Personality traits as risk factors for treatment-resistant depression

（難治性うつ病患者の性格特徴に関する研究）

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CONTENTS

1. GENERAL INTRODUCTION

Treatment resistant depression

Treatment resistant depression is an important problem in clinical practice. Antidepressants are commonly used in the treatment of major depression. A model of stage was proposed and differential levels of resistance exist in treatment resistant depression (Thase and Rush, 1995). Treatment resistant depression was defined as major depression with poor response to two or more adequate trials of different class of antidepressant (Souery et al., 1999). It is estimated that treatment resistant depression occurs about 30% to 40% of depressive episode after adequate treatments with first or second antidepressant therapy, respectively in 50% response of HAM-D (Souery et al., 1999). Thus, almost 10% of patients with depression cannot attain remission or recovery (HAM-D<7) despite availability of an increasing number of antidepressants.

It was found that a set of 11 relevant clinical variables is associated with treatment resistant major depressive disorder (for example, comorbid anxiety disorder and personality disorder) (Souery et al., 2007). In addition, it was suggested that extraversion, rumination, and external locus of control were differentiating psychological characteristics for chronicity of depression (Wiersma et al., 2011).

Neural mechanism and depression

It is well documented that smaller hippocampal volumes were found in the patients with longer cumulative duration of lifetime depression, total number of recurrent episodes, and early age of onset of depression (Sheline et al., 1999). Furthermore, MDD subjects have shown abnormally reduced activity in lateral prefrontal cortices during explicit voluntary control of emotional experience (Rive et al., 2013). Nucleus accumbens is also noted as a

candidate of site for depression (Shirayama and Chaki, 2006). Increased amygdala volume in the patients with depression is also noted (Frodl et al., 2002).

Relationship of the cognitive model of depression was proposed by Beck, and neural mechanisms have been elucidated (Disner et al., 2011). For example, it is likely that biased attention to negative stimulus is related to increased amygdala and anterior cingulate cortex, and to decreased right lateral prefrontal cortex and superior parietal cortex (Disner et al., 2011).

Psychological factor (resilience and personality)

Resilience is as dynamic and adaptive process that subserves maintaining, regaining, or homeostasis in conditions. Furthermore, resilience entails a process of sustain-ability that prevents or attenuates disturbance of mental health after exposure to sever adversity (Rutten et al., 2013). In the psychological factors of resilience, secure attachment, experiencing positive emotions, having a purpose in life, cognitive processes, personality traits, and active coping mechanism are known to be important (Rutten et al., 2013; Wu et al., 2013). Resilience is associated with favorable treatment outcome in patients with depression (Min et al., 2012). Depressive disorder was helped by resilience-enhancing intervention (Stallard and Buck, 2013).

Positive emotions are active ingredients within trait resilience, which reduce the risk of depression (Fredrickson et al., 2003). Increases in positive emotion during the first week of pharmacological treatment in depressed patient predicted improved depression scores and recovery from depression 6weeks later (Geschwind et al., 2011). In neuroimaging study, positive emotion was found to be related with activity of subgenual cingulated-centered limbic cortical network that affect sad mood induction (Keightley et al., 2003).

Resilience was negatively associated with neuroticism, and positively related to

extraversion and conscientiousness, in their relations to personality (Campbell-Sills et al., 2006). Previous studies reported that depressed patients demonstrate high neuroticism, and low extraversion and conscientiousness compared to healthy control. The biological and psychological basis of neuroticism was recently reviewed (Ormel et al., 2013). Furthermore, neuroticism was quantified by neuroimaging studies (Servaas et al., 2013). In functional connectivity of limbic system, it has been revealed that right amygdala-medial prefrontal cortex connectivity was positively correlated with neuroticism score in response to negative emotional facial expressions (Cremers et al., 2010). For a while, extraversion had positive correlations with whole-brain functional networks and a relationship with response in somatosensory cortex (Gao et al., 2013; Schaefer et al., 2012).

There are a variety of ways in which personality features may play a role in development and treatment of major depression. There are five etiological models (Vulnerability model, Pathoplasty model, Complication model, Spectrum model, Common-Cause model) to account for relation between personality and major depression (Bagby et al., 2008a). Many research demonstrated that personality features could be useful in diagnosis and treatment (Bagby et al., 2008a). For example, neuroticism is associated with negative outcome in general (Mulder, 2002), whereas extraversion appears to be consistently associated with a more favorable outcome to treatment (Bagby et al., 1995). Personality dysfunction is associated with impaired short-term response to antidepressant treatment in major depression (Gorwood et al., 2010)

In the relationships between personality traits and treatment response, cognitive behavior therapy might be superior to interpersonal psychotherapy for depressed patients with high harm avoidance (Joyce et al., 2007). Additionally, treatment resistant depressive patients with high neuroticism are more likely to respond pharmacotherapy compared to cognitive behavioral therapy (Bagby et al., 2008b). The results suggest that treatment response for

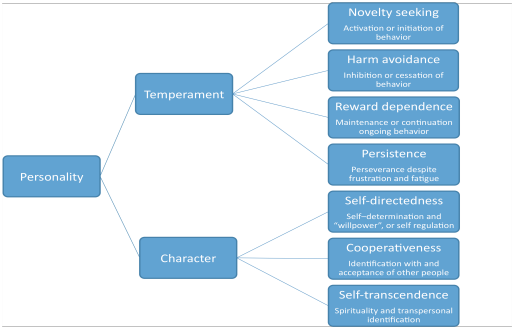

Figure 1. Structure of Temperament Character Inventory (TCI)

patients with major depression may be optimized if patient personality traits are taken into account.

TCI and NEO in depression

In many research and clinical situation, Temperament and Character Inventory (TCI), and NEO Personality Inventory Revised (NEO) have been used widely as personality assessment tool.

TCI was developed by Cloninger based on seven factor model of personality (Figure 1). In TCI, personality is divided into temperament dimension and character dimension. Temperament was postulated to be independently heritable, manifest in early life, and individual difference in associative learning in response to novelty, danger or punishment, and reward. Temperament dimension include novelty seeking, harm avoidance, reward dependence and persistence. Character is defined as second domain of personality, which is

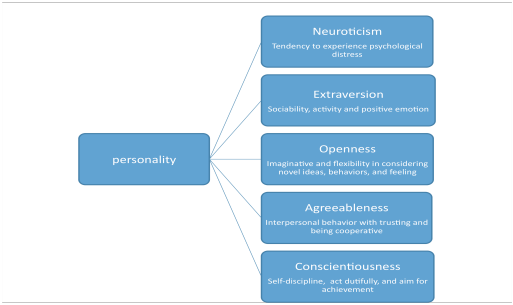

Figure 2. Structure of NEO Personality Inventory Revised (NEO)

predominantly determined by socialization processes during the life-span. Character dimension include self-directedness, cooperativeness and self-transcendence. Previous research consistently reported that high levels of harm avoidance and low levels self-directedness were consistently found in patients with major depression (Please see the text, Chapter I pp.10).

NEO assesses five domains of personality based on big five model of personality structure (Figure 2). The NEO was the end product of many years of factor analytic studies that had as their goal to distill personality into a set of valid and reliable dimensions. NEO is comprised neuroticism, extraversion, openness, agreeableness and Conscientiousness. Previous studies reported high neuroticism, and low extraversion and conscientiousness in depressed patients (Please see the text, Chapter II pp.24).

