Towards an improvement of the differentiation of depressive disorders. A multidimensional approach

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Character and temperament in major depressive disorder and a highly anxious-retarded subtype derived from melancholia.

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Abstract

Background: An anxious-retarded subtype of major depressive disorder, defined by high scores for both anxiety and retardation, has been derived from melancholia and appeared to have higher external validity in terms of poor outcome and vasopressinergic stress hormone regulation. A specific personality could enhance the validity of this subtype, and the association with melancholia suggested the absence of a personality disorder. As 2 character dimensions of the Temperament and Character Inventory (TCI), self-directedness (SD) and cooperativeness, parsimoniously predict the presence of a personality disorder, the primary aim was to test whether patients with the highly anxious-retarded subtype of depression have both normal SD and normal cooperativeness. A secondary aim was to optimally account for the general personality characteristics of patients with a major depressive disorder.
Methods: Eighty-six patients with major depressive disorder and matched healthy controls were selected. Seventy patients were eventually recruited for a 2-year follow-up encompassing 5 assessments of personality (TCI) and psychopathology (Comprehensive Psychopathological Rating Scale). Full remission of depression was defined by the presence of less than 3 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition items of depression during 2 weeks.
Results: State-dependent changes of SD and harm avoidance (HA) scores were found in all depressed patients. Fully remitted patients had only high HA compared with healthy controls. Unexpectedly, fully remitted patients with the highly anxious-retarded subtype, in addition, had low SD.
Conclusion: The temperament of high HA may be the predisposing TCI trait for major depressive disorder in general. Low SD may be a specific presumably premorbid character trait for the highly anxious-retarded subtype derived from melancholia.

Key words: Melancholia, dimensions, anxiety, psychomotor retardation, Personality

1 Introduction

Major depression with melancholic features according to Diagnostic and Statistical Manual of Mental Disorders (DSM), Fourth Edition (DSM-IV) represents the current definition of endogenous depression. Its clinical description is entirely based on signs and symptoms, in which it differs from DSM, Revised Third Edition (DSM-III-R) melancholia, and resembles the earlier DSM, Third Edition version. A major difference characterizing the DSM-III-R version is the presence of the item "absence of a personality disturbance before the first depressive episode." This item refers to a classic view of melancholic or endogenous depression, which implies that this subcategory is related with an "adequate" personality (Carney et al. 1965, Charney et al. 1981). The absence of a premorbid personality disorder was included in the DSMIII-R criteria because it had repeatedly been associated with favorable somatic treatment outcome, which was the guiding principle in the discussion of candidate nonsymptom features of the DSM-III-R melancholic subtype (Zimmerman & Spitzer 1989). The decision to drop this DSM-III-R item in the DSM-IV version of the melancholic subtype was not made on scientific but on practical grounds because of the difficulty felt to reliably evaluate this absence of a personality disorder (Rush & Weisenberger 1994). There are therefore reasons to assume that the discussion of this topic is not closed by adopting the DSM-IV criteria. These reasons are the inherent heterogeneities of DSM-IV melancholia, resulting from the operationalization of the syndrome by the criterion of at least 4 of 7 signs and symptoms (van Praag 1998), as well as the difficulty to assess the personality of depressed patients.

In the present study, we used an improved "melancholic" subcategory called highly anxious-retarded depression and tested the normality of the personality after full remission of the depressive episode. The multidimensionally defined highly anxious-retarded subcategory has been derived from DSM-IV melancholia (De Winter et al. 2004). It is defined by above median scores on basic symptom dimensions of autonomic dysregulation (anxiety) and motivational inhibition (retardation) assessed by the Comprehensive Psychopathological Rating Scale (CPRS) (Goekoop et al. 1992) and has appeared to be better validated than DSM-IV melancholia because it was characterized by correlated plasma vasopressin (AVP) and cortisol concentrations and a long time to full remission within 2 years (De Winter et al. 2003, De Winter et al. 2006). It may therefore be seen as a better validated version of DSM-IV melancholia. This suggested that it would also be characterized by the absence of a personality disturbance. To test this hypothesis, we used the 2 character dimensions of the Temperament and Character Inventory (TCI) (Cloninger et al. 1993) that specifically predict the presence of a personality disorder (Svrakic et al. 1993). The TCI differentiates 3 character dimensions: self-directedness (SD), cooperativeness (CO) and self-transcendence (ST), and 4 temperament dimensions: novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (PER). Several studies have shown that low scores on SD and CO predict the presence of a DSM personality disorder (Cloninger et al. 1993, Svrakic et al. 1993, Bayon et al. 1996, Joyce et al 2003). Continuous scores of SD and CO predict with nearly equal weight the risk (11%-94%)(Cloninger et al. 1993) of a personality disorder by the logistic regression function: $X = -6.21 + 0.11$ (SD score) $+ 0.10$ (CO score). Dichotomized scores have been found to have a sensitivity and specificity of 0.77 and 0.79 for low SD and 0.73 and 0.59 for low CO, resulting in hit rates of 77% and 68%, respectively (Gutierrez et al. 2002). We therefore hypothesized both normal SD and normal CO in fully remitted patients with the highly anxious-retarded subtype. The use of these measures to detect personality disorder style was preferred above the use of a standardized axis-II interview for reasons of economy (self-report) and parsimony (2 dimensions). The hypothesis of normal personality in the highly anxiousretarded subtype would be refuted by either low SD or low CO. These low character scores, which would

refer to the inevitable comorbidity of personality disorders in patients with major depression (Corruble & Ginestet 1996), were expected in the group of non–highly anxious-retarded patients.

Secondary aims of this study were the maximally attainable elimination of state-dependent report bias and the maximally attainable differentiation between subtypespecific traits and general presumably premorbid traits of depression in fully remitted patients. In this context, we investigated whether known relations between depression and TCI scores could be replicated and whether the differentiation of different sorts of relation could be optimized. We recognized at least 4 types of relation (Veling & Goekoop 2000): that of a vulnerability factor (a personality trait predisposing to the development of a depressive disorder), pathoplastic factor (a preexisting personality trait influencing intensity, subtype, or outcome), complication of the depressive disorder (a state-dependent personality change during the acute episode), and a scar (a state-independent personality change after ≥1 acute episodes). A personality characteristic that changes during the course of remission towards normality can be conceived as a complication of depression. A personality characteristic in fully remitted patients compared with healthy controls may be a candidate for a vulnerability factor, pathoplastic factor, or a scar. If it is related to recurrent depression or the number of previous episodes, it may be interpreted as a scar, and if it differentiates a depressive subcategory from all other patients, it may have the role of a pathoplastic or even specific vulnerability factor for that subcategory.

