Neuroscience Letters 471 (2010) 30–33

Contents lists available at ScienceDirect

Neuroscience Letters

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

Sham or real—Post hoc estimation of stimulation condition in a randomized transcranial magnetic stimulation trial

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ARTICLE INFO

Article history:
Received 27 October 2009
Received in revised form 7 December 2009
Accepted 5 January 2010

Keywords:
Transcranial magnetic stimulation
Treatment trials
Depression
Sham condition

ABSTRACT

Selecting a suitable sham condition within the frame of repetitive transcranial magnetic stimulation (rTMS) treatment trials is a central issue. On the one hand, the ideal sham condition should not have a real stimulation effect; on the other hand, it should not be recognized as sham by patients, particularly when considering that real stimulation conditions come along with rTMS specific side effects. Within the course of a multi-centre trial assessing the antidepressant effects of rTMS, patients were randomized to sham or real stimulation, in both cases using a standard stimulation coil. In one centre, patients ($n = 33$) were asked about their impression whether they received the sham or the real treatment, and if they would recommend the treatment to others. 29 patients returned the questionnaires and were included into the analysis. From 15 subjects with real stimulation, 11 suggested to have obtained real, and 4 to have obtained sham. From 14 sham stimulated subjects, 9 suggested to have obtained the real condition and 5 to have been sham stimulated. This difference was not significant ($p = 0.60$, chi square test). In addition, the major part of patients in both stimulation conditions would recommend rTMS to others. In both conditions, real and sham, the majority of subjects believed to have obtained the real condition. This implies suitability of the sham condition used since subjects appeared not to be able to identify the condition. The results imply the feasibility of a valid sham condition with a "real" coil.

Major depression belongs to the leading causes of disease burden worldwide [4]. Repetitive transcranial magnetic stimulation (rTMS) was introduced as a promising treatment option for depression and showed beneficial but at most moderate effects in single- and multi-centre trials [7,10,11,13,18,19]. Its application in depressed patients had recently been approved by the U.S. Food and Drug Administration and it is increasingly offered in psychiatric services. However, till now it remains difficult to draw consistent conclusions about the antidepressant efficacy of rTMS based on present publications. This is firstly due to inconsistent results, secondly due to methodological issues [8,16,19]. A primary issue, evident in each randomized stimulation trial, is the sham condition. On the one hand, real stimulation and sham stimulation have to be different concerning their efficacy: real should cause an effective stimulation, sham should not. On the other hand, sham and real should not differ concerning the subjective experience of the stimulation. The first aspect can be fulfilled by dislocating the coil or using a so-called "sham coil", the second one by inducing the characteristic noise and the sensory, sometimes painful artefact [5]. That sensory artefact, however, is not present when using commercially available sham coils or it is of a different character when attempting to mimic the sensory impression [2]. Further, it is impossible to blind the experimenter because he or she has to apply the stimulation and has to know how and where to do that. The term "double-blind", within rTMS trials, thus refers only to patient and rater, who are unaware of the stimulation condition. Still, the experimenter might have an unintentional influence on the patient. Since stimulation conditions have to be different between each other to establish sham and real, the patient, too, might identify the applied condition. Accordingly, in randomized controlled trials (RCTs) the question often arises whether patients are able to guess their treatment condition. In the present study we aimed to clarify whether patients participating an rTMS RCT would be able to successfully guess which kind of stimulation they received: sham or active. Additionally, we also considered interesting to know whether the patients believed to benefit from the stimulation and would recommend the stimulation to others, and whether their expectation towards the stimulation might have biased treatment outcome.

Within the frame of a randomized, double-blind, placebo-controlled, multi-centre trial to assess the antidepressant effect

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doi:10.1016/j.neulet.2010.01.003

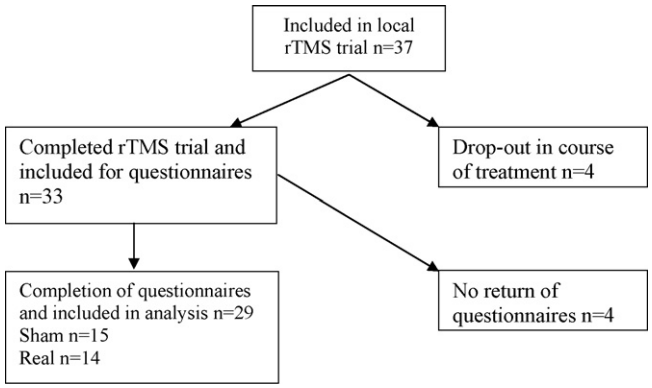

Fig. 1. Diagram illustrating the inclusion patients in questionnaire assessment.

of rTMS [11], the patients within one centre (Ulm, $n = 37$, 4 drop-outs, 33 completed the treatment trial, 29 of these returned the questionnaires, Fig. 1), were asked in the weeks afterwards by a questionnaire about their experience of rTMS, particularly concerning the stimulation condition. All patients gave written informed consent. The trial was performed according to the latest version of the Declaration of Helsinki and was approved by the local ethics committee. Inclusion criteria were: age 18–75 years, a moderate or severe major depressive episode according to ICD-10 and DSM-IV and a score of 18 points or more in at least two of the three depression rating scales: Becks' depression inventory (BDI) [3], Hamilton depression scale (HAM-D 21-items version) [9], Montgomery-Åsberg depression rating-scale (MADRS) [17]. The detailed methodology with exclusion criteria and add-on design onto parallel established antidepressant medication and the clinical results of the trial were reported earlier [11]. Included patients were given an identification number linked to a centralised computer-generated randomisation code determining real or sham stimulation condition.

