HHS Public Access

Author manuscript

J Psychiatr Pract. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

J Psychiatr Pract. 2016 May ; 22(3): 193–202. doi:10.1097/PRA.0000000000000150.

Use of the Temperament and Character Inventory to Predict Response to Repetitive Transcranial Magnetic Stimulation for Major Depression

Shan H. Siddiqi, MD, **Ravikumar Chockalingam, MD**, **C. Robert Cloninger, MD**, **Eric J. Lenze, MD**, and **Pilar Cristancho, MD**

Department of Psychiatry, Washington University School of Medicine in St. Louis, St. Louis, MO

Abstract

Objective—. The goal of this study was to investigate the utility of the Temperament and Character Inventory (TCI) in predicting antidepressant response to repetitive transcranial magnetic stimulation (rTMS).

Background—Although rTMS of the dorsolateral prefrontal cortex (DLPFC) is an established antidepressant treatment, little is known about predictors of response. The TCI measures multiple personality dimensions (harm avoidance, novelty seeking, reward dependence, persistence, self-directedness, self-transcendence, and cooperativeness), some of which have predicted response to pharmacotherapy and cognitive-behavioral therapy. A previous study suggested a possible association between self-directedness and response to rTMS in melancholic depression, although this was limited by the fact that melancholic depression is associated with a limited range of TCI profiles.

Methods—. Nineteen patients with a major depressive episode completed the TCI prior to a clinical course of rTMS over the DLPFC. Treatment response was defined as ≥50% decrease in scores on the Hamilton Rating Scale for Depression (HAM-D). Baseline scores on each TCI dimension were compared between responders and non-responders via analysis of variance. Pearson correlations were also calculated for temperament/character scores in comparison with percentage improvement in HAM-D scores.

Results—Eleven of the 19 patients responded to rTMS. T-scores for persistence were significantly higher in responders than in non-responders (P=0.022). Linear regression revealed a correlation between persistence scores and percentage improvement in HAM-D scores.

Conclusions—Higher persistence scores predicted antidepressant response to rTMS. This may be explained by rTMS-induced enhancement of cortical excitability, which has been found to be decreased in patients with high persistence. Personality assessment that includes measurement of TCI persistence may be a useful component of precision medicine initiatives in rTMS for depression.

Please send correspondence to: Shan Siddiqi, MD, Department of Psychiatry, Washington University School of Medicine in St. Louis, Box 8134, 660 S Euclid Ave., St. Louis, MO 63110 (cristanp@psychiatry.wustl.edu).

Keywords

depression; major depressive disorder; temperament; character; Temperament and Character Inventory (TCI); transcranial magnetic stimulation (TMS); repetitive TMS (rTMS); dorsolateral prefrontal cortex

The antidepressant efficacy of repetitive transcranial magnetic stimulation (rTMS) has been supported by a growing number of clinical trials,[1–3] leading to its approval by the U.S. Food and Drug Administration for the treatment of major depressive disorder in 2008.[4] More recent studies have demonstrated that differential treatment parameters are effective for patients with varying degrees of treatment-resistant illness.[5–7] When rTMS is effective, its antidepressant effects have been demonstrated to persist well beyond the initial course of treatment.[8] However, the utility of rTMS is somewhat limited by the fact that not all studies have found positive results, although this has been associated with methodological variability; as a result, more recent treatment protocols have found better results than older studies.[9]

A major limitation for the widespread use of rTMS is that it is difficult to predict which patients will improve, thereby necessitating significant financial and/or time investment despite uncertainty regarding potential efficacy for any given patient. To this effect, some factors that might predict response to rTMS have been thoroughly investigated. For example, baseline clinical characteristics that are associated with higher response rates include concurrent antidepressant pharmacotherapy,[10] fewer earlier treatment failures, a shorter duration of the current mood episode, and absence of a concurrent anxiety disorder.[11] Impaired response is associated with the converse of these factors, as well as with benzodiazepine or anticonvulsant pharmacotherapy.[10] Response in older patients is improved when increased doses are used to overcome the higher coil-to-cortex distance caused by cerebral atrophy in these populations.[12]

Several biomarkers that may predict some degree of treatment response have also been identified. Studies have reported algorithms involving various electroencephalographic parameters for this purpose, although these studies have yet to be replicated in a prospective design.[13,14] Anterior cingulate cortex activity and prefrontal cortex activity have shown predictive capability in various neuroimaging studies, but these findings are not unique to rTMS and are also found in patients more likely to respond to other treatments.[15–20] Electromyography-based motor cortex excitability has also demonstrated some limited utility in predicting response.[21] More recent data have suggested involvement of functional network connectivity, including activity of frontostriatal networks[22,23] and the default mode network.[24] While most of these variables are promising tools, none of them has yet been validated to the point of routine clinical utility.

