Transcranial Magnetic Stimulation (TMS) for Mental Illness

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Neuromodulation

• Use of magnets, electricity and ultrasound in the brain.
• TMS, microcurrents and ultrasound are below the threshold to cause seizures so there is no need for an anaesthetic.
• Magnetic energy can penetrate the skull and can be focussed to stimulate the brain so it should have few side effects.
• Electrical microcurrents e.g. cranial electrical stimulation or CES can be used at home safely
• Transcranial magnetic stimulation (TMS) discovered in 1985; CES in 1970s. TMS primarily used for depression.
• Currently a few but a growing number of NHS clinics in UK provide TMS but much private provision.
Vision

• Promising new popular, safe, effective magnetic, ultrasound and electric therapies whose mechanism of action is amenable to study using brain imaging such as MRI connectivity, MRI spectroscopy (GABA/glutamate), MEG and EEG.

• Personalise therapy to individual, condition, comorbidity - versatile.

• Predict who might respond to what e.g. biotypes, predictor of early response.

• Improve duration of clinical improvement and speed of action.

• Can combine with psychological and digital therapies.

• Can safely use in developing brains, improved or no change in cognition, can be used when other treatments can’t e.g. breast feeding
What is TMS?

- Application of powerful magnetic pulses to the scalp, generally to left dorsolateral prefrontal cortex (DLPFC) of the head (near temple)
- Figure of 8 coil
- Person is conscious, tries to relax
- Loud clicking noise (need earplugs)
- rTMS 45 minutes, TBS 20 minutes
- 16-20 daily sessions over 4 weeks for TRD
- Can drive or resume usual activities afterwards.
- Adverse effects – temporary headache sometimes, 1 in 10,000 cases syncope or seizure. No memory problems (may improve cognition).
- 96% complete 20 sessions.
TMS and neuronavigation
NICE appraisal of TMS for depression

• Safe, effective, few cognitive side-effects versus sham TMS.
• Cost effective compared to other treatments for depression especially in early treatment resistance (lack of response to 2 antidepressants).
• NICE approved all types of TMS for use for depression in the NHS (IPG 542, December 2015) but recommended research on new forms of its delivery.
• In 2016 16 RCTs, 510 TRD patients rTMS robustly effective vs sham TMS.
• However effectiveness is relatively short lived with standard rTMS without brain imaging improving 25% TRD patients for 3 months.
Adult major depression

- Mutz et al (2019). Network meta-analysis of effectiveness and acceptability of TMS and tDCS.
- 56 RCTs, n=3,051.
- Effective: high frequency rTMS over the left DLPFC (OR = 3.75, 95% CI [2.44; 5.75]), little heterogeneity, n=32 RCTs (relative hypoactivity of the left DLPFC and relative hyperactivity of the right DLPFC in depression).
- Right-sided low-frequency rTMS (OR = 7.44, 95%CI [2.06; 26.83])
- Bilateral rTMS (OR = 3.68,95%CI [1.66; 8.13]),
- Deep TMS (OR = 1.69, 95%CI [1.003; 2.85]),
- Intermittent TBS (OR = 4.70, 95%CI [1.14; 19.38])
- tDCS (OR = 4.17, 95% CI [2.25; 7.74]).
Repetitive Transcranial Magnetic Stimulation (rTMS) and Theta Burst Stimulation (TBS)

- iTBS = bursts of high and low frequency stimulation (3 pulses at 50 Hz) repeated at intervals of 200 ms. 3-10 minute treatment
- Inhibitory intermittent theta burst stimulation has long-term potentiation and plasticity far away from site of stimulation.
- iTBS>rTMS alters brain chemistry, ratio of inhibitory GABA to excitatory glutamate.
Theta Burst Stimulation in Depression

• Meta-analysis of 5 RCTs of TBS versus sham in 221 participants with TRD (Berlim et al, 2017).

• Unilateral iTBS to left DLPFC and unilateral iTBS to left DLPFC plus continuous TBS applied to right DLPFC both more effective than sham.

• Blumberger et al (2018) Lancet. 414 participants with TRD, 20 daily iTBS and rTMS equally effective on all outcomes and adverse effects at 1, 4, 6 and 12 weeks after 20 treatments to left DLPFC.