Previous TCI studies in depression have found the following. During the acute episode, low SD and high HA have been found most consistently, whereas incidentally, high ST and low CO, NS, and PER were present (Hansenne et al. 1999, Hansenne et al. 2001, Richter et al. 2000, Hirano et al. 2002, Marijnissen et al. 2002). These results do not enable the differentiation between complication, pathoplastic or vulnerability factor, or scar.

Harm avoidance and SD have been found related with depression intensity (Richter et al. 2000, Hirano et al. 2002), which implies their involvement as a complication. At time of remission, only high HA has reproducibly been found. Low SD was present in only 2 studies, whereas both low and high CO were found in 2 separate studies (see Table 1). Only 1 study investigated TCI relations with (remitted) melancholia, and no specific association has been found (Sato et al. 2001. These results suggest that high HA after remission may correspond with a general vulnerability factor for major depression. Low SD after remission could refer to the premorbid trait of a subgroup of patients with a personality disorder. An analogous relationship between low CO and a subcategory of depression cannot be refuted. The state-dependent changes of HA and SD scores imply that the investigation of relations between depression and presumably premorbid traits requires cautious elimination of this report bias. Most TCI studies of the relation between depression and personality, however, did not investigate patients in full remission and generally relied on a too-short period to follow-up (2-52 weeks) (Table 1). As a consequence, part of the high HA or low SD in "remitted" but not fully remitted patients could still be due to state dependent changes.

To optimize the differentiation between state-dependent report bias and presumably premorbid personality of the highly anxious-retarded subtype and depression in general, we analyzed the relation between personality and depression after full remission. In addition, we asked the patient to rate himself as if in his premorbid condition, and we used strict criteria for full remission (Frank et al. 1991). To optimize the percentage of fully remitted patients, we used a long (2-year) follow-up period. To control for a

potential scar effect, we controlled for the relation between TCI score after full remission and recurrence of major depressive episode.

The main question of the present study was, do fully remitted patients with a highly anxious-retarded depression have both normal SD and normal CO compared with healthy controls? Secondary questions were related with the optimal elimination of state-dependent report bias and differentiation between subtype-specific and general traits after full remission. These were: do all eventually fully remitted patients with depression differ from normal control subjects on HA (replication of high HA as presumably premorbid factor)? Do these remitted patients exhibit a change of selfreport on TCI dimensions during the 2-year follow-up period (replication of complications concerning HA and SD)? For global comparison with previous findings during the acute episode, we, in addition, investigated on which TCI dimensions patients with major depression differ from normal control subjects (replication study of low SD and high HA most relevant and, to a lesser extent, ST, CO, NS, and PER). Melancholic patients were similarly investigated as the highly anxious-retarded subtype.

Table 1
Review of differences of TCI scores between depressed patients and controls, TCI changes during follow-up, and TCI differences between remitted patients and controls. – = data not available.

Author(s) and year	N	follow-up period in weeks	definition of remission	depressed patients vs controls	change during follow-up	remitted patients vs controls
Black & Sheline (1997)	15	6 - 10	completer	-	↑ SD	-
Richter et al. (2000)	126	-	discharge	↑HA, ↓NS, ↓PER, ↓SD	↓HA, ↑SD	↑HA, ↓SD, ↓ST
Sato et al. (2001)	121	26	HDRS < 8	-	-	↑HA, ↓SD,↓CO
Hirano et al. (2002)	108	16	HDRS < 8	↑HA, ↓SD, ↓CO	↓HA, ↑SD, ↑CO	↑HA
Marijnissen et al. (2002)	35	6	HDRS < 16, < 8	↑HA, ↓SD	-	↑HA
Corruble et al. (2002)	57	4 - 52	>50% reduction MADRS, MADRS <15	-	↓HA,↑SD, ↑CO, ↓ST	-
Agosti & McGrath (2002)	154	2 - 10	responder (CGI)	-	-	↑HA, ↓PER, ↑CO

2 Method

2.1 Subjects

Newly referred in- and outpatients of the psychiatric institute GGZ Leiden/Rivierduinen were referred for the study by a psychiatrist who made the initial diagnosis of depressive disorder. The diagnosis was confirmed by the investigator (RFP deW) using a semistandardized interview, the CPRS(Asberg et al. 1978, Goekoop et al. 1991, APA 1994), which, in this context, was used to operationalize the presence of the symptoms of a major depressive disorder according to DSM-IV. DSM-IV symptoms that were not covered by the CPRS were separately scored using a similar gradation of item severity to score the clinically meaningful presence of a symptom. Each symptom or set of symptoms was checked for its presence during the last 2 weeks before assessment using the criterion ≥3 for each CPRS item score (range, 0-6). Patients were included if they fulfilled criteria for major depressive disorder according the DSM-IV (APA 1994) and had a score of at least 21 on the depression rating scale of the CPRS, the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgommery & Asberg 1997). Seventy patients were included for the initial cross-sectional and 2-year follow-up parts of the study. Nineteen were additionally recruited for the initial cross-sectional part only because of limited time availability, 3 of whom were excluded because of invalid TCI data. This resulted in 86 patients for the initial cross-sectional part. Of the 70 follow-up patients, 12 dropped out of the follow-up, leaving 58 patients after 2 years. Patients with organic, bipolar, schizoaffective, or schizophrenic or other primary psychotic disorder were excluded, as were patients with somatic disorders that could influence AVP concentration, such as the syndrome of inappropriate antidiuretic hormone secretion. Depressed patients with a panic disorder were not included because they participated in a different research project. The presence of a severe personality disorder that, by the first psychiatrist, was assumed to hamper the treatment of the mood disorder, was an additional exclusion criterion. The exact number of patients excluded this way is not known, but they generally comprise less than 5% of all patients with major depression. No patients had to be excluded because of the syndrome of inappropriate antidiuretic hormone secretion. Written informed consent was obtained from all patients. The Ethical Committee of Leiden University Medical Centre approved the consent protocol.