In addition to direct biological measures, response to various treatments has also been predicted by the Temperament and Character Inventory, an objective questionnaire that assesses a seven-factor psychobiologic model of quantifiable personality traits (Fig 1), which have been validated on the basis of various genetic and neurobiologic data. Four temperament dimensions—harm avoidance, novelty seeking, reward dependence, and

persistence—are rooted primarily in various neurobiologic data. Three character dimensions —self-directedness, cooperativeness, and self-transcendence—develop based on social learning.[25] Harm avoidance, which tends to be associated with baseline anxiety, has been correlated with serotonin transporter polymorphisms[26] and has repeatedly been shown to predict response to serotonergic pharmacotherapy.[27–30] In addition, self-directedness has been correlated with response to cognitive-behavioral therapy in major depressive disorder[31] and various other illnesses, such as obsessive-compulsive disorder and eating disorders.[32,33]

One previous study has also reported improved rTMS response in patients with melancholic treatment-resistant depression who demonstrated high self-directedness as measured by the TCI, but this study was limited by the restricted range of temperaments and characters inherent in patients with melancholic depression.[34] The results of other studies that have investigated a five-factor personality model previously suggested that extraversion may be associated with improved response to both rTMS[35] and deep TMS,[7] although the significance of this finding was somewhat limited by the fact that extraversion is generally associated with improved outcomes independent of treatment modality.[36] To summarize, further characterization of personality profiles that may predict response to rTMS is warranted. The goal of this study was to investigate the utility of the TCI in predicting antidepressant response to rTMS in a general clinical sample of patients receiving rTMS during a major depressive episode.

METHODS

Subjects

We used a convenience sample of outpatients treated in the Transcranial Magnetic Stimulation Program at Washington University in St. Louis. Patients' diagnoses and appropriateness for treatment were assessed by the senior author (P.C.). All patients were determined to be in a major depressive episode as defined by DSM-IV-TR criteria and had no absolute contraindications to rTMS. All patients agreed to serial assessments during clinical treatment with rTMS and signed informed consent to allow naturalistic data collection as they were undergoing rTMS treatments. This protocol was approved by the Washington University School of Medicine Institutional Review Board. Patients bore the treatment costs.

Instruments

Subjects completed a baseline written version of the TCI, the TCI-R 140, which was scored by the Center for Well-Being at Washington Univerity in St. Louis. The instrument contains 140 questions about personality traits that patients rate on a 5-point scale. Scoring of these responses is based on statistical norms of the 4 temperament dimensions (harm avoidance, novelty seeking, reward dependence, and persistence) and the 3 character dimensions (self-directedness, cooperativeness, self-transcendence). (Figure 1).[37] Investigators were blinded to the results of the TCI until after completion of the treatment course.

Severity of depression and improvement in depression symptoms were assessed by the senior author using the 16-item Hamilton Rating Scale for Depression (Ham-D).[38] The

Ham-D was completed at the initial visit, after 2 weeks (after 10 rTMS sessions), and at the end of treatment. Treatment response was defined as ≥50% decrease in Ham-D scores.

rTMS Treatment

All subjects received a clinical protocol with high frequency (10Hz) rTMS over the left dorsolateral prefrontal cortex (DLPFC) at 4000 pulses on consecutive weekdays for up to 20 treatments using a Magpro R30 device (MagVenture, Tonica Elektronik, Denmark). Additional slow (1Hz) rTMS at 600 to 1200 pulses over the right DLPFC was used for augmentation in subjects who had not achieved at least 25% improvement in Ham-D scores after 10 high frequency unilateral treatments, to complete 20 treatments. Some subjects received a longer treatment course for up to 30 rTMS sessions.

Statistical Analyses

Baseline scores on each TCI dimension and baseline clinical characteristics were compared between responders and nonresponders via single-measure analysis of variance (ANOVA) with significance at $P<0.05$. The relationship between temperament/character scores and percentage improvement in Ham-D scores was also analyzed using linear regression analysis. Pearson correlation coefficients were compared for each temperament/character score against baseline Ham-D score and percentage improvement in Ham-D. Statistical analysis was completed using SPSS version 23 (IBM Corp, Armonk, NY).

RESULTS

Twenty patients were enrolled and received a course of rTMS, 1 of whom did not complete the treatment course and was excluded from analysis due to missing data. Baseline clinical characteristics of this sample are summarized in Table 1. The response rate to rTMS was 58% (11/19). A subgroup of 8 patients received augmentation with right-sided rTMS treatment. The mean improvement in scores on the Ham-D was 46% (95% CI 26%–67%) in the overall group, 1% in non-responders (95% CI 19%–22%), and 79% in responders (95% CI 71%–87%). No significant differences in clinical characteristics were found between responders (subjects with ≥50% decrease in Ham-D scores) and nonresponders, although the number of features indicating treatment-resistant illness, such as previous trials of electroconvulsive therapy and antidepressant resistance, were higher in the nonresponders group. (Table 1). Treatments were well-tolerated with no serious side effects or seizures.

Pearson correlations of baseline personality characteristics with baseline Ham-D scores and improvement in Ham-D scores are summarized in Table 2. Persistence was directly correlated with improvement in Ham-D scores ($R=0.55$, $P=0.015$), while self-directedness was inversely correlated with baseline Ham-D scores ($R=-0.65$, $P=0.0025$).

