Personality dimensions and deep repetitive transcranial magnetic stimulation (DTMS) for treatment-resistant depression: A pilot trial on five-factor prediction of antidepressant response

Alexander McGirr [a], Frederique Van den Eynde [c], Eduardo Chachamovich [b], Marcelo P.A. Fleck [c], Marcelo T. Berlim [b,c,*]

[a] Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada [b] Depressive Disorders Program, Douglas Mental Health University Institute and McGill University, Montréal, QC, Canada [c] Neuromodulation Research Clinic, Douglas Mental Health University Institute, Montréal, QC, Canada

a b s t r a c t

Background: Prognostication is poor in repetitive transcranial magnetic stimulation (rTMS) treatment for major depressive disorder (MDD). Personality traits, particularly extraversion and neuroticism, have attracted increasing attention for both trait- and state-dependent characteristics in predicting response to pharmacotherapy, psychotherapy, and more recently to therapeutic neuromodulation for MDD. The advent of deep rTMS (DTMS) allows stimulation of deeper cortical regions, and we aimed to prospectively characterize personality dimensions and antidepressant response to DTMS in treatment-resistant MDD.

Methods: A convenience sample of 15 patients with treatment-resistant MDD received four weeks of daily sessions of DTMS (20Hz, 3000 pulses/session) of the left dorsolateral prefrontal cortex (DLFPC). At baseline and at the conclusion of treatment, patients completed the Big Five Inventory, a five-factor assessment of major personality dimensions. Clinical response was measured using the 21-item Hamilton Depression Rating Scale.

Results: Four weeks of DTMS treatment were not associated with changes in personality measures. Clinical remission was associated with higher baseline levels of agreeableness (score ≥29:100% sensitive and 72.7% specific) and conscientiousness (score ≥30:75% sensitive and 81.8% specific). Levels of agreeableness and extraversion were linearly associated with antidepressant response. Neuroticism was not associated with the antidepressant effects of DTMS in this cohort.

Conclusions: Five-factor personality assessment may have prognostic value in DTMS for resistant MDD. Agreeableness, extraversion, and conscientiousness are associated with decreases in depressive symptoms during treatment with DTMS.

1. Background

Medical management of major depressive disorder (MDD) is effective overall, however as many as 60% of patients will not experience remission from their depressive episodes following the first trial with an antidepressant medication [32]. Further, 20–30% will go on to experience significant impairment despite several adequate medication and psychotherapeutic trials [4]. In recent years, novel so matic methods of treating MDD have emerged [29]. Among these, neuromodulatory treatments have shown great promise, particularly repetitive tr anscranial magnetic stimulation (rTMS). rTMS is an attractive treatment modality for its ability to safely and non-invasively modulate the activity of cortical

* Corresponding author at: Douglas Mental Health University Institute, 6875

LaSalle Blvd., FBC-3 Pavilion, Rm. F-3131-2, Montréal, Québec H4H 1R3, Canada. E-mail address: nrc.douglas@me.com (M.T. Berlim).

Table 1
Sample demographic characteristics.

	N (%) or mean ± standard deviation (M ± SD)
Gender	–
Male	3 (20%)
Female	12 (80%)
Age	44.87 ± 12.35 years
Education	15.20 ± 4.19 years
Duration of current depressive episode	34.60 ± 23.85 months
Number of depressive episodes	1.60 ± 1.45 episodes

