Towards an improvement of the differentiation of depressive disorders.

A multidimensional approach

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Aan:
alle patienten die deelgenomen hebben aan dit onderzoek
Voor:
mijn ouders
Elisa, Carmen, Gabor en Mareen

Contents

List of abbreviations

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ACTH	AdrenoCorticoTropic Hormone
AD	Autonomous Dysregulation
ANOVA	ANalysis Of VAriance
AR	Anxious-Retarded
AMDP	Arbeitsgemeinschaft für Methodik und Documentation in der Psychiatrie
APA	American Psychiatric Association
ANA	Above Normal Arginine vasopressin
AVP	Arginine VasoPressin
BDI	Beck Depression Inventory
CBT	Cognitive Behavioural Therapy
CGI	Clinical Global Impression Scale
CO	COoperativeness
CPRS	Comprehensive Psychopathological Rating Scale
CSF	CerebroSpinal Fluid
CRH	Corticotrophin-Releasing Hormone
DAPP	Dimensional Assessment of Personality Pathology
Dex-CRH	Dexamethasone-Corticotrophin-Releasing Hormone
DSM	Diagnostical Statistical Manual
DST	Dexamethasone Suppression Test
DSD	Depressive Spectrum Disease
ED	Emotional Dysregulation
EPQ	Eysenck Personality Questionnaire
FH-RDC	Family History-Research Diagnostic Criteria
FPDD	Familial Pure Depressive Disease
GAD	General Anxiety Disorder
HA	Harm-Avoidance
HAB	High Anxiety-related Behaviour
HAR	Highly Anxious-retarded
HDRS	Hammilton Depression Rating Scale
HPA	Hypothalamic-Pituitary-Adrenal
HPLC	High Performance Liquid Chromatography
ICD	International Classification of Disease
IPT	Interpersonal PsychoTherapy
LUMC	Leiden University Medical Center
MADRS	Montgomery Asberg Depression Rating Scale
MANCOVA	Multiple ANalysis of COVAriance
MASQ	Mood and Anxiety Symptom Questionnaire
MPT	Münchener Personality Test
NEO-PI	Neuroticism-Extraversion-Openness Personality Inventory
NA	Negative Affect
NS	Novelty-Seeking
PER	Persistence
PA	Positive Affect
PH	Physiological Hyper arousal
PVN	ParaVentricular Nucleus
RIA	Radio-Immuno-Assay

RD	Reward-Dependence
RDC	Research Diagnostic Criteria
ROC	Receiver Operating Characteristic
SD	Self-Directedness
SD	Standard Deviation
SNP	Single Nucleotide Polymorphism
SNRI	Serotonergic and Noradrenalin Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
ST	Self-transcendence
TCA	TriCyclic Antidepressant
TCI	Temperament and Character Inventory
V1b	Vasopressine 1b
WHO	World Health Organization

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General introduction

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I) Description of major depressive disorder

Depressive disorder is an illness with low or depressed mood and loss of interest as its major symptoms. At present the most used description or classification for this disorder according to the Diagnostic Statistical Manual (DSM) is Major depressive disorder (see below). It is a serious health problem for which the lifetime risk for adults is estimated at approximately 15-17% (WHO 2000, Simon et al. 2002). Major depressive disorder has been linked to shorter life expectancy, significantly reduced quality of life and economic burden (WHO 2000, Simon et al.2002, Sobocki et al. 2006, Baan et al. 2003). At present, major depressive disorder is the fourth leading cause of disease burden or disability and it is expected that the disease will rise by 2020 to second place worldwide (Ustun et al. 2004, WHO 2001). Despite the impact that this disease has on society and the interest it incites, achieving a full and satisfactory description of the disorder remains complex and depressive disorder is hard to define the fundamental nature or origin is still unclear and uncertain (Eysenck 1970, Kendell 1976, 1978, Parker 2000b, 2005a).

Current classification

At present, major depressive disorder is mostly "operationalised" in international literature and throughout western medicine in a "dichotomous" categorical manner. The categorical system for the classification of psychiatric diseases that was developed in the United States, the Diagnostic and Statistical Manual of Mental Disorders (DSM), is the world's leading diagnostic system (Pichot 1997). It contains 5 domains of classification or scores (called axes). The first axis (axis-I) describes the mental clinical disorders (like major depressive disorder) as well as developmental and learning disorders. The second axis (axis-II) describes underlying pervasive or personality conditions (personality disorders) as well as mental retardation. The third axis (axis-III) describes the medical conditions that may be relevant to the understanding and treatment of a mental disorder. The fourth axis (axis- IV) describes the environmental and psychosocial aspects that contribute to the disorder. The last and fifth axis (axis- V) is the global assessment of functioning (on a scale from 0-100, GAF score).

The International Classification of Disease (ICD) is another important categorical classification system, mainly developed in Europe, in this system, the manner of diagnosing major depressive disorder resembles and overlaps the DSM classification system quite strongly (Andrews 1999, Pichot 1997, Paykel 2002). The DSM is the dominant diagnostic system for classifying psychiatric disorders (also within the Dutch language areas) (Jongedijk 2001). See **table I** for the criteria for depressive disorders according to the latest version of the DSM.

Both systems, the DSM and ICD, classify by means of several core symptoms that are present, and other accompanying symptoms that persist for a certain minimum period of time. In this way, the possible combinations of symptoms of major depressive disorder could lead to 326 variations of depression. Exactly how the symptoms are weighed up in order to reach a diagnosis is not clear. A recent study showed that not all symptoms for major depressive disorder according to the DSM-IV contribute to the final diagnosis in an equal weight (Zimmerman et al. 2006a).

Moreover, it should also be noted that the choice of the symptoms included in the DSM is not founded on empirical scientific research; these have been collected non-empirical on

the basis of clinical presentations and practical experience (Cassidy et al. 1957, Feighner et al. 1972, Spitzer 1991, Nelson & Charney 1981, Andreasen 2007). Following the publication of the DSM-III (APA 1980), Boyd described that there was more overlap of psychiatric disease entities within the DSM system than would be possible based on coincidence alone and that the empirical base for the isolation of psychiatric disorder units was weak (Boyd et al. 1984).

Table 1
Criteria for Major Depressive Episode according DSM-IV (and DSM-IV-TR) (APA 1994, 2000a)

A Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either Depressed mood or loss of interest or pleasure.
Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1 Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.
2 Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3 Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
4 Insomnia or Hypersomnia nearly every day.
5 Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6 Fatigue or loss of energy nearly every day.
7 Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8 Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9 Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B The symptoms do not meet criteria for a Mixed Episode.
C The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
E The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

The usual psychiatric treatment currently given for a depressive disorder classified according to the DSM is not strongly differentiated, possible only except for treatment given for a season-bound depressive disorder and the major depressive disorder with psychotic features (APA 2000b, Trimbos-instituut 2005). Treatment of major depressive disorder in general, consists of protocolled somatic interventions and psychotherapeutic interventions (cognitive behavioural therapy, CBT) and/or interpersonal psychotherapy (IPT) accompanied by supporting professional services that may help to dispel stress such as behavioural activation, social work, debt management, self-system therapy etc. (Trimbos-instituut 2005, APA 2000).

If a better definition of depression and its subtypes were available, then improved treatment could be developed that is more finely tuned. Moreover, specific scientific research could then also be conducted. One solution towards this would be to make a better differentiation between the various depressive disorders (Zimmerman et al. 2006b). The American Psychiatric Association (APA) and administrator of the DSM is apparently aware of the limitations of the categorical diagnostic method, considering the decision it has made on the DSM-V (expected in 2012) to leave behind the categorical diagnostics for axis II and implement personality disorders in a multidimensional way (Westen & Shedler 1999, Trull et al. 2007). A next step in the development could be a multidimensional approach for the categorisation of axis I or further development of a system by combining elements of axis I and axis II.

II) Categorical subtypes of depression and the concept of endogenicity

For the development of differentiation between diseases in general medicine, Kendel (1989) has provided some historical analogies:

"*It was only after Sydenham had demonstrated that "the pox" was actually two distinct syndromes, chicken pox and small pox, that it was possible to predict with any accuracy who would remain scarred for life and was in danger of dying. And only after physicians had learned to distinguish between the renal and cardiac forms of dropsy was it possible to predict which patients were likely to benefit from digitalis.*"

It is more difficult to pinpoint the distinguishing phenotypical and etiological characteristics for the subcategories of depressive disorders than those of non-psychiatric medical disorders. This is partly due to the fact that psychiatry does not usually carry the options of classifying a disease on the basis of physical diagnostic examination, validated laboratory testing and/or additional diagnostic tests such as imaging technology tests. In spite of this, attempts have always been made to classify psychiatric disorders and to make sub-categories within these disorders. The conceptual problem is not just restricted to major depressive disorder, but applies to other psychiatric diseases such as schizophrenia, anxiety disorders, etcetera (Blom 2003, Harvey & Bryant 2002).

As far as the depressive disorders are concerned, there is a rough historically classic categorical subdivision or subtyping, namely the difference in endogenous and exogenous subtypes (Akiskal & McKinney 1975, Carney & Sheffield 1976, Coryell 2007, Shorter 2007). The so-called endogenous subtype is, for example, a subtype or form of depression with various biological abnormalities, a genetic predisposition and the clinical

picture does not often present with prior stress and/or an abnormal personality (Nelson et al. 1981, Young et al., 1986, Joyce et al. 2002).

The exogenous subtype is characterised by a more etiological connection with psycho-social factors and their resulting stress and is less likely to be accompanied by biological and genetic changes. In addition, this depression would be more often associated with an abnormal coping pattern and its emerging maladaptive personality development (Coryel 2007, Tedlow et al. 2002, Charney el al. 1981, Fink & Taylor 2007), although this vision is not based on empirical data. According to the DSM-IV, the classic term endogenous depression is reproduced as the subtype with melancholic characteristics (Parker 2005b, Akiskal & Akiskal 2007) see **table 2**. The validity of this "melancholic" subclassification of depression was used as a point of departure for this thesis in order to see whether other methods of clinical description would provide a better validated differentiation of major depressive disorder.

Table 2
Criteria for Melancholic Features according DSM-IV (and DSM-IV-TR)

Specify if: With Melancholic Features (can be applied to the current or most recent Major Depressive Episode in Major Depressive Disorder and to a Major Depressive Episode in Bipolar I or Bipolar II Disorder only if it is the most recent type of mood episode)

A. Either of the following, occurring during the most severe period of the current episode:

1 loss of pleasure in all, or almost all, activities
2 lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens)

B. Three (or more) of the following:

1 Distinct quality of depressed mood (i.e., the depressed mood is experienced as distinctly different from the kind of feeling experienced after the death of a loved one)
2 depression regularly worse in the morning
3 early morning awakening (at least 2 hours before usual time of awakening)
4 marked psychomotor retardation or agitation
5 significant anorexia or weight loss
6 excessive or inappropriate guilt

III) External validation of diagnostic concepts

Robins and Guze formulated a method for improving diagnostic validity (Robins & Guze 1970). Their proposal was to validate a psychiatric diagnostic concept with the following levels of investigation:

1) the clinical description, with phenotype, personality and eventually precipitated stress
2) laboratory findings,
3) family history,
4) outcome/ follow-up study

Higher validity of a diagnostic concept is the consequence of better interrelations between the various levels. The development of validity would therefore progress according to a cyclic process. Diagnostic concepts would be developed with increasing higher validity and better differentiation. Improvements in the relations between the various layers are, at the same time, be accompanied by improvements of the etiological and pathogenetic theories. With this strategy the first set of diagnostic criteria was formulated in 1972 in the United States for 14 phenotypically-defined categories (Feighner et al. 1972). In 1980 and in a similar fashion, the operationalised definition of the whole psychiatric spectrum followed in terms of classifications described in the DSM-III (APA 1980). One positive element of this operationalisation was that the classification no longer stemmed from the idea of disease entities with a prerequisite for coherence between syndrome, course, etiology and response to treatment. The DSM-III classification was based almost exclusively on the combination of clinical syndromes with course criteria. Thanks to the clear conceptual advance made in the system, the weak validity of the new categories was not at all strong and it seemed as if the criteria formulated by Robins and Guze -- that were at the foundation of the system -- ultimately became its weakness. This weakness was even more demonstrated by the higher rate of comorbidity of the "so called" independent categories of the DSM-III (Boyd 1984).

Later on it was also shown that for depression, the cut-off criterion for the border between sick and healthy was merely arbitrary (Kendler & Gardner 1998). After all, this resulted in a situation where approximately 20 years after the introduction of the DSM-III, the hope of creating a strong boundary with normality had become untenable. Research using the DSM criteria once more confirmed that we neither cannot define clinically sharp disease categories with this system nor their delineation from normality.

Convincing arguments against the current form of classification have been put forward by van Praag (van Praag 1999). He concludes that holding on to the DSM classification is the reason that external validation in the area of depressive disorders has never really taken off, and that this way of classification is the most significant obstacle in the development of knowledge on depression (van Praag 1998, 2001).

IV) External validity of the melancholic subcategory according the DSM.

One of the first, laboratory based, discoveries that supported the melancholic subclass, was it's relation with disturbances found in the hypothalamus-pituitary-adrenal axis (HPA axis) (Carroll et al. 1981). This came about by an increase in the levels of plasma cortisol following suppression of the hypothalamus-pituitary-adrenal axis with the glucocorticoid antagonist dexamethasone. The relevant test, known as the dexamethasone suppression test (DST), had been used previously in endocrinology for diagnosing Cushing's syndrome. This test proved to be only moderately specific for diagnosing the melancholic subtype. Moreover, differences were found in test results depending on which version of the DSM was used (Zimmerman et al. 1989, Rush en Weissenburger 1994).

Another partial step into validation research could cover aspects of personality. One traditional clinical view in psychiatry is that melancholic and/or endogenous depression excludes a disturbed premorbid personality (Carney et al 1965, Charney et al. 1981, Joyce et al. 2002). In the DSM-III-R the diagnosis of the melancholic subtype was partially based on the absence of a personality disorder (APA 1987). This has naturally made research

into the relation between depression and personality traits more difficult. According to Robins and Guze, a third step into validation research should cover family history. As far as familial depression is concerned, two subcategories have been identified (Winokur 1978). In one of these, alcoholism or antisocial behaviour is present in the family (depression spectrum disorder) whilst in the other subcategory, only depression occurs in the family (familial pure depressive disease). Non-suppression detected by the DST was found to have limited specificity for familial pure depressive disease (Rush et al. 1995). Based on the non-suppression in both melancholic and this type of familial depression, the melancholic phenotype, non-suppression and the familial depression could be all characteristics of one and the same subcategory of depression.

The absence of strong reciprocal connections between the melancholic phenotype, the DST and a family history for major depressive disorder, means that no high validity can be given to this subclassification of depression. One final step in the validation study is to study outcome of major depression. This area of research does not show distinctive results for the melancholic subtype. The results vary – there are studies that associate the melancholic subcategory with worse outcome (Tuma 2000) but there are also studies that show good outcome (Parker et al. 2000a). Most studies concerning the melancholic subtype did not find any relation with outcome. It could be that a non categorical diagnostic approach instead of a categorical approach is more fruitfull for a better validated description of melancholic depression.

V) The nosological view of Karl Jaspers

Jaspers (1883-1969) proposed that it was unlikely that strong natural boundaries would exist between psychiatric diseases. He postulated that "krankheitsbilder" or disease entities were probably a mixture of primary symptom dimensions and that they developed gradually. He proposed describing the clinical pictures first and foremost as clinical phenotypes. These phenotypes could be developed by specifically merging the symptom dimensions already mentioned. Should this type of description of phenotypes be further developed, then a subsequent step would be to look for connections with pathogenetic and etiological characteristics (Jaspers, translated 1997). Subsequently, on the basis of Jasper's theoretical model, researchers started to look for these primary symptom dimensions. The most of this early research is done by the "Arbeitsgemeinschaft für Methodik und Documentation in der Psychiatrie" (ADMP) system and has been summarised in several publications (Mombour et al. 1972, Troisfontaines et al., 1984, Troisfontaines en Bobon, 1987).

They found 7 major primary symptom dimensions of psychopathology;

1. Anxiety
2. Depression
3. Apathy-retardation/inhibition
4. Hostility/Dysphoria
5. Mania
6. Perceptual dysregulation
7. Behavioural disorganisation

There has been no concrete empirical follow-up to this research and it has also not led to a revision of current diagnostic categories.

VI) Main questions of this thesis

The primary aim of this research was to reformulate the melancholic subtype (according to the DSM) from the perspective of a multidimensional approach on the basis of Jasper's theoretical model.This multidimensional revised phenotype was there after be tested for validity according to the steps of the validation model drawn up by Robins and Guze. The Comprehensive Psychopathological Rating Scale (CPRS) (Asberg et al. 1978) (Goekoop et al. 1991, 1994b) was used for this multidimensional construction. The CPRS is a research instrument for determining psychiatric symptoms through a semi-standardised interview. The scale consists of 40 items that refer to the psychopathology that is reported by the patient as well as 25 observational items (see table 3). Based on the CPRS, a heterogeneous group of patients has been sought using the principle of component factor analysis for a multidimensional structure present in the group. In this way, 6 out of 9 main dimensions (see page 14) were found that had previously been detected with another instrument (Troisfontaines et al. 1987). The multidimensional structure that was found consisted of 5 global dimensions for psychopathology for which one dimension could be interpreted in a negative and positive part. These dimensions are: emotional dysregulation (dimension I), motivational dysregulation that can be divided into inhibition and disinhibition (dimension IIa/b), perceptual disintegration (dimension III), behavioural disintegration (dimension IV) and finally autonomic dysregulation (dimension V), (Goekoop et al. 1992) see **table 3**. The dimensions 1, 2, and 5 can be regarded as non-psychotic dimensions of psychopathology. Moreover, it appeared that there is a hierarchical structure within these 5 dimensions (Goekoop et al. 1994b).

Table 3
Signs and symptoms of the CPRS encompassed by 6 dimensions of psychopathology (Goekoop & Zwinderman 1994). Underlined signs and symptoms are part of the MADRS. *Italic signs and symptoms* are present in more than one dimension

Dimension I (emotional dysregulation)	**Dimension III (perceptual disintegration)**
Inner tension	Ideas of persecution
Concentration difficulty	Disrupted thoughts
Sadness	Delusional mood
Pessimistic thoughts	Depersonalization
Reduced sexual interest	Rituals
Inability to feel	Other delusions
Reduced sleep	Commenting voices
Indecision	Feeling controlled
Apparent sadness	Other auditory hallucinations
Fatiquability	Visual hallucinations
Failing memory	Other hallucinations
Lassitude	Hallucinatory behaviour
muscular tension	
reduced appetite	**Dimension IV (behavioural disintegration)**
loss of sensation or mood	*Slowness of movement*
Phobias	*Lack of appropriate emotion*
suicidal thoughts	*Reduced speech*
worrying over trifles	Withdrawal
Compulsive thoughts	Agitation
Depersonalisation	Perplexity
Derealisation	Perseverations
	Blank spells
Dimension IIa Motivational inhibition	Distractibility
Inability to feel	Incoherent speech
Apparent sadness	
Slowness of movement	**Dimension V (autonomic dysregulation)**
Lack of appropiate movement	*Inner tension*
Reduced speech	Autonomic disturbance
	muscular tension
Dimension IIb Motivational disinhibition	*Reduced sleep*
Pressure of speech	Aches and pains
Flight of ideas	Autonomic disturbance
Labile emotional responses	
Elation	
Ideas of grandeur	
Elated mood	
Overactivity	
Increased sexual interest	
Ecstatic experiences	

The first research question was: how does the melancholic subtype according to the DSM-IV criteria depend on these non-psychotic symptom dimensions? Subsequently, we constructed a multidimensional subcategory which was based on these findings. Thereafter we tested in 89 patients with major depression, whether this new subcategory has better external validation aspects than the original DSM-IV subcategory:

Step 1a analysis of the melancholic subtype and construction of a multidimensionally defined phenotype *(chapter 2)*

In the first step, we started at the phenotypic level by a multi-dimensional reconstruction of the DSM-IV defined melancholic subcategory. We analyzed the dependence of the melancholic subcategory on the non-psychotic CPRS dimensions and their interactions. After this we constructed a multidimensional phenotype. This new "description" of the melancholic/vital subtype could be seen as a refinement and its external validity in terms of the next validation steps by Robins and Guze.

Step 1b clinical description of personality *(chapter 5)*

The Temperament and Character inventory (TCI) differentiates three character dimensions: Self-directedness (SD), Cooperativeness (CO) and Self-transcendence (ST), and four 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 personality disorder classified by the DSM-IV (Cloninger et al. 1993, Svrakic et al. 1993, Bayon et al. 1996, Joyce et al. 2003). We primary used the two character dimensions in order to validate the multidimensional phenotype in this direction.

Step 2 laboratory findings (*chapter 3****)***

The vasopressinergic theory of depression formed the background of this step. Arginine vasopressin (AVP) is a synergizer of the activation of the hypothalamus-pituitary-adrenal-axis (HPA-axis) by corticotrophin-releasing hormone (CRH) (Antoni, 1993). Repeated stress may increase the synthesis of AVP (de Goeij et al 1992). In previous study plasma AVP and Cortisol have been found to be correlated in suicidal depressed patients (Inder 1997 et al). Van Londen had previously found an increased plasma AVP level in depressed patients compared with control subjects (van Londen et al. 1997) and a weak relation to DSM-IIIR melancholia. Plasma Arginine vasopressin (AVP) and basal cortisol levels were used as laboratory parameters in this step and chapter III contains a further in depth description of the background and rationale for these parameters for validating the multidimensional model.

Step 3 family studies *(chapter 2)*

We used the family history of depression corresponding to the criteria for Family History Research Diagnostic criteria (FH-RDC) Depressive Disorder (Andreasen et al. 1986a, b) for the validation of the multi-dimensional phenotype (on a possible genetic level).

Step 4 outcome *(chapter 4)*
For the last step we investigate the long-term outcome of the multidimensional phenotype. We investigated the outcome criteria for full-remission of depression according to Frank et al. (1991) during a follow-up period of 2-years.

Further diagnostic development based on endophenotypical characteristics.
According to Robins and Guze a higher validity of a diagnostic concept could results from better interrelations between the parameters of the various levels. This means that an improvement made at one level of investigation, as formulated by Robins & Guze could lead to improvement in the relation with another or more levels, and this, in turn could lead to improvements in previous levels. The development of diagnostic concepts could therefore progress according to a cyclic validation process. New findings from these former researches would also be tested in the validation cyclus of Robins and Guze.

For this reason, we finally investigated if above-normal plasma AVP could also be a more useful endophenotypic parameter than plasma AVP as a continuous variable in relation with dimensions of psychopathology, family history and personality as external validation parameters (step 1,2 and 3 of the validation cyclus of Robins&Guze)((chapter 6 and 7).

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2

Anxious-Retarded Depression: Relation to Family History of Depression.

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Abstract

Anxious-retarded depression is a two-dimensionally defined subcategory of depression based on high scores for both anxiety and retardation. This anxious-retarded subcategory is related to melancholia as defined by DSM-IV. Patients with this diagnosis exhibit elevated plasma arginine vasopressin (AVP) and a high correlation between plasma vasopressin and cortisol, which suggests vasopressinergic overactivation of the hypothalamus-pituitary-adrenal (HPA) axis. In this report we present the multi-dimensional derivation of the anxious-retarded subcategory from DSM-IV melancholia, and a second step in the validation of this anxious-retarded subcategory by exploring its relation to family history of depression. The patient sample comprised 89 patients with major depression and encompassed 66 patients investigated previously regarding plasma AVP and cortisol. All patients were rated for the following three dimensions of psychopathology: autonomic dysregulation (anxiety), motivational inhibition (retardation), and emotional dysregulation, as well as for family history of depression. The dependence of DSM-IV melancholia on the sum scores and the dichotomized scores on the three dimensions was investigated by multiple logistic regression. Thereafter, the dependence of the family history for depression on the same parameters was also investigated. The melancholic subcategory depended on the interaction between the sum scores, as well as on the interaction between the dichotomized scores for anxiety and retardation that constitute the anxious-retarded subcategory. Family history for depression depended only on the interaction of the dichotomized scores, and thus on the anxious-retarded subcategory.

Key words: Depression, melancholia, anxiety, retardation, family history

1 Introduction

The validity of psychiatric diagnoses is based on studies of clinical description, laboratory studies, follow-up study, and family studies (Robins and Guze 1970). A fifth criterion for validity mentioned by Robins and Guze is delimitation from other disorders or subtypes. This delimitation may be dichotomous like the DSM-IV categories, or gradual. These phases of investigation interact with one another so that new findings in any of them may lead to modifications in one or more of the other phases. Since major depression is a heterogeneous disorder, and the validity of its clinically defined subcategories is low, we adopted a multi-dimensional approach to redefine clinical pictures in terms of mixtures of basic dimensions of psychopathology as proposed by Jaspers (1953). Six basic dimensions were previously found in a heterogeneous patient sample using the semi-standardized interview of the Comprehensive Psychopathological Rating Scale (CPRS) (Asberg et al. 1978) (Goekoop et al. 1992). Three non-psychotic dimensions of this CPRS, called autonomic dysregulation, emotional dysregulation and motivational inhibition were used in the present study. Autonomic dysregulation comprises inner tension and somatic anxiety items, emotional dysregulation general neurotic symptoms, and motivational inhibition anhedonia and psychomotor retardation items (Goekoop et al. 1992). The three dimensions correlate highly with dimensions of anxiety, depressive mood, and psychomotor retardation (Goekoop et al.1994) (De Weme and Goekoop 1996), and all three dimensions conform to the hierarchy of the Rasch model (Goekoop and Zwinderman 1994). The latter finding means that cut-off values on these dimensions represent different stages of development of the underlying dysregulation. These characteristics of the CPRS dimensions make them suitable for studies of the hypothesized multi-dimensional mixtures composing clinical pictures like melancholia as defined in DSM-IV.

As part of our search for enhanced validity of differentiations within the group of depressive disorders, we started at the phenotypic level by a multi-dimensional reconstruction of the DSM-IV melancholia. We analyzed the dependence of the melancholic subcategory on the three CPRS dimensions and their interactions. The potential usefulness in these analyses of dichotomized scores in relation to sum scores was suggested by the finding that DSM-IV melancholia, itself a dichotomous phenotypic delimitation, is related to relatively high scores on the single dimension of psychomotor retardation (Parker et al. 2001). From a multi-dimensional perspective this clinical picture of DSM-IV defined melancholia could be related to the combination of high scores on more than one dimension of psychopathology.

In a previous publication we reported on a subgroup of the patients of the present study (de Winter et al. 2003). The 66 depressed patients of that report were selected on the basis of full hormonal data and the absence of oral contra-conception. We found that the subcategory of depression defined by the combination of high autonomic dysregulation and high motivational inhibition, called anxious-retarded depression, is moderately associated with the melancholic subcategory according to DSM-IV (de Winter et al. 2003). In addition we found that patients with anxious-retarded depression exhibited a high correlation between plasma vasopressin and cortisol as well as an elevated level of plasma vasopressin, compared with other depressed patients (de Winter et al. 2003). These data presumable reflect vasopressinergic overactivation of the hypothalamus-

pituitary-adrenal (HPA) axis. Melancholic patients had only a low correlation between plasma vasopressin and cortisol. The anxious-retarded subcategory could therefore be seen as a phenotypic refinement of the DSM-IV melancholic subcategory, with increased external validity at the biochemical level.

In the present study we present the derivation of the anxious-retarded subcategory from the melancholic subcategory as well as a further step in the validation of this anxious-retarded depression. This study was based on the complete sample of 89 patients, which encompasses the earlier reported subsample of 66 patients.We first investigated the dependence of DSM-IV melancholia on the three CPRS dimensions and their interaction. In contrast to our previous study, in which we presented only the Cohen's kappa statistics (de Winter et al. 2003) of the association between melancholia and anxious-retarded depression, we now present the multiple logistic regressions, which eventually result in the derivation of the anxious-retarded subcategory from melancholia. We first used the sum scores on the three dimensions and their interactions, and thereafter the dichotomized scores. In this way we could account for the possibility that dichotomization might entail loss of power.

For the second validation step of the anxious-retarded subcategory we investigated the dependence of the family history of depression on the same CPRS dimensions, and we likewise used dimensional sum scores, dichotomies and their interactions. For comparison we also investigated the dependence on DSM-IV melancholia. Since familial depression has been found associated with recurrent depression, the number of previous episodes and the psychotic subtype of depression (Winokur 1997), these parameters were used as covariates. A positive family history or genetic factors have not been found related to DSM-IV melancholia (Rush an Weissenburger 1994) or to psychomotor retardation alone (Rush an Weissenburger 1994) (Kendler 1997). Therefore we hypothesized that in the present study neither DSM-IV melancholia nor high motivational inhibition alone would be related to family history of depression.

In searching for a relationship between anxious-retarded depression and family history we recognized that the assumption of a relationship between a certain phenotype and family history is at odds with the general conclusions that family history for depression is not related to any form of endogenous depression (Andreasen 1986b) and that depression is clinically homogeneous and only etiologically heterogeneous (Winokur 1997). We nevertheless endeavored to investigate this relationship for the following reasons: because we adopted a new, multi-dimensional method to formulate the clinical phenotype, because in using this method we had found a relationship at the biochemical level, and because we wanted to systematically follow the steps of the validation programme proposed by Robin and Guze (1970).

2 Materials and methods

2.1 Patients

Patients (n = 134) who fulfilled DSM-IV criteria for major depression and scored > 20 on the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979; Hartong and Goekoop 1985), were recruited for a cross-sectional study of depression. The diagnosis of major depression (DSM-IV) was primarily made by

psychiatrists at the inpatient or outpatient clinic. If R.F.P. de W. confirmed this diagnosis, the patient was asked to participate in the study. Patients with organic disorder and patients with bipolar, schizoaffective, or schizophrenic or other primary psychotic disorder were excluded. Depressed patients with a panic disorder were not included, since they participated in a different research project. The Ethical Committee of the Leiden University Medical Center (LUMC) approved the informed consent protocol. Written informed consent was obtained from all patients. Eighty-nine patients (66.4%) remained in the study after exclusion because of lithium usage (n=3), alcohol consumption above three drinks a day (n=3), the use of drugs or corticosteroids (n=2), or non-consent (n=37). Compared with an independent sample of 48 patients and with those 45 patients who did not remain in the study, these 89 patients did not differ on the scores for the MADRS, emotional dysregulation, autonomic dysregulation or motivational inhibition.