• Inhibitory TBS more focussed, delayed response, greater long-term potentiation in neurons: excitatory TBS, less focussed, faster.
TBS versus rTMS
Targets of TMS on brain circuits for depression

dlPFC – dorsolateral prefrontal cortex, mPFC medial prefrontal cortex, PCC posterior cingulate cortex, sgACC subgenual anterior cingulate gyrus

Anterior insula in salience network – heightened response to negative stimuli, influences sleep, modulates default mode network (rumination, low self-worth) and central executive network (emotional disinhibition, poor concentration/planning).
Economics, pros and cons

• TAU for treatment resistant depression costs approximately £4K per year with 15% response rate (Morriss et al, 2016).
• iTBS costs £786.30 per course with 30% response rate (Mendlowitz 2019)
• rTMS costs £1308.60 per course with 30% response rate.

• Pros – some patients will respond to TMS but not to other treatment or only with considerable adverse effects or medical risk. Popular.

• Cons – set up costs (machine £50-75K) plus staffing, requires skill, training and practice. Inconvenient for some.
Importance of sham or active control in TMS research

• Procedure of getting up each day at a similar time to attend TMS on a daily basis can be seen as a form of behavioural activation.
• Behavioural activation – typically one task per day that gives a sense of mastery or pleasure.
• Behavioural activation is a highly effective treatment for depression in its own right.
• Therefore high responses in case series may be highly misleading.
• Response rates in sham can be high so it is difficult to show a clinically important difference – need adequately powered RCTs.
Approaches to improve response rate or duration of response in adult depression.

- Accelerated TMS - 2-10 times per day (courses 10 to 5 days)
- Increasing the energy delivered.
- Adapt coil size to go deeper into brain.
- Use neuronavigation to stimulate exactly the same site- 5% better response.
- Vary the form of TMS.
- Personalise the site of TMS – use fMRI, EEG (at time of TMS)
- Personalise the course due to underlying condition.
- Evidence of each mostly from small case series rather than RCTs with a substantial sample size.
Accelerated TMS

• Williams et al (2018) 22 TRD – resting fMRI to select site based on maximum connectivity between left DLPFC and subcallosal cingulate, 10 x 3 minute iTBS with 50 minute breaks over 5 days. 76% response rate.

• Meta-analysis of 3 RCTs of accelerated iTBS or rTMS applied to left DLPFC more effective than sham (Sonmez et al, 2019).
BRIGhtMIND RCT

• Full title: Randomised double-blind controlled trial of connectivity guided theta burst transcranial magnetic stimulation versus repetitive transcranial magnetic stimulation for treatment resistant moderate to severe depression: evaluation of efficacy, cost effectiveness and mechanism of action.

• Funded by NIHR/MRC EME programme £2 million, NHS treatment costs and Magstim (equipment, maintenance, training).

• Aim – can personalised iTBS based on site of maximum connectivity between L-DLFPC and right anterior insula result in a longer duration of improvement in depression symptoms than standard rTMS at L-DLFPC.
Pilot RCT of fMRI guided cgiTBS versus non-fMRI rTMS

- Clinicaltrials, NCT02016456 : n=29, treatment resistant major depression, Nottingham only, HDRS-17 response (50% drop)
  - cgiTBS, 69% at 4 wks, 88% at 12 wks
  - rTMS, 56% at 4 wks, 44% at 12 wks

10% dropped out of TMS, 10% loss to follow up or scan
Baseline to 3 month change in depression symptoms (HDRS) after TMS associated with changes in functional connectivity and GABA.

