms of numbers of patients. Adverse events were not reported in 38 studies. There was a high variability in sample size (1 to 164) and rTMS protocol (0.2 to 50 Hz, 120 to 5,200 stimuli per day, study duration 1 day to 8 weeks).

Adverse rTMS-related events were categorised as follows: seizure induction, other serious adverse events, symptom exacerbation, mild adverse events, and no adverse events. Analysis was limited to the crude per-person risk with a 95% confidence interval (CI), truncated when appropriate to remain within natural limits when approaching 0 or 100%.

Other issues: There is patient overlap with the systematic review by Kennedy et al. (2018).

Key efficacy and safety findings

Safety

Number of patients analysed: **1,815 (393 for auditory hallucinations)**

- **Seizure induction**=0.16% (3/1,815); 95% CI 0 to 0.19%

  None of the patients with seizures had rTMS for auditory hallucinations: 1 patient had rTMS for tinnitus and 2 had complex regional pain syndrome.
- **Other serious adverse events**: 1 patient had ischaemic chest pain that was not considered to be related to rTMS. One patient had optic neuritis during a study on rTMS for migraine; the event happened before treatment started and was thought not to be a result of rTMS.
- **Aggravation of sensory symptoms**=1.54% (28/1,815); 95% CI 0.97 to 2.11%

  In patients with auditory hallucinations, the crude risk for high frequency rTMS was 0% (0/21) and the crude risk for low frequency rTMS was 1.07% (4/373); 95% CI 0.03 to 2.11%

  A case report described a single patient who had an increase in auditory hallucinations for 1 month, described as 'tolerable' after the final low frequency rTMS session to the left temporoparietal cortex.
- **Other adverse events**=14.9% (271/1,815); 95% CI 13.29 to 16.57%

Adverse events reported in patients who had rTMS for auditory hallucinations

- Abdominal pain=0.25% (1/393)
- Clicking noise persistence=0.25% (1/393)
- Concentration difficulty=0.76% (3/393)
- Dizziness=0.76% (3/393)
- Earache=0.25% (1/393)
- Fatigue/drowsiness=0.25% (1/393)
- Headache=9.92% (39/393)
- Hearing problems=0.51% (2/393)
- Ischaemic chest pain=0.25% (1/393)
- Light headedness=1.27% (5/393)
- Memory difficulty=1.02% (4/393)
- Muscle twitching=3.56% (14/393)
- Nausea=0.25% (1/393)
- Psychiatric symptom exacerbation=1.53% (6/393)
- Restlessness=0.25% (1/393)
- Scalp discomfort=0.25% (1/393)

- **Adverse events during placebo rTMS**=5.25% (67/1,275); 95% CI 4.03 to 6.47%

These included deterioration of psychological clinical state in 3 patients (0.23%, 95% CI 0 to 0.49%) and symptom exacerbation in 2 auditory hallucination studies. The most common adverse event was headache (1.88% [24/1,275]; 95% CI 1.13 to 2.63%).

One study did not clarify which adverse events corresponded to placebo or real rTMS.

Abbreviations used: rTMS, repetitive transcranial magnetic stimulation

Validity and generalisability of the studies

- Most of the RCTs included in the meta-analysis were small.
- Sham coils may produce a larger placebo effect than tilted coils because they can produce auditory and somatic sensations similar to an active coil.
- Some studies used low frequency rTMS and others used high frequency TMS. One study used theta burst rTMS.[4]
- Stimulation parameters and duration of treatment varied between studies.
- Different areas were targeted for stimulation within and between studies.
- The definition of response varied between studies.
- Most of the studies reported outcomes at the end of treatment. One study followed patients for up to 24 weeks.[5]

Existing assessments of this procedure

In 2013, the Canadian Agency for Drugs and Technologies in Health published a rapid response report on 'Repetitive Transcranial Magnetic Stimulation for Specific Patient Populations: Clinical and Cost-Effectiveness and Safety'.[8] For auditory hallucinations, the report identified 1 relevant systematic review and 3 randomised controlled trials.

The report concluded:

'*For patients with auditory hallucination or obsessive compulsive disorder there appears to be no significant improvement with rTMS treatment of duration >2 weeks or >10 sessions when compared to sham. No relevant evidence was identified for substance use disorders. Generally, the side effects with rTMS were mild and there appear to be no issues with respect to tolerance of the procedure. No robust evidence was identified on the cost effectiveness of rTMS compared with sham or pharmacotherapy.*

Several factors such as comorbidities, concomitant medication, refractoriness to pharmacotherapy, disease condition and individual patient characteristics may impact outcomes with rTMS and may be worth considering when deciding on an optimal treatment strategy.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Repetitive transcranial magnetic stimulation for depression. NICE Interventional procedures guidance 542 (2015). Available from http://www.nice.org.uk/guidance/IPG542

- Transcranial magnetic stimulation for treating and preventing migraine. Interventional procedures guidance 477 (2014). Available from http://www.nice.org.uk/guidance/IPG477