Mean T-scores for comparisons of individual personality characteristics between responders and nonresponders are presented in Table 3 Persistence scores were significantly higher in responders (T-score 47, 95% CI 40–54) than in non-responders (T-score 34, 95% CI 22–45), $F(1,17) = 6.3$, $P=0.022$. Of note, 1 subject who demonstrated response despite a low persistence score had a rapid response, demonstrating remission (improvement in Ham-D

score from 18 to 6) within 2 weeks of starting treatment. None of the other personality traits predicted rTMS response.

The only personality characteristic that was associated with a significant improvement in Ham-D scores was persistence. A comparison of linear regression of T-scores for persistence with percentage improvement in Ham-D scores is shown in Figure 2; the associated Pearson correlation coefficients for all temperament/character traits are summarized in Table 2.

DISCUSSION

On the basis of analysis of baseline TCI personality traits before a course of rTMS, persistence was the only trait found to be correlated with rTMS response. Of note, persistence was not correlated with severity of depressive symptoms at baseline, suggesting that this effect is independent of illness severity. In contrast, self-directedness was correlated with depression severity at baseline, which is consistent with earlier literature demonstrating that major depression is associated with lower self-directedness.[39–41] Patient characteristics that were examined, which included age, history of electroconvulsive therapy (ECT), suicide attempts, and inpatient hospitalizations, treatment-resistant illness (defined by failure to respond adequately to 3 previous antidepressant trials); and baseline Ham-D scores, were not associated with treatment response in this sample. Although this result contrasts with existing literature indicating that treatment resistance is a predictor of response to TMS,[11] we suspect that the effect of treatment resistance was not significant in this study due to the small sample size.

While response to rTMS has previously been reported to be correlated with TCI self-directedness,[34] the study in which this was found investigated only patients with melancholic depression, which tends to be associated with decreased persistence (Fig 1). Therefore, that study did not investigate general major depression with a full distribution of persistence scores. The authors of that study also postulated that the improvement may have been related to the fact that low self-directedness is associated with personality disorders, which were not specifically excluded in the study.[34] In contrast, our study investigated a convenience sample of patients referred for rTMS treatment, which may have led to selection bias introduced by the possibility that a patient's primary psychiatrist may be less likely to refer a patient for a brain stimulation treatment such as rTMS when symptoms appear to be attributable to a personality disorder. Of note, prior literature has also suggested a lower probability of ECT response in patients with melancholic features in the absence of psychosis (contrary to the popular conception that melancholic features are a predictor of ECT response, which was found to be true only when considering presence of psychosis),[42] suggesting that a similar phenomenon may be at play in the role of melancholia in ECT response.

As noted earlier in the article, an earlier study investigated the utility of personality traits as measured using the Big Five Questionnaire (BFQ) for predicting response to rTMS,[35] and a subsequent study by the same group used the same methodology to analyze BFQ traits as predictors of response to deep TMS.[43] However, these studies found that multiple personality traits rather than any single specific trait were somewhat predictive of response.

The only trait that was found to be somewhat predictive of response in both studies was extraversion, which has also been shown to be correlated with improved prognosis for major depressive disorder in general, without consideration of treatment modality.[36] This variability may be related to the fact that the BFQ is not based on a specific theoretical model,[44] suggesting that individual traits may not be associated with specific neurbiological changes[45] that are being targeted by rTMS. To our knowledge, our study is the first to demonstrate the predictive capability of a psychobiologic personality model such as the TCI in predicting response to rTMS in a broad range of patients with MDD.

The association of persistence with response to rTMS may be explained by the fact that persistence has been found to be inversely proportional to baseline left hemispheric motor cortical reactivity, as measured by optical neuroimaging.[46] Because rTMS enhances ipsilateral cortical excitability[47] in a manner that is subject to interindividual variation,[48] patients with lower baseline excitability and/or interhemispheric differences in activity may be more likely to respond to rTMS.[49,50]

rTMS responders have also been shown to have greater fluctuations in resting motor threshold, lending further credence to the notion that the degree of modulation of motor cortical excitability is related to response to rTMS.[51] This finding may also provide some explanation for the effect of age on probability of response to rTMS,[52] since interindividual and interhemispheric variation in cortical excitability has been attributed in part to age-related changes.[53] In combination with this earlier research, our study suggests that persistence may be used as a proxy marker for cortical reactivity, particularly in the dominant hemisphere, thus being a potential predictor of rTMS response. However, this speculative hypothesis is limited by the fact that there was no relationship between rTMS response and novelty seeking, which was shown to be directly correlated with cortical reactivity in the study mentioned above that showed an inverse correlation between persistence and cortical reactivity.[46]

An alternate explanation for the effect observed in our study is that higher persistence is associated with increased functional connectivity between the prefrontal cortex and the ventral striatum.[54] A recent study found that successful rTMS for major depressive disorder decreases connectivity in affective divisions of frontostriatal loops,[23] suggesting that depressed patients with higher baseline connectivity may be more likely to respond to rTMS. This effect was attributed to a earlier finding by the same group showing that rTMS attenuated baseline hyperactivity in the default mode network,[24] which is thought to be modulated via dopamine release from the striatum.[55]

Our findings are distinct from the TCI profiles associated with antidepressant response to other treatments. For instance, response to selective serotonin reuptake inhibitors has been found to be correlated with high levels of harm avoidance,[27–30] whereas response to cognitive behavioral therapy has been found to be correlated with high levels of self-directedness.[31] These findings suggest that a identifying a high level of persistence may be a useful tool for determining which patients are likely to respond to rTMS despite having failed other treatments.