As mentioned above, it is well established that there exist personality traits of depressed patients. However, psychological features of treatment-resistant depressive patients have never been reported. The aim of study is to clarify personality bias of patients with

treatment-resistant depression. In these studies, we revealed the psychological features of treatment resistant depressive patients and remitted depressive patients compared to healthy control. We divided this study into two chapters and report them here.

Chapter I:

We investigated the possibility of personality biases in treatment-resistant patients with MDD, using TCI. In addition, internal correlations of TCI were investigated in each group.

Chapter II:

We investigated the possibility of personality biases in treatment-resistant patients with MDD, using NEO Personality Inventory Revised (NEO-PI-R). In addition, internal correlations of NEO were investigated in each group. Furthermore, we examined relationships between TCI and NEO in treatment-resistant depressive patients.

2. CHAPTER I

Personality Traits as Risk Factors for Treatment-Resistant Depression

1. ABSTRUCT

Background: The clinical outcome of antidepressant treatment in patients with major depressive disorder (MDD) is thought to be associated with personality traits. A number of studies suggest that depressed patients show high harm avoidance, low self-directedness and cooperativeness, as measured on the Temperament and Character Inventory (TCI). However, the psychology of these patients is not well documented.

Methods: Psychological evaluation using Cloninger's TCI, was performed on treatment-resistant MDD patients (n=35), remission MDD patients (n=31), and age- and gender-matched healthy controls (n=174).

Results: Treatment-resistant patients demonstrated high scores for harm avoidance, and low scores for reward dependence, self-directedness, and cooperativeness using the TCI, compared with healthy controls and remission patients. Interestingly, patients in remission continued to show significantly high scores for harm avoidance, but not other traits in the TCI compared with controls. Moreover, there was a significant negative correlation between reward dependence and harm avoidance in the treatment-resistant depression cohort, which was absent in the control and remitted depression groups.

Conclusions: This study suggests that low reward dependence and to a lesser extent, low cooperativeness in the TCI may be risk factors for treatment-resistant depression.

2. INTRODUCTION

Antidepressants are commonly used in the treatment of major depressive disorder (MDD). Between 60 and 70 percent of depressed patients respond to treatment with the first prescribed antidepressant at maximal doses for at least 2 months, and 80 to 90 percent of these patients respond to the first or second choice prescribed antidepressant. The 5 to 15 percent of patients who do not respond to treatment are deemed to have treatment-resistant depression (Thase and Rush, 1995). It is noteworthy that response is defined as a reduction to less than 50 percent in depressive symptoms, but not necessarily recovery. Remission is defined as a full recovery, classified as a score of less than 7 on the Hamilton Rating Scale for Depression (HAM-D) (Thase and Rush, 1995). In order to study the psychopathological aspects of treatment-resistant depression, it is necessary to extract the core features of treatment-resistant depression.

Cloninger and his colleagues developed a dimensional psychosocial model of personality. This Temperament and Character Inventory (TCI) defines four dimensions of temperament: novelty seeking, harm avoidance, reward dependence, and persistence, and three dimensions of character: self-directedness, cooperativeness, and self-transcendence (Cloninger et al., 1993). Personality is considered to affect the outcome of mood disorder. It is well established that depressed patients showed high scores of harm avoidance and that the severity of depression correlates positively with harm avoidance scores on the TCI (Mulder et al., 1994; Chien and Dunner, 1996; Hansenne et al., 1999; Richter et al., 2000; Hirano et al., 2002; Marijnissen et al., 2002; Farmer et al., 2003; Smith et al., 2005; Celikel et al., 2009; Spittlehouse et al., 2010; Sasayama et al., 2011). Furthermore, scores in the harm avoidance section are altered by depression and antidepressant treatment (Chien and Dunner, 1996; Hirano et al., 2002; Marijnissen et al., 2002; Joffe et al., 1993). In a meta-analysis of MDD study data, harm avoidance scores showed a clear negative change from baseline to endpoint

(Kampman and Poutanen, 2011). Similarly, it is known that depressed patients showed low scores of self-directedness and that the severity of depression correlates negatively with self-directedness scores on the TCI (Hansenne et al., 1999; Richter et al., 2000; Hirano et al., 2002; Marijnissen et al., 2002; Farmer et al., 2003; Smith et al., 2005; Celikel et al., 2009; Spittlehouse et al., 2010; Sasayama et al., 2011; Svrakic et al., 1993).

Favorable outcomes after antidepressant treatment are associated with personality score changes. Depressive patients with low harm avoidance scores on the TCI tend to have good outcomes (Joyce et al., 1994; Kampman et al., 2012). Typical TCI scores indicating a favorable outcome, show decreases in harm avoidance and self-transcendence and increases in self-directedness and cooperativeness, from baseline to post- treatment values (Corruble et al., 2002). Furthermore, the harm avoidance rate in treatment-resistant patients is significantly higher than that of the treatment-response group (Kampman et al., 2012; Nelsen and Dunner, 1995). However, no significant personality changes were observed in patients with poor outcome after antidepressant treatment (Corruble et al., 2002). Both non-responders and responders showed increased harm avoidance scores, and decreased self-directedness and cooperativeness scores on the TCI (Hirano et al., 2002). However, it remains unclear which components of personality influence treatment-resistance in MDD patients.

The purpose of this study was to evaluate the psychological features of treatment-resistant patients with MDD. Here, we investigated the possibility of personality biases in treatment-resistant patients with MDD, using Cloninger's seven-factor model, TCI (Cloninger et al., 1993).

Table 1-1. **Demographic information of subjects**

	Healthy Control	Remitted depression	Treatment-resistant depression	p values
Current age (years)	36.76 ± 9.52 (17-60)	40.58 ± 7.88 (28-55)	38.74 ± 9.42 (22-53)	0.080
Sex (male/female)	135/39	18/13	24/11	0.056
Age on set (years)		38.00 ± 8.42 (25-54)	35.94 ± 8.93 (17-50)	0.366
Duration of depressive state (months)		19.04 ± 24.26 (3-49)	36.46 ± 21.32 ** (9-98)	< 0.001
Duration of treatment (months)		23.31 ± 22.32 (3-103)	30.06 ± 26.23 (4-97)	0.235
HAM-D		4.38 ± 1.63 (2-7)	18.31 ± 4.04 **(14-28)	< 0.001
Trial numbers of antidepressants		1.20 ± 0.40 (1-2)	2.60 ± 1.56 **(2-9)	< 0.001

Data are shown as mean ± SD. Parenthesis is the range.

**p<0.001 as compared to the remitted group (Student's t-test)

HAM-D: Hamilton Rating Scale for Depression

3. METHODS

3.1. Ethics Statement

The study was approved by the ethics committee of Teikyo University Chiba Medical Center (study number 09-30) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after the procedures had been fully explained.

3.2. Participants

A total of 174 healthy subjects, 35 antidepressant treatment-resistant depressive patients, and 31 remitted depressive patients were enrolled in this study (Table 1-1). All patients were recruited from the outpatient clinics of Teikyo University Chiba Medical Center (Ichihara, Chiba, Japan), and met the DSM-IV criteria for MDD (first episode) (American Psychiatric Association, 1994). Two senior-level psychiatrists assessed patients' psychopathology. Patients were all physically healthy and free of alcohol or drug abuse. Inclusion criteria required symptoms of moderate depression, after treatment with at least two antidepressants, for 8 weeks. Patient scores were 14 or more on the 17-item HAM-D scale, where the definition of remission (recovery) was 7 or less (Thase and Rush, 1995). Healthy control

subjects with no past history of psychiatric disorders or drug dependence were recruited. Clinical information regarding the subjects is provided in Table 1. The duration of depression in treatment-resistant patients was significantly longer than in remitted depression (Table 1-1).

