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Psychiatry Research

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

Self-directedness: An indicator for clinical response to the HF-rTMS treatment in refractory melancholic depression

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ARTICLE INFO

Article history:

Received 30 January 2014

Received in revised form

27 July 2014

Accepted 31 July 2014

Available online 8 August 2014

Keywords:

Self-directedness

HF-rTMS

Unipolar depression

Melancholia

Treatment resistance

ABSTRACT

Although well-defined predictors of response are still unclear, clinicians refer a variety of depressed patients for a repetitive Transcranial Magnetic Stimulation (rTMS) treatment. It has been suggested that personality features such as Harm Avoidance (HA) and self-directedness (SD) might provide some guidance for a classical antidepressant treatment outcome. However, to date no such research has been performed in rTMS treatment paradigms. In this open study, we wanted to examine whether these temperament and character scores in particular would predict clinical outcome in refractory unipolar depressed patients when a typical high-frequency (HF)-rTMS treatment protocol is applied. Thirty six unipolar right-handed antidepressant-free treatment resistant depressed (TRD) patients, all of the melancholic subtype, received 10 HF-rTMS sessions applied to the left dorsolateral prefrontal cortex (DLPFC). All patients were classified as at least stage III TRD and were assessed with the Temperament and Character Inventory (TCI) before a HF-rTMS treatment. Only the individual scores on SD predicted clinical outcome. No other personality scales were found to be a predictor of this kind of application. Our results suggest that refractory MDD patients who score higher on the character scale SD may be more responsive to the HF-rTMS treatment.

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1. Introduction

Major depressive disorder (MDD) is a severe mental health problem affecting millions worldwide. In spite of a variety of treatment modalities, not all patients respond to current pharmacotherapy or psychotherapy interventions (Papakostas, 2009). Furthermore, when challenged by antidepressant (AD) non-response, treatment options are limited (Shelton et al., 2010; Ward and Irazoqui, 2010; Kupfer et al., 2012). Repetitive Transcranial Magnetic Stimulation (rTMS) has become an established non-invasive treatment for patients suffering from MDD (Lefaucheur et al., 2011, in press; Berlin et al., 2014).

Although most of the former rTMS trials have been carried-out in MDD patients with some level of treatment-resistance, 20 years

of clinical experience indicates that beneficial predictors are a limited history of treatment resistance, younger age (< 65 years), and a relatively short period of clinical depression (< 1 year) (Brakemeier et al., 2007; George and Post, 2011). In daily clinical practice however, when confronted with partial or non-response, instead of a quick referral to such non-invasive approaches, clinicians tend to hold on changing or combining AD. However, this approach does not dramatically increase response and remission rates (von Wolff et al., 2012; Turner et al., 2014). As a consequence, a large number of MDD patients referred to the rTMS treatment settings range from some history of treatment resistance to chronic treatment resistant depression (TRD) or refractory MDD, including patients with unsuccessful electroconvulsive therapy (ECT) in the past (Baeken et al., 2009a, 2010, 2013; Zeeuws et al., 2011).

Typical rTMS treatment protocols follow daily sessions, spread over 2 weeks or more, applying high frequency (HF)-rTMS on the left dorsolateral prefrontal cortex (DLPFC) or low frequency (LF) rTMS to its right counterpart (George and Post, 2011; Fitzgerald

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and Daskalakis, 2012). Although some demographic variables may provide some indication for a beneficial rTMS treatment outcome, given the logistic issues of daily applications for patients and clinicians the availability of response predictors would not only be very valuable but may result in more individually adapted applications.

In pharmacotherapy research, personality features and/or personality disorders based on the Temperament and Character Inventory (TCI; Cloninger, 1987; Cloninger et al., 1994) have been evaluated to examine their ability to guide or even predict clinical outcome in MDD (Mulder, 2002; Mulder et al., 2003; Newton-Howes et al., 2006; Kaneda et al., 2011). With regard to MDD, in particular the temperament dimension Harm Avoidance (HA) and the character scale self-directedness (SD) have been related to depression, and both scales are usually negatively correlated (Hansenne et al., 1999; Hirano et al., 2002; Nery et al., 2009; Spittlehouse et al., 2010). In general, when clinically depressed, MDD patients compared to healthy controls score higher on HA and lower on SD. Successful treatment interventions may 'normalize' the two TCI scales (Hirano et al., 2002), although no effects have been reported as well (Marijnissen et al., 2002). According to Cloninger's psychobiological theory on personality, HA is related to behavioral inhibition and it implies a genetically determined bias towards being cautious, apprehensive and overly pessimistic (Cloninger et al., 1994). Individuals scoring higher on this personality dimension seem to be more vulnerable to develop mood and anxiety disorders during life-time (Cloninger et al., 2006; Kampman and Poutanen, 2011). The character dimension SD refers to higher cognitive processes that modulate emotional conflicts such as being responsible, purposeful, and resourceful, having willpower and determination (Cloninger et al., 1994). Besides that lower scores on self-directedness may be associated with an elevated risk for personality disorders, individuals with lower SD scores are more at risk to become depressed. Furthermore, in MDD samples these two TCI scales have been reported to be indicative of treatment response (Cloninger et al., 2006; Celikel et al., 2009; Margetić and Jakovljević, 2013). However, although less straightforward, also the temperament dimension Reward Dependence (RD: approval seeking vs. aloof), and the character scale Cooperativeness (CO: helpful and empathic vs. hostile and aggressive) have been linked with therapeutic outcome (for a review see Mulder, 2002). The temperament dimensions Novelty Seeking (NS: exploratory and impulsive vs. reserved and stoical), Persistence (P: industrious and determined vs. lazy and underachiever) and the character scale Self-Transcendence (ST: creative and spiritual vs. alienated and skeptical) have not been clearly associated with clinical outcome in MDD. Importantly, no studies yet have examined the influence of these personality scales on the clinical outcome of a typical HF-rTMS treatment protocol in a sample of unipolar MDD patients, documented to be resistant to several psychotropic interventions.

