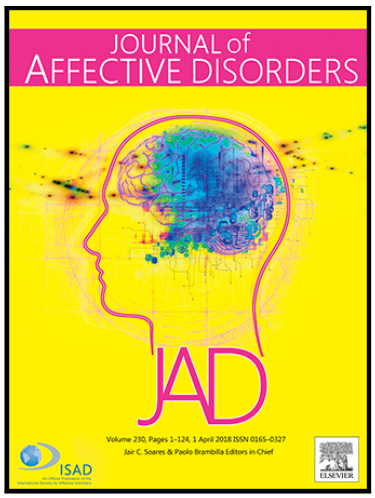

TEMPERAMENT AND CHARACTER INFLUENCE ON DEPRESSION TREATMENT OUTCOME

Martina Balestri , Stefano Porcelli , Daniel Souery , Siegfried Kasper , Dimitris Dikeos , Panagiotis Ferentinos , George N. Papadimitriou , Dan Rujescu , Giovanni Martinotti , Marco Di Nicola , Luigi Janiri , Elisabetta Caletti , Gian Mario Mandolini , Alessandro Pigoni , Riccardo Augusto Paoli , Matteo Lazzaretti , Paolo Brambilla , Michela Sala , Vera Abbiati , Marcella Bellani , Cinzia Perlini , Maria Gloria Rossetti , Sara Piccin , Carolina Bonivento , Dora Fabbro , Giuseppe Damante , Clarissa Ferrari , Roberta Rossi , Laura Pedrini , Francesco Benedetti , Stuart Montgomery , Joseph Zohar , Julien Mendlewicz , Alessandro Serretti

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HIGHLIGHTS

- Temperament and Character Inventory (TCI) personality features may predict depression treatment outcome.
- Non remission seemed to be related to high Harm Avoidance (HA) and Self Transcendence (ST) and low Persistence (P) and Self Directedness (SD) in MDD patients
- HA, Reward Dependence (RD) and SD could predict Non Response, while RD, P and Cooperativeness (C) could be associated with Resistance.
- The inclusion of such personality traits, together with other socio-demographic and clinical predictors, could ameliorate the accuracy of the prediction models available to date.

TEMPERAMENT AND CHARACTER INFLUENCE ON DEPRESSION TREATMENT OUTCOME

Martina Balestri [1], Stefano Porcelli [1], Daniel Souery [2], Siegfried Kasper [3], Dimitris Dikeos [4], Panagiotis Ferentinos [4], George N. Papadimitriou [4], Dan Rujescu [5], Giovanni Martinotti [6], Marco Di Nicola [7], Luigi Janiri [7], Elisabetta Caletti [8], Gian Mario Mandolini [8], Alessandro Pigoni [8], Riccardo Augusto Paoli [8], Matteo Lazzaretti [8], Paolo Brambilla [8], Michela Sala [9], Vera Abbiati [10], Marcella Bellani [11], Cinzia Perlini [11], Maria Gloria Rossetti [11], Sara Piccin [12], Carolina Bonivento [12], Dora Fabbro [13], Giuseppe Damante [13], Clarissa Ferrari [14], Roberta Rossi [15], Laura Pedrini [15], Francesco Benedetti [16], Stuart Montgomery [17], Joseph Zohar [18], Julien Mendlewicz [19], Alessandro Serretti [1]

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ABSTRACT

Background: personality features have been repeatedly associated with depression treatment outcome in Major Depressive Disorder (MDD), however conclusive results are still lacking. Moreover, as for Bipolar Disorder (BD), results are only few and preliminary.
Aim: the aim of the present study was to perform an exploratory investigation of the influence of personality traits as assessed by the Temperament and Character Inventory (TCI), on principal depression treatment outcomes (non remission, non response and resistance).
Methods: 743 mood disorders patients (455 MDD (61.24%) and 288 BD (38.76%)) were recruited in the context of 6 European studies. Generalized logit models were performed to test the effects of TCI dimensions on treatment outcomes, considering possible confounders such as age, gender and education. Positive results were controlled for comorbidities (anxiety and substance use disorders) as well.
Results: MDD Non-Remitters showed high Harm Avoidance (HA) and Self Transcendence (ST) ($p=0.0004$, $d=0.40$; $p=0.007$, $d=0.36$ respectively) and low Persistence (P) and Self Directedness (SD) ($p=0.05$; $d=0.18$; $p=0.002$, $d=0.40$, respectively); MDD Non-Responders showed a slightly different profile with high HA and low Reward Dependence (RD) and SD; finally, MDD Resistants showed low RD, P and Cooperativeness (C). In BD patients, only higher HA in non response was observed.
Limitations: the retrospective cross-sectional design, the TCI assessment regardless of the mood state and the small number of bipolar patients represent the main limitations.
Conclusion: specific TCI personality traits are associated with depression treatment outcome in MDD patients. The inclusion of such personality traits, together with other socio-demographic and clinical predictors, could ameliorate the accuracy of the prediction models available to date.

Keywords: Major Depressive Disorder; Bipolar Disorder; Treatment Resistance Depression; treatment outcomes.

1. INTRODUCTION

Mood Disorders, including Major Depressive Disorder (MDD) and Bipolar Disorder (BD), are highly prevalent and recurrent disorders associated with increased morbidity and mortality (Whiteford et al., 2013). Major Depressive Episodes (MDEs), characterizing MDD, are also the most common mood states in the BD illness course, related to increased suicidal risk as well as to diminished role functioning and quality of life (Vieta et al., 2018).

Despite the effectiveness of available therapies, only half of MDD patients shows a response to treatment (Souery et al., 1999) and about 70% fails to achieve complete remission (Rush et al., 2006). Even lower rates of response/remission are reported for bipolar depression (Garnham et al., 2007, Mendlewicz et al., 2010). Moreover, a considerable proportion of mood disorder patients do not respond/remit after two or more subsequent antidepressant treatments. Literature data estimated that up to 33% of patients do not respond to multiple interventions, rate that increases if remission is considered as principle outcome (Berlim et al., 2008, Cain, 2007). Taken together, these findings have increased the attention on Treatment Resistant Depression (TRD) in the last years and its possible predictors (Kautzky et al., 2018).

To date, most part of available studies investigated predictors of non response and remission to a single antidepressant (AD) (De Carlo et al., 2016), without taking into account multiple treatment failures in the same depressive episode, with the notable exception of our Group for the Study of Resistant Depression (GSRD) (Dold et al., 2017).

