Journal of Affective Disorders 200 (2016) 6–14

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: A fast road to remission?

Romain Duprat [a,b,1], Stefanie Desmyter [a], De Raedt Rudi [c], Kees van Heeringen [a], Dirk Van den Abbeele [a], Hannelore Tandt [a], Jasmina Bakic [c], Gilles Pourtois [c], Josefien Dedoncker [a,b], Myriam Vervaet [a], Sara Van Autreve [a], Gilbert M.D. Lemmens [a], Chris Baeken [a,b,d,*,1]

[a] Department of Psychiatry and Medical Psychology, Ghent University, Ghent, Belgium
[b] Ghent Experimental Psychiatry (GHEP) Lab, Ghent University, Ghent, Belgium
[c] Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium
[d] Department of Psychiatry, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Laarbeeklaan 101, 1090 Brussels, Belgium

ARTICLE INFO

Article history:
Received 18 December 2015
Accepted 11 April 2016
Available online 19 April 2016

Keywords:
Accelerated rTMS
Intermittent theta-burst stimulation
Treatment resistance
Left DLPFC
Major depression

ABSTRACT

Although accelerated repetitive Transcranial Magnetic Stimulation (rTMS) paradigms and intermittent Theta-burst Stimulation (iTBS) may have the potency to result in superior clinical outcomes in Treatment Resistant Depression (TRD), accelerated iTBS treatment has not yet been studied. In this registered randomized double-blind sham-controlled crossover study, spread over four successive days, 50 TRD patients received 20 iTBS sessions applied to the left dorsolateral prefrontal cortex (DLPFC). The accelerated iTBS treatment procedure was found to be safe and resulted in immediate statistically significant decreases in depressive symptoms regardless of order/type of stimulation (real/sham). While only 28% of the patients showed a 50% reduction of their initial Hamilton Depression Rating Scale score at the end of the two-week procedure, this response rate increased to 38% when assessed two weeks after the end of the sham-controlled iTBS protocol, indicating delayed clinical effects. Importantly, 30% of the responders were considered in clinical remission. We found no demographic predictors for response. Our findings indicate that only four days of accelerated iTBS treatment applied to the left DLPFC in TRD may lead to meaningful clinical responses within two weeks post stimulation.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is currently an evidence-based and accepted treatment option to treat patients suffering from Major Depressive Disorder (MDD) (Lefaucheur et al., 2014). Since two decades, evidence of supremacy of rTMS over placebo stimulation is accumulating, and the most compelling data have been provided by large, multisite, and randomized sham-controlled trials including pharmacotherapy resisting MDD patients (O'Reardon et al., 2007; George et al., 2010). On the other hand, the effects sizes are rather limited and remission rates are relatively small (De Raedt et al., 2015). Comparing classical HF-rTMS treatment to sham, applying daily rTMS sessions averagely over 2–4 weeks, shows moderate effect sizes on depressive symptoms of 0.39 (Schutter, 2009) or 0.55 (Slotema et al., 2010), depending on the meta-analysis. Generally, for left high frequency (HF) rTMS this yields an average rate of 29% responders in the active condition and 10% for sham (Berlim et al., 2014). Although the average rate of responders patients receiving active and sham right low frequency (LF) rTMS was respectively 38% and 15% in another meta-analysis (Berlim et al., 2013a), left HF-rTMS only received an A level of evidence in recent guidelines on the therapeutic use of rTMS (Lefaucheur et al., 2014). Notwithstanding that no meta-analyses have been carried out yet for accelerated designs (given the limited amount of available accelerated HF-rTMS data), in a recent open – label study response rate was 43%, with 29% remission immediately following treatment (15 sessions administered over 2 days) (Holtzheimer et al., 2010), and 35% response and 15% remission after a placebo-controlled HF-rTMS crossover study (Baeken et al., 2013). Of note, as treatment resistant depression (TRD) may not be the primary indication for rTMS treatment and may negatively influence the clinical outcome (George and Post, 2011), it is important to mention that these patients were not all treatment resistant.

The optimization in stimulation parameters, using more

* Correspondence to: Department of Psychiatry and Medical Psychology Ghent University, De Pintelaan 185 – 9000, Ghent, Belgium.
E-mail address: chris.baeken@UGent.be (C. Baeken).
[1] Equally contributing authors.

http://dx.doi.org/10.1016/j.jad.2016.04.015
0165-0327/

accurate methods to localize the stimulation area (Gershon et al., 2003; Fitzgerald et al., 2009; Levkovitz et al., 2015), and also introducing intensified or accelerated rTMS treatment algorithms have been evaluated to increase clinical responses, but seem to produce similar response rates (Baeken et al., 2013). For the latter, instead of the usually applied daily sessions, spread over two – to four weeks, accelerated stimulation protocols significantly reduce the time-period of stimulation. In sum, accelerated HF-rTMS treatment protocols in MDD may be able to yield clinical improvements similar to the classic treatment protocols, but within a significant shorter amount of time.

Recently, a new form of rTMS has been introduced, i.e. theta-burst stimulation (TBS), thought to produce similar if not greater effects on brain activity than standard rTMS protocols. Recent data indeed suggest that TBS has similar or superior clinical efficacy in treating MDD when compared to rTMS (Di Lazzaro et al., 2011; Chung et al., 2015; Prasser et al., 2015). Reduced administration duration may be a major advantage of TBS when compared to conventional rTMS procedures. Conventional TMS sessions may last between 20 and 45 min, while TBS paradigms may require less than 5 min of stimulation (Chung et al., 2015). Intermittent theta-burst stimulation (iTBS) uses bursts of high frequency stimulation at repeated intervals, usually on a 2 seconds on/8 seconds off cycle applying 50 Hz triplet bursts five times per second (Di Lazzaro et al., 2008; Bakker et al., 2015). Similar to HF-rTMS, iTBS may have excitatory effects on neurons, possibly matching or and exceeding the more classical HF-rTMS paradigms in antidepressant effectiveness (Di Lazzaro et al., 2011; Oberman et al., 2011; Bakker et al., 2015). Neurophysiological data suggest that iTBS affects cortical and subcortical neuroplasticity via long-term potentiation (Huang et al., 2005; Chistyakov et al., 2010). In theory, it may thus be possible that the strongest antidepressant effects may have a delayed onset. Interestingly, it has been suggested that TBS, at least the continuous form (cTBS), with effects comparable to the low frequency application of rTMS, may obey a dose-response function, suggesting that higher numbers of delivered stimuli may be needed to optimize clinical outcomes in MDD patients (Chistyakov et al., 2010). On the other hand, it has to be noted that the excitatory effects of iTBS may not be that straightforward, as prolonged iTBS sessions applied to the motor cortex in healthy individuals may result in inhibitory effects rather than excitation (Gamboa et al., 2010), although dose-dependent effects resulting in neuronal excitation have been reported as well (Nettekoven et al., 2014). Although at this stage no firm conclusion can be drawn, the effects of iTBS treatment may result in an even better clinical outcome than cTBS or rTMS (Li et al., 2014).

