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Short Communication

Implementation of rTMS in the treatment of depression in Denmark

Poul Erik Buchholtz*

Department of Affective Disorders, Aarhus University Hospital, Denmark

*Author for correspondence:
Email: poulhans@rm.dk

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Repetitive transcranial magnetic stimulation (rTMS) has appeared as a new non-invasive antidepressant method, which implies non-convulsive focal stimulation of the brain through a time-varying magnetic field. Research indicates, that rTMS of the prefrontal cortex has a significant antidepressant effect and is associated with minimal side effects. An increasing number of scientific original works [1-17] and meta-analyses [18-28] have in recent years substantiated the evidence of the antidepressant effect of the method, and rTMS is today approved for the treatment of depression in an increasing number of countries all over the world.

Aarhus University Hospital in Denmark has used rTMS in a research context for the past almost 20 years and was in 2015 the first psychiatric Danish psychiatric center to offer rTMS as add-on to selected patient groups for the treatment of depression in daily clinical practice. With the aim of introducing the method in the treatment of depression in Denmark a review and update (Tables 1-3) on the scientific evidence for the antidepressant effect that was published in the Danish medical journal, Ugeskrift for Laeger in 2019 [29].

Eligible articles were identified by systematic searching PubMed, Embase and Cochrane for original studies and meta-analyses from 1999 to 2019 and included Randomized controlled trials (RCT´s) comparing the antidepressive effect of High frequency (HF) rTMS of the left dorsolateral prefrontal (DPFC) cortex or low frequency (LF) rTMS of the right DPFC (International accepted and approved models of stimulation) with placebo or antidepressant drug treatment in a double-blind design. The included trials were restricted to RCT´s with sufficient statistical power (including ≥ 20 patients in each group) and comprised patients with a diagnose of major depression (uni-or bipolar) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) criteria. Age 18-80 years. Antidepressant effect was expressed in the Hamilton depression scale or Montgomery-Aasberg depression scale score as remission (total score ≤7 or 10) and /or response (total score reduced ≥ 50%). The included meta- analyses were restricted to randomized, placebo-controlled, blinded trials comparing the antidepressant effect of the above-mentioned models of stimulation, but without a lower threshold for the number of Individuals in the compared groups.

The majority of the RCT studies included (Table 1) used high frequency stimulation of the left DLPC [2-8,10-15], and 75% of them achieved an antidepressant effect, which was statistically significantly superior to placebo. In the few studies [1,2,9] on LF-rTMS of right DLPC, it was found consistent with other studies [15-17] that the two stimulus models had an antidepressant effect at the same level. In addition, LF stimulation has been shown to be associated with a gentler side-effect profile than HF stimulation [3,8,30]. The efficacy of rTMS expressed in remission and response rates were generally in line with the efficacy of antidepressant drug treatment [3,16,17]. The lower remission and response rates in studies covering patients who had not previously responded to at least 1-2 medical treatment courses suggest in accordance with previous studies, treatment resistance a negative predictor of antidepressant effect [31]. The included studies meet a number of scientific quality requirements. The distribution of patients based on randomness counteracts an uneven distribution of confounders that may influence the outcome of the treatment leading to misinterpretations and bias. However, several studies are weakened by placebo-technical challenges and varying degrees of

Tabel 1: Randomized controlled double blind trials comparing the antidepressive effect of rTMS with placebo (Sham).