Our study is limited by the small sample size, the use of a convenience sample, and the lack of biomarkers other than personality traits. Future research should include baseline optical neuroimaging to prospectively investigate the relationship between rTMS response, persistence, and cortical excitability. In the meantime, we plan to use this paradigm involving the TCI to predict response to ECT to elucidate whether it may be possible to determine the appropriateness of different neuromodulatory therapies based on a patient's TCI profile.

CONCLUSIONS

Higher levels of persistence predicted antidepressant response to rTMS. Personality assessment that includes measurement of persistence may be a useful component of future precision medicine initiatives in rTMS for depression.

Acknowledgments

The authors thank the Barnes-Jewish Hospital Foundation for its support of the Transcranial Magnetic Stimulation Program at Washington University. We also thank Kathryn Money for assistance with scoring TCIs.

Research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under award R34MH101433. The Content is solely the responsibility of the authors and does not neccesarily represent the official views of the National Institutes of Health. The authors acknowledge the Center for Well-Being, Washington University in St. Louis, for administration and scoring of Temperament and Character Inventories (TCI) as well as travel support to Dr. Siddiqi to present preliminary findings at the 2015 meeting of the International Society for ECT and Neuromodulation 2015 meeting in Toronto.

References

1. George MS, Wassermann EM, Williams WA, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport. 1995; 6:1853–1856. [PubMed: 8547583]
2. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry. 2010; 67:507–516. [PubMed: 20439832]
3. Connolly KR, Helmer A, Christancho MA, et al. Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center. J Clin Psychiatry. 2012; 73:e567–573. [PubMed: 22579164]
4. George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. Curr Opin Psychiatry. 2013; 26:13–18. [PubMed: 23154644]
5. Pascual-Leone A, Rubio B, Pallardó F, et al. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet. 1996; 348:233–237. [PubMed: 8684201]
6. Fitzgerald PB, Benitez J, de Castell A, et al. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiatry. 2006; 163:88–94. [PubMed: 16390894]
7. McGirr A, Van den Eynde F, Tovar-Perdomo S, et al. Effectiveness and acceptability of accelerated repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant major depressive disorder: an open label trial. J Affect Disord. 2015; 173:216–220. [PubMed: 25462419]
8. Mantovani A, Pavlicova M, Avery D, et al. Long-term efficacy of repeated daily prefrontal transcranial magnetic stimulation (TMS) in treatment-resistant depression. Depress Anxiety. 2012; 29:883–890. [PubMed: 22689290]

