Syndromes versus symptoms : towards validation of a dimensional approach of depression and anxiety

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Summary:

Depressive and anxiety disorders are very common in the general population and cause a great deal of disability and health-related costs. The disorders often have a chronic-intermittent course with interchanging periods of remission and recurrence. These course characteristics make the disease burden of depression and anxiety especially heavy, because the disorders are long-lasting and hard to cure completely. Unfortunately, the knowledge about the etiological mechanisms that underlie the onset and course of depression and anxiety are largely unknown. In addition, although general guidelines exist, the treatment of patients often relies on trial and error, since well-defined one-to-one treatment indications are still unavailable.

A large amount of research has been conducted to investigate the underlying mechanisms that cause depression and anxiety. In recent years, research has come to focus especially on biological mechanisms, including: the stress-system, genetics, structural and functional neuro-imaging and more. In addition, environmental aspects that have been investigated are childhood trauma and life-events. Psychological mechanisms that have been proposed, include: coping mechanisms and the experience of social support. More recently, studies have looked at the interactions between genetic and environmental factors in causing psychopathology. Despite many results and a large volume of suggestive evidence, etiological research has yielded relatively little results. In addition, effect sizes of the few consistent findings have been small.

Several reasons for the lack of progress in understanding the etiology of depression and anxiety have been proposed, including lack of statistical power and focus on the wrong mechanisms. However, it has also become clear that the nature of the currently used Diagnostic and Statistical Manual (DSM)-diagnoses hampers scientific research in three important ways. First, an inherent problem of DSM-diagnoses is the occurrence of comorbidity. Depressive and anxiety disorders co-occur more often than expected by their strict separation in the DSM. In fact, depression and anxiety show considerable overlap in their symptomatology and it is likely that, given their frequent co-occurrence, they share a considerable part of their etiology. The latter is further supported by the similar treatment indications for depression and anxiety (usually selective serotonin reuptake inhibitors and/or cognitive therapy). Restricting research to either depression or anxiety is bound to limit the insight that can be gained in their shared etiology. A second issue of DSM disorders is their large within-diagnosis heterogeneity: no two depression patients are the same. This has important implications for research and clinical practice. Etiological research is hampered by diagnostic heterogeneity because within-diagnosis differences are likely to obscure between-group differences (e.g. patients vs. controls). In other words: DSM-diagnoses decrease the statistical power to detect effects of etiological and/or cinical factors. In addition, the large variability in symptomatology across patients with similar diagnoses suggests that different underlying mechanisms play a role. In addition, in clinical practice, within-diagnosis heterogeneity leads to unspecific treatment indications, forcing clinicians to rely

on prior experience and/or trial-and-error. To better capture symptom-specific etiological effects, the specificity of the clinical description should be increased. The third and final problem of the DSM categories is the assumed discontinuity between ill and non-ill. In reality, symptoms of depression and anxiety are continuously distributed in the general population without a clear cut-off between depressed and non-depressed. The implication of dichotomising these continuous phenomena is that the statistical power to detect any etiological/treatment effect is seriously decreased. In addition, a large group of sub-threshold patients, who do not meet DSM-criteria but have relevant problems are excluded from research and have no formal diagnostic status or treatment indication in clinical settings.

Several attempts have been made to solve the problems summarized above in new and/or upcoming versions of the DSM. For instance, depression subtypes were proposed to decrease diagnostic heterogeneity. Also, the diagnosis of mixed depression-anxiety was proposed to overcome comorbidity between the two disorders and sub-threshold categories were proposed to cover persons, who do not meet full disorder criteria. However, these measures do not address the elemental problems of the DSM, but only tackle specific problems in a piecemeal fashion. To really overcome the abovementioned problems, the approach of the DSM should be changed on a more elemental level. A viable alternative could be a dimensional approach to describe individuals' patterns of symptomatology. Dimensions have two defining characteristics. First, they are continuous without a fixed cut-off between healthy and diseased. Second, they cover specific symptom-domains. A dimensional approach assumes that multiple dimensions coexist and that an individual's clinical state can be described by the pattern of scores on the dimensions.

A well-known and simple dimensional model to describe the symptomatology of depression and anxiety is the *tripartite model*, developed by Clark & Watson in 1991. This model was developed to describe common and specific symptom-dimensions of depression and anxiety with three dimensions. A dimension of General Distress (GD) included symptoms of negative affect and general psychological distress, which are common for depression and anxiety and account for much of their overlap and/or comorbidity. In addition, two more specific dimensions were proposed. The dimension of Anhedonic Depression (AD) includes the lack of positive affect and energy, which is specific to depression. The dimension of Anxious Arousal (AA) includes symptoms of somatic hyperarousal, which are specific to anxiety, and panic in particular. This three-dimensional structure has been shown to be a valid - although simplified - description of the symptomatology of depression and anxiety. The initial model was followed by a series of model-elaborations (e.g. the hierarchical model), which have been successfully used to describe the latent structure of DSM-disorders and uncover the shared basis of both depression and anxiety. Thus, the tripartite model and its cousins have been shown internally valid by a large body of scientific work, supporting the validity of a dimensional approach to depressive and anxiety disorders.

One of the most urgent problems of the current DSM-diagnoses is the lack of correspondence between the diagnoses and underlying etiological mechanisms and between diagnoses and clinical implications. If dimensions were shown to have consistent associations with etiological mechanisms and clinical characteristics, this would indicate that they are *externally valid* and that they better explain the way symptoms occur in reality. Although there is ample support for the internal validity of dimensional approaches such as the tripartite model, the external validity of the dimensions has not been thoroughly evaluated. For dimensions to be implemented as standard diagnostic tools, they should first be shown to be internally and externally valid beyond reproach, especially given the reservations many working clinicians still hold against dimensions.

The aim of this dissertation was to evaluate the internal and external validity of a dimensional approach to depression and anxiety. Different approaches were taken: the optimal measurement of dimensions was investigated (Chapters 2 and 3), the associations between dimensions and etiological factors were investigated (Chapters 4-6) and the associations between dimensions and clinical course were investigated (Chapters 7 and 8).

The first two chapters were intended to evaluate and, if necessary, to improve the measurement of dimensions. In **Chapter 2**, the development and validation of a measure of the tripartite dimensions was described: the 30-item adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ-D30). The scales were shown to have good internal consistency across healthy and anxious/depressed groups. Also, construct validity and convergent validity were found to be adequate. Therefore, the MASQ-D30 was used in several of the subsequent chapters as the main dimensional measure. In **Chapter 3**, a different approach was taken to the development and validation of dimensional measures. Here, the best-fitting factor-structure of the widely used Inventory of Depressive Symptomatology was identified with confirmatory factor analyses. A 3-factor structure was shown to fit best and most consistently. Of these 3 factors, two were shown to be usable as reliable one-dimensional subscales with item-response analyses (Rasch). These dimensional scales were: 'mood/cognition' and 'anxiety/arousal'. Importantly, these results showed that more specific dimensional measurement does not have to rely on specialized instruments but is also possible with an existing and already widely used questionnaire.

In the next three chapters, the validated dimensional measures from chapter 2 were associated with biological and environmental etiological factors. In **Chapter 4**, the association between the tripartite dimensions and the activity of the Hypothalamo-Pituitary-Adrenal (HPA) axis was investigated. The HPA-axis activity was assessed with a series of saliva samples, taken across one day (at awakening and after 30, 45 and 60 minutes; at 22.00 and 23.00 pm) and the next morning after awakening, following dexamethasone ingestion the evening before. These data enabled assessment of the cortisol awakening rise (CAR) curve, basal cortisol and dexamethasone suppression. The

results showed that the tripartite dimensions were only associated with the CAR and that this association had the shape of an inverted U. These non-linear associations persisted after adjustment for demographic, psychiatric (including DSM-diagnosis) and sampling factors. These results indicated that the CAR first increased with increasing dimensional severity, but from a certain point started to decrease again, which indicated the existence of a negative feedback system. These findings could explain why both increased and decreased HPA-axis activity have previously been observed in depressed patients and showed the dynamic role of the HPA-axis in psychopathology. In **Chapter 5**, the association between the tripartite dimensions and the metabolic syndrome and its components were investigated. There has been a well-documented bidirectional link between depression and the metabolic syndrome and the present study was intended to see which symptom-specific associations underlie this general association. The metabolic syndrome (elevated waist circumference, increased triglycerides, increased blood pressure, and fasting glucose, and reduced high-density lipoprotein [HDL] cholesterol) was present in 20.1% of participants. Only increases on the AA dimension were associated with increased risk of having the complete metabolic syndrome. In addition, AA was only significantly associated with three of the five individual components (waist circumference, triglycerides and blood-pressure). This indicated that the generally observed association between depression and the metabolic syndrome was primarily driven by more specific underlying associations between AA and particular metabolic syndrome components.

Chapter 6 focused on environmental etiological factors. Life events have repeatedly been suggested to play a role in the onset and course of depression and anxiety. A longitudinal approach was used to model the change over time of dimensional scores in reaction to both negative and positive life events that occurred between repeated measurements. The results showed that GD most consistently increased in response to negative life events and that AD most consistently decreased in response to positive life-events. The life event induced changes were seen across groups with different course-trajectories (i.e. early remission, late remission/recurrent, chronic). This indicated that by modeling within-person change, specific effects of life events were captured that would not be captured by single measurements and/or DSM-defined course-trajectories. Closer inspection of the associations of individual life events showed that some life events affected all dimensions and some had dimension-specific effects, illustrating the complexity of the relationship between life events and mental well-being.

The next chapters dealt with the prediction of the course of depression and anxiety. Despite similar DSM-diagnoses, two patients can have different prognoses due to the large within-diagnosis heterogeneity of symptomatology, severity and context. Dimensions could be used to more specifically describe patients' clinical picture and, thus, to increase the specificity of patients' prognoses. This approach was evaluated in Chapters 7 and 8, using different dimensional models. In **Chapter 7**, the added value of the tripartite model dimensions to predict course and outcome after 2 years was

evaluated. The dimensional scores were assessed at baseline and the course over the following 2 years was assessed with standardized diagnostic interviews and a life-chart method. Two outcome variables were used: (1) diagnosis after two years (healthy, single depression, single anxiety and comorbid depression-anxiety) and (2) course-trajectory (early remission, late remission/recurrence and chronic course). The results showed that AD specifically predicted increased risk of single depression, AA predicted single anxiety (mainly panic disorder) and GD predicted comorbid depression-anxiety after two years. In addition, GD predicted an increased risk of less favorable overall course-trajectories (late remission or chronicity). These results persisted after adjustment for traditionally used prognostic factors at baseline, such as DSM-diagnosis. Taken together, these results indicated that specific dimensions have added value as prognostic factors. In **Chapter 8**, a similar approach was taken, but here the IDS dimensions of mood-cognition and anxiety-arousal were used and their prognostic ability was compared with the IDS total score. The results showed that the IDS total scale predicted single depression, anxiety and comorbid depression-anxiety after two years. The dimensions showed more specific associations. Mood/cognition at baseline predicted an increased risk of single depression and worse course trajectories of depressive symptomatology. Anxiety/arousal predicted single anxiety (mainly panic) after two years and worse course trajectories of anxiety symptomatology during follow-up. Both dimensions predicted comorbid depression-anxiety after two years. All associations persisted when adjusted for other well-known prognostic factors. These results supported the idea that breaking up generic instruments into more specific dimensions enables us to better specify prognosis.

Together, the presented chapters were intended to validate a dimensional approach to depression and anxiety. Chapters 2 and 3 clearly showed that it is possible to validly measure dimensions with optimized instruments. Chapters 4 and 5 showed that the use of dimensions benefits the investigation of complex (non-linear) biological associations and the identification of symptom-specific associations. Importantly, the results could explain previous inconsistencies in the literature. Chapter 6 showed that dimensions capture the dynamic and complex effects of life events on depressive and anxiety symptomatology. In addition, chapter 6 showed the potential of modeling within-person change on dimensions as a very useful outcome variable to capture etiological effects. Chapters 7 and 8 showed that dimensions could be used to predict the prognoses of depressive and anxiety disorders more specifically.

This research project had several strengths (e.g. validated dimensional measurements, large sample sizes and careful adjustment for confounders/mediators). However, the results should also be interpreted in the light of some limitations including: limited generalizability outside outpatient populations, the use of simplified dimensional models and sample attrition over time.

In conclusion, the results of this dissertation provided a comprehensive overview of the added value of dimensions in depression and anxiety research. The results also

confirmed that dimensions are not merely internally, but also externally valid. Importantly, the results showed that dimensions can have much added value in research, without taking very much time and effort to assess.