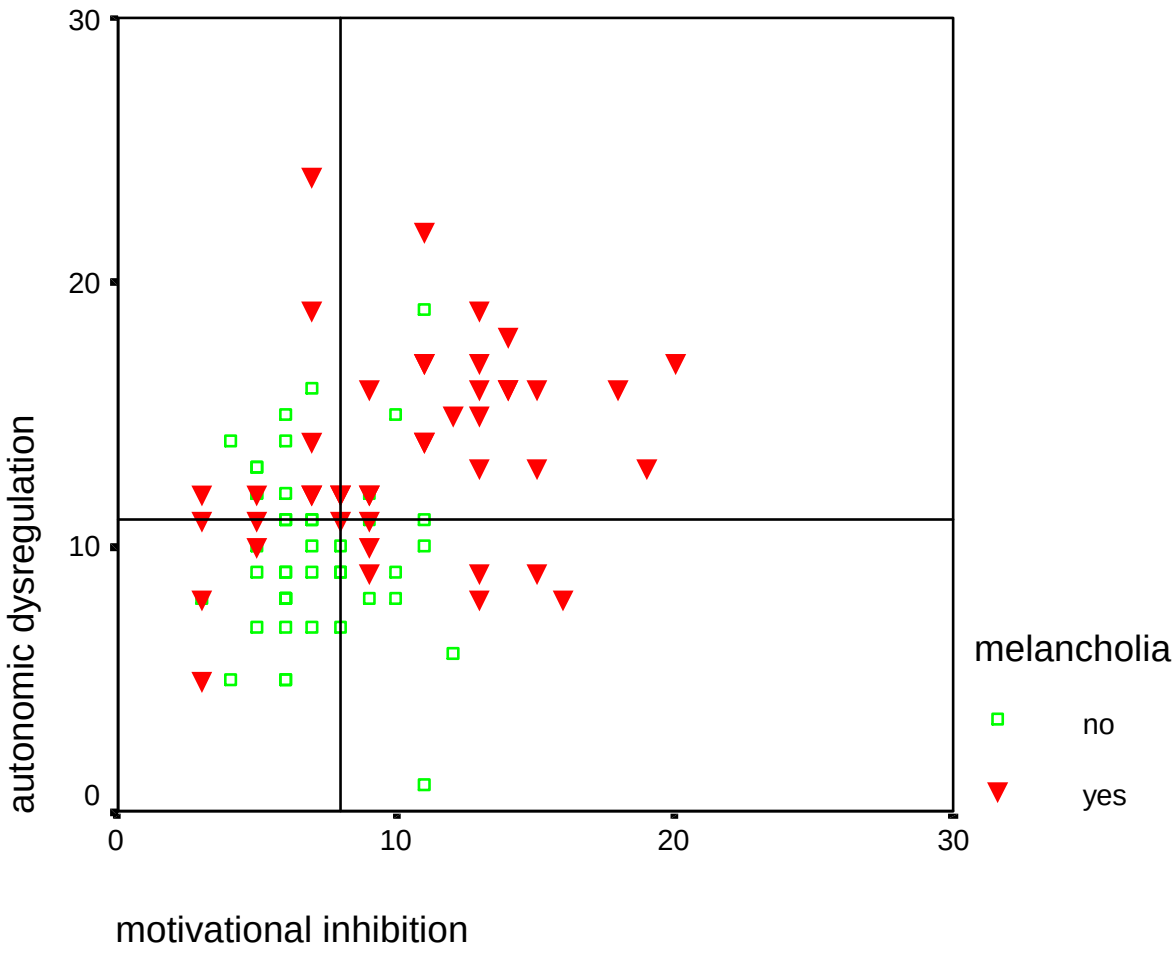
2.2 *Psychopathological assessment*

The semi-standardized CPRS interview (Asberg et al. 1978) (Goekoop et al. 1992) was used to assess the three non-psychotic dimensions of psychopathology: motivational inhibition (retardation), autonomic dysregulation (anxiety) and emotional dysregulation. Motivational inhibition comprises the items apparent sadness, anhedonia, retarded movements, reduced speech, and inappropriate emotional expression. Autonomic dysregulation comprises inner tension, reported autonomic symptoms, observed muscle tension, reduced sleep, aches and pains, and observed autonomic symptoms. The dimension, emotional dysregulation, comprises the items inner tension, concentration difficulties, reported sadness, pessimistic thoughts, reduced sexual interest, inability to feel, reduced sleep, indecision, apparent sadness, fatigability, failing memory, lassitude, reported muscular tension, reduced appetite, phobias, suicidal thoughts, worrying over trifles, compulsive thoughts, depersonalization and derealization. Each CPRS item was scored from 0-6. The inter-rater reliability of the CPRS items scores is good to excellent and comparable to that of the Present State Examination, despite using more grades per item (Goekoop et al. 1991). The face validity of the 3 non-psychotic dimensions is supported by the detection of 3 similar non-psychotic dimensions in anxious-depressed patients (Watson et al. 1995).

First sum scores and thereafter dichotomized scores on these three dimensions were used to test the dependence of the melancholic subcategory and family history of depression on these dimensions. The dichotomized scores were computed based on median scores. Median and above median values were called ‘high’ scores, below median scores ‘low’ scores. Eventually, four subcategories were constructed based on combinations of high or low anxiety and high or low retardation (**see figure 1**). These subcategories were called: anxious-retarded, anxious (non-retarded), retarded (non-anxious) and undifferentiated depression.

Figure 1

Scatter plot of the distribution of depressed patients in the two-dimensional structure defined by autonomic dysregulation ('anxiety') and motivational inhibition ('retardation'). The upper right quadrant is called anxious-retarded depression. Melancholic patients are marked by triangles.



The DSM-IV criteria for melancholic and psychotic subtypes were used in a standardized diagnostic interview, in which each symptom or set of symptoms was checked for its presence during the last 2 weeks of the present episode.

2.3 Family history

A. Semi-standardized procedure for family history taking of first-degree family members was adopted corresponding with the criteria for FH-RDC Depressive Disorder (Andreasen et al. 1986a) with a minimal modification in the direction of the DSM-IV. All patients were asked by RFP de W, whether a depressive disorder fulfilling the criteria ever occurred in one of the parents, siblings, or children. In case of doubt by the patient (n=4) about the presence or absence of symptoms in a family member, a family member as 'best informant' for the latter was asked the same question to avoid false negative diagnoses. For confirmation of familial depression at least one first-degree family member had to fulfill the following criteria (A –D): A (1) Evidence of a depressive mood or loss of interest; and (2). Three additional signs or symptoms such as sleep change, appetite or weight change, loss of energy, psychomotor agitation or retardation, guilt or self-reproach, impaired concentration, or suicidal behavior.

B. At least one of the following associated with the symptoms in A: (1). Electroconvulsive therapy or antidepressant medication; (2) hospitalization; (3) treated for A1 or A2; (4) gross impairment in work, housework, or school, or social withdrawal; (5) four associated symptoms in A2.

C. No evidence of a chronic non-affective deteriorating course (but may have some residual symptoms) other than accounted for by alcoholism.

D. Duration of at least 2 weeks; this criterion was used for all symptoms described in A. In this way diagnoses of familial depression were made conservatively and the sensitivity was slightly enhanced by introducing a second informant in 4 cases.

We did not perform a reliability study of the family history interview, a potential limitation of the study. However the diagnosis of definite depression according to the FH-RDC interview generally has been shown to have an excellent level of interrater reliability (Kappa's: 0.88- 0.94) (Andreasen et al. 1977).

2.4 Statistics

Sum scores and dichotomized scores for each of the three CPRS dimensions were used. Multiple logistic regressions were applied to identify the dependence of DSM-IV melancholia and family history on the three dimensions of psychopathology or their interactions. The results of these multiple regression analyses are presented in terms of Wald tests and Odds Ratio's for main effects stratified in subgroups in the presence of interaction effects. The relationship between anxious-retarded depression and family history was corrected by an additional multiple regression analysis for potential confounding effects of gender, age at present episode, duration of present episode, age first episode, number of previous episodes, in-or outpatient status and psychotic subtype. Relative Risks as well as Odds Ratio's were computed and confidence intervals were set at 95%. Chi squares were used to test relations between subcategories of depression and

dichotomous characteristics, and Student's t-tests were used to test differences regarding dimensional scores. All analyses were performed with the Statistical Package for Social Sciences (SPSS, 9.0).

3 Results

3.1 Demographic and clinical characteristics

Of the study sample of 89 patients, 58 patients (65%) were female and 31 were male. Thirty-nine patients (44 %) had a first episode. Mean age at present episode was 40.1 years (range 20-64y). Mean age at the first episode was 30.5 years (range 10-59y). The mean duration of the index episode was 6,9 months. The mean number of previous episodes was 1.66 (range 0-10). Fifty-two (58%) were outpatients and 37 inpatients. The excluded 45 patients, who did not differ on the three dimensions of psychopathology, more often were admitted to the clinic (Chi square: p = 0.002) and more often had a recurrent depressive episode (Chi square: p = 0.003). These parameters were included in multiple regression analyses as covariates. Forty-four patients (49%) had a melancholic subtype of depression and 11 patients (12 %) had a psychotic subtype. These two subcategories were significantly related to one another (see Table 1). Forty–two patients (47%) had a positive family history of depression. Table 2 shows how melancholic, psychotic and anxious-retarded depression are related to family history.

The median scores for the three CPRS dimensions emotional dysregulation, autonomic dysregulation (anxiety) and motivational inhibition (retardation) were 51 (range 32-89), 11 (range 1-24) and 8 (range 3-20), respectively. Forty-eight patients (54%) had high emotional dysregulation, 53 patients (60%) had high anxiety and 47 patients (53%) high retardation. After the multiple regression analyses that showed the dependence on the interaction between dichotomized anxiety and retardation, four two-dimensionally defined subcategories were constructed based on combinations of the dichotomies for anxiety and retardation: Thirty-one patients had anxious-retarded depression, 22 anxious (non-retarded) depression, 16 retarded (non-anxious) depression and 20 undifferentiated depression. The reason why relatively many patients had either anxious or anxious-retarded depression was due to the fact that many patients had median anxiety scores.

Mean age at present episode and mean age of first episode for anxious-retarded depression were 42.7 years (sd: 12.7 y; range 20-64 y) and 31.6 years (sd: 14.4 y; range 10-59 y), respectively. For the melancholic patients these ages were 43.4 years (sd: 11.7 y; range 20-6 4y) and 32.9 years (sd: 12.7 y; range 11-59 y), and for the patients with familial depression 38.7 years (sd: 11.78 y; range 20-59 y) and 26.1 years (sd: 10.7 y; range 10-50 years). Compared with the age at present episode of non-melancholic patients (36.8 years, sd: 10.3 years) the age at present episode of melancholic patients (43.4 y, sd: 11.7 years) was significantly higher (t = 2.817; df = 87; p = 0.006). Compared with the age of first episode non-familial depression (34.4 y; sd: 12.95 y) the age of first episode familial depression (26.12 years; sd: 10.74 y) was significantly lower (t = -3.246; df = 87; p = 0.002).

Table 1
Inter-relations between 3 subcategories of major depression.

	Melancholic	Psychotic	Anxious-retarded
Melancholic	44/44 (100 %)	9/44 (21 %) [a]	26/44 (59 %) [b]
Psychotic	9/11 (82 %) [a]	11/11 (100 %)	6/11 (55 %)
Anxious-retarded	26/31 (84 %) [b]	6/31 (19 %)	31/31 (100 %)

Numbers of the denominators represent patients of the categories in the rows; numbers of the numerators represent patients of the categories in the columns.
[a] Chi square: $p = 0.02$; [b] $p < 0.001$.

Table 2
The division of the patients with and without a family history of depression over the anxious-retarded, melancholic, and psychotic subcategories, as well as their complementary subcategories.

	positive family history		Negative family history		Total N
anxious-retarded	20	(64.5%)	11	(35.5%)	31
non-anxious-retarded	22	(37.9%)	36	(62.1%)	58
melancholic	23	(54.8%)	21	(45.2%)	44
non-melancholic	19	(42.2%)	26	(57.8%)	45
psychotic	7	(63.6%)	4	(36.4%)	11
non- psychotic	35	(44.9%)	43	(55.1%)	78

3.2 *Relationships between DSM-IV melancholia and the 3 CPRS dimensions as well as the two-dimensionally defined subcategories*

Multiple logistic regression using sum scores for the three non-psychotic dimensions (autonomic dysregulation, motivational inhibition and emotional dysregulation) as independent parameters showed that the DSM-IV defined melancholic subcategory depended only on the interaction between autonomic dysregulation and motivational inhibition (Wald = 17.4074; df=1; p <0.001). Multiple logistic regression using dichotomous scores for these two dimensions as independent parameters showed that the melancholic subcategory depended slightly more strongly on the interaction between dichotomized autonomic dysregulation and dichotomized motivational inhibition (Wald 18.771; df=1; p <0.001. Odds ratio 11.6; 95% CI 3.8-35.0). Figure1 shows a scatter plot of the scores of the 89 patients in the two-dimensional structure defined by autonomic dysregulation (anxiety) and motivational inhibition (retardation), and the distribution of the patients with DSM-IV defined melancholia within this two-dimensional structure. The four quadrants based on combinations of high or low autonomic dysregulation and motivational inhibition are constructed by reference lines representing the median scores of 11 and 8, respectively. The upper right quadrant is called anxious-retarded depression. The fact that DSM-IV defined melancholia depended not on whether patients were only anxious or retarded, but especially on whether they were both highly anxious and highly retarded, basically meant that DSM-IV defined melancholia was more prevalent in the anxious-retarded quadrant than in the other quadrants. Twenty-six of the 31 anxious-retarded patients (83.9%) had a melancholic depression, and these 26 patients represented 59.1% of the 44 melancholic patients (see table 1).

3.3 *Relationships between family history and the 3 CPRS dimensions as well as the two-dimensionally defined subcategories and DSM-IV melancholia*

Multiple logistic regression using the sum scores on the three dimensions or their interactions did not result in a relation with family history of depression. However, when using dichotomized scores for autonomic dysregulation, motivational inhibition and emotional dysregulation, then family history for depression appeared to be related to the interaction of autonomic dysregulation and motivational inhibition (Wald 5.551; df=1; p=0.0185. Odds Ratio 3.0; 95% CI: 1.2-7.4). Univariately, neither dichotomized autonomic dysregulation nor dichotomized motivational inhibition, nor dichotomized emotional dysregulation score was related to family history.

Using the 4 subcategories constructed by combinations of high or low autonomic dysregulation and motivational inhibition (anxiety and retardation) showed that the anxious-retarded subcategory had far more patients with a positive family history (Wald: 5.551; df =1; p=0.018) than the other subcategories. Table 2 shows how family history is distributed over anxious-retarded and non-anxious retarded patients. From the 31 anxious-retarded patients 64.5% (n=20) had a family history of depression (Relative Risk 2.0; 95% CI: 1.1=3.7). For the remaining 58 patients, this percentage was 37.9 % (n=22) (Relative Risk 0.7; 95% CI: 0.5-1.0). The Odds ratio was therefore 3.0 (95% CI: 1.2-7.4). Multiple regression also showed that age, gender, intensity of depression (MADRS), psychotic depression, duration of present episode, recurrent depression, the number of previous episodes, and the in-outpatient status did not confound the relation between family history and anxious-retarded depression (Wald 5.551; df=1; p=0.0185; Odds ratio 3.00; 95% CI: 1.2-9.0). No relationship was found between the melancholic subcategory and family history of depression (Wald 0.9017; df=1; p= 0.342). Table 2 also shows the (non-significant) relationships between family history of depression and the DSM-IV defined melancholic and psychotic subcategories of depression.

4 Discussion

This study showed that the DSM-IV defined melancholic subcategory depended on the interaction between both the sums cores and dichotomized scores for autonomic dysregulation ('anxiety') and motivational dysregulation ('retardation'). The Odds Ratio of the dependence on this interaction was 11.6. Family history of depression, on the other hand, depended only on the interaction between the dichotomized scores for anxiety and retardation. From the four subcategories that can be constructed by combinations of high or low scores for anxiety and retardation, only the anxious-retarded subcategory was related to familial depression. The Odds Ratio of the relation between family history and anxious-retarded depression was 3. Neither age, sex, the intensity of the depression, assessed by the MADRS, nor a history of recurrent depression, the number of previous episodes, in- or outpatient status, nor psychotic subtype in the index patient did confound this relationship. As far as we know this is the first evidence of a non-psychotic phenotype that is related to family history for depression. The finding should be treated cautiously, since a limitation of the present study could be the absence of inter-rater reliability data of the family history interview. On the other hand, this fact may probably be of limited importance since the diagnosis of definite depression according to the FH-RDC interview generally has an excellent inter-rater reliability (Kappa's: 0.88- 0.94) (Andreasen et al. 1977). Based on these data we conceived our data as sufficiently strong to warrant further investigations in this direction.

As predicted, the DSM-IV defined melancholic subcategory, despite its dependence on the interaction between anxiety and retardation, was not related to family history. Moreover, no relationship with family history was found for one of the three non-psychotic CPRS dimensions separately. This general negative finding regarding to single dimensions of psychopathology is an extension of the previous finding in the field of the dimension motivational inhibition, where psychomotor changes in depressed patients were not related to the risk of depressive illness in co-twins (Kendler 1997). The meaning of the relationship between anxious-retarded depression and family history is largely genetic, since shared family environment has not been found a causal factor in the pathogenesis of depression (McGuffin et al. 1996). This probable role of genetics, however, does not preclude the pathogenetic significance of early or late stress in at least a subgroup of the anxious-retarded patients.

Finally, the present finding may be of importance for the enhancement of the validity of specific subcategories of familial depression. Familial depression has etiologically been divided in 'depressive spectrum disease' (DSD) and the 'familial pure depressive disease' (FPDD) (Winokur 1997). Compared with DSD FPDD has a somewhat higher rate of the symptom 'loss of interest' in one study, and a higher rate of 'psychomotor retardation', 'anhedonia', and 'lack of reactivity' in a second study. These signs and symptoms are typically part of the dimension motivational inhibition. We hypothesize that the differentiating value of the items of this single dimension may be enhanced by the combination with items of the dimension autonomic dysregulation. In other words, the relationship we found in the present study between the anxious-retarded subcategory and family history for depression suggests that the combination of these two dimensions could enable a better formulation of the phenotype of FPDD. Moreover FPDD has a higher rate of overactivation of the HPA axis assessed by non-suppression in the dexamethasone suppression test (DST) than DSD (Winokur 1997). If anxious-retarded depression would appear a better phenotype for FPDD than high motivational inhibition alone, then the vasopressinergic overactivation of the HPA-axis found in anxious-retarded depression (De Winter et al. 2003) could also be more specifically present in FPDD than in DSD.

Summarizing, anxious-retarded depression has been found to exhibit elevated plasma vasopressin and a high correlation between vasopressin and cortisol (De Winter et al. 2003). We now found in addition a relation to family history of depression. These data suggest that the two-dimensionally defined anxious-retarded phenotype may open the way for the discovery of more precise interrelations between the phenotypic level, HPA-axis overactivation, and the genetic level of investigation.

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3

Anxious-retarded depression. Relations to Plasma Vasopressin and Cortisol.

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Abstract

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is related to melancholic or endogenous depression; however the strength of this relationship depends on the definition of the specific depression subcategory. A two-dimensionally defined subcategory, anxious-retarded depression is related to melancholic depression. Since arginine vasopressin (AVP) activates the HPA-axis, and both major depression and the melancholic subcategory are associated with elevated plasma AVP, we investigated whether the plasma AVP is also elevated in anxious-retarded depression, melancholic depression and anxious-retarded melancholic patients, and whether plasma AVP and cortisol are correlated in these subcategories. A total of 66 patients with major depression not using oral contraception were investigated. Patients with anxious-retarded depression had a highly significant AVP-cortisol correlation, while no such correlation was found in patients with nonanxious-retarded depression. Log-transformed mean plasma AVP values were higher in anxious-retarded than in patients with nonanxious-retarded patients. Patients with anxious-retarded melancholic also had a significantly elevated plasma AVP and a highly significant correlation between plasma AVP and cortisol levels. The correlation was low in patients with melancholic depression patients. Anxious-retarded depression may be a useful refinement of the melancholic subcategory with regard to dysregulation of the HPA-axis and plasma AVP release.

Keywords: Depression, melancholia, anxiety, retardation, vasopressin, cortisol

1 Introduction

Hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis is a robust characteristic of major depression (Holsboer 1999, Scott and Dinan 1998). Basal plasma levels of cortisol and urinary excretion of cortisol are raised (Carroll et al. 1976a,b) and the secretion of corticotrope releasing hormone is increased (CRH) (Holsboer 1999, Scott and Dinan 1998). Several studies have shown that the HPA axis is dysregulated in depression. For example, the HPA axis is resistant to suppression by dexamethasone in the dexamethasone suppression test (DST) (Carroll et al. 1981), the release of adrenocorticotrope hormone (ACTH) after CRH challenge is diminished (Thalen et al. 1993), and CRH-induced release of ACTH and cortisol is increased after dexamethasone in the Dex-CRH test (Heuser et al. 1994). In, on average 30%-50% of depressed patients the HPA axis is not suppressed in the DST, with the highest rates of non-suppression being found in patients with melancholic, endogenous, familial or psychotic subcategories of depression (Nelson and Davis 1997, Rush et al. 1996). The failure to suppress the HPA axis may be cause of reduced negative feedback via glucocorticoid receptors, facilitation of CRH-induced ACTH release or both. It may be partially mediated by increased CRH release. This suggestion is supported by the finding that cerebrospinal fluid (CSF) levels of CRH are higher in patients in whom the HPA axis is suppressed in the DST (Pitts et al. 1995). Reduced CRH-dependent ACTH release has also been associated with DST non-suppressor status (Thalen et al. 1993), and has been attributed to negative feedback by high basal cortisol levels and/or down regulation of pituitary CRH receptors (Ur et al. 1992). The Dex-CRH test is a more sensitive test for detecting changes in HPA axis regulation. Depending on age and sex, 90% of depressed patients exhibit increased release of ACTH and cortisol (Heuser et al. 1994). Possible as a result of increased CRH release and reduced negative feedback by down-regulated glucocorticoid receptors (Modell et al. 1997). An increased release of CRH and reduced glucocorticoid feedback, however, cannot fully explain nonsuppression of the HPA axis or a positive Dex-CRH test. Numerous animal data obtained under physiological and pathophysiological conditions support the view that this dysregulation of the HPA axis may involve amplification of the effect of CRH by AVP (Scott and Dinan 1998). AVP produced by parvocellular and magnocellular hypothalamic neurons synergizes with CRH at the pituitary level to stimulate ACTH release (Antoni 1993). Chronic psychological stress induces a 5-fold increase of the number of AVP containing CRH neurons (de Goeij et al. 1992). Moreover, highly anxious Wistar rats and old Wistar rats have a positive response in the Dex-CRH test, which appears to depend on increased synthesis and release of AVP from parvocellular neurons of the hypothalamic paraventricular nucleus (PVN) (Hatzinger et al. 2000, Keck et al. 2002). Pathological conditions such as adrenalectomy or CRH1 receptor deficiency likewise result in an increased number of AVP containing neurons in the PVN and in the synthesis and release of AVP from the PVN, respectively (Kiss et al. 1984, Muller et al. 2000). Finally in humans CRH cannot override dexamethasone-induced suppression of the HPA axis, where as the addition of (lysine) vasopressin leads to non-suppression of the HPA axis in the DST, like that seen in depressed patients (Von Bardeleben et al. 1985).

Thus AVP has become a peptide of major interest in depression research and may be specifically involved in the hyperactivity of the HPA axis in certain subcategories of major depression. In support of this hypothesis, plasma AVP levels are elevated in patients with major depression and in patients with the melancholic subcategory compared with healthy control subjects (Van Londen et al. 1997). Moreover, plasma AVP and cortisol levels are positively correlated in depressed patients (Inder et al. 1997a). Interestingly, plasma AVP levels are higher in hypercortisolemic depressed patients than in patients with normal cortisol levels and healthy controls (Inder et al. 1997a). The finding that CSF AVP is non-significantly elevated in patients in whom the HPA axis is not suppressed in the DST (Pitts et al. 1995) suggests that AVP release may be increased in these individuals.

These data suggest that increased AVP release is related to a specific subcategory of depression in which the HPA axis is not suppressed during the DST, rather than to depression in which responses are increased in the Dex-CRH test.

Investigations of DST non-suppression in subcategories of major depression have shown that the strength of the relationship between non-suppression and endogenous or melancholic subcategory depends on the definition used. The nonsuppression rate is lower if the endogenous or melancholic subcategory is defined according to the Diagnostic and Statistical Manual for Mental Disorders (DSM)-III (American Psychiatric Association 1980) or DSM-IV (American Psychiatric Association 1994) than if melancholic depression is defined according to Research Diagnostic Criteria (RDC) or Newcastle criteria (Rush and Weissenburger 1994). In another study, we found that anxious-retarded depression had a significant overlap with melancholic depression according to the DSM-IV (De Winter et al. 2004). The definition of anxious-retarded depression was based on median scores for two dimensions anxiety and retardation, and appeared to be associated with a family history of depression (De Winter et al., 2004). Since plasma AVP levels are raises in major depression and melancholic depression (Van Londen et al. 1997), the present study primarily investigated whether plasma AVP levels are raised in anxious-retarded depression. Since plasma AVP and cortisol levels are correlated (Inder et al. 1997) we also investigated whether this is the case for anxious-retarded depression. Patients with non-anxious-retarded were used as control subjects. We also measured plasma AVP and cortisol levels, and their correlation, in patients with melancholic depression (DSM-IV) and in patients with non-melancholic depression, hypothesizing that elevated plasma AVP levels and a positive correlation between AVP and cortisol levels would be found in the melancholic patients. We further explored whether the relation between plasma AVP and anxious-retarded depression was due to a relation between plasma AVP and melancholic depression or vice versa. We therefore compared the AVP levels and AVP-cortisol correlations in patients with anxious-retarded melancholic depression and in the category of all other depressed patients.

2 Methods

2.1 Subjects

A total of 81 patients with major depression recently admitted to the in- and out-patient university clinic of the Rijngeest Groep were recruited for a 2-year cross-sectional, prospective follow-up study of the role of stress hormones in the outcome of depression. All patients were referred to the study by the psychiatrist who made the initial diagnosis of major depression. After confirmation of the diagnosis by RFPdeW, using a semi-standardized interview, the patient was asked to participate in the study. Written informed consent was obtained for all patients, and the Ethical Committee of Leiden University Medical Center (LUMC) approved the informed consent protocol.

Patients were included if they fulfilled DSM-IV criteria for major depressive episode (American Psychiatric Association 1994) and scored at least 21 on the Montgomery Åsberg Depression Rating scale (MADRS) (Montgomery and Asberg 1979). Exclusion criteria were bipolar disorder, treatment with lithium, carbamazepine or valproate; first episode of major depression at or above the age of 60 years; alcohol or drug abuse or dependence; pregnancy; or clinical evidence of a medical illness that could be associated with abnormal plasma AVP release, such as the syndrome of Inappropriate Secretion of Anti Diuretic Hormone.

Because short term drug withdrawal may influence the regulation of the HPA axis (Kraus and Grof 1985), and we considered long term withdrawal to be not feasible as it may lead to a high drop-out rate among patients with severe depression, patients continued to

take their prescribed medication during the investigation. In exploratory analyses we confirmed that oral contraceptives decrease plasma vasopressin levels (Ekstrom et al. 1992) (Kostoglou-Athanassiou et al. 1998), and increase plasma cortisol levels (Amin et al. 1980). Therefore, 15 patients taking oral contraceptives were excluded, as were patients with depression in relation to panic disorder not included, since they participated in a different research project.

2.2 *Demographic, clinical and treatment characteristics*

Of the 66 depressed patients with a mean age of 41 years (SD 11.7), 59% were female, 53% had a positive family history, and 56% were outpatients (n = 37). The mean number of previous episodes was 1.59 (SD 1.95). A total of 29 experienced their first episode of major depression. The average duration of the current episode was 6.8 (SD 7.0) months. A total of 31 patients smoked more then one cigarette a day. Altogether 45 patients did not use alcohol, 20 patients consumed one to three alcoholic beverages daily, and one patient consumed maximally four alcoholic beverages daily in the month before the investigation. Alcohol consumption was thus lower than that associated with an increased risk of depression (5 consumptions) (Wang and Patten 2001). All patients refrained from using alcohol for 12 h before the investigation.

Of the 66 patients, nine used a neuroleptic drug, 39 an antidepressant drug,16 a selective serotonin reuptake inhibitor, 15 a serotonergic and noradrenergic reuptake inhibitor, and 8 a tricyclic drug) and 38 a benzodiazepine. For correlational studies currently accepted equivalent values of the dosages were computed (Moleman and Birkenhaeger 1998). Of the patients on antidepressant treatment, five additionally used a neuroleptic plus a benzodiazepine, two a neuroleptic, and 20 a benzodiazepine. Two psychotically depressed patients used only an antipsychotic drug and 13 patients used only a benzodiazepine

2.3 *Assessments*

2.3.1 *Psychopathology*

RFPdeW performed the psychopathological assessments using a semi-standardized interview. This interview encompassed the DSM-IV criteria for depressive disorder, subcategorisation of DSM-IV melancholic depression, and the Comprehensive Psychopathological Rating Scale (CPRS) (Asberg et al. 1978; Goekoop et al. 1992). The CPRS is a widely used scale for the assessment of psychopathological signs and symptoms. The inter-rater reliability is comparable with that of the Present State Examination (Goekoop et al. 1991), and factor-analysis in a heterogeneous patient sample has shown that its 65 items may be reduced to five global factors of psychopathology, one of which is a bipolar component (Goekoop et al. 1992). Three of these 5 components represent non-psychotic psychopathology. They are called emotional dysregulation, motivational dysregulation (the bipolar component comprising 2 dimensions of inhibited and disinhibited motivational dysregulation, respectively) and autonomic dysregulation. The 2 psychotic dimensions are called perceptual disintegration and behavioral disintegration (Goekoop et al. 1992). All 6 dimensions conform to the Rasch model (Goekoop and Zwinderman 1994) and confirmatory factor analysis has shown that all dimensions except behavioral disintegration are confirmed in the domain of unipolar major depression (Goekoop et al. unpublished data).