Building further on our previous studies of accelerated HF-rTMS (Baeken et al., 2013), the current crossover study aimed at investigating whether an accelerated iTBS treatment protocol (sham-controlled) could result in fast and meaningful beneficial clinical effects in a group of TRD patients. Because we wanted not only to include 'last resort' TRD patients, all patients were considered at least stage I treatment resistant (Rush et al., 2003). To evaluate the immediate influences of iTBS, mood was assessed daily. To evaluate delayed clinical effects, all patients were assessed two weeks after the end of the (two week) protocol. Patients were randomized to receive in the first week either 20 real or sham iTBS sessions (5 sessions/day), delivering a fixed amount of pulses amounting in total 32.400 stimuli over 4 days' time (1620 pulses per session). The choice for the prolonged iTBS parameters within a stimulation session was based on the rationale of delivering a similar amount of pulses - as we performed in our former accelerated HF-rTMS study (Baeken et al., 2013)-in order to compare the two neurostimulation protocols for clinical outcome, rather than examining the inhibitory or excitatory effects of prolonged iTBS.

We hypothesized that the application of this accelerated iTBS protocol would result in fast and meaningful clinical outcomes, especially so after the real when compared to the sham iTBS treatment sessions. Secondly, during the real iTBS sessions, we expected to detect significant mood improvements even before the end of the 4-day stimulation protocol. Thirdly, given the possible large-scale neuroplasticity effects induced by iTBS, we expected that beneficial clinical changes brought about by iTBS would survive and possibly even increase two weeks after the end of the treatment.

2. Methods and materials

This registered study (http://clinicaltrials.gov/show/NCT01832805) was approved by the local Ghent University Hospital ethics committee and in accordance with the declaration of Helsinki (2004). All patients gave written informed consent. This study was part of a larger project investigating the influence of iTBS on neuro-cognitive markers.[2]

2.1. TRD patients

Fifty right-handed antidepressant-free depressed patients (35 females), age 42 years (SD = 12), were included in the iTBS study.[3] Depression was diagnosed using the structured Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). All patients were at least stage I treatment resistant: they had a minimum of one unsuccessful treatment trial with serotonin reuptake inhibitors/ noradrenaline or serotonin reuptake inhibitors (SSRI/ NSRI). For details see Table 1. Exclusion criteria were current or past history of epilepsy, neurosurgical interventions, having a pacemaker or metal or magnetic objects in the brain, having had electroconvulsive therapy (ECT), alcohol dependence and suicide attempts occurring within 6 months before the start of the study. Bipolar and psychotic depressed patients were excluded. Because concomitant antidepressant treatment can confound outcome results, all patients went through a medication washout before entering the study. All TRD patients were free from any antidepressant (AD), neuroleptic and mood stabilizer for at least two weeks before entering the iTBS treatment protocol. As proposed by Fitzgerald and Daskalakis (2012), only habitual benzodiazepine agents were allowed. In practice, the benzodiazepines were mostly prescribed as sleeping medication. The maximum allowed dose of benzodiazepines was the equivalent of 40 mg diazepam. These benzodiazepines equivalent doses are described by the British National Formulary (No. 66, London: British Medical Association and Royal Pharmaceutical Society of Great Britain; September 2013, pp. 218–226). Any changes in benzodiazepine treatment during the stimulation sessions resulted in dropout from the

[2] Part of this data set, including 22 TRD patients, was also used in a conference paper reporting preliminary results on the effects of accelerated iTBS on suicidal ideation (Desmyter et al., 2014). Because of the specific literature concerning suicide, the complete results of this iTBS protocol on suicidal ideation will be published elsewhere.

[3] Given that an estimation of the expected effect size is necessary to calculate the power and that there are currently no studies available on which we can rely to estimate the effect size, we started from the assumption that we would be able to find a clinically meaningful medium effect size, which corresponds to f = .25 in an ANOVA (corresponds to d = .50). For the parallel design part of our study with within-between interaction to observe the effects at week one (2 pre-post X 2 sham-real), with our total sample of 47 patients and the α error probability set at 0.05, the power to find an effect was.92 (calculated with G-Power 3.1.9.2.), which is very high. Even when we are very conservative and start from the meta-analysis of Schutter (2009) based on a regular rTMS intervention (as compared to our accelerated design with iTBS), in which a mean effect size d = .39 was found (which corresponds to an f of.195 in ANOVA), the power of our study was 0.74.

Table 1
Demographic data and individual rating scores of the 17-item Hamilton Depression Rating Scale (HDRS), the Beck Depression Inventory (BDI). F: Female. M: Male. rMT: resting Motor Threshold. R > S: First real iTBS, then sham iTBS. * Two patients were considered Stage IV (unsuccessful trial with MAO-I), but were included in the stage III group. ** Based on 44 patients. Clinical response is defined as a 50% decrease of the initial 17-item HDRS score. Clinical remission is defined as a score on the 17-item HDRS ≤ 7 post treatment. Where appropriate *F*, *T* or X^2 tests were used to indicate group differences. The p-values with significance level were set at $p < 0.05$, two-tailed.

	All	Stage I	Stage II	Stage III		Responder	Non-responder	
					p-values			*p*-values
Number *	47	9	24	14		18	29	
Gender (F/M)	33/14	8/1	19/5	6/8	**0.02**	14/4	19/10	0.37
Age	41.72 (11.80)	40.89 (11.54)	37.88 (11.33)	48.86 (10.05)	**0.02**	40.41 (12.18)	43.83 (11.19)	0.34
Duration current depressive episode (years)**	3.87 (6.08)	1.26 (1.12)	3.17 (3.36)	2.62 (2.49)	0.87	3.46 (3.19)	2.17 (2.64)	0.16
Number depressive episodes	3.15 (2.65)	3.22 (2.99)	2.75 (2.31)	3.79 (3.02)	0.27	3.00 (2.43)	3.24 (2.81)	0.81
Stage (I/II/III)	9/24/14	–	–	–	–	5/9/4	4/15/10	0.43
Hospitalized patients	13	3	8	2	0.41	4	8	0.51
Melancholic depression	31	7	13	11	0.22	13	18	0.48
Order (R > S)	22	7	12	3	**0.03**	8	14	0.80
Benzodiazepine intake (number)	15	2	7	6	0.54	5	10	0.63
Benzodiazepine intake (mg/day)	5.41 (9.70)	2.78 (6.67)	4.38 (10.03)	9.15 (10.38)	0.31	2.65 (5.63)	7.04 (11.21)	0.35
rMT (%)	59.17 (8.18)	58.00 (9.79)	59.29 (8.23)	59.71 (7.54)	0.89	59.06 (7.97)	59.24 (8.45)	0.94
HDRS T_1	21.34 (5.26)	17.33 (4.87)	21.71 (5.15)	23.29 (5.89)	**0.04**	21.28 (5.10)	21.38 (6.00)	0.95
HDRS T_2	17.72 (6.63)	15.78 (7.36)	17.33 (4.98)	19.64 (6.69)	0.30	15.72 (6.24)	18.97 (5.65)	0.07
HDRS T_3	14.72 (6.03)	12.00 (5.94)	14.88 (6.31)	16.21 (7.47)	0.33	10.28 (4.42)	17.48 (6.31)	< **0.01**
HDRS T_4	12.87 (7.41)	8.44 (4.80)	13.30 (7.26)	15.15 (8.28)	0.07	6.50 (2.33)	17.10 (6.49)	< **0.01**
BDI T_1	30.96 (8.95)	35.11 (6.90)	29.30 (9.56)	31.00 (8.73)	0.26	32.11 (8.80)	30.19 (9.12)	0.49
BDI T_2	27.64 (10.80)	28.00 (12.00)	26.82 (10.67)	28.77 (10.96)	0.88	28.12 (12.23)	27.33 (10.03)	0.82
BDI T_3	24.38 (11.41)	28.50 (11.34)	21.09 (11.07)	27.43 (11.14)	0.14	19.11 (10.57)	27.89 (10.73)	**0.01**
BDI T_4	21.25 (11.11)	19.13 (11.49)	20.00 (11.72)	24.43 (9.94)	0.38	14.11 (10.10)	25.46 (9.05)	< **0.01**
Responder T_3	12	3	7	2	0.67	–	–	–
Responder T_4	19	5	10	4	0.43	–	–	–
Remission T_3	6	2	3	1	0.58	–	–	–
Remission T_4	14	4	6	4	0.44	–	–	–

study. For the record, no patients dropped-out according this criterion.