2.1.1 Normal controls

Normal control subjects (n = 86) were selected from 339 normative controls (Duijsens et al. 2000) who were randomly selected from the national telephone book. They represented the population with its inherent frequency of psychopathology and vulnerability. The 86 control subjects were blindly and individually selected by matching on age and sex of each depressive patient.

2.2 Assessments

2.2.1 Subcategories and dimensions of psychopathology.

The DSM-IV melancholic subtype (n = 42) was diagnosed by a semistandardized diagnostic interview, the CPRS (Asberg et al. 1978, Goekoop et al. 1991), which, in this context, was used to operationalize the presence of the symptoms of the melancholic subtype. DSM-IV symptoms that were not covered by the CPRS were separately scored using a similar gradation of item severity to score the clinically meaningful presence of a symptom. Each symptom or set of symptoms was checked for its presence during the last 2 weeks before assessment, corresponding with a CPRS item score of 3 or higher (range, 0-6). A slightly modified version of the Family History of the Research Diagnostic Criteria (RDC) Interview by Andreasen et al (Andreasen et al. 1986 was used to assess familial depression (De Winter et al. 2004).

The CPRS was used for rating severity of depression by means of the MADRS and for rating basic dimensions of psychopathology. To this end, all CPRS items were scored from 0 to 6. Of the 6 factor-analytic subscales of the CPRS the following 3 scales were scored: emotional dysregulation, motivational dysregulation (inhibition and disinhibition), and autonomic dysregulation (Goekoop et al. 1992). The highly anxious-retarded subcategory of depression (n = 30) was defined by ratings (≥median) on the dimensions autonomous dysregulation (≥11) and motivational inhibition (≥8), hereafter called anxiety and retardation.

2.2.2 *Personality*

The Dutch translation (Duijsens et al. 2000) of Cloninger's TCI (Cloninger et al. 1993) was used to assess the 3 dimensions of character and 4 dimensions of temperament. The questionnaire was filled in within 2 weeks after recruitment and, subsequently, every 6 months until 2 years after recruitment. Patients were asked to answer the questions as if they were in their premorbid state to minimize state-dependent effects.

2.3 *Treatment*

The treatment protocol has been described extensively before (De Winter et al. 2006). In short, all patients were treated according to a standard pharmacotherapeutic protocol and a standardized treatment with cognitive behavioral therapy, starting with behavioral activation. If necessary, relational therapy, daytime treatment, or clinical treatment was added. If a patient was already taking an antidepressant, this treatment was continued and increased after t1 to a maximal therapeutic dose. If the antidepressant drug at entrance of this study had to be changed because of lack of treatment effect at the start of this study, drug withdrawal was performed after the first assessment of the study. To account for potential drug effects on the TCI scores, antipsychotic, antidepressant, and benzodiazepine drug dosages at t1 and t7 were transformed into equivalent dosages (haloperidol, imipramine, and chlordiazepoxide equivalents) according to standard dosage ranges (Birkenhager & Moleman 1998). Both effects of drug treatment and drug dosage were analyzed.

2.4 *Follow-up and outcome measures*

Psychopathology was assessed with the CPRS at the beginning of the treatment (t1); after 6 weeks (t2); and then after 3, 6, 12, 18, and 24 months (t3-t7), as described before (De Winter et al. 2006). TCI data were only available for t1, t4, t5, t6, and t7. Full DSM-IV remission of depression was defined by a maximum of 2 symptoms for major depression during at least the last 2 weeks. These full remission criteria as representation of the current state were chosen, instead of criteria covering a longer period, because the aim was only to maximally enhance the percentage of patients with current state remission. The background assumption that this short period would suffice was based on the clinical impression that the state-dependent fluctuation of character deficiencies immediately parallel depressive state fluctuations. Partial remission was defined by a minimum of 3 and a maximum of 4 symptoms of major depression according DSM-IV during at least the last 2 weeks (Frank et al. 1991).

DSM-IV criteria were assessed by using corresponding CPRS items. For this purpose, the scores on the individual items were dichotomised: scores of 3 or higher were taken as representing the DSM-IV severity criterion of a symptom being more present than absent. Increased appetite and weight were rated separately. The absence of a DSM-IV symptom was defined by a CPRS item score of 2 or lower.

2.5 *Data analysis*

Because in the general population sex has been found related with RD, ST, NS, and HA, and age has been found related with NS, CO, and ST (Peliso et al. 2000, Cloninger et al. 1997), we analyzed covariate effects for age and sex in all comparisons. Multiple analysis of covariance (MANCOVA) was used to analyze, in the depressed patients, relations between scores on the 7 TCI dimensions and MADRS score, age, time since first episode of depression, number of previous episodes, and level of education, as well as the dichotomous variables sex, family history, marital status, out- or inpatient status, and recurrent depression. Separate assessments were used to detect whether significant relations with TCI scores were based on higher or lower scores or on positive or negative correlations (Pearson's correlation). These analyses resulted in using age and sex as covariates in all investigations, as well as level of education, MADRS score, and recurrence in all analyses at t1 that compared subgroups of depressed patients. In addition, psychotropic treatment and dosage were analyzed for their relation with the highly anxious-retarded subtype and the TCI scores.

MANCOVA with the 7 TCI scores as dependent variables was used to compare depressed patients and healthy controls, as well as subgroups of patients, at t1 and t7. As in fully remitted patients at t7 level of education and MADRS were not related to any dimension, and time since first episode emerged as covariable, we added the latter and eliminated the former covariables from analyses at t7. Separate assessments were used to detect whether significantly differing TCI scores were higher or lower. Since only lower SD or CO in patients with fully remitted highly anxious-retarded depression would refute the 0-hypothesis, α was primarily set at .10 for this 1-sided difference on each of these dimensions. As this refutation could be realized by both low SD and low CO, an α of .05 was eventually required to a avoid chance finding. MANCOVA with repeated measures (double multivariate analysis), using the 7 TCI scores at t1, t4, t5, t6, and t7 as dependent variables and full-remission vs non–full remission as independent variable, was used to detect the general characteristics of changed report bias in depression. All tests were carried out using SPSS for windows 12.0 (SPSS Inc, Chicago, IL).