targets through the principals of electromagnetic induction [10]. rTMS is a diverse tool, a treatment modality that can be applied to numerous cortical targets with various stimulation parameters. The most common stimulation site in MDD is the dorsolateral pre- frontal cortex (DLPFC) due to evidence suggesting dysregulation in this brain region [12,19], and meta-analyses of randomized controlled trials have demonstrated efficacy for both high- [7] and low-frequency [5] protocols in MDD.rTMS is a resource inten- sive intervention requiring significant material and human capital, in addition to extended daily time commitments on the part of patients. While effective for MDD, response to rTMS is difficult to predict and there are several negative placebo-controlled trials in the literature [9,15,18,27,28]. In light of this, improved prognostication may lead to better allocation of rTMS resources. Personality traits have garnered increasing attention in the treatment of MDD, both as prognostic tools relating to their trait characteristics but also as corollaries of response due to state-dependent characteristics. Indeed, as personality traits are associated with distinct neuroanatomical correlates and patterns of resting state brain activity [34] there is growing interest in their potential as neurophysiologial markers of pathway or circuit integrity, or of identification of suitable cortical regions for neuromodulation treatments. Both pharmacotherapy [1,38] and psychotherapy [38] have been associated with changes in neuroticism and extraversion. This finding has also been reported with rTMS for MDD, with decreases in neuroticism [3,37] and increases in extraversion [37] following treatment. Clearly, personality traits characterized in the context of an active psychiatric disorder will be subject to both state- and trait-influences. Indeed, of the primary personality dimensions in the five-factor model, neuroticism is most subject to state influences, while extraversion, agreeableness, conscientiousness and openness are less so [23]. In accordance with this, we have previously reported that baseline extraversion is proportionally related to antidepressant response with rTMS [3]. Until recently, cortical electromagnetic induction has been limited to superficial targets [17,28] as deeper brain regions require levels of energy for stimulation that are often not tolerated by subjects [30]. The new "H1 coil" (and its associated therapeutic procedure named deep transcranial magnetic stimulation [DTMS]) allows direct modulation of larger and deeper brain regions, at the expense of reduced focality [25] and has been shown to be effective in MDD [25,26]. To our knowledge, personality prediction of clinical response to DTMS treatment for MDD has not been yet characterized. We aimed to prospectively characterize personality traits in the prediction of antidepressant response to DTMS in treatment-resistant MDD. We hypothesized that DTMS would be associated with decreases in neuroticism, and that extraversion would predict clinical response.

2. Methods

2.1. Patients

Our open label clinical study was registered at www.clinicaltrials.gov (#NCT01409304) and was approved by the Douglas Mental Health University Institute's (DMHUI) Research Ethics Board. Written informed consent was obtained from all participants. Patients were recruited between October 2011 and November 2012 from the Depressive Disorders Program at the DMHIU – a tertiary care outpatient clinic providing specialized follow up for individuals with moderate to severe MDD. All participants had a primary diagnosis of at least a moderate unipolar major depressive episode (MDE) as assessed by the Mini International Neuropsychiatric Interview (MINI) [35], based on the DSM-IV, and the 21-item Hamilton Depression Rating Scale

(HAMD-21; i.e., a score ≥18) [20]. Also, they had to have failed to respond to at least three adequate courses of antidepressants (in terms of dose, duration and compliance) in the current MDE (as assessed by the Antidepressant Treatment History Form [33]). A total convenience sample of 17 depressed subjects was recruited. Of these, 15 completed the personality assessment at baseline, and 14 completed the reassessment at the conclusion of the study (one patient did not return the completed instrument).

2.2. Instruments evaluation

A psychiatrist (M.T.B.) performed baseline medical and psychiatric history assessments and safety screenings. Data was gathered at the conclusion of the study by a second psychiatrist (E.C.). The HAMD-21 [21] was used as a clinician-rated measure of depressive symptoms. Clinical response was defined as ≥50% reduction in HAMD-21 scores and clinical remission was defined as HAMD-21 score <9 [31]. Personality dimensions were assessed using the Big Five Inventory (BFI) [2], a self-report measure based on the FFM [39]. Reliability analyses revealed very good internal consistency for extraversion (= .85), agreeableness (= .81), conscientiousness (= .84), neuroticism (= .86), and openness (= .82).

2.3. Deep rTMS treatment

DTMS treatment for treatment resistant depression has been described elsewhere [6]. Briefly, DTMS was administered using a Magstim Rapid 2® magnetic stimulator (Magstim Company Ltd., U.K.) connected to an H1 coil. Over 4 weeks, patients received 20 daily DTMS sessions over the left dorsolateral prefrontal cortex (DLPFC) consisting of 75 trains (2 s, 20 s intertrain interval, and 3000 pulses per session) delivered at a frequency of 20 Hz and an intensity of 120% of the measured motor threshold, for a total of 60,000 magnetic pulses.