3.3. Personality Scores and Psychological Tests

Personality was assessed using the TCI-125 (a shortened version of the TCI) (Cloninger et al., 1993; Smith et al., 2005; Tome et al., 1997; Black and Sheline, 1997). The Japanese version of TCI has been validated and tested for reliability in Japan (Kijima et al., 2005; Takeuchi et al., 2011). Items were rated on a four-point scale (1; totally disagree, 2; disagree, 3; agree and 4; totally agree). This test covers four dimensions of temperament, namely: harm avoidance, novelty seeking, reward dependence, and persistence, and three dimensions of character: self-directedness, cooperativeness, and self-transcendence. To obtain normative data, this test was performed on the 174 healthy controls.

3.4. Statistical Analysis

Data from the seven TCI dimensions were first analyzed using multiple analysis of variance (MANOVA), to determine the simultaneous existence of significant differences. Statistical differences among the three groups were determined by a one-way factorial analysis of variance (ANOVA), followed by a multiple comparison test (Scheffe's test). Chi-square test was used for categorical variables. Statistical evaluation between the two groups was performed using a two-tailed Student's t-test. Coefficients among scores of TCI were estimated by Pearson coefficient. Differences were considered to be significant when p values were less than 0.01.

4. Results

MANOVA indicated a significant group effect ($F=9.101$, $p<0.0001$). Subsequent one-way ANOVA demonstrated that treatment-resistant patients showed significantly altered scores on harm avoidance, reward dependence, self-directedness and cooperativeness, but not novelty seeking, persistence, or self- transcendence compared with remitted depression patients and healthy controls (Figure 1-1). Relative to healthy controls, patients in remission only showed significantly increases in scores for harm avoidance (Figure 1-1).

The subscales of each dimension of the TCI are shown in Table 1-2. Treatment-resistant patients showed significantly high scores for anticipatory worry, fear of uncertainty and fatigability in the harm avoidance, and low scores for attachment in reward dependence, responsibility, purposefulness, resourcefulness and congruent second nature in the self-directedness, and empathy, helpfulness and pure-heartedness in the cooperativeness category, compared to remitted depression patients and healthy controls.

Interestingly, harm avoidance, self-directedness and self-transcendence correlate significantly with HAM-D scores in all MDD patients (harm avoidance, $r=0.434$, $p<0.0001$; self-directedness, $r=0.485$, $p<0.0001$; self-transcendence, $r=0.343$, $p<0.001$). In contrast, there were no correlations between TCI scores and severity of depression in patients with treatment-resistant depression (data not shown).

There was a significant negative correlation between reward dependence and harm avoidance in treatment-resistant depression patients. This correlation was not present in healthy controls and remitted depression patients (Table 1-3). Furthermore, there was a significant negative relationship between cooperativeness and the dimensions of novelty seeking and harm avoidance, in the treatment-resistant group, but not in the healthy control and remitted depression groups (Table 1-3). Conversely, there was a significant negative

correlation between novelty seeking and harm avoidance scores in the healthy control and remitted depression groups, but not in the treatment-resistant depression group (Table 1-3).

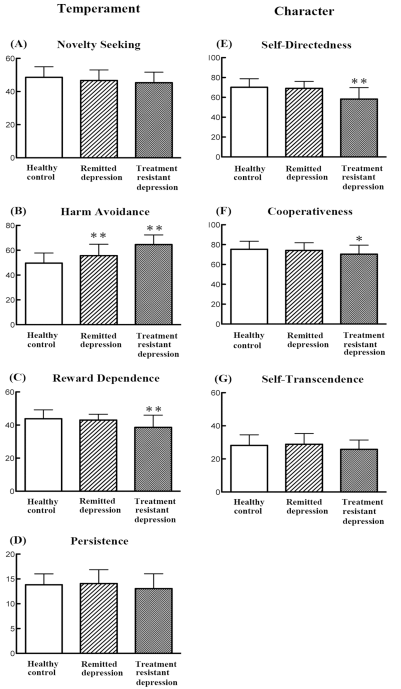

Figure 1-1. The data of TCI

Analysis of variance (ANOVA) shows a significant difference between three groups for (B) Harm Avoidance (F (2,237)=50.58; p<0.001), (C) Reword Dependence (F (2,237)=13.19; p<0.001), (E) Self-Directedness (F (2,237)=25.98; p<0.001), and (F) Cooperativeness (F (2,237)=5.42; p=0.005). There are not significant differences between three groups in (A) Novelty seeking, F (2,237)=4.44, p=0.013, (D) Persistence, (F (2,237)=1.81, p=0.167, and (G) Self-transcendence, F (2,237)=2.51, p=0.084. *p<0.01, **p<0.001 compared to control (ANOVA followed by Scheffe's test).

Table 1-2. Comparison of TCI subscales in subjects

	Healthy control (n = 174)	Remitted depression (n = 31)	Treatment resistant depression (n = 35)	F	p
< Novelty seeking >	48.58 ± 6.40	46.65 ± 6.35	45.31 ± 6.37	4.44	0.013
Exploratory excitability	12.60 ± 1.96	12.36 ± 2.11	11.49 ± 2.12	4.54	0.012
Impulsiveness	12.43 ± 2.26	11.65 ± 2.32	10.69 ± 2.78**	8.66	< 0.001
Extravagance	12.68 ± 2.81	12.45 ± 2.40	12.71 ± 2.86	0.09	0.916
Disorderliness	10.78 ± 2.22	10.19 ± 2.65	10.23 ± 1.82	1.58	0.208
< Harm avoidance >	49.62 ± 8.15	55.65 ± 9.16**	64.59 ± 7.81**,##	50.58	< 0.001
Anticipatory worry	11.79 ± 2.39	13.17 ± 2.40	16.03 ± 2.07**,##	48.70	< 0.001
Fear of uncertainty	13.98 ± 2.34	14.78 ± 2.94	16.67 ± 2.17**,#	18.65	< 0.001
Shyness	11.97 ± 2.96	13.45 ± 2.95	14.97 ± 3.11**	16.25	< 0.001
Fatigability	11.92 ± 2.60	14.26 ± 2.61**	16.94 ± 2.24**,##	61.32	< 0.001
< Reward dependence >	43.82 ± 5.35	43.00 ± 3.51	38.60 ± 7.36**,#	13.19	< 0.001
Sentimentality	14.23 ± 2.17	14.32 ± 2.24	13.00 ± 2.99	4.36	0.014
Attachment	14.39 ± 2.67	14.07 ± 2.00	11.29 ± 3.55**,##	18.64	< 0.001
Dependence	15.17 ± 2.26	14.61 ± 1.63	14.34 ± 2.95	2.31	0.102
< Persistence >	13.83 ± 2.20	14.07 ± 2.79	13.06 ± 2.98	1.81	0.167
< Self-directedness >	70.16 ± 8.64	69.03 ± 7.06	58.28 ± 11.51**,##	25.98	< 0.001
Responsibility	15.79 ± 2.41	13.25 ± 2.98	13.26 ± 2.98**	16.60	< 0.001
Purposefulness	14.34 ± 1.93	14.03 ± 2.09	11.14 ± 2.84**,##	33.81	< 0.001
Resourcefulness	14.21 ± 2.07	13.42 ± 2.55	11.14 ± 2.57**,##	28.14	< 0.001
Self-acceptance	11.91 ± 3.46	12.90 ± 3.24	11.17 ± 3.86	2.03	0.134
Congruent second nature	13.83 ± 2.00	14.00 ± 1.97	11.51 ± 2.23**,##	19.93	< 0.001
< Cooperativeness >	75.33 ± 8.03	74.10 ± 7.81	70.37 ± 9.07*	5.42	0.005
Social acceptance	15.83 ± 2.33	15.00 ± 2.56	14.66 ± 2.29	4.56	0.011
Empathy	13.22 ± 1.87	12.90 ± 2.21	11.97 ± 2.27*	5.84	0.003
Helpfulness	15.23 ± 2.07	14.74 ± 2.00	13.37 ± 2.77**	10.66	< 0.001
Compassion	15.11 ± 2.73	16.07 ± 2.63	15.66 ± 2.63	1.96	0.143
Pure-heartedness	15.95 ± 1.93	15.39 ± 2.00	14.77 ± 2.39*	5.42	0.005
< Self-transcendence >	28.18 ± 6.38	29.61 ± 7.49	25.80 ± 5.65	3.09	0.047
Self-forgetfulness	8.62 ± 2.59	9.23 ± 2.68	8.20 ± 2.69	1.28	0.279
Transpersonal identification	10.03 ± 2.41	10.29 ± 2.82	8.80 ± 2.11	4.23	0.017
Spiritual acceptance	9.65 ± 2.42	10.07 ± 2.63	8.89 ± 2.35	2.59	0.125