Technology appraisals

- Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years. NICE technology appraisal 213 (2011). Available from http://www.nice.org.uk/guidance/TA213

NICE guidelines

- Psychosis and schizophrenia in adults: prevention and management. NICE clinical guideline 178 (2014). Available from http://www.nice.org.uk/guidance/CG178
- Psychosis and schizophrenia in children and young people: recognition and management. NICE clinical guideline 155 (2013; updated: October 2016). Available from http://www.nice.org.uk/guidance/CG155

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One professional expert questionnaire for transcranial magnetic stimulation for auditory hallucinations was submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 3 companies who manufacture or distribute a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- Ongoing trials:
  - Transcranial Magnetic Stimulation (TMS) for Patients With Treatment Resistant Auditory Verbal Hallucination (TMS) (NCT03762746); RCT; Indonesia; n=40; estimated study completion date: February 2019
  - Repetitive Transcranial Magnetic Stimulation (rTMS) Treatment for Schizophrenia Patients With Auditory Hallucinations (NCT02863094); RCT; China; n=30; estimated completion date: January 2021
- There is a TMS device that is CE marked for auditory hallucinations (Neuro-MS/D), but none of the published evidence summarised in table 2 named this

device. Other devices that are not currently CE marked for treating auditory hallucinations are available.

References

1. Kennedy NI, Lee WH, Frangou S (2018) Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: A meta-analysis of randomized controlled trials. European Psychiatry 49: 69–77
2. Dollfus S, Jaafari N, Guillin O et al. (2018) High-frequency neuronavigated rTMS in auditory verbal hallucinations: a pilot double-blind controlled study in patients with schizophrenia. Schizophrenia Bulletin 44: 505–14
3. Bais L, Vercammen A, Stewart R et al. (2014) Short and long term effects of left and bilateral repetitive transcranial magnetic stimulation in schizophrenia patients with auditory verbal hallucinations: a randomized controlled trial. PloS one 9: e108828
4. Koops S, van Dellen E, Schutte MJL et al. (2016) Theta burst transcranial magnetic stimulation for auditory verbal hallucinations: negative findings from a double-blind-randomized trial. Schizophrenia Bulletin 42: 250–7
5. Hoffman RE, Wu K, Pittman B et al. (2013) Transcranial magnetic stimulation of Wernicke's and Right homologous sites to curtail "voices": a randomized trial. Biological Psychiatry 73: 1008–14
6. Slotema CW, Blom JD, de Weijer AD et al. (2011) Can low-frequency repetitive transcranial magnetic stimulation really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial. Biological Psychiatry 69: 450–6
7. Muller PA, Pascual-Leone A, Rotenberg A (2012) Safety and tolerability of repetitive transcranial magnetic stimulation in patients with pathologic positive sensory phenomena: a review of literature. Brain Stimulation 5: 320–9.e27
8. Canadian Agency for Drugs and Technologies in Health (2013). Repetitive Transcranial Magnetic Stimulation for Specific Patient Populations: Clinical and Cost-Effectiveness and Safety. CADTH Rapid Response Service.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	12/02/2020	Issue 2 of 12, February 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	12/02/2020	Issue 2 of 12, February 2020
MEDLINE (Ovid)	12/02/2020	1946 to February 11, 2020
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	12/02/2020	1946 to February 11, 2020
EMBASE (Ovid)	12/02/2020	1974 to 2020 week 07
PsycINFO	12/02/2020	1806 to February Week 1 2020

Trial sources searched 9th July 2019

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	exp Schizophrenia/
2	Paranoid Disorders/
3	Psychotic disorder/
4	Hallucinations/
5	AVH.tw.
6	((auditor* or Sound* or hear*) adj4 hallucinat*).tw.

7	(schizophren* or schizoaffective*).tw.
8	((paranoid or psychot* or emotion*) adj4 disorder*).tw.
9	(auditor* adj4 verb* adj4 hallucinat*).tw.
10	or/1-9
11	magnetic field therapy/ or transcranial magnetic stimulation/
12	(rTMS or dTMS or TMS).tw.
13	((repetit* or deep*) adj4 transcran* magnetic stimulat*).tw.
14	((repetit* or deep*) adj4 trans-cran* magnetic stimulat*).tw.
15	(Magneti* adj4 field* adj4 Therap*).tw.
16	or/11-15
17	10 and 16
18	DuoMAG.tw.
19	Neuro MS.tw.
20	Neurosoft.tw.
21	eNeura.tw.
22	MagVenture.tw.
23	Nexstim.tw.
24	BrainsWay.tw.
25	or/18-24
26	17 or 25
27	Animals/ not Humans/
28	26 not 27