Since we were specifically interested in the major differentiation of unipolar depression, we used three non-psychotic dimensions: Emotional dysregulation, motivational inhibition and autonomic dysregulation. Emotional dysregulation comprises *general neurotic* signs and symptoms of inner tension, concentration difficulties, reported sadness, pessimistic thoughts, reduced sexual interest, inability to feel, reduced sleep,

indecision, apparent sadness, fatigability, failing memory, lassitude, reported muscular tension, reduced appetite, phobias, suicidal thoughts, worrying over trifles, compulsive thoughts, depersonalization and derealization. Motivational inhibition comprises the signs and symptoms related to psychomotor retardation apparent sadness, inability to feel (particularly anhedonia), slowness of movement, reduced speech, and inappropriate emotional expression (including affective flattening). Autonomic dysregulation comprises signs and symptoms of predominantly somatic anxiety, such as inner tension, reported autonomic symptoms, observed muscle tension, reduced sleep, aches and pains, and observed autonomic symptoms. Correlational analysis has shown that the major differentiation of depressive disorders is due to autonomic dysregulation ('anxiety') and motivational inhibition ('retardation'), while emotional dysregulation is a more general dimension (Goekoop et al. unpublished data). We therefore used the former two dimensions for the present study. To make four two-dimensionally defined subcategories of depression we used dichotomous ratings based on median scores for the dimensions autonomic dysregulation ('anxiety') and motivational inhibition ('retardation'). These subcategories were called anxious-retarded, (non-retarded) anxious, retarded (non-anxious) and undifferentiated depression. The anxious-retarded subcategory was selected for the present study because of its high association with the melancholic subcategory (Goekoop et al. unpublished data, see also Results).

2.3.2 Biochemical assay procedures

Within 7 days after the CPRS interview blood samples were drawn on a single day under standardized rest conditions between 09.00h and 9.30h and between 15.30h and 16.00h. All patients refrained from the use of alcohol and abnormal motor activity (sports) during the 12-h period preceding the study. They were seated 15 minutes before venipuncture, and smoking was prohibited during 30 minutes preceding the venipuncture. Eating and drinking were ad libitum.

Blood was sampled by venipuncture in 10-ml vacutainer tubes and immediately stored at 4 °C. Within 30 minutes plasma was separated and stored at -80 °C until AVP and cortisol analysis. Plasma AVP was determined by radio-immuno-assay (RIA), and total plasma cortisol was measured by high performance liquid chromatography (HPLC) with UV detection as previously described (Van Londen et al. 1997). For plasma AVP the detection limit was 0.5pg/ml for plasma (extracted assay), and the intra-and interassay coefficients of variation were 9.9% and 15.9%, respectively. For cortisol the detection limit was 0.01 mg/l and the intra-assay coefficient of variation was 2.9 %. In the present study plasma osmolality was not assessed since in our previous study of depressed patients no association had been found with plasma AVP (Van Londen et al. 1997).

2.4 Statistical analyses

The association between anxious-retarded depression and melancholia was quantified by Cohen's kappa. Plasma AVP and cortisol levels were calculated as the average of the morning and afternoon values. Plasma AVP values were not normally distributed. Therefore differences between subcategories were analyzed by Mann-Whitney U tests and correlations with plasma cortisol and psychotropic drug dosage were analyzed with Spearman's rank correlations. For multivariate analysis, plasma AVP values were log-transformed into ln(AVP). Differences in ln(AVP) and cortisol between anxious-retarded and non-anxious-retarded, melancholic and non-melancholic, as well as anxious-retarded melancholic and all other patients were analyzed with Students' t tests. Pearson's correlations were used for the correlations between ln(AVP) and cortisol. The effects of medication, age (dichotomized as older or younger than the median of 42 years, as well as older or younger than the menopausal age of 50 years) and sex on ln(AVP) were investigated by analysis of variance (ANOVA). The effects of these parameters on the correlation between ln(AVP) and cortisol were analyzed by ANOVA using ln(AVP) as the

dependent variable and cortisol as the covariate. The association between ln(AVP) and anxious-retarded depression or melancholic depression was also investigated by ANOVA. All calculations were carried out using SPSS 9.0 (SPSS INC, Chicago)

3 Results

Relation between anxious-retarded depression and melancholic depression
In all, 25 patients had anxious-retarded depression and 34 had melancholic depression. Totally, 22 patients (88% of the patients with anxious-retarded depression and 65% of the patients with melancholic depression) fulfilled the criteria for both subcategories. The correspondence between the anxious-retarded and melancholic subcategories was 0.549 (Cohen's kappa, $p < 0.001$).

3.1 Plasma AVP and Cortisol in major depression

Mean values, and effects of drug treatment, age and sex
Table 1 shows plasma AVP and cortisol levels and AVP-cortisol correlations in patients with different subcategories of major depression. The mean plasma AVP concentration was 4.5 pg/ml (S.D. 4.87). In subgroups of patients on different medications, Spearman's correlations between drug dosage and plasma AVP were 0.267 for the SSRI subgroup (n = 16, p = 0.317), -0.231 for the SNRI subgroup (n = 15, p = 0.408), -0.771 for the TCA group (n = 8, p = 0.025), 0.124 for the antipsychotic subgroup (n = 9, p = 0.750) and -0.162 for the benzodiazepine subgroup (n = 38, p = 0.333). ANOVA showed that in the whole group, treatment with SSRI, SNRI, TCA, antipsychotic drug or benzodiazepine was not related to ln(AVP). F values (p values between brackets) related to these drug treatments were 0.134 (p=0.715), 0.007 (p=0.935), 0.818 (p=0.369), 0.069 (p=0.794) and 0.105 (p=0.747) respectively. Likewise ln(AVP) did not depend on the dosage of these psychotropic drugs. F values (p values between brackets) were 0.682 (p=0.412), 0.330 (p=0.568), 0.532 (p=0.468), 2.263 (p = 0.138) and 0.171 (p=0.680), respectively finally there was no interaction between antidepressants and antipsychotics, antidepressants and benzodiazepines, and antipsychotics and benzodiazepines. F values were 0.554 (p=0.460), 0.468 (p=0.497) and 0.445 (p=0.507), respectively. Neither age (< or ≥ 42 years) nor sex, nor their interaction, were related to ln(AVP). F values were 0.011 (p=0.918), 0.348 (p=0.557) and 0.238 (p=0.628), respectively. If a menopausal age criterion of 50 years was used, then the F values were 2.349 (p=0.130), 0.165 (p=0.686) and 0.003 (p=0.957), respectively.

Table 1
Plasma AVP and Cortisol with standard deviation (SD) and Spearman correlations between plasma AVP and Cortisol for all patients, as well as for anxious-retarded versus non-anxious-retarded, and melancholic versus non-melancholic patients.

(Sub)categories	n	AVP pg/ml		Cortisol mg/ml		AVP-Cortisol	
		Mean	SD	Mean	SD	Correlation	p
Major depression	66	4.50	(4.87)	145.4	(41.2)	.35	0.005
Anxious-retarded	25	6.25[a]	(7.06)	148.6	(44.6)	.56	0.004
Non-anxious-retarded	41	3.44[a]	(2.38)	143.4	(39.5)	.24	0.126
Melancholic	34	5.50	(6.22)	148.5	(41.4)	.39	0.024
Non-melancholic	32	3.44	(2.53)	142.1	(42.4)	.27	0.133
Anxious retarded melancholic	22	6.75[b]	(7.39)	148.6	(47.3)	.59	0.004
All other patients	44	3.38[b]	(2.31)	143.8	(38.4)	.25	0.098

Differences between means (Mann Whitney) [a]: p=0.09; [b]: p=0.046

The mean plasma cortisol concentration was 145.4 mg/ml (41.2). In subgroups of patients on different medications, Spearman's correlations between drug dosage and plasma cortisol were 0.302 for the SSRI subgroup (*n* = 16, p = 0.255), -0.011 for the SNRI subgroup (*n* = 15, p = 0.969), 0.072 for the TCA group (*n* = 8, p = 0.691), 0.080 for the antipsychotic subgroup (*n* = 9, p = 0.838) and -0.126 for the benzodiazepine subgroup (*n* = 38, p = 0.451).

Treatment with SSRI, SNRI, TCA, antipsychotic drug or benzodiazepine was not related to plasma cortisol concentration. F values (p values between brackets) related to these drug treatments were 0.222 (p=0.639), 0.347 (p=0.558), 1.129 (p=0.292), 1.133 (p=0.291) and 0.108 (p=0.743) respectively. Similarly, plasma cortisol concentration was not associated with psychotropic drugs dosage. F values (p values between brackets) were 0.119 (p=0.732), 0.022 (p=0.881), 0.442 (p=0.508), 1.439 (p=0.227) and 0.149 (p=0.701) respectively. Interaction effects were analyzed for antidepressants and antipsychotics, antidepressants and benzodiazepines, and antipsychotics and benzodiazepines. F values were 0.596 (p=0.443), 1.439 (p=0.235) and 0.956 (p=0.332), respectively. Neither age (< or ≥ 42 years) nor sex, nor their interaction, were related to ln(AVP). F values were 0.013 (p=0.908), 0.020 (p=0.999) and 0.013 (p=0.909), respectively. If the menopausal age criterion of 50 years was used, then the F values were 1.799 (p=0.185), 0.040 (p=0.841) and 0.062 (p=0.804), respectively

3.2 Correlations between plasma AVP and cortisol, and effects of drug treatment, age and sex

A statistically significant positive correlation (Spearman's r= 0.35, p=0.005) was found between plasma AVP and cortisol for all 66 patients with major depression. After logarithmic transformation of AVP concentrations the Pearson's correlation was 0.37 (p=0.002). ANOVA further showed that neither medication with SSRI, SNRI, TCA, antipsychotic drug and benzodiazepine nor the above mentioned interactions of drug treatments were related to the correlation between ln(AVP) and plasma cortisol, the significance of the association being only slightly reduced (p=0.004) after correction for these factors. ANOVA of age (< or ≥ 42 years), sex and their interaction and cortisol as covariate of ln(AVP) showed that the significance of the covariation between cortisol and

ln(AVP) in depression again was only slightly reduced (p=0.003). If the menopausal age criterion of 50 years was used, then the significance of the covariation was again slightly reduced (p = 0.005).

3.3 Plasma AVP and Cortisol in patients with anxious-retarded depression, melancholic depression or anxious-retarded melancholic depression

Differences between mean values, and effects of drug treatment, age and sex. Patients with anxious-retarded patients had a higher plasma AVP concentration than patients with non-anxious-retarded patients (Mann-Whitney U test, p= 0.09, two-tailed). After logarithmic transformation of AVP concentrations the difference was statistically significant (t test: p=0.031, two-tailed). The difference in plasma AVP or ln(AVP) between patients with melancholic or non-melancholic depression was not significant, (p= 0.090, Mann Whitney, and 0.130, t-test, respectively). Patients with anxious-retarded melancholic depression had a significantly higher plasma AVP and ln(AVP) than all other patients (p = 0.046 and 0.013 respectively). ANOVA showed that the dosage of SSRI, SNRI, TCA, antipsychotic drug and benzodiazepine did not have a confounding effect on the relation between ln(AVP) and anxious-retarded depression. F values (p values between brackets) were 1.787 (p=0.386), 1.778 (p=0.198), 0.680 (p=0.420), 1.855 (p=0.189) and 0.026 (p=0.874) respectively. Similarly, dosage of SSRI, SNRI, TCA, antipsychotic or benzodiazepine did not affect the relation between plasma cortisol level and anxious-retarded depression. F values (p values between brackets) were 0.005 (p=0.945), 1.279 (p=0.272), 1.136 (p=0.300), 0.252 (p=0.621) and 0.738 (p=0.401) respectively.

ANOVA showed that age (< or ≥ 42 years), sex and their interaction did not have a confounding effect on the relation between ln(AVP) and anxious-retarded depression, melancholic depression or anxious-retarded melancholic depression. F values (p values between brackets) related to age, sex and their interaction were 0.707 (p=0.410), 0.011 (p=0.916) and 1.265 (p= .0273) for the anxious retarded subcategory, 0.109 (p=0.743), 0.562 (p=0.459) and 0.555 (p=0.462) for the melancholic subcategory, and 0.001 (p=0.975), 0357 (p=0.558) and 2.554 (p=0.127) for the anxious-retarded melancholic depression. ANOVA with anxious-retarded depression and melancholic depression as independent variables showed that ln(AVP) was only associated with the anxious-retarded subcategory of depression (p=0.031). There was no association between cortisol level and subcategory of depression.

3.4 Correlations between plasma AVP and cortisol, and effects of age and sex

In patients with anxious-retarded depression, Spearman's correlations between plasma AVP and cortisol were 0.56 (n= 25; p=0.004) and 0.24 (n=41; n.s.), respectively. In patients with melancholic or non-melancholic depression, these correlations were 0.39 (n=34; p=0.024) and 0.27 (n= 32; n.s.), respectively. The correlation between plasma AVP and cortisol levels in the 22 patients with anxious-retarded melancholic depression was0.59 (p=0.004), while in the 44 other patients it was 0.253 (p=0.098). After logarithmic transformation of AVP concentrations, the Pearson's correlations between ln(AVP) and plasma cortisol were 0.61 (p=0.001) and 0.17 (p=0.302) for patients with anxious-retarded or non-anxious-retarded patients, 0.43 (p=0.011) and 0.27 (p=0.141) for patients with melancholic or non-melancholic depression, and 0.63 (p=0.002) and 0.16 (p=0.289) for patients with anxious-retarded melancholic patients and all other patients. After correction for age (< or ≥ 42 years), sex and their interaction, ANOVA with concentration as covariate revealed a slightly lower association between cortisol concentration and ln(AVP) in anxious-retarded patients (p=0.005), melancholic depression (p= 0.017) or anxious-retarded melancholic depression (p=0.004).

4 Discussion

We replicated the finding that major depression is associated with a positive correlation between plasma AVP and cortisol (Inder et al. 1997). This correlation was due to a highly significant correlation between plasma AVP and cortisol in patients with anxious-retarded depression. We also showed that this anxious-retarded subcategory of depression was associated with a higher of plasma AVP level than the complementary non-anxious-retarded subgroup, but it was only significant when logarithmic-transformed AVP values were used.

In patients with melancholic depression (65% of the patients had anxious-retarded depression), there was a low correlation between plasma AVP and cortisol. These patients had a non-significantly higher plasma level of AVP than the patients with non-melancholic depression. Like the patients with anxious-retarded depression, the patients with anxious-retarded melancholic depression (88% of the patients with anxious-retarded depression) had a significantly higher plasma AVP level and a highly significant AVP-cortisol correlation. This suggests that anxious-retarded depression may be a two-dimensional refinement of the melancholic subcategory and a more useful clinical phenotype than the melancholic subcategory as far as external validity involving plasma AVP related HPA-axis dysregulation is concerned.

The increased plasma AVP level combined with the correlation between plasma AVP and cortisol levels in the patients with anxious-retarded depression is the third report supporting the hypothesis that AVP is involved in the dysregulation of the HPA-axis in depression. As already mentioned, one study demonstrated a correlation between plasma AVP and cortisol in major depression (Inder et al. 1997), and another study showed that the number of CRH neurons coexpressing AVP in the PVN of the hypothalamus was almost three times higher than in a control group (Raadsheer et al. 1994). However, in an earlier study (Van Londen et al. 1997), we found no correlation between plasma AVP and cortisol levels. The reason for this difference is unclear. Whether drug withdrawal may have played a role will have to be investigated. The previously reported statistically significant elevation of plasma AVP in melancholic depression (Van Londen et al. 1997) was not reproduced in the present study. This may be because this relationship was only found for plasma AVP levels at 23.00, a time not assessed in the present study. Another reason is that DSM-III-R criteria for melancholic depression were used in our previous study.

The specific phenotypic characteristic of patients with high plasma AVP and high AVP-cortisol correlation appears to be the combination of both high anxiety and high retardation. This differentiates these patients from highly anxious or highly retarded patients, as well as from highly anxious, low-retarded patients and highly retarded low-anxious patients. The combination of high anxiety, high retardation, and high plasma AVP with positive AVP–cortisol correlation suggests a common pathogenetic pathway that involves disinhibition of the HPA-axis as well as disinhibition of the two coping systems for fight/flight and behavioral inhibition (Bohus and Koolhaas 1993). Since these two systems centrally involve CRH and AVP neurotransmission, respectively, reduced negative feedback or increased release of both CRH and AVP may occur in the anxious-retarded subcategory of depression. This could be due to reduced hippocampal and/or hypothalamic glucocorticoid feedback function (Sapolsky and Plotsky 1990,Kovacs et al. 2000) and/or to enhanced noradrenergic activation (Scott and Dinan 1998). Although it is generally accepted that peripheral plasma AVP levels reflect osmotic regulation activity of the magnocellular neurosecretory system, the elevated plasma AVP in the anxious-retarded depression could be because of a disinhibited response to psychological stress. In this case the response could originate in the parvocellular neurons in the hypothalamic

PVN and reach the pituitary via the portal circulation, as indicated by the results of animal studies of 'psychological' stress (Keck et al. 2002, Scott and Dinan 1998). The higher correlation between plasma AVP and cortisol may be because of synergy between AVP derived from the parvocellular PVN and CRH at the level of the pituitary. However, increased plasma AVP levels may also directly stimulate adrenocortical glucocorticoid secretion (Guillon et al. 1995). Altough we have no evidence for this from this study. Increased plasma AVP levels could also originate from the magnocellular system. The lack of a correlation between plasma AVP levels and plasma osmolality in our earlier study (Van Londen et al. 1997), makes the latter explanation unlikely.

Psychotropic agents may have confounded the association between plasma AVP levels, or the correlation between plasma AVP and plasma cortisol levels and anxious-retarded depression, because the SSRI fluoxetine has been shown to reduce hypothalamic AVP release *in vitro* (Altemus et al. 1992) and in some studies antipsychotic drugs have been shown to influence plasma cortisol and AVP levels (Gattaz et al. 1995, Raskind et al. 1987). In these 66 patients with major depression, we only found a negative correlation between TCA dosage and plasma AVP level in the whole group of depressed patients. This finding was no longer significant after correction for multiple assessments. To detect the effects of treatment on plasma AVP levels, it may be better to measure plasma AVP levels of those drugs whose antidepressant is known to be related to their plasma concentration. The finding that neither age (< 42 or ≥ 42 years; < 50 or ≥ 50 years) sex, nor their interaction explained the elevated plasma AVP levels in patients with anxious-retarded depression, and that no difference was found between young men and women, suggests that postmenopausal nor perimenstrual effects did not confound the data.

We found that the mean plasma AVP level was 4.5 pg/ml, which may seem rather high compared to data reported by others. Our healthy control group of 17 subjects, however, had a mean plasma AVP level of 3.17 pg/ml (range 1.20 –9.11pg/ml; SD 1.97), which is similar to previously reported concentrations (ranging from 1.2 pg/ml ± 0.6 to 3.5 ± 0.6 pg/ml) measured by RIA plasma extraction (Glanzer et al. 1984, Viinamaki et al. 1986) . This suggests that it is unlikely that the RIA method used resulted in systematically higher plasma AVP values, and that the high mean plasma AVP level in this depressed patient group was due to a subgroup with extraordinary high levels (the anxious-retarded depression subgroup).

In conclusion, anxious-retarded depression, which has been related to family history, appeared to be a phenotypic subcategory showing a correlation with high plasma AVP levels and a high AVP-cortisol correlation. Anxious-retarded depression was significantly associated with melancholia and patients with anxious-retarded melancholic depression also had high plasma AVP levels and a high correlation between plasma AVP and cortisol levels. These findings suggest that this two-dimensional refinement of the melancholic subcategory of depression may be useful for further investigations of plasma AVP-related dysregulation of the HPA axis in familial depression.

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4

Anxious-retarded depression: Relation to two-year outcome of major depressive disorder.

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Abstract

Background: Anxious-retarded depression is a two-dimensionally defined subcategory of depression derived from DSM-IV melancholia. It is related to increased plasma vasopressin, correlative plasma vasopressin and cortisol levels, and a positive family history. We now explored its relation with outcome. Methods: Seventy depressed patients were included to follow-up for two years. Outcome was defined by time until full-remission of depression. Cox regression analyses were used to compare patients with anxious-retarded and non-anxious-retarded depression, as well as melancholic and non-melancholic patients. Results: Anxious-retarded depression had a poor outcome. Limitations: The number of patients was small. Conclusion: The relation with poor outcome further supports the validity of the anxious-retarded subcategory.

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

1 Introduction

An anxious-retarded subcategory of depression has been derived from DSM-IV melancholia by using a multidimensional structure of psychopathology (De Winter et al. 2004). The validity of this subcategory is supported by correlative plasma vasopressin (AVP) and cortisol levels, elevated plasma AVP (De Winter et al. 2003), and a relation with family history of depression (De Winter et al. 2004). The melancholic subcategory was less or not related to these parameters.

We now describe a next step of the validation programme proposed by Robins and Guze (Robins and Guze 1970), by investigating the long-term outcome of this anxious-retarded subcategory. Since anxious-retarded depression has been derived from melancholia, we additionally investigated the outcome in melancholic patients. Many factors have been found to predict poor outcome of depression: The melancholic subcategory (Tuma, 2000), endogenous depression (O'Leary 1996), symptom severity and duration of illness (Keller et al. 1992), retardation (van Londen et al. 1998), anxiety (Coryell et al. 1992), neuroticism (Scott et al., 1992), a positive family history of depression (Kendler et al. 1997), female gender (Sargeant et al. 1990), older age and lower education (Ronalds et al. 1997), family history of mental disorder (Duggan et al. 1998), and psychiatric and somatic co-morbidity (Keitner et al, 1991). In the present outcome study we investigated the role of these factors (except for the last two) as covariates of poor outcome. In addition we investigated the effect of insufficient treatment. Outcome was defined as the time to full-remission (Frank et al.1991).

2 Methods

2.1 Patients

The patient sample was a sub-sample of that investigated in preceding cross-sectional analyses (De Winter et al. 2003; De Winter et al. 2004). Inclusion criteria were DSM-IV major depression, Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg 1979) score > 20, age 18-65 years, and first episode before the 60th years. A psychiatrist at the inpatient or outpatient clinic primarily made the diagnosis of major depression (DSM-IV). If R.F.P.de W. confirmed the diagnosis in an individual subject (see Section 2.2), the patient was asked to participate in the study. Inclusion and exclusion criteria have been published before (De Winter et al. 2003, De Winter et al. 2004). The Medical Ethics Committee of the Leiden University Medical Centre approved the research protocol. Written informed consent was obtained from each patient.

2.2 Assessment and outcome measures

Psychopathology was assessed with the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al. 1978) at the start of the study (t1), six weeks later (t2) and than after 3, 6, 12 18 and 24 months (t3 – t7)). All CPRS items were rated from 0 – 6, covering the two weeks preceding the assessment. DSM-IV criteria for major depression were assessed by using corresponding CPRS items. A score ≥ 3 was taken as representing the DSM-IV severity criterion of a symptom being more present than absent. Increased appetite and weight were rated separately. Full remission was defined by a maximum of 2 symptoms during at least the last 2 weeks. Partial remission was defined by a minimum of 3 and a maximum of 4 symptoms (Frank et al. 1991). DSM-IV subcategories were assessed by semi-standardized interviews.

The anxious-retarded subcategory was defined as the combination of above median scores for anxiety and retardation, assessed by two scales from the CPRS (Goekoop et al. 1992): autonomic dysregulation (≥11) and motivational inhibition (≥8) (De Winter et al. 2003). A positive family history was quantified by the presence or absence major

depressive disorder in any first degree using a slightly modified version of the Family History interview by Andreasen (Andreasen et al. 1986; De Winter et al. 2004). Neuroticism was assessed by Eysenck's Personality Questionnaire (Eysenck and Eysenck 1975). Educational level was classified in six categories (level 1 = no or low education until level 6 = university or postgraduate).
Depressive intensity was rated with the MADRS. Duration of current episode was assessed by history taking of the individual patient, and was defined by the number of months with preceding depressive symptoms. The number of episodes was also assessed by history taking. Each episode was defined by treatment necessity.

2.3 Treatment
Treatment was carried out after t1 according to a standardised treatment guideline comprising cognitive behavioural therapy or/and antidepressant drug treatment depending on severity, second antidepressant, lithium addition, MAO-inhibitor. Insufficient treatment was defined by the absence of antidepressant treatment when fully depressed (or not fully remitted), or the absence of antipsychotic treatment in a patient with psychotic depression. This insufficiency was quantified as the sum of the time points of its occurence.

2.4 Data analysis
Mann-Whitney U, *t* tests and χ^2 were used for differences between subgroups of patients. Kaplan-Meier curves were made and Cox regression analyses (forward stepwise) were used to test whether outcome differed between subcategories and their patient control groups, accounting for the effect of covariates. The Statistical Package for Social Sciences version (SPSS 9.0 INC, Chicago) was used for all analyses.

3 Results

Patients lost in the follow-up and those remaining in the follow-up did not differ on clinical or demographic parameters (neuroticism, number of previous episodes, duration of current episode, family history of depression, psychotic depression, atypical depression, melancholia and anxious-retarded subtype, or age, gender and education) (χ^2, *t* test or Mann-Whitney U, P> 0.05). There were also no clinical or demographic differences between the anxious-retarded or melancholic subcategories and their patient control groups (χ^2, *t* test or Mann-Whitney U, P> 0.05). From the 24 anxious-retarded patients 20 patients fulfilled criteria for the melancholic subcategory (χ^2 = 19.2, df = 1 and P < 0.0001) and six had psychotic features (χ^2 = 3.42, df = 1 and P = 0.064).

Figure 1 and Table 1 show rates of full remission and non-remission in anxious-retarded and non-anxious-retarded depression during follow-up. The patients with anxious-retarded depression differed significantly from all other patients in time to full remission (Wald = 7.85, df = 1 and p = 0.005). Analysis of covariate effects, including initial MADRS score, did not result in altered Wald and P values (Table 2). The strength of the relation between poor outcome and anxious-retarded depression was slightly reduced by insufficient antipsychotic (Wald = 6.634; df=1; p=0.010) or antidepressant (Wald 6.583; df=1; p=0.010) treatment as covariates. The use of both covariates resulted in the same Wald as the latter.

The dichotomised scores of initially high versus low anxiety, and high versus low retardation, were not related to time to full remission (Wald = 1.162, df = 1 and p = 0.204, and Wald = 2.080, df = 1 and p = 0.149), neither was melancholia related to this outcome measure (Wald = 3.21, df = 1 and p = 0.073).

Figure 1
Remission and MDD rates for anxious-retarded and non-anxious-retarded patients during follow-up

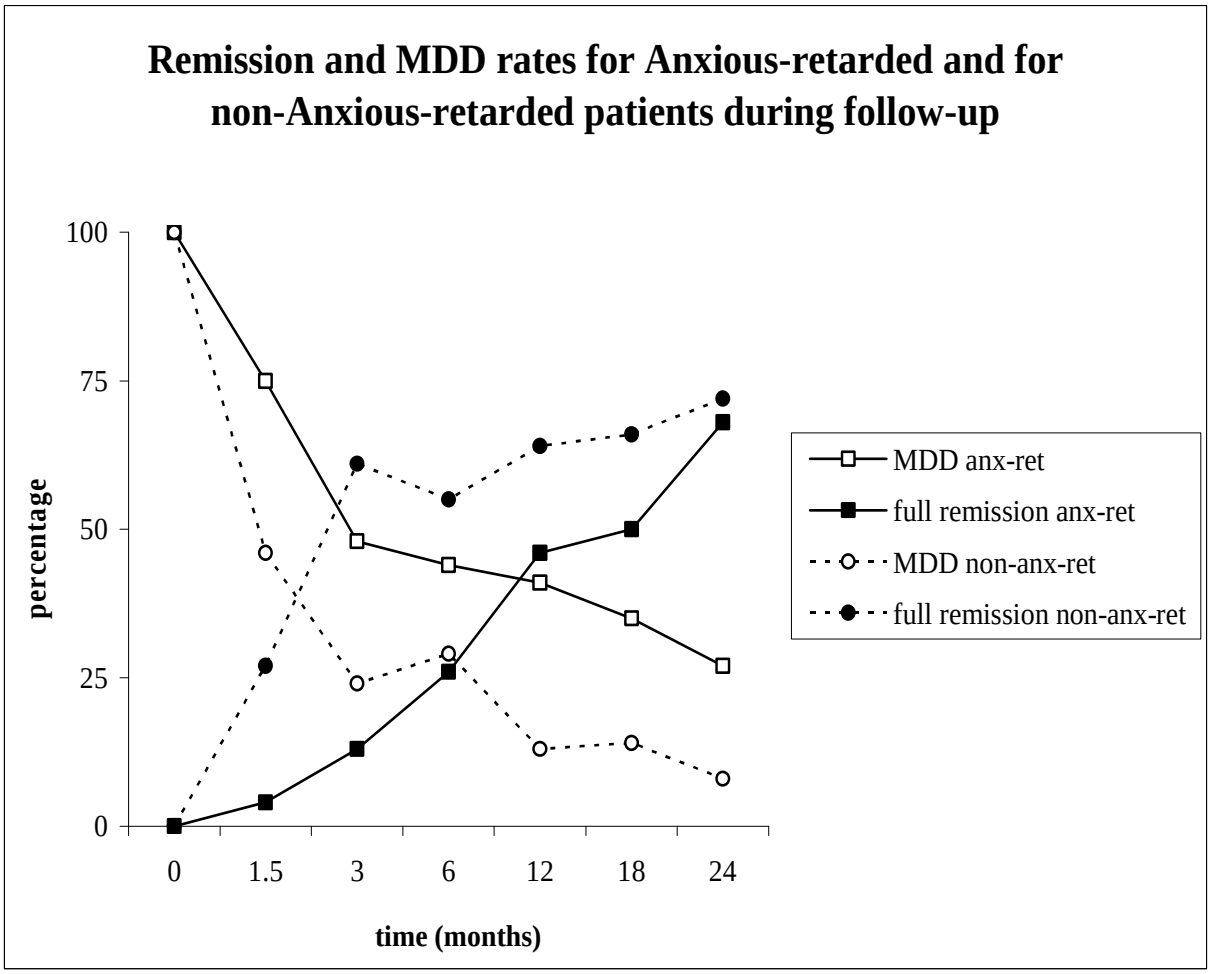

Table 1

Percentages of patients fulfilling criteria for MDD criteria, partial remission and full remission in all patients, patients with the melancholic subcategory and patients with anxious-retarded depression

MDD and subcategory	6 weeks percentage (n)	3 months % (n)	6 months % (n)	1 year % (n)	18 mnths % (n)	2 years % (n)
All patients:						
MDD	56% (37)	33% (21)	34% (22)	23% (14)	22 % (12)	16 % (9)
Partial remission	25% (16)	23% (15)	21% (14)	20% (12)	18% (10)	14% (8)
Full remission	19% (12)	44% (28)	45% (29)	57% (35)	60% (33)	71% (41)
Melancholic:						
MDD	69% (22)	40% (12)	39% (12)	27% (8)	19% (5)	18% (5)
Partial remission	25% (8)	33% (10)	32% (10)	27% (8)	15% (4)	14% (4)
Full remission	6% (2)	27% (8)	29% (9)	47% (14)	65% (17)	68% (19)
Anxious-retarded:						
MDD	75% (18)	48% (11)	44% (10)	41% (9)	35% (7)	27% (6)
Partial remission	21% (5)	39% (9)	30% (7)	14% (3)	15% (3)	5% (1)
Full remission	4% (1)	13% (3)	26% (6)	46% (10)	50% (10)	68% (15)
Non-anxious-retarded						
MDD	46% (19)	24% (10)	29% (12)	13% (5)	14% (5)	8% (3)
Partial remission	27% (11)	15% (6)	17% (7)	23% (9)	20% (7)	19% (7)
Full remission	27% (11)	61% (25)	55% (23)	64% (25)	66% (23)	72% (26)

Table 2
Wald values of relations between anxious-retarded depression as well as covariates and poor outcome.