Although personality features have a modulating influence on mood disorders as observed in clinical practice, they are not commonly included in predictive algorythms. However, during the last decades, they have been investigated as possible predictors of depression treatment outcome. Earlier research mainly seemed to underline the negative influence of comorbid personality disorders (PD) on treatment outcome in depression (Pilkonis and Frank, 1988). This negative influence was also confirmed by subsequent review articles, where PDs were associated with worse social functioning, higher levels of residual symptoms (Shea et al., 1990, Kleindienst et al., 2005a) and poorer response to various forms of treatment (Shea et al., 1992, Reich and Green, 1991). More recent investigations, focusing on both pharmacological and psychological therapies, reported, however, contrasting results (Erkens et al., 2018, van Bronswijk et al., 2018, Mulder et al., 2017, Newton-Howes et al., 2014, Unger et al., 2013, Latalova et al., 2013, Beatson and Rao, 2013, Souery et al., 2007, Kool et al., 2005). Several factors like the quality of personality assessment, the small sample size and the heterogeneity of the studies could have modulated all findings. Moreover, PDs are quite heterogeneous regarding personality features/symptoms and a high comorbidity among PD diagnoses is frequently observed (Bagby et al., 2004, Ryder et al., 2002). In addition, the PDs do not appear to be very stable over time (Kjaer et al., 2016, Skodol et al., 2010) and the inter-rater reliability of the specific personality assessment instruments is generally poor (Clark et al., 1997, Livesley, 1985). Many of these problems could be the result of imposing a categorical system on dimensional phenomena and could be overcome using a dimensional approach.

Several personality models have been developed independently of the Diagnostic and Statistical Manual (DSM) categorical system, identifying a normal range of broad personality traits. The latter should be considered as pathological when reaching extreme levels in terms of intensity and frequency and when are associated with significant distress and/or functional impairment (Markon et al., 2005). Among these models, the Cloninger biosocial one, with its evaluation instrument (i.e., Temperament and Character Inventory (TCI)), has been widely applied to mood disorder patients

(Zaninotto et al., 2016, Zaninotto et al., 2015), also considering its relationship with phenomenological, biological, and genetic evidence (Prillwitz et al., 2018, Eric et al., 2017, Balestri et al., 2014, Bagby et al., 2008).

Several studies investigated the associations between TCI personality traits and depression treatment outcomes in MDD, leading, however, to contrasting results. While in one of the first review of literature data the role of Harm Avoidance (HA) or other TCI traits as predictors of outcome seemed to be weak (Mulder, 2002), a recent meta-analysis emphasized the association between high HA scores and non response, in particular to AD treatments (Kampman and Poutanen, 2011). Similarly, high Novelty Seeking (NS) scores were associated with a more favorable treatment outcome in some (Tome et al., 1997) but not all (Takahashi et al., 2013b, Mulder, 2002, Corruble et al., 2002) studies. It was also suggested that AD treatment could exert a direct positive impact on HA, as a reduction in HA scores was responsible for the improvement of depressive symptoms (Quilty et al., 2010). Among other personality traits, Self Directedness (SD) was associated with response to antidepressant treatment and to a combination of medication and psychotherapy (Paavonen et al., 2016, Takahashi et al., 2013a, Kaneda et al., 2011, Corruble et al., 2002, Sato et al., 1999, Black and Sheline, 1997), low scores of the latter being related to worse outcome. Positive results were also reported for Persistence (P), Reward Dependence (RD), Cooperativeness (C) and Self Transcendence (ST), where the association with depression outcome mainly resulted from changes in trait scores after AD treatment and specifically in responder subjects (Paavonen et al., 2018, Takahashi et al., 2013a, Corruble et al., 2002, Sato et al., 1999). However, most part of studies investigating such personality traits in the prediction of response failed to confirm these findings (Tomita et al., 2015, Kampman and Poutanen, 2011, Mulder, 2002). Interestingly, low P was found to predict, even if minimally, poor response to Cognitive Behavioural Therapy (CBT), while high HA and low RD and SD seemed to predict negative response to Interpersonal Therapy (IPT) (Joyce et al., 2007). Specifically considering BD, results were few and preliminary. Like for MDD, high HA scores, alone or in combination with genetic variants, were related to poor AD treatment outcome in BD patients meeting criteria for MDE (Mandelli et al., 2012, Mandelli et al., 2009). Similarly, in the meta-analysis by Kleindienst and colleagues, higher neuroticism score, related to HA, were suggested as a possible risk factor for non response to prophylactic lithium (Kleindienst et al., 2005b).

These findings suggested that clinical research about TCI personality traits influence on depression treatment outcome is far from being conclusive. The lack of unequivocal results could be related to several factors, including the small sample size of some studies, the heterogeneity in their designs or in the definition of specific outcome (i.e., response), variations in follow-up time as well as differences in treatment strategies. In addition, it should be considered that variations in personality trait scores in mood disorder patients could be also related to the mood state (Bajraktarov et al., 2017, Zaninotto et al., 2016, Sauer et al., 1997) and persist, as a "scar", after symptom resolutions (Hakulinen et al., 2015). The lack of a consistent control for covariates (i.e., age, gender and education), with known influence of personality traits, and for comorbidities, like Anxiety Disorders or Substance Use Disorders, could have affected main results as well. In addition, most part of the studies did not consider the number of treatments administered to MDD or BD patients in the evaluation of outcome, with consequent difficulties in the identification of personality traits which could consistently predict TRD. Finally, traditional outcomes in clinical studies on depression mainly focused on symptomatic improvement or response rather than on full remission,

failing to emphasize the substantial impact of residual symptoms on psychosocial dysfunction and poor prognosis.

For all these reasons, the aim of the present study was to investigate the role of TCI personality traits on principal depression treatment outcomes in a large sample of mood disorder patients recruited in the context of various European studies. In particular, our primary objective was to test the TCI influence on remission in MDD patients, while the secondary ones were to evaluate the role of TCI on response and resistance in MDD and BD subjects and in the whole sample.