A magnetic stimulator with a figure-of-eight coil was used for rTMS (Medtronic Magpro; Medtronic Inc., Minneapolis, MN, USA; coil: MC-B70). Patients were seated in a comfortable chair during stimulation. Stimulations were performed with a frequency of 10 Hz, trains of 2 s, inter-train-intervals of 8 s, 100 trains per session, 2000 stimuli per day on 15 subsequent working days. The real stimulation was applied above the left dorsolateral prefrontal cortex (DLPFC), targeted by guiding the coil to the position F3 according to the International 10-20 system for electroencephalography electrode placement [12]. The real stimulation intensity was determined as 110% of the individual resting motor threshold (MT) [22]. Sham stimulation was applied 5 cm lateral to F3, perpendicular to the parasagittal plane, above the left temporal muscle. To reduce a possible effectiveness of sham stimulation, the coil was angled at 45°, touching the skull not with the centre but with the rim opposite the handle, and the stimulation intensity was reduced to 90% MT. In this position, the coil–cortex distance also is essentially larger (more than 3 cm versus 1–1.5 cm) than above F3, such that the electromagnetic field, if at all reaching the cortex, due to technical reasons was substantially weaker and far outside the target region.

Within the weeks after the antidepressant stimulation, all patients that completed treatment in the centre should answer and return a questionnaire concerning their experience with rTMS, with a particular focus on the stimulation condition. If patients did not return the questionnaire upon the estimated time of 4 weeks, they were contacted by phone and asked the same questions. The following questions were posed (original in German, here English translation):

a. Which expectation did you have concerning successful treatment prior to rTMS? Range 1 to 4, with 1 being no, and 4 being very high expectations
b. Two stimulation conditions were possible, real and sham, which one do you think you received? Sham/real
c. Would you recommend rTMS treatment to others? Yes/no
d. Did you have the impression that rTMS overall helped you? Yes/no

Treatment outcome dependent on treatment conditions as measured with the three rating scales were analyzed with Mann–Whitney *U*-test due to non-parametric distribution. In order to assess (i) whether the patients estimated to have received real or sham stimulation, (ii) whether they would recommend rTMS, and (iii) how they felt after rTMS, the data were analyzed with a chi square test. The hypothesis was that 'real' and 'sham' should not be discriminated by the patients as reflected in comparable amounts of estimations with no statistical differences concerning the questions of guessing the condition and of recommendation (assuming that one would not recommend a treatment not considered to be effective). To assess the influence of expectation on treatment outcome irrespective of condition, we pooled the groups with low and medium low expectation versus high and medium high expectation into two groups and subjected the data to a chi square test.

From 37 patients that were enrolled in the centre, 33 completed stimulation. Within this group responses from 29 patients, i.e. 88%, were obtained, 4 patients did not answer (Fig. 1). These 29 were included in further analyses (demographic data in Table 1). They responded to all questions except the question concerning recommendation which was not answered by 4 patients. Regarding the antidepressant treatment outcome, the patients did not show significant differences between real and sham in all three scales, whenever one might observe a descriptive improvement particularly of HAM-D and BDI scores (Table 1). Concerning the HAM-D score, the sham group was slightly less depressed prior stimulation than the real group which was not the case in BDI and MAD.

Regarding whether patients considered real to be real and sham to be sham, from 15 real stimulated patients, 11 suggested to have received real, and 4 sham. From 14 sham stimulated patients, 9 also estimated to have received the real condition and 5 to have been sham stimulated (Table 1). This difference was not significant ($p = 0.60$, chi square test). Further, the majority of patients in both stimulation conditions would recommend rTMS to others: 10

Table 1
Demographic and clinical data of included patients.

	Real	Sham	sign., *p*
N	15	14	
Age *m*/sd	51.1/12.1	52.6/13.4	n.s. (0.74)
Gender	7m/8f	5m/9f	n.s. (0.36)
BDI pre *m*/sd	29.9/9.4	32.0/7.3	n.s. (0.50)
HAM pre *m*/sd	24.3/3.9	21.1/4.1	0.036
MAD pre *m*/sd	29.1/3.8	27.8 4.9	n.s. (0.43)
BDI diff *m*/sd	−14.9/9.2	−10.6/11.4	n.s. (0.25)
HAM diff *m*/sd	−13.7/7.5	−10.5/8.2	n.s. (0.29)
MAD diff *m*/sd	−16.5/7.8	−14.9/8.5	n.s. (0.91)
Co venlafaxine	8	7	n.s. (0.86)
Co mirtazapine	7	7	
Consid. real *n* (%)	11 (73%)	9 (64%)	n.s. (0.60)
Consid. sham *n* (%)	4 (27%)	5 (36%)	
Recom. Yes *n* (%)	10 (67%)	9 (64%)	n.s. (0.16)
Recom. no/miss. (%)	5	5	
Benefit yes	11 (73%)	5 (36%)	0.042
Benefit no	4 (27%)	9 (64%)	

Abbreviations: m: mean; sd: standard deviation; diff: difference pre–post; co: co-medication; consid.: consideration (question 1); recom.: recommendation (question 2); miss.: missings. *Statistics:* *t*-test for age, Mann–Whitney *U*-test for rating data, chi square test for categorical data.