9. Gross M, Nakamura L, Pascual-Leone A, et al. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. Acta Psychiatr Scand. 2007; 116:165–173. [PubMed: 17655557]
10. Dumas R, Padavoni R, Richieri R, et al. Repetitive transcranial magnetic stimulation in major depression: response factor. Encephale. 2012; 38:360–368. [PubMed: 22980479]
11. Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. Neuropsychopharmacology. 2009; 34:522–534. [PubMed: 18704101]
12. Nahas Z, Li X, Kozel FA, et al. Safety and benefits of distance-adjusted prefrontal transcranial magnetic stimulation in depressed patients 55–75 years of age: a pilot study. Depress Anxiety. 2004; 19:249–256. [PubMed: 15274174]
13. Arns M, Drinkenburg WH, Fitzgerald PB, et al. Neurophysiological predictors of non-response to rTMS in depression. Brain Stimul. 2012; 5:569–576. [PubMed: 22410477]
14. Khodayari-Rostamabad A, Reilly JP, Hasey GM, et al. Using pre-treatment electroencephalography data to predict response to transcranial magnetic stimulation therapy for major depression. Conf Proc IEEE Eng Med Biol Soc. 2011; 2011:6418–6421. [PubMed: 22255807]
15. Langguth B, Wiegand R, Kharraz A, et al. Pre-treatment anterior cingulate activity as a predictor of antidepressant response to repetitive transcranial magnetic stimulation (rTMS). Neuro Endocrinol Lett. 2007; 28:633–638. [PubMed: 17984932]
16. Micoulaud-Franchi JA, Richieri R, Boyer L, et al. Combining neurophysiological and functional neuroimaging biomarkers to predict rTMS non-response in depression. Brain Stimul. 2013; 6:461–463. [PubMed: 22910170]
17. Hernández-Ribas R, Deus J, Pujol J, et al. Identifying brain imaging correlates of clinical response to repetitive transcranial magnetic stimulation (rTMS) in major depression. Brain Stimul. 2013; 6:54–61. [PubMed: 22417767]
18. Kito S, Hasegawa T, Koga Y. Cerebral blood flow ratio of the dorsolateral prefrontal cortex to the ventromedial prefrontal cortex as a potential predictor of treatment response to transcranial magnetic stimulation in depression. Brain Stimul. 2012; 5:547–553. [PubMed: 22019081]
19. Richieri R, Boyer L, Farisse J, et al. Predictive value of brain perfusion SPECT for rTMS response in pharmacoresistant depression. Eur J Nucl Med Mol Imaging. 2011; 38:1715–1722. [PubMed: 21647787]
20. Weiduschat N, Dubin MJ. Prefrontal cortical blood flow predicts response of depression to rTMS. J Affect Disord. 2013; 150:699–702. [PubMed: 23707032]
21. Fitzgerald PB, Brown TL, Marston NA, et al. Motor cortical excitability and clinical response to rTMS in depression. J Affect Disord. 2004; 82:71–76. [PubMed: 15465578]
22. Salomons TV, Dunlop K, Kennedy SH, et al. Resting-state cortico-thalamic-striatal connectivity predicts response to dorsomedial prefrontal rTMs in major depressive disorder. Neuropsychopharmacology. 2013; 39:488–498. [PubMed: 24150516]
23. Avissar, M.; Powell, F.; Casey, BJ., et al. Annual Meeting of the International Society for ECT and Neurostimulation. Toronto, ON: 2015. TMS over the left dorsolateral prefrontal cortex modulates frontostriatal connectivity in depression.
24. Liston C, Chen AC, Zebley BD, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. Biol Psychiatry. 2014; 76:517–526. [PubMed: 24629537]
25. Cloninger CR, Svrakic DM. Integrative psychobiological approach to psychiatric assessment and treatment. Psychiatry. 1997; 60:120–141. [PubMed: 9257353]
26. Mandelli L, Mazza M, Martinotti G, et al. Harm avoidance moderates the influence of serotonin transporter gene variants on treatment outcome in bipolar patients. J Affect Disord. 2009; 119:205–209. [PubMed: 19332357]
27. Quilty LC, Godfrey KM, Kennedy SH, et al. Harm avoidance as a mediator of treatment response to antidepressant treatment of patients with major depression. Psychother Psychosom. 2010; 79:116–122. [PubMed: 20090398]

28. Kampman O, Poutanen O, Illi A, et al. Temperament profiles, major depression, and response to treatment with SSRIs in psychiatric outpatients. Eur Psychiatry. 2012; 27:245–249. [PubMed: 20933372]
29. Joyce PR, Mulder RT, McKenzie JM, et al. Atypical depression, atypical temperament and a differential antidepressant response to fluoxetine and nortriptyline. Depress Anxiety. 2004; 19:180–186. [PubMed: 15129420]
30. Hirano S, Sato T, Narita T, et al. Evaluating the state dependency of the Temperament and Character Inventory dimensions in patients with major depression: a methodological contribution. J Affect Disord. 2002; 69:31–38. [PubMed: 12103449]
31. Johansson R, Lyssarides C, Andersson G, et al. Personality change after Internet-delivered cognitive behavior therapy for depression. PeerJ. 2013; 1:e39. [PubMed: 23638375]
32. Corchs F, Corregiari F, Ferräo YA, et al. Personality traits and treatment outcome in obsessive-compulsive disorder. Rev Bras Psiquiatr. 2008; 30:246–250. [PubMed: 18833426]
33. Anderson CB, Joyce PR, Carter FA, et al. The effect of cognitive-behavioral therapy for bulimia nervosa on temperament and character as measured by the temperament and character inventory. Compr Psychiatry. 2002; 43:182–188. [PubMed: 11994835]
34. Baeken C, Desmyter S, Duprat R, et al. Self-directedness: an indicator for clinical response to the HF-rTMS treatment in refractory melancholic depression. Psychiatry Res. 2014; 220:269–274. [PubMed: 25175912]
35. Berlim MT, Mcgirr A, Beaulieu MM, et al. Are neuroticism and extraversion associated with the antidepressant effects of repetitive transcranial magnetic stimulation (rTMS)? An exploratory 4-week trial. Neurosci Lett. 2013; 534:306–310. [PubMed: 23291399]
36. Spinhoven P, Elzinga B, Roelofs K, et al. The effects of neuroticism, extraversion, and positive and negative life events on a one-year course of depressive symptoms in euthymic previously depressed patients versus healthy controls. J Nerv Ment Dis. 2011; 199:684–689. [PubMed: 21878783]
37. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry. 1993; 50:975–990. [PubMed: 8250684]
38. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23:56–62. [PubMed: 14399272]
39. Zaninotto L, Souery D, Calati R, et al. Temperament and character profiles in bipolar I, bipolar II and major depressive disorder: impact over illness course, comorbidity pattern and psychopathological features of depression. J Affect Disord. 2015; 184:51–59. [PubMed: 26070046]
40. Hansenne M, Reggers J, Pinto E, et al. Temperament and character inventory (TCI) and depression. J Psychiatr Res. 1999; 33:31–36. [PubMed: 10094237]
41. Takahashi M, Shirayama Y, Muneoka K, et al. Personality traits as risk factors for treatment-resistant depression. PLoS One. 2013; 8:e63756. [PubMed: 23717477]
42. Fink M, Rush AJ, Knapp R, et al. DSM melancholic features are unreliable predictors of ECT response: a CORE publication. J ECT. 2007; 23:139–146. [PubMed: 17804986]
43. McGirr A, Van den Eynde F, Chachamovich E, et al. Personality dimensions and deep repetitive transcranial magnetic stimulation (DTMS) for treatment-resistant depression: a pilot trial on five-factor prediction of antidepressant response. Neurosci Lett. 2014; 563:144–148. [PubMed: 24486892]
44. Block J. The five-factor framing of personality and beyond: some ruminations. Psychological Inquiry. 2010; 21:2–25.
45. Eysenck HJ. Four ways five factors are not basic. Pers Individ Dif. 1992; 13:667–673.
46. Ito M, Fukuda M, Suto T, et al. Increased and decreased cortical reactivities in novelty seeking and persistence: a multichannel near-infrared spectroscopy study in healthy subjects. Neuropsychobiology. 2005; 52:45–54. [PubMed: 15942263]
47. Pell GS, Roth Y, Zangen A. Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: influence of timing and geometrical parameters and underlying mechanisms. Prog Neurobiol. 2011; 93:59–98. [PubMed: 21056619]