2.4. Statistical analyses

Statistical analyses were performed with IBM SPSS 19. Continuous variables were compared using Student's t-test, and dichotomous comparisons were performed using 2 comparisons. Change in personality variables as a function of DTMS was performed using repeated measures ANOVA. The utility of baseline personality variables in predicting DTMS antidepressant response was tested with multiple linear regressions. Statistical significance was set at ≤ 0.05.

3. Results

Sociodemographic characteristics of our sample are presented in Table 1. The clinical outcomes from this study are reported elsewhere [6]. Succinctly, response (≥50% reduction in HAMD-21 scores) and remission rates (HAMD-21 score <9) were 70.60% and 41.20%, respectively.

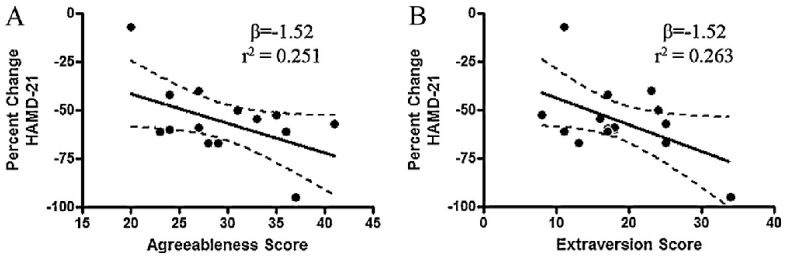
Table 2
Pearson correlation between depressive symptoms and personality.

	Baseline HAMD-21	Extraversion	Agreeableness	Conscientiousness	Neuroticism
Baseline HAMD-21	–	–	–	–	–
Extraversion	–.023	–	–	–	–
Agreeableness	–.435	.425	–	–	–
Conscientiousness	–.097	.768***	.290	–	–
Neuroticism	–.072	–.603*	.053	–.672**	–
Openness	–.666**	.402	.379	.458	–.307

* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table 3
Personality traits and clinical remission.

	Remission ($n = 4$) M ± SD	Non-remission ($n = 11$) M ± SD	t; p
Extraversion	22.25 ± 9.28	17.12 ± 5.52	1.33; $p = .205$
Agreeableness	35.75 ± 4.99	26.91 ± 4.57	3.24; $p = .006$
Conscientiousness	32.25 ± 5.90	24.00 ± 5.74	2.44; $p = .030$
Neuroticism	30.25 ± 7.32	32.27 ± 4.86	0.62; $p = .542$
Openness	37.56 ± 5.96	31.90 ± 4.53	1.94; $p = .076$



Pearson's correlations between baseline depressive symptoms and personality dimensions are presented in Table 2. Comparisons of baseline personality factors are presented in Table 3. Patients who went on to experience remission from their depressive symptoms had higher baseline agreeableness scores ($p < .01$) and higher conscientiousness scores ($p < .05$). An agree- ableness score ≥29 had 100% sensitivity and 72.7% specificity for clinical remission with DTMS. A conscientiousness score ≥30 had 75% sensitivity and 81.8% specificity for clinical remission with DTMS. Linear regressions with pre-intervention personality dimensions predicting percent change in HAMD-21 scores at the end of DTMS treatment and significant associations are illustrated in Fig. 1. Higher levels of extraversion ($F(1, 13) = 4.67$, $p = .050$, ˇ = −1.39; constant $p = .036$) and a trend towards higher levels of agree- ableness ($F(1,14) = 4.37$, $p = .057$, ˇ = −1.52; constant ns therefore removed) predicted greater antidepressant response with DTMS treatment. No other pre-intervention personality dimension pre- dicted anti-depressant response ($p > .188$). Finally, repeated measures ANOVA examining change in per- sonality dimensions as a function of DTMS. No significant changes in personality dimensions were identified ($.919 > p > .126$) nor were changes indentified after controlled for change in depressive symp- toms (% change in HAMD-21 scores; $p > .321$).