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Case reports were excluded.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Aleman A, Sommer IE, Kahn RS (2007) Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. The Journal of Clinical Psychiatry 68: 416-21	Systematic review n=212 10 studies	There was a statistically significant mean weighted effect size for rTMS versus sham, d=0.76 (95% CI=0.36 to 1.17). When only studies were included that used continuous stimulation (9 studies), the mean effect size increased to d=0.88 and heterogeneity disappeared. There was no significant effect of rTMS on a composite index of general psychotic symptoms.	A more recent review is included (Kennedy N et al., 2018).
Arumugham SS, Thirthalli J, Andrade C (2016) Efficacy and safety of combining clozapine with electrical or magnetic brain stimulation in treatment-refractory schizophrenia. Expert Review of Clinical Pharmacology 9: 1245-52	Review	rTMS can be safely combined with clozapine, although its efficacy in patients with clozapine-refractory auditory hallucinations is equivocal. Further studies with novel protocols are needed.	Descriptive review.
Bais L, Liemburg E, Vercammen A et al. (2017) Effects of low frequency rTMS treatment on brain networks for inner speech in patients with schizophrenia and auditory verbal hallucinations. Progress in Neuropsychopharmacology & Biological Psychiatry 78: 105–13	RCT n=24	rTMS of the left temporoparietal area is associated with decreased involvement of the stimulated region during auditory-verbal processing. Sham stimulation showed different patterns of change compared with active rTMS.	Small RCT, focused on neural networks.
Bagati D, Nizamie SH, Prakash R (2009) Effect of augmentatory repetitive transcranial magnetic stimulation on auditory hallucinations in schizophrenia: randomized controlled study. The Australian and New Zealand Journal of Psychiatry 43: 386-92	RCT n=40	A statistically significant improvement was found in auditory hallucinations in the experimental group as compared to the control group	Larger or more recent studies are included.
Blumberger DM, Christensen BK, Zipursky RB et al. (2012) MRI-targeted repetitive transcranial magnetic stimulation of Heschl's gyrus for refractory auditory	RCT n=54	The findings suggest that neither priming nor low frequency left sided rTMS of Heschl's gyrus are effective at ameliorating refractory auditory hallucinations in schizophrenia.	Small RCT, which is included in review by Kennedy N et al., 2018.

hallucinations. Brain Stimulation 5: 577-85			
Brunelin J, Poulet E, Bediou B et al. (2006) Low frequency repetitive transcranial magnetic stimulation improves source monitoring deficit in hallucinating patients with schizophrenia. Schizophrenia Research 81: 41-5	RCT n=24	Compared to sham, active rTMS statistically significantly improved auditory hallucinations.	Small RCT, which is included in review by Kennedy N et al., 2018.
Chibbaro G, Daniele M, Alagona G et al. (2005) Repetitive transcranial magnetic stimulation in schizophrenic patients reporting auditory hallucinations. Neuroscience Letters 383: 54-7	RCT n=16	The main finding was the long-term reduction in auditory hallucinations in the active group, with a return to the baseline in the sham group. The improvements in auditory hallucinations and positive symptomatology increased and lasted during the follow-up till the end-point.	Larger or more recent studies are included.
Chiu Y-H, Hsu C-Y, Lu M-L et al. (2020) Augmentation strategies for clozapine-resistant patients with schizophrenia. Current Pharmaceutical Design 26: 218-227	Review	No definite effective augmentation strategy was found for clozapine-resistant patients.	Only 3 studies on TMS are discussed, all of which are included in the appendix of the overview.
d'Alfonso AAL, Aleman A, Kessels RPC et al. (2002) Transcranial magnetic stimulation of left auditory cortex in patients with schizophrenia: effects on hallucinations and neurocognition. The Journal of Neuropsychiatry and Clinical Neurosciences 14: 77-9	Case series n=9	A statistically significant improvement was observed on a hallucination scale after 10 days of TMS at the left auditory cortex.	Small case series.
de Jesus DR, Gil A, Barbosa L et al. (2011) A pilot double-blind sham-controlled trial of repetitive transcranial magnetic stimulation for patients with refractory schizophrenia treated with clozapine. Psychiatry Research 188: 203-7	RCT n=17	There was a statistically significant reduction in Brief Psychiatric Rating Scale (BPRS) scores in the active group compared with the sham group. There was no significant difference between active and sham rTMS on Quality of Life Scale (QLS), Auditory Hallucinations Rating Scale (AHRS), Clinical Global Impressions (CGI) and functional assessment staging (FAST) scores. Compared with sham stimulation, active rTMS of the left temporoparietal cortex in clozapine-treated patients showed a positive effect on general psychopathology. However, there was no effect on refractory auditory hallucinations.	Small RCT, which is included in review by Kennedy N et al., 2018.