48. Nettekoven C, Volz LJ, Leimbach M, et al. Inter-individual variability in cortical excitability and motor network connectivity following multiple blocks of rTMS. Neuroimage. 2015; 118:209–218. [PubMed: 26052083]

49. Cheeran B, Talelli P, Mori F, et al. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. J Physiol. 2008; 586:5717–5725. [PubMed: 18845611]

50. Spampinato C, Aguglia E, Concerto C, et al. Transcranial magnetic stimulation in the assessment of motor cortex excitability and treatment of drug-resistant major depression. IEEE Trans Neural Syst Rehabil Eng. 2013; 21:391–403. [PubMed: 23559064]

51. Pallanti S, Di Rollo A, Antonini S, et al. Low-frequency rTMS over right dorsolateral prefrontal cortex in the treatment of resistant depression: cognitive improvement is independent from clinical response, resting motor threshold is related to clinical response. Neuropsychobiology. 2012; 65:227–235. [PubMed: 22653158]

52. Pallanti S, Cantisani A, Grassi G, et al. rTMS age-dependent response in treatment-resistant depressed subjects: a mini-review. CNS Spectr. 2012; 17:24–30. [PubMed: 22790115]

53. Bashir S, Perez JM, Horvath JC, et al. Differential effects of motor cortical excitability and plasticity in young and old individuals: a Transcranial Magnetic Stimulation (TMS) study. Front Aging Neurosci. 2014; 6:111. [PubMed: 24959141]

54. Gusnard DA, Olinger JM, Shulman GL, et al. Persistence and brain circuitry. Proc Natl Acad Sci U S A. 2003; 100:3479–3484. [PubMed: 12626765]

55. Dang LC, Donde A, Madison C, et al. Striatal dopamine influences the default mode network to affect shifting between object features. J Cogn Neurosci. 2012; 24:1960–1970. [PubMed: 22640392]

