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

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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).

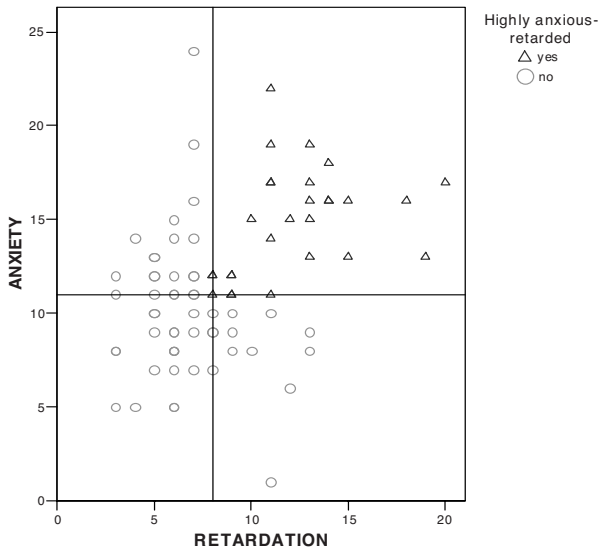
According to this data, emotional dysregulation seems to be the general dimension of dysregulation in depression. The two other basic symptom dimensions, retardation and anxiety, appear to play more of a differentiating role in depression.

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.

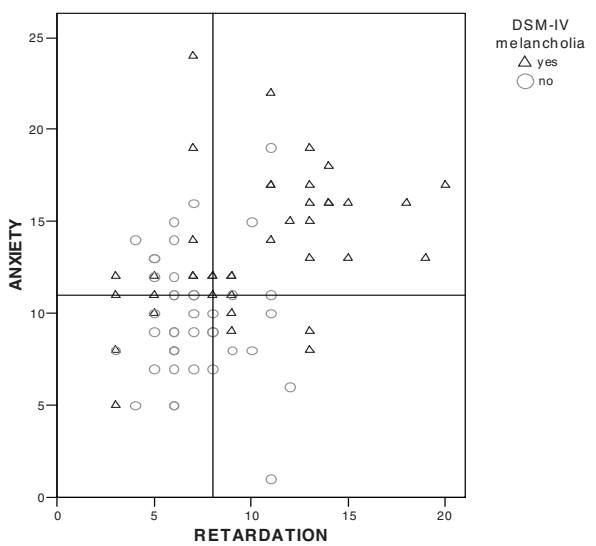
Based on the dependency of the melancholic subtype on the combination of above-median scores for anxiety and retardation a highly anxious-retarded subcategory was constructed on the basis of this phenotypical combination (chapter 2, De Winter et al. 2004) (see upper-right quadrant in **Figure IA**). 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).

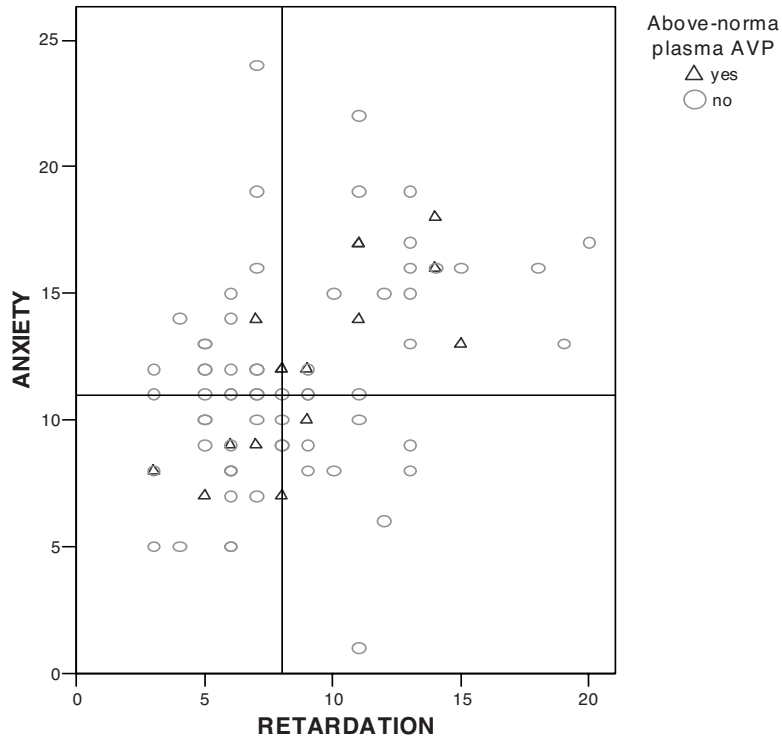
This relationship was indeed stronger than the relationship between this highly anxious-retarded subcategory and the AVP concentration as a continuous variable. The significance of this relationship was however lost on its turn after correction for the dose of antipsychotic treatment as a covariate. 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.

Figure 2
The anxious-retarded clinical picture in depression with above-normal plasma AVP concentration characterized by the increased correlation between anxiety and retardation. Reference lines correspond with median scores.



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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