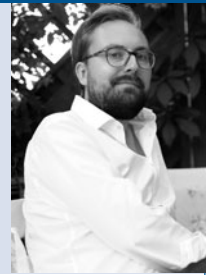


## Editorial

# Repetitive transcranial magnetic stimulation in non-treatment-resistant depression

Maximilian Kiebs, René Hurlmann and Julian Mutz



## Summary

Repetitive transcranial magnetic stimulation (rTMS) has been investigated as treatment for major depressive episodes since the early 1990s. Using data from a recent meta-analysis, we show that most patients included in randomised trials display relatively high degrees of treatment resistance. This might have unfavourably biased the clinical reputation of rTMS.

## Declaration of interests

M.K. has received a lecture fee from Innomed Medizintechnik in 2017 and 2018.

## Keywords

Transcranial magnetic stimulation; treatment resistance; depression; rTMS; medication-naive.

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**Maximilian Kiebs** (pictured) is pursuing a PhD concerning neuromodulation through non-invasive brain stimulation in depression and the prediction of undesired effects of electroconvulsive therapy at the Medical Psychology Department of the University Hospital Bonn. **Professor René Hurlmann** is Head of the Medical Psychology Division and Vice Head of the Psychiatry Department at the University Hospital Bonn with a focus on developing innovative neuromodulatory and neuroendocrine therapies. **Julian Mutz** is a doctoral researcher at the Institute of Psychiatry, Psychology & Neuroscience at King's College London. His research focuses on brain stimulation in mood disorders, evidence synthesis and prediction of healthy ageing.

Current treatment modalities for people with treatment-resistant depression include repetitive transcranial magnetic stimulation (rTMS). rTMS uses electromagnetic fields, generated by a coil that is placed over the patient's head, to depolarise superficial neurons which potentially leads to prolonged modulation of neural activity. Meta-analyses of randomised clinical trials support the antidepressant efficacy of rTMS and find the treatment to be generally well tolerated by patients, e.g.<sup>1</sup>. Common undesired effects are limited to transient headaches, dizziness and mild discomfort at the site of stimulation. Countries including Australia, Brazil, Canada, Israel and the USA have approved rTMS as second-line treatment for major depressive disorder (MDD), while others have included rTMS in their guidelines for good clinical practice (e.g. Finland, Germany, Serbia, UK). Initially thought of as a less-invasive alternative to electroconvulsive therapy, rTMS has been investigated primarily in people with treatment resistance. Staging models define levels of treatment resistance by the number of failed pharmacological interventions at adequate duration and dosage, with more failed antidepressant trials – which sometimes include class switching and augmentation – reflecting higher degrees of treatment resistance.

In a recent meta-analysis, we examined the antidepressant efficacy and acceptability of several non-invasive brain stimulation techniques for the treatment of unipolar and bipolar depression.<sup>2</sup> Of the 42 randomised sham-controlled trials ( $N = 1703$  patients) that investigated rTMS without co-initiation of another treatment, only three trials ( $n = 49$  patients) recruited exclusively patients who were not treatment resistant. To the best of our knowledge, no randomised controlled trial has investigated the antidepressant efficacy of rTMS without co-initiation of pharmacotherapy in patients with medication-naive and/or first-onset depression. This highlights an important gap in the literature.

The Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial, which enrolled 4041 outpatients with nonpsychotic

depression, has shown that remission rates decline with each successive treatment step. In STAR\*D, the first-line remission rate was 36.8% compared with 13% after the fourth treatment step. We found that only 5% of the studies ( $n = 41$  patients) that were included in our meta-analysis and reported on the level of treatment resistance used an inclusion criterion of at least one failed medication trial. The majority of trials (64%;  $n = 702$  patients) required participants to have failed at least two pharmacological treatments. Moreover, 33% of all participants included in this analysis stem from two trials that recruited patients with one to four failed antidepressant trials.

Given this empirical background, it seems evident that (a) there is a lack of trials investigating rTMS as a treatment for medication-naive nonpsychotic MDD and (b) that most studies to date primarily recruited patients with high degrees of treatment resistance, reflecting its historical roots as a potential therapeutic alternative to electroconvulsive therapy. This has unfavourably biased the clinical reputation of rTMS, leading many clinicians to believe that rTMS is a less powerful treatment modality for nonpsychotic MDD. Although the need for treatment alternatives in people with treatment resistance is considerable, it is also clear from our observations that the patient population included in randomised clinical trials of rTMS represents a group characterised by one of the most reliable clinical predictors of poor response to treatment: treatment resistance. Several studies have indicated lower degrees of treatment resistance to be a reliable predictor of increased response to rTMS, e.g.<sup>3</sup>. As some people do not tolerate pharmacotherapy due to undesired effects – including sexual dysfunction, weight gain and insomnia – we contend that trials with participants showing lower degrees of treatment resistance are needed. We also suggest that studies ought to investigate the comparative efficacy of rTMS and standard first-line pharmacological treatments, similar to the work comparing transcranial direct current stimulation with escitalopram.

Current barriers to a more widespread use of rTMS are the need for specialised equipment and infrastructure, associated costs, as well as the duration and labour intensity of treatment (typically administered 5 days a week for 4–6 weeks), with high-frequency rTMS requiring up to 37.5 min per treatment session. However, Blumberger *et al*<sup>4</sup> have recently shown in a large randomised trial including 414 participants that a 3 min theta-burst stimulation protocol is not statistically inferior to 37.5 min of high-frequency rTMS. This advance in reduced treatment duration could represent a key step in bringing non-invasive brain stimulation to a wider group of people with MDD. A more

widespread use of rTMS may be considered, especially for groups in which antidepressant pharmacodynamics may be cause for concern, e.g. during pregnancy or breastfeeding, in adolescents or in the context of somatic contraindications (e.g. pre-existing liver damage).

rTMS was first introduced in 1985 and studies in MDD have been conducted since the early 1990s, with rTMS receiving Food and Drug Administration approval for treatment-resistant depression in 2008. Although the decision to extend any treatment to a new patient population demands careful evaluation, findings to date suggest that rTMS has very few undesired effects. Moreover, although this finding cannot be extrapolated to treatment-naïve patients, evidence from health-economic modelling suggests that rTMS may be cost-effective compared to pharmacotherapy in a non-treatment-resistant population.<sup>5</sup> Since future research may facilitate the accessibility of rTMS through portable devices or community care providers, we conclude that it is important to conduct clinical trials that investigate rTMS in less treatment-resistant and/or medication-naïve patients with depression.

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## References

- 1 Mutz J, Vipulanathan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. *BMJ* 2019; **364**: l1079.
- 2 Mutz J, Edgcombe DR, Brunoni AR, Fu CHY. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: a systematic review and meta-analysis of randomised sham-controlled trials. *Neurosci Biobehav Rev* 2018; **92**: 291–303.
- 3 Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology* 2009; **34**: 522–34.
- 4 Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet* 2018; **391**: 1683–92.
- 5 Voigt J, Carpenter L, Leuchter A. Cost effectiveness analysis comparing repetitive transcranial magnetic stimulation to antidepressant medications after a first treatment failure for major depressive disorder in newly diagnosed patients – A lifetime analysis. *PLOS ONE* 2017; **12**: e0186950.