3 Results

3.1 Demographic and clinical data

Table 2 shows the relevant demographic and clinical data of the 86 patients. Forty-2 patients (49%) fulfilled criteria for melancholic subtype according to DSM-IV, and 30 patients (35%) had a highly anxious-retarded depression. From the 42 patients with melancholic depression, 25 patients (60%) also had highly anxious-retarded depression, whereas 83% of the latter subtype fulfilled criteria for DSM-IV melancholia. No significant differences were found between the highly anxious-retarded subtype and the group of all other patients, except for the MADRS score, which was higher in the highly anxious-retarded subgroup than in the non–highly anxious-retarded patients ($t = 8.097$; $df = 84$; $P < .001$). The 70 patients who were recruited for the follow-up study (De Winter et al. 2006) did not differ in any of these respects from the 86 patients of the cross-sectional study at initial measurement. The 16 patients who were not included in the follow-up study differed in age (37 years, standard deviation = 13 vs 29 years, standard deviation = 12; $P = .023$) from the 70 patients of the follow-up study. The 12 dropouts from the follow-up did not differ on any demographic or clinical measure from those who remained in the study. **Table 3** presents the numbers of patients with depression and the initially melancholic, anxious-retarded patients and in- or outpatients, as well as of those with recurrent depression, at the 5 time points of the follow-up and the numbers and percentages of nonremission, partial remission, and full remission as well as the MADRS scores at these time points.

No relation was found between the highly anxious-retarded subtype and any pharmacologic treatment variable at t1 or t7.

Table 2
Demographic and clinical data of acutely depressed patients, and the subgroups with the highly anxious-retarded subtype, all other patients and recurrent depression. Age in years (y); theoretical range for level of education: 1-6.

	Major depression n = 86		Highly anxious-retarded n = 30		All other patients n = 56		Recurrent depression n = 48	
age	40 y	(sd =12 y)	42 y	(sd = 13 y)	39 y	(sd = 11 y)	43 y	(sd = 12 y)
female	56	(65%)	18	(60%)	38	(68%)	33	(69%)
educational level	3.4	(sd = 1.5)	3.7	(sd = 1.6)	3.2	(sd = 1.5)	3.4	(sd = 1.6)
inpatients	36	(42%)	12	(40%)	24	(43%)	20	(42%)
recurrence	48	(56%)	19	(63%)	29	(52%)	48	(100%)
MADRS	30	(sd = 6)	36	(sd = 5)	27	(sd = 4)	31	(sd = 6)
number of previous episodes	1.7	(sd = 2.1)	1.8	(sd = 2.3)	1.6	(sd = 2.0)	2.8	(sd = 2.1)
generalized anxiety disorder	22	(26%)	7	(23%)	15	(27%)	14	(29%)
dysthymic disorder	9	(11%)	3	(10%)	6	(11%)	5	(10%)

Table 3
Numbers of patients with depression and the initially melancholic, anxious-retarded patients, and in- or outpatients, as well as of those with recurrent depression at the 5 time points of the follow-up, and numbers and percentages of remission rates as well as MADRS scores.

	Start		6 months		12 months		18 months		24 months	
All patients	70		64		61		55		58	
non-remission	70	100%	22	34%	14	23%	12	22 %	9	16 %
partial remission		-	14	22%	12	20%	10	18%	8	14%
full remission		-	28	44%	35	57%	33	60%	41	71%
MADRS	30		20		16		16		13	
Melancholic	33		31		30		26		28	
non-remission	33	100%	12	39%	8	27%	5	19%	5	18%
partial remission		-	10	32%	8	27%	4	15%	4	14%
full remission		-	9	29%	14	47%	17	65%	19	68%
MADRS	34		22		18		16		15	
Anxious-retarded	24		23		22		20		22	
non-remission	24	100%	10	44%	9	41%	7	35%	6	27%
partial remission		-	7	30%	3	14%	3	15%	1	5%
full remission		-	6	26%	10	46%	10	50%	15	68%
MADRS	36		23		20		19		17	
Outpatients	42		39		39		32		35	
non-remission	42	100%	12	31%	9	23%	7	21%	4	11%
partial remission		-	6	15%	7	18%	6	18%	4	11%
full remission		-	20	54%	23	59%	21	62%	27	77%
MADRS	29		19		15		15		13	
Recurrent	41		36		36		33		35	
non-remission	41	100%	12	33%	9	25%	7	21%	6	17%
partial remission		-	8	22%	7	19%	3	8%	2	6%
full remission		-	16	44%	20	56%	23	70%	27	77%
MADRS	31		20		16		15		13	

3.2.1 Temperament and Character Inventory scores and demographic and clinical data in depressed patients at t1

MANCOVA in the 86 patients with major depression at t1, with age, level of education, MADRS score, number of previous episodes, and time since first episode as covariates and sex, marital status, recurrence, in- or outpatient status and familial depression as fixed factors, showed that female patients had different CO and RD compared with male patients ($F = 25.011$; $df = 1$; $P < .001$) and $F = 7.341$; $df = 1$; $P = .008$). Separate comparison showed higher CO and RD in females. Patients with recurrent depression had different SD and HA ($F = 6.738$; $df = 1$; $P = .011$ and $F = 6.003$; $df = 1$; $P = .017$). SD was lower and HA was higher than in first-episode patients. Level of education was significantly related with CO ($F = 4.339$; $df = 1$; $P = .041$). The correlation between CO and educational level was positive. Age related significantly with SD ($F = 4.305$; $df =1$; $P = .041$) and NS ($F = 4.276$; $df =1$; $P = .042$). The correlation with SD was positive and, with NS, negative. The MADRS related significantly and positively with ST ($F = 10.132$; $df =1$; $P = .002$). No relations were found between TCI dimensions and number of previous episodes, time since first episode, out- or inpatient status, marital status, and family history of depression. These data resulted in the use of age and sex as covariates in analyses comparing patients with healthy controls, and in age, sex, level of education, recurrence, and MADRS as covariates in analyses comparing subgroups of patients (see Table 2).