Because of a severe suicide attempt (overdose of medication) in the weekend after one week of stimulation (sham iTBS), one female patient was considered dropout from the study. One male patient erroneously received two times real stimulation. Although he was responder at T_2 and remitter at T_4, we did not include his data into the final analyses. Finally, after inclusion, one female patient spontaneously improved after her AD washout and it was decided not to start the stimulation protocol and no follow-up data were collected.

2.2. Stimulation protocol

Intermittent TBS stimulation was applied using a Magstim Rapid[2] Plus[1] magnetic stimulator (Magstim Company Limited, Wales, UK) with a figure-of eight-shaped coil. The Brainsight neuronavigation system (Brainsight™, Rogue Resolutions, Inc) was used to identify the site of stimulation ((i.e., the center part of the midprefrontal gyrus [Brodmann 9/46]) based on structural MRI of each individual in order to accurately target the left DLPFC. Before the first session, the resting motor threshold (rMT) of each individual was determined using surface electromyography. Given the dose-dependency effect (Chistyakov et al., 2010), a stimulation intensity of 110% of the subject's rMT of the right abductor pollicis brevis muscle was used and this MT was maintained throughout

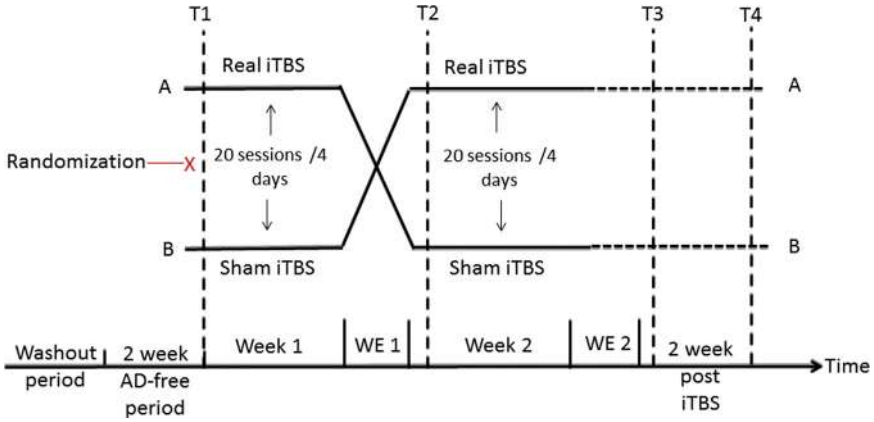

Fig. 1. Flow chart of the experimental iTBS treatment procedure. After a washout period, all patients are at least two weeks antidepressant (AD) free before they are randomized to receive real or sham iTBS treatment respectively. Baseline measurements were assessed at T_1 (on Monday afternoon) before the first week of iTBS treatment. iTBS treatment is spread over the four succeeding afternoons (5 daily sessions on Tuesday, Wednesday, Thursday and Friday). In the second week, strictly the same treatment schedule is followed but with a change of stimulation: line AB=a TRD patient who first received real iTBS now receives sham; line BA=a patient who first received sham treatment now receives real iTBS. A second assessment day is performed exactly 1 week after the first week (time T_2) and a third time exactly after 2 weeks (time T_3), always on a Monday afternoon. No stimulation or assessment was performed during the weekend (WE). Two weeks after finishing the real iTBS week at T_4 all measurements were reassessed.

the experimental procedure. The treatment protocol consisting of in total 20 iTBS sessions was spread over 4 days at five sessions per day, mounting a total of 32.400 stimuli. See Fig. 1. In each session, patients received 1620 pulses per session in 54 triplet bursts with train duration of 2 seconds and an intertrain interval of 8 seconds. For the sham condition, a specially designed sham coil identical to the real coil was placed exactly on the same target/anatomical location in the same position, but without any active stimulation. Throughout the whole iTBS treatment (real and sham), patients were blindfolded, wore earplugs and were kept unaware of the type of stimulation they received. Between two sessions, there was a pause of approximately 15 min.

2.3. Clinical assessment

To assess the short-term clinical effects of the sham-controlled iTBS treatment protocol three strategies were followed.

First, to evaluate the effects of iTBS on (negative) mood after each week of stimulation, depression severity was assessed with the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) by a certified psychiatrist, blinded to the actual treatment of the patient. After the initial assessment at baseline (T_1), patients were randomized (flipping a coin) to receive in the first week either real or sham iTBS delivered on the left DLPFC. All patients were re-assessed after 1 week of real or sham treatment (T_2) and at the end of the second week of the stimulation protocol (T_3). Following standard practice, we defined clinical response as a 50% reduction of the baseline HDRS score. At each of these time points patients were also asked to score themselves on depressive symptoms with the Beck Depression Inventory (BDI-I; Beck et al., 1961) assessing how they felt over the previous week. To evaluate possible delayed clinical effects of accelerated iTBS, patients were reassessed two weeks after end of the protocol (T_4). See Fig. 1. Within the two-week period, with the exception of the current benzodiazepine intake at steady dose, patients were psychotropic free and any change was considered as drop out of the study.

Secondly, to detect acute changes on depression severity symptoms over 24 h on a daily basis we used an adapted version of the BDI-I so that patients scored themselves on depression symptoms over the last 24 h. This BDI-I 24 h was filled in before the start of each stimulation day (before the 5 iTBS sessions).

Thirdly, to evaluate immediate changes in mood on a daily basis, within the same day directly before and after each of the five daily iTBS sessions, mood ratings were administered using seven visual analogue scales (VAS) providing measures of fatigue, power, anger, cheerfulness, tension, depression, and happiness (McCormack et al., 1988). Patients were asked to describe from "totally not" to "very much" how they felt "at that moment" using 10 cm horizontal lines for each of the abovementioned mood states.

3. Statistical analyses

All collected data were analyzed with SPSS 22 (Statistical Package for the Social Sciences; IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY). Whenever the assumption of sphericity was violated, we applied the Greenhouse-Geisser correction. The significance level was set at $p < 0.05$, two-tailed, for all analyses. Given the intention-to-treat protocol all analyses were completed by a last observation carry forward approach (LOCF) when applicable. See also Table 1.