Author	Number of Patients N rTMS/sham	Stimulated area	Intensity % of MT [f]	Frequency Hz	Number of Pulses total	Days of Treatment number	Sham Coil model	Drug-resistens [ta]	Model of Treatment	Patients in remission %	Response HamD-17/ [d] MADRS [e] %
Klein (1999) [1]	36/34	Right PFC [c]	110	1	1.200	10	90^0 [g]	No	Add-on	rTMS: 46%* Sham. 19%	rTMS: 49%* Sham: 25%
Rumi (2004) [3]	22/24	Left PFC	120	5	25.000	20	Blind Coil	No	Add-on	rTMS: 4%** Sham:12%	rTMS: 95%** Sham: 46%
Rossini (2005) [15]	50/49	Left PFC	100	15	9.000	20	90^0	No	Add-on	rTMS: 7%** Sham:11%	rTMS: 51%** Sham: 21%
Avery (2006) [4]	35/33	Left PFC	110	10	24.000	15	90^0	yes	Add-on	rTMS: 20%* Sham: 3%	rTMS: 31%** Sham: 6%
Herwig (2007) [5]	62/65	Left PFC	110	10	30.000	15	45^0 [h]	yes	Add-on	Unknown	rTMS: 31% # Sham: 31%
O'Reardon (2007) [6]	155/146	Left PFC	110/120	10	90.000	30	Blind [i] coil	yes [b]	Mono-Therapy	rTMS: 15%* Sham: 8%	rTMS: 25%* Sham: 14%
George (2010) [7]	92/98	Left PFC	120	10	45000	15	Blind coil	yes	Mono-Therapy	rTMS: 14%* Sham: 5%	rTMS: 15% * Sham: 5%
Mogg (2008) [8]	29/30	Left PFC [c]	110	10	10.000	10	Blind coil	yes	Add-on	rTMS: 25% * Sham:10%	unknown
Pallanti (2010) [9]	20/20	Right PFC	110	1	6.300	15	Blind coil	yes	Add-on	rTMS: 30%* Sham. 5%	rTMS :35% * Sham: 10%
Ray (2011) [10]	20/20	Left PFC	90	10	12.000	10	45^0	unknown	Add-on	rTMS: 75%** Sham: 10%	unknown
Blumberger (2012) [11]	24/22	Left PFC	100/120	10	21.750	15	90^0	yes	Add-on	rTMS: 5% # Sham: 5%	rTMS: 5% # Sham: 10%
Huang (2012) [12]	28/28	Left PFC	90	10	8.000	10	90^0	No	Add-on	rTMS: 39% # Sham: 29%	rTMS: 39%# Sham: 29%
Wang (2017) [13]	22/21	Left PFC	80	10	16.000	20	Blind coil	No	Add-on	rTMS:68%** Sham: 38%	rTMS:96%* Sham: 71%
Theleritis (2017) [14]	52/44	Left PFC	100	20	24.000/ 48.000	15	90^0	yes	50% Add-on	rTMS: 25%*** Sham:0%	rTMS: 59%** Sham: 3%

[a]: insufficient antidepressant response to at least two different types of antidepressant drugs used in sufficient time and dose; [b]: insufficient antidepressant response to at least one antidepressant drugs used in sufficient time and dose; [C]: Prefrontal cortex; [d]: Hamilton 17-item rating scale score for depression; [e]: Montgomery & Aasberg Depression rating scale score; [f]: Motor threshold; [g]: the coil is angled 90 degrees; [h]: the coil is angeled 45 degrees; [i]: sham coil; # insignificant, $p< 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 2: Randomized controlled double blind trials comparing the antidepressive effect of low frequency repetitive transcranial magnetic stimulation (rTMS) with that of Venlafaxin.

Author	Number of patients N	Stimulated Part of the scalp	Intensity % af MT	Frekvens Hz	Number of Pulses total	Number of Treatment days	Model of blinding	Drug resistant	Share of patients obtaining effect Ham-D/MADRS	
									Remission	response
Bares (2009) [16]	rTMS: 29 AD: 31	right PFC	100	1	24.000	20	90^0	yes	rTMS: 19% * Venlafaxin:23%	:33% ** :39%
Brunelin (2014) [17]	rTMS +AD: 55 Placebo+AD:55 rTMS+placebo:60	right PFC	120	1	5.400-10.800	15-30	Blind coil	yes	rTMS+Venlafaxin: 28 % *** Sham +Venlafaxin:43% rTMS + placebo : 41%	:54% **** :60% :59%
AD: Venlafaxin; MT: Motor Threshold; PFC: Prefrontal cortex; * P=0.76; ** P=0.36; *** P=0.59; **** P = 1.0										

Table 3: Meta-analyses of randomized controlled double blinded trials comparing the antidepressive effect of rTMS with placebo (Sham).

Author	Number of trials (number of patients)	Share of studies covering > 20 patients in the compared groups %	Number of studies by model of stimulation HFLP[a] /LFRP[b]	Share of studies using stimulus Intensity ≥ 100 % af MT[c]. %	Share of studies covering Treatment Resistant patients %	Share of studies Using a Treatment period ≤ 2 weeks %	Effect rTMS vs. Placebo Evaluation
Martin (2003) [19]	12 (217)	14	13/1	33	50	100	rTMS > placebo * Small populations, short treatment periods. Low quality trials. Inconclusive
Lam (2008) [20]	24 (1092)	42	24/0	67	100	79	rTMS > placebo * Low levels of remission and response, small populations, short treatment periods. Inconclusive.
Schutter (2008) [21]	30 (1164)	27	30/0	27	57	83	rTMS > placebo **** Effect at the level of antidepressant drugs. The method is evaluated as safe.
Berlim (2013) [22]	8 (263)	38	0/8	88	88	63	rTMS > placebo **** The effect of HFLP rTMS at the level of LFRP stimulation and antidepressant drugs. LFRP has less side effects

