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Chapter 9: Discussion

9.1   Background

The current categorical DSM-diagnoses have brought marked advantages to the field of psychiatry. However, they also have had clear disadvantages, which have hampered research into the underlying mechanisms of diagnostic categories and, in clinical practice, have led to unclear and unspecific treatment indications (Clark et al., 1995; Widiger & Clark, 2000; Widiger & Samuel, 2005). Therefore, the interest for other paradigms to classify patients has been growing. An alternative dimensional approach has gained consistent and serious attention (e.g. Kendell, 1989). Multi-dimensional symptom-patterns to describe patients are very specific, do justice to continuity of psychopathological phenomena and do not have the problem of comorbidity (Widiger & Samuel, 2005). The idea of dimensional diagnostics appeals to many and it was even considered for inclusion in the DSM-V (Helzer et al., 2008). However, it was concluded that the evidence for a fixed set of valid and clinically useful dimensions is presently too limited to merit a paradigm-shift in psychiatric diagnostics (First, 2005; Frances, 2009). Dimensions should first be shown to be valid beyond reproach and to have considerable added value compared to the existing system (Frances, 2009).

9.2   Aims of this dissertation

Thus far, the majority of dimensional research has focussed on the structure of symptom dimensions on a phenomenological level (e.g. Clark & Watson 1991; Watson 2005; Krueger, 1999; Kotov et al., 2011). Although very important, these investigations of internal validity should be expanded with investigations of *external validity*: the dimensions should be associated with other, hypothetically related variables that were not used to define them. In addition, it should be evaluated whether dimensional associations explain more variation in putative etiological variables than associations with DSM-categories. This is the only way to find out to what extent research has thus far been hampered by a flawed categorical diagnostic system. Therefore, the current project was aimed to gain more insight in the overall validity and added value of dimensions in depression and anxiety research.

The first part of this thesis focused on the issue of dimensional measurements and structural validity of dimensions. The rest of the studies were to investigate the external validity and added value of dimensions in etiological and clinical research. Also, it was evaluated whether dimensions capture dynamic symptom changes over time, enabling a new kind of research into the factors that affect mood and emotionality. Overall, the aim of the current project was to provide a substantiated overview of the possibilities of dimensions and, more importantly, a *proof-of-concept* for their use in depression and anxiety research.

9.3   Measuring dimensions

Although much is known about the internal validity of dimensional models, in the areas of actual model-operationalisation and measurement, studies have been sparse and results have been variable (e.g. Shankman & Klein, 2000). The original mood and anxiety symptoms questionnaire (MASQ; Watson et al., 1995) was developed to measure the dimensions of the tripartite model. However, results on the psychometric quality and construct validity of the MASQ have been mixed (e.g. Buckby et al., 2008; Boschen et al., 2006). In addition, the MASQ was very long (90 items) making it cumbersome and time-consuming, and therefore expensive to administer. Therefore, we made several alterations and improvements, resulting in a shortened 30-item adaptation: the MASQ-D30. In chapter 2, we showed that the MASQ-D30 had good and consistent psychometric characteristics. In addition, the results had two generic implications with regard to dimensional measurement. First, the results showed that, to achieve better differentiation between dimensions, scales should have limited and well-specified symptom coverage. This might seem very logical, but it is likely that previous tests of the tripartite model have been hampered by the fact that the used scales overlapped substantially and were too heterogeneous (e.g. Keogh & Reidy, 2000; Boschen & Oei, 2006; Buckby et al., 2008), making them unsuitable to measure distinct dimensions, with potentially distinct underlying mechanisms. Second, the case of the MASQ-D30 showed that measurement of dimensions is possible with simple 10-item scales and does not require elaborate questionnaires, clinician ratings or interviewing. Thus, including dimensions in research or clinical settings can be easy and quick, taking away some of the reservations against the use of dimensions (e.g. Frances, 2009).

In chapter 3, using an existing and widely used generic depression severity questionnaire, we developed and validated specific dimensional measures. This approach to dimensional measurement yielded additional insights in the way dimensions can be identified and measured. The results showed that the symptom coverage of the total IDS-SR is heterogeneous, multi-dimensional and falls apart into three distinct sets of items with different symptom-coverage. After fine-tuning with item-response theory (IRT) analyses, two of these item-sets ('mood/cognition' and 'anxiety/arousal') were shown to function well as dimensional measures, and thus, as IDS-SR subscales.

In addition to their practical use, these results had some general implications for the measurement of dimensions. First, the study showed that dimensions of depression and/or anxiety could be measured with existing severity scales, without having to resort to a new and specialized instrument. A downside of this approach could be that the number and coverage of the dimensions depend more on the available instrument than theory-driven instruments, such as the MASQ-D30. However, data-driven methods could be very helpful to verify if hypothesized distinctions between symptom-domains are generalizable and occur across different depression severity scales. Indeed, the distinction between mood/cognition and anxiety/arousal underlying the IDS-SR was in line with

much previous research using other scales (e.g. Shafer, 2006; Mineka et al., 1998). A second interesting implication stems from the fact that item-response theory (IRT)/Rasch analyses were used in addition to traditional factor analyses. These methods enabled the investigation of the actual unidimensionality and psychometric quality of each of the identified factors. Unlike popular belief, factor-analyses do not identify dimensions but latent structures. A *factor* is not a dimensional entity with a scale of measurement, but focuses on clumping items together on one point, based on optimisation of their covariance. Therefore, it cannot be assumed that the items falling onto one factor function together as a unidimensional additive subscale, with items lined up along an underlying severity dimension and with a higher score actually indicating higher severity (Wright & Masters, 1982). IRT/Rasch analyses can be done to evaluate whether items function in this way and the items can be added up to a truly unidimensional additive measurement scale. The IDS-SR results showed that after factor-analyses, thorough fine-tuning in the form of item-deletion or rescoring based on IRT/Rasch analyses was needed to achieve this optimal dimensional measurement. This indicates that the development of dimensional measurements should go further than only the establishment of factor structures. Initially, item response theory analyses were only conducted for the IDS-SR subscales and not for the MASQ-D30. Later Rasch-analyses of the MASQ-D30 showed that its subscales could indeed be regarded as unidimensional measurement scales (all items fit to the Rasch model; data not shown)

Taken together, dimensional measurement could be markedly improved and optimised by aiming for adequate differentiation between subscales and checking their unidimensionality. Also, measurement of dimensions does not have to be overly complex or time-consuming in daily practice.

9.4   Dimensions of depression and anxiety and biological factors

If dimensions were shown to have more specific or simple biological underpinnings than traditional diagnoses, this would support the assumption that specific symptom dimensions of disease rather than complete diagnoses are the natural end-points of pathological pathways. Therefore, the current dissertation set out to investigate the associations between dimensions and different biological pathways. In the next paragraphs, the results for two biological pathways are discussed.

9.4.1   Dimensions and the Hypothalamo-Pituitary-Adrenal (HPA) axis

In chapter 4, we described findings on the association between the tripartite dimensions and HPA-axis activity. The results showed that all three dimensions were associated with cortisol exposure during the hour after awakening in the morning. Interestingly, all associations had an inversed U-shape and were consistent across DSM-IV defined diagnostic groups.

Previous studies on the association between the HPA-axis and depression have yielded varied results. Part of these studies observed increased cortisol in patients (e.g.

Bhagwagar et al., 2005; Vreeburg et al., 2009; Holsboer et al., 2010). However, others found lower HPA-axis activity in depressed patients than in controls (Stetler & Miller, 2005; Huber et al., 2006; Knight et al., 2010) or found no difference between the groups (Strickland et al., 2002). Thus, so far findings have been inconsistent when using DSM-IV diagnoses. Interestingly, our findings in chapter 4 could explain this observed inconsistency. Depending on symptomatology, a group of patients can either have a low or high HPA-axis activity. In hindsight, previous finding need not be seen as inconsistent, but rather as only partly informative. The used categorical approach could only be used to detect point-to-point differences without seeing the much larger underlying continuum on which these points are located.

Our findings were in line with previous research. Veen et al (2010) used similar measures in a smaller sample and found a similarly shaped association with HPA-axis activity. In addition, of the studies that looked at severely affected inpatients, some found decreased HPA-axis activity (Posener et al., 2000) and some found increased HPA-axis activity (Maes et al., 1994; Posener et al., 2000). Also, within groups of elderly depressed patients, evidence was found for both hypo- and hypercortisolemia (Penninx et al., 2007; Bremmer et al., 2007). Although varied, these findings are all in line with the central implication of chapter 4: HPA-axis activity can vary within patient-groups as a function of symptom severity. Interestingly, Vreeburg et al (submitted) showed that outpatients with a low HPA-axis activity had a worse prognosis than those with a high HPA-axis activity. This is in line with the results in this dissertation, which showed that increased severity on e.g. General Distress is associated with lower HPA-axis activity (chapter 4) and worse prognosis (chapter 7).

Several possible mechanisms may contribute to lower HPA-axis activity in severely ill patients. It is most plausible that following prolonged severe stress, a decrease or downregulation of HPA-axis activity occurs (Oldehinkel et al., 2001; Meinlschmidt & Heim, 2005). The underlying mechanism is yet unknown but could consist of downregulation of CRH receptors in the pituitary, reduced synthesis or depletion of CRH, or increased sensitivity to negative feedback (Heim, 2000). Because the current results were based on epidemiological data, no conclusions could be drawn about this. However, the results did indicate how dimensions enable us to detect and incorporate the dynamic of these systems in psychiatric research.

9.4.2 Dimensions and the Metabolic Syndrome

The study described in chapter 5 was aimed to break down the previously reported association between depression and the metabolic syndrome into more specific parts. Earlier findings on this association have been mixed with reports of increased prevalence in depressed patients compared to healthy controls (e.g. Heiskanen et al., 2006) and others reporting no difference (e.g. Reedt-Dortland et al, 2010a; 2010b). These inconsistent findings were not surprising, given the observed heterogeneity of both DSM-defined depression and of the metabolic syndrome concept. In chapter 5, we decreased

this heterogeneity by associating specific symptom dimensions (General Distress, Anhedonic Depression and Anxious Arousal) with separate metabolic syndrome components (waist circumference, triglyceride level, HDL-cholesterol level, glucose level and blood pressure). The results showed that of the tripartite dimensions, only Anxious Arousal was associated with increased odds of the metabolic syndrome and with an increased number of metabolic syndrome components. Moreover, the associations were only significant for three of the five metabolic syndrome components (waist circumference, triglycerides and blood-pressure). These findings were replicated with the somatic symptoms subscale of the Beck Anxiety Inventory (BAI-som). Both in the analyses with the tripartite dimensions and the BAI, non-somatic anxiety symptoms were not associated with metabolic factors. Also, these findings were consistent across diagnoses and not explained by confounders.

Our results were in line with previous work. De Jonge et al (2006) proposed a specific somatic subtype of depression in patients with CVD, and Vogelzangs et al. (2011) suggested a metabolic subtype of chronic depression. The current results indicated that somatic symptoms are associated with CVD risk, irrespective of DSM-diagnosis, thus expanding these previous results.

Several possible mechanisms are thought to underlie the association between metabolic factors and psychiatric symptoms. From one direction, depressed/anxious state could lead to metabolic dysregulations through various pathways. Increased inflammatory markers have been found to be associated with more depression (