De Weijer A, Sommer I, Meijering A et al. (2014) High frequency rTMS; a more effective treatment for auditory verbal hallucinations? Psychiatry Research: Neuroimaging 224: 204–10	RCT n=18	Both groups (1 Hz and 20 Hz) showed a decrease in AVH after 1 week of rTMS. No treatment type was superior.	Small RCT, comparing low and high frequency rTMS.
Dollfus S, Lecardeur L, Morello R et al. (2016) Placebo response in repetitive transcranial magnetic stimulation trials of treatment of auditory hallucinations in schizophrenia: a meta-analysis. Schizophrenia Bulletin 42: 301–8	Meta-analysis n=303 (21 articles)	Placebo effect should be considered a major source of bias in the assessment of rTMS efficacy.	Analysis only includes patients who had sham treatment.
Dougall N, Maayan N, Soares-Weiser K et al. (2015) Transcranial magnetic stimulation (TMS) for schizophrenia. The Cochrane database of systematic reviews 8: cd006081	Systematic review n=1,473 41 studies	Based on this review, there is insufficient evidence to support or refute the use of TMS to treat symptoms of schizophrenia. Although some evidence suggests that TMS, and in particular temporoparietal TMS, may improve certain symptoms (such as auditory hallucinations and positive symptoms of schizophrenia) compared to sham TMS, the results were not robust enough to be unequivocal across the assessment measures used. There was insufficient evidence to suggest any added benefit with TMS used as an adjunctive therapy to antipsychotic medication. The overall quality of evidence was graded as very low due to risk of bias, and this was accompanied by an imprecision in estimates because of the relatively small number of participants in the studies.	A more recent review is included (Kennedy N et al., 2018).
Fitzgerald PB, Benitez J, Daskalakis JZ et al. (2005) A double-blind sham-controlled trial of repetitive transcranial magnetic stimulation in the treatment of refractory auditory hallucinations. Journal of Clinical Psychopharmacology 25: 358-62	RCT n=33	rTMS was safe with no adverse effects on memory and cognitive parameters assessed. Active treatment did not result in a greater therapeutic effect than sham on any measure except for the loudness of hallucinations where there was a significant reduction in the active versus the sham group over time.	Small RCT, which is included in review by Kennedy N et al., 2018.
Freitas C, Fregni F, Pascual-Leone A (2009) Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. Schizophrenia Research 108: 11-24	Systematic review and meta-analysis	When specifically analysing auditory hallucinations, the effect size for the sham-controlled studies was large and statistically significant (1.04, p=0.002). There is a need for further controlled, larger trials to assess the clinical efficacy of rTMS on negative and positive symptoms of	A more recent review is included (Kennedy N et al., 2018).

		schizophrenia, while suggesting the need for exploration for alternative stimulation protocols.	
He H, Lu J, Yang L et al. (2017) Repetitive transcranial magnetic stimulation for treating the symptoms of schizophrenia: A PRISMA compliant meta-analysis. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology 128: 716-724	Systematic review and meta-analysis 20 studies	Although there may appear to be a therapeutic effect for 1-Hz rTMS on auditory hallucinations of schizophrenia, this needs to be confirmed by large-scale randomised controlled trials before this finding can be recommended in clinical practice.	A more recent review is included (Kennedy N et al., 2018).
Hoffman RE, Gueorguieva R, Hawkins KA et al. (2005) Temporoparietal transcranial magnetic stimulation for auditory hallucinations: safety, efficacy and moderators in a fifty patient sample. Biological Psychiatry 58: 97-104	RCT n=50	Hallucination Change Score was more improved for rTMS relative to sham stimulation (p=0.008) as was the Clinical Global Impressions Scale (p=0.0004). Hallucination frequency was significantly decreased during rTMS relative to sham stimulation (p=0.0014) and was a moderator of rTMS effects (p=0.008). There was no evidence of neurocognitive impairment associated with rTMS.	Small RCT, which is included in review by Kennedy N et al., 2018.
Hoffman RE, Hawkins KA, Gueorguieva R et al. (2003) Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. Archives of General Psychiatry 60: 49-56	RCT n=24	Auditory hallucinations were robustly improved with rTMS relative to sham stimulation. Frequency and attentional salience were the 2 aspects of hallucinatory experience that showed greatest improvement. Duration of putative treatment effects ranged widely, with 52% of patients maintaining improvement for at least 15 weeks. rTMS was well tolerated, without evidence of neuropsychological impairment.	More recent studies by the same author are included in review by Kennedy N et al., 2018.
Horacek J, Brunovsky M, Novak Tet al. (2007) Effect of low-frequency rTMS on electromagnetic tomography (LORETA) and regional brain metabolism (PET) in schizophrenia patients with auditory hallucinations. Neuropsychobiology 55: 132-42	Case series n=12	The findings suggest that the effect is connected with decreased metabolism in the cortex underlying the rTMS site, while facilitation of metabolism is propagated by transcallosal and intrahemispheric connections.	Small case series, focused on neuroimaging.
Hovington C, McGirr A, Lepage M et al. (2013) Repetitive transcranial magnetic stimulation (rTMS) for treating major depression and schizophrenia: a systematic review of recent meta-analyses. Annals of Medicine 45: 308–21	Systematic review n=5 meta-analyses on schizophrenia	The majority of meta-analyses support the efficacy of active rTMS over sham when applied to the temporo-parietal cortex in the context of auditory verbal hallucinations. Three of the 4 meta-analyses concluded efficacy of the therapy compared with sham.	A more recent review is included (Kennedy N et al., 2018).