2. METHODS

2.1. SAMPLE

The total sample was collected from 6 different sources and was composed by 743 subjects (age ≥ 18 years) with mood disorders (455 patients with MDD (61.24%) and 288 patients with BD (38.76%). For details see also Supplementary Methods.
The first sample was composed by 287 MDD and BD patients (n=228, 79.44%; n=59, 20.56%, respectively), recruited in the context of a European Multicenter Study, conducted by the GSRD between January 2000 to February 2004 (for details about the study and the recruitment procedures see (Souery et al., 2007)).
The second sample was composed by 197 MDD patients, recruited within an international, multicenter, cross-sectional study conducted by the previously mentioned GSRD between November 2011 and September 2016 (Kautzky et al., 2018, Dold et al., 2018).
The third sample was composed by 112 BD outpatients recruited in the context of an Italian, naturalistic, observational, case-control, multi-centric study (GECO-BIP study) (Porcelli et al., 2018).
The fourth sample included 90 BD patients consecutively referred to the Psychiatric Day-Care unit at Gemelli Hospital, Department of Psychiatry and Addiction Center, Catholic University of Rome and consecutively recruited in the period between June 2006 and December 2013 (Zaninotto et al., 2015).
The fifth sample included 42 mood disorder patients (15 MDD and 68 BD patients, 35,71% and 64.29%, respectively) consecutively admitted to the Department of Neuropsychiatry at the Institute H. San Raffaele (Serretti et al., 2008).
The sixth sample was composed by 15 MDD outpatients recruited at the Department of Biomedical and NeuroMotor Sciences, Bologna University (Fabbri et al., 2013).
Written informed consent was obtained from all subjects after a detailed and extensive description of the study. All studies were approved by the local ethics committee and carried out in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki.

2.2. ASSESSMENT

2.2.1. Socio-demographic and Clinical variables

Current and lifetime diagnosis, course of illness and psychiatric comorbidities according to DSM IV diagnostic criteria (A.P.A., 1994) were assessed by experienced clinicians on the basis of structured and unstructured diagnostic interviews and medical records following the best estimate procedure (Leckman et al., 1982). In particular, the Structured Clinical Interview for DSM IV Axis I Disorder (SCID-I) (First et al., 1995) was used for the *Sample III and IV*, while the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), including a modified version for the GSRD, was administered to S*ample I, II and VI*. When compared, the latter showed high validation and reliability scores (Sheehan et al., 1997). Personality Disorders (PD) diagnosis was obtained with the Structured Clinical Interview for DSM IV Axis II Disorder (SCID-II) (First et al., 1990), while medical illness were assessed through unstructured clinical interviews and medical records. Only baseline assessment was taken into account without examining changes in diagnosis overtime

(i.e. from MDD to BP). Socio-demographic and clinical information, including current and previous medications, were also collected by clinical investigation using all possible sources of information, considering previous charts, family members and previous treating clinicians as well. Severity of mood symptoms was assessed both with clinical judgment and with specific scales at different treatment times according to the different study designs.

As for depressive symptoms, the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) (17 or 21 item version) was administered to all patients, while the Mongomery & Asberg Depression Rating Scale (Montgomery and Asberg, 1979) only to a subsample of MDD patients. As for manic symptoms, the Young Mania Rating Scale (YMRS) (Young et al., 1978) or the Bech-Rafaelsen Mania Rating Scale (BRMRS) (Bech et al., 1979) were administered to BD patients. All patients were treated as usual according to the current clinical practice in a tertiary care center. Adequacy of treatment was controlled when possible according to available data (see "Outcome variables" paragraph). HDRS and MADRS scores were obtained for each patient after at least four weeks of adequate treatment. For the present study both clinical judgment and severity scales were used to determine treatment outcome.

2.2.2. Temperament and Character Inventory (TCI)

The Temperament and Character Inventory (TCI) was administered to all patients considered for the present study, independently of their clinical status (euthymia, depression or hypo-mania), after at least one adequate treatment according to the current clinical practice (a description of the TCI with its different versions is reported in Supplementary Methods).

Outliers (i.e., values representing erroneous data) or patients with > 5% of TCI missing data were excluded and, when possible, missing data were replaced by the mean scores of the corresponding lower order traits. Different TCI versions were used across studies. In order to standardize results, T-scores (range 0-100) were created to reflect a mean score of 50 and standard deviation (SD) of 10 (Zaninotto et al., 2015).

2.3. OUTCOME VARIABLES

2.3.1. Remission

As for MDD (*Sample I, II, V, VI*), we considered Remitters those patients with a HDRS total score ≤7.

As for BD *of the Sample I, IV and V* we considered Remitters patients with a HDRS total score ≤7 and the concomitant exclusion of a current hypo-manic episode during the clinical assessment. When possible, clinical data were also supported by those of the severity scales (YMRS total score ≤7)

As for BD of the *Sample III*, we considered Remitters patients in stable euthymia according to a clinical assessment carried out by experienced Psychiatrists. Due to the lack of missing data, the latter was preferred to that one based on severity scales (HDRS and BRMRS) reporting, however, similar evaluations (data not shown).

2.3.2. Response

As for MDD, we considered Responders patients with a decrease in HDRS (*Sample V and VI*) or MADRS (*Sample II*) total score ≥ 50%. As for the *Sample I*, because of the lack of the severity scale at the beginning of the depressive episode (considered as moderate or severe according to DSM IV), we defined Responders patients with a HDRS ≤ 17 after at least an adequate AD treatment.
As for BD (*Sample I, IV and V)*, we considered Responders patients with a decrease in HDRS total score ≥ 50% and the concomitant exclusion of a current hypo-manic episode during the clinical assessment. A decrease in YMRS total score ≥ 50% was considered as well in *Sample IV*.
Sample III was not considered because of the lack of data about the severity scale variations with consequent difficulty in the distinction of these patients from remitters.

2.3.3. Resistance

As for MDD, we considered as Resistant those patients with a decrease in HDRS (*Sample V, VI*) or MADRS (*Sample II*) total score ≤ 50% after at least two adequate AD treatments. As for the *Sample I*, because of the lack of the severity scale at the beginning of the episode (considered as moderate or severe according to DSM IV), we defined as resistant patients with a HDRS ≥ 17 after at least two adequate AD treatments.
As for BD (*Sample I*), we considered resistant those patients with a decrease in HDRS total score ≤ 50% after at least two adequate AD treatment and the concomitant exclusion of a current hypo-manic episode during the clinical assessment. *Sample III, IV and V* were excluded because of the lack of data of adequacy of at least two treatments.

Considering the more relevant clinical impact and the available data concerning severity scales and treatments, our primary aim was to test the TCI influence on remission in MDD patients, while the secondary ones were to evaluate the role of TCI on response and resistance in MDD and BD subjects and in the whole sample.