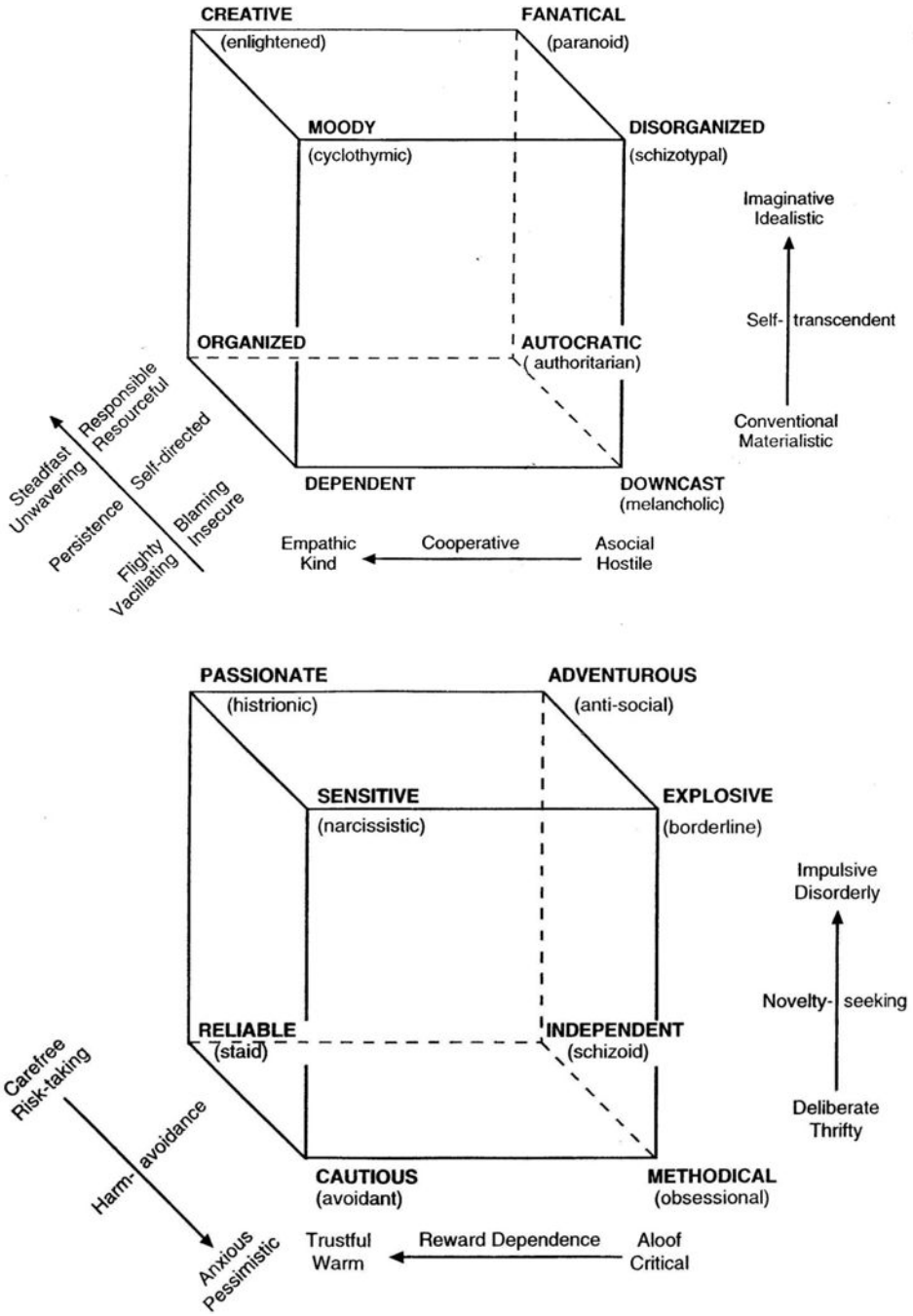

Figure 1. Temperament and Character Cubes (Reproduced with permission of the Center for Well-Being, Washington University in St. Louis)

Summary of specific personality traits and psychopathology associated with variability in each temperament and character score as measured by the Temperament and Character Inventory (TCI). Individual TCI traits have been validated on the basis of various genetic and neurobiological data.

