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

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

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Abstract

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

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

1 Introduction

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

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

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

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

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

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

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

2 Materials and methods

2.1 Patients

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

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

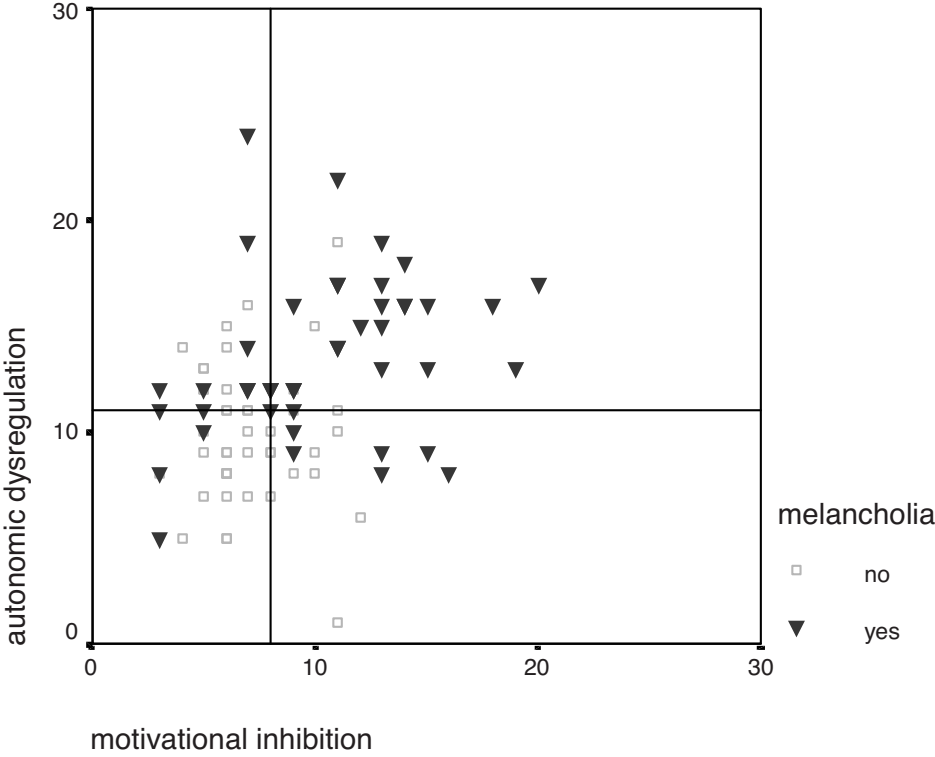
2.2 Psychopathological assessment

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

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

Figure 1

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



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

2.3 Family history

- A. Semi-standardized procedure for family history taking of first-degree family members was adopted corresponding with the criteria for FH-RDC Depressive Disorder (Andreasen et al. 1986a) with a minimal modification in the direction of the DSM-IV. All patients were asked by RFP de W, whether a depressive disorder fulfilling the criteria ever occurred in one of the parents, siblings, or children. In case of doubt by the patient (n=4) about the presence or absence of symptoms in a family member, a family member as 'best informant' for the latter was asked the same question to avoid false negative diagnoses. For confirmation of familial depression at least one first-degree family member had to fulfill the following criteria (A–D): A (1) Evidence of a depressive mood or loss of interest; and (2). Three additional signs or symptoms such as sleep change, appetite or weight change, loss of energy, psychomotor agitation or retardation, guilt or self-reproach, impaired concentration, or suicidal behavior.
- B. At least one of the following associated with the symptoms in A: (1). Electroconvulsive therapy or antidepressant medication; (2) hospitalization; (3) treated for A1 or A2; (4) gross impairment in work, housework, or school, or social withdrawal; (5) four associated symptoms in A2.
- C. No evidence of a chronic non-affective deteriorating course (but may have some residual symptoms) other than accounted for by alcoholism.
- D. Duration of at least 2 weeks; this criterion was used for all symptoms described in A. In this way diagnoses of familial depression were made conservatively and the sensitivity was slightly enhanced by introducing a second informant in 4 cases.

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

2.4 Statistics

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

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

3 Results

3.1 Demographic and clinical characteristics

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

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

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

Table 1

Inter-relations between 3 subcategories of major depression.

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

Numbers of the denominators represent patients of the categories in the rows; numbers of the numerators represent patients of the categories in the columns.

^a Chi square: $p = 0.02$; ^b $p < 0.001$.

Table 2

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

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

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

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

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

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

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

4 Discussion

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

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

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

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

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