First, to examine the clinical effects of accelerated iTBS treatment on a weekly basis, we performed a mixed 2×4 ANOVA with the depression severity scores (HDRS) at the 4 different clinical assessments as the dependent variable, and Time (T_1 at baseline; T_2 after the first week of stimulation; T_3 after the second week of stimulation, and T_4 two weeks after the end of the stimulation protocol) and Order (first sham then real vs. first real then sham) as between-subjects factors. To follow-up significant interaction effects, we anticipated to use separate Time (baseline; after stimulation) X Stimulation (real; sham) mixed ANOVA's separately for week 1 and 2 separately, followed by *T*-tests. A similar approach was performed with the BDI-I, indicating how they felt over the last week.

Secondly, to evaluate the impact of 5 iTBS sessions over 24 h, a mixed $2 \times 2 \times 4$ ANOVA was performed with an adapted version of the BDI-I over 24 h depression severity scores (BDI-I 24 h) assessed at the start of the 4 different stimulation days as dependent variable. Week (week 1 vs. week 2) and Day (T_1 day one; T_2 day two; T_3 day three; T_4 day four) were the within-subjects factors and Order (first sham then real vs. first real then sham iTBS) the between-subjects factor. This was also followed by *T*-tests to further examine significant effects.

Thirdly, to examine whether the daily iTBS sessions affected mood without any delay, when mood was measured with VAS, mood changes were analyzed with a mixed $2 \times 2 \times 4$ MANOVA. Within-subject factors were Week (week 1 vs. week 2) and Day (T_1, T_2, T_3 and T_4). The between subjects factor was Order (first real then sham vs. first sham then real iTBS). Significant results would be followed-up by *T*-tests. The seven VAS mood scales were the multiple dependent variables. On every stimulation day before and after each individual session every VAS subscale was assessed 6 times. For each stimulation day, mean values were calculated for each VAS subscale separately at T_1, T_2, T_3, and T_4.

Fourthly, to examine whether demographic and individual physiological data predicted clinical outcome we used two approaches. 1) With a categorical approach (only with the 17-item HDRS), we wanted to identify baseline group differences between responders and non-responders (clinical response defined as a 50% reduction of the baseline HDRS score) at T_4 at the end of the entire iTBS protocol (2 weeks after T_3). We ran separate analyses for Gender (dichotomous), age, duration of the current depressive episode (years), subtype of depression diagnosis (melancholic/non-melancholic), level of treatment-resistance (Stage I, II, and III), and individual differences in motor threshold. When appropriate, we applied independent *T* or X^2 tests with the same variables (See also Table 1). 2) To substantiate the relationship between changes in depressive symptoms and individual features we used stepwise linear regression analysis (probability-of-*F*-to-enter ≤ 0.05, probability-of-*F*-to-remove ≥ 0.10), adopting a continuous approach with HDRS change scores. We calculated the clinical change as delta HDRS (HDRS scores at baseline T_1 – HDRS scores two weeks after the procedure (T_4)). Then, we used this score as dependent variable. Gender (dichotomous), age, duration of the current depressive episode and individual differences in motor threshold were the independent predictors. A similar approach was performed with the delta BDI-I.

4. Results

Although the iTBS treatment was found to be safe and generally well tolerated, a majority of patients, especially at the start of the first session, mentioned some discomfort such as superficial pain sensations at the stimulation site, or headache. These complaints spontaneously disappeared after a short period of time or shortly after the intake of a common analgesic such as paracetamol.

Given the three drop-out patients, we performed all analyses on the remaining 47 patients. Twenty-five participants first received sham then real iTBS treatment during the second week, while 22 TRD patients had the opposite order. Mean HDRS scores before entering the study at baseline (T_1) were 21.34 (SD = 5.26),

indicating moderate to severe depression. Demographic and clinical characteristics of the patients are summarized in Table 1.

According to the definition of clinical response, from the 47 included patients at the end of the two-week study protocol (T_3) 13 were identified as clinical responders (28%), with only 7 in remission (15%) defined as a 17-item HDRS (score ≤ 7). However, two weeks after the iTBS trial (T_4) the amount of clinical responders (n=18) increased to 38%. Fourteen patients were considered in remission at T_4 (30%).

From the 22 patients who received real iTBS in the first week, 4 were considered to be in response at T_2 (18%). Convinced of having had real stimulation, only one Stage II female patient out of 25 (4%) responded to the first week of placebo iTBS (HDRS from T_1: 24 to T_2: 10) and further reaching remission at T_3 (HDRS: 7) and at T_4 (HDRS: 7). Four patients responded after the second week of real iTBS, and another 3 after the second week of sham treatment. Two male patients who responded after real iTBS at T_2 were above the 50% response threshold again at T_3 and remained at these scores at T_4, and did not meet the criteria for clinical response. One female patient was considered responder after the second week of stimulation (real iTBS, HDRS: 10), but 2 weeks later at T_4 she was clinically depressed again (HDRS: 23). All other patients who responded at T_3 remained responder or were remission at T_4.

Although baseline HDRS and BDI-I were not correlated $r=0.24$, n=47, $p=0.11$, the clinical changes (Δ HDRS, Δ BDI-I) after the two week iTBS procedure were significantly correlated: at T_3 (HDRS T_3-HDRS T_1 and BDI-I T_3 – BDI-I T_1) $r=0.67$, n=44, $p<0.01$ and at T_4 (HDRS T_4-HDRS T_1 and BDI-I T_4 – BDI-I T_1) $r=0.69$, n=43, $p<0.01$. Due to some missing BDI-I values, the number of included patients varied across time points. A LOCF approach including 45 patients did not influence this outcome.

4.1. Clinical effects of accelerated iTBS treatment on depression severity on a weekly basis

The 4 (Time) x 2 (Order) ANOVA with the HDRS scores as dependent variable showed a significant main effect of Time $F(3, 41)=23.57$, $p<0.01$, but not of Order $F(1, 43)=0.54$, $p=0.47$. Importantly, the two-way interaction between Time and Order was not significant $F(3, 41)=1.36$, $p=0.27$, suggesting that the order of stimulation had little to no impact on clinical improvements as a function of time. The significant main effect of time showed linear decreases on the 17-item HDRS scores over time, suggesting that the accelerated iTBS procedure, regardless whether it was real or sham, was associated with significant improvement regarding depression severity. See Fig. 2. Using the individual BDI-I scores as dependent variable, a similar outcome was evidenced: a significant main effect of Time $F(3, 38)=10.36$, $p<0.01$, but not of Order $F(1, 40)=0.01$, $p=0.93$ and no significant two-way interaction between these two factors was observed $F(3, 38)=0.88$, $p=0.46$. Due to missing data, 42 TRD patients were included (22 received first real). A LOCF analysis including 45 patients (22 received first real) did not influence this outcome. Of note, when performing a 2 (Time: pre/post) x 2 (Intervention: real/sham) ANOVA, to examine the effects of one week of real and one week of sham iTBS, but this time between subjects, again we observed a significant main effect of Time $F(1, 45)=19.14$, $p<0.01$, not of Order $F(1, 45)=1.05$, $p=0.31$ and not for the two-way interaction between Time and Order $F(1, 45)=1.79$, $p=0.19$. A similar outcome we found with the BDI-I.