Predictors	Wald	p
Anxious-retarded depression	7.85	.005
Age	0.26	ns
Gender	0.30	ns
Neuroticism	0.06	ns
Education	0.28	ns
Number of previous episodes	1.07	ns
Duration of current illness	0.10	ns
Family history	0.38	ns
Psychotic depression	0.22	ns
Melancholia	0.27	ns
Depression Severity (MADRS)	1.93	ns

4 Discussion

The anxious-retarded subcategory had a poor outcome in terms of time to full remission. Intensity of depression assessed by the MADRS did not affect this relation. Neither did the weak influences of insufficient antipsychotic and antidepressant treatment explain this relation.This multidimensionally defined subcategory is therefore now not only validated by by increased plasma vasopressin, correlative plasma vasopressin and cortisol levels (De Winter et al., 2003) and a positive family history (De Winter et al., 2004), but also by a poor outcome.

The combination of high anxiety and high retardation was required for this prediction, since the dichotomised scores for anxiety and retardation separately were not significantly related. The present results can be seen as adding information to previous findings relating anxiety or anxiety disorder comorbidity (Bakish, 1999; Clayton et al., 1991; Coryell et al., 1992) and retardation (Parker et al., 1992; van Londen et al., 1998) to poor outcome of depression.

In contrast with the non-anxious-retarded subgroup outcome in the anxious-retarded subcategory appeared not homogeneously distributed. After two years anxious-retarded patients were generally either fully remitted or still depressed. Only one patient was partially remitted (5%). Although the number of patients involved in this study is relatively small, these data suggest a differentiation of outcome specific for the anxious-retarded subcategory. The number of patients was also too small for the analysis of the confounding effect of the melancholic subcategory.

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5

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 anxiousretarded subtype and the TCI scores.

MANCOVAwith 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 Means and changes t1 - t7	P	Remitted n = 41 Means and changes t1- t7	P	Non-remitted n = 17 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).

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6

Depression with above-normal plasma vasopressin: Validation by relations with family history of depression and mixed anxiety and retardation.

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Abstract

An anxious-retarded subtype of depression has been derived from the DSM-IV category of melancholia. It is defined by combined high scores for anxiety and retardation, and is related to family history of depression and increased plasma vasopressin (AVP) levels. Central problems concerning this hypothesized subcategory are whether elevated plasma AVP is related to family history, whether it would be better operationalized by a cut-off level for plasma AVP than as continuous variable, and whether the anxious-retarded phenotype would be better described in terms that account for full variability of mixed anxiety and retardation. A previous study suggested that above-normal plasma AVP was a more useful endophenotypic parameter than plasma AVP as a continuous variable. To answer these and related questions, 81 patients were investigated. Receiver Operating Characteristic analyses yielded a cut-off value of 5.56 pg/ml for above-normal plasma AVP, log-transformed plasma AVP (ln (AVP)) was used as continuous variable, and the correlation between anxiety and retardation was used to account for full variability of the anxious-retarded phenotype. Family history was related to above-normal plasma AVP (n =16) and nonsignificantly to ln(AVP). Depression with above-normal plasma AVP, as well as familial depression with above-normal plasma AVP, showed a high correlation between anxiety and retardation, and this correlation was significantly higher than that found in the depressed patient control groups. The data support the delimitation of a largely familial depression with above-normal plasma AVP, vasopressinergic activation of the hypothalamus–pituitary–adrenal axis and a variable anxious-retarded phenotype.

Key words: Depression, melancholia, dimensions, vasopressin, family history

1 Introduction

The purpose of this study was to search for a more valid subcategory of depression than DSM-IV melancholia, the DSM-IV variant of endogenous depression. The necessity for such a study has been put forward by Van Praag (1998, 1993). He identified the description of the DSM classification to be a key factor hampering biological research into depression. Research would benefit from dissecting clinical pictures into their component parts. In our strategy, we followed the method of Robins and Guze (1970) to assess diagnostic validity. This approach implies that development at one level of investigation (e.g., the phenotypic level) may enhance relations with other levels of investigation (e.g., the endophenotypic level and family history of depression), and that developments at or between these other levels in their turn may result in developments at the former level.Theories of the multidimensional structure of clinical pictures and of a vasopressinergic drive of the hypothalamic–pituitary–adrenal (HPA) axis in melancholia formed the background of developments at the phenotypic and endophenotypic levels in the present study.

The theory of Jaspers (1953) motivated our phenotypic investigations. He stated that clinical pictures are constituted by mixtures of basic symptom dimensions, and that these mixtures have variable levels of intensity. This theory guided an earlier factor- analytic investigation of the global dimensions of psychopathology (Goekoop et al. 1992), and the multiple logistic regression analysis of the melancholic subtype using three of these independent dimensions: "emotional dysregulation", "autonomic dysregulation" and "motivational inhibition" (De Winter et al. 2004). The latter study resulted in the refinement of DSM-IV melancholia into a highly anxious-retarded subtype. This subtype was defined by above median scores for "autonomic dysregulation" and "motivational inhibition". Since the former comprises items of somatic anxiety and the latter symptoms of psychomotor retardation and anhedonia, these global dimensions have subsequently been called "anxiety" and "retardation" for easier comprehension.

In the present study, we compare the highly anxious-retarded subtype with a phenotype defined to cover full intensity variation of mixed anxiety and retardation. For that purpose we used the correlation between the scores on the dimensions of "anxiety" and "retardation". The vasopressinergic theory of depression formed the background of our choice of plasma vasopressin (AVP) concentration as the endophenotypic parameter.The origin and function of stress-related AVP release is well documented in animal research. AVP from the parvocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus functions as a synergizer of the activation of the HPA axis by corticotropinreleasing hormone (CRH) (Antoni 1993). Repeated stress may enhance the synthesis of AVP (De Goeij et al. 1992), and genetic factors may be involved in the enhanced synthesis and release of AVP in hyperanxious rats (Keck et al. 2002). In healthy human subjects, high levels of exogenous vasopressin cause cortisol escape from dexamethasone suppression (Von Bardeleben et al. 1985).

Evidence supporting vasopressinergic HPA-axis activation in depressed patients has also been reported. For instance, more CRH neurons co-express AVP (Raadsheer et al. 1994), the concentration of AVP in the cerebrospinal fluid (CSF) is correlated with the level of CRH (Pitts et al. 1995), and plasma AVP and plasma cortisol levels are correlated in suicidal depressed patients (Inder et al. 1997), as well as in patients with anxious-retarded depression (De Winter et al. 2003). Finally, increased plasma AVP has been found in drug-free depressed patients compared with control subjects (Van Londen et al. 1997). Thus, elevated plasma AVP levels in depression could reflect stress-related or genetically determined release of AVP, leading to AVP-driven HPA axis activation, and this would

explain the correlation between the plasma levels of AVP and cortisol in depression. The origin and function of that elevated plasma AVP concentration in depression have not yet been determined. It is not likely to be a response to above-normal plasma osmolality, because plasma osmolality is decreased in depressed patients compared with normal control subjects (Van Londen et al. 1997).

Since depressed patients may experience severe stress, stress-related AVP release from the PVN could occur, in parallel to AVP necessary for osmostasis. In a previous study relating plasma AVP as a continuous variable to phenotypic characteristics of depression, we found a relation to DSM-III-R melancholia (Van Londen et al. 1997), as well as to daytime immobility in both depressed patients and healthy control subjects (Van Londen et al. 1998). In contrast, above-normal plasma AVP was found to be related to a particular motor pattern (increased sleeptime motility) in depressed patients only (Van Londen et al. 1998).

In the present study, we therefore hypothesized that above-normal plasma AVP would be a more useful endophenotypic parameter than plasma AVP as a continuous variable. The first steps of our search for a more valid subclass of depression were formed by relations found between the highly anxious-retarded subtype and family history of depression (De Winter et al. 2004) as well as log-transformed plasma AVP concentration (De Winter et al. 2003). Patients with the highly anxious-retarded subtype also showed a significant correlation between AVP and cortisol (De Winter et al. 2003). The melancholic subtype was only weakly or not at all related to these parameters. Although these results do not necessarily mean that increased plasma AVP and family history of depression are also related to one another, they suggest the possibility of such a relation. If a relation between plasma AVP and family history indeed was present, then a subcategory of depression could exist, that is characterized by the triple interrelation between an anxious-retarded phenotype, elevated plasma AVP and family history of depression. This triple interrelation would enhance diagnostic validity compared with the "bilateral" relations found with the highly anxious-retarded subtype only. Two major questions about such a subcategory are whether elevated plasma AVP would be better operationalized by a cut-off level for above-normal plasma AVP than by plasma AVP as a continuous variable, and whether the anxious-retarded phenotype would be better described in terms that account for the full variability of mixed anxiety and retardation. The first hypothesis was that plasma AVP would be related to a family history of depression. The second hypothesis was that above-normal plasma AVP would prove to be a more useful parameter for relations with family history of depression and the anxious-retarded phenotype than plasma AVP as a continuous variable. The third hypothesis was that depression with abovenormal plasma AVP would show a high correlation between anxiety and retardation, and that this correlation would be higher than that found in the complementary group of all other patients. Finally, since the highly anxious-retarded subtype was characterized by a significant correlation between plasma AVP and cortisol (De Winter et al. 2003), and this correlation might be due to increased AVP release, we investigated whether the correlation between plasma AVP and cortisol was also present in the subcategory of depression with above-normal plasma AVP, accounting for the overlap with the highly anxious-retarded subtype. We also investigated whether the correlation between plasma AVP and cortisol in patients with the highly anxious-retarded subtype was influenced by above-normal plasma AVP.

2 Methods

2.1 Subjects

Eighty-one patients with unipolar depression were recruited. This sample comprised the patients with complete AVP measures from the 89 patients in whom the relation was found between the highly anxious-retarded subtype and family history (De Winter et al. 2004). All patients were referred to the study by the psychiatrist who made the initial diagnosis of major depression according to DSM-IV criteria (American Psychiatric Association 1994). After confirmation of the diagnosis (RFP de W) using a semistandardized interview, the patient was asked to participate in the study. Patients with depression in the course of a panic disorder were not included because they participated in a different research project. For the study of the correlation between plasma AVP and cortisol, 15 patients who were taking oral contraceptives were not included in the analyses, because these drugs affect plasma cortisol levels (Amin et al. 1980). Since these drugs could also influence plasma AVP levels (Ekstrom et al. 1992, Kostoglou-Athanassiou et al. 1998), oral contraception was used as a covariate in multivariate analyses. Written informed consent was obtained from all patients, and the Ethics Committee of the Leiden University Center (LUMC) approved the informed consent protocol. Patients were included if they fulfilled criteria for major depression (American Psychiatric Association 1994) and scored at least 21 on the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979, Hartong and Goekoop 1985). Exclusion criteria were organicity; schizophrenic, schizoaffective, and bipolar disorder; first episode of major depression at age 60 years or older; alcohol or drug dependence; pregnancy; clinical evidence of a condition with abnormal AVP release, such as the syndrome of Inappropriate Secretion of Anti-Diuretic Hormone; or treatment with lithium, carbamazepine, or valproate, which could influence AVP concentration. Because acute drug withdrawal may influence the regulation of the HPA axis (Kraus and Grof 1985) and the phenotypic expression of depression, and because we considered long-term withdrawal not feasible as it may lead to high drop-out rates among patients with severe depression, patients continued to take their prescribed medication during the investigation.

2.2 Demographic, clinical and treatment characteristics

Of the 81 patients (mean age=40 years, S.D.=11.5, range=20–64 years), 67% were female, 51% had a positive family history, and 59% were outpatients (n =48). The mean number of previous depressive episodes was 1.69 (S.D.=2.08), and 47 patients (58%) had a recurrent episode. Eleven patients received an antipsychotic drug, 47 an antidepressant drug (21 a selective serotonin reuptake inhibitor, 15 a serotonergic and noradrenergic reuptake inhibitor, and 11 a tricyclic antidepressant), and 47 a benzodiazepine. For analysis of variance correcting for the effect of psychotropic drug dosage, equivalent values of the dosages were computed based on currently accepted maximum dosages (Moleman and Birkenhaeger 1998). Seven patients used antihypertensive drugs. Mean antidepressant dosage in 47 patients on antidepressant treatment was 158 mg amitriptyline (median=150, range=37.5–375), mean benzodiazepine dosage in 47 patients was 39 mg clorazepate (median=30, range=4–200), and mean antipsychotic dosage in 11 patients was 3.3 mg haloperidol (median=2, range=1–9). Thirty-nine patients smoked one or more cigarettes a day. Fifty-one patients did not consume alcoholic beverages, 27 patients consumed one to three alcoholic beverages daily, and three patients consumed four beverages daily in the month before the study. Alcohol consumption was thus lower than the five consumptions associated with the risk of depression (Wang and Patten 2001).

2.3 *Assessments*

2.3.1. Psychopathology

Severity of depression was assessed with the MADRS (Montgomery and Asberg 1979, Hartong and Goekoop 1985), and the psychotic and melancholic subtypes of depression with DSM-IV criteria (American Psychiatric Association 1994). Multidimensional psychopathological assessment (performed by RFP de W) was performed using the semi-standardized interview of the Comprehensive Psychopathological Rating Scale (CPRS) Asberg et al. 1978). The CPRS is a widely used scale for the assessment of psychopathological signs and symptoms. The interrater reliability is comparable to that of the Present State Examination (Goekoop et al.1991), and factor analysis in a heterogeneous patient sample has shown that its 65 items can be reduced to five global components of psychopathology, one of which is a bipolar component (Goekoop et al. 1992). The resulting six CPRS dimensions are autonomic dysregulation (anxiety), emotional dysregulation, motivational inhibition (retardation), motivational disinhibition, perceptual disintegration, and behavioral disintegration. Each dimension conformed to the hierarchy of the Rasch model (Goekoop and Zwinderman 1994), which implies that the scores on these dimensions represent different levels of dysregulation. Only the dimensions 'motivational inhibition" (retardation) and "autonomic dysregulation" (anxiety) were used in the present study. All items of the CPRS were rated on a scale from 0 to 6 instead of the customary scale from 0 to 3. The highly anxious-retarded subtype (n =28) was defined by a score of 11 or higher on the dimension "anxiety" and a score of 8 or higher on the dimension "retardation" (De Winter et al. 2003).

2.3.2 Vasopressin and cortisol

Within 7 days of the CPRS interview, blood samples were drawn on a single day under standardized conditions between 09.00 and 9.30 h and between 15.30 and 16.00 h. All patients refrained from ingesting alcohol and from undertaking strenuous physical exercise (sports) for 12 h before the study. They sat down 15 min before venipuncture. Smoking was not allowed for 30 min before venipuncture; eating and drinking were allowed ad libitum. Blood was collected in 10-ml vacutainer tubes and immediately stored at 4 °C. Within 30 min, plasma was separated, in a cooled centrifuge, and stored at -80 °C. Plasma AVP was determined as described previously (Van Londen et al. 1997) by radioimmunoassay (RIA) following peptide extraction using C-8 Bond ElutR cartridges (Analytichem International, USA). The RIA was performed using a rabbit antiserum (coded W1E) with the following cross-reactivities: vasotocin 100%; [Cyt^6]AVP-(3–9) 50%; [$pGlu^4$, Cyt^6]AVP-(4–9) 25%; [Cyt^6]AVP-(5–9) 13%; AVP- (1–8), AVP-(1–7) and oxytocin undetectable. The detection limit of the extracted assay was 0.5 pg/ml plasma, and the intra- and inter-assay coefficients of variation were 9.9% and 15.9%, respectively. Patient and control samples were coded and assayed in a single run. Total plasma cortisol was measured by high-performance liquid chromatography (HPLC) with UV detection as previously described (Van Londen et al. 1997). The detection limit was 0.01 ng/ml, and the intra- and inter-assay coefficients of variation were 2.9% and 5.8%, respectively. For each patient, mean daytime plasma AVP and cortisol levels were computed from the morning and afternoon values. A survey of data from healthy human subjects (Van Londen 2003) has resulted in the estimated upper limit of normal for the plasma AVP level of 5.0 pg/ml. Because of the global nature of this estimation, we used Receiver Operating Characteristic (ROC) parameters to define the nearest plasma AVP level that was optimally related to the highly anxious-retarded subtype, and compared the resulting cut-off level with that found in relation to familial depression. Patients with a mean daytime plasma AVP level lower than this cut-off level were considered to have a normal plasma level of AVP, whereas those with higher or equal levels had an above-normal

level. To account for the potential influence of postmenopausal alteration of plasma AVP, we used the interaction between age ≥ 50 years and gender in multiple logistic regression analysis. For the purpose of parametric analyses, the values of plasma AVP, which were not normally distributed, were transformed into log-transformed values (ln AVP). After this operation, ln AVP values were normally distributed (one-sample Kolmogorow–Smirnov test; Z =1.269, P=0.080).

2.3.3. Family history of depression

As described elsewhere (De Winter et al. 2004), a semi-standardized procedure for taking the family history from first-degree family members was adopted, corresponding to the criteria for Family History Research Diagnostic Criteria (FH-RDC) Depressive Disorder (Andreasen et al. 1986) with a minimal modification according to the DSM-IV criteria. All patients were asked (by RFP de W) whether a depressive disorder fulfilling the criteria had ever occurred in one of the parents, siblings, or children. If the patient (n =4) was uncertain about the presence or absence of symptoms in a family member, a family member, who functioned as dbest informantT for the patient, was asked the same question to avoid false-negative diagnoses. For confirmation of familial depression, at least one firstdegree family member had to fulfill the following criteria (A–D): A1. Evidence of a depressive mood or loss of interest; and A2. Three additional signs or symptoms such as sleep change, appetite or weight change, loss of energy, psychomotor agitation or retardation, guilt or self-reproach, impaired concentration, or suicidal behavior. B. At least one of the following associated with the symptoms in A: 1. Electroconvulsive therapy or antidepressant medication, 2. hospitalization, 3. treated for A1 or A2, 4. gross impairment in work, housework, or school, or social withdrawal, 5. four associated symptoms in A2. C. No evidence of a chronic non-affective deteriorating course (but may have some residual symptoms) other than accounted for by alcoholism. D. Duration at least 2 weeks; this criterion was used for all symptoms described in A. In this way, diagnoses of familial depression were made conservatively. The sensitivity was increased slightly by using a second informant in four cases. To avoid potentially confounding effects of parameters associated with family history (Winokur, 1997), the effects of inpatient or outpatient status, severity of depression, and psychotic features were analyzed in covariate analysis involving family history. 2.4. Statistical analyses All data are given as means Fstandard deviation (S.D.), and P values are two-tailed. Mean daytime plasma AVP (plasma AVP) levels were not normally distributed. Therefore, for correlations and multivariate analyses, plasma AVP levels were log-transformed into ln(AVP). Plasma cortisol values were normally distributed and did not need transformation. Pearson's chi-square test was used to investigate the relation between above-normal plasma AVP and both family history and the highly anxious-retarded subtype. Analysis of variance (ANOVA) was used to investigate the relation between ln(AVP) as dependent variable and family history or anxious-retarded subtype as fixed factor, and multiple logistic regression was used to analyze the relation between above-normal plasma AVP as dependent variable and family history or anxious-retarded subtype as group factor. In these analyses, covariates were used to account for potential effects of factors related to plasma AVP (smoking, sex, age, or interaction between age above 50 years and sex as measure of menopausal status, and oral contraception), familial depression (recurrence, the number of previous episodes, psychotic depression; Winokur, 1997), severity of depression (inpatient versus outpatient status, and MADRS score (only when familial depression was the fixed factor)), and drug treatment (equivalent dosages of benzodiazepines, antidepressants, and antipsychotics). Spearman's correlation coefficient was used to analyze the correlation between anxiety and retardation. Fisher's Z-transformation was used to test whether the correlations found in two patient groups differed significantly.

Correlations between ln(AVP) and plasma cortisol level were analyzed with Pearson's correlation coefficient. Cohen's kappa was used to assess the degree of overlap between depression with above-normal plasma AVP levels and the highly anxious-retarded subtype of depression. Partial correlations were used to control for effects of age, smoking, and the highly anxiousretarded subtype, and Fisher's Z to test whether the correlations between ln (AVP) and cortisol levels in two patient groups differed significantly. All calculations were carried out using SPSS 9.0 (SPSS Inc. Chicago).

3 Results

3.1 Plasma AVP levels and optimal cut-off level

3.1.1 Plasma AVP and relation to drug treatment

Table 1 shows mean plasma AVP concentrations of healthy control subjects and depressed patients, as well as mean plasma AVP concentrations in subgroups of patients on antidepressant, benzodiazepine or antipsychotic treatment, and their combinations. These data do not support an effect of one type of drug nor any combination of drug on mean plasma AVP. Correlational analyses showed a positive correlation between antipsychotic dosage and ln (AVP) in the group of patients being treated with these drugs (Pearson's r =0.738, n =11, P=.009).

3.1.2 Definition of cut-off value for above-normal plasma AVP

ROC parameters showed that AVP levels ≥ 5.56 pg/ ml were optimally related to the highly anxious-retarded subtype, the anxious-retarded subtype having a sensitivity of 32% and a specificity of 87% for high AVP. By this criterion, 16 of the 81 patients (20%) had above-normal plasma AVP levels, and 65 patients had normal plasma AVP levels. An independent ROC analysis relating plasma AVP to family history of depression showed that the same cut-off level (≥ 5.56 pg/ml) could be used for the relation with family history, family history having a sensitivity of 29% and specificity of 90% for high AVP. Therefore we used plasma AVP ≥ 5.56 pg/ml as the general cut-off level for above-normal plasma AVP in the present study.

3.2 Relation between depression with above-normal plasma AVP and family history of depression

Twelve of the 16 patients with above-normal AVP, and 29 of the 65 patients with normal AVP had familial depression (see Table 2, Pearson's χ^2 = 4.742, df =1, P=0.029). Positive and negative predictive values of above normal plasma AVP for familial depression were 75% and 55%, respectively. ANOVA showed a statistically non-significant relation between ln(AVP) as dependent variable and family history as group factor (F =3.666; df =1, 79; P=0.059). If covariate effects of age, sex, outpatient or inpatient status, recurrence, number of previous episodes, MADRS score, psychotic features, number of cigarettes, and dosages of antipsychotics, antidepressants and benzodiazepines were accounted for, then a nonsignificant relation was found between ln(AVP) and antipsychotic dosage (F =3.491; df =1, 68; P=0.066) as well as MADRS score (F =3.796; df =1,68; P=0.055), while the strength of the relation with family history was reduced (F =2.318; df =1, 68; P=0.133). If the 11 patients on antipsychotic treatment were excluded, then ln(AVP) significantly depended on MADRS score (F =5.254; df =1, 58; P=0.026) and number of cigarettes smoked (F =3.654; df =1, 58; P=0.061), while the strength of the relation with family history remained the same (F =2.657; df =1, 58; P=0.109). Logistic regression confirmed that above-normal plasma AVP as dependent variable was related to family history (Wald=4.3701, df =1, P=0.037), and multiple logistic regression showed that from the added covariates (age, sex, outpatient or inpatient status, recurrence, number of previous episodes, MADRS score, psychotic features, number of cigarettes, and dosages of antipsychotics, antidepressants and benzodiazepines), both family history (Wald=4.593, df =1, P=0.032) and antipsychotic dosage (Wald=3.827, df =1, P=0.050) were related to above-normal plasma AVP. A separate analysis using age above 50 years (instead of age) and the interaction of age above 50 years and sex, showed no effect of these parameters. The relation with antipsychotic dosage did not influence that with family history of depression. If the 11 patients on antipsychotic treatment were excluded, then above-normal plasma AVP appeared to depend a little more on family history (Wald=5.752, df =1, P=0.016).

Table 1
Mean plasma AVP concentration (pg/ml) and standard deviation (S.D.) in healthy controls and depressed patients, as well as depressed patients on antidepressant (AD), benzodiazepine (BENZ) or antipsychotic (AP) treatment, and their combinations (+=on drug; -= not on drug).

	n	Plasma AVP	(SD)
controls	17	3.17	(1.97)
all depressed patients	81	4.25	(4.58)
AD	47	4.10	(3.96)
BENZ	47	4.49	(5.54)
AP	11	4.48	(3.70)
+ AD + BENZ + AP	6	3.38	(1.45)
+ AD + BENZ - AP	24	4.48	(5.18)
+ AD - BENZ + AP	3	3.97	(2.65)
+ AD - BENZ - AP	14	3.76	(2.35)
- AD + BENZ + AP	2	8.53	(8.49)
- AD + BENZ - AP	15	4.41	(6.94)
- AD - BENZ - AP	17	4.04	(3.30)

Table 2
Number of patients with a positive or negative family history of depression and with above-normal or normal plasma AVP.

	Above-Normal AVP	Normal AVP	Total
Positive family history	12	29	41
Negative family history	4	36	40
	16	65	81

3.2.1 Conclusion

The data confirmed the first hypothesis that elevated plasma AVP is related to family history of depression, and also confirmed part of the second hypothesis by showing that above-normal plasma AVP is a better parameter than ln(AVP) as a continuous variable to establish this relationship.

3.3 Relations between depression with above-normal AVP, as well as familial depression with above-normal AVP, and two anxious-retarded phenotypes

3.3.1 Depression with above-normal AVP and the highly anxious-retarded subtype

Nine of the 16 patients with above-normal AVP (≥ 5.56 pg /ml), and 19 of the 65 patients with normal AVP had the highly anxious-retarded phenotype (Pearson's χ^2 =4.144, df =1, =0.042). Positive and negative predictive values of above-normal plasma AVP for the highly anxious-retarded subtype were 56% and 71%, respectively. ANOVA showed that the relation between ln(AVP) as dependent variable and the highly anxious-retarded subtype as group factor just failed to reach statistical significance (F =3.892; df =1, 79; P=0.052). If covariate effects of age, sex, outpatient or inpatient status, recurrence, number of previous episodes, psychotic features, number of cigarettes, and dosages of antipsychotics, antidepressants and benzodiazepines were accounted for, then a non-significant relation was found between. ln (AVP) and antipsychotic dosage (F =3.361; df =1, 69; P=0.071), while the strength of the relation with the anxious-retarded subtype was reduced (F =3.122; df =1, 69; P=0.082). If the 11 patients on antipsychotic treatment were excluded, then ln(AVP) was nonsignificantly related to the highly anxious-retarded subtype (F =3.033; df=1, 68; P=0.086). Addition of the covariates showed a further reduction of the relation with the anxious-retarded subtype (F =2.289; df =1, 59; P=0.136). Logistic regression showed that above-normal plasma AVP was related to the highly anxiousretarded subtype (Wald=3.927, df =1, P=0.048). Multiple logistic regression showed that from the added covariates (age, sex, outpatient or inpatient status, recurrence, number of previous episodes, psychotic features, number of cigarettes, and dosages of antipsychotics, antidepressants and benzodiazepines), antipsychotic dosage related non-significantly to above-normal plasma AVP (Wald= 3.380, df =1, P=0.066), and that as a consequence the relation between above-normal plasma AVP and the anxious-retarded subtype lost its statistical significance (Wald=3.548, df =1, P=0.060). A separate analysis using age above 50 (instead of age) and the interaction of age above 50 years and sex showed no effect of these parameters. Also after exclusion of the 11 patients on antipsychotic treatment, only a non-significant relation with the anxious-retarded subtype remained (Wald=3.188, df =1, P=0.074).

3.3.1 Conclusion

The data further confirmed our second hypothesis. Above-normal plasma AVP had a stronger relation with the highly anxiousretarded phenotype than the continuous variable ln(AVP) had. However, this relation between above-normal plasma AVP and the highly anxiousretarded subtype lost statistical significance after correction for the effect of antipsychotic treatment.

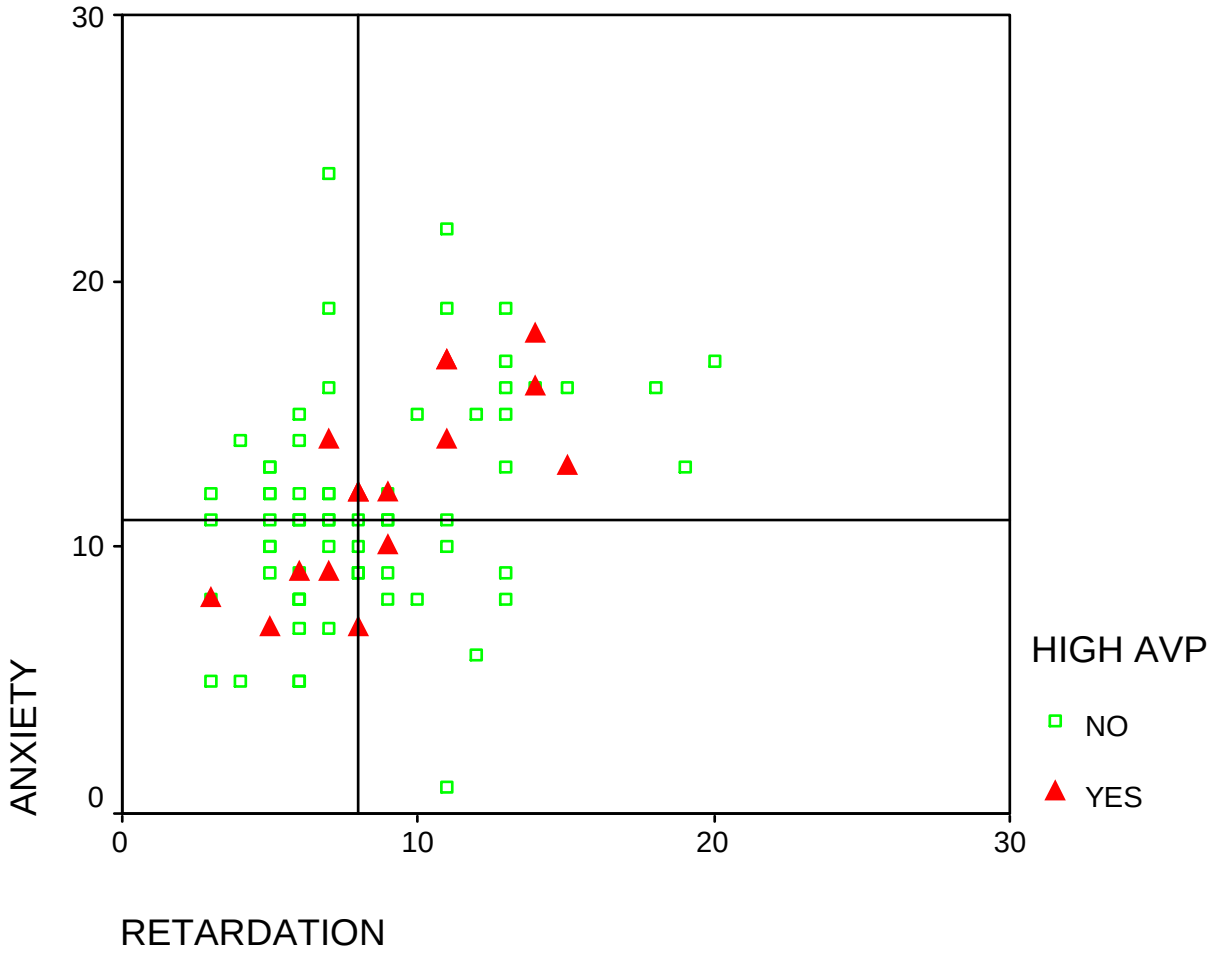
3.3.2 Depression with above-normal AVP and the correlation between anxiety and retardation

The correlation between anxiety and retardation in the 81 depressed patients was 0.43 (P ≤ 0.001). In the subcategory of depression with above-normal AVP levels (≥5.56 pg/ml), this correlation between anxiety and retardation was 0.768 (n =16, P=0.001). This value differed significantly from that in the subcategory of depression with normal AVP (r =

0.341, n =65, P=0.005) (Fisher's Z =2.16, P=0.03). **Figure. 1** shows a scatterplot for these patients with abovenormal AVP within the two-dimensional structure defined by anxiety and retardation. If the 11 patients with antipsychotic treatment were excluded, then the correlation between anxiety and retardation in patients with above-normal plasma AVP was 0.859 (n =13, P ≤ 0.001), and that in patients with normal plasma AVP was 0.367 (n =57, P=0.005).
Fisher's Z was 2.63 (P=0.01). Finally, in the group of patients with familial depression and above-normal plasma AVP, the correlation between anxiety and retardation was 0.841 (n =12, P ≤ 0.001), and in the group of all other patients, the correlation was 0.377 (n =69, P ≤ 0.001). This difference was also statistically significant (Fisher's Z =2.33, P=0.02).