Consequently, we examined the predictive value of the TCI scales – with a special focus on HA and SD – in a sample of melancholic TRD patients referred for the HF-rTMS treatment. According to the Thase and Rush criteria (Rush et al., 2003), all patients were at least stage III treatment resistant. All had had a minimum of two unsuccessful treatment trials with serotonin reuptake inhibitors/noradrenaline and serotonin reuptake inhibitors (SSRI/NSRI) and one failed clinical trial with a tricyclic antidepressant (TCA). A substantial part of these patients ($n=10$) were unsuccessfully treated with ECT, classifying them as stage V TRD, indicating maximum resistance. Based on former pharmacological research, we hypothesized that lower scores on HA and higher scores on SD would be indicative for beneficial HF-rTMS outcome. We did not expect that the other TCI scales would predict clinical outcome. For exploratory objectives, we also examined stage III and stage V TRD patients separately.

2. Methods

2.1. Participants

The study was approved by our ethics committee (UZBrussel) and all subjects gave written informed consent. This study was part of a larger project investigating several neurobiological and neurocognitive markers in depressed patients. Thirty six medication-free unipolar TRD patients (Female: Male=26:10; age=46.2, S.D.=10.4 years) were selected by using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). By using this structured clinical MINI, all patients fulfilled the criteria of Major Depressive Episode with melancholic features (ICD-9-CM code 296.23 and 296.33). This type of depression is characterized by anhedonia, and other characteristics such as distinct quality of depressed mood, depression symptoms worse in the mornings, early morning awakenings, psychomotor retardation, weight loss, and excessive feelings of guilt (Gold and Chrousos, 2002). Patients with bipolar, atypical and psychotic depression were not included. Based on our earlier research on lateralization effects of DLPFC HF-rTMS on psychomotor and on brain functioning only right-handed TRD patients were selected (Baeken et al., 2009b, 2011, 2012). Right handedness was assessed with the Van Strien questionnaire (Van Strien and Van Beek, 2000). As described by Rush et al. (2003), all included MDD patients were considered at least stage III treatment resistant: they had had a minimum of two unsuccessful treatment trials with an SSRI/NSRI and one failed clinical trial with a TCA. Ten of these TRD patients had also undergone an unsuccessful trial ECT, indicating maximum treatment resistance (stage V). Probably just a coincidence, and due to the fact physicians do not regularly prescribe monoamine oxidase inhibitors (MAO-I), no TRD patient qualified for stage IV. For details see Table 1. To avoid influences of concomitant antidepressant (AD) medication, before entering the study all patients went through an AD washout and they were AD free for at least 2 weeks before the HF-rTMS treatment. Only habitual steady dose benzodiazepine agents were allowed.

2.2. Assessment

Before and after the HF-rTMS treatment, depression severity was assessed with the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) by a certified psychiatrist, unrelated to the study. Before the start of the study, patients were also assessed with the Temperament and Character Inventory (TCI; Cloninger et al., 1994), using a Dutch version of the TCI (de la Rie et al., 1998). The TCI is

Table 1
Demographics. Ratio's, means and standard deviations are provided.

MDD patients	Gender (F:M)	age	Duration current episode	NS	HA	RD	P	SD	CO	ST	HDRS before	HDRS after	ΔHDRS
All	26:10	46.2 (10.4)	4.2 (4.3)	15.2 (5.2)	27.8 (5.8)	16.6 (3.5)	4.9 (2.3)	23.6 (6.9)	31.1 (5.5)	10.5 (5.1)	24.2 (4.8)	15.9 (7.8)	8.3 (7.0)
Stage III	20:5	44.9 (10.0)	3.4 (3.5)	15.4 (4.8)	26.9 (6.0)	17.7 (2.9)	5.4 (2.2)	23.2 (6.4)	32.6 (3.7)	11.7 (5.1)	24.4 (4.3)	16.1 (7.7)	8.4 (7.4)
Stage V	6:5	49.1 (11.1)	6.4 (5.8)	14.8 (6.2)	29.5 (4.9)	14.5 (6.2)	3.9 (2.6)	24.5 (8.2)	28.0 (7.3)	8.1 (4.1)	23.7 (6.2)	15.5 (7.6)	8.3 (6.1)
HF-rTMS responders	11:3	45.5 (9.0)	4.3 (5.3)	16.1 (5.7)	27.6 (5.6)	17.1 (3.2)	5.0 (2.4)	24.7 (5.7)	30.4 (6.4)	10.3 (5.2)	24.8 (5.1)	9.1 (3.3)	15.6 (3.3)
HF-rTMS non-responders	15:7	46.6 (11.3)	4.1 (3.6)	14.6 (4.9)	27.9 (6.1)	16.3 (3.8)	4.9 (2.3)	22.7 (7.7)	31.6 (4.8)	10.7 (5.1)	23.9 (4.7)	20.2 (6.3)	3.7 (4.1)

MDD: major depressive disorder, F: female, M: male, NS: Novelty Seeking, HA: Harm Avoidance, RD: Reward Dependence, P: Persistence, SD: self-directedness, CO: Cooperativeness, ST: Self-Transcendence, HDRS: Hamilton Depression Rating Scale. HF-rTMS: high-frequency repetitive Transcranial Magnetic Stimulation.

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