2.4. STATISTICAL ANALYSES

All statistical analyses were performed by using the STATISTICA software package (Dell Software, Tulsa, OK, USA). T-scores (range 0-100) were computed for all TCI traits in order to compare different versions of the same scale as previously reported (Zaninotto et al., 2015). Differences in socio-demographic and clinical variables among groups were evaluated by Chi-square test for categorical variables and by Student T-test and one-way analysis of variance (ANOVA) for continuous variables with normal distribution, while non parametric analyses were also performed for variables departing from normal distribution. Since age (Chen et al., 2013, Mikolajczyk et al., 2008, Cloninger et al., 1994, Cloninger et al., 1993), gender (Gutierrez-Zotes et al., 2004, Brandstrom et al., 2001, Mendlowicz et al., 2000) and education (Mikolajczyk et al., 2008, Cloninger et al., 1994) were previously reported to affect temperament and character, we investigated any association between continuous variables, including age, education, severity scales, and T-scores of TCI dimensions which was determined by Pearson's correlation. The last-observation-carried-forward method of analysis was conservatively used, when baseline and at least two subsequent severity measures were present.

Multivariate generalized linear models (Logit Model for binomial distributions) were used to test the effects of TCI dimensions on treatment outcomes, considering possible confounders such as age, gender, education, and diagnosis. As for response, we performed a sub-analysis excluding *Sample 1* for the lack of the severity scale at the beginning of the depressive episode. Positive results were also controlled for principal comorbidities. This was performed because of the influence of such variables on TCI scores (Cloninger et al., 1994), confirmed by our sample, and their different distribution across the investigated groups.

Given the lack of a prospective serial evaluation and in order to partially control for possible influences of depressive symptomatology on TCI scores, we calculated Pearson's correlations between TCI personality traits and symptoms severity at the time of assessment. In order to avoid a spurious correlation with the disease status, we included in this analysis only non remitter, non responder and resistant subjects.

All p values were 2-tailed and statistical significance was set at the standard level of $p=0.05$, considering the explorative role of the present investigation. Results were however weighted for their relative significance despite the absence of a formal multiple testing correction.

With these parameters we had sufficient power (0.80) (as calculated with G*Power 3.1.2 (Faul, 2007), as an example for t-test given $\alpha=0.05$ to detect a medium-small effect size ($d=0.35$) between Remitters and Non Remitters in MDD patients, that corresponds to a difference in the TCI scale of HA of 3.8 points (Cohen, 1988). As for BD sample, the power was marginally lower. For significant findings effect size d values were reported.

3. RESULTS

3.1. SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE

We included 743 mood disorder patients, of which 455 (61.24%) with MDD. Socio-demographic and clinical features of the total sample are reported in Table 1 as well as differences between MDD and BD patients. Most part of BD patients in illness status reported a MDE.
As for their clinical outcome, 200 (26.92%) patients were Remitters, 260 (41.20%) were Responders and 128 (26.89%) were Resistants.

3.2. POSSIBLE CLINICAL AND DEMOGRAPHIC STRATIFICATION FACTORS ON TCI SCORES

We preliminary performed a series of univariate analyses to test age, gender and education associations with the standardized scores of all TCI dimensions (T-score) (see Supplementary Table 1 and 2 for associations with age and gender; education correlated with RD, P and C (data not shown)). Correlations between TCI T-scores and severity scales at assessment were also evaluated as described above in order to control for a possible modulatory effect of depression symptomatology in separated analyses including Non Remitters, Non Responders and Resistants, considering MDD patients, BD patients and the whole sample. Indeed, as previously reported, personality profile was found to be only marginally influenced by the mood state (Elovainio et al., 2004, Hansenne et al., 1999, Peselow et al., 1995, Hirschfeld et al., 1983) thus supporting the predictive value of this feature (Supplementary Table 3).
On the basis of these findings, TCI trait T-scores were investigated in MDD and BD patients, using the Generalized Logit Model and controlling for age, gender, education and severity scales. Results are shown in Supplementary Table 4. As expected, MDD and BD patients showed differences in NS, HA, P, SD, C and ST. The greatest significances were found for NS ($p=0.0009$), higher in BD patients, and SD ($p<0.0000001$), higher in MDD patients. Moreover, no difference in TCI trait scores was found between BDI and BDII patients (data not shown), suggesting not to consider separately the latter in further investigations on TCI dimensions.
Despite of the missing data, no differences in TCI T-scores between patients with and without Axis II comorbidities emerged (data not shown).

3.3. EFFECT OF TEMPERAMENT AND CHARACTER ON OUTCOME

3.3.1. Association between TCI personality traits and depression treatment outcomes in MDD patients

As for MDD patients, results were reported in Table 2, 3 and 4. In particular, Non-Remitters showed higher Harm Avoidance (HA) and Self Transcendence (ST) ($p=0.0004$, $d=0.40$; $p=0.007$, $d=0.36$ respectively) and lower Persistence (P) and Self Directedness (SD) ($p=0.05$, $d=0.18$; $p=0.002$, $d=0.40$ respectively); Non-Responders reported higher HA ($p=0.01$, $d=0.26$) and lower Reward Dependence (RD) and SD ($p=0.03$, $d=0.16$; $p=0.01$, $d=0.27$ respectively); finally, Resistants showed lower RD, P and Cooperativeness (C) ($p=0.04$, $d=0.17$; $p=0.01$, $d=0.22$; $p=0.01$, $d=0.21$, respectively). Results about response were confirmed by the sub-analysis which excluded

Sample I for the lack of the severity scale at the beginning of the depressive episode (HA: p=0.01, d=0.27; RD: p=0.01, d=0.19 and SD: p=0.01, d=0.24).

3.3.2. Association between TCI personality traits and depression treatment outcomes in BD patients

As for BD patients (Supplementary Tables 5, 6 and 7), the only marginal association was found between HA and Response, with Non Responders having higher HA scores (p=0.04, d=0.46).

3.3.3. Association between TCI personality traits and depression treatment outcomes in the whole sample

Results for the whole sample were reported in Supplementary Table 8, 9 and 10. No relevant association between TCI trait T-scores and all outcomes was observed, as expected given the differences we observed between MDD and BD patients.

A summary of the main results was reported in figure 1.

4. DISCUSSION

In the present study, we investigated the influence of TCI personality traits on depression treatment outcome in a large sample of mood disorder patients recruited in the context of various European studies. First, we evaluated their general influence in the prediction of remission. Furthermore, we explored their role in treatment response and resistance. While we primarily focused on MDD patients, we also considered BD patients and the whole sample composed by both mood disorders.
As for MDD, Non-Remitters showed higher HA and ST and lower P and SD, Non-Responders reported higher HA and lower RD and SD, while Resistants showed lower RD, P and C. In BD and the whole sample only minor effects were observed.