3.2.2 Depressed patients at t1 vs healthy controls

MANCOVA showed that patients and healthy controls differed significantly on SD ($F = 77.35$; $df = 1$; $P < .001$) and HA ($F = 97.79$; $df = 1$; $P < .001$) and weaker on CO ($F = 6.34$; $df = 1$; $P = .013$), as well as on NS ($F = 4.26$; $df = 1$; $P = .041$) and RD ($F = 7.07$; $df = 1$; $P = .009$). Sex related most strongly with CO ($F = 12.15$; $df = 1$; $P = .001$) and RD ($F = 10.09$; $df = 1$; $P = .002$) and to a lesser degree with HA ($F = 4.78$; $df = 1$; $P = .03$). Age was only related with NS ($F = 15.03$; $df = 1$; $P < .001$). Separate assessment showed higher values for CO, RD, and HA in females and lower NS in aged subjects. The main findings are summarized in **Table 4**. The question whether psychotropic drugs could influence the TCI scores in depressed patients was primarily answered within the group of all depressed patients. Relations between psychotropic treatment and TCI dimensions at t1 were found in MANCOVAs using all TCI scores as dependent variables; sex and recurrence as fixed factors; age, level of education, and MADRS at t1 as covariates; and finally, psychotropic treatment or dosage as additional covariates. Antidepressive treatment was not associated with any TCI dimension. Antipsychotic treatment was related with SD ($F = 6.356$; $P = .014$), HA ($F = 5.976$; $P = .017$), and CO ($F = 4.741$; $P = .033$), and benzodiazepine treatment, with NS ($F = 7.208$; $P = .009$). Self-directedness and CO were relatively low, HA was high in patients on antipsychotics, and NS was relatively high in patients on benzodiazepine treatment. If psychotropic dosage was used as independent variable instead of psychotropic treatment, then the significance of the relation between CO and the antipsychotic drug increased slightly (CO [$F = 4.027$; $df = 3$; $P = .012$]), whereas all other relations lost significance. We therefore used psychotropic treatment as covariate in the following analyses. Level of education related only with CO in these depressed patients ($F = 4.210$; $P = .046$).

3.2.3 Highly anxious-retarded patients at t1 vs healthy controls and all other patients at t1.

MANCOVA, accounting for the effect of age and sex, showed that highly anxious-retarded patients had different SD ($F = 35.40$; $df = 1$; $P < .001$) and HA ($F = 38.13$; $df = 1$ and $P < .001$) compared with healthy controls. Separate tests showed lower SD and higher HA in this subcategory. MANCOVA showed that melancholic patients also had significantly different SD ($F = 55.74$; $df = 1$; $P < .001$) and HA ($F = 51.00$; $df = 1$; P b 0.001), and a slightly different CO ($F = 5.13$, $df = 1$; $P = .025$). Separate analyses showed lower SD and CO and higher HA. The highly anxious-retarded and melancholic patients therefore had the same

lower SD and higher HA as all patients compared to healthy controls. When comparing the subgroup of patients with the highly anxious-retarded subtype and the group of all remaining patients, then no significant difference was found on any TCI dimension between these subgroups (age, sex, level of education, MADRS and recurrence, as well as psychotropic treatments as covariates). The same was found for the melancholic subtype.

3.3 General state-dependent personality change in patients with major depression

Multiple analysis of variance with repeated measures (double multivariate analysis) using the 7 TCI scores at t1, t4, t5, t6, and t7 as dependent variables and full remission at t7 as independent variable showed that eventually remitted patients differed from nonremitted patients by change of both SD ($F = 5.538$; $df = 4$; $P < .001$) and HA ($F = 6.070$; $df = 4$; $P = .001$). If MANCOVA was used, controlling for the effects of age, sex, level of education, MADRS score at t1 and recurrence, then these differences had lower strength but were still statistically significant ($F = 3.557$; $df = 4$; $P = .008$ and $F = 3.938$; $df = 4$; $P = .004$). Separate assessment (see Table 4) showed that SD increased and HA decreased in eventually remitted patients and that HA increased in all nonremitted patients.

Table 4
Means and changes of TCI scores between t1 and t7 in all patients, fully remitted patients, and non-fully remitted patients. t1 = initial measurement, t7 = after 2 years.

TCI dimension	All patients n = 58		Remitted n = 41		Non-remitted n = 17	
	Means and changes t1 - t7	P	Means and changes t1- t7	P	Means and changes t1 – t7	P
Novelty Seeking (NS)	17.7 - 19.3 - 1.6	0.008	18.5 – 20.1 - 1.6	0.023	15.9 – 17.4 - 1.5	ns
Harm-Avoidance (HA)	25.4 - 23.2 2.2	0.014	25.7 – 21.7 4.0	<0.001	24.5 – 26.9 - 2.4	0.003
Reward-Dependence (RD)	14.5 – 15.1 - 0.6	ns	14.8 – 15.5 - 0.7	ns	13.7 – 14.1 - 0.4	ns
Persistence (PER)	4.8 – 4.5 0.3	ns	4.8 – 4.6 0.2	ns	4.9 – 4.3 0.6	ns
Self-Directedness (SD)	23.7 – 28.4 4.7	<0.001	22.9 – 29.8 - 6.9	<0.001	25.5 – 25.0 0.5	ns
Cooperativeness (CO)	32.0 – 32.6 - 0.6	ns	32.4 - 32.9 - 0.5	ns	31.1 – 31.9 0.5	ns
Self-Transcendence (ST)	9.7 - 8.9 0.8	ns	9.6 - 8.8 0.8	ns	9.9 – 9.1 0.8	ns

3.4 *Cross-sectional analyses after 2 years (t7)*

3.4.1 *Temperament and Character Inventory scores and demographic and clinical data in fully remitted patients at t7*