Data are shown as mean ± SD.

*p<0.01, **p<0.001 compared to control (ANOVA followed by Scheffe's test).

#p<0.01, ##p<0.001 compared to remitted depression (ANOVA followed by Scheffe's test)

Table 1-3. Correlates of TCI variables

Healthy control (n=174)	NS	HA	RD	P	SD	C	ST
Novelty seeking (NS)	–						
Harm avoidance (HA)	-.463**	–					
Reward dependence (RD)	.063-	.115	–				
Persistence (P)	-.018-	.146	.109	–			
Self-directedness (SD)	-.142	-.399**	.232*	.093	–		
Cooperativeness (C)	-.093	-.169	.639**	.177	.358**	–	
Self-transcendence (ST)	.194	-.043	.007	.148	-.308**	.041	–

Remitted depression (n=31)	NS	HA	RD	P	SD	C	ST
Novelty seeking (NS)	–						
Harm avoidance (HA)	-.525*	–					
Reward dependence (RD)	.376	-.173	–				
Persistence (P)	.287	-.401	.252	–			
Self-directedness (SD)	.292	-.334	.466*	.027	–		
Cooperativeness (C)	.071	-.055	.486*	-.069	.396	–	
Self-transcendence (ST)	.438	-.288	.383	.263	.105	.314	–

Treatment-resistant depression (n=35)	NS	HA	RD	P	SD	C	ST
Novelty seeking (NS)	–						
Harm avoidance (HA)	.034	–					
Reward dependence (RD)	-.074	-.466*	–				
Persistence (P)	-.246	-.366	.330	–			
Self-directedness (SD)	-.407	-.603**	.512*	.290	–		
Cooperativeness (C)	-.437*	-.519*	.599**	.368	.577**	–	
Self-transcendence (ST)	.377	-.121	.119	.295	-.023	.121	–

*p<0.01, **p<0.001

5. Discussion

In this study, we found a number of psychological features that appeared to be associated with treatment-resistant MDD. Firstly, we found treatment-resistant patients showed higher scores for harm avoidance and lower scores for self-directedness on the TCI, consistent with previous reports on depressed patients (Hansenne et al., Richter et al., 2000;

Table 1-4. Summary of TCI scores of depressed patients

	NS	HA	RD	P	SD	C	ST
Hansenne et al., 1999 [5]	−	↑	−	−	↓	↓	↑
Richiter et al., 2000 [6]	↓	↑	−	↓	↓	−	−
Farmer et al., 2003 [9]	↓	↑	−	−	↓	↓	−
Smith et al., 2005 [10]	−	↑	−	−	↓	−	−
Celikel et al., 2009 [11]	−	↑	−	−	↓	−	−
Sasayama et al., 2011 [13]	↑	↑	−	−	↓	↓	−
Kampman et al., 2012 [18]	−	↑	↑	−	−	−	−
This study (treatment-resistant)	−	↑	↓	−	↓	↓	−

NS: Novelty seeking, HA: Harm avoidance, RD: Reward dependence, P: Persistence,
SD: Self-directedness, C: Cooperativeness, ST: Self-transcendence
↑ : Increase, ↓ : Decrease, −: No change

Farmer et al., 2003; Smith et al., 2005; Celikel et al., 2009; Sasayama et al., 2011). We also found that harm avoidance and self-directedness correlate significantly with HAM-D scores in both remitted and treatment-resistant patients with depression, replicating previous studies (Richter et al., 2000; Hirano et al., 2002; Celikel et al., 2009; Spittlehouse et al., 2010). Of the seven published studies on TCI scores in depression (Table 1-4), all found significant alterations in the score for harm avoidance and all but one in the score for self-directedness, indicating that this is a common pattern in depression. Since treatment-resistant patients suffer from depressive symptoms, it is not surprising that these non-responders showed the same pattern of high harm avoidance and low self-directedness as depressed patients.

Secondly, treatment-resistant patients demonstrated low scores for reward dependence on the TCI. To the best of our knowledge, this is the first report showing this feature in treatment-resistant MDD patients, and there are no equivalent reports in depressed patients groups (Table 1-4). This is suggestive of low reward dependence being a characteristic feature of treatment-resistant MDD. Looking more closely at reward dependence, the subscale altered between remitted patients and healthy controls is attachment. Thus, it is likely that the dimension of attachment in reward dependence could be specific to treatment-resistant patients. In a recent study of the antidepressant treatment responders, scores for reward

dependence had a small overall positive change from baseline to endpoint (Kampman and Poutanen, 2011). This is supportive of other studies where depressive patients showing high reward dependence on the TCI, also showed a good outcome after antidepressant treatment (Joyce et al., 1994; Tome et al., 1997). Interestingly, scores for reward dependence in non-depressive siblings of depressed patients, were significantly higher than for siblings with a history of depression, suggesting that high reward dependence may protect against the development of depression (Farmer et al., 2003). However, it is unknown whether the enduring characteristics of non-responders are primary or secondary to the disease. A long history of treatment-resistant depression may induce character changes within patients and these changes may persist after the recovery from disease. Future studies will be needed to elucidate these points.