4. Discussion

We performed a prospective characterization of personality dimensions according to the five-factor model in an open label trial of DTMS for treatment-resistant MDD. To our knowledge, this is the first study to address this issue in the literature. Yet, similar characterizations have been reported in standard rTMS highlight- ing the importance of extraversion and neuroticism [3,37], but a paucity of findings related to other personality domains. Our analyses revealed that personality characterization has prognostic utility in DTMS for treatment-resistant MDD. Agreeable- ness and extraversion were proportionally associated the degree of antidepressant response to DTMS. Meanwhile, higher agree- ableness scores (score ≥29:100% sensitive and 72.7% specific) and conscientiousness scores (score ≥30:75% sensitive and 81.8% spe- cific) were associated with eventual clinical remission. Agreeableness relates to an aggregation of pro-social traits such as altruism, theory of mind, and empathy [8]. In our study, higher levels of this personality trait were both categorically related to clinical remission and linearly related to the degree of antidepres- sant response. While we did not initially hypothesize the predictive importance of agreeableness, it has interesting implications for DTMS. Experimental standard TMS has revealed that stimulation of the left DLPFC (our stimulation site) results in inter-hemispheric propagation proportional to the individual's level of agreeableness [22]. Higher levels of agreeableness, therefore, may reflect a neu- roanatomical correlate, such as integrity of the corpus callosum, of suitability for neuromodulation as a treatment for MDD. Conscientiousness, in turn, relates to a constellation of behaviours consistent with delayed gratification, self-discipline and cognitive control [8]. In volumetric studies, this personality domain has been linked to DLPFC [11], and therefore it is perhaps unsurprising that conscientiousness was related to antidepressant response with DTMS of the left DLPFC. As such, it may serve as a marker of pre-morbid neuropsychological function [11] and thus

a marker of potential for improvement in MDD-related cognitive impairment. Extraversion is considered an aggregation of traits that are related to sensitivity to reward and a tendency to experience pos- itive emotions [8]. Our findings with respect to extraversion were consistent with our hypotheses and with our previous analyses in standard rTMS [3]. Our design cannot exclude the possibility of extraversion predicting antidepressant response independent of DTMS. Indeed, there is data to suggest that higher degrees of extraversion are associated with a higher likelihood of positive life events, and that this association moderates the relationship between extraversion and improved clinical outcomes [36]. Simi- larly, DTMS may act in concert with the structured environment in which it takes place as a form of behavioral activation therapy [24]. Contrary to previous pharmacotherapy [1,38], psychotherapy
[38] and rTMS [3,37] trials in MDD reporting decreases in neuroti- cism, our analyses did not reveal changes in any of the five-factor personality domains with DTMS, including neuroticism. Given the small sample size, it is premature to conclude that DTMS is not associated with alterations in neuroticism, however in light of sig- nificant effects emerging from even smaller standard rTMS samples [3,37], DTMS may have a lesser effect on neuroticism. This will require replication and investigation in larger samples.

5. Limitations

This study is limited by a small sample size, a convenience sam- ple, and the absence of a control group. However, in regards to the latter, indirect evidence suggests that the placebo response rates are much lower in subjects with resistant MDD as compared to those with uncomplicated MDD [13,14,16]. Randomized, sham-controlled evidence is needed to determine the independent role of personality dimensions in DTMS and standard rTMS for treat- ing MDD. Our assessment of personality traits was during a major depressive episode, and while it is reflective of information that may be used for clinical decision-making and prognostication, it is complicated by both trait and state-dependent influences.

6. Conclusion

Five-factor personality assessment may have prognostic value in DTMS treatment for MDD. Agreeableness, extraversion, and consci- entiousness are associated with decreases in depressive symptoms in resistant MDD during treatment with DTMS.

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