Jandl M, Steyer J, Weber M et al. (2006) Treating auditory hallucinations by transcranial magnetic stimulation: a randomized controlled cross-over trial. Neuropsychobiology 53: 63-9	RCT n=16	Treatment responses were observed after left hemisphere rTMS only. The 5 patients who showed a response did so after 2 days. However, group mean hallucination scores did not differ across treatment conditions. No significant changes were found in EEG after rTMS.	Larger or more recent studies are included.
Kim E-J, Yeo S, Hwang I et al. (2014) Bilateral repetitive transcranial magnetic stimulation for auditory hallucinations in patients with schizophrenia: A randomized controlled, cross-over study. Clinical Psychopharmacology and Neuroscience 12: 222-228	RCT n=23	The findings suggest that bilateral rTMS at the temporoparietal area or Broca's area with high- or low-frequency does not produce superior effects in reducing AHs compared to sham stimulation.	Small RCT.
Kimura H, Kanahara N, Takase M et al. (2016) A randomized, sham-controlled study of high frequency rTMS for auditory hallucination in schizophrenia. Psychiatry Research 241: 190-4	RCT n=30	The present study's rTMS protocol was ineffective. However, several previous studies demonstrated that high-frequency rTMS is a possible strategy to ameliorate pharmacotherapy-resistant AVH.	Small RCT, which is included in review by Kennedy N et al., 2018.
Kindler J, Homan P, Flury R et al. (2013) Theta burst transcranial magnetic stimulation for the treatment of auditory verbal hallucinations: results of a randomized controlled study. Psychiatry Research 209: 114-7	RCT n=24	Theta burst TMS demonstrated equal clinical effects compared to 1Hz TMS.	Small RCT, comparing theta burst TMS with rTMS.
Kindler J, Homan P, Jann K et al. (2013) Reduced neuronal activity in language-related regions after transcranial magnetic stimulation therapy for auditory verbal hallucinations. Biological Psychiatry 73: 518-24	RCT n=30	TMS treated patients showed positive clinical effects, which were indicated by a reduction in AVH scores ($p \leq 0.001$). Cerebral blood flow was statistically significantly decreased in the primary auditory cortex ($p \leq 0.001$), left Broca's area ($p \leq 0.001$) and cingulate gyrus ($p \leq 0.001$).	Small RCT, focusing on the effect of rTMS on cerebral blood flow.
Klein E, Kolsky Y, Puyerovsky M et al. (1999) Right prefrontal slow repetitive transcranial magnetic stimulation in schizophrenia: a double-blind sham-controlled pilot study. Biological Psychiatry 46: 1451-4	RCT n=35	No serious adverse effects were reported; however, rTMS was not superior to sham treatment on any of the clinical ratings.	Small RCT, which is included in review by Kennedy N et al., 2018.
Klirova M, Horacek J, Novak T et al. (2013) Individualized rTMS neuronavigated according to regional brain metabolism (^{18}FGD PET) has better treatment effects on auditory hallucinations than standard positioning of rTMS: a double-blind, sham-controlled study. European Archives of	RCT n=10	The intention-to-treat analysis of AHRS score change revealed superiority of the ^{18}FDG PET-guided rTMS over both the standard and the sham rTMS. The analyses of the PANSS scores failed to detect significant difference among the treatments. Our data showed acute efficacy	Small RCT, which is included in review by Kennedy N et al., 2018.