Thirdly, treatment-resistant patients showed low scores for cooperativeness. Significant scores for low cooperativeness in depressed patients were reported in three of the seven studies examining this issue (Table 1-4) (Hansenne et al., 1999, Farmer et al., 2003; Sasayama et al., 2011). This lower concordance suggests that low cooperativeness is a less common characteristic of depressed patients compared with high harm avoidance and low self-directedness. Within the subscale of cooperativeness, the most significantly altered dimensions in comparison with healthy controls, were empathy, helpfulness and pure-heartedness. These results should prove useful in tailoring psychotherapy for MDD treatment-resistant patients. The cooperativeness score correlated negatively with the severity of depression among depressive patients (Hansenne et al., 1999). Other studies showed large increases in cooperativeness and self-directedness scores among treatment responders in MDD, with relative stability of these features among non-responders during treatment (Hirano et al., 2002; Corruble et al., 2002; Black and Sheline, 1997). A recent study demonstrated that cooperativeness was strongly associated with perceived social support

(Cloninger et al., 2011). As mentioned before, it remains unknown whether low cooperativeness is related primarily to treatment-resistant depression or is a secondary effect due to the long duration of illness. Previous studies using TCI showed that low scores for cooperativeness and self-directedness strongly predicted personality disorders in patients with mood disorders (Svrakic et al., 1993; Black and Sheline, 1997). Furthermore, low cooperativeness could be a predictor for hostility and paranoia (Conrad et al., 2009). Low reward dependence is strongly associated with cluster A symptoms, such as paranoid, schizoid and schizotypal personality disorders (Svrakic et al., 1993). It is well known that personality disorders have negative effects on the course and outcome of MDD (Mulder, 2002; Gorwood et al., 2010; Skodol et al., 2011). Therefore, treatment-resistant patients with MDD may suffer from some underlying personality disorder traits, although patients with overt personality disorders were excluded from this study at recruitment.

Fourthly, our results showed significant negative correlations between reward dependence and harm avoidance and between cooperativeness and novelty seeking in the treatment-resistant depression group, which were absent in healthy controls and remitted depression patients. This newly highlighted relationship in treatment-resistant depression patients indicates that low scores for reward dependence and cooperativeness could at least in part be due to harm avoidance and novelty seeking, respectively.

Finally, patients in remission still showed high scores for harm avoidance, compared with normal controls, although the difference was small. In this case, the altered subscale between remitted patients and controls was fatigability. This finding is supported by a previous study demonstrating that even though a significant reduction occurred, higher harm avoidance among unipolar depression patients persisted after treatment, compared with healthy controls (Richter et al., 2000). Future studies will be needed to elucidate whether harm avoidance plays a role in the relapse of depression.

In conclusion, treatment-resistant patients with MDD demonstrated high scores for harm avoidance, and low scores for reward dependence, self-directedness, and cooperativeness, using the TCI. It is well known that depressed patients show high harm avoidance and low self-directedness, and sometimes low cooperativeness on the TCI. Patients with treatment-resistant MDD show persistent symptoms of depression. Our findings suggest that low reward dependence and to a lesser extent, cooperativeness on the TCI may constitute possible risk factors of treatment-resistant depression.

3. CHAPTER II

Low Openness on the Revised NEO Personality Inventory as a Risk Factor for Treatment-Resistant Depression

1. ABSTRACT

Background: Recently, we reported that low reward dependence, and to a lesser extent, low cooperativeness in the Temperature and Character Inventory (TCI) may be risk factors for treatment-resistant depression. Here, we analyzed additional psychological traits in these patients.

Methods: We administered Costa and McCrae's five-factor model personality inventory, NEO Personality Inventory-Revised (NEO-PI-R), to antidepressant-treatment resistant depressed patients (n=35), remitted depressed patients (n=27), and healthy controls (n=66). We also evaluated the relationships between scores on NEO and TCI, using the same cohort of patients with treatment-resistant depression, as our previous study.

Results: Patients with treatment-resistant depression showed high scores for neuroticism, low scores for extraversion, openness and conscientiousness, without changes in agreeableness, on the NEO. However, patients in remitted depression showed no significant scores on NEO. Patients with treatment-resistant depression and low openness on NEO showed positive relationships with reward dependence and cooperativeness on the TCI.

Conclusions: Many studies have reported that depressed patients show high neuroticism, low extraversion and low conscientiousness on the NEO. Our study highlights low openness on the NEO, as a risk mediator in treatment-resistant depression. This newly identified trait should be included as a risk factor in treatment-resistant depression.

2. INTRODUCTION

It is well documented that 60 to 70 percent of depressed patients respond to first line antidepressant treatment at maximum dose, for at least two months. Between 80 and 90 percent of these patients respond to first or second choice prescribed antidepressant medication. The remaining 10 to 15 percent of patients who do not respond to therapy are deemed to have treatment-resistant depression (Thase and Rush, 1995; Souery et al., 2007). Response is defined as a reduction in depressive symptoms to less than 50 percent, but not necessarily recovery. Remission is described as a full recovery. We recently reported that low reward dependence and to a lesser extent, low cooperativeness in the Temperature and Character Inventory (TCI) may be risk factors for treatment-resistant depression (Cloninger et al., 1993). Furthermore, patients with remitted depression show high scores for harm avoidance, relative to healthy controls (Takahashi et al., 2013). It is likely that additional psychological factors associated with depression are yet to be identified from this group of patients.

Another personality inventory, the NEO Personality Inventory-Revised (NEO-PI-R) is also in common use (Costa et al., 2005). This five-factor model of personality structures personality in terms of five traits: neuroticism, extraversion, openness, agreeableness, and conscientiousness. Numerous studies have reported that depressed patients show high scores for neuroticism and low scores for extraversion and conscientiousness using the NEO (Bagby et al., 1998; Enns et al., 2000; Petersen et al., 2001; Du et al., 2002; Duberstein and Heisel, 2007; Chopra et al., 2005; Tang et al., 2009; Rector et al., 2012). The severity of depression correlates positively with neuroticism and negatively with extraversion (Du et al., 2002; Duberstein and Heisel, 2007; Bagby et al., 1995; Griens et al., 2002). The personality traits of neuroticism and extraversion are associated with negative and positive emotional experiences, respectively (McCrae and Costa, 2003). Furthermore, neuroticism scores differed between the

depressed and post antidepressant treatment states (Du et al., 2002; Griens et al., 2002; Costa et al., 2005; Quilty et al., 2008).

Chronically depressed patients also reported higher levels of neuroticism and lower levels of extraversion, agreeableness, and conscientiousness, compared with those suffering acute forms of the disease (Wiersma et al., 2011). Treatment-resistant depression patients had significantly higher neuroticism and lower extraversion scores (Bagby et al., 1995). Interestingly, the duration of depressive episodes significantly correlates with high levels of premorbid neuroticism (Scott et al., 1995). Scores of neuroticism increased, while scores of extraversion and conscientiousness decreased with the occurrence of depression, but the scores for conscientiousness changed very little on recovery from depressive disorders (Karsten et al., 2012). At times, individuals with remitted depression showed significantly more neuroticism than healthy controls (Elliott et al., 2012). It is well known that residual symptoms during remission have a strong prognostic value (Fava et al., 2007). These results indicate that some psychological features are resistant to treatment and persistent in patients with remitted depression.

The purpose of this study was to investigate in more depth, the presence of personality biases in patients with treatment-resistant depression, using the NEO-PI-R (Costa and McCrae, 1997). Additionally, we evaluated the relationships between scores obtained using NEO in this study, and those obtained using TCI in our previous study (Takahashi et al., 2013), using the same cohort of treatment-resistant depression patients.