MANCOVA in the 41 patients with fully remitted depression at t7, with age, level of education, MADRS score, number of previous episodes, and time since first episode as covariates and gender, marital status, ecurrence, in-or outpatient status and familial depression as fixed factors, showed that female patients had different CO and RD compared with male patients ($F = 16.267$; $df = 1$; $P < .001$, and $F = 4.982$; $df = 1$; $P = .033$). Separate comparison showed higher CO and RD in females. Age related significantly with persistence SD ($F = 5.624$; $df = 1$; $P = .024$), and this correlation was negative. Time since first episode related negatively with CO ($F = 4.812$; $df = 1$; $P = .036$). No relations were found between TCI dimensions and number of previous episodes, recurrence, out- or inpatient status, MADRS score, level of education, marital status, and family history of depression. The latter finding suggests that HA and SD in fully remitted patients are generally not influenced by a scar effect. The data resulted in the use of age and sex as covariates in analyses comparing patients with healthy controls and in age, gender, and time since first episode as covariates in analyses comparing subgroups of patients. If the 3 psychotropic treatments were added to the MANCOVA model, then no relation was found between any type of treatment and any TCI dimension.

3.4.2 *Temperament and Character Inventory in fully remitted and non–fully remitted depressed patients at t7 vs healthy controls.*

MANCOVA showed that fully remitted patients after 2 years ($n = 41$) scored only significantly different on HA ($F = 19.94$, $df = 1$ and $P = b.001$) and on ST ($F = 4.03$, $df = 1$; $P = .047$) compared with healthy controls ($n = 86$).Separate comparison showed that HA was higher, whereas ST was lower in remitted patients. MANCOVA showed that the non–fully remitted patients ($n = 17$) after 2 years still scored different on HA ($F = 42.94$; $df = 1$; $P < .001$) and SD ($F = 17.38$; $df = 1$; $P < .001$) compared with healthy controls. Post hoc tests showed a higher HA and lower SD.

3.4.3 *Temperament and Character Inventory in fully remitted highly anxious-retarded patients at t7 compared with healthy controls.*

MANCOVA showed that after 2 years, the fully remitted highly anxious-retarded patients ($n = 15$) scored different on HA compared with healthy controls ($n = 86$) ($F = 9.595$, $df = 1$; $P = .003$). Separate comparison showed higher HA in the remitted highly anxious-retarded patients. As far as the character dimensions are concerned, SD ($F = 4.804$; $df = 1$; $P = .031$) was different in fully remitted highly anxious-retarded patients compared with healthy controls, whereas CO was not related to either highly anxious-retarded or non–highly anxious-retarded patients. Separate comparison against expectation showed lower SD in the highly anxious-retarded subtype. Mean SD score of the fully remitted non–anxious-retarded subgroup was 30.6 ($SD = 7.7$) and of the highly anxious-retarded subgroup 28.4 ($SD = 7.9$), and mean HA score was 21.8 ($SD = 7.9$) and 21.5 ($SD = 7.6$), respectively. MANCOVA also showed that fully remitted melancholic patients scored only different on HA ($F = 8.256$, $df = 1$; $P = .005$) compared with healthy controls. Separate comparison showed an increased HA.

3.4.4 *Temperament and Character Inventory in fully remitted highly anxious-retarded patients at t7 compared with fully remitted non–anxious-retarded patients at t7*

Within the group of full remitted patients, MANCOVA showed no significant relation between SD or any other TCI dimension at t7 and the highly anxious-retarded subcategory, when the effect of age, sex, and time since first episode was accounted for. The addition of psychotropic treatment variables to the analysis did not change this

finding. The mean MADRS score of the fully remitted non– anxious-retarded patients was 8.3 (n = 26; standard deviation = 5.0) and of the highly anxious-retarded patients 11.1 (n = 15; standard deviation = 5.9). This means a statistically nonsignificant difference of 2.8, corresponding with 1 item now and then present in low intensity, and a dubiously or very rarely present second item. Within the fully remitted non–anxious-retarded subgroup, the residual MADRS score correlated with the HA score (r = 0.623; P = .001) and not with SD (r = −0.233; P = .253), and also, in the anxious-retarded subgroup, the residual MADRS score correlated better with the HA (r = 0.466; P = .080) than with the SD (r = −0.317; P = .250) score. This implies that the lower SD in the highly anxious-retarded subgroup was not due to residual psychopathology.

4 Discussion

This study confirms previous findings that HA and SD are most generally involved in acutely depressed patients (Hansenne et al. 1999, Richter et al. 2000, Hirano et al. 2002, Marijnissen et al. 2002). We also found lower scores on RD, NS, and CO. The latter 2 findings can be seen as a confirmation of previous inconsistent findings and may relate to subgroups of depressed patients. One of these is characterized by low CO and RD scores and will be discussed separately (Goekoop et al. submitted). The comparison between fully remitted patients and healthy controls showed that the dimensions of SD and HA are not involved in the same way in their relation to depression. Although the scores on both dimensions changed in the direction of normality during the time to full remission, only HA remained higher than healthy controls at time of full remission. At that time, the difference on the character dimension SD had disappeared. This means that reduced SD is generally involved as a complication of a major depressive episode, whereas increased or high HA is involved as a general complication and as a presumably premorbid trait. We interpret the state-dependent complications as state-dependent report bias. The follow-up data further showed that HA in eventually nonremitted patients increased over time. This increase may therefore be seen as a complication of chronic depression. Subtype analysis after full remission showed that, like all other patients, those with the highly anxious-retarded and melancholic subtypes also had high HA after full remission. The highly anxious-retarded subtype, however, was, in addition, characterized by low SD and normal CO at time of full remission compared with healthy controls, while the melancholic subcategory did not differ on any character dimension. We assume that these findings, that directly and indirectly depend on the diagnosis of DSM-IV melancholia, are sufficiently representative, as the percentages of melancholic patients (49% of all patients, 60% of the inpatients, and 40% of the outpatients) is comparable with that found in the other TCI study of melancholic subjects (53% of a sample of outpatients) (Sato et al 2001), which, as already entioned, also did not detect any TCI relation.