The most significant results emerged for the primary outcome, in particular for HA and SD, being higher scores of the former and lower scores of the latter associated with non remission in MDD patients. The same traits were associated with non response, while a trend for HA was also detected in Resistants. Patients with high HA and low SD strive for order and perfection, showing harsh self-criticism of failure, pessimism and a reduced tolerability for stressful life events. These features were associated with both mood disorders (Zaninotto et al., 2016, Nowakowska et al., 2005) and poor depression treatment outcome. Nevertheless, few studies specifically focused on non remission (de Winter et al., 2007, Corruble et al., 2002), despite its strong implications for better functioning and prognosis (Rush et al., 2006). Interestingly, high levels of neuroticism, closely related to HA, were associated with non remission to subsequent AD trials in first depressive episode (Bock et al., 2010), emphasizing the role of the anxiety-avoidant dimension in the prediction of the recovery. The role of both HA and SD seemed to be more evident when non response was taken into account (Baeken et al., 2014, Kampman et al., 2012, Joyce et al., 2007), also considering different treatment strategies (SSRI, TCA, psychotherapies or r-TMS). Main findings were observed for HA and were resumed by a recent meta-analysis (Kampman and Poutanen, 2011). Low HA and high SD scores seemed also to characterize Early Responders from Late or Non Responders (Kaneda et al., 2011). Nevertheless, in most part of the studies, both traits were related to the mood state, with consequent difficulties in determining if the different personality profile showed by patients with residual symptoms was a consequence of the depressive state rather than represented a real risk factor for a poor prognosis. However, as both HA and SD, with particular evidence for the former, were also considered as vulnerability factors for mood disorders, regardless of their association with depression, and a reduction in HA scores after AD treatment was observed irrespective of the depressive symptom improvement (Quilty et al., 2010), a role of HA and SD traits in the prediction of non remission, non response, but also resistance cannot be excluded, requiring further investigations, especially with longitudinal study design. Indeed, in a recent study aiming to investigated if treatment response during the acute phase of MDD was predictable by TCI temperament dimensions, HA scores after 6 weeks of SSRI treatment was found to be more strongly explained by HA baseline scores rather than by MADRS endpoint scores (Kampman et al., 2012), underling the specific role of this trait in the prediction of response to AD therapy. In support of this hypothesis, in the present study, neither HA nor SD showed a significant correlation with the depression severity scale (HDRS) in MDD patients.
In BD patients, however, results were basically negative and inconclusive. The fact that higher HA scores were only marginally associated with non response suggested to consider this result as a false positive finding, related to the small sample size (Resistants, n=11) and possibly to the

heterogeneity of the BD sample, composed by patients with hypo/manic symptoms and treated with different strategies. Moreover, in our sample, HA scores showed a marginal negative correlation with hypo/manic symptom severity in Non Remitters (data not shown), while SD negatively correlated with depression severity in Non Responders and Resistants. Although most of these correlations were small, they introduced a further element of bias in the interpretation of the results. We could also hypothesize that in BD patients, showing a personality profile characterized by higher HA and NS on the one hand (expression of approach-avoidance conflicts), and lower SD, C and higher ST on the other one (denoting vulnerability to moodiness and psychosis), the influence of TCI personality traits on depression treatment outcome could be more difficult to detect. However, the few literature results considering BD were in line with our finding (Mandelli et al., 2012, Mandelli et al., 2009, Kleindienst et al., 2005b).

When both mood disorders were considered as a whole, some results disappeared, suggesting that the inclusion of BD patients could have represented a possible confounder. Indeed, MDD and BD were recently considered as different disorders in terms of symptomatology, family history, and genetics (Vieta et al., 2018, Han et al., 2018, Gatt et al., 2015) and for this reason they were primarily separately investigated in the present analyses.

As for the other traits or secondary outcomes, results were less strong, but worth to be briefly discussed.

Higher ST was related to non remission in MDD patients. This finding, however, disappeared when both non response and resistance were considered. Higher ST, representing spirituality and creativity (Cloninger, 2013, Cloninger and Zohar, 2011), in presence of low SD and C as in our sample, could be associated with proneness to psychosis (Bayon et al., 1996) or sub-threshold psychotic symptoms in turn related to more severe form of depressions, poor AD response and remission (Buoli et al., 2013, Cassano et al., 2013), longer time for remission (Falola et al., 2017, Rush et al., 2006) and higher frequency of residual symptoms (Ostergaard et al., 2014). Unfortunately, in the present study, the assessment of the treatment outcome required a minimum of four weeks, but did not include details of the follow-up period. In other words, some patients reported a short follow-up time, which could be regarded as sufficient for the evaluation of response, but less appropriate when investigating remission. A similar consideration could be made for resistant patients. Although a correlation between ST score and residual depressive or hypo/manic symptoms were excluded in the present study, we did not control for the presence/absence of psychosis, possibly confounding our results.

The association between lower P and non remission in MDD patients deserve a particular attention, as that the same trait was related also to TRD. Indeed, patients with low levels of P are found to be indolent, inactive and low perseverant when faced with frustration or when rewards are infrequent or occur in the long time (Cloninger et al., 1994). While partial response to AD treatment is generally rapid, more time is sometime needed to achieve complete response and overall full remission. The compliance in long term therapies as well, generally required to achieve and maintain the remission state, could be impaired by low P scores (Li et al., 2018), particularly when more than one treatment was prescribed, especially in case of TRD. Indeed, high P scores were related to response to rTMS in TRD-MDD patients (Siddiqi et al., 2016), while most studies focusing on non response reported negative results (Tomita et al., 2015, Takahashi et al., 2013a, Kampman and Poutanen, 2011).

