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Simultaneous rTMS and psychotherapy in major depressive disorder: Clinical outcomes and predictors from a large naturalistic study

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) is considered an efficacious non-invasive neuromodulation treatment for major depressive disorder (MDD). However, little is known about the clinical outcome of combined rTMS and psychotherapy (rTMS + PT). Through common neurobiological brain mechanisms, rTMS + PT may exert enhanced antidepressant effects compared to the respective monotherapies.
Objective: The current naturalistic study aimed to evaluate feasibility and clinical outcome of rTMS + PT in a large group of MDD patients. The second aim was to identify clinical predictors of response and remission.
Methods: A total of 196 patients with MDD were treated with at least 10 sessions of simultaneous rTMS and PT. rTMS was applied over the DLPFC, either 10 Hz left or 1 Hz right. Psychotherapy was based on principles of cognitive behavioral therapy (CBT). Symptoms were measured using the BDI each fifth session until end of treatment and at 6-month follow-up. Comparisons were made between responders and non-responders, as well as between the 10 Hz and 1 Hz protocol. Additionally, baseline variables and early BDI change were evaluated as predictors of response/remission.
Major findings and conclusions: 1) Combining rTMS and PT resulted in a 66% response and a 56% remission rate at the end of treatment with 60% sustained remission at follow-up. Compared to previous findings in RCTs, these rates are relatively high; 2) No differences were found between the 10 Hz and 1 Hz TMS regarding clinical outcome; 3) Clinical baseline variables were not predictive of treatment outcomes; 4) Early symptom improvement (at session 10) was highly predictive of response, and may therefore be used to guide rTMS + PT continuation; 5) Based on the current findings in a large naturalistic study, future studies employing a more standardized method are warranted to draw solid conclusions on the unique effect of rTMS + PT.

Introduction

The application of repetitive transcranial magnetic stimulation (rTMS) in major depressive disorder (MDD) as an augmentation treatment strategy for treatment-resistant patients has been extensively investigated in the past decades. In rTMS, a magnetic coil is placed on a specific location on the scalp to modify target brain networks by applying magnetic pulses, inducing an electrical current in underlying cortex [1]. The efficacy of rTMS over the dorsolateral prefrontal cortex (DLPFC) has been established in large multicenter randomized controlled trials (RCTs) [2,3] and meta-analyses [4–7], and is considered an evidence-based treatment

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approach for MDD [8]. A few studies have investigated the generalizability of the effects of rTMS in clinical settings. In a multisite observational study, the response rate in the short term was comparable to those in research populations [9], and a 1-year follow-up study of the same population demonstrated that these effects remained similar in the long term [10]. These studies highlight the clinical significance of rTMS for the treatment of MDD patients. Currently, rTMS is usually applied either as monotherapy or as augmentation to pharmacotherapy. Although response to this approach is better than sham in RCTs, a large proportion of patients does not respond [5]. It is therefore important to seek optimization of the treatment protocol.

The effects of rTMS are exerted through modulating network connectivity [1]. MDD is associated with dysregulation of medial/orbitofrontal networks, including the default mode network (DMN), central executive network (CEN) and salience network (SN) [11,12]. In these networks, hyperconnectivity between prefrontal and anterior cingulate regions is associated with symptoms of MDD, such as rumination and negative bias [13]. Numerous studies have shown that connectivity from the DLPFC to the anterior cingulate cortex (ACC) changes as a result of rTMS [14]. Similarly, symptom changes as a result of psychotherapy (PT) are associated with changes in functional connectivity in fronto-limbic and fronto-cingulate circuitry, particularly from the medial PFC to the ACC and the amygdala [15]. Thus, both rTMS and PT are targeting the same networks through different pathways, inducing changes through neuroplasticity [16,17]. These observations give rise to the question whether simultaneous application of rTMS and PT (rTMS + PT) could lead to more robust and prolonged antidepressant effects.

Such an enhanced effect has been observed in studies combining PT with pharmacotherapy [18,19] and rTMS with pharmacotherapy [20]. Even stronger additive effects may be expected from rTMS + PT, as both target network plasticity in a similar way through different pathways. Furthermore, PT may be a preferable add-on strategy to rTMS, as it is desirable for many patients to quit medication. The main disadvantages of pharmacological treatment consist of undesirable side effects, cumulative drop-out rates, and non-response in a significant proportion of the patients, as demonstrated in the systematic antidepressant treatment of STAR*D [21]. Moreover, psychotherapy is often better tolerated as a next-step treatment than medication augmentation and switch strategies [22]. Although psychotherapy and medication are equally effective in the short term, follow-up outcomes are favorable for psychotherapy [18,19,23]. It may therefore be hypothesized that a combination of rTMS and PT could lead to stronger and longer lasting effects, using a well-tolerated treatment approach.