The absence of a relation between SD scores and psychotropic treatment at t7 suggests that the low SD in fully remitted patients with the highly anxious-retarded subtype is not due to drug treatment. The absence of any relation between psychotropic treatment and TCI dimensions after full remission permits the following conclusion about relations found during the acute episode. The association at t1 between antipsychotic treatment and low SD and CO as well as high HA may be interpreted as due to the antipsychotic treatment chosen to control the psychopathology of the patients with these personality scores, rather than as a personality change induced by antipsychotic treatment. The same may be said of the association at t1 between benzodiazepine treatment and high NS. The low SD score we found during full remission in the highly anxious-retarded subtype could not be related to minimal residual symptoms but could correspond to a preexisting immature personality (Cloninger et al. 1993, Svrakic et al. 1993, Bayon et al. 1996, Joyce et al 2003). Since remitted highly anxious-retarded patients combine low SD

with normal CO, their personality may be interpreted as dependent (Cloninger et al. 2006). Their high HA predicts that they would have an increased risk of a C-cluster personality disorder according to DSM-IV. These patients are not impulsive or aloof but rather purely dependent and depressive, so that the personality abnormality may be primarily typical of pure depressive disorders. Their low self-directedness may mean that they tend toward dependency and helplessness. Finally, it should be recognized in this context that, in the present study, only a few patients with severe comorbid personality disorder were not included because of severe cluster B disorder. If these cases would have been included, then the association between the highly anxious-retarded subtype and low SD compared with healthy controls would probably not have been influenced, although it could have further decreased the difference compared with non–anxious-retarded patients.

A limitation of this study is the small number of patients, which may have hampered the detection of low SD in fully remitted highly anxious-retarded patients, compared with all other depressed patients. A second limitation could be that only the DSM-IV definition of full remission was used (De Winter et al. 2006). Recovery was not assessed, which is defined by a period of full remission during 8 weeks or longer. On the other hand, the time to follow-up was much longer, and the definition of full remission we have used in this study was more precisely and generally accepted than the time to follow-up and remission criteria used up to now in most follow-up studies of TCI scores (Table 1). Moreover, as already mentioned, the choice for current state criteria of full remission was based on the clinical impression that state-dependent fluctuation of character deficiency immediately parallels depressive state fluctuation. Several other potential limitations of the design of this study deserve discussion. First, matching of healthy controls on level of education could have been useful, although low SD will rather contribute to low level of education than the other way round (Gruzca et al. 2005). Secondly, the group of healthy controls could not be the optimal control group because they would not have the same amount of residual sychopathology, and this could have caused subtle alteration of personality scores in the patient sample. However, as far as after full remission such an alteration could have played a role in this study, the relation with the MADRS shows that this would only have applied to the high HA score in all patients and not to the low SD in the fully remitted highly anxious-retarded subgroup.

In summary, this study shows that low SD is generally involved as a reversible complication of depression. This finding is in agreement with the state-dependent change of the percentage of personality disorders in patients with depression (Corruble et al. 1996). The present study further shows that high HA may be involved in several ways: as a general presumably premorbid factor for depression, as a complication of the acute episode, and as a complication of chronic depression. The most specific finding of the present study is that low SD after full remission may function as an additional presumably premorbid factor for the highly anxious-retarded subcategory of depression. These results may complement the finding of a recent prospective study in adults representative of the general population in which particularly high HA and low SD were found to predict about 44% of the variance of the change of depressive symptoms after 1 year (Cloninger et al . 2006). The present study confirms the involvement of these 2 premorbid personality traits in depressive disorders but, in addition, supports their differential meaning for major depression in general and the highly anxious-retarded subtype in particular. This suggests a remarkable difference of the meaning of the relations between character and temperament in personality disorder and depression. Although in personality disorders the presence of the disorder is predicted by low scores on character dimensions of SD or CO and the subtype by temperamental scores, in depression, the temperament of high HA would predict the disorder and character

dimensions would define the subtype. This difference may be of importance for optimal preventive and therapeutic measures.

Finally, as far as the highly anxious-retarded subtype is concerned, this subcategory has already been shown to exhibit a correlation between AVP and cortisol (De Winter et al. 2003), which supports the involvement of a vasopressinergic activation of the hypothalamus pituitary adrenal axis. In addition, this subtype has been found to be associated with a longer time to full remission compared with non–highly anxious-retarded patients (De Winter et al. 2006). The low SD may further support the validity of this highly anxious-retarded subcategory. Since no relation between this low SD and high AVP concentration is involved, as this appeared to be specifically related to low CO (Goekoop et al. submitted), the low SD of the highly anxious-retarded subcategory may play a role in the acquirement of stressinduced up-regulation of the pituitary vasopressin receptor (Volpi et al. 2004), evidence of which has been found in melancholia (Dinan et al. 2004).

References

Agosti, V., McGrath, P.J. 2002. Comparison of the effects of fluoxetine, imipramine and placebo on personality in atypical depression. J Affect Dis 71, 113-20.

American Psychiatric Association. 1994. Diagnostic and Statistical Manual Of Mental Disorders. 4th ed. Washington (DC): American Psychiatric Press.

Andreasen, N.C., Rice, J., Endicott, J., Reich, T., Coryell, W. 1986. The family history approach to diagnosis. How useful is it? Arch Gen Psychiatry 143, 421-9.

Åsberg. M., Montgomery, S.A., Perris, C., Shalling, D., Sedvall, G.A. 1978. A comprehensive psychopathological rating scale. Acta Psychiatr Scand 271(Suppl), 5-27.

Bayon, C., Hill, K., Svrakic, D.M., Przybeck, T.R., Cloninger, C.R. 1996. Dimensional assessment of personality in an out-patients sample: relations of the system of Millon and Cloninger. J Psychiatry Res 30, 341-52.

Birkenhäger, T.K., Moleman, P. 1998. Praktische psychofarmacologie. Houten: Bohn Stafleu Van Loghum.

Black, J.K., Sheline, Y.I. 1997. Personality disorder scores improve with effective pharmacotherapy of depression. J Affect Disord 43, 11-8.

Carney, M.W.P., Roth, M., Garside, R.F. 1965. The diagnosis of depressive syndromes and the prediction of E.C.T. response. Br J Psychiatry 111, 659-74.

Charney, D.S., Nelson, J.G., Quinlan, D.M. 1981. Personality traits and disorder in depression. Am J Psychiatry 138, 1601-4.

Cloninger, C.R., Svrakic, D.M., Przybeck, T.R. 1993. A psychobiological model of temperament and character. Arch Gen Psychiatry 50,975-90.

Cloninger, C.R., Svrakic, N.M., Svrakic, D.M. 1997. Role of personality selforganization in development of mental order and disorder. Dev Psychopathol 9(4),881-906.

Cloninger, C.R., Svrakic, D.M., Przybeck, T.R. 2006. Can personality assessment predict future depression?. A twelve-month follow-up of 631 subjects. J Affect Disord 92, 35-44.

Corruble, E., Ginestet, D. 1996. Comorbidity of personality disorders and unipolar major depression: a review. J Affect Disord 37, 157-70.

Corruble, E., Duret, C., Pelissolo A., Falissard, B., Guelfi, J.D. 2002. Early and delayed personality changes associated with depression recovery? A one-year follow-up study. Psychiatry Res 109,17-25.

De Winter, R.F., van Hemert, A.M., DeRijk, R.H., Zwinderman, K.H, Frankhuijzen-Sierevogel, A.C., Wiegant, V.M., Goekoop, J.G. 2003. Anxious-retarded depression. Relation to plasma vasopressin and cortisol. Neuropsychopharmacology 23,140-7.

De Winter, R.F., Zwinderman, K.H., Goekoop, J.G. 2004. Anxious-retarded depression: relation to family history. Psychiatry Res 127,111-9.

De Winter, R.F., Zitman, F.G., Houwelingen van, J.C., Wolterbeek, R., Goekoop, J.G. 2006. Anxious-retarded depression: relation to two-year outcome of major depressive disorder. J Affect Disord 90, 77-81.

Dinan, T.G., O'Brien, S., Lavelle, E., Scott, L.V. 2004. Further neuroendocrine evidence of enhanced vasopressin V3 receptor responses in melancholic depression. Psychol Med 34,169-72.

Duijsens, I.J., Spinhoven, P.H., Goekoop, J.G., Spermon, A., Eurelings-Bontekoe, E.H.M. 2000.. The Dutch temperament and character inventory (TCI): dimensional structure, reliability and validity in a normal and psychiatric outpatient sample. Pers Individ Differ 28,487-99.

Frank, E., Prien, R.F., Jarrett, R.B., Keller, M.B., Kupfer, D.J., Lavori, P.W. 1991. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 48,851-5.

Goekoop, J.G., Knoppert, van der Klein, E.A.M., Hoeksema, T., Klinkhamer, R.A., van Gaalen, H.A.E., van der Velde, E.A.1991. The interrater reliability of a Dutch version of the comprehensive psychopathological rating scale. Acta Psychiatr 83, 202-5.

Goekoop JG, Hoeksema T, Knoppert van der Klein EAM, Klinkhamer RA, van Gaalen HAE, Van Londen L, et al. Multidimensional ordering of psychopathology: a factor-analytical study using the comprehensive psychopathological rating scale. Acta Psychiatr Scand 1992;86: 306-12. 77-81.

Gruzca RA, Przybeck TR, Cloninger CR. Personality as mediator of demographic risk factors of suicide attempts in a community sample. Compr Psychiatry 2005;46:214-22.

Gutiérrez F, Sangorrin J, Martin-Santos R, Torres X, Torrens M. Measuring the core features of personality disorders in substance abusers using the temperament and character inventory (TC1). J Personal Disord 2002;16:344-59.

Hansenne M, Reggers J, Pinto E, Kjiri K, Ajamier A, Ansseau M. Temperament and character inventory (TCI) and depression. J Psychiatr Res 1999;33:31-6.

Hansenne M, Ansseau M. Contingent negative variation and personality in depression. Neuropsychobiology 2001;44:7-12.

Hirano S, Sato T, Narita T, Kusunoki K, Ozaki N, Kimura S, et al. Evaluating the state dependency of the temperament and character inventory dimensions in patients with major depression: a methodological contribution. J Affect Disord 2002;69:31-8.

Joyce PR, Mulder RT, Luty SE, McKenzie JM, Sullivan PF, Cloninger CR. Borderline personality disorder in major depression: symptomatology, temperament, character, differential drug response, and 6-month outcome. Compr Psychiatry 2003;44:35-43.

Marijnissen G, Tuinier S, Sijben AE, Verhoeven WM. The temperament and character inventory in major depression. J Affect Disord 2002;70:219-23.

Montgomery S, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1997;134:382-9.

Pélissolo A, Lépine J. Normative data and factor structure of the temperament and character inventory (TCI) in the French version. Psychiatry Res 2000;94:67-76.

Richter J, Eisemann M, Richter G. Temperament and character during the course of unipolar depression among inpatients. Eur Arch Psychiatry Clin Neurosci 2000;250:40-7.

Rush AJ,Weissenburger JE. Melancholic symptom features and DSMIV. Am J Psychiatry 1994;151:489-98.

Sato T, Narita T, Hirano S, Kusinoki K, Sakado K, Uehara T. Is interpersonal sensitivity specific to melancholic depressions? J Affect Disord 2001;64:133-44.

Svrakic DM, Whitehead C, Przybeck TR, Cloninger CR. Differential diagnosis of personality disorders by the seven-factor model of temperament and character. Arch Gen Psychiatry 1993; 50:991-9.

Van Praag HM. The diagnosis of depression in disorder. Aust NZ J Psychiatry 1998;32:767-72.

VelingWA, Goekoop JG. Relaties tussen persoonlijkheid en unipolaire depressie. Een multidimensionele benadering. Tijdschr Psychiatrie 2000;11:825-35.

Volpi S, Rabadan-Diehl C, Aguilera G. Vasopressinergic regulation of the hypothalamic pituitary adrenal axis and stress adaptation. Stress 2004;7:75-83.

Zimmerman BA, Spitzer RL. Melancholia: from DSM-III to DSM-IIIR. Am J Psychiatry 1989;146:20-28.