Psychiatry and Clinical Neuroscience 263: 475-84		of ^{18}FDG PET-guided rTMS in the treatment of AHs. Neuronavigated rTMS was found to be more effective than standard, anatomically guided rTMS.	
Lai I-C, Yang CCH, Kuo TBJ et al. (2010) Transcranial magnetic stimulation for auditory hallucination in severe schizophrenia: partial efficacy and acute elevation of sympathetic modulation. Psychiatry and Clinical Neurosciences 64: 333-5	Case series n=8	Three patients reported a 50% or greater reduction of auditory hallucinations after rTMS. The ratio of low-frequency power to high-frequency power, an index of sympathetic modulation, increased significantly after rTMS.	Small case series.
Lee S-H, Kim W, Chung Y-C et al. (2005) A double blind study showing that two weeks of daily repetitive TMS over the left or right temporoparietal cortex reduces symptoms in patients with schizophrenia who are having treatment-refractory auditory hallucinations. Neuroscience Letters 376: 177-81	RCT n=39	The study suggests that 10 days of low-frequency rTMS applied daily for 20 min to either temporoparietal cortex significantly reduces the symptoms in patients with schizophrenia who are having refractory AH, but the left sided rTMS is not superior to right or sham rTMS.	Small RCT, which is included in review by Kennedy N et al., 2018.
Loo CK, Sainsbury K, Mitchell P et al. (2010) A sham-controlled trial of left and right temporal rTMS for the treatment of auditory hallucinations. Psychological Medicine 40: 541-6	RCT n=18	The study did not demonstrate an advantage for left temporal rTMS compared to right temporal and sham stimulation, over a 3-day stimulation period, but found modest improvement in hallucinations during continued open label treatment.	Small RCT.
Marzouk T, Winkelbeiner S, Azizi H et al. (2019) Transcranial magnetic stimulation for positive symptoms in schizophrenia: a systematic review. Neuropsychobiology DOI: 10.1159/000502148	Systematic review n=803 (active TMS)	Of the 30 studies included, 25 investigated auditory verbal hallucinations (AVH). In 12 studies, there was evidence for a positive treatment effect of TMS on positive symptoms. In the other 18 there was not enough evidence to conclude that TMS is effective for positive symptoms. However, the small sample size of most of the studies was a limiting factor.	The review did not include a meta-analysis.
Matheson SL, Green MJ, Loo C et al. (2010) Quality assessment and comparison of evidence for electroconvulsive therapy and repetitive transcranial magnetic stimulation for schizophrenia: a systematic meta-review. Schizophrenia Research 118: 201-10	Systematic meta-review 5 reviews	High quality evidence suggests a short-term, medium to large treatment effect of rTMS for auditory hallucinations (d=0.88).	A more recent review is included (Kennedy N et al., 2018).
McIntosh AM, Semple D, Tasker K et al. (2004) Transcranial magnetic stimulation for auditory	RCT n=16	Patients' hallucination scores improved from baseline with both real and sham TMS, and there was no statistically significant	Small RCT, which is included in review by

hallucinations in schizophrenia. Psychiatry Research 127: 9-17		difference between real and sham treatments.	Kennedy N et al., 2018.
Montagne-Larmurier A, Etard O, Maiza O et al. (2011) Repetitive transcranial magnetic stimulation in the treatment of auditory hallucinations in schizophrenic patients. Current Opinion in Psychiatry 24: 533-40	Review 15 studies	Using rTMS for auditory hallucinations currently seems less promising than it did 10 years ago because of the variable clinical effects.	A more recent review with most of the same studies is included (Kennedy N et al., 2018).
Montagne-Larmurier, A; Etard, O; Razafimandimby, A; et al. (2009) Two-day treatment of auditory hallucinations by high frequency rTMS guided by cerebral imaging: a 6 month follow-up pilot study. Schizophrenia Research 113: 77-83	Case series n=11 FU=6 months	A significant reduction in global severity and frequency of auditory hallucinations between baseline and post-treatment day 12 was observed. Auditory hallucinations were entirely relieved at 6-month follow-up in 2 patients. The treatment was well tolerated in all patients.	Small case series.
Nathou C, Etard O, Dollfus S (2019) Auditory verbal hallucinations in schizophrenia: Current perspectives in brain stimulation treatments. Neuropsychiatric Disease and Treatment 15: 2105-2117	Review	rTMS seems to be the most efficacious non-invasive brain stimulation to offer patients with persistent AVH as an add-on therapeutic strategy.	No meta-analysis.
Otani VHO, Shiozawa P, Cordeiro Q et al. (2015) A systematic review and meta-analysis of the use of repetitive transcranial magnetic stimulation for auditory hallucinations treatment in refractory schizophrenic patients. International Journal of Psychiatry in Clinical Practice 19: 228-32	Systematic review and meta-analysis n=246 10 studies	There was a positive sized effect in favour of rTMS [random-effects model Hedges' g=0.011, I^2=58]. There was some variability between study effect sizes, but the sensitivity analysis concluded that none of them had sufficient weight to singularly alter the results of the meta-analysis.	A more recent review is included (Kennedy N et al., 2018).
Paillere-Martinot M-L, Galinowski A, Plaze M et al. (2017) Active and placebo transcranial magnetic stimulation effects on external and internal auditory hallucinations of schizophrenia. Acta psychiatrica Scandinavica 135: 228-238	RCT n=28	A marked placebo effect of rTMS was observed in patients with resistant AVH. Patients with prominent external AVH may be more likely to benefit from both active and placebo interventions. Cortical effects related to non-magnetic stimulation of the auditory cortex are suggested.	Small RCT.
Poulet E, Brunelin J, Bediou B et al. (2005) Slow transcranial magnetic stimulation can rapidly reduce resistant auditory hallucinations in schizophrenia. Biological Psychiatry 57: 188-91	RCT n=10	AVH were robustly improved (56%) by 5 days active rTMS, whereas no variation was observed after sham. Seven patients were responders to active treatment, five of whom maintained improvement for at least 2 months.	Small RCT, which is included in review by Kennedy N et al., 2018.
Rachid F (2017) Safety and efficacy of theta-burst stimulation in the treatment of psychiatric disorders: a review of the	Review	Theta-burst stimulation (TBS) is a form of rTMS and is thought to induce more rapid and longer-lasting effects on synaptic plasticity than conventional rTMS	Descriptive review.