3. Methods

3.1. Ethics statement

The study was approved by the ethics committee of Teikyo University Chiba Medical Center (study number 09-30) and performed in accordance with the Declaration of Helsinki.

Written informed consent was obtained from all participants, after procedures had been fully explained.

3.2. Subjects

Sixty six healthy subjects, 27 depressed patients in remission, and 35 antidepressant treatment-resistant depressed patients were enrolled on this study (Table 2-1). The treatment-resistant depressed patients were the same sample used in our previous study (Takahashi et al., 2013). All patients met the DSM-IV criteria for major depressive disorder (MDD) (first episode) (American Psychiatric Association, 1994). Patients were recruited from the outpatient clinics of Teikyo University Chiba Medical Center. All patients were physically healthy and free of alcohol or drug abuse. Inclusion criteria required symptoms of moderate depression, after treatment with at least two antidepressants, for 8 weeks (Souery et al., 2007). Scores for patients were 14 or more on the 17-item Hamilton Rating Scale for Depression (HAM-D), on which remission or recovery was scored at 7 or less (Thase and Rush, 1995). Healthy control subjects with no past history of psychiatric disorders or drug dependence were recruited. Clinical information on all subjects is provided in Table 2-1. The duration of depressive states in patients with treatment-resistant depression was significantly longer than in those with remitted depression.

Table 2-1. **Demographic information of subjects**

	Healthy control	Remitted depression	treatment-resistant depression	p values
Current age (years)	38.09 ± 8.46 (23-61)	39.07 ± 9.19 (22-56)	38.74 ± 9.42 (22-53)	0.821
Sex (male/female)	56/10	18/9	24/11	0.073
Age on set (years)		36.07 ± 9.27 (22-54)	35.94 ± 8.93 (17-50)	0.955
Duration of depressive state (months)		19.44 ± 15.67 (3-68)	36.46 ± 21.32* (9-98)	0.002
Duration of treatment (months)		26.63 ± 24.34 (6-54)	30.06 ± 26.23 (4-97)	0.517
HAM-D		4.48 ± 2.76 (3-7)	18.31 ± 4.04** (14-28)	< 0.001
Trial numbers of antidepressants		1.26 ± 0.45 (1-2)	2.54 ± 1.25** (2-9)	< 0.001

Data are shown as mean ± SD. Parenthesis is the range.

**p<0.001 as compared to the remitted group (Student's t-test)

HAM-D: Hamilton Rating Scale for Depression

3.3. Personality Scores and Psychological Tests

Personality was assessed using NEO PI-R. NEO PI-R utilized the five-factor model of personality: neuroticism, extraversion, openness, agreeableness, and conscientiousness (Costa and McCrae, 1997). Each domain scale is comprised of six item facets. The NEO-PI-R consists of 240 items answered on a five- point Likert scale, ranging from absolutely disagree to strongly agree. Raw scores were converted to T-scores for standardization. The mean and SD for each dimension are 50 and 10, respectively.

TCI Scores in patients with treatment-resistant depression were taken from our recently reported study. In this study, we used TCI-125, a shortened version of the TCI (Cloninger et al., 1993; Kijima et al., 2000; Takeuchi et al., 2011). Items are rated on a four-point scale. This test covers four dimensions of temperament: harm avoidance, novelty seeking, reward dependence, and persistence, and three dimensions of character: self-directedness, cooperativeness, and self-transcendence.

3.4. Statistical Analysis

Data from five domains of the NEO were first analyzed using multiple analysis of variance (MANOVA), to check for the simultaneous existence of significant differences. Statistical differences among the three groups were determined by one-way factorial analysis of variance (ANOVA), followed by multiple comparison testing (Scheffe's test). Chi-square test was used for categorical variables. Statistical evaluation between the two groups was performed using a two-tailed Student's t-test. Coefficients among scores for NEO and TCI were estimated by Pearson coefficient. Differences were considered to be significant when p values were less than 0.01.

4. Results

4.1. Psychological Features assessed by NEO

MANOVA indicated a significant groupeffect ($F=5.777$, $p<0.0001$). Subsequent one-way ANOVA demonstrated that patients with treatment-resistant depression showed significantly high scores for neuroticism and lower scores for extraversion, openness and conscientiousness on the NEO, compared with healthy controls or patients with remitted depression (Figure 2-1). Patients in remission showed no significant differences in NEO scores, compared to healthy controls (Figure 2-1).

The subscales of each domain on the NEO are shown in Table 2-2. Patients with treatment-resistant depression showed significantly higher scores for anxiety, depression, self-consciousness and vulnerability in the neuroticism subset. They also showed low scores for warmth, gregariousness, assertiveness, activity, excitement-seeking, and positive emotion in the extraversion subset, feelings and actions in the openness subset, modesty in the agreeableness subset, and competent, achievement striving and self-discipline in the conscientiousness subset, compared with remitted depression and healthy control subjects (Table 2-2).

Neuroticism correlated significantly with HAM-D scores in all MDD patients including both remitted and treatment-resistant groups (neuroticism, $r=0.341$, $p<0.01$; extraversion, $r=0.497$, $p<0.001$). In contrast, there was no correlation between NEO scores and the severity of depression in patients with treatment- resistant depression (data not shown).

A significant negative correlation between neuroticism and extraversion was seen in healthy controls and remitted depression patients, but not in treatment-resistant depression patients (Table 2-3). Significant positive correlation between extraversion and openness was seen in healthy controls, but not in the remitted depression and treatment-resistant depression groups (Table 2-3).

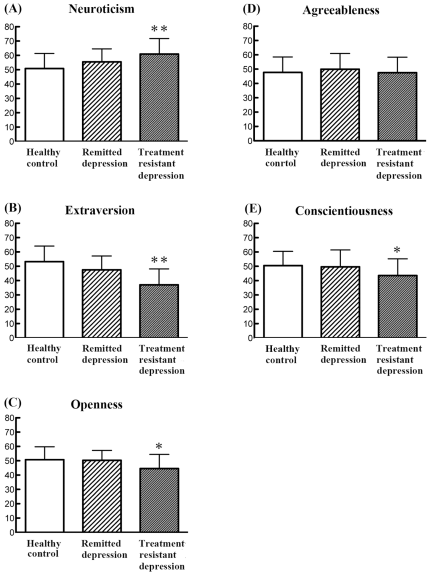

Figure 2-1.
Analysis of variance shows a significant difference between three groups for (A) Neuroticism ($F(2,125)=11.10$; $p<0.001$), (B) Extraversion ($F(2,125)=26.42$; $p<0.001$), (C) Openness ($F(2,125)=5.93$; $p=0.004$), and (E) Conscientiousness ($F(2,125)=4.88$; $p=0.009$). In (D) Agreeableness, there is not a significant difference between three groups ($F(2,125)=0.49$; $p=0.616$). *$p<0.01$, **$p<0.001$ compared to control (ANOVA followed by Scheffe test).