4.2. Clinical effects of accelerated iTBS treatment on depression severity over 24 h

To evaluate the iTBS clinical effects over 24 h (BDI-I 24 h) the mixed ANOVA with Week (week 1 vs. week 2) and Day (T_1 day one; T_2 day two; T_3 day three; T_4 day four) as within-subjects factors and Order (first sham then real vs. first real then sham) as between-subjects factor, showed a main effect of Week $F(1, 40)=5.04$, $p=0.03$, and Day $F(3, 120)=2.88$, $p=0.04$ but not of Order $F(1, 40)=0.33$, $p=0.57$. The two-way interactions between Week and Order $F(1, 40)=0.12$, $p=0.73$, between Day and Order $F(3, 120)=2.36$, $p=0.08$, and between Week and Time were not significant $F(3, 120)=0.77$, $p=0.51$. The three-way interaction between Week, Day, and Order was not significant either, $F(3, 120)=0.46$, $p=0.71$. Due to missing data, 42 TRD patients were included (22 received first real). A LOCF approach with 43 patients (22 received first real) did not influence this outcome. Paired T-tests (LOCF) did not show significant differences between the 2 different week and days ($p's > 0.05$).

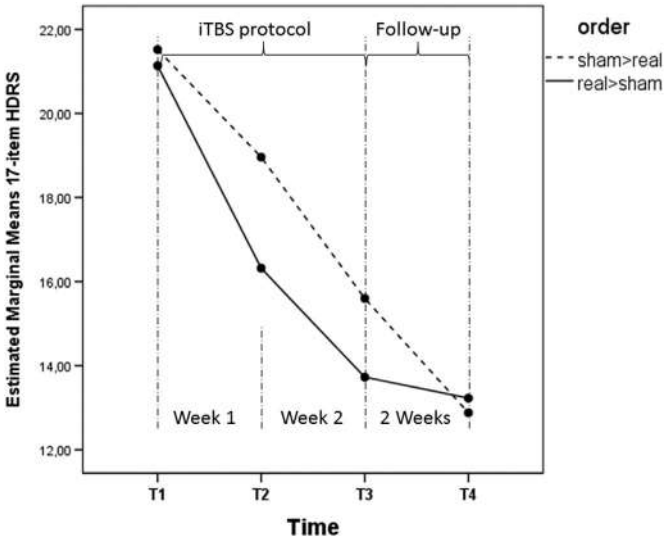

Fig. 2. Graphical representation of the 2×4 ANOVA with Time (HDRS scores at baseline (T_1), after one week (T_2) and two weeks of stimulation (T_3), and 2 weeks after the end of the treatment protocol (T_4)) as within-subjects factor and Order (first sham then real vs. first real then sham) as between-subjects factors.

4.3. Immediate daily clinical effects of accelerated iTBS treatment on mood

The mixed MANOVA evaluating the immediate iTBS effects on mood (VAS) showed a marginal significant main effect of Week $F(7, 36)=2.04$, $p=0.08$, but no significant main effect of Day $F(21, 366)=0.81$, $p=0.71$ or of Order $F(7, 36)=0.76$, $p=0.62$. The interaction effects between Week and Order $F(7, 36)=0.76$, $p=0.62$, between Day and Order $F(21, 366)=0.42$, $p=0.99$, and between Week and Day $F(21, 366)=1.23$, $p=0.22$ were not significant either. Furthermore, the interaction effect between Week, Day and Order was not significant $F(21, 366)=1.11$, $p=0.33$. See Table 2. Of note, mixed ANOVAs performed for each VAS subscale separately did not show any significant effects, neither real nor sham iTBS therapy.

4.4. Demographic influences on clinical outcome of accelerated iTBS treatment

For the categorical approach, Pearson Chi-Square tests showed no significant association between responders/non-responders and Gender $X^2(47)=0.80$, $p=0.37$, Order $X^2(47)=0.07$, $p=0.80$, hospitalization/ ambulatory treatment $X^2(47)=0.43$, $p=0.51$, benzodiazepine intake (yes/no) $X^2(47)=0.23$, $p=0.63$, type of depression (melancholic/non-melancholic) $X^2(47)=0.51$, $p=0.48$, or Staging (I, II, III) $X^2(47)=1.70$, $p=0.43$.

Table 2
Mean ratings and standard deviations for the BDI-I assessed every day before iTBS stimulation (BDI-I 24 h) and the visual analogue (VAS) subscales assessed just before and just after each stimulation session.

Daily assessment		**Sham > Real**				**Real > Sham**			
Week 1		**T_1**	**T_2**	**T_3**	**T_4**	**T_1**	**T_2**	**T_3**	**T_4**
BDI-I 24 h		28.18 (9.42)	27.57 (9.30)	27.70 (10.95)	28.70 (11.42)	28.46 (7.90)	26.41 (7.82)	27.19 (7.76)	27.41 (10.38)
VAS	*Tiredness*	6.88 (1.78)	6.98 (1.62)	7.20 (1.80)	7.42 (1.93)	6.62 (2.26)	6.44 (2.41)	6.40 (2.29)	6.65 (1.95)
	Power	2.21 (1.36)	2.09 (1.39)	1.82 (1.23)	1.80 (1.32)	1.69 (1.07)	1.56 (1.12)	1.71 (1.24)	1.69 (1.54)
	Anger	3.27 (2.49)	3.36 (2.94)	2.99 (2.83)	3.11 (3.05)	3.03 (2.29)	2.40 (2.48)	3.00 (2.92)	2.78 (2.66)
	Cheerfulness	2.92 (2.08)	2.76 (1.98)	2.53 (2.08)	2.28 (2.15)	2.16 (2.05)	1.89 (1.43)	1.80 (1.21)	1.77 (1.55)
	Tension	5.25 (2.53)	5.17 (2.74)	5.09 (2.68)	5.35 (3.25)	5.26 (1.96)	4.66 (1.99)	4.91 (2.45)	4.62 (2.05)
	Depression	5.96 (2.32)	5.61 (2.23)	5.58 (2.84)	6.07 (2.70)	6.11 (1.71)	5.87 (2.14)	6.02 (2.28)	5.79 (2.43)
	Happiness	2.16 (1.26)	1.93 (1.29)	1.79 (1.16)	1.62 (1.27)	1.55 (0.95)	1.61 (1.28)	1.68 (1.29)	1.71 (1.59)
Week 2		**T_1**	**T_2**	**T_3**	**T_4**	**T_1**	**T_2**	**T_3**	**T_4**
BDI-I 24 h		26.32 (10.54)	26.43 11.17)	25.91 (10.83)	27.14 (10.64)	28.50 (10.28)	24.95 (10.58)	25.14 (10.71)	25.91 (9.65)
VAS	*Tiredness*	7.36 (1.85)	7.01 (1.99)	6.95 (2.00)	7.06 (2.11)	6.36 (2.17)	5.92 (2.37)	6.25 (2.30)	5.68 (2.07)
	Power	1.91 (1.20)	2.23 (1.47)	2.39 (1.65)	2.21 (1.59)	1.84 (1.69)	2.40 (1.83)	2.26 (2.09)	1.86 (1.70)
	Anger	3.17 (2.98)	2.71 (2.93)	2.80 (2.92)	2.97 (3.15)	3.29 (3.03)	2.79 (2.58)	2.87 (2.92)	2.86 (2.99)
	Cheerfulness	2.51 (2.18)	2.68 (2.14)	2.97 (2.25)	2.63 (2.29)	1.93 (1.72)	2.63 (1.91)	2.49 (2.09)	1.99 1.76)
	Tension	5.45 (2.69)	5.27 (2.61)	5.40 (2.69)	5.37 (2.82)	4.69 (2.21)	4.38 (2.27)	4.59 (2.62)	4.92 (2.46)
	Depression	5.79 (2.62)	5.71 (2.57)	5.85 (2.44)	5.94 (2.32)	5.98 (2.77)	5.49 (2.39)	5.61 (2.58)	6.01 (2.54)
	Happiness	1.93 (1.40)	2.23 (1.56)	2.23 (1.72)	2.20 (1.80)	1.88 (1.71)	2.37 (1.81)	2.34 (2.03)	1.90 (1.84)