Considering secondary outcomes, we found a relationship between RD levels and both non response and resistance. Low RD scores, characterizing practical, tough-minded, cold and socially

insensitive patients, was strongly associated with cluster A symptoms, such as paranoid, schizoid and schizotypal personality disorders (Svrakic et al., 1993), with possible negative effects on the course and outcome of MDD (Skodol et al., 2011). These data supported first studies (Tome et al., 1997, Joyce et al., 1994). Contrary to HA and SD, there is less evidence for an association between low RD score and the depressive state (Kampman and Poutanen, 2011), as confirmed by our study showing no correlation with HDRS. Interestingly, in non-depressive siblings of depressed patients, RD scores were significantly higher than in siblings with a history of depression, suggesting that high RD may also protect against the development of depression (Farmer et al., 2003). For these reasons, RD trait could represent a possible predictor of depression treatment outcome. However, it is unknown whether the personality characteristics of Non Responders were primary or secondary to the disease. A long history of depression, with multiple episodes or resistance to treatment, may induce personality changes within patients, which can be stable over time (Teraishi et al., 2015, Zaninotto et al., 2015) and influence the results concerning the role of TCI traits also in the prediction of TRD. In the present study, lower RD scores together with lower P and C levels were associated with resistance to treatment in MDD. Our findings seemed to confirm those reported by a very small sample of TRD-MDD patients compared with remitter patients and healthy controls, where low RD scores, and to a lesser extent, low C levels were related to TRD (Takahashi et al., 2013b). Some data associated the increase in C scores with the response to treatment in MDD (Kampman and Poutanen, 2011, Hirano et al., 2002, Corruble et al., 2002), while others correlated this trait with symptoms severity (Kronstrom et al., 2011, Hirano et al., 2002). In the present sample, C was not correlated with the severity of depressive symptoms, suggesting that its influence on TRD was independent of the illness severity. In particular, patients with low C scores are self-absorbed, intolerant, critical, and revengeful (Cloninger et al., 1994). All these features could compromise the therapeutic alliance and interfere with the benefit of social support during treatments. These personality characteristics, together with those ones associated with low RD, as shown by TRD patients, may depict a specific form of depressive illness, more similar to psychotic disorders and therefore more difficult to treat.

Therefore, among TCI personality traits, HA and SD could more specifically predict non remission in MDD patients. The same traits should have a role also in non response, while RD, P and C could be related to resistance. As for BD, our preliminary results suggested a possible role of HA in the prediction of non response. Despite these interesting findings, how these traits exert their influence on depression treatment outcome remains unknown. Some hypotheses could be derived from genetic studies. For example, as S (short) allele of the 5-HTTLPR (a polymorphism of the promoter region of the serotonin transporter gene), which has been repeatedly associated with the AD treatment response (Fabbri and Serretti, 2015), was also associated with higher HA levels (Balestri et al., 2014), the worse outcome observed in MDD patients carrying SS genotype may be modulated by its effect on anxiety-avoidant temperament. Similarly, 5-HT2 receptor sensitivity was positively related to HA and negatively associated with SD (Peirson et al., 1999), suggesting that both traits could be regulated by the serotoninergic system, known to influence AD response (Kao et al., 2018, Andrews et al., 2015). Interestingly, common polymorphisms of the glutamate transporter gene were found to contribute to certain aspect of the empathy trait (Kim et al., 2018), a component of the cooperativeness dimension in the TCI. Moreover, schizotypal features, which could be regarded as aspects of low RD, were associated with and imbalance of excitatory glutamate and inhibitory γ-aminobutyric acid (GABA) concentrations in right and left hemisphere superior temporal (ST)

voxels (Ford et al., 2017), while higher glutamine levels were related to greater impairments in social cognition (Cochran et al., 2015). As the glutamatergic system was found to mediate the antidepressant response in particular in TRD (DeWilde et al., 2015), the response to ketamine (i.e., NMDA receptor antagonist), could be partially modulated by both C and RD traits. Clearly, further studies are needed to test these speculations also on the light of the complex relationship between personality and treatment outcomes.

Despite the large sample size, in particular of MDD patients, including Non Remitters and TRD patients, this study presented several limitations. First, the sample was collected from different studies designed for other purposes, both with prospective and retrospective designs. Unfortunately, it was not possible to test the rater reliability or if assessments or clinical treatments were comparable or standardized across psychiatric centers. However, all patients were recruited and treated by experienced Psychiatrists and many of the investigators previously collaborated in multicenter studies were training was performed**.** In addition, due to the cross-sectional design of the present investigation, personality traits were not serially evaluated before and after treatments and not always in a condition of stable euthymia. Indeed, the TCI assessment was made at different time points (even if after at least an adequate treatment), independent of the mood state, which is known to possibly influence the personality trait scores. However, our correlation analysis between TCI traits and the severity scales administered to all mood disorder patients did not evidence a relevant bias in our sample, thus supporting its possible predictive validity. Second, the heterogeneous definition of response, with the use of different scales in the evaluation of both depression in all samples and mania in BD patients could have affected our findings. For example, MADRS could be a more reliable tool than the HDRS for the assessment of depressive symptoms and their reduction after treatment (Carneiro et al., 2015). Unfortunately, MADRS scores were not available for all patients. However, results from severity scales were also compared with the clinical evaluation, primarily taken into account in the definition of remission and response. Another limitation, when considering response, was the lack of a depression severity rating scale at baseline for some patients. A more consistent definition of remission prompted us to evaluate this outcome as the primary one of the present study, paired with the more relevant clinical impact. Third, some patients showed a short follow-up time (4 weeks), with consequent influence on the reliability of the outcome. Even if the AD response usually occurs after 2–4 weeks, it cannot be fully evaluated until the treatment has been administered for 8–12 weeks (Cipriani et al., 2009). Full response and overall remission generally require longer periods, also for testing the stability of the outcome, especially in TRD (Rush et al., 2006). However, the cut-off of 4 weeks is typically used in clinical practice and it is a reliable proxy for later outcome. Fourth, several other factors could have modulated our results and should be taken into account in the interpretation of findings. Severe and recurrent episodes, higher number of previous hospitalizations and chronic illness course were found to independently predict poor AD response (Balestri et al., 2016, Kohler et al., 2015, Riedel et al., 2011). It was also suggested that long-standing (ie, chronic) depressions could take longer to remit or be less likely to remit (Rush et al., 2006). These features were not considered. In particular, the severity of the episode at baseline was used to evaluate response and resistance and could not be introduced in the multivariate models. Although a number of strategies have been adopted to minimize this possible bias, it was not possible to rule out the effect of pretreatment severity of the depressive state on TCI traits as shown in a number of studies. In addition, both high number of previous episodes and depression chronicity were associated with comorbid personality disorders