Table 2-2. Comparison of NEO subscales in subjects

	Healthy control (n=66)	Remitted depression (n=27)	Treatment-resistant depression (n=35)	F	p
< Neuroticism >	50.82 ± 10.55	55.44 ± 9.04	60.94 ± 10.83**	11.10	< 0.001
Anxiety	51.24 ± 10.88	56.11 ± 9.72	60.57 ± 9.89**	9.50	< 0.001
Angry Hostility	50.62 ± 12.16	53.93 ± 8.10	55.63 ± 11.98	2.42	0.094
Depression	50.79 ± 10.49	55.93 ± 10.27	62.57 ± 10.12**	14.96	< 0.001
Self-consciousness	50.42 ± 10.48	51.85 ± 8.97	58.00 ± 10.75*	6.38	0.002
Impulsiveness	51.88 ± 10.16	53.07 ± 7.34	51.03 ± 12.34	0.30	0.741
Vulnerability	49.53 ± 10.65	55.22 ± 10.53	62.11 ± 11.07**	15.86	< 0.001
< Extraversion >	53.26 ± 10.85	47.48 ± 9.66	37.00 ± 11.16**	26.42	< 0.001
Warmth	52.79 ± 11.75	49.00 ± 8.79	41.09 ± 12.84**	11.81	< 0.001
Gregariousness	52.33 ± 12.54	47.44 ± 10.67	40.89 ± 10.71**	11.04	< 0.001
Assertiveness	50.62 ± 11.16	48.30 ± 11.18	41.43 ± 10.34**	8.13	< 0.005
Activity	52.00 ± 10.79	50.59 ± 9.07	40.46 ± 11.65**,#	13.92	< 0.001
Excitement-Seeking	54.86 ± 11.65	46.00 ± 10.41*	42.31 ± 10.52**	16.38	< 0.001
Positive Emotions	52.65 ± 11.10	48.48 ± 10.54	39.31 ± 9.48**,#	18.24	< 0.001
< Openness >	50.76 ± 9.01	50.33 ± 6.90	44.60 ± 9.83*	5.93	0.004
Fantasy	48.71 ± 8.46	50.00 ± 8.55	48.09 ± 10.36	0.35	0.706
Aesthetics	46.85 ± 10.69	49.26 ± 9.28	43.29 ± 9.41	2.83	0.063
Feelings	52.82 ± 9.71	52.15 ± 9.38	46.27 ± 9.34*	5.66	0.004
Actions	54.03 ± 10.65	50.00 ± 10.36	46.11 ± 9.47*	6.95	0.001
Ideas	49.91 ± 9.95	49.33 ± 8.43	44.31 ± 11.23	3.76	0.026
Values	53.26 ± 8.03	54.15 ± 9.21	51.26 ± 10.21	0.91	0.405
< Agreeableness >	47.71 ± 10.77	49.96 ± 11.02	47.54 ± 10.83	0.48	0.973
Trust	51.29 ± 11.70	47.63 ± 10.23	44.14 ± 12.15	4.50	0.013
Straightforwardness	46.58 ± 10.31	50.41 ± 9.10	49.20 ± 6.77	2.00	0.140
Altruism	48.77 ± 10.57	48.82 ± 9.28	43.74 ± 10.25	3.09	0.049
Compliance	49.58 ± 10.51	50.74 ± 10.65	49.17 ± 11.89	0.17	0.134
Modesty	46.55 ± 10.44	51.63 ± 12.45	56.23 ± 10.70**	9.20	< 0.001
Tender-Mindedness	48.05 ± 10.52	49.44 ± 11.69	48.03 ± 12.03	0.17	0.846
< Conscientiousness >	50.47 ± 9.94	49.63 ± 11.82	43.54 ± 11.82*	4.88	0.009
Competent	51.23 ± 10.78	49.15 ± 11.04	41.94 ± 12.65**	7.32	< 0.001
Order	51.71 ± 9.45	51.92 ± 10.07	50.91 ± 12.14	0.09	0.913
Dutifulness	47.96 ± 9.28	49.07 ± 9.20	43.86 ± 9.29	3.03	0.052
Achievement Striving	52.96 ± 10.87	48.48 ± 10.69	40.06 ± 12.73**	14.71	< 0.001
Self-Discipline	50.82 ± 10.21	50.07 ± 13.83	41.37 ± 10.99**	8.58	< 0.001
Deliberation	48.15 ± 9.94	48.89 ± 9.77	52.23 ± 10.98	1.87	0.158

Data are shown as mean ± SD.

*p<0.01, **p<0.001 compared to control (ANOVA followed by Scheffe test).

#p<0.01, ##p<0.001 compared to remitted depression (ANOVA followed by Scheffe test)

Table 2-3. Correlates of NEO factors

Healthy control (n=66)	N	E	O	A	Co
Neuroticisms (N)	–				
Extraversion (E)	-.395**	–			
Openness (O)	.001	.457**	–		
Agreeableness (A)	-.346*	.277	.265	–	
Conscientiousness (Co)	.489**	.304	.125	.022	–

Remitted depression (n=27)	N	E	O	A	Co
Neuroticisms (N)	–				
Extraversion (E)	-.610**	–			
Openness (O)	.122	.136	–		
Agreeableness (A)	.201	-.188	.291	–	
Conscientiousness (Co)	-.543*	.088	-.126	-.246	–

Treatment-resistant depression (n=35)	N	E	O	A	Co
Neuroticisms (N)	–				
Extraversion (E)	-.239	–			
Openness (O)	.026	.411	–		
Agreeableness (A)	-.469*	.142	.376	–	
Conscientiousness (Co)	-.670**	.369	-.037	.167	–

*p<0.01, **p<0.001

4.2. Relationship between scores on the NEO and the TCI in Patients with Treatment-Resistant Depression

As shown in Table 2-4, there were significant, strong relationships between NEO and TCI factors, in the patients with treatment-resistant depression. Openness on NEO correlated positively with reward dependence and cooperativeness in TCI. Similarly, agreeableness on the NEO correlated positively with reward dependence and cooperativeness on TCI. Neuroticism on the NEO showed positive correlation with harm avoidance and negative correlation with self-directedness and cooperativeness on the TCI. Extraversion on the NEO

Table 2-4. Correlates of TCI variables in treatment-resistant depressive patients.

	<TCI>						
	Novelty seeking	Harm avoidance	Reward dependence	Persistence	Self-directedness	Cooperativeness	Self-transcendence
<NEO>							
Neuroticism	.343	.682**	-.123	-.344	-.699**	-.502*	-.091
Extraversion	.130	-.574**	.694**	.435*	.416	.406	.353
Openness	.079	-.215	.542**	.042	.057	.505*	.207
Agreeableness	-.260	-.408	.446*	.178	.338	.618**	.051
Conscientiousness	-.369	-.486*	.233	.598**	.563*	.277	.226

*p<0.01, ** p<0.001

correlated negatively with harm avoidance and positively with reward dependence and persistence on the TCI. Conscientiousness on the NEO showed negative correlation with harm avoidance and positive correlation with persistence and self-directedness on the TCI.

5. Discussion

We found that patients with treatment-resistant depression showed significantly altered scores in neuroticism, extraversion, openness and conscientiousness, as measured by NEO. Previous studies using the NEO show that depressed patients scored highly for neuroticism, low extraversion and low conscientiousness (Bagby et al., 1998; Petersen et al., 2001; Du et al., 2002; Chopra et al., 2005; Rector et al., 2012; Griens et al., 2002). Of the six published studies using this scale in depression (Table 2-5), all found significant alterations in scores for extraversion and conscientiousness, and all but one found significant changes in scores for neuroticism, highlighting a common pattern in depression. Since treatment-resistant patients suffer from depressive symptoms, it is not surprising that non-responders showed the same pattern of high scores for neuroticism and low scores for extraversion and conscientiousness, as depressed patients. It is also highly likely that the remaining factor, low openness, could be specific to patients with treatment-resistant depression. Examining the finding for openness, the subscales scores altered are feelings and actions (Table 2-2). Thus, it is likely that altered feelings and actions could be specific to treatment-resistant patients. It should be noted that low openness was associated with high ratios of self-reported, to observer-rated mood symptoms (Duberstein and Heisel, 2007). Although only one of six published studies detected low openness in depressed patients (Table 2-5) (Griens et al., 2002), the subjects in Griens's study seemed to involve patients with chronic or repetitive episodes of depression, based on the recorded long mean duration of illness (over 6 years), the repeated depressive episodes, but without high neuroticism.