Furthermore, baseline measurements were not different between responders and non-responders (detected at T_4) for depression severity HDRS: $T(45)=0.06$, $p=0.95$ and BDI-I: $T(43)=0.70$, $p=0.49$, age $T(45)=0.97$, $p=0.34$, number of depressive episodes (including the current one)$T(45)=0.30$, $p=0.77$, age of first depressive episode $T(45)=0.06$, $p=0.49$, rMT $T(45)=0.08$, $p=0.94$. For three chronically depressed patients (one Stage I, one Stage II and one stage III) no clear-cut point of timing of current depressive episode could be established as they claimed to be depressed over the last 20 years or longer and they did not remember episodes of feeling better or less severely depressed. Therefore, we decided to exclude these patients from these analyses concerning depression duration. Nevertheless, we found no significant differences of duration of the current depressive episode between responders and non-responders $T(42)=1.42$, $p=0.16$. Of note, one-way ANOVA's did not show significant group differences between the 3 groups (Staging I, II, and III) ($p's > 0.05$) for the number of episodes, the age of the first episode, the duration of the current episode, rMT, BDI-I at T_1, except for HDRS at T_1 $F(2, 46)=3.53$, $p=0.04$. Bonferroni corrected T-tests showed that Stage III patients scored significantly higher on 17-item HDRS than Stage I TRD patients ($p=0.04$).

Finally, for the continuous approach, the stepwise multiple linear regression analysis for delta HDRS did not identify any of the variables as significant predictor. This was the same for the delta BDI-I. LOCF approaches did not change these outcomes.

5. Discussion

Given that the majority of the iTBS studies typically use (sub) threshold stimulation intensities (% MT of 100% or less) (Oberman et al., 2011; Chung et al., 2015), this iTBS study shows that suprathreshold iTBS is safe, and it can even be applied several times a day with short time intervals between sessions. No seizures or any other major adverse events were observed. Minor transient complaints such as fatigue and headache were reported mainly after the first treatment sessions, but none required medical attention.

Concerning the overall clinical improvements, this study showed no statistical significant differential effects between sham and real stimulation on depression severity symptoms, assessed with the 17-HDRS and the BDI-I on a weekly basis. Moreover, no differential immediate mood changes occurred during the iTBS sessions when examined on a daily basis (VAS, BDI-I 24 h). Overall, these results are in line with our former accelerated HF-rTMS treatment protocol (Baeken et al., 2013), also using a within subjects sham-controlled crossover design, performing in total 20 sessions of suprathreshold HF-rTMS spread over 4 days performed 5 times daily (yielding a similar amount of pulses). Indeed, at the group level all TRD patients experienced clinical improvement to some extent, regardless of order, real/sham stimulation, substantiating our former findings that such accelerated protocols may be prone to stronger placebo effects (Baeken et al., 2013). Regardless of the stimulation protocol, accelerated protocols with several sessions a day, providing a lot of time, care, and attention to the patients may accumulate to a stronger placebo effect. Placebo responses in neurostimulation designs are not uncommon, also following the more classic sham-controlled rTMS studies offering daily treatment over weeks (Berman et al., 2000). The daily VAS results also agree with recent findings of an accelerated HF-rTMS study where over a 3-day period of 3 daily stimulation sessions yielding up to 54.000 stimuli in total, 20 patients were allocated to real stimulation and 21 allocated to receive sham HF-rTMS (George et al., 2014). These authors could also not find significant differences between the two groups on the VAS measurements. Unlike inventories or questionnaires like the HDRS or BDI, it has been claimed that VAS used to detect mood change may not be sensitive enough to capture discrete moods changes caused by rTMS (George et al., 1996). Nevertheless, our daily assessment on depression severity symptoms (BDI-I 24 h) also did not indicate that the application of real or sham iTBS immediately changed the patient's impression of feeling less or more depressed.

Importantly, and also in line with our former accelerated HF-rTMS study (Baeken et al., 2013), when using a categorical approach - defining clinical response by as a 50% decrease following treatment of the initial 17-item HDRS score −26% of the TRD patients were considered to be clinical responders after the two-week iTBS treatment protocol (at T_3). Although this number seems somewhat modest and numerically lower than our former accelerated HF-rTMS treatment study (in which 35% of these TRD patients responded after the two-week procedure), the follow-up assessment showed increases in clinical response rising to 38% at T_4. Importantly, confirming our former findings, with these kinds of accelerated treatment protocols a vast number of patients (30%) were considered to be in remission (17-item HDRS scores ≤ 7). In the Hadley et al., (2011) study, a comparable proportion of MDD patients (i.e., 33%) showed remission after one week of HF-rTMS

treatment (delivering 34.000 stimuli spread over 5 daily sessions). Furthermore, in the Holtzheimer trial (2010) 36% of the responders also were found to be in remission 3 weeks post last stimulation. Therefore, our current study adds to these findings by showing that the meaningful clinical effects resulting from the accelerated iTBS treatment performed over 4 days may actually occur later in time, indicating a possible delayed plasticity as a function of iTBS. This latter interpretation is not at odds with the proposed neurophysiological effects of TBS where it is assumed that this kind of neurostimulation may create more potent neuroplasticity effects, which may become apparent later in time following the treatment (Chung et al., 2015). We note however that brain imaging or neurophysiological studies will be needed to confirm these assumptions. Using an intensified HF-rTMS protocol, Hadley and colleagues (2011) who delivered daily 6800 stimuli/session and 34.000 stimuli in 5 days (which is comparable to the number of stimulation reached here), encouraged their patients to carry on with this protocol for at least five weeks. After 8 weeks of treatment, 66% of the total sample of patients showed clinical remission. Although this was an open add-on to psychopharmacotherapy as usual study, these observations suggest indirectly that more potent clinical improvements may be obtained when accelerated stimulation is used during several weeks.

The current study did not confirm our previous finding of a predictive effect of a younger age and a shorter depressive period as predictors of beneficial outcome of accelerated HF-rTMS treatment (Baeken et al., 2013). Moreover, none of the demographic variables considered in our study turned out to explain (in part) the variance accounting for the distinction between responders and non-responders, nor clinical outcome more generally. Accordingly, these findings do not support the assumption that beneficial neuroplasticity effects created by rTMS are especially visible in (relatively) younger patients (George and Post, 2011), and/or with a relatively short current depressive episode, or lower level of treatment resistance (Holtzheimer et al., 2004; Brakemeier et al., 2007). One could argue that compared to our previous study (Baeken et al., 2013), including only Stage III melancholic TRD patients, the current sample may have been more heterogeneous, with MDD patients showing different degrees of treatment resistance. We note however that neither depression staging nor the type of depression appeared to influence reliably the rate of clinical response in the current study. Furthermore, it should be emphasized that discrepant or sometimes opposite results were previously reported in the literature regarding the modulatory role (or the lack thereof) of demographic variables on TBS treatment efficacy in MDD patients. With some studies reporting a deleterious or hindering effects with increasing levels of treatment resistance (Li et al., 2014), while other studies failed to evidence significant contributions of variables such as therapy resistance, age, or duration of the current depressive episode as predictors (Plewnia et al., 2014). At any rate, it seems therefore parsimonious to conclude tentatively that clinical improvements in MDD resulting from an accelerated iTBS treatment may eventually be different (in either magnitude or content, or both) from the beneficial effects brought about by more classical iTBS/HF-rTMS protocols.