- $r=0.57$, $p<0.05$ – also effective connectivity right anterior insula to left DLPFC

- $r=0.68$, $p<0.05$ – also BDI-1 cognitive symptoms of depression

- $r=0.63$, $p<0.05$
Comparison of TMS Treatment

TMS
Transcranial Magnetic Stimulation

• Standard Care Treatment
  Repetitive TMS (rTMS)
  • Standard site of stimulation on the scalp is determined with neuro navigation
  • Different stimulation pattern to cgiTBS

• Novel Treatment
  Connectivity Guided Intermittent Theta Burst (cgiTBS)
  • Site of Stimulation on the scalp determined using neuro navigation from the MRI scan.
  • Different stimulation pattern to rTMS

HDRS-17 change from baseline, 8, 16 and 26 weeks, n=266 TRD
Adolescent depression

• Croakin et al (2021). 103 adolescents (aged 12-21 with TRD) randomised to 30 daily rTMS or sham for 6 weeks.
• Mean (sd) drop in HDRS-24, 11.1 (2.03) for rTMS and 10.6 (2.00) for sham; p = 0.8; difference [95% CI], - 0.5 [-4.2 to 3.3].
• Response rates and remission rates also similar.
• rTMS is ineffective.
• No iTBS RCTs
Obsessive Compulsive Disorder

- NICE August 2020, no safety concerns but evidence of effectiveness insufficient in quantity and quality.
- Rehn et al (2018), meta-analysis of 18 RCTs comparing active rTMS versus sham TMS involving 484 patients.
- Active rTMS more effective than sham on Y-BOCS but high heterogeneity due to 2 RCTs. If removed active rTMS no more effective than sham.
- Carni et al (2019) active deep H7 coil versus sham, task induced obsessions while having TMS. 29 sessions in 99 participants (11 sites). Significant drop in Y-BOCS at end of treatment and 4 weeks (36% versus 11% response).
- 6 other small RCTs since Rehn et al (2018) – heterogenous results and TMS protocols.
Schizophrenia and non-affective psychosis

• Marzouk et al (2020). 23 RCTs. Just under half show some effect on positive symptoms, most consistently verbal auditory hallucinations.

• However, no consistency in site of stimulation, type of TMS, number or frequency of sessions so no conclusions can be drawn.
Other mental disorders

- **PTSD.** 9 RCTs, largest only 31 participants. No conclusion can be drawn on effectiveness (Harris and Reece, 2021).
- **GAD.** 3 RCTs (1 MDD and GAD) 25-36 sessions right DLPFC or bilateral rTMS versus sham, effect size 2.06 (95% CI 1.48, 2.64) (Cirillo et al, 2019)
- **Bipolar depression.** 1 RCT, inconclusive.
- **Psychotic depression.** rTMS less effective than non-psychotic depression.
- **Cognitive function.** Small effect of TMS on working memory (25 RCTs, n=875) across diagnostic groups. No effect on attention, executive function, processing speed, verbal fluency or verbal learning (Begemaan et al, 2020).
Other mental disorders

• **Autistic Spectrum Disorder.** 10 RCTs versus waiting list sham, all very small (largest n=25). Tolerated TMS. Moderate effects on social behaviour and stereotyped behaviours.

• **Alcohol craving.** 15 RCTs. No effect on alcohol craving or behaviour. Low quality, small in size, variable TMS protocols (Mostafasi et al, 2020).

• **Stimulant craving.** 12 RCTs. Significant effect on craving but high heterogeneity and low quality. rTMS applied to LDLPFC may be effective (Ma et al, 2019).

• **Suicidality.** 2 RCTs in 156 patients with depression and suicidal ideation (Weissman et al, 2018). High dose rTMS bilateral 40.4% remission of suicidal ideation vs 26.8% unilateral DLPFC, 18.8% sham.

• **Eating disorder.** 8 RCTs rTMS to left DLPFC and deep TMS versus sham reduces BMI, craving for food and energy intake. Unclear if related to depression and heterogeneity so findings are preliminary. Pilot work with other eating disorders only so inconclusive.
Conclusions

• Both rTMS and iTBS NICE approved with robust evidence of clinical effectiveness for depression and treatment resistant depression.
• Highly acceptable, safe. Of value to patients unable to tolerate or not responsive to other treatments.
• Cost saving in treatment resistant depression, especially theta burst.
• Various research approaches underway to increase duration of response and overall response rate.
• Evidence of small benefits in working memory in depression and some neurological disorder.
• Maybe effective in OCD but evidence not yet robust.
• Evidence inconclusive in other conditions, possibly effective in GAD, PTSD, stimulant use, obesity, treatment resistant auditory hallucinations, autism.