Moreover, non-invasive brain stimulation techniques including rTMS exert effects on cognitive functions that psychotherapy may rely on, such as explicit learning or top-down emotional control [24]. In neurorehabilitation, combined application of rTMS and cognitive rehabilitation therapies has been shown to result in beneficial effects [25], mainly in the motor [26] and language domain [27,28] as well as unilateral neglect [29]. A similar effect may apply to the behavioral effect of rTMS + PT in psychiatry. Indeed, a case report demonstrated that combined rTMS and CBT is feasible and possibly more effective than either treatment alone [30], supporting this hypothesis, but no other studies to date have reported on the clinical outcome of this promising approach.

Therefore, the present study aimed to evaluate the feasibility and clinical outcome of the simultaneous application of rTMS + PT in a large, representative population of MDD patients. The second aim was to identify possible predictors of treatment outcome.

Method

Design and participants

The current study was a naturalistic open-label study. All patients enrolled at three outpatient mental health care clinics (neuroCare Clinic Nijmegen, neuroCare Clinic The Hague, and Psychologenpraktijk Timmers Oosterhout) between May 2007 and November 2016 were screened for inclusion. Inclusion criteria were 1) a primary diagnosis of non-psychotic MDD or dysthymia, 2) BDI$\geq$14 at baseline, 3) treatment with at least 10 sessions of rTMS over the DLPFC or response within these 10 sessions, and 4) informed consent. Exclusion criteria to ensure safety for rTMS were previous ECT treatment, epilepsy, traumatic brain injury, current psychotic disorder, wearing a cardiac pacemaker or metal parts in the head, and current pregnancy.

Treatment procedure

Prior to treatment, patients completed an intake procedure, including a structured clinical interview (MINI International Neuropsychiatric Interview (MINI)) [31] for the diagnosis of MDD or dysthymia; if the MINI could not be completed due to time limits, patients with a diagnosis in accordance with DSM-IV or DSM-5 criteria obtained elsewhere were considered eligible for treatment as well. In addition, EEG was used to rule out contraindications for rTMS.

All patients were treated with either a high frequency (HF) protocol over the left DLPFC or a low frequency (LF) protocol over the right DLPFC, or both sequentially. rTMS was performed using a Magstim Rapid2 (Magstim Company, Spring Gardens, UK) or a Deymed DuoMag XT-100 stimulator with a figure-of-8 coil, 70 mm diameter. For the HF protocol, rTMS was administered at 10 Hz over the left DLPFC, 110–120% of the resting motor threshold (MT), 30 trains of 5s duration, inter-train interval (ITI) 30s, 1500 pulses per session. The LF protocol consisted of rTMS at 1 Hz over the right DLPFC, 110–120% MT, 120 trains of 10s duration, ITI 1s, 1200 pulses per session. In case of both protocols, the LF protocol was administered first with a shorter duration of 1000 pulses per session and subsequently the HF protocol at full length. The DLPFC was localized using either the 5-cm rule or the Beam F3/F4 method (see Ref. [32] for details).

Furthermore, rTMS treatment was complemented with psychotherapy by a psychologist trained in both rTMS and CBT. The therapist performed psychotherapy while the rTMS protocol was running (as shown in Fig. 1). Psychotherapy always consisted of evidence-based methods, mainly cognitive-behavioral therapy (CBT) [33,34], but the specific approach was tailored to the clinical needs of the patient, according to a decision procedure as usual in mental health care, in some cases including other evidence-based techniques indicated for comorbidities such as schema therapy or EMDR. Each treatment session had a total duration of 45 min. An rTMS protocol lasted 20 min, but psychotherapy was continued until 45 min. Sessions took place with a minimum frequency of two to three times per week and a maximum frequency of two per day.

The total number of sessions was guided by clinical decisions and thus varied for each individual patient. Decisions to continue treatment were based on response to treatment (satisfactory or unsatisfactory response could both be a reason to end treatment), clinical evaluation of symptom severity, and the patient's own request. The first decision rule was to continue rTMS if a decrease of at least 20% in BDI score was obtained after 10 sessions; the effect was evaluated each subsequent fifth session. If no response occurred by session 20–25, it was advised to abort treatment. If the BDI indicated remission over the course of sessions, defined as a

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