Some limitations warrant comments nonetheless. First, one major limitation is the lack of long-term follow-up data. By design, the T_4 time point represents different duration of delay from real treatment across the two groups, thus essentially preventing direct comparison (See Fig. 1). Another important limitation is related to the possibility that patients were actually aware of real vs. sham stimulations and thus not completely blind to these two different conditions. Although we took great care to minimize this possibility (including the use of a coil in the sham condition that was allegedly identical to the one used for the real stimulation condition, blindfolding and sound attenuation by means of earplugs), the sham condition necessarily differs from the real iTBS condition regarding skin sensations for example, a difference which may become especially obvious (for the patients) when using a crossover design like in the present case. Although not formally assessed, patients gave us such feedback. Despite the theoretical assumption that in contrast to a parallel group design, a crossover study comparing the same participants before versus after the intervention is not 'contaminated' by the variability between subjects - since the comparison is carried out on each individual - increasing dramatically study power, for our study it could have accounted for a disadvantage. For this accelerated iTBS study, we anticipated long term clinical effects meaning that the effect of a stimulation condition given in the first time period persists into the second period. However, possible delayed clinical effects of real iTBS when applied during the first week could only be measured at week two. For patients who received real stimulation during the second week, the delayed effects could not be measured. Secondly, although Berlim et al., (2013b) in a meta-analysis reported no significant differences between depressed patients who after treatment correctly guessed their actual condition allocation (real or sham rTMS) and those who did not, in our study it was clear that a majority of patients were eventually aware of this skin sensation difference across the two conditions, as reported at the subjective level. Given the specificities of (accelerated) TBS designs, this problem might even be more salient with these designs than those based on (more standard) rTMS protocols. Lastly, as it is currently unclear whether the separate iTBS sessions applied on the left DLPFC in TRD patients evoked excitatory or inhibitory neuronal activity under the stimulation coil and/or in the connected regions, or even whether the net effect of the total accelerated iTBS treatment is predominantly excitatory or inhibitory, neurophysiological measures are needed to verify this influence on our results.

In conclusion, in spite that mood-related improvements may partly be explained by a placebo effect, nevertheless, accelerated iTBS treatment resulted in "fast" meaningful clinical responses with some delayed effect. The fact that the clinical effects of accelerated iTBS are comparable to those of accelerated HF-rTMS, which was recently confirmed in studies comparing directly these two neurostimulation techniques (Bakker et al., 2015), is promising because it paves the way for using an effective neurostimulation protocol to treat MDD patients, which is less time consuming than more regular rTMS ones. In this context, additional empirical (and clinical) work is needed to optimize these parameters during iTBS (e.g., stimulation frequency, number of cycles, duration) and eventually improve further clinical outcomes in MDD. To ascertain the specificity of the neuroplasticity effects created by accelerated iTBS and providing in turn protective mechanisms against MDD, the use of crossover experimental designs incorporating a proper sham condition appears as a 'conditio sine qua non'.

Author disclosure

None.

Role of funding source

There were no commercial or financial involvements relevant to this study (a full financial disclosure has been included with the submission, and is included in this document).

This work was supported by the Ghent University Multidisciplinary Research Partnership "The integrative neuroscience of behavioral control". No other sponsors were included. Therefore, the authors report no conflict of interest.

Contributors

All authors contributed substantially to conception and design, or acquisition of data, or analysis and interpretation of data and drafted the article or revised it critically for important intellectual content and gave final approval of the version to be published.

Specifically,

Duprat Romain, Prof. Dr. De Raedt Rudi, and Prof. Dr. Baeken Chris

- Designed the study, acquired, analyzed, and interpreted the data; and
- drafted a first version of the article; and
- gave final approval of the version to be published.

Dr. Bakic Jasmina, Prof. Dr. Pourtois Gilles, and Dedoncker Josefien

- Contributed substantially to conception and design, analysis and Interpretation of data; and
- critically revised the manuscript for important intellectual content; and
- gave final approval of the version to be published.

Desmyter Stefanie, van Heeringen Kees, Van den Abbeele Dirk, Tandt Hannelore, Vervaet Myriam, Van Autreve Sara, Lemmens MD Gilbert

Contributed substantially to the acquisition of data, and interpretation of data; and

- critically revised the manuscript for important intellectual content; and
- gave final approval of the version to be published.

Acknowledgments

This work was supported by the Ghent University Multidisciplinary Research Partnership "The integrative neuroscience of behavioral control". GP is supported in part by a 2015 NARSAD Independent Investigator Grant from the Brain & Behavior Research Foundation.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2016.04.015.

References

Baeken, C., Vanderhasselt, M.A., Remue, J., Herremans, S., Vanderbruggen, N., Zeeuws, D., Santermans, L., De Raedt, R., 2013. Intensive HF-rTMS treatment in refractory medication-resistant unipolar depressed patients. J. Affect. Disord. 151, 625–631.

Bakker, N., Shahab, S., Giacobbe, P., Blumberger, D.M., Daskalakis, Z.J., Kennedy, S.H., Downar, J., 2015. rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. Brain Stimul. 8, 208–215.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.

Berlim, M.T., Van den Eynde, F., Daskalakis, Z.J., 2013a. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. Neuropsychopharmacology 38, 543–551.

Berlim, M.T., Broadbent, H.J., Van Den Eynde, F., 2013b. Blinding integrity in randomized sham-controlled trials of repetitive transcranial magnetic stimulation for major depression: a systematic review and meta-analysis. Int. J. Neuropsychopharmacol. 16, 1173–1181.

Berlim, M.T., van den Eynde, F., Tovar-Perdomo, S., Daskalakis, Z.J., 2014. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol. Med. 44, 225–239.

Berman, R.M., Narasimhan, M., Sanacora, G., Miano, A.P., Hoffman, R.E., Hu, X.S., Charney, D.S., Boutros, N.N., 2000. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. Biol. Psychiatry 47, 332–337.

Brakemeier, E., Luborzewski, A., Danker-Hopfe, H., Kathmann, N., Bajbouj, M., 2007. Positive predictors for antidepressive response to prefrontal repetitive transcranial magnetic stimulation (rTMS). J. Psychiatr. Res. 41, 395–403.

Chistyakov, A.V., Rubicsek, O., Kaplan, B., Zaaroor, M., Klein, E., 2010. Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. Int. J. Neuropsychopharmacol. 13, 387–393.

Chung, S.W., Hoy, K.E., Fitzgerald, P.B., 2015. Theta-burst stimulation: a new form of TMS treatment for depression? Depression Anxiety 32, 182–192.

De Raedt, R., Vanderhasselt, M.A., Baeken, C., 2015. Neurostimulation as an intervention for treatment resistant depression: from research on mechanisms towards targeted neurocognitive strategies. Clin. Psychol. Rev. 41, 61–69.