(Shea et al., 1992), in turn related to poor depression treatment outcomes (Newton-Howes et al., 2006). Unfortunately, due to the high number of missing data in some of the included samples, we did not control for PD as possible confounder. On the contrary, both anxiety disorders and SUDs were used as covariates. Further, patients with chronic depression seemed to show a different personality profile if compared with patients with acute episode (Wiersma et al., 2011), while comparing TCI traits in patients with recurrent or single MDD episode during remission, some personality differences were detected, in particular for the HA trait (Teraishi et al., 2015). Fifth, as for BD, some patients reported hypo-manic symptoms, a possible bias, but full hypo-manic episodes were excluded. Sixth, as not all mood disorder patients who fulfilled inclusion criteria for the studies included in the present work completed the TCI assessment and some patients were recruited in studies focusing on TRD, it is not possible to consider our sample as representative of the population of MDD or BD patients treated in a naturalistic setting. In addition, due to the different study designs, it was not possible to investigate resistance to treatment for all patients. Further, TRD patients showed different levels of resistance according to the number of failed trials with consequent difficulty in the generalization of the results concerning this group of patients. Finally, we should underline that we did not correct for multiple testing, so possible false positive results may not be ruled out. In particular, concerning non response and resistance, we reported and discussed findings which would not survive a rigorous multiple testing correction. In this regard we considered: 1) the confirmative role of the present investigation; 2) the fact that we took into account both non remission and resistance as outcomes and BD as diagnosis, all poorly evaluated in literature; 3) the presence of discrepant results in literature which need further confirmation. For all these reasons a more strict correction could have been poorly informative. In any case, our primary results would have survived multiple testing corrections, while secondary results should be considered with more caution. However, the prediction power of TCI personality traits, also for the strongest results, was found to be basically low, suggesting the importance to combine personality with other socio-demographic, clinical or genetic predictors to increase the prediction accuracy, also considering different approaches (i.e., machine learning algorithms) in addition to the clinical evaluation (Kautzky et al., 2018).

In conclusion, TCI personality dimensions could be useful predictors of depression treatment outcomes, in particular considering MDD. Indeed, due to their trait property, which make them stable over time and only moderately modulated by symptoms severity, they seem to represent ideal variables to test for the association with non remission, non response and resistance. Further studies are required to confirm our findings, in particular using prospective evaluations of TCI personality traits. Although the role of the single personality dimension could be low, its evaluation, together with other socio-demographic, clinical or genetic predictors, could ameliorate the recognition of patients at high risk for poor outcome, guiding clinicians in the choice of optimal and personalized treatments.

Contributors

All authors were actively involved in the design of the study, the analytical method of the study, the selection and review of all scientific content. All authors had full editorial control during the writing of the manuscript and finally approved it.

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None

Conflict of Interests

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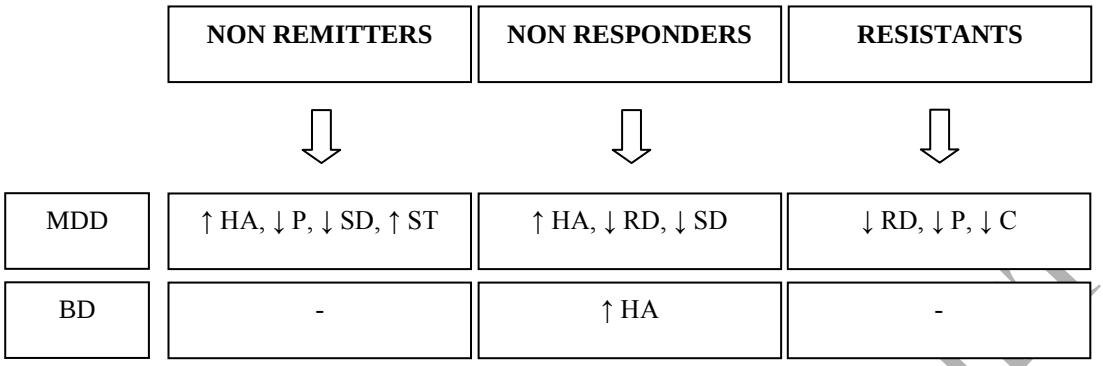
FIGURES

Figure 1. Summary of the main results



TABLES

SOCIO-DEMOGRAPHIC and CLINICAL FEATURES	MDD PATIENTS (N=455, 61.24%)	BD PATIENTS (N=288, 38.76%)	TOTAL SAMPLE (N=743)	STATISTICS		
				$t/x^2/z$	d.f.	p
Age	47.38 ± 12.75	45.18 ± 12.37	46.53 ± 12.64	2.32	741	**0.02**
Gender						
Female	332 (72.97%)	161 (55.90%)	493 (66.35%)	23.02	1	**<0.0001**
Education* (N=731)						
Low	195 (43.72%)	91 (31.93%)	286 (39.12%)	16.14	2	**0.0003**
Medium	107 (23.99%)	105 (36.84%)	212 (29.00%)			
High	144 (32.29%)	89 (31.23%)	233 (31.87%)			
Marital status (N=602)						
Single	84 (19.44%)	40 (23.53%)	124 (20.60%)	3.93	2	0.14
Married/ partnership	274 (63.43%)	93 (54.71%)	367 (60.96%)			
Divorced/ widow	74 (17.13%)	37 (21.76%)	111 (18.44%)			
Ethnicity (N=589)						
Caucasian	418 (95.00%)	147 (98.66%)	565 (95.93%)	9.98	4	**0.04**
Asian	2 (0.45%)	0 (0.00%)	2 (0.34%)			
African	17 (3.86%)	0 (0.00%)	17 (2.89%)			
North-American	1 (0.23%)	2 (1.34%)	3 (0.51%)			
Latin-American	2 (0.45%)	0 (0.00%)	2 (0.34%)			
Inpatients (N=589)	172 (39.09%)	53 (35.57%)	225 (38.20%)	34.80	2	**<0.0001**
Illness course						
Duration current episode (days) (N=521)	205.61 ± 194.16	103.38 ± 162.60	177.55 ± 191.40	7.67	-	**<0.0001**
MDE lt (nr) (N=546)	3.72 ± 4.50	4.00 ± 6.19	3.79 ± 4.98	1.38	-	0.17
Manic Episode lt (nr) (N=122)	-	1.46 ± 2.01	1.46 ± 2.01	-	-	-
Age at onset (N=417)	35.40 ± 14.01	29.33 ± 10.19	32.87 ± 12.90	4.87	415	**<0.0001**
Hosp. for MDE (n=293)	161 (68.80%)	51 (86.44%)	212 (72.35%)	7.32	1	**0.007**
Hosp. for Hypo/Manic Episode (N=72)	-	15 (38.46%)	15 (20.83%)	-	-	-
Comorbidities						
Axis I disorders						
Anxiety Disorders (N=738)	118 (25.93%)	27 (9.54%)	145 (19.65%)	29.70	1	**<0.0001**
PD (N=742)	68 (14.98%)	19 (6.60%)	87 (11.73)	11.96	1	**0.0005**
SP (N=652)	36 (7.93%)	11 (5.56%)	47 (7.21%)	1.16	1	0.28
OCD (N=650)	9 (1.99%)	9 (4.55%)	18 (2.77%)	3.33	1	0.07
PTSD (N=653)	11 (2.42%)	8 (4.04%)	19 (2.91%)	1.29	1	0.25
GAD (N=705)	43 (10.46%)	14 (5.02%)	57 (8.09%)	5.85	1	**0.02**
SUD (N=743)	34 (7.47%)	60 (20.83%)	94 (12.65%)	28.49	1	**<0.0001**
AN *(N=612)*	0 (0.00%)	2 (1.05%)	2 (0.33%)	4.46	1	**0.03**
BN *(N=612)*	3 (0.71%)	5 (2.63%)	8 (1.78%)	3.75	1	**0.05**
Axis II disorders (N=211)	53 (63.86%)	56 (43.75%)	109 (51.66%)	8.15	1	**0.004**
Medical illness (N=307)	112 (48.28%)	32 (42.67%)	144 (46.91%)	0.72	1	0.40
Outcomes						
Remitters	80 (17.58%)	120 (41.67%)	200 (26.92%)	52.00	1	**<0.0001**
Responders (N=631)	161 (35.38%)	99 (56.25%)	260 (41.20%)	22.80	1	**<0.0001**