literature. The Journal of Nervous and Mental Disease 205: 823-839		protocols. Despite the fact that studies were heterogeneous in terms of design and results, some of them are promising mostly for treatment-resistant depression and auditory hallucinations. Future well-designed sham-controlled studies are needed to confirm the long-term safety and efficacy of TBS in the treatment of such conditions.	
Ray P, Sinha VK, Tikka SK (2015) Adjuvant low-frequency rTMS in treating auditory hallucinations in recent-onset schizophrenia: A randomized controlled study investigating the effect of high-frequency priming stimulation. Annals of General Psychiatry 14: 8	RCT n=40	Low-frequency rTMS alone and high-frequency priming of low-frequency rTMS do not elicit significant differences in treatment of overall psychopathology, particularly AVH when given in recent onset schizophrenia patients. Add on priming however, seems to have a faster reduction in loudness of AVH.	Small RCT, focusing on the effect of priming.
Rosa MO, Gattaz WF Rosa MA et al. (2007) Effects of repetitive transcranial magnetic stimulation on auditory hallucinations refractory to clozapine. The Journal of Clinical Psychiatry 68: 1528-32	RCT n=11	Active rTMS in association with clozapine can be administered safely to treat auditory hallucinations, although its clinical utility is still questionable. No significant clinical effects were observed in the sample studied, possibly because it was too small or because of its high refractoriness.	Small RCT, which is included in review by Kennedy N et al., 2018.
Rosenberg O, Gersner R, Klein LD et al. (2012) Deep transcranial magnetic stimulation add-on for the treatment of auditory hallucinations: A double-blind study. Annals of General Psychiatry 11: 13	RCT n=18	Auditory hallucination scores of both groups improved; however, there was no statistical difference in any of the scales between the active and the sham treated groups.	Small RCT, which is included in review by Kennedy N et al., 2018.
Rosenberg O, Roth Y, Kotler M et al. (2011) Deep transcranial magnetic stimulation for the treatment of auditory hallucinations: A preliminary open-label study. Annals of General Psychiatry 10: 3	Case series n=8	This preliminary study demonstrated an improvement in AHRS score (an average reduction of 32% +/- 32%) and to a lesser extent improvement in SAPS results (an average reduction of 17% +/- 20%).	Small case series.
Saba G, Verdon CM, Kalalou K et al. (2006) Transcranial magnetic stimulation in the treatment of schizophrenic symptoms: a double blind sham controlled study. Journal of Psychiatric Research 40: 147-52	RCT n=18	All patients were improved at the end of the trial but no statistically significant group differences were found. Patients receiving sham stimulation showed the same pattern of improvement compared to active condition on all the subscales of the positive and negative syndrome scale and clinical global impression scores (p>0.05).	Small RCT, which is included in review by Kennedy N et al., 2018.

Schonfeldt-Lecuona C, Gron G, Walter H et al. (2004) Stereotaxic rTMS for the treatment of auditory hallucinations in schizophrenia. Neuroreport 15: 1669-73	RCT n=12	rTMS did not lead to a significant reduction of hallucination severity.	Small RCT
Slotema CW, Blom JD, van Lutterveld R et al. (2014) Review of the efficacy of transcranial magnetic stimulation for auditory verbal hallucinations. Biological Psychiatry 76: 101-10	Review 19 studies	rTMS versus sham treatment for AVH yielded a mean weighted effect size of 0.44. For patients with medication-resistant AVH, the mean weighted effect size was 0.45. rTMS applied at the left temporoparietal area with a frequency of 1 Hz yielded a moderate mean weighted effect size of 0.63, indicating superiority of this paradigm. Various other paradigms failed to show superior effects. rTMS applied at the right temporoparietal area was not superior to sham treatment. rTMS, especially when applied at the left temporoparietal area with a frequency of 1 Hz, is effective for the treatment of AVH, including in patients with medication-resistant AVH. The results for other rTMS paradigms are disappointing thus far.	A more recent review with most of the same studies is included (Kennedy N et al., 2018).
Slotema CW, Blom JD, de Weijer AD et al. (2012) Priming does not enhance the efficacy of 1 Hertz repetitive transcranial magnetic stimulation for the treatment of auditory verbal hallucinations: results of a randomized controlled study. Brain Stimulation 5: 554-9	RCT n=23	The severity of AVH and other psychotic symptoms in the group with priming was not statistically significantly lower after 3 weeks of treatment in comparison to baseline. The group treated with standard rTMS showed a trend toward improvement after 3 weeks of treatment. No statistically significant differences were observed on any of the rating scales between the group with and without priming.	Small RCT, assessing the effect of priming.
Slotema CW, Aleman A, Daskalakis ZJ et al. (2012) Meta-analysis of repetitive transcranial magnetic stimulation in the treatment of auditory verbal hallucinations: update and effects after one month. Schizophrenia Research 142: 40-5	Meta-analysis 5 studies FU=1 month	The mean weighted effect size of rTMS directed at the left temporoparietal area was 0.44 (95% CI 0.19 to 0.68). A separate meta-analysis including studies directing rTMS at other brain regions revealed a mean weighted effect size of 0.33 (95% CI 0.17-0.50) in favour of real TMS. The effect of rTMS was no longer significant at one month of follow-up (mean weighted effect size=0.40, 95% CI −0.23 to 0.102). Side effects were mild and the number of dropouts in the real TMS group was not	A more recent review with most of the same studies is included (Kennedy N et al., 2018).