3.3.4 Conclusion.
Depression with above-normal plasma AVP, and familial depression with above-normal plasma AVP, had a high correlation with anxiety and retardation, and these correlations were significantly higher than those in their respective patient control groups. Combined with the negative finding of the previous section, this finding confirms our third hypothesis: The anxious-retarded phenotype of depression with above-normal plasma AVP is better defined by the correlation between anxiety and retardation than by the combination of high scores for both dimensions.

Figure 1
Scatterplot of 81 depressed patients within the two-dimensional structure based on anxiety and retardation scores. The right-upper quadrant defines the highly anxious-retarded subtype. High AVP means plasma AVP ≥ 5.56 pg/ml.



3.4 Depression with above-normal AVP, as well as familial depression with above-normal AVP, and the correlation between plasma AVP and cortisol

In this study 15 patients on oral contraception were excluded. Patients with above-normal plasma AVP (n =14) and those with normal AVP (n =52) did not differ on mean plasma cortisol concentration (164.10 ± 56.65 vs. 141.36 ± 36.25 ng/ml, respectively; Student's t test: P=0.16). The correlation between plasma ln(AVP) and plasma cortisol in the whole sample of patients was 0.37 (P=0.002). In the subcategory of depression with above-normal plasma AVP levels, this correlation was 0.56 (n =14, P=0.036), and in the subgroup with normal AVP levels, it was 0.181 (n =52, P=0.199). After controlling for age and smoking habit, the correlation between ln(AVP) and cortisol in the subcategory depression with above-normal plasma AVP was 0.55 (n =11, P=0.050) and 0.48 (n =11, P=0.096), respectively. If both variables were controlled for, the correlation was 0.46 (n =10, P=0.129). (The reduction of the n in these analyses is related to the number of effects controlled for.) These variables had no effect in the subcategory depression with normal plasma AVP levels.

Nine of the 14 patients with a plasma AVP level higher than 5.56 pg/ml fulfilled the criteria for the highly anxious-retarded subtype (Cohen's kappa= 0.211, P=0.042). Partial correlation correcting for the effect of this overlap showed that it did not influence the correlation between plasma AVP and cortisol levels in depression with above-normal plasma AVP levels (r =0.55, n =11, P=0.05). Analogously, above-normal plasma AVP did not influence the correlation between ln (AVP) and plasma cortisol in patients with the highly anxious-retarded subtype (Pearson's r =0.61, n =25, P=0.001 in the absence of a correction, and r =0.61; n =22; P= 0.002 in partial correlation correcting for abovenormal plasma AVP). In the subcategory familial depression with above-normal plasma AVP levels (≥ 5.56 pg/ml), the correlation between plasma ln(AVP) and cortisol levels was 0.61 (n =12, P=0.037); in the group of all other patients, it was r = 0.21 (n =54, P=0.120). The difference between these correlation coefficients was not statistically significant (z =1.37, P=0.17). Partial correlation controlling for the potential effect of anxious-retarded depression did not influence the correlation between plasma ln(AVP) and plasma cortisol level in the subgroup with familial depression and above-normal plasma AVP levels (r =0.60, n =9, P=0.049).

3.4.1 Conclusion

The two biologically defined subcategories of depression, namely depression with above-normal plasma AVP and familial depression with above-normal AVP, both had a significant correlation between plasma AVP and cortisol, corresponding with vasopressinergic activation of the HPA axis. The small effects of age and smoking did not explain the difference with patients with normal AVP levels, but reduced the statistical significance. The highly anxious-retarded subtype did not influence the correlation between ln(AVP) and cortisol; neither did above-normal plasma AVP influence that correlation in patients with the highly anxious-retarded subtype.

4 Discussion

Above-normal plasma AVP appeared to be a useful parameter for the development of a subcategory of depression based on interrelations between plasma AVP, family history and an anxious-retarded phenotype. ROC analyses searching for optimal sensitivity–specificity relations with the highly anxious retarded subtype and family history of depression showed that a value of 5.56 pg/ml plasma AVP could be used to define dabove-normal plasma AVPT. In support of our first hypothesis, this above normal plasma AVP was more significantly related to family history of depression. Corresponding with our second hypothesis, above-normal plasma AVP was more strongly related to family history and the highly anxious-retarded subtype than the continuous variable ln(AVP) was. Though depression with above normal plasma AVP was not significantly related to the highly anxious-retarded phenotype if antipsychotic dosage was used as a covariate, the correlation between anxiety and retardation appeared to be higher in depression with above-normal plasma AVP than in all other depressed patients, even after correction for the potential effect of antipsychotic dosage. This confirmed the third hypothesis, that a phenotypic description of mixed anxiety and retardation without a threshold for intensity would be more appropriate than the highly anxious-retarded subtype, which is defined by the combination of above median scores for both anxiety and retardation. In addition, depression with above-normal AVP had a statistically significant correlation between. ln (AVP) and cortisol, in the same range as previously found in the highly anxious-retarded subtype (De Winter et al. 2003). As in the highly anxious-retarded subtype, this correlation did not differ significantly from the control group of all other patients. Nonetheless, the correlation between ln(AVP) and cortisol in patients with above-normal AVP supports the view that the increased plasma AVP levels reflect vasopressinergic activation of the HPA axis.

Finally, the subgroup of patients with familial depression and above-normal AVP was characterized by both a significantly higher correlation between anxiety and retardation than was found in its patient control group, and a significant correlation between ln(AVP) and cortisol. These findings support the existence of a subcategory of depression validated by triple interrelations between family history, above-normal plasma AVP, and a variable anxious retarded phenotype, involving enhanced vasopressinergic activation of the HPA axis.

As far as we know, this is the first study using a mixture of basic dimensions of psychopathology operationally defined by the correlation between these dimensions. The results support Jaspers' theory of clinical pictures as mixtures of basal symptom dimensions (Jaspers 1953). The reason dichotomized plasma AVP levels proved more useful than plasma AVP as a continuous parameter is probably that osmoregulatory AVP and depression-related AVP have different origins, and that measures of plasma AVP within the normal range will be a mixture of both, while in the above-normal range variations of plasma AVP will be less influenced by osmotic admixture. The non-significance of the relation between ln (AVP) and the highly anxious-retarded subtype in the present sample of 81 patients differs from the statistical significance previously found in the subsample of the 66 patients, which had resulted from the exclusion of all patients on oral contraception from the 81 patients (De Winter et al. 2003). This difference will be due to a low percentage of patients on oral contraception having the highly anxious-retarded subtype, while they all had nearly the same mean value of ln(AVP). Since the cortisol response in the dexamethasone- CRH test is increased in non-depressed family members of patients with major depression (Holsboer et al. 1995), the present findings suggest that this may be due to increased AVP release reducing the dexamethasone-induced blockade of the HPA axis. Further investigations are needed to determine

whether one of the two subcategories of familial depression (Winokur 1997) is specific to above-normal plasma AVP and a high correlation between anxiety and retardation. Further study is warranted to unravel the genetic and stress-related mechanisms involved in the correlation between plasma levels of AVP and cortisol, particularly in depression with above-normal plasma AVP and the highly anxious-retarded subtype with normal AVP levels, respectively. At the phenotypic level, the subcategory with above-normal plasma AVP shows overlap with the highly anxious-retarded subtype, previously derived from DSM-IV melancholia, in the high range of the mixture of anxiety and retardation. The fact that the correlation between ln(AVP) and cortisol in both groups was not influenced by this overlap suggests that a different mechanism than increased AVP release may be operative in the highly anxiousretarded subtype with normal plasma AVP. A recent finding suggests that this mechanism could be increased vasopressin-receptor responsivity (Dinan et al. 2004). Future studies will be necessary to replicate the present findings in an independent patient sample.

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7

Reduced cooperativeness and reward-dependence in depression with above-normal plasma vasopressin concentration.

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Abstract

The neuropeptide vasopressin is centrally involved in the regulation of social behaviour and response to stress. We previously found support for a subcategory of depression defined by above-normal plasma vasopressin (AVP) concentration. This subcategory is validated by a positive family history of depression and correlating plasma AVP and cortisol concentrations. The data support the validity of above-normal plasma AVP concentration as a genetically determined biological marker for a subcategory of depression. The aim of the present study was to test whether above-normal plasma AVP concentration in depression is related to personality characteristics reflecting a specific social behaviour style.

The data of 78 patients from a previously investigated sample were reanalysed. Fifty-eight patients were available after 2 years, 15 of whom with initially above-normal plasma AVP. The dimensions of the Temperament and Character Inventory (TCI) were scored, with particular focus on the dimensions of Cooperativeness (CO) and Reward-dependence (RD). Normative subjects and other depressed subjects were used as controls. After full remission, patients with initially above-normal AVP had low CO compared with normal and patient controls. During depression, these patients had both low CO and low RD compared with normal controls and low RD compared with patient controls. Low CO is a presumably premorbid trait and reduced RD a state-dependent characteristic in depression with above-normal plasma AVP. The low CO further supports the validity of above-normal plasma AVP concentration as a genetically determined biological marker for a subcategory of depression.

Keywords: Depression, personality, dimensions, socialization, vasopressin

1 Introduction

This study is a part of a series of investigations, in the same patient sample that aims to detect biological markers of diagnostic subclasses of depression with higher validity than the current subclasses of the Diagnostic and Statistical Manual IV (DSM-IV; American Psychiatric Association, 1994). We assumed that higher validity of depressive subcategories could be achieved by multi-dimensional description of clinical pictures using global dimensions of psychopathology (Goekoop et al. 1992), relations with a positive family history of depression, and multi-dimensionally defined personality profiles using the dimensions of the Temperament and Character Inventory (TCI) (Cloninger et al. 1993).

Because depression is conceived as a disorder of the response to stress and vasopressin (AVP) plays a major role in the response to severe stress conditions (Antoni 1993), the biological markers of depressive subcategories were sought at the level of vasopressinergic activation of the hypothalamus–pituitary–adrenal (HPA)-axis. Because AVP is also centrally involved in the regulation of social behaviour (Young 2002), genetically deficient vasopressinergic mechanisms could play a role in both the premorbid personality and the pathophysiology of subcategories of depressive disorders.

At the vasopressinergic level of analysis, we used the following parameters: a high correlation between plasma AVP and cortisol concentrations, which could be a parameter of increased responsivity of the pituitary vasopressin-1b (V1b) receptor, as it has been found after severe stress (Volpi et al.2004), and above-normal plasma AVP concentration, which, because of its relation with familial depression (Goekoop et al. 2006), could be a parameter of genetically increased AVP synthesis and/or release, as it has been found in highlyanxious inbred rats (Murgatroyd et al. 2004).

Up to now, we found support for two better-validated subcategories of depression than the melancholic subtype according to the DSM-IV: a highly anxious-retarded subcategory (De Winter et al. 2004) and a subcategory defined by above-normal plasma AVP concentration (Goekoop et al. 2006). Both subcategories showed a correlation between plasma AVP and cortisol (De Winter et al. 2003, Goekoop et al. 2006). The highly anxious-retarded subcategory was further related to melancholia (De Winter et al. 2004) and was characterized by poor long-term outcome (De Winter et al. 2006), familial depression (De Winter et al. 2004) and a low score on the dimension of self-directedness (SD) of the TCI after full remission (De Winter et al. 2007). The second subcategory, depression with above-normal plasma AVP, was defined by the optimal cut-off level of the plasma AVP concentration for familial depression, and the clinical picture of this subcategory was characterised by correlating anxiety and retardation scores (Goekoop et al. 2006).

In this study, we tested whether the patients with depression with above-normal plasma AVP concentration are characterized by a personality dimension of the TCI representing a specific style of social behaviour. The TCI comprises three character dimensions, self-directedness (SD), cooperativeness (CO) and self-transcendence (ST), as well as four temperament dimensions, harm-avoidance (HA), novelty seeking (NS), reward-dependence (RD) and persistence (PER) (Cloninger et al. 1993). The dimensions of CO and RD represent selfreported styles of social behaviour. The subscales of the CO dimension assess 'social acceptance' versus 'intolerance', 'empathy' versus 'social disinterest', 'helpfulness' versus 'unhelpfulness', 'compassion' versus 'revengefulness' and 'pure-heartedness' versus 'self-serving'. The subscales of the RD dimension assess 'sentimentality' versus 'insensitivity', 'attachment' versus 'detachment' and

'dependence' versus 'independence'. Examples of items of these scales are: 'I can usually accept other people as they are, even if they are very different from me' or 'I like to help find a solution to problems so that everyone comes out ahead' and 'I would like to have warm and close friends with me most of the time' or 'If I am feeling upset I usually feel better around friends than when left alone'. A substantial contribution of genetic factors has been found in both dimensions (Ando et al. 2002, Ando et al. 2004, Gillespie et al. 2003). Although the dimension of HA has been found to predict general social adaptation in dyadic interaction (Tse et al. 2005), this dimension was hypothesized not to contribute to the validation of the subcategory of depression with above-normal plasma AVP as it represents the general vulnerability trait for all depressive disorders (De Winter et al. 2007).

Similar to our previous study of the relation between a subcategory of depression and TCI scores (De Winter et al. 2007), we were primarily interested in the TCI scores after full remission of depression. This method maximally eliminates state-dependent report bias and therefore offers an optimal estimation of the presumed premorbid personality. In addition, we searched for evidence of state-dependent reversible changes on the CO and RD dimensions during the transition from the depressed state to the condition of full remission.

2 Methods and materials

2.1 Subjects

We reanalysed the data of a subsample of the 89 patients investigated in a previous analysis (De Winter et al. 2004). All patients were newly referred to an in- and out-patient's clinic of Rivierduinen GGZ Leiden. They were recruited if a psychiatrist had made an initial diagnosis of major depression according to the DSM-IV, and if this diagnosis was subsequently confirmed by the investigator (RFP de W) using a semi-standardised interview. This among others comprised the DSM-IV criteria for major depression (American Psychiatric Association 1994), subtypes of major depression, and the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al. 1978, Goekoop et al. 1992). Patients were included if they in addition rated at least 21 on the Montgomery Åsberg Depression Rating scale (MADRS) (Montgomery and Åsberg 1979), and consented to the protocol. Patients with organic disorder and patients with bipolar, schizoaffective or schizophrenic or other primary psychotic disorder were excluded, as were patients with a somatic disorder that could influence plasma AVP concentration, such as inappropriate anti-diuretic hormone (ADH) 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.

In all, 86 of the 89 patients had full TCI data, 81 full AVP data and 78 full TCI and AVP data. These 78 patients were investigated in the first cross-sectional analysis of the present study. The first 70 of them were recruited for a 2-year longitudinal study (De Winter et al. 2006), and 58 patients were eventually available for cross-sectional evaluation after two years of follow-up. Written informed consent was obtained from all patients. The Ethical Committee of Leiden University Medical Centre (LUMC) approved the study protocol. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Educational level was classified in six categories (level 1 = low education to level 6 = University or postgraduate).

Normal control subjects (n = 86) were selected from a normative sample (Duijsens et al. 2000), which was at random recruited from the national telephone book as described in the study of the relation between the highly anxious-retarded depressive subcategory and personality (De Winter et al. 2007). For reason of comparability, the number of control subjects was kept the same as in that study.

2.2 *Personality*

The Dutch translation (Duijsens et al. 2000) of Cloninger's Temperament and Character Inventory (Cloninger et al. 1993) was used to assess the temperament dimensions of novelty seeking (NS), harm-avoidance (HA), reward-dependence (RD) and persistence (PER), and the character dimensions of self-directedness (SD), cooperativeness (CO) and selftranscendence (ST). The lists were filled in within 2 weeks after recruitment and every 6 months until 2-years after recruitment. Patients were asked to respond to the items 'as if they were in their premorbid state', to maximally reduce statedependent changes of response tendency.

2.3 *Treatment*

The therapy comprised pharmacotherapy or cognitive behavioural therapy in mild cases and both in more severe depression. If necessary, relational therapy, daytime treatment or clinical treatment was added. If at entrance a patient was already taking an antidepressant, that treatment was continued and increased to maximal dose. If this drug had to be changed because of lack of effect, drug withdrawal was performed after the first assessment of the study. The steps after the initial antidepressant comprised: 1) venlafaxine, 2) amitriptylin, 3) amitriptylin and lithium, 4) lithium and tranylcypromine and 5) electroconvulsive therapy.

To account for potential drug effects on plasma AVP and the cut-off level in particular, antipsychotic, antidepressant and benzodiazepine drug dosages at t1 were used as covariates in the analyses. To this end, they were transformed into equivalent dosages (haloperidol, imipramine and chlordiazepoxide equivalents) according to standard dosage ranges (Moleman and Birkenhaeger 1998).

2.4 *Plasma AVP*

As described before (De Winter et al. 2003), within 7 days of the CPRS interview, blood samples were drawn on a single day under standardised conditions between 09.00 a.m. and 9.30 a.m. and between 3.30 p.m. and 4.00 p.m. All patients refrained from ingesting alcohol and from undertaking strenuous physical exercise (sports) for 12 h before the study. They sat down 15 min before venipuncture. Smoking was not allowed for 30 min before venipuncture; eating and drinking were allowed ad libitum.

Blood was collected in 10-mL vacutainer tubes and immediately stored at 4 °C. Within 30 min, plasma was separated in a cooled centrifuge and stored at −80 °C. The determination of plasma AVP was based on radioimmunoassay (RIA) following peptide extraction using C-8 Bond ElutR cartridges (Analytichem International, Harbor City, CA, USA RIA was performed using a rabbit antiserum (coded W1E) with the following cross-reactivities: vasotocin 100%; (Cyt6)AVP-(3–9) 50%; (pGlu4, Cyt6)AVP-(4–9) 25%; (Cyt6)AVP-(5–9) 13%; AVP-(1–8), AVP-(1–7) and oxytocin undetectable. The detection limit of the extracted assay was 0.5 pg/mL plasma, and the intra-and inter-assay coefficients of variation were 9.9% and 15.9%, respectively. Patient and control samples were coded and assayed in a single run. For each patient, mean daytime plasma AVP level (plasma AVP) was computed from the morning and afternoon values. Above-normal plasma AVP was defined as any value >5.56 pg/mL corresponding with the ROC analysis relating familial depression to above-normal plasma AVP (Goekoop et al. 2006).

2.5 *Follow-up and outcome*

All patients were assessed with the CPRS at the beginning of the treatment (t1), after 6 weeks (t2) and than after 3, 6, 12, 18 and 24 months (t3–t7) as described before (De Winter et al. 2006, De Winter et al. 2007). TCI data were available for t1,t4, t5, t6 and t7. Intensity of depression was described by means of the MADRS. Outcome was defined as DSM-IV depression in full remission, defined by a maximum of two DSM-IV symptoms during at least the last 2 weeks (Frank et al. 1991). Partial remission was defined by a minimum of three and a maximum of four symptoms of major depression during at least the last 2 weeks. DSM-IV criteria were defined by corresponding CPRS items. For this purpose, the scores on the individual items were dichotomised: scores ≥ 3 were taken as representing the presence of a DSM-IV symptom. Increased appetite and weight were rated separately.

2.6 *Data analysis*

The analyses were identical to those of our previous TCI study (De Winter et al. 2007). We used only gender and age as covariates in analyses comparing depressed patients with normal controls, and in addition, recurrent depression, MADRS score and educational level in investigations comparing subgroups of depressed patients. As in a previous analysis of this sample, antipsychotic dosage at t1 was, after elimination of other treatment variables, eventually used, in addition, in analyses comparing depressed subgroups.

Pearson's chi-square was used to analyse the relation between subcategories of depression. MANCOVA using TCI scores as dependent variables and above-normal plasma AVP as independent variable was used to compare subcategories of depressed patients with normal controls and to compare subgroups of depressed patients at t1 and t7. Separate comparisons were used to detect the direction of differences found. Doubly multivariate analysis was used to test TCI differences over 2 years between depression with above-normal AVP and depression with normal AVP. These analyses were all carried out by SPSS for Windows 12.0 (SPSS Inc, Chicago, USA).

3 Results

3.1 Demographic and clinical data

Table 1 shows demographic characteristics of the 78 depressed patients. No statistically significant differences were found between the patients with above-normal and those with normal plasma AVP concentration. These 78 patients at t1 did not differ in these respects from the 70 patients at t1 who consented to participate in the follow-up study. The characteristics of these 70 patients have been described elsewhere (De Winter et al. 2006). In all, 16 of the 78 patients had above-normal plasma AVP at t1. Of the 70 patients who entered the follow-up study, 15 patients had above-normal plasma AVP at t1. They were the same 15 patients with initially above-normal AVP who could be evaluated after 2 years.

Table 2 shows the percentage of the patients who had antipsychotic, antidepressant and anxiolytic treatments, as well as the dosages of these treatments at t1. No significant differences were found between the subgroups with normal and above-normal plasma AVP concentration. Mean MADRS score at t1 was 30 (range: 21–47). Mean MADRS of depression with above-normal AVP was 33 (range 23–41).

Table 1
Demographic data of acutely depressed patients and the subgroups with above-normal and normal plasma vasopressin (AVP).

	Major Depression	Above-normal AVP	Normal AVP
	n = 78	n = 16	n = 62
age	39 (sd =12)	41 (sd = 12)	39 (sd = 11)
female	52 (67%)	10 (63%)	42 (68%)
educational level	3.4 (sd = 1.5)	3.4 (sd = 1.6)	3.4 (sd = 1.5)
inpatients	32 (41%)	6 (38%)	26 (42%)
recurrent depression	45 (58%)	10 (63%)	35 (57%)
MADRS t1	30 (sd = 6)	33 (sd = 7)	30 (sd = 6)

(Age in years (y); theoretical range for level of education: 1-6; MADRS = depression severity rating scale; sd = standard deviation).

Table 2
Number and percentages of patients with psychotropic drug treatment, as well as mean haloperidol, imipramine and chlordiazepoxide equivalent dosages and standard deviations (sd) in acutely depressed patients and subgroups with above-normal and normal plasma vasopressin (AVP).

	Major Depression	Above-normal AVP	Normal AVP
Antipsychotic treatment	11 (14%)	3 (19%)	8 (13%)
Haloperidol equivalents	0.5 (sd = 1.5)	1.2 (sd = 2.9)	0.3 (sd = 0.8)
Antidepressant treatment	45 (58%)	9 (56%)	36 (58%)
Imipramine equivalents	90.5 (sd = 101.7)	81.3 (sd = 101.8)	93.0 (sd = 102.3)
Anxiolytic treatment	41 (53%)	8 (50%)	33 (53%)
Chlordiazepoxide equivalents	20.8 (sd = 32.8)	13.6 (sd = 18.7)	22.6 (sd = 35.4)

3.2 *Treatment data*

At t1, 9 of the 16 patients with above-normal plasma AVP had an antidepressant drug and 36 of the 62 patients with normal plasma AVP. At t1, four patients with above-normal AVP had selective serotonin reuptake inhibitor (SSRI) treatment, three venlafaxine and two a tricyclic antidepressant (TCA). At t3, no patient had SSRI treatment (chi-square 4.521; P = 0.033) compared with 12 of the 49 patients with normal AVP), 7 had venlafaxine and 1 had a TCA. This shift towards venlafaxine may have been related with insufficient change of the high MADRS score at t1 of the patients on SSRI treatment (mean MADRS = 41 range: 40–41). The data suggest insufficient SSRI response in depression with above-normal plasma AVP.

3.3 *TCI scores in depression with above-normal plasma AVP at t1*

MANCOVA at t1, during the acute episode, showed that all depressed patients (n = 78) differed from matched controls on HA (F = 92.755; P < 0.001) and SD (F = 76.625; P < 0.001) and less strongly on RD (F = 5.885; P = 0.016) and CO (F = 5.118; P = 0.025). Covariates used were gender and age. Patients with above-normal AVP (n = 16) differed significantly from matched control subjects on HA (F = 23.956; P < 0.001), SD (F = 21.166; <0.001), RD (F = 8.466; P = 0.004) and CO (F = 8.052; P = 0.006) and rather weakly on NS (F = 4.354; P = 0.040).

The acutely depressed patients with above-normal plasma AVP (n = 16) differed also from all other depressed patients (n = 62) on RD (F = 5.183; P = 0.031) but not significantly on CO (F = 2.615; P = 0.110) if relations with age, gender, level of education, recurrent depression and MADRS score were accounted for. Separate logistic regression analyses showed that antidepressant and benzodiazepine dosages were not related with above-normal plasma AVP. However, antipsychotic dosage was non-significantly related (Wald = 3.226; P = 0.072) with above-normal AVP. If this variable was added to the MANCOVA as covariate, then the strength of the relation with RD increased slightly (F = 6.330; P = 0.014), whereas the relation with CO became slightly weaker (F = 2.050; P = 0.157). Separate comparison showed both RD and CO to be lower in depression with above-normal AVP than in the group of all other depressed patients (RD = 12.81 (SD = 4.32) versus RD = 15.13 (SD = 3.70) and CO = 29.19 (SD = 5.59) versus CO = 32.00 (SD = 6.13)). Separate analyses of the correlation between RD and CO at t1 and plasma AVP concentration at t1 showed that there was no such correlation in the whole group of depressed patients or in depression with above-normal plasma AVP.

3.4 *TCI scores in fully remitted patients with initially above-normal plasma AVP after 2 years (t7)*

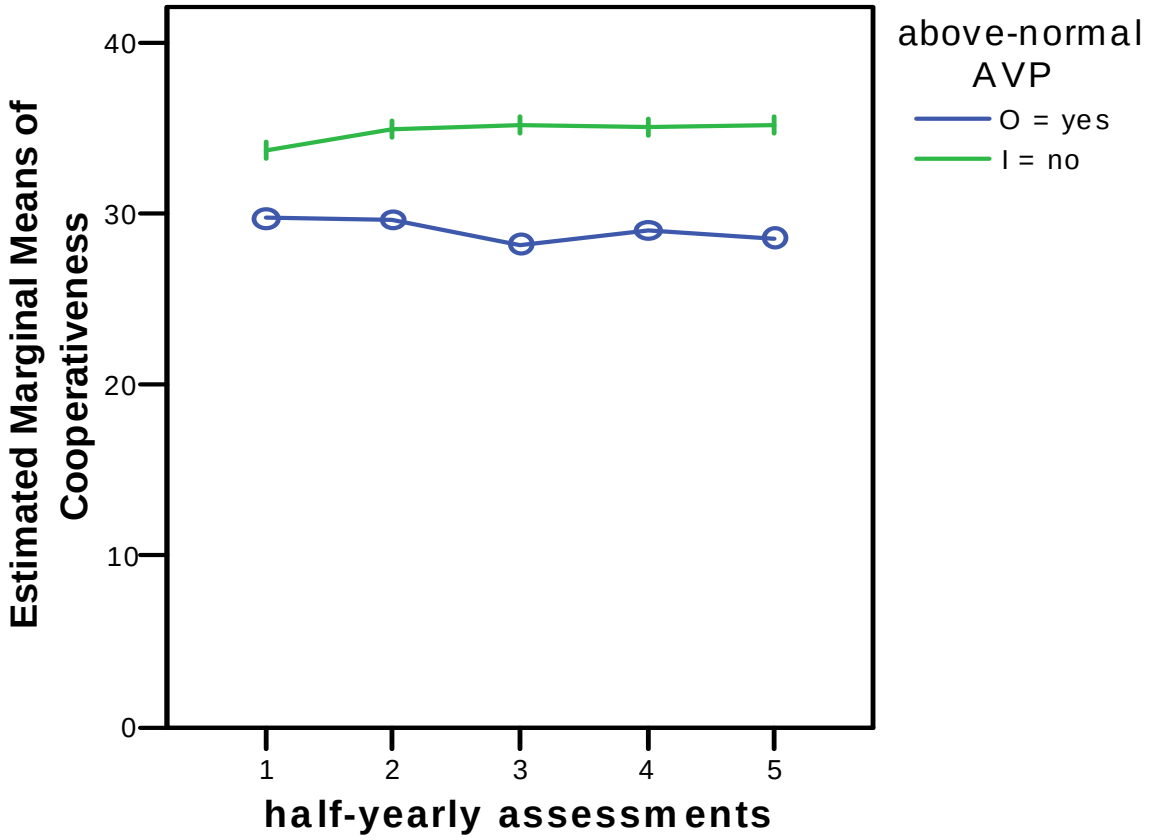
MANCOVA showed that fully remitted patients at t7 (n = 41) had only significantly higher HA compared with control subjects (MANCOVA: F = 19.94, df = 1 and P < 0.001; De Winter et al. 2007). MANCOVA also showed that after 2 years, fully remitted patients with initially above-normal plasma AVP (n = 11) had different CO (F = 9.357; P = 0.003) and HA (F = 4.387; P = 0.039) compared with control subjects, corrected for a significant effect of gender on HA (F = 18.286; P < 0.001) and RD (F = 4.129; P = 0.045) and a significant effect of age on CO (F = 9.357; P = 0.003) and HA (F = 4.387; P = 0.039). Separate comparison showed a lower CO (CO = 28.45; SD = 3.36 versus CO = 33.30; SD = 5.18) and a higher HA (HA = 20.45; SD = 8.52 versus HA = 15.38; SD = 7.13) in depression with above-normal AVP.

