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

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1

General introduction

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I) Description of major depressive disorder

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

Current classification

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

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

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

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

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

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

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

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

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

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

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

II) Categorical subtypes of depression and the concept of endogenicity

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

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

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

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

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

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

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

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

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

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

B. Three (or more) of the following:

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

III) External validation of diagnostic concepts

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

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

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

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

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

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

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

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

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

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

V) The nosological view of Karl Jaspers

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

They found 7 major primary symptom dimensions of psychopathology;

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

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

VI) Main questions of this thesis

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

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

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

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

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

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

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

The Temperament and Character inventory (TCI) differentiates three character dimensions: Self-directedness (SD), Cooperativeness (CO) and Self-transcendence (ST), and four temperament dimensions: Novelty-seeking (NS), Harm-avoidance (HA), Reward-dependence (RD) and Persistence (PER). Several studies have shown that low scores on SD and CO predict the presence of a personality disorder classified by the DSM-IV (Cloninger et al. 1993, Svrakic et al. 1993, Bayon et al. 1996, Joyce et al. 2003). We primary used the two character dimensions in order to validate the multidimensional phenotype in this direction.

Step 2 laboratory findings *(chapter 3)*

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

Step 3 family studies *(chapter 2)*

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

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

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

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

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