Resistants (N=476)	117 (27.79%)	11 (20.00%)	128 (26.89%)	1.50	1	0.22

Table 1. **Socio-demographic and Clinical characteristics of the sample and differences between UD and BD patients.** MDD=Major Depressive Disorder; BD=Bipolar Disorder; Lt=Lifetime; PD=Panic Disorder with or without Agoraphobia; SP=Social Phobia; OCD=Obsessive-Compulsive Disorder; PTSD=Post-Traumatic Stress Disorder; GAD=Generalized Anxiety Disorder; SUD=Substance Use Disorders; AN=Anorexia Nervosa; BN=Bulimia Nervosa. *Low=secondary school or technical school inferior degree fulfilled or less; Middle=secondary school or technical school superior degree fulfilled; High=university degree or post-secondary school degree.

MAJOR DEPRESSIVE DISORDER PATIENTS					
TCI traits	**REMITTERS** (N=80, 17.58%)	**NON REMITTERS** (N=375, 82.42%)	**STATISTICS**		
			ß/Stat.	s.e.	p
NS	50.31 ± 10.81	49.30 ± 9.62	0.02/2.00	0.01	0.16
HA	46.70 ± 11.91	50.97 ± 9.32	-0.05/12.22	0.01	**0.0004**
RD	49.85 ± 8.27	49.67 ± 10.23	0.01/0.37	0.01	0.54
P	51.52 ± 9.24	49.78 ± 9.91	0.03/3.85	0.01	**0.05**
SD	53.64 ± 10.49	49.68 ± 9.74	0.04/9.79	0.01	**0.002**
C	50.88 ± 8.70	49.58 ± 10.41	0.02/1.62	0.01	0.20
ST	46.81 ± 7.63	49.94 ± 9.86	-0.04/7.34	0.01	**0.007**

Table 2. **Differences in the standardized scores (T-score (range 0-100)) of all TCI traits between Remitter and Non Remitter in MDD patients.** NS=Novelty Seeking; HA=Harm Avoidance; RD=Reward Dependence; P=Persistence; SD=Self-Directedness; CO=Cooperativeness; ST=Self-Transcendence. s.e.=standard error. Age, gender and education were added as covariates. Similar results were obtained also including anxiety and SUD disorders as covariate.

MAJOR DEPRESSIVE DISORDER PATIENTS					
TCI traits	**RESPONDERS** (N=161, 35.38%)	**NON RESPONDERS** (N=294, 64.62%)	**STATISTICS**		
			ß/Stat.	s.e.	p
NS	49.65± 10.46	49.38 ± 9.53	0.01/0.81	0.01	0.37
HA	48.56 ± 10.54	51.12 ± 9.16	-0.03/5.93	0.01	**0.01**
RD	50.64 ± 8.92	49.14 ± 10.38	0.02/4.83	0.01	**0.03**
P	50.68 ± 9.41	49.77 ± 10.04	0.02/2.18	0.01	0.14
SD	52.11 ± 10.14	49.45 ± 9.74	0.03/6.27	0.01	**0.01**
C	50.35 ± 9.58	49.44 ± 10.42	0.01/2.07	0.01	0.15
ST	48.46 ± 9.20	49.90 ± 9.75	-0.02/2.15	0.01	0.14

Table 3. **Differences in the standardized scores (T-score (range 0-100)) of all TCI traits between Responders and Non Responders in MDD patients.** NS=Novelty Seeking; HA=Harm Avoidance; RD=Reward Dependence; P=Persistence; SD=Self-Directedness; CO=Cooperativeness; ST=Self-Transcendence. s.e.=standard error. Age, gender and education were added as covariates. Similar results were obtained also including anxiety and SUD disorders as covariate.

MAJOR DEPRESSIVE DISORDER PATIENTS					
TCI traits	**RESISTANTS** (N=117, 27.79%)	**NON RESISTANTS** (N=304, 72.21%)	**STATISTICS**		
			ß/Stat.	s.e.	P
NS	49.41 ± 9.44	49.46 ± 10.03	-0.003/0.06	0.01	0.39

HA	51.42 ± 9.63	49.89 ± 9.79	0.02/2.43	0.01	0.12
RD	48.52 ± 11.12	50.26 ± 9.60	-0.02/4.23	0.01	**0.04**
P	48.48 ± 10.55	50.71 ± 9.52	-0.03/6.53	0.01	**0.01**
SD	49.69 ± 10.49	50.70 ± 9.86	-0.01/0.88	0.01	0.34
C	48.23 ± 11.64	50.46 ± 9.58	-0.03/6.12	0.01	**0.01**
ST	48.85 ± 9.50	49.26 ± 9.41	0.002/0.0001	0.01	0.98

Table 4. **Differences in the standardized scores (T-score (range 0-100)) of all TCI traits between Resistants and Non Resistants in MDD patients.** NS=Novelty Seeking; HA=Harm Avoidance; RD=Reward Dependence; P=Persistence; SD=Self-Directedness; CO=Cooperativeness; ST=Self-Transcendence. s.e.=standard error. Age, gender and education were added as covariates. Similar results were obtained including also anxiety and SUD disorders as covariate.