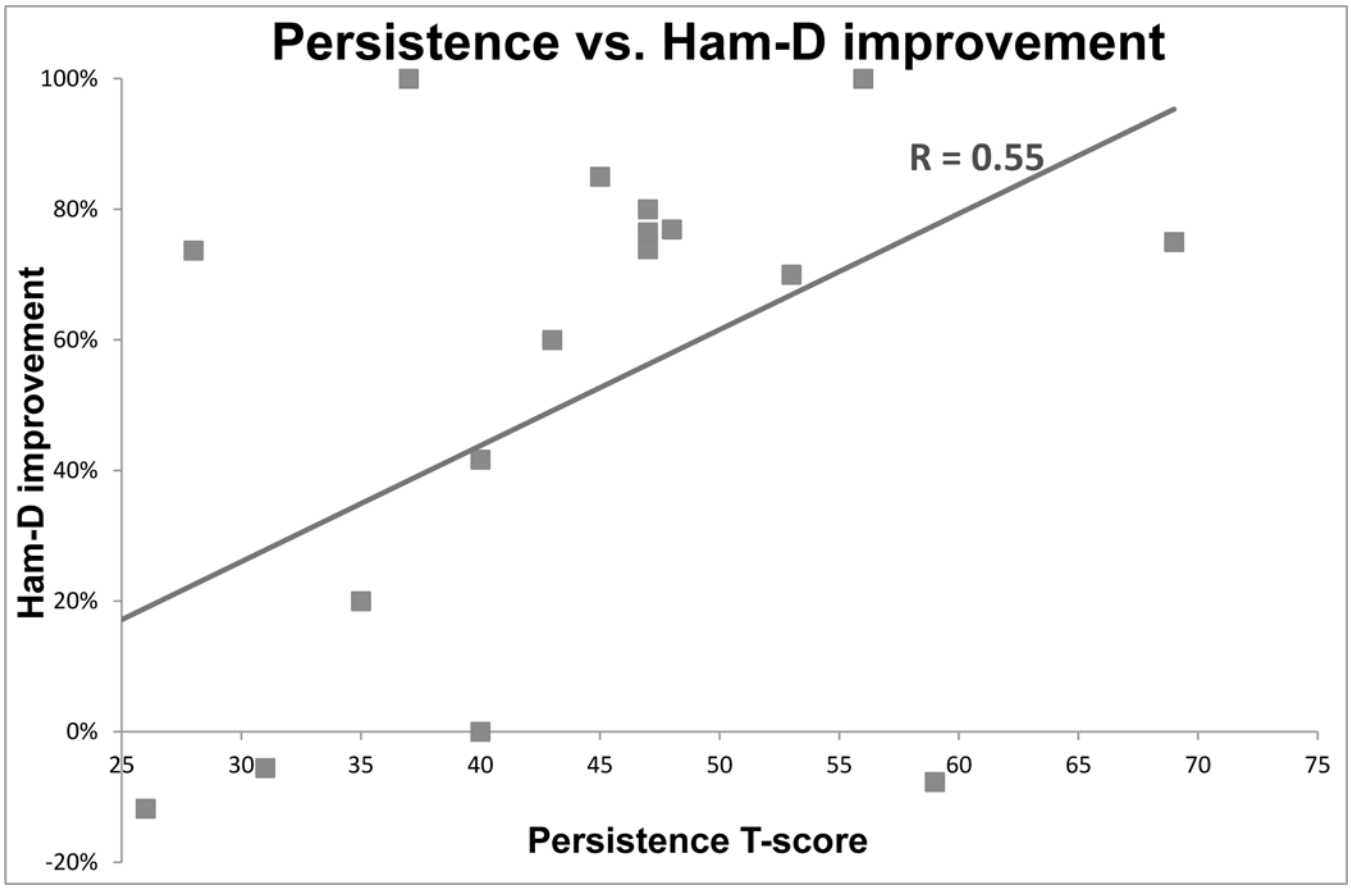

Figure 2. Temperament and character scores vs. percent improvement in Ham-D scores

Ham-D: Hamilton Rating Scale for Depression

Persistence demonstrated a significant correlation with percentage improvement in Ham-D scores on the basis of linear regression (R=0.55).

Table 1

Clinical characteristics of patients receiving rTMS

	Overall *n*=19		Non-responders *n*=8		Responders *n*=11		*P*
Characteristic	**Mean±SD**	**95% CI**	**Mean±SD**	**95% CI**	**Mean±SD**	**95% CI**	
Age (y)	47±17	38.1–54.9	49±17	34.6–63.9	45±18	32.5–56.6	0.58
Sex[1]	68% F	n/a	62% F	n/a	73% F	n/a	0.64[2]
Previous ECT trials (lifetime)	0.2±0.4	0.01–0.4	0.4±0.5	−0.1–0.8	0.1±0.3	−0.1–0.3	0.10
Suicide attempts (lifetime)	0.3±0.7	0–0.6	0.1±0.4	−0.2–0.4	0.4±0.8	−0.2–0.9	0.51
Hospitalizations (lifetime)	0.9±0.8	0.5–1.2	0.7±0.8	0.02–1.4	1.0±0.8	0.5–1.5	0.45
Treatment resistance[1,3]	84%	n/a	100%	n/a	73%	n/a	0.11[2]
Baseline Ham-D	15±5	13.0–17.6	15±3	12.0–18.0	16±6	11.8–19.3	0.81

CI: confidence interval; n/a: not applicable; ECT: electroconvulsive therapy; Ham-D: Hamilton Rating Scale for Depression

No significant difference was found in baseline demographics, severity of illness, or treatment resistance between responders and nonresponders.

[1] Percentages reported rather than mean/SD/CI.

[2] Chi square uesd in lieu of t-test for categorical variables.

[3] Treatment resistance was defined as failure to achieve an adequate response to more than 3 previous antidepressant trials.

Table 2

Pearson coefficients indicating correlation between baseline TCI personality characteristics and baseline depression severity and between baseline TCI personality characteristics and improvement in depression

	Correlation with baseline Ham-D score	*p*	Correlation with percentage improvement in Ham-D scores	*p*
Harm avoidance	−0.24	0.32	0.11	0.66
Novelty seeking	0.24	0.32	−0.22	0.37
Reward dependence	0.10	0.68	−0.32	0.19
Persistence	0.03	0.89	**0.55**	**0.015**
Self-directedness	**−0.65**	**0.0025**	0.08	0.74
Cooperativeness	−0.06	0.82	−0.11	0.66
Self-transcendence	−0.07	0.77	0.40	0.093

TCI: Temperament and Character Inventory; Ham-D: Hamilton Rating Scale for Depression

Self-directedness was correlated with severity of baseline depression. Persistence demonstrated significant correlation with percentage improvement in Ham-D scores.

Table 3

Comparison of TCI characteristics in rTMS responders and nonresponders

Temperament/character	Non-responders (T-score) *n=8*		Responders (T-score) *n=11*		*p*
	Mean±SD	95% CI	Mean±SD	95% CI	
Harm avoidance	68±11	58–77	65±7	60–69	0.48
Novelty seeking	45±11	35–54	47±13	38–55	0.75
Reward dependence	54±11	45–63	47±9	41–53	0.11
Persistence	34±13	22–45	47±10	40–54	0.022
Self-directedness	32±14	21–44	37±10	30–43	0.44
Cooperativeness	49±13	38–59	45±9	38–52	0.47
Self-transcendence	38±7	32–43	43±7	38–48	0.11

TCI: Temperament and Character Inventory; CI: confidence interval

Significant differences in TCI scores on persistence were found between responders and nonresponders. No other traits demonstrated a statistically significant difference.