Gaynes (2014)	18 (676)	6	14/4	NA	100	6	rTMS > placebo Small populations, short treatment periods. Pooled RR[d] for remission=2.8. (95% CI, 1.8 - 4.3) #
Berlim (2014) [23]	29 (1371)	28	29/0	72	62	62	HF rTMS > placebo **** a clinical significant antidepressant effect. Few and acceptable side effects
Health Quality Ontario (2016) [24]	23 (1156)	NA	23/0	70	74	35	HF rTMS > placebo ** A statistical significant antidepressive short term effect
Wei (2017) [25]	29 (1659)	69	24/5	58	0	28	rTMS > placebo ** a statistical significant but variating antidepressive effect
Mutz (2018) [26]	38 (1510)	24	35/3	66	71	50	rTMS > placebo # a statistical significant antidepressive effect of HFLP as well as LFRP rTMS
Eunethta (2018) [27]	25 (1180)	48	25/0	80	64	68	HF rTMS > placebo *** a small but statistical significant antidepressant effect at the limit of being clinical significant. The method is safe and well tolerated
Sehatzadeh (2019) [28]	20 (1146)	50	19/1	60	100##	50	HF rTMS > placebo RRd for remission =2.33 (95% CI 1.5–3.6) A statistical significant moderate antidepressant effect #

[a]: HFLP= High frequency Left Prefrontal; [b]: LFRP= Low Frequency Right Prefrontal; [c]: MT= Motor Threshold; [d]: RR= Relative Risk; * P < 0.05; ** p < 0.001; *** p = 0.0003; **** p < 0.0001; # p = unknown; ## 20% failed 1 antidepressant (AD) courses, 80% failed 2 AD courses

blinding. The use of blind coils, which are identical to active coils in terms of appearance and accompanying sensory impressions but produce no magnetic field, has in recent years limited the risk of bias due to insufficient blinding. Some studies deserve special mention. A US placebo-controlled multi-center study [6] was conducted with total blindness at all joints and included patients, who had responded insufficiently to at least one prior drug treatment trial. In the rTMS group, 16% achieved remission and 25% response on the Hamilton's depression scale. The corresponding values in the placebo group were 9% and 14%, respectively. The relatively limited effect of rTMS compared to placebo may reflect that the sample included drug-resistant patients. Based on the findings of the 2008 study, the US Food and Drug Administration approved HF-rTMS of the left DLPFC to treat patients with unipolar depression.

The result was challenged by a concurrent German multi center study by Herwig et al. [5] who found that rTMS and placebo were equivalent in antidepressant efficacy. The result should be evaluated in the light of the used placebo model, which with just a 45-degree angle of the coil may have stimulated the brain in the placebo group. In addition, the effect of concomitant antidepressive drug treatment initiated in parallel with the rTMS may have erased the power difference further. Since then, two other RCT´s [11,12] has been questioning the antidepressant potential of the two rTMS stimulus models. Huang et al. [11] found a significant faster reduction in HAM-D 17 item score in active rTMS compared to placebo, but the difference in remission and response did not reach the level of significance. The relatively small samples, and short period of treatment may have contributed to the outcome. Further Blumberger et al. carried out an RCT comparing the antidepressant effect of Left frontal HF rTMS with sham. The study failed to show any significant difference in rates of remission and response between the two groups. However, the study was weakned by small samples combined by an unusually high drop-out rate.

In 2010, Pallanti et al. [9] published a randomized, double-blind study comparing LF right-sided prefrontal rTMS with placebo. The study included 20 treatment refractory patients with moderate-severe depression in each group. After 15 sessions, 30% received remission and 35% response to active treatment against respectively 5% and 10% in the placebo group. The difference was statistically significant. The antidepressant potential of LF-rTMS is further supported by a 2009 Czech study [16] and a later French multicenter study [17] comparing the antidepressant effect of LF right-sided prefrontal rTMS with venlafaxine in a randomized controlled double-blind design. Both studies found an antidepressant effect of LF-rTMS of the prefrontal cortex at the same level as venlafaxine (Table 2).

The meta-analyzes (Table 3) confirm the results of the original studies cited, but a lower antidepressant effect is generally obtained [19-28]. Thus, in two comprehensive meta-analyzes [24,27] the response rates to HF-rTMS were found to be approximately twice as high as on placebo, but on the borderline to be clinically significant. The results should be seen in the light of the fact that the studies included patients with drug treatment refractory depression, which has been shown to be a negative predictor of the antidepressive effect. Further the majority of the studies included ≤ 10 sessions.

The main conclusion of the review was that both HF stimulation of the left and LF stimulation of the right DLPC have an antidepressant effect that is on the level of the effect of antidepressant medication and has a documented potential for the treatment of drug treatment refractory depression. Given this and the very gentle side effect profile of the method, rTMS was found to be a relevant treatment option in the management of depression primarily as add-on to other antidepressant treatment in daily clinical practice.

In 2021 National Danish guidelines for the treatment of difficult-to-treat depression [32] approved the method with a weak recommendation for this category of depressions and an increasing number of rTMS treatment unites is subsequently being established in the Danish regions.

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