Table 2-5. The published data of NEO scores of depressed patients

	N	E	O	A	C
Bagby et al., 1998	↑	↓	−	−	↓
Petersen et al., 2001	↑	↓	−	−	↓
Du et al., 2001	↑	↓	−	−	↓
Griens et al., 2002	−	↓	↓	−	↓
Chopra et al., 2005	↑	↓	−	−	↓
Rector et al., 2012	↑	↓	−	−	↓
This study (treatment-resistant)	↑	↓	↓	−	↓

N: Neuroticism, E: Extraversion, O: Openness, A: Agreeableness, C: Conscientiousness

↑ : Increase, ↓ : Decrease, −: No change

We also detected a significant negative correlation between neuroticism and extraversion, in the healthy control and remitted depression groups, but not in the treatment-resistant depression group (Table 2-3). This negative relationship was also detected in depressed patients, in a previous study (Duberstein and Heisel, 2007). The absence of a relationship between neuroticism and extraversion in treatment-resistant depression may indicate that these patients have lost an adaptive mechanism that still functions in healthy controls. We speculate that neuroticism and extraversion on the NEO are probably less dependent on each other than originally thought in treatment-resistant depression. Furthermore, it appears that neuroticism and extraversion act together with cooperativeness and reward dependence, respectively (Table 2-4), when assessing treatment-resistant depression using TCI, as our previous study reported that both reward dependence and cooperativeness may be risk factors for treatment-resistant depression (Takahashi et al., 2013).

Patients with treatment-resistant depression showed a negative relationship between neuroticism and agreeableness, which also was seen in healthy controls, but not in remitted depressed patients (Table 2-3) or in depressed patients examined in different study (Duberstein and Heisel, 2007). We put forward that there may be a new connection between

neuroticism and agreeableness, rather than between neuroticism and extraversion, leading to psychosocial isolation. These connected characteristics may partially contribute to the psychological features of treatment-resistant depression. Future studies will be needed to elucidate the roles of extraversion and agreeableness in the depressive state.

Here, openness on the NEO showed a positive relationship with reward dependence and cooperativeness on the TCI, in the treatment-resistant depression group (Table 2-4). Again, it should be noted that low scores for reward dependence and cooperativeness on the TCI are characteristic features in patients with treatment-resistant depression (Takahashi et al., 2013). A previous study showed that openness on the NEO has significant relationships with novelty seeking, harm avoidance and self-transcendence on the TCI, in healthy volunteers (De Fruyt et al., 2000). Therefore, the remaining relationships between openness on the NEO and reward dependence, and cooperativeness on the TCI indicate that these factors may act together in treatment-resistant depression. Agreeableness on the NEO also showed a similar pattern for reward dependence and cooperativeness on the TCI, and with openness on the NEO, in treatment-resistant depression, although agreeableness on the NEO did not reach statistically significant levels in this study. A recent study reported that agreeableness on the NEO did not show a significant relationship with reward dependence on the TCI in healthy controls (De Fruyt et al., 2000). Therefore, agreeableness, as well as openness might play a role in the pathology of treatment-resistant depression.

We also found significant relationships between neuroticism on the NEO and harm avoidance and self-directedness on the TCI in treatment-resistant depression. Additionally, we detected association between extraversion on the NEO, and harm avoidance and reward dependence on the TCI, and between conscientiousness on the NEO and harm avoidance, persistence and self-directedness on the TCI in the same group of patients (Table 2-4). These same patterns were also seen in the healthy controls of a previous study (De Fruyt et al.,

2000), indicating that these characteristics are common to both groups. It is likely that this pattern represents the norm and is therefore seen in patients and normal controls. By contrast, significant relationships between neuroticism on the NEO and cooperativeness on the TCI, and between extraversion on the NEO and persistence on the TCI, were seen only in treatment-resistant depression. In addition, these patterns were not seen in healthy volunteers of the previously mentioned study (De Fruyt et al., 2000). These newly detected relationships in treatment-resistant depression patients indicate that high neuroticism and low extraversion on the NEO interact with low cooperativeness and persistence on the TCI, respectively, in the pathology of treatment-resistant depression. However, it remains unknown whether personality bias occurs as a result of long illness or exists as a cause of treatment-resistance.

Finally, this study failed to show any significant factors in remitted depression patients, using the NEO (Figure 2-1). However, our previous study using the TCI revealed that remitted patients still showed high scores for harm avoidance on the TCI, compared with normal controls (Takahashi et al., 2013). Another study using the Maudsley Personality Inventory showed that personality traits do not change after a typical episode of major depression (Shea et al., 1996). Future studies will be needed to examine the psychological factors which contribute to the relapse of depression.

We put forward that patients with treatment-resistant depression display lower levels of resilience, compared with healthy subjects and remitted depression patients. A previous study showed that resilient individuals exhibit lower levels of denial, avoidant coping, pessimism and behavioral disengagement (Alimi et al., 2008). Positive emotions, which are generally seldom seen in depression, promote adaptive coping, openness to social support and flexible thinking (Ong et al., 2006). Negative, rather than positive, life events predict a longer time to remission of depression, however, personality traits do not influence the effect of life events on disease course indicators (Spinghoven et al., 2011). Social support and educational levels

were associated with long-term outcome of treatment-resistant depression (Fekadu et al., 2012). Furthermore, personality dysfunction was also associated with poor response to antidepressant treatment in major depression (Gorwood et al., 2010). Future studies are required to aid identification of factors related to resilience in treatment-resistant depression.

In conclusion, patients with treatment-resistant depression demonstrated high scores for neuroticism, low scores for extraversion, openness and conscientiousness using the NEO. Previous studies report that depressed patients show high neuroticism, low extraversion and low conscientiousness on the NEO. This would strongly imply that the remaining factor, namely, low openness is a specific feature of treatment-resistant depression. Openness on the NEO has positive relationships with reward dependence and cooperativeness on the TCI, in treatment-resistant depression. Our results indicate that these three factors are important mediators in treatment-resistant depression.

5. CONCLUSION

In conclusion, patients with treatment-resistant depression demonstrated high harm avoidance (TCI) and neuroticism (NEO), and low self-directedness (TCI), reward dependence (TCI), cooperativeness (TCI), extraversion (NEO) and conscientiousness (TCI). Previous studies report that depressive patients show high harm avoidance and neuroticism, and low self-directedness, extraversion and conscientiousness. These results suggest low levels of reward dependence (TCI), cooperativeness (TCI) and openness (NEO) may risk factors for treatment-resistant depression. Furthermore, positive relationships between Openness (NEO) and, reward dependence (TCI) and cooperativeness (TCI) may act together in treatment-resistant mechanism of depression.

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