		significantly higher than in the sham group.	
Slotema CW, Blom JD, Hoek HW et al. (2010) 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. The Journal of Clinical Psychiatry 71: 873-84	Meta-analysis 7 studies on AVH	In the treatment of AVH, rTMS was superior to sham treatment, with a mean weighted effect size of 0.54 ($p<0.001$).	A more recent review with most of the same studies is included (Kennedy N et al., 2018).
Sommer IEC, de Weijer AD, Daalman K et al. (2007) Can fMRI-guidance improve the efficacy of rTMS treatment for auditory verbal hallucinations? Schizophrenia Research 93: 406-408	Case series n=12	The results of this study suggest that fMRI-guidance for rTMS treatment of AVH is feasible in most patients with frequent AVH. This may indicate that fMRI-guidance can improve efficacy of rTMS treatment, though replication in a larger sample is needed.	Small case series.
Subramanian P, Burhan A, Pallaveshi L et al. (2013) The experience of patients with schizophrenia treated with repetitive transcranial magnetic stimulation for auditory hallucinations. Case Reports in Psychiatry 2013: 183582	Case series n=4	All 4 participants noted some improvements in their well-being after treatment and none reported a worsening of their symptoms. Only 2 participants noted an improvement in the auditory hallucinations and only 1 of them reported an improvement that was sustained after treatment completion.	Small case series.
Tranulis C, Sepehry A, Galinowski Andre et al. (2008) Should we treat auditory hallucinations with repetitive transcranial magnetic stimulation? A metaanalysis. Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie 53: 577-86	Meta-analysis n=232 10 studies	Low-frequency rTMS over the left temporoparietal cortex has a medium effect size action on medication-resistant auditory hallucinations. This result has implications for understanding the pathophysiology of psychotic symptoms and supports the use of rTMS as a complementary treatment approach in patients suffering from treatment-resistant auditory hallucinations.	A more recent review with most of the same studies is included (Kennedy N et al., 2018).
van Lutterveld R, Koops S, Schutter DJLG et al. (2012) The effect of rTMS on auditory hallucinations: clues from an EEG-rTMS study. Schizophrenia Research 137: 174-9	Case series n=24	Stimulation of the temporoparietal cortices was not more effective in reducing AVH-severity than control-site stimulation. In addition, EEG-related power and connectivity measures were not affected differently across stimulation sites and changes in neuronal activity did not correlate with changes in AVH-severity.	Small case series.
Vercammen A, Knegtering H, Liemburg EJ et al. (2010) Functional connectivity of the temporo-parietal region in schizophrenia: effects of rTMS	RCT n=18	Application of 1 Hz rTMS to the left TPJ region may affect functional connectivity of the targeted region. However, the relationship between these	Small RCT, focusing on functioning connectivity.

treatment of auditory hallucinations. Journal of Psychiatric Research 44: 725-31		functional changes during the resting state and the rate of clinical improvement needs further clarification.	
Vercammen A, Knegtering H, Bruggeman R et al. (2009) Effects of bilateral repetitive transcranial magnetic stimulation on treatment resistant auditory-verbal hallucinations in schizophrenia: a randomized controlled trial. Schizophrenia Research 114: 172-9	RCT n=38	Compared to bilateral or sham stimulation, rTMS of the left temporo-parietal region appears most effective in reducing auditory hallucinations, and additionally may have an effect on general psychopathology. Placebo effects should however not be ruled out, since sham stimulation also led to improvement on a number of AVH parameters.	Small RCT, which is included in review by Kennedy N et al., 2018.
Zhang Y, Liang W, Yang S et al. (2013) Repetitive transcranial magnetic stimulation for hallucination in schizophrenia spectrum disorders: a meta-analysis. Neural Regeneration Research 8: 2666–76	Systematic review and meta-analysis n=398 (17 RCTs)	Overall mean weighted effect size for active rTMS versus sham stimulation was statistically significant (mean difference −0.42, 95% CI −0.64 to −0.20, p=0.0002). Patients who had active rTMS responded more frequently than those who had sham (OR 2.94, 95% CI 1.39 to 6.24, p=0.005). Compared with sham stimulation, active rTMS had equivocal outcome in cognitive function and commonly caused headache and facial muscle twitching.	A more recent review with most of the same studies is included (Kennedy N et al., 2018).