Compared with fully remitted patients with normal AVP at t7 (n = 30), fully remitted patients with initially above-normal plasma AVP (n = 11) differed on CO (F = 9.116; P = 0.005) and HA (F = 4.559; P = 0.040) (the effects of age, gender, level of education, recurrent depression and MADRS at t7 score being accounted for). MADRS score at t7 and recurrent depression were not related with CO at t7. Separate comparison showed that CO and HA were lower in remitted depression with above-normal AVP than in the

group of all other remitted patients (CO = 28.45 (SD = 3.36) versus CO = 34.53(SD = 54.89), and HA = 20.45 (SD = 8.52) versus HA = 22.13 (SD = 7.46)). If antipsychotic dosage at t1 was added to the MANCOVA as covariate, to account for its effect on above normal plasma AVP, then the strength of the relation with CO increased slightly ($F = 9.462$; $P = 0.005$), whereas the relation with HA became slightly weaker ($F = 3.551$; $P = 0.070$). If all patients with initially above-normal AVP concentration at t7 (n = 15) were compared with all other patients (n = 43), then they still differed uniquely on CO ($F = 10.212$; $P = 0.003$), despite the inclusion of the four not-fully-remitted patients (age, gender, level of education, recurrent depression and MADRS at t7 score, as well as the effect of antipsychotic at t1 accounted for).

Figure 1 illustrates the highly significant difference ($F = 27.501$; $P < 0.001$) between the CO scores of all patients with above-normal plasma AVP and all other patients during 2 years in the 53 patients with complete data (doubly multivariate analysis; repeated measures design with all TCI scores at five time points as dependent variables, above-normal plasma AVP as fixed factor and age, gender, level of education, recurrent depression, MADRS at t1 and antipsychotic dosage at t1 as covariates).

Figure 1
Cooperativeness in patients with above-normal plasma vasopressin (AVP) and all other patients assessed at 5 time points during 2 years of follow-up in 53 patients with complete data set.



4 Discussion

After full remission of depression, the subgroup of patients with initially above-normal plasma AVP concentration was characterised by low CO compared with both normal controls and the group of fully remitted patients with initially normal plasma AVP. This finding was strengthened by the highly significant difference between the repeated CO scores in the subcategory of depression with above-normal plasma AVP and the group of all other patients during the 2-year follow-up period. The low CO score after full remission did not relate to recurrent depression or depression severity and may therefore maximally correspond with the patient's premorbid personality. The combination of low CO and normal SD in this subcategory implies that their personality may be called autocratic or authoritarian (Cloninger et al. 1997; Cloninger et al. 1998). For the full picture of this presumably premorbid personality, one should further recognise that these patients also had the general personality characteristics of all patients with major depression: decreased SD and increased HA during the acute episode and high HA after full remission (De Winter et al. 2007). Regretfully, there are no plasma samples available to relate plasma AVP at t7 with HA and CO during full remission.

During the acutely depressed episode, the patients with above-normal plasma AVP concentration had low RD and low CO scores compared with normal controls and low RD compared with all other patients. The much lower statistical significance of the low CO score during the acute episode compared with the remitted state may be due to state-dependent response bias on the CO dimension in other patient group.

The contrast between low CO being detected both during the acute episode and after full remission and low RD being detected uniquely during the acute episode suggests a selectively state-dependent change in response tendency on the dimension of RD. The absence of a correlation between RD and plasma AVP concentration at t1 may be due to the incentive to score the TCI items as if in the premorbid condition but may also imply that other factor is involved. This factor could be reduced oxytocin release, as is suggested by the positive correlation between RD and plasma oxytocin in depression (Bell et al. 2006). The potential relation in this subcategory between increased concentration of plasma AVP and decreased concentration of plasma oxytocin, the two principal neurohypophyseal hormones that are centrally involved in social behaviour, is a question that deserves further investigation. Regretfully, there are no more plasma samples available to test the role of oxytocin.

The relations found between the biological marker of above-normal plasma AVP concentration on the one hand and familial depression (Goekoop et al. 2006), high HA and low CO and an anxious-retarded phenotype without intensitythreshold (Goekoop et al. 2006) on the other hand support a diagnostic concept that suggests a pathogenetic pathway centrally involving genetically increased AVP release. This warrants prospective investigations in subjects at increased familial risk, in which hypotheses are tested of the relation between the basal vasopressinergic regulation and both the premorbid social behaviour style and the response to stress. The differentiation between 'Pure Familial Depressive Disease' and 'Depression Spectrum Disorder' (Winokur 1997) may be useful in this context of familial depression, but also the potential association with bipolar disorder, which has been found related with an increased post-dexamethasone AVP concentration (Watson et al. 2006). The hypothesis that genetic factors determining AVP synthesis and release are involved in the low CO of depression with above-normal AVP is testable in principle because genetic factors have unexpectedly been found to explain the familial source of variation not only of the temperaments but also of the character

dimensions (Ando et al. 2002, Ando et al. 2004, Gillespie et al. 2003). Because of the high inter-assay variability of the basal AVP concentration, individual assignment may be improved by using postdexamethasone concentrations (Watson et al. 2006).

The emerging concept of a familial depressive disorder, involving genetically enhanced AVP release, low socialization and further inhibition of social behaviour during stressinduced increase of AVP release, suggests an analogy with the AVP-related behaviour of montane voles (Young 2002). Although it is not known whether these animals have by themselves already increased AVP release, they have a genetic polymorphism of the vasopressin-1a (V1a) receptor, basically restricted social behaviour, a severely reduced expression of the V1a receptor in brain structures involved in social reward related behaviour and increased self-grooming after administration of AVP (Young 2002) instead of the increase of social behaviour that is induced by AVP in the highly socialised prairie voles. A second animal model with potential relevance for genetic factors in depression with above-normal AVP may be that of the genetically increased release of AVP in the highly anxious inbred rat (Murgatroyd et al. 2004). The behavioural phenotype of this animal model has been found related with altered regulation of the promoter region of the AVP gene resulting in over-expression of AVP in the parvo- and magnocellular subdivisions of the hypothalamic paraventricular nucleus, which controls the activity of the HPA-axis. This animal model shows a remarkable analogy with that of depression with above normal plasma AVP as the former critically involves the combination of anxiety and passive avoidance and the latter mixed anxiety and retardation (Goekoop et al. 2006). Finally, depression with above-normal plasma AVP concentration may have an analogous genetic origin to that of autism, with its microsatellites of the V1a receptor gene (Yirmiya et al. 2006) and increased plasma AVP concentration (Momeni et al. 2007). The present findings support the validity of the depressive subcategory with above-normal plasma AVP, and the primary role in it of a genetically deficient vasopressinergic regulation of both the stress response and premorbid social behaviour. If these results are replicated, including the presumably insufficient SSRI response, this biological marker may be useful for the development of specific pharmacological treatment.

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8

General discussion

Towards an improvement of the differentiation of depressive disorders. A multi-dimensional approach.

1 Introduction of the general discussion

This dissertation addresses the validity and consequence of the diagnostic category of major depressive disorder with melancholic or vital features (APA, 2000). This subtype of depressive disorder used to be called endogenous depression (Joyce et al. 2002). The validity of this diagnosis is weak (Rush and Weisenberger 1994, Rasmussen 2007). The objective of this research was to develop a subtype with higher clinical validity. This was done by using the methodology according to Robins & Guze (Robins & Guze 1970). We tried to develop a clinical description with higher external validity, which means a description that is related to other characteristics of the disorder such as biological factors, heredity and prognosis. In other words, our research was focussed on the relationships between the following levels of investigation:

1. the clinical description, comprising the areas of phenotype, personality and precipitated stress
2. laboratory findings
3. family history
4. Long time outcome

According to the suggestions by Robins and Guze, this type of investigation is a cyclical process. It starts, for example, with the development of a new phenotypical description with a higher validity and a better phenotypical demarcation. If this subtype in biochemical research shows a weak relationship to a biochemical parameter, this can lead to additional biochemical research. Subsequently, this can immediately result in improvement of the external validity of this new phenotypical description, but may also motivate to further improve the new description. The same applies to the role of family history and outcome studies. In this dissertation we followed various steps in this cyclical process:

1) A multi-dimensional reconstruction of the melancholic subtype according to DSM-IV by:
   i. a demonstration of the dependence of this subtype on high scores on two basic symptom dimensions of psychopathology, autonomous dysregulation (anxiety) and motivational inhibition (retardation), eliminating the meaning for this subclassification of the third basic dimension, emotional dysregulation
   ii. the definition of a new phenotype of melancholic depression based on this combination of high anxiety and retardation.
2) External validation of this highly anxious-retarded subcategory based on the following characteristics: increased correlation of plasma arginine-vasopressin (AVP) and cortisol concentrations, family history of depression, low Self-directedness (SD) combined with high Harm-avoidance (HA) in the 'Temperament and Character Inventory' (TCI) (Cloninger et al. 1993) during full remission after a follow-up of 2 years.
3) Optimizing an initially weak relationship between plasma AVP and the highly anxious-retarded subtype by subdivision of the concentration of plasma AVP in high and low AVP using Receiver Operating Characteristic (ROC) analysis. Loss of significance of the relationship between AVP concentration and highly anxious-retarded depression (HAR) initially found without several specific confounders.
4) Discovery of a stronger relationship between above-normal AVP concentration and familial depression than between above-normal AVP concentration and the highly anxious-retarded subtype.
5) Further support for a second subtype of depression, defined by above-normal AVP concentration and validated by: a relationship to familial depression, increased correlation between plasma AVP and cortisol concentrations,

increased correlation of the dimensions of autonomous dysregulation (anxiety) and (motivational) inhibition, and a presumably premorbid low score on the character dimension of Cooperativeness (CO) and a low score on the temperament dimension of Reward-dependence (RD) during the acute episode (see also table 3).

These findings will be discussed below separately.

2 Background of the above mentioned research areas

2.1 Multi-dimensional reconstruction of the melancholic subtype

In previous studies six dimensions of psychopathology were found in a heterogenous group of psychiatric patients (clinical patients/outpatients with psychotic disorders, affective disorders and anxiety disorders) using the Dutch translation of the semi-standardized interview of the Comprehensive Psychopathological Rating Scale (CPRS) (chapter 1, Asberg et al.1978) (Goekoop et al.1992, 1994). These dimensions seemed analogous to six of the seven large non-organic dimensions of psychopathology that were discovered earlier with the semi-standardized interview of the Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie (AMDP-system) (Goekoop et al. 1994). Only the dimension 'Hostility' was not found in this investigation with the CPRS.
The six-dimensional structure of psychopathology that was discovered using the CPRS encompasses four non-psychotic dimensions:

1) emotional dysregulation (in addition to 9 of the 10 items of the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979), this also comprises specifically neurotic symptoms.
2) motivational inhibition (apathy-retardation/inhibition) and
3) motivational disinhibition (mania)
4) autonomic dysregulation ((somatic) anxiety)

and two psychotic dimensions:

5) perceptual disintegration (perceptual dysregulation)
6) behavioural disintegration (behavioural disorganisation)

The hypothesized composition of fundamental symptom dimensions, that would characterize DSM-IV melancholia, was analysed using the three non-psychotic and non-disinhibited symptom dimensions in the heterogeneous group of patients mentioned above (chapter 2, De Winter et al. 2004).

From the perspective of a multi-dimensional structure of symptoms, all patients have their own set of scores on all dimensions (Goekoop & Zwinderman 1994). In this manner, every patient could be represented by a certain point within this multi-dimensional structure. Similarly each cluster of related patients (such as the group with a depressive disorder and the subtype with DSM-IV melancholia) can be located in this multi-dimensional symptom structure.

The investigation for this dissertation showed that in the entire group of depressive patients, motivational inhibition (retardation) and autonomous dysregulation (anxiety) were moderately correlated with each other ($r = 0.362$), while both dimensions independently showed a high correlation with emotional dysregulation ($r = 0.630$ and $r = 0.614$ respectively).

According to this data, emotional dysregulation seems to be the general dimension of dysregulation in depression. The two other basic symptom dimensions, retardation and anxiety, appear to play more of a differentiating role in depression.

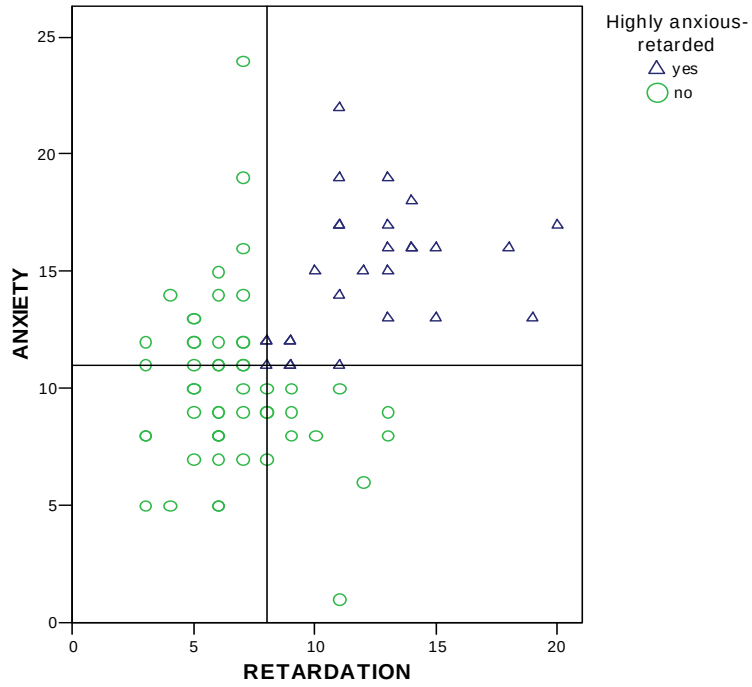
It turned out that the melancholic subtype according to the DSM-IV is indeed characterized by the combination of scores on the latter two fundamental symptom dimensions. With multiple regression, it turned out that the melancholic subtype is only characterized by the interaction between scores on autonomous dysregulation (anxiety) and motivational inhibition (retardation) (chapter 2, De Winter et al. 2004). This relationship was strongest when the anxiety and retardation scores were dichotomized around the median. The third dimension, the central dimension of emotional dysregulation, played no part in the multi-dimensional characterization of the melancholic subtype. In the past, other researchers have shown that within the depressive disorders, the dimensions of anxiety and retardation - independently of each other - play a part in differentiation; the significance of the combinations of higher scores on both dimensions, however, has never investigated before.

Based on the dependency of the melancholic subtype on the combination of above-median scores for anxiety and retardation a highly anxious-retarded subcategory was constructed on the basis of this phenotypical combination (chapter 2, De Winter et al. 2004) (see upper-right quadrant in **Figure IA**). Of the 89 patients with a depressive disorder that were examined, 33 patients (37 per cent) belonged to the highly anxious-retarded subtype, 16 were highly-retarded and not-anxious, 20 were highly-anxious and not-retarded, and 20 were not-anxious and not-retarded. Eighty-four per cent of the patients in the highly anxious-retarded subcategory had DSM-IV melancholia, whereas this highly anxious-retarded subcategory made up no more than 60 per cent of the original melancholic subcategory (see **Figure 1B**) (chapter 3, De Winter et al. 2003).
We assumed that the highly anxious-retarded subtype would be a more valid phenotype within the depressive spectrum than the melancholic subtype according the DSM-IV. This was investigated by examining the relationships between this new phenotype and several parameters of the other levels of investigation using the methodology according to Robins & Guze: personality, possible vasopressinergic endophenotypes, family history and outcome after two years.

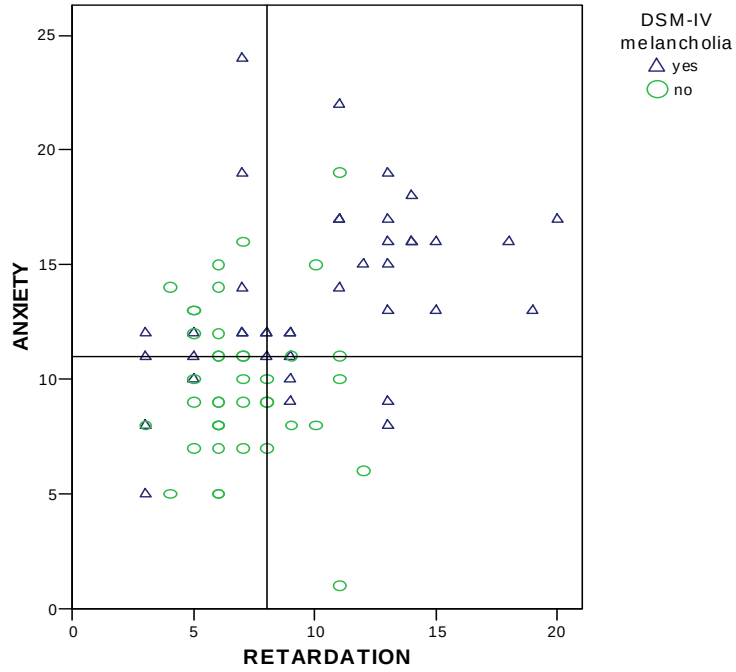
Figure 1

Two-dimensional quadrants and distribution of A) highly anxious retarded depression and B) DSM-IV melancholia. Reference lines represent median scores of autonomous dysregulation (anxiety) (11) and motivational inhibition (retardation) (8)

A



B



3 Considerations regarding the external validation of the highly anxious-retarded subcategory

3.1 Relationship with personality

A traditional hypothesis is that endogenous depression is associated with an adequate premorbid personality (Carney ea 1965, Charney et al. 1981, Coryell 2007). In this dissertation, that hypothesis was tested in patients during full remission of depression. We used the criteria for full remission according to the DSM-IV (Frank et al. 1991). The assumption was that we would find the same personality during full remission as would be present in the premorbid condition, if there were no relevant residual symptoms and if there was no indication of scars caused by relapses or extended duration of the depressive episode. In order to test the hypothesis of an adequate personality, we used (chapter 5, De Winter et al. 2007) Cloninger's personality model, the so-called 'Temperament and Character Inventory' (TCI) (Cloninger et al. 1993). The TCI differentiates three character dimensions: Self-directedness (SD), Cooperativeness (CO) and Self-transcendence (ST); and four temperament dimensions: Novelty-Seeking (NS), Harm-Avoidance (HA), Reward-Dependence (RD) and Persistence (PER). Different studies have shown that the presence of a DSM personality disorder can be predicted by low scores on the character dimensions of Self-Directedness (SD) and Cooperativeness (CO) (Cloninger et al. 1993; Svrakic et al. 1993). Therefore, we hypothesized that patients with highly anxious-retarded depression have normal SD and CO during full remission of major depressive disorder.

During the acute phase, the entire group of patients with depression, in comparison with a matched 'healthy' control group, showed a highly significantly elevated HA and a highly significantly reduced SD. Significantly reduced CO, NS, and RD were found as well. During the acute phase, there was no difference between the patients with highly anxious-retarded depression and the group of all other depressed patients on any of the TCI dimensions.

After two years, during full remission, there was a highly significantly increased HA and a significantly decreased ST in all patients in comparison with the healthy control group. The highly anxious-retarded subcategory had had a significantly increased HA during remission, but also a significantly decreased SD in comparison with the healthy control group. At this point there was no significantly different ST in this subcategory. During full remission, the melancholic subtype had a significantly elevated HA and no difference on ST. Therefore, the highly anxious-retarded subtype was better differentiated from controls than the melancholic subcategory during full remission.

The combination of the decreased SD score with a normal CO can be interpreted as to predict a dependent personality (Cloninger et al. 1997). In terms of the DSM criteria this implies an increased risk for a Cluster C personality disorder. To the extent that the highly anxious-retarded subcategory is a refinement of the melancholic subtype of depression, and to the extent that the patients were adequately classified as fully remitted by the criteria according to Frank et al. (1991), this means a refutation of the classical hypothesis of an adequate personality in an endogenous subtype of depression.

The higher association of a maladaptive personality with the multi-dimensionally derived endogenous phenotype needs to be replicated, like the other findings of this dissertation.

3.2 Relationship with biological parameters of the regulation of stress reactions

Chapter 3 (De Winter et al. 2003) decribes the external validation step regarding laboratory parameters. We selected the concentration of plasma cortisol, plasma arginine-vasopressin (AVP), and the correlation between plasma cortisol and AVP concentrations, as laboratory parameters.

We selected vasopressinergic parameters because the endogenous depression, according to the New Castle criteria (Carney & Sheffield 1972), as well as the melancholic depression, according to DSM, are characterized by an altered regulation of the Hypothalamic-Pituitary-Adrenal axis (HPA axis). This altered regulation has been investigated mainly through the concentration of the stress hormone cortisol (Holsboer 2001, De Kloet, 2003), either as a basal value or after suppression of the HPA axis by the synthetic glucocortocoid dexamethasone (Caroll et al. 1985, Zimmerman et al. 1986, Rush & Weisenberger 1994). The relationship between these values and subcategories turned out to be weak (Rush et al. 1996). Since AVP can influence the escape of the cortisol secretion from suppression by dexamethasone (von Bardeleben & Holsboer 1985), the plasma concentration of AVP and the correlation between AVP and cortisol concentrations were selected as parameters of possible vasopressinergic mechanisms. The plasma concentration of AVP could be a parameter of the synthesis and release of AVP, and the correlation between plasma AVP and cortisol concentrations could be a parameter of the sensitivity of the pituitary vasopressin receptor.

The patients in the highly anxious-retarded subgroup showed a significantly increased AVP concentration in comparison with the group of all other depressive patients. The melancholic subgroup showed no significantly increased AVP concentration. Therefore, using this relationship, it turned out that the highly anxious-retarded subgroup had a stronger external validation than the melancholic subgroup.

In a later chapter (chapter 6, Goekoop et al. 2006) we used the dichotomized concentration of plasma AVP, expecting to find a stronger relation with the anxious-retarded subtype (see below, section 2.3). Despite the expected increase of the strength of this relationship, we eventually found that the highly anxious-retarded subgroup lost the statistical significance of this relationship with plasma AVP after correction for the dose of antipsychotic prescription as confounder (chapter 6, Goekoop et al. 2006).

3.3 Relationship with the family history of depression

The Family History Research Diagnostic Criteria for depression (FH-RDC) in first degree family members were used to define a family history of major depressive disorder (Andreasen et al. 1992) (chapter II).We modified the RDC criteria for the classification for major depressive disorder into the DSM-IV criteria for depression (Chapter 2, De Winter et al. 2004).

Fourty-seven per cent of the 89 patients with a depressive disorder met the criteria for a positive family history. Of the patients with the melancholic subtype according to DSM-IV, 55 per cent met the criteria for a positive family history. Of the highly anxious-retarded subtype, 65 per cent met the criteria for a positive family history. After multiple regression analysis (covariants: age, sex, severity of depression, psychotic depression, duration of the current period, clinical/outpatient status) only the highly anxious-retarded subcategory was significantly associated with a positive family history for depression.

3.4 Relationship with outcome

Chapter 4 (De Winter et al. 2006) describes the investigation of the long-term outcome of the highly anxious-retarded subcategory and the melancholic subgroup. There were seven measurements: t1 at the start, t2 after six weeks, t3 after 13 weeks, t4 after six months, t5 after one year, t6 after 18 months and t7 after two years. For the outcome analysis, we controlled for the effect of diverse factors: age, sex, familial history, degree of severity, duration of illness, number of episodes and education level.
For the outcome measure, we used the criteria for complete remission according to Frank et al. (Frank et al.1992). This meant that maximally two DSM-IV symptoms for depressive disorder were allowed to be present for the last two weeks. The highly anxious-retarded subgroup showed a significantly longer time until full remission (Wald = 7.85, df = 1 and p = 0.005). Covariance analysis resulted in an unaltered outcome. The anxiety and retardation dimensions independently predicted no alterations in the course of events. The melancholic subgroup had no difference in duration until full remission of major depressive disorder.

This validation step showed that the highly anxious-retarded subgroup had a more poor long-term outcome compared with all other patients, in contrast to the melancholic subgroup.

3.5 An attempt to optimize the validity of highly anxious-retarded depression based on a dichotomy of the concentrations of plasma AVP. Evidence for a second subcategory within the domain of endogenous depressions

In the first part of this dissertation, it is demonstrated that a development in the area of clinical description based on the construction of a combination of basic dimensions of psychopathology can lead to a better externally validated endogenous/melancholic subcategory. This new highly anxious-retarded subcategory has been phenotypically defined on the basis of the combination of above-median scores for anxiety and retardation. The combination of an increased correlation between plasma AVP and cortisol concentrations and an elevation of the plasma AVP concentration was initially assumed to be the endophenotype of this subcategory. The additionally found relationship between highly anxious-retarded depression and a positive family history of depression suggested that the highly-anxious-retarded phenotype, these vasopressinergic parameters and the family history of depression all concern one single subcategory of endogenous depression.

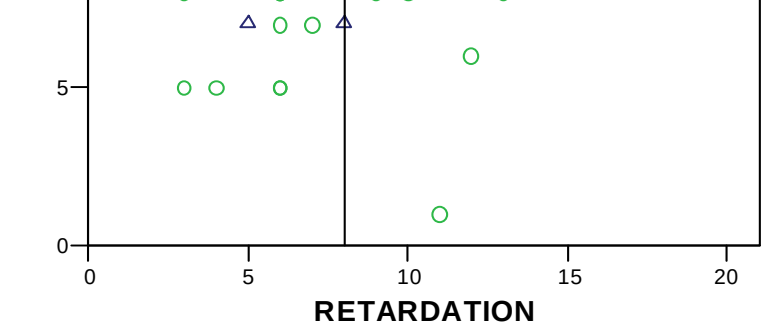
Since the relationship between the highly anxious-retarded phenotype and the plasma AVP concentration was weak, we searched for improvement of this relationship in a following study, expecting to find stronger interrelations between the three levels of investigation (chapter 6). In a previous investigation of patients with depression, it had been found that above-normal AVP concentration is specifically related to an increased pattern of motor activity during the night in a group of depressive patients in comparison with healthy volunteers, opposed to the relation between plasma AVP as continuous variable and psychomotor retardation that was seen in both depressed and healthy persons (Van Londen et al. 1998). These previous results lead to the hypothesis of an improved strength of the interrelations between the highly anxious-retarded phenotype, plasma AVP and familial depression after dichotomizing the plasma AVP concentration values. In the research for this dissertation, ROC analysis provided an optimized cut-off value (5.56 pg/ml) for the relationship between high AVP and the highly anxious-retarded phenotype (chapter 6).

This relationship was indeed stronger than the relationship between this highly anxious-retarded subcategory and the AVP concentration as a continuous variable. The significance of this relationship was however lost on its turn after correction for the dose of antipsychotic treatment as a covariate. In our previous investigation, we had corrected only for the use of several categories of psychotropic medication in the analysis (chapter 3), but not for the dosage of these psychotropic medications. The negative finding regarding the optimized relationship between the highly anxious-retarded phenotype and plasma AVP suggested that the above-normal AVP concentration could still be a characteristic of another subgroup within the domain of endogenous depression, more specifically that an above-normal AVP concentration could be related with familial depression and with an other type of anxious-retarded depression, given the non-significant relationship with the highly anxious-retarded phenotype.

3.5.1 Validation of a subcategory with above-normal AVP concentration by relations with familial depression and an anxious-retarded phenotype without severity criterion

In the investigation that is described in chapter 6 we found the same cut-off level (5.56 pg/ml) for the plasma AVP concentration for the subgroup with familial depression, as for the highly anxious-retarded subcategory. After correction for the effect of antipsychotic medication dosage, it even turned out that the significance of the relationship between familial depression and the above-normal AVP concentration had increased. These findings rejected the hypothesis of one single subcategory of familial depression with a highly anxious-retarded phenotype and above-normal plasma AVP concentration, and supported the presence of two subcategories of depression: the previously found highly anxious-retarded subtype with increased correlation between AVP and cortisol concentrations combined with normal AVP concentration, and a second subcategory with above-normal plasma AVP concentration and a relationship with familial depression.

The hypothesis that this second subcategory would have a different anxious-retarded phenotype was confirmed**. Figure 2** shows the anxious-retarded phenotype that was found in depression with above-normal AVP concentration, and that was characterized by an increased correlation between anxiety and retardation.
From this point in the investigation, the second subcategory, in contrast to the still phenotypically defined highly anxious-retarded subcategory, was defined biologically on the basis of the cut-off criterion of plasma AVP (5.56 pg/ml) for the relationship with familial depression.