Desmyter, S., Duprat, R., Baeken, C., Bijttebier, S., Van Heeringen, K., 2014. The acute effects of accelerated repetitive transcranial magnetic stimulation on suicide risk in unipolar depression: preliminary results. Psychiatr. Danub. 26 (1), S48–S52.

Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Oliviero, A., Mazzone, P., Insola, A., Ranieri, F., Meglio, M., Tonali, P.A., Rothwell, J.C., 2008. The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. J. Physiol. 586, 3871–3879.

Di Lazzaro, V., Dileone, M., Pilato, F., Capone, F., Musumeci, G., Ranieri, F., Ricci, V., Bria, P., Di Iorio, R., de Waure, C., Pasqualetti, P., Profice, P., 2011. Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation. J. Neurophysiol. 105, 2150e6.

Fitzgerald, P.B., Hoy, K., McQueen, S., Maller, J.J., Herring, S., Segrave, R., Bailey, M., Been, G., Kulkarni, J., Daskalakis, Z.J., 2009. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. Neuropsychopharmacology 34, 1255–1262.

Fitzgerald, P.B., Daskalakis, Z.J., 2012. A practical guide to the use of repetitive transcranial magnetic stimulation in the treatment of depression. Brain Stimul. 5, 287–296.

Gamboa, O.L., Antal, A., Moliadze, V., Paulus, W., 2010. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp. Brain Res. 204, 181–187.

George, M.S., Wassermann, E.M., Williams, W.A., Steppel, J., Pascual-Leone, A., Basser, P., Hallett, M., Post, R.M., 1996. Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. J. Neuropsychiatry Clin. Neurosci. 8, 172–180.

George, M.S., Lisanby, S.H., Avery, D., McDonald, W.M., Durkalski, V., Pavlicova, M., Anderson, B., Nahas, Z., Bulow, P., Zarkowski, P., Holtzheimer 3rd, P.E., Schwartz, T., Sackeim, H.A., 2010. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch. Gen. Psychiatry 67, 507–516.

George, M.S., Post, R.M., 2011. Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression. Am. J. Psychiatry 168, 356–364.

George, M.S., Raman, R., Benedek, D.M., Pelic, C.G., Grammer, G.G., Stokes, K.T., Schmidt, M., Spiegel, C., Dealmeida, N., Beaver, K.L., Borckardt, J.J., Sun, X., Jain, S., Stein, M.B., 2014. A two-site pilot randomized 3 d trial of high dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients. Brain Stimul. 7, 421–431.

Gershon, A.A., Dannon, P.N., Grunhaus, L., 2003. Transcranial magnetic stimulation in the treatment of depression. Am. J. Psychiatry 160, 835–845.

Hadley, D., Anderson, B.S., Borckardt, J.J., Arana, A., Li, X., Nahas, Z., George, M.S., 2011. Safety, tolerability, and effectiveness of high doses of adjunctive daily left prefrontal repetitive transcranial magnetic stimulation for treatment-resistant depression in a clinical setting. J. ECT 27, 18–25.

Hamilton, M., 1967. Development of a Rating Scale for primary Depressive Illness. Br. J. Soc. Clin. Psychol. 6, 278–296.

Holtzheimer 3rd, P.E., Russo, J., Claypoole, K.H., Roy-Byrne, P., Avery, D.H., 2004. Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation. Depression Anxiety 19, 24–30.

Holtzheimer 3rd, P.E., McDonald, W.M., Mufti, M., Kelley, M.E., Quinn, S., Corso, G., Epstein, C.M., 2010. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. Depression Anxiety 27, 960–963.

Huang, Y.A., Edwards, M.I., Rounis, E., Bhatia, K.P., Rothwell, J.C., 2005. Theta burst stimulation of the human motor cortex. Neuron 45, 201–206.

Lefaucheur, J.P., André-Obadia, N., Antal, A., Ayache, S.S., Baeken, C., Benninger, D.H., Cantello, R.M., Cincotta, M., de Carvalho, M., De Ridder, D., Devanne, H., Di Lazzaro, V., Filipović, S.R., Hummel, F.C., Jääskeläinen, S.K., Kimiskidis, V.K., Koch, G., Langguth, B., Nyffeler, T., Oliviero, A., Padberg, F., Poulet, E., Rossi, S., Rossini, P.M., Rothwell, J.C., Schönfeldt-Lecuona, C., Siebner, H.R., Slotema, C.W., Stagg, C.J., Valls-Sole, J., Ziemann, U., Paulus, W., Garcia-Larrea, L., 2014. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. 125, 2150–2206.

Levkovitz, Y., Isserles, M., Padberg, F., Lisanby, S.H., Bystritsky, A., Xia, G., Tendler, A., Daskalakis, Z.J., Winston, J.L., Dannon, P., Hafez, H.M., Reti, I.M., Morales, O.G., Schlaepfer, T.E., Hollander, E., Berman, J.A., Husain, M.M., Sofer, U., Stein, A., Adler, S., Deutsch, L., Deutsch, F., Roth, Y., George, M.S., Zangen, A., 2015. Efficacy

and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry 14, 64–73.
Li, C.T., Chen, M.H., Juan, C.H., Huang, H.H., Chen, L.F., Hsieh, J.C., Tu, P.C., Bai, Y.M., Tsai, S.J., Lee, Y.C., Su, T.P., 2014. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain 137, 2088–2098.
Mccormack, H.M., David, J., Horne, L., Sheater, S., 1988. Clinical applications of visual analogue scales: a critical review. Psychol. Med. 18, 1007–1019.
Nettekoven, C., Volz, L.J., Kutscha, M., Pool, E.M., Rehme, A.K., Eickhoff, S.B., Fink, G. R., Grefkes, C., 2014. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J. Neurosci. 34, 6849–6859.
Oberman, L., Edwards, D., Eldaief, M., Pascual-Leone, A., 2011. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. J. Clin. Neurophysiol. 28, 67–74.
O'Reardon, J.P., Solvason, H.B., Janicak, P.G., Sampson, S., Isenberg, K.E., Nahas, Z., McDonald, W.M., Avery, D., Fitzgerald, P.B., Loo, C., Demitrack, M.A., George, M. S., Sackeim, H.A., 2007. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol. Psychiatry 62, 1208–1216.
Plewnia, C., Pasqualetti, P., Große, S., Schlipf, S., Wasserka, B., Zwissler, B., Fallgatter, A., 2014. Treatment of major depression with bilateral theta burst stimulation: a randomized controlled pilot trial. J. Affect. Disord. 156, 219–223.
Prasser, J., Schecklmann, M., Poeppl, T.B., Frank, E., Kreuzer, P.M., Hajak, G., Rupprecht, R., Landgrebe, M., Langguth, B., 2015. Bilateral prefrontal rTMS and theta burst TMS as an add-on treatment for depression: a randomized placebo controlled trial. World J. Biol. Psychiatry 16, 57–65.
Rush, A.J., Thase, M.E., Dubé, S., 2003. Research issues in the study of difficult-to-treat depression. Biol. Psychiatry 53, 743–753.
Schutter, D., 2009. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol. Med. . 39, 65–75.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 20, 22–57.
Slotema, C.W., Blom, J.D., Hoek, H.W., Sommer, I.E.C., 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. J. Clin. Psychiatry 71, 873–884.