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

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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 ^{o}C. Within 30 min, plasma was separated, in a cooled centrifuge, and stored at -80 ^{o}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 "best informant" for the patient, 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): 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 ± standard 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 anxious-retarded 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.

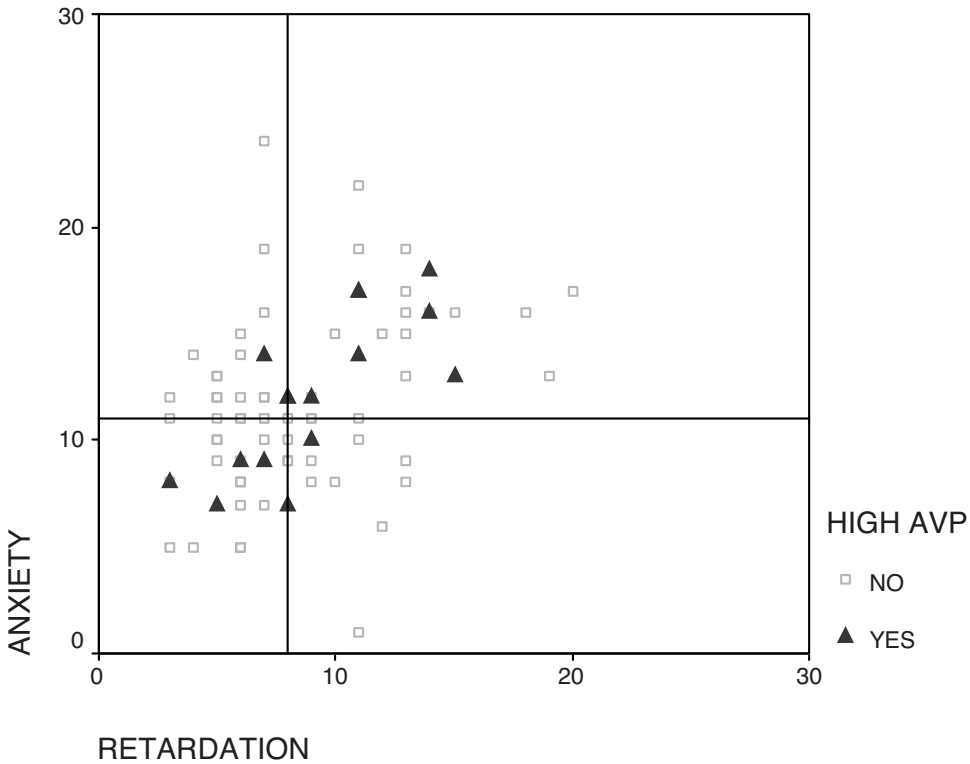
3.3.2 Depression with above-normal AVP and the correlation between anxiety and retardation

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 "above-normal plasma AVP". 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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