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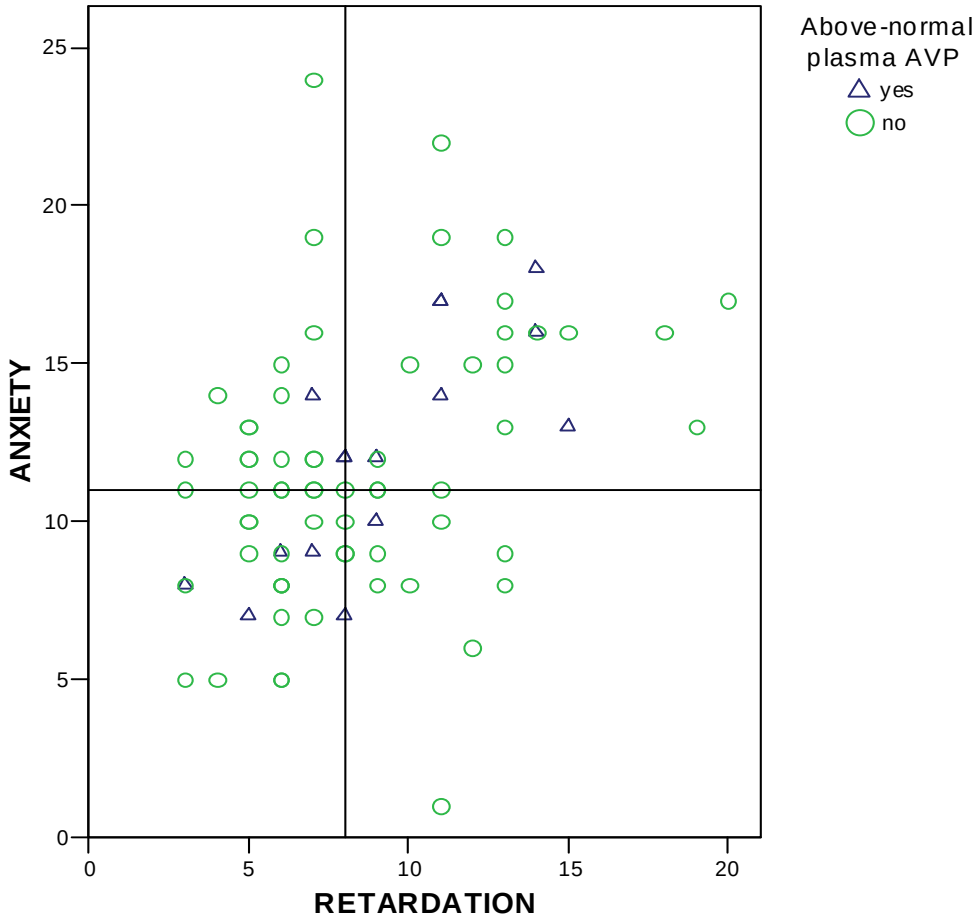

3.5.2 Further external validation of depression with above-normal AVP concentration

In addition to the relationship with familial depression and the anxious-retarded phenotype without severity criterion, two more validation relationships with depression with an above-normal AVP concentration were investigated. We found support for an increased correlation between plasma AVP and cortisol concentrations as described at the end of 2.4. In comparison with patients with a normal AVP concentration, patients with above-normal AVP concentration had a significantly increased correlation between plasma AVP and cortisol concentrations, which remained after correction for the effect of the correlation between both parameters in the highly anxious-retarded subgroup. In the study with the TCI (see 3.1 of this chapter for an earlier description), we found that the subgroup with above-normal AVP had a lower Reward-Dependence (RD) and Cooperativity (CO) score during depression, in addition to which the low CO remained after full remission of the depression (chapter 7, Goekoop et al. 2008). According to Cloninger's model, a low CO combined with a normal SD corresponds to an autocratic or authoritarian personality.

The results of the subgroups are summarized in **table 1.**

Table 1

Interrelations between parameters of investigation in three subgroups of depression (melancholic, highly anxious-retarded and above normal AVP). **Bold** is the defining characteristic of a subcategory and *italic are* the external validation characteristics.

Phenotype	Familial depression	Personality	AVP	Increased AVP-cortisol-correlation	Outcome
Melancholic	-	-	-	-	-
Highly anxious-retarded	+	SD↓	-	+	Poor long-term outcome
Anxious-retarded correlation	+	CO↓ RD ↓	**Above normal**	+	-

AVP = Arginine Vasopressin; SD = Self-Directedness; CO = Cooperativeness; - = no relation; + = relation; ↓ = decreased score

Discussion and considerations

4 Development of the vasopressinergic theory of depression

The external validation of highly anxious-retarded depression and depression with above-normal AVP concentration support the presence of two subcategories, with a different vasopressinergic endophenotype, in stead of one within the domain of melancholic/endogenous depression. The endophenotype of the highly anxious-retarded subcategory is the AVP cortisol correlation without significantly elevated AVP concentration. This correlation is supposed to be a parameter of elevated expression of the pituitary V1b receptor. Chronic stress (Volpi et al. 2004) as well as a genetic polymorphism (Dempster et al. 2007) could play a causal role here. The endophenotype of the second subcategory is the above-normal AVP concentration. The endophenotype of the animal model with above-normal AVP synthesis, the High Anxiety-related Behaviour (HAB) rat (Landgraf et al. 2007, Keck et al. 2002, Frank & Landgraf 2008), could be analogous to this endophenotype in humans. Depression with above-normal AVP concentration could therefore be related to a genetically elevated AVP synthesis.

The independent relationship of two vasopressinergic characteristics in two subgroups of depression implies an extension of Scott and Dinan's theory about the role of vasopressin during depression (Scott & Dinan 2002). This theory is primarily based on an elevated reaction of the HPA axis on administration of the vasopressinergic substance desmopressin during melancholic depression. This elevated reaction is probably caused by an elevated expression of the pituitary V1b receptor. The previously found support for elevated AVP release (Van Londen et al.1997) in depression and the elevated synthesis of AVP in the Paraventricular Nucleus (PVN) of the hypothalamus (Raadsheer et al. 1994; Purba et al. 1996) were mentioned by Scott and Dinan (2002), but they were not clearly distinguished from the elevated receptor expression. Another finding, that unequivocally fits the theory of changed vasopressin-receptor expression, is the increased correlation between the plasma AVP and cortisol concentrations in suicidality (Inder et al. 1997). The recently found genetic polymorphormism of the V1b receptor in early onset depression (Dempster et al. 2007) also fits the conceptualization formulated by Scott en Dinan (2002). The extension of the vasopressinergic theory which is suggested by the results of this dissertation consists in the support for for the presence of two different vasopressinergic endophenotypes in two different subcategories. These endophenotypes are:, increased AVP cortisol correlation combined with normal plasma AVP concentration, and above-normal plasma AVP concentration combined with increased AVP cortisol correlation. This differentiation is analogous to the differentiation of the two vasopressinergic mechanisms in the previously described animal models.

As indicated above, earlier investigations have shown an elevated AVP concentration in depressive patients in comparison with a healthy control group (Van Londen et al. 1997). When the AVP concentration was expressed as continuous parameter, it was weakly related to the melancholic subtype according to DSM-III-R. But this study also found that an above-normal AVP concentration was related to increased motor activity during the night, that was only found in patients (Van Londen et al. 1998). In contrast, the correlation between plasma AVP concentration as continuous parameter and psychomotor retardation was not specific for a depressive disorder, because it was also present in the healthy control group. This was the first indication that plasma AVP concentration as a dichotomized variabele could be a better endophenotypical measure for a subgroup of depression than plasma AVP as continuous variable. The finding in this manuscript that above-normal AVP concentration is associated specifically with familial depression, confirmed and specified this conclusion in an independent patient sample. In a further validation of depression with above-normal AVP concentration, we found

relationships with low CO and RD (chapter 7) and an anxious-retarded phenotype without severity criterion. These two results corroborate the independence of a subcategory of depression which is defined by the endophenotype of an above-normal AVP concentration. The results of this dissertation combined with the previous finding of increased activity during the night for above-normal AVP concentration in depressed patients (Van Londen et al. 1998) imply an extension of the vasopressinergic theory of depression.

The results that are described in this dissertation were made possible by a combination of multi-dimensional measurements on the level of psychopathology, temperament, character and HPA axis, which has not previously been applied in psychiatry. The chosen instruments will be discussed individually later on. First, we shall discuss the choice we made in searching for endophenotypes by means of an improvement of the description of manifest psychopathology, together with the choice of the melancholic subtype of depression as a starting point for the intended improvement in the diagnostics of depressive disorders.

5 Multi-dimensional description of manifest psychopathology for the detection of endophenotypes in subgroups of depression

The method of searching for improvement of clinical description through mixtures of fundamental symptom dimensions has been proposed by Jaspers (1959) as described in chapter 1 and in the beginning of this chapter. In our investigation we assumed that a multi-dimensional clinical description is a necessary condition for the development of diagnostic concepts with better validity in comparison with the description according to the present DSM classification. The expected increase in validity should be demonstrated by better relations between clinical phenotype, endophenotype, personality, family history and outcome.

The multi-dimensional approach of the phenotype shows similarities with the method used in recent research of animal models of depression with a genetically elevated synthesis of AVP. In these animal models, a multi-dimensional description of behaviour (a combination of anxiety and immobility) was related to a neurobiological parameter (elevated AVP synthesis) (Landgraf et al. 2007). In psychiatry, the combination of two 'dimensions' of psychopathology (aggression and fear) in depressive patients has already earlier been related to one neurobiological characteristic: hyposerotonergic function (Van Praag 2005). Since the hyposerotonergic activity is probably not just linked to a subgroup of depression, but rather to a general maladaptive premorbid personality trait (Lyons-Ruth et al. 2007, Hamer et al. 1999), the role of this hyposerotonergic activity can be seen as a reinforcing factor concerning the role of the vasopressinergic mechanisms, that have been found in this dissertation regarding the different subgroups of depression.
The expectation in this dissertation was to arrive, through a multi-dimensional description of manifest psychopathology, at the detection of related endophenotypes. This expectation is not in agreement with Van Praag's assumption that this method would lead to a phenotypical swamp (Van Praag 2008).

According to Van Praag (2008), the testing of a causal relation between the discovered endotypes and the development of the two depressive disorders would require proof that they are involved in the emergence of a functional deficit. According to our view in this field, this deficit should be the necessary precondition for the emergence of the general manifest symptoms of depression, as well as for the specific anxious-retarded phenotypical mixtures in both subcategories.

The hypothesis of a functional deficit as a precondition for the emergence of manifest symptoms was already mentioned by Jaspers. He refers explicitly to Kraepelin and implicitly to Hughlings Jackson (Jaspers 1959), saying that a causal explanation of the emergence of symptoms in symptom dimensions might be found on the one hand in the genetically determined cerebral disposition, and that, according to Kraepelin, a layered order, or rather a dynamic relation between a disturbed higher cerebral function and remaining lower functions, should be involved here. These functions are called 'higher' and 'lower' with respect to their phase in the ontogenesis of the cerebrum. According to this neurologically recognized explanation of the generation of symptoms (Hughlings Jackson), a disturbance in the function of higher levels of cerebral organization (functional deficit) would induce the manifest symptoms to arise by disinhibition of healthy lower structures (Jaspers 1959).

The research of the relationship between endophenotypes, functional deficits and manifest phenotypes requires a theory formulation and testing that lie outside the scope of this manuscript.

6 Improvement of the melancholic subtype as a starting point in our search for endophenotypes of depression

As we saw earlier, the intention was to gather more knowledge about the endophenotype for a subgroup of depression. Improvement of the melancholic subtype was chosen as the first step because this concerns a rather large subcategory of depression (Kahn et al. 2008) that has more relations with neurobiological parameters than the non-melancholic subgroup. The relationship between the melancholic subtype according to the DSM classification and neurobiology has particularly been found in terms of moderately strong relationships with non-suppression in the DST (Carroll 1985, Rush et al. 1996) and a changed Rapid Eye Movement (REM) sleep latency (Antonijevic 2008). Not everyone agrees that the melancholic subtype might be suitable for neurobiological research of depression. Some researchers have the opinion that "psychotic depression" would be a better subcategory, even though this concerns a smaller subgroup (Contreras et al. 2007). They argue that psychotic depression is the most severe form of depression and therefore would be related to a greater number of biological changes. This theory is based on a different fundamental concept regarding the classification of depressive disorders than the multi-dimensional concept that we use. This other theory states that all depressive disorders can be ordered along one general dimension of psychopathology according to a hierarchical phenotypical continuum. Depending on the severity, symptoms of retardation and psychotic dysregulation would arise subsequently. The retardation would be accompanied by the DSM diagnosis of the melancholic subtype. An increase in the severity of this retardation would lead to the additional emergence of psychotic dysregulation (Parker 2007).

In our investigation we assumed that the group of depressive disorders contains qualitatively different subtypes that are phenotypically characterized by different mixtures of a few fundamental symptom dimensions, and that these mixtures are related to qualitatively different endophenotypical parameters. This hypothesis is confirmed by the results of our investigation. If our results are replicated, they will imply the refutation of the one-dimensional hierarchical theory of depression.

7 The selection of three fundamental symptom dimensions of the CPRS for the multi-dimensional description

Next, we shall compare the structure of three fundamental symptom dimensions of the CPRS with a few alternative multi-dimensional and uni-dimensional structures of psychopathology. The multi-dimensional structures are the structures of the

psychopathology according to the AMPD system (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie) (Troisfontanes et al. 1984,1987) and the tripartite model of 'mood and anxiety' of the Mood and Anxiety Symptom Questionnaire (MASQ) according to Clark & Watson. The uni-dimensional structure is the structure of the 'general neurotic syndrome' (Tyrer et al. 1992)

7.1 Multi-dimensional symptom structure of the CPRS versus the AMDP system

From a face validity perspective, the 6 CPRS dimensions correspond to 6 of the 7 large non-organic fundamental dimensions of the extended semi-standardized interview of the AMDP system. A difference with these 6 dimensions of the AMDP system is that the dimension of Emotional Dysregulation (ED) of the CPRS, next to depressive items, also contains items of specifically neurotic symptoms. The reason why we chose the CPRS instead of the AMDP system is based on psychometric criteria such as scale construction and the usage (possibility of general scoring from 0 to 6, and a clear description of the items in ordinary language), and on the usefulness for scoring by non-physicians or non-psychologists such as research nurses. In addition, the interview of the AMDP system is unnecessarily long in view of the purpose of the analysis of melancholia. There is a theoretical reason why we did not choose the MADRS as the dimension for depression, but instead the fundamental symptom dimension Emotional Dysregulation (ED) that consists of 21 items, among which are 9 of the 10 MADRS items. In this way, only fundamental symptom dimensions were used, and not a hybrid combination of fundamental symptom dimensions and an intensity rating scale comprising items that are selected for the measurement of a quick recovery from depression. For the analyses, we used the following 3 CPRS dimensions: Emotional Dysregulation (ED), Psychomotor retardation (retardation) and Autonomous Dysregulation (anxiety). It turned out that, contrary to the dimensions anxiety and retardation, the general dimension ED did not differentiate between subcategories. Earlier two-dimensional models according to which depressive disorders might be ordered, contained a mixture of symptom items and historical and/or personality items (Bech & Allerup 1986; Paykel 2008). On the basis of the methodological standard of Robbins and Guze these dimensions cannot be considered very useful.

7.2 The three dimensions (anxiety, retardation and emotional dysregulation) of the CPRS versus the tripartite structure of anxiety and depression according to the MASQ

The three-dimensional structure of the CPRS contains information that differs qualitatively and quantitatively from the tripartite structure of the MASQ (Clark & Watson 1991, Watson et al. 1995). The latter consists of a general dimension: Negative Affect (NA), and two specifying dimensions: Physiological Hyperarousal (PH) and Positive Affect (PA). According to the authors, the MASQ in a qualitative sense only covers affects regardless of the transition from normal to dysproportional regulation, whereas the CPRS structure covers more of the evident psychopathology.

From a qualitative point of view, the MASQ only offers a twodimensional structure for the prediction of subtypes in the domain of the depressive psychopathology, namely a differentiation based on the separate dimensions PH and PA pointing to anxiety disorder and depression respectively. This structure allows only a qualitative differentiation of depression in terms of combinations of depression and anxiety.

Contrary to this two-dimensional psychopathological prediction of the MASQ, the three-dimensional non-psychotic structure of the CPRS, in addition to the psychopathology of the dimension Emotional Dysregulation (that contains most of the depression items of the MADRS) and the dimension of Autonomous Dysregulation (anxiety), contains the

dimension of retardation as well. This three-dimensional structure yields more potential mixtures of symptom dimensions than only the combination of anxiety and depression that is enabled by the MASQ, more specifically the combination of anxiety and retardation and the combination of depression and retardation.

The authors of the MASQ interpreted the general MASQ dimension of Negative Affect (NA) merely as a measure of the severity of the general stress-induced strain, which can be seen as a precondition for the emergence and severity of the two specific dimensions (depression/low PA and anxiety/PH) (Watson et al. 1995). NA should therefore represent something other than the general symptom dimension ED, that represents general symptoms of depression and specifically neurotic symptoms.

We can conclude that the MASQ, which can (according to recent investigations) represent the three emotions of anger, anxiety and sadness (De Beurs et al. 2007), lacks the dimension of retardation, which appears to be an important component of depressive disorders, especially for the differentiation into melancholic and psychotic depression (Parker & Hadzi-Pavlovic 1996). The MASQ is therefore too limited for a study of subtyping 'severe' forms of depression.

8 The choice of the personality dimensions of the TCI

In studies of the relationship between multi-dimensional personality models and depression, 4 personality models are used in particular (Bagby et al. 2000). These are:

1. The model of Eysenck & Eysenck (1976), measured by the Eysenck Personality Questionnaire (EPQ). This model contains the dimensions Extraversion/Introversion (E), Neuroticism (N), Psychoticism (P), and Lie-Scale (L).
2. The model of Von Zerssen et al. (1988), measured by the Münchener Personality Test (MPT). This contains Neuroticism, Extraversion, Frustration tolerance, Rigidity, and Schizoidy.
3. The model of Costa & McCray (1990), the Big 5, measured with the Neuroticism-Extraversion-Openness Personality InventoryNEO-PI. This contains the dimensions Neuroticism, Extraversion, Openness, 'Agreeableness' and Conscientiousness.
4. The model of Cloninger et al. (1993). This model has been extensively discussed under 3.1. It differs from the other models in its differentiation in personality between the temperament, which is already present at birth, and the character that develops later in life. Of the four temperamental dimensions, three are supposed to be linked to different neurotransmitter systems. Novelty-seeking could be associated to the dopaminergic system, Harm-avoidance to the serotonergic system and Reward-dependence mainly to the noradrenergic system (Cloninger 1994). With the TCI, it is possible to differentiate between character and temperament. Due to the relation between low SD and low CO and a personality disorder, this distinction provides an efficient possibility to estimate the presence of a maladaptive personality, with the smallest possible number of variables. Yet another possibility would have been to use Livesley's Dimensional Assessment of Personality Pathology (DAPP) (Livesley et al. 1998). But in that case the presence of personality disorders would have got too much emphasis, and it would not have been possible to describe the combination of normal premorbid traits such as an elevated HA, and maladaptive personality traits such as a reduced SD or CO.

The most common criticism of Cloninger's model concerns psychometric weaknesses, such as the dichotomic yes/no structure of the answers to the questions, the fact that in several studies only a moderate internal consistency was found, in particular for the dimension RD, and that often an imperfect to moderate differentiation between dimensions was found, more specifically between the dimensions HA and SD and the dimensions RD and CO (Farmer and Goldberg 2008). The most critical reaction (Farmer and Goldberg 2008) comes down to a rejection of the relevance of the difference between character and temperament, in spite of the repeatedly demonstrated significance of a low character score as a predicting factor of a personality disorder (Cloninger 2008). This criticism must be reviewed with due carefulness, because the researchers rely on the coincidence of the HA and SD subscales in their factor-analytical investigation of a convenience sample of community volunteers (shoppers at a mall) and they completely ignored the fact that, within that same sample, the TCI still provided a better prediction of the difference between 'maturity' and 'clinical disorder' than other personality inventories (Cloninger, 2008).

In time, the knowledge of the biological meaning of the TCI scores has been revised. It turned out that not only all temperament dimensions are determined by genetic factors, but also allcharacter dimensions had a substantial genetic contribution (Ando et al. 2004). Furthermore, temperament dimensions turned out to be not exclusively related to variations within separate monoaminergic systems (Cloninger, 2004). Finally, some support has been found for the assumption that the maximum differentiation between temperament and character is achieved on the basis of environmental influences that are not shared within families, rather than on a genetical basis (Ando et al. 2004)

9 Plasma concentrations of AVP and cortisol, cortisol-AVP correlation and above-normal AVP concentration

An important argument for the application of HPA-axis related parameters such as plasma AVP concentration, above-normal AVP concentration, in addition to the plasma cortisol concentation, is that the vasopressinergic parameters could, more specifically than the (post-dexamethasone) cortisol values, represent the activating mechanisms used by the organism to maintain a continuous activation of the HPA axis after high or persistent stress, when after some time the sensitivity for the primarily activating Corticotrope Releasing Hormone (CRH) begins to decrease (Aquilera & Rabadan-Diehl 2000).

In the course of this investigation we found that the increased correlation between the plasma AVP and cortisol concentrations, the elevated basal plasma AVP concentration and the basal above-normal plasma AVP concentration could be indicators of the upregulation of the pituitary vasopressin receptor (Dinan & Scott 2005), the elevated hypothalamic AVP synthesis (Raadsheer et al. 1994) in depression, and a form of elevated AVP release in a specific group of patients (Van Londen 1998), respectively. In this way, three potentially relevant vasopressinergic parameters might be available, together with the afternoon value of plasma cortisol as a parameter, which would correspond best with the aspecific Dexamethasone Suppression Test (DST) (Burke et al. 2005).

The separate afternoon value of plasma cortisol has not been included in the analyses discussed in this thesis. The same applies to the slope of the regression line of the AVP cortisol correlation in the highly anxious-retarded subgroup. This slope should be steeper in the group of patients with an elevated AVP - cortisol correlation and a normal AVP concentration in comparison to all other patients, because it should represent the upregulation of the V1b receptor. The number of patients was too small to detect a statistically significant difference in this slope.

A further restriction might be that, through the applied definition of the cut-off for above-normal AVP concentration, an important overlap may remain between a stress-induced elevated normal AVP secretion and a genetically elevated AVP secretion in patients with familial elevated AVP secretion. We would wish that, in the future, better group and individual parameters can be applied to these two kinds of elevated AVP release. The slope of the regression line of the correlation between AVP and cortisol concentrations could be used as a measure for the elevated V1b receptor on group level, as has been indicated above. An individual measure of this receptor responsivity could be the strength of the stimulation of ACTH secretion by a standardized stress with the vasopressinergic substance of desmopressin, or conversely, the strength of the inhibition of the HPA axis by a vasopressin antagonist (Simon et al. 2008). As an individual measure for elevated AVP synthesis and release the post-dexamethasone release of AVP may be useful, as has been done for bipolar disorders and chronic depression (Watson et al. 2006).

10 Possible therapeutic implications of the two subcategories with different vasopressinergic mechanisms

Since in the highly anxious-retarded subcategory an elevated V1b receptor expression is expected, a specific V1b receptor antagonist could in this first subcategory (highly axious-retarded) be a remedy with an optimum therapeutic effect. Since the second subcategory (above normal AVP) is supposed to have an elevated AVP synthesis and release that could lead to stimulation of V1b as well as V1a receptors, for this subgroup a combined V1a and V1b receptor-antagonist could be therapeutical.

11 General limitations of the study set-up

The selection of depressive patients was done on the basis of the DSM IV classification for depression. It was a combined second and third line sample from unremitted patients after initial treatment by a general practitioner and/or a first line mental health worker. The mean duration of the index episode was 6,9 months (Chapter 2, de Winter et al 2004). Therefore, the selection was performed on the basis of insufficient recovery within six months (Ormel et al. 1993), and this could have been a factor in the strength of the stress-induced upregulation of the V1b receptor.

In addition, more attention will have to be paid to the effects of medication. In an earlier study where patients without medication were included, a higher average AVP level was found than in the present investigation (Van Londen et al. 1998). This might have been caused by medication withdrawal in the earlier study. The effect of medication withdrawal (antidepressants) on AVP levels needs further investigation. In future studies, a highly anxious-retarded subgroup may be found on the basis of the optimum cut-off scores for anxiety and retardation in relation to the melancholic subtype. A second subgroup could be detected through an optimum cut-off level for plasma concentration of AVP in relation to familial depression.

As long as it is impossible to select patients on the basis of sufficiently validated measurements of the V1b receptor expression and genetically elevated AVP release, the most useful criteria shall be those described above.

12 Suggestions for further investigation

In future studies, the validation relationships may be improved if the overlap between the highly anxious-retarded subcategory and the subcategory with above-normal AVP concentration is removed. In addition, it is necessary to test the hypothesis that endophenotypical parameters provide a better delimitation than the phenotypical ones. As long as no proper measure for elevated V1b receptor expression is available, the

hypothesis that the already detected validation relationships become stronger when the overlap between these two subcategories is removed can be tested as follows: highly-anxious depression with a normal AVP concentration on the one hand, and depression with an above-normal AVP concentration on the other.

In the future, genetic analogies of the two new subcategories of depression and animal models of depression and fear may become available. The genetics of depression with above-normal AVP concentration could correspond with those of the animal model of the HAB rat (High Anxiety related Behaviour) (Landgraf et al. 2007), and conversely, we can study animals for a vulnerability to depression-like behaviour with an elevated V1b receptor expression and look for an analogy of depression that starts during early youth (Dempster et al. 2007). These findings may indicate the direction for studies of expected single nucleotide polymorphisms (SNP's) concerning the expression of the V1b receptor and the promotor area of the AVP gene.

Using the multi-level explanation in which the development of a higher cerebral deficit is supposed to be the precondition for the transition from normal affect to disturbed affective regulation (Jaspers, 1957), the various vasopressinergic mechanisms have no pathological meaning unless they contribute directly to the development of this deficit. As in depression a general decrease of SD occurs (De Winter et al. 2007), SD is associated with prefrontal function (Cloninger. 2000, Van Heeringen et al. 2003, Gusnard et al. 2003), and a deficit in the prefrontal area can lead to the loss of inhibitory control over the amygdala (LeDoux, 1996) and the HPA axis (Diorio et al. 1993), the causal role of the elevated AVP synthesis and the elevated V1b expression must be extended to the medial prefrontal cortex. Testing this causal hypothesis will require a prospective design in which persons with a familial elevated expression of AVP or V1b–receptor in a stress condition will be tested for this medial prefrontal function.

Finally, the meaning of hyposerotonergically determined anxiety/aggression-driven depression (Van Praag et al. 2005) needs investigation in relation to the two new subcategories with their anxious-retarded phenotypes and vasopressinergic mechanisms. In order to do this, the phenotypical description of the depressive subcategories must be supplemented with a measure for hostility or anger. Since hyposerotonergic hostility or anger seems to be based on a general premorbid personality trait (Van Praag et al. 2005).This has also been associated with antisocial and borderline traits (Lyons-Ruth et al. 2007) as well as with low CO and SD (Hamer et al. 1999), which corresponds perfectly with the prediction according to the TCI (Cloninger et al. 1997). The most probable outcome is that the combination of premorbid hyposerotonergic function with one of the two vasopressinergic endophenotypes will confound the specificity of the premorbid traits of low SD and low CO with a common decrease of both character traits. On the level of symptoms, this combination will have the pathoplastic effect of strengthening the anxiety combined with hostility that occurs during depression.

A multilevel multidimensional description of psychopathology yields depressive subtypes with higher validity. It is probable that this approach is not limited to depression and that this kind of development may also be of importance for the differentiation and subtyping of more psychiatric disorders. It therefore seems worthwhile to further investigate this multilevel multidimensional description. A dimensional approach for personality disorders, axis II in DSM-V, will play an important supplemental role (Widiger et al. 2005, Trull et al. 2007) and perhaps this will also apply to the first and general axis of psychopathology, beyond the DSM-V.

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Nederlandse Samenvatting

Hoofdstuk 1, Inleiding

Een klassieke indeling van de depressieve stoornis is die in endogene depressie, waarvan gesuggereerd wordt dat het meer van "binnenuit" zal worden veroorzaakt en exogene depressie, welke meer van "buitenaf" zou worden veroorzaakt.
Er wordt verondersteld dat het endogene subtype vaker samen zal gaan met biologische afwijkingen en een genetische predispositie. Ook wordt gesuggereerd dat het endogene subtype minder vaak voorafgegaan wordt door diverse vormen van stress of een verstoorde persoonlijkheidsontwikkeling.
Het endogene subtype wordt in het huidige meest gebruikte classificatie systeem voor psychiatrische ziekten, de Diagnostic Statistical Manual (DSM), het beste benaderd door het melancholische (= vitale) subtype. Het melancholische subtype volgens de DSM heeft echter weinig sterke consistente valideringskenmerken en er is overlap met andere psychiatrische ziekten. De huidige wijze van classificeren, met de DSM, middels een categoriale dichotome wijze (aan- of afwezig zijn van een stoornis) lijkt een belemmering te zijn voor de ontwikkeling van onder andere een meer biologisch gevalideerde diagnostiek bij depressie.

Het centrale uitgangspunt van dit proefschrift is dat een andere benadering dan de huidige categoriale diagnostiek van psychiatrische ziekten een oplossing zal kunnen bieden voor dit probleem. Karl Jaspers, psychiater en filosoof, heeft voor de 2^{e} wereldoorlog een theoretisch model ontwikkeld, waarbij hij psychiatrische ziekten beschreef als verschijningsvormen, welke ontstonden door de interactie van het beïnvloedend milieu en de erfelijkheid. De variatie van deze verschijningsvormen (=fenotypen) ontstonden in zijn opinie door verschillende mengingen van onderliggende basale symptoomdimensies. Verschillende onderzoekers hebben onderzoek gedaan naar deze basale symptoomdimensies. De uitkomsten van deze onderzoeken hebben uiteindelijk geen gevolgen gehad voor de wijze van diagnostiek in de Psychiatrie.

Gebaseerd op het theoretische model van Karl Jaspers hebben we onderzocht of het mogelijk was om, uitgaande van het melancholisch subtype, binnen de depressieve stoornis te differentiëren, met gebruikmaking van basale symptoomdimensies.
Met de Comprehensive Psychopathological Rating Scale (CPRS), een semi-gestandaardiseerd psychiatrisch diagnostisch interview, is eerder bij een psychiatrische patiëntengroep met verschillende psychiatrische aandoeningen (depressie, psychotische stoornissen, angststoornissen etc.) onderzoek verricht naar het bestaan van basale symptoomdimensies. Er werden zes basale symptoomdimensies van psychopathologie gevonden:

1) emotionele ontregeling
2) motivationele remming,
3) motivationele ontremming,
4) autonome dysregulatie,
5) perceptuele desintegratie en
6) desintegratie van het gedrag.

Met behulp van deze dimensies werd in een eerste stap de samenstelling van het melancholische subtype volgens de DSM-IV onderzocht. Vervolgens werd onderzocht of een gevonden differentiatie een sterkere empirische onderbouwing heeft met externe

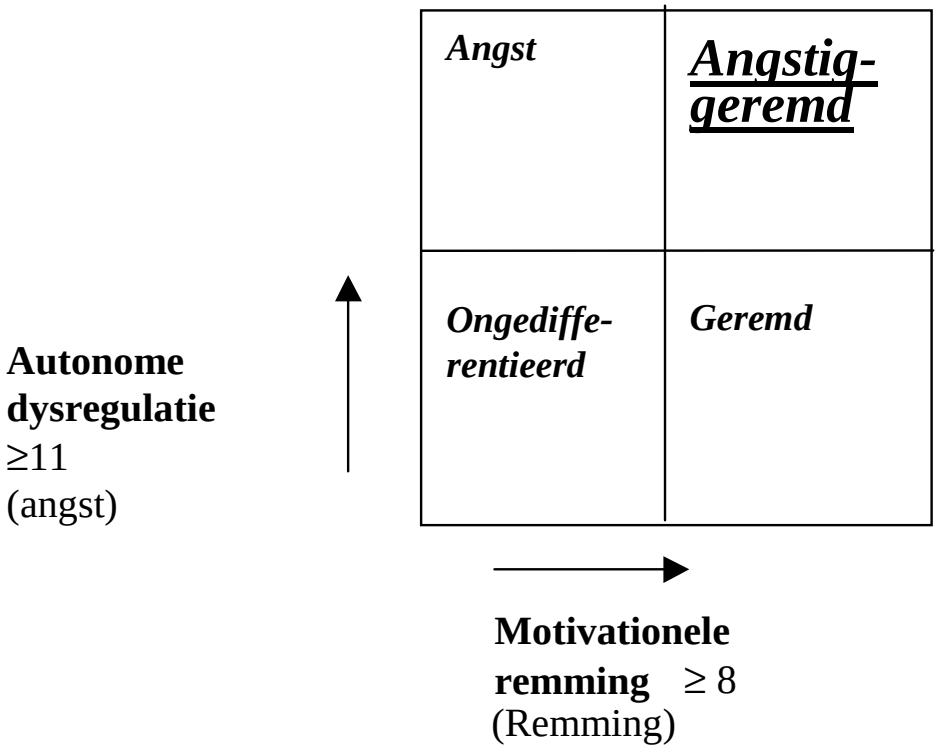
valideringskenmerken. We gebruikten daartoe het model van Robins & Guze voor de validering. Dit model onderscheidt de volgende valideringsniveaus:

1) de klinische beschrijving - met fenotype,
2) familieonderzoek,
3) laboratorium bevindingen,
4) uitkomstonderzoek,
5) persoonlijkheid en stressfactoren als onderscheidbare gebieden

Het melancholische subtype bleek gekenmerkt te zijn door de interactie tussen scores op de dimensies autonome ontregeling (Angst) en motivationele inhibitie (Remming).
Het bleek dat het melancholische subtype een relatie had met de combinatie van hoge (boven de mediaan) scores voor angst en remming. Vanuit deze 2 dimensies werden 4 (multidimensionele) subcategorieën geconstrueerd. Op basis van deze twee hoge dimensie scores werden 4 subgroepen gecreëerd. In verband met de overlap van hoge scores van angst en remming met het melancholische subtype, lag de nadruk van dit onderzoek op de hoog angstig-geremde subgroep in het rechterboven quadrant (**Figuur I**). We suggereerden dat deze subgroep een herdefinitie zou kunnen zijn van het melancholische subtype.

In de hoofdstukken 2 t/m 5 worden van het nieuwe multidimensionele subtype, hoog angstig-geremde depressie, de diverse valideringsniveaus verder uitgewerkt. Hoofdstuk 6&7 beschrijven een herziening van dit subtype.

Figuur 1: Vier dimensionele kwadrant van angst en remming



Het hoog angstig-geremde subtype

Hoofdstuk 2, Het hoog angstig-geremde subtype als fenotype en de relatie met familiair voorkomen van depressie.

We beschouwden het hoog angstig-geremde subtype als een herdefinitie van het melancholische subtype en hypothetiseerden we dat dit subtype of fenotype hogere externe validiteit zou hebben dan het melancholische subtype volgens de DSM-IV, wat zich in deze validatiestap zou tonen in een sterkere relatie met familiair voorkomen van depressie.
Voor het beoordelen van familiair voorkomen van depressie gebruikten we de Family History Research Diagnostic Criteria voor depressie (FH-RDC) bij eerstegraads familieleden. Van alle patiënten voldeed 47.2 procent aan criteria voor een positieve familieanamnese. Van de patiënten met het melancholische subtype volgens de DSM-IV, voldeed 54.8% en van de hoog-angstig geremde subgroep voldeed 64.5% aan de criteria voor een positieve familieanamnese. Na correctie waren alleen nog patiënten met het hoog angstig-geremde subtype significant gerelateerd aan een positieve familieanamnese voor depressie.

Hoofdstuk 3, Laboratorium bevindingen

In dit hoofdstuk werd de valideringsstap met betrekking tot laboratoriumuitkomsten beschreven. Als uitkomstmaten kozen we voor het hormoon plasma cortisol en het neuropeptide plasma Arginine Vasopressine (AVP). Eerder is gevonden dat depressie in het endogene spectrum (dus ook volgens de DSM) werd gekenmerkt door een veranderende sturing van de Hypothalamus-Hypofyse-Bijnieras (HHB-as) met als centrale hormoon cortisol. AVP lijkt een belangrijke rol te spelen bij de biologische ontregeling van affectieve stoornissen. De stof heeft een modulerende rol op de HHB-as en bij stress zijn er aanwijzingen dat er een verhoging van de productie plaatsvindt. Sturing van de modulerende werking van AVP op de HHB-as wordt dan ook van belang gezien bij de toekomstige ontwikkeling van de farmacologische behandeling van depressie.
De hoog angstig-geremde subgroep vertoonde een significant verhoogd plasma AVP . De melancholische subgroep liet geen verhoogd AVP zien. Verder vonden we binnen de gehele patiëntengroep een significante correlatie tussen cortisol en AVP, waarbij de hoog angstig geremde subgroep de sterkste correlatie vertoonde.

Hoofdstuk 4, Uitkomst-onderzoek

In dit hoofdstuk beschrijven we de follow-up en lange termijn uitkomst. Er waren 7 meetmomenten over twee jaar. Als uitkomstmaat gebruikten we internationaal geaccepteerde criteria voor volledige remissie. Alleen de hoog angstig-geremde subgroep vertoonde een significant langere duur tot volledige remissie. Onafhankelijk gaven de dimensies angst en remming geen verschil in het beloop. Met deze valideringsstap toonde we aan dat de hoog angstig-geremde subgroep zich differentieert door een langer durend herstel.

Hoofdstuk 5, De klinische beschrijving met persoonlijkheid

Een traditionele visie is dat voorafgaande aan depressie, “bij normale toestand”, endogene depressie, in tegenstelling tot exogene depressie, zal samengaan met een normale

persoonlijkheidsstructuur. Tijdens volledig herstel van een depressie zal er dan, bij het ontbreken van restverschijnselen, wederom dezelfde persoonlijkheidstoestand zichtbaar zijn als dat deze was voor de ziekte. Bij de hoog angstig-geremde subgroep zal er, "als herdefinitie" van endogene depressie, dus hypothetisch sprake kunnen zijn van een normale persoonlijkheid. Er is echter nog nooit op een empirische wijze aangetoond dat endogene depressie minder vaak zal samengaan met een afwijkende persoonlijkheid.
Om de hypothese te toetsen hebben we in dit hoofdstuk gebruik gemaakt van het persoonlijkheidsmodel van Robert Cloninger, de Temperament and Character Inventory (TCI). De karakterschalen verwijzen naar dimensies, welke de persoonlijke en sociale effectiviteit beïnvloeden en geassocieerd zijn met het verwerven van een bewust zelfconcept. De dimensies ontwikkelen zich, door diverse psychologische en sociale factoren in combinatie met diverse interne factoren, tot de volwassen leeftijd. De temperamentschalen meten die aspecten van de persoonlijkheid, die waarschijnlijk erfelijk beïnvloed worden, automatisch zijn, onbewust de leerprocessen beïnvloeden en al vroeg in de kinderjaren geobserveerd kunnen worden.
Er zijn in dit model drie karakterdimensies; Coöperativiteit (Cooperativeness, CO), Zelf-stuurbaarheid (Self-directedness, SD) en Zelftranscendentie (Self-transcendence, ST), en vier temperament dimensies; Prikkelzoekend (Novelty-seeking, NA), Leedvermijdend (Harm-avoidance, HA), Sociaalgericht (Reward-dependence, RD) en Volhardend (Persistence, PER).
Verschillende studies hebben aangetoond dat de aanwezigheid van een DSM persoonlijkheidstoornis voorspeld kan worden door lage scores van de karakterdimensies SD en CO. Gedurende depressie vertoonde de gehele groep patiënten in vergelijking met een "gezonde" controlegroep een sterk verhoogde HA en sterk verlaagde SD.
Gedurende depressie was er geen duidelijk onderscheid tussen de patiënten met angstig geremde depressie en de andere patiënten met een depressie. Na 2 jaar beloop was er bij de gehele groep van patiënten tijdens volledige remissie een sterk verhoogde HA en een verlaagde ST ten opzichte van de controlegroep. De hoog angstig-geremde subgroep had gedurende remissie een verhoogde HA en een verlaagde SD in vergelijking met de controlegroep.
De melancholische subgroep had gedurende remissie alleen een verhoogde HA.
De angstig geremde subgroep differentieert zich dus gedurende remissie, met een lagere SD.
Voorzichtig kan worden geconcludeerd dat het subtype, als herdefinitie van endogene depressie, in tegenstelling tot de eerder genoemde traditionele visie, juist een verhoogde kans heeft op een afwijkende persoonlijkheid.

Herziening van het mutidimensionele hoog angstig-geremde subtype

Hoofdstuk 6, Validering van een subtype gebaseerd op hoog AVP met familiair voorkomen en dimensies van angst en remming als mengvorm.

Robins & Guze hebben bij de ontwikkeling van hun valideringsmodel geopperd dat verdere positieve ontwikkelingen van de diagnostiek waarschijnlijk leiden tot betere extern gevalideerde psychiatrische ziektebeelden. Dit zou vervolgens resulteren in verbeterde afgrenzingen van de ziektebeelden. Vervolgens zal dit weer kunnen leiden tot verdere verbeteringen in de kennis van relaties met externe parameters.
De verbetering van deze kennis zal dan eveneens weer positief kunnen bijdragen aan een verdere externe validering. Er zou dus een positieve cyclus gevormd kunnen worden, waardoor de kennis en de inzichten van psychiatrische ziektebeelden steeds meer kunnen gaan toenemen.

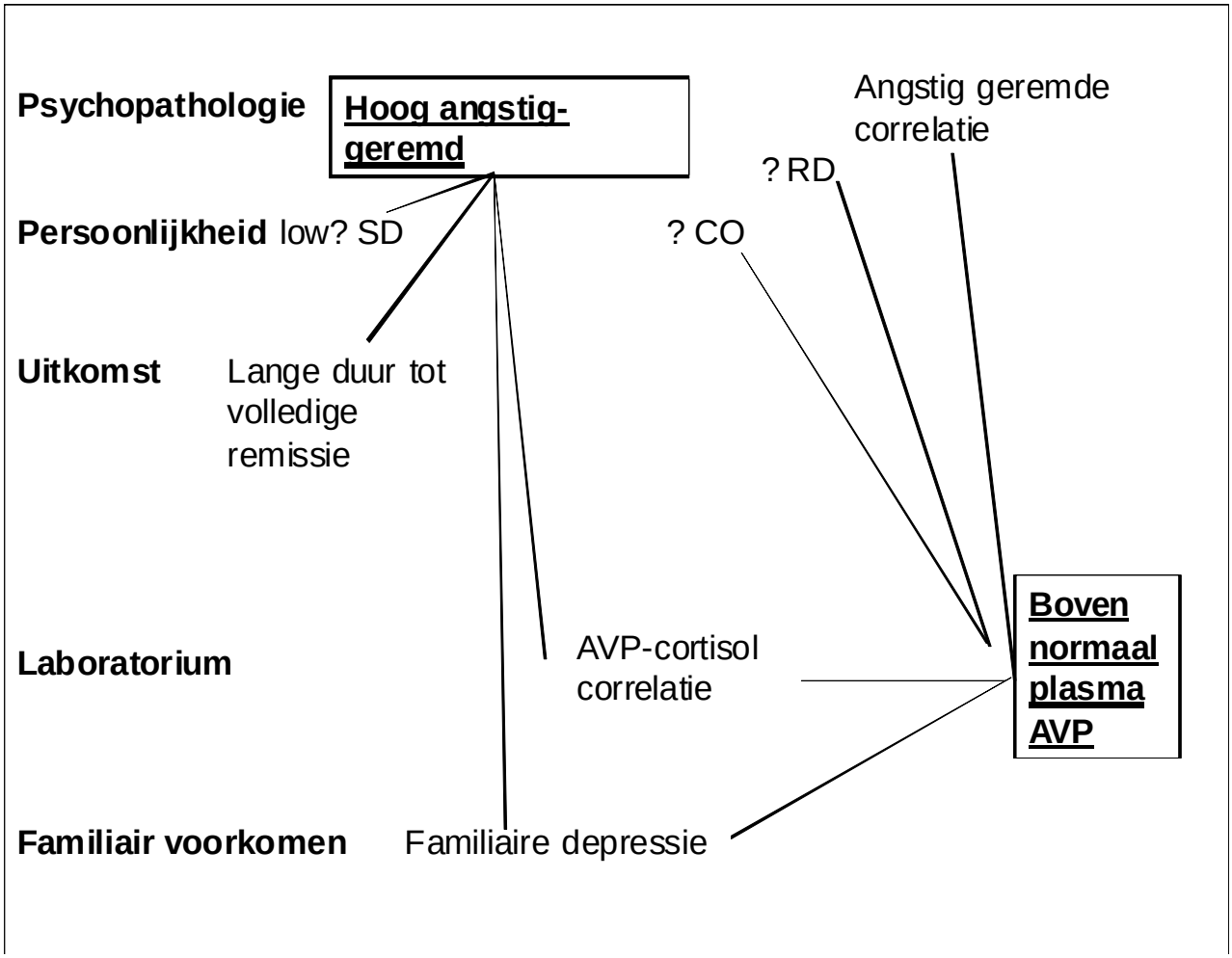
De vorming van het dichotome, hoog angstig-geremde subtype was een eerste stap van onderzoek. Doordat we scores van de dimensies angst en remming redelijk grof dichotomiseerden, was er de vraag of we op deze manier geen verlies van informatie kregen.
Bij statistische analyse bleek dat depressie met boven-normaal plasma AVP een significant hogere correlatie van angst met remming vertoonde dan de subgroep met normaal AVP. Deze bevinding kon betekenen dat patiënten met hoog AVP een meer variabele mengvorm van angst en remming zonder minimumintensiteit zouden kunnen hebben, dit was reden om het fenotype met een hoog AVP verder te onderzoeken.
We vonden eveneens een verhoogd familiair voorkomen van depressie bij patiënten met bovennormaal plasma AVP. In deze analyse verloor de hoog angstig-geremde subgroep de relatie met een verhoogd AVP, indien we corrigeerden voor dosishoogte van antipsychoticagebruik.

Hoofdstuk 7, Validering van een subgroep gebaseerd op hoog AVP met persoonlijkheid

In dit hoofdstuk werd net als bij hoofdstuk 5, voor relaties tussen de subgroep met bovennormale AVP en de persoonlijkheid, gebruik gemaakt van de TCI. Bij het persoonlijkheidsonderzoek met de TCI vonden we dat de subgroep met bovennormale AVP een lagere reward-dependence (RD) en coöperativiteit (CO) had tijdens depressie. De lage CO bleef bestaan tijdens het beloop over 2 jaar bij herstel van depressie. De subgroep met bovennormale AVP had dus eveneens een afwijkende karakterdimensie tijdens remissie.
Bij het belooponderzoek vonden we bij de subgroep met bovennormale AVP geen verandere relatie met de uitkomst.

Conclusie en toekomstig onderzoek

Bij de zoektocht naar een mutidimensionele herziening van het melancholische subtype, hebben we een aantal verbeteringen gevonden voor de differentiatie van het endogene spectrum bij de depressieve stoornis **(Figuur 2).**
De dichotoom gevormde, hoge angstig geremde subgroep kenmerkte zich in eerste instantie door een verhoogd AVP, een sterke correlatie tussen cortisol en AVP, vaker familiair voorkomen van depressie en een langere duur tot herstel en met één afwijkende karakterdimensie. In een 2^{e} stap vonden we een subcategorie met boven-normaal plasma AVP. Dit bleek een grotendeels familiair bepaalde depressieve subcategorie, welke zich verder kenmerkte door een menging van angst en remming, uitgedrukt in een significante correlatie tussen de dimensies angst en remming, een pecifieke verlaagde temperamentdimensie en karakterdimensie tijdens depressie, waarbij voor deze subgroep één onderscheidende verlaagde karakterdimensie bleef bestaan bij remissie.



Figuur 2 Samenvatting van de externe validatie van de hoog angstig-geremde subgroep en de subgroep met boven normaal plasma AVP . Vijf niveaus van onderzoek: psychopathologie (fenotype), persoonlijkheid, uitkomst, laboratorium en familiair voorkomen. (SD = Self-directedness; CO = Cooperativeness; RD = Reward-dependence; Angstig-geremde correlatie = Angstig-geremde fenotype zonder intensiteitscriteria)(*naar J.G. Goekoop 2009*)

In vergelijking met de melancholische subtypering volgens DSM-IV blijkt de fenotypering op basis van een tweedimensionele beschrijving een subdifferentiatie van depressie mogelijk te maken met een hogere validiteit. De theoretische betekenis van deze serie onderzoeken is dan ook dat blijkt dat een multidimensionele fenotypering een oplossing kan bieden voor de belemmering, die de DSM fenotypering vormt voor een externe validering.

Vanuit deze multidimensionele gevormde subgroepen en/of fenotypen zal verder biologisch, genetisch, beeldvormend en/of farmacologisch onderzoek meer kunnen opleveren dan de minder goed gevalideerde subgroepen, welke zijn gecategoriseerd volgens de DSM. Ook is er waarschijnlijk meer aansluiting met de modellen, welke worden gebruikt in het proefdieronderzoek.

De hoge AVP-cortisol correlatie zonder significante verhoogd AVP concentratie bij het hoog angstig geremde subtype kan het gevolg zijn van een verhoogd voorkomen van de V1b receptor in de hypofyse, dit veroorzaakt door langdurige stress en een familiaire kwetsbaarheid. Het boven normale plasma AVP subtype zou meer kunnen samenhangen met een genetisch verhoogde AVP synthese.
Deze en andere veelbelovende ontwikkelingen op het gebied van vasopressinerge mechanismen bij depressie zullen in de toekomst mogelijk leiden tot een specifiekere behandeling van deze ernstige ziekte.

Bij de vernieuwde versie van de DSM (DSM-V) wil men een aanvullend dimensioneel model gaan gebruiken voor de persoonlijkheidsstoornissen en wellicht zal in de versies daarna een aanvullend dimensioneel model gebruikt kunnen worden voor alle psychiatrische ziekten, en in het bijzonder voor de differentiatie van depressie.

Curiculum Vitae

Curriculum Vitae

Remco de Winter werd op 3 februari 1966 geboren in Leiden. In 1983 behaalde hij het MAVO diploma, in 1985 het HAVO diploma en vervolgens in 1987 het VWO diploma. Vervolgens was hij van 1987 t/m 1988 dienstplichtig militair. Na het afzwaaien startte Remco met de studie Geneeskunde aan de Universiteit Leiden. In 1993 begon hij met een onderzoeksstage in het Antoni van Leeuwenhoekziekenhuis (olv Dr. E.M. Rankin) gecombineerd met een laboratorium stage op het CLB (olv Prof. Dr. C.E. Hack) te Amsterdam met een onderzoek naar monoklonale antilichamen bij non-Hodgkin lymfoom. In 1994 behaalde hij zijn doctoraal en in 1996 behaalde hij het arts examen. Vervolgens begon hij als AGNIO op de Jelgersmapolikliniek (toenmalig behorende bij het APZ Endegeest, thans Rivierduinen) te Oegstgeest, dit was een combinatiebaan als behandelaar en als artsonderzoeker waarbij hij ook het eerste gedeelte van het onderzoek begon en waarvan in 2003 de eerste publicatie verscheen en wat leidde tot het proefschrift wat 3 december 2009 in het openbaar wordt verdedigd. In 2000 begon hij met de opleiding tot psychiater bij het Haags Leids Onderwijs Consortium. Het eerste jaar was op de acute opname afdeling (APA) van Parnassia te den Haag met als opleider Prof. dr. H.W. Hoek . De rest van de basisopleiding werd gevolgd in de Robert Fleury (thans Rivierduinen) met als hoofdopleider Dr.P.F. Bouvy, het tweede jaar werd verricht bij de Robert Fleury in Gouda, het derde jaar werd verricht op de polikliniek van de Robert Fleury te Leidschendam. Het keuzejaar werd verricht op de afdeling Ouderen Psychiatrie van de Robert Fleury te Leidschendam. De laatste stage Sociale Psychiatrie vond plaats bij de crisisdienst van Parnassia te den Haag met als opleider sociale Psychiatrie Prof. dr. A.M. van Hemert, dit werd eind 2004 afgerond. Eén januari 2005 werd Remco geregistreerd als psychiater. Vervolgens bleef hij werken bij de crisisdienst als coördinator van de spoedpoli (tot eind 2008) waarbij hij ook de spoedzorg bij PsyQ in Zoetermeer opzette. Aan het einde van dat jaar werd hij afdelingshoofd van het KCAP van PsyQ en bleef hij coördinator van de spoedpoli van de crisisdienst tot eind 2008. In juli 2007 werden de afdelingen KCAP en APA samengevoegd in een nieuwe kliniek als één gesloten acute opname afdeling met 52 gesloten bedden. Hiermee werd dit de grootste acute gesloten opname afdeling van Nederland. Deze kliniek valt nu onder de divisie volwassene van het zorgbedrijf Parnassia. Vanaf oktober 2008 is Remco Afdelingshoofd Zorg van deze afdeling. Verder is hij op dit moment bezig met het toewerken naar een Topreferent predicaat voor deze kliniek en coördineert hij een onderzoeksteam met enkele onderzoekslijnen op o.a. het gebied van suïcidaliteit en diagnostiek in de acute Psychiatrie.

Nawoord

Nawoord

Bij de totstandkoming van dit Proefschrift ben ik zoveel mensen dank verschuldigd. Het schrijven van dit proefschrift is een zeer lang en intens proces geweest waarbij er veel zaken gedurende deze periode mijn leven zijn gepasseerd. Getrouwd, vader geworden van 3 kinderen, de opleiding tot Psychiater gevolgd allerlei persoonlijke perikelen, zoals mijn lieve vader die op zijn 58e jaar in een zeer korte periode overleed aan een maligniteit, twee weken voor de geboorte van onze zoon. Er zijn perioden dat ik zeer intensief aan het proefschrift heb gewerkt maar ook perioden dat ik er gevoelsmatig veel te weinig aan deed en het niet meer kon voorstellen dat het ooit tot een goed einde zou komen en voor de zoveelste keer een klaagzang hield!
Ik wil mijn ouders bedanken en het spijt me zo dat mijn lieve vader veel te vroeg is gestorven zodat hij dit niet meer mag meemaken! Mijn moeder die zo belangrijk is en waar ik zoveel tegen aan kan zeuren, we elkaar wel en niet altijd begrijpen. Mijn lieve vrouw die soms een zeer sikkeneurige man had die wanhopig was en niet meer wist hoe het met dit boekje moest gaan lopen. Hoewel het nu af is kan ik echter niet beloven dat het sikkeneurige voor altijd weg zal zijn. Mijn lieve drie kinderen, bewust heb ik bijna nooit gewerkt aan mijn proefschrift als ze wakker waren, want hun jeugd is er maar één keer en daar kan ik zo van genieten. Twee van hen zijn nu zelfs bij de plechtigheid. En wat vind ik het jammer dat mijn schoonmoeder ook vorig jaar veel te vroeg is gestorven ik mis haar relativering zo vaak.
Al die lieve patiënten die voor de wetenschap een intensief onderzoek ondergingen. Waar ze twee jaar lang aan mee deden, 28 keer (84 buisjes) bloed gaven, meer dan 650 vragen beantwoordden, meerdere lijsten invulden met ruim 2200 vragen, diverse geheugenonderzoeken ondergingen, in de ochtend nuchter bij me kwamen en na afloop met een paar krentenbollen en een kop koffie weg gingen. Mijn dank is enorm en ik hoop oprecht dat niemand achteraf spijt heeft gehad van de enorme inspanning die dit tijdens één van de zwaarste perioden in een leven heeft gekost. Zonder de steun van de patiënt is de wetenschapsbeoefening in de Geneeskunde nergens.
Mijn vrienden die me steunden, de een meer dan de ander. Ik ben trots dat twee van hen me vandaag als Paranimf vergezellen. De één, een vriendschap die lang geleden op de middelbare school begon, en misschien was ik zelfs zonder deze vriend nooit aan een universitaire studie begonnen. Ik promoveer alsnog eerder (maar niet sneller!), ik koester je, en ook dank aan je ega. De ander, mijn grote studievriend, peetvader van mijn kinderen en nu ook psychiater waarmee ik heel veel deel, je (en ook weer niet!). Je bent al veel langer geleden gepromoveerd en ik hoop ook ooit nog iets op wetenschappelijk gebied samen met je kunnen doen, de toenemende concurrentie tussen GGZ instellingen maakt dit voor ons echter niet gemakkelijker. Jouw vrouw mag ik niet vergeten, altijd vriendelijk en opgeruimd en zonder haar was mijn leven heel anders verlopen, dan had ik mijn vrouw niet ontmoet.
Veel mensen uit Leiden-II en de deelgenoten in Baarn die altijd interesse bleven houden. Mijn hardloop maatjes, is het nu rennen of praten ik hoop nog dat we lang met elkaar fit mogen blijven. Mijn grote vrienden in Zoetermeer, jouw vader de anatoom was op verschillende wijze inspirerend, moge hij verder rusten in vrede. Mijn buren, in het bijzonder die hun huis ter beschikking stelden als ik rustig moest werken.
Mijn Norton en BSA vriendje die in al zijn bescheidenheid een duidelijke rol speelt, zie de omslag. De man die nu eindelijk een echte Triton heeft, heeft een unieke plaats in mijn

leven. Mijn studievrienden waarvan er velen zijn uitgewaaierd, ik hoop enkelen daarvan vandaag weer te ontmoeten. Mijn zwager en zijn vrouw die een unieke positie innemen. Mijn zwager die nooit moe en bang is, zonder hem was deze dag een stuk minder snel en goed georganiseerd. Mijn verre overbuurvrouw en overbuurman, die weten dat zonder hen dit proefschrift hier niet had gelegen. Het secretariaat van de Jelgersma polikliniek. De wetenschappelijk vruchtbare noodbarak waarin we gehuisvest waren, het was achteraf een wereldplek zo half verscholen in het bos, en wat was deze poli professioneel maar ook gezellig. De andere medewerkers, de artsen in opleiding, psychiaters en psychologen waarvan er hoogleraar zijn geworden en een daarvan heeft me ook bijzonder geholpen bij een publicatie. De Jelgersma Kliniek, het secretariaat met in het bijzonder de medewerkers van de toenmalige afdeling Querido. De studenten die me holpen, kostenloos met zeer veel inspanning. Trots kan ik er op zijn dat een van hen mij allang gepasseerd is en ik hoop weer ooit met hem te mogen samenwerken. Een ander is gelijk met mij aan de opleiding begonnen en ik koester zeer goede herinneringen aan deze tijd. De tijdelijke hoogleraar van de vakgroep Psychiatrie in Leiden, die het mogelijk maakte dat ik een verlenging kreeg met een "schaduwplaats" voor de opleiding.
De toenmalige aan de kliniek verbonden medewerkers en 2 hoogleraren. De medewerkers van het onderzoekslaboratorium, gewone laboratorium en in het bijzonder het toenmalige hoofd van het Lab. De neuropsycholoog, ik zie hem nog denken in zijn donkere met boeken en artikelen gevulde werkkamer. De collega's op het LUMC, veel goede herinneringen heb ik aan de relatief korte tijd op de kantoortuin. Diegene die ik volgens het reglement niet mag noemen, je hebt me erdoor heen gesleept mijn dank is zeer groot. De hooggeleerde farmacoloog en de laborante van het Rudolf Magnus instituut.
Mijn maatjes tijdens mijn opleiding en enkelen met wie ik nu nog goed bevriend ben.
Mijn collega's van het APA in Den Haag, waar ik mijn eerste opleidingsjaar doorbracht, mijn supervisoren. De mede assistent de laatste helft van het eerste jaar, jongen het heeft veel betekend het is jammer dat de wetenschap je niet trok ondanks je eindreferaat gerelateerd aan dit onderzoek. De collega's in Gouda. Veel dank naar mijn opleider, hij heeft er altijd in gelooft, ik heb op diverse terreinen heel veel van hem geleerd!
De medewerkers op de Hoge Roest, het secretariaat en mijn toenmalige supervisor en Kuifje fan aan wie ik veel goede herinneringen heb en de andere psychiater die ik nog veelvuldig in de stad tegenkom.
De medewerkers van de Crisisdienst. Wat was deze plek een verademing het was de perfecte afsluiting van mijn opleiding. Het toenmalige afdelingshoofd bedrijfsvoering. Het afdelingshoofd zorg van de crisisdienst die recent hoogleraar is geworden. Zonder hem was mijn eerste internationale artikel nooit verschenen. PsyQ Zoetermeer en een persoon in het bijzonder. De managers en directie van PsyQ voordat we opgingen binnen de divisie Parnassia. De ruimte die ik van hen heb gekregen. De Raad van Bestuur die voor innovatiegeld hebben gezorgd waardoor mijn huidige afdeling een "great place to be is" en daardoor de kans om het KCAP naar een toprefente kliniek te kunnen brengen. De medewerkers buiten KCAP, de voorzitter van het ochtendrapport, mijn enthousiaste collega met snor en een Guzzi, mijn evenknie op het KCVG en zijn mede AMT-er. De opleiders en net afgezwaaide opleider bij de ParnassiaBavogroep in Den Haag, ook jij en je ega zijn nog ;ang niet van me! De collega AMT op het CDP en de overijverige daar werkende SPV. Mijn huidige divisie management. Mijn voorganger, die erg dichtbij woont. Maar weinig mensen zijn zo gastvrij. De directie die me in de gelegenheid heeft gesteld

om meer praktisch georiënteerd onderzoek te doen. Alle artsen en psychiaters in opleiding die op mijn huidige afdeling het fort versterken, mijn supervisanten die altijd weer luisteren. De geneesheer-directeur. Mijn collega's op de Poortmolen. Mijn mede KCAP psychiaters, een goede combinatie, ik ben blij dat jullie ook geïnteresseerd zijn in de wetenschap en vooral dat we het samen kunnen doen.
Diegene die nu onderzoek gaan doen ik ben uitermate blij met jullie. Mijn TKZ maatjes! De collega's waarmee ik in diverse commissies zit. Mijn collega die altijd weer van alles weet te regelen. De neurologen in opleiding en die ene neuroloog i.o. die maar weer altijd veel geduld moet hebben maar het gaat lukken... Mijn mede AMT waarvan er ook één een punthoofd heeft gekregen en de ander weer haar, van de perikelen rondom dit boekje. Het "kernteam" en secretariaat van het KCAP die zoveel raad weten met de laatste loodjes. En als laatste de rest van mijn huidige afdeling al die medewerkers die mij maar bezig zien zijn met andere zaken "buiten de afdeling" en zich misschien afvragen wat doet die man nou, dank voor het geduld en ik hoop dat het KCAP nog "grootser" zal worden dan het al is. En tja ik besef dat ik toch een aantal mensen vergeet! Maar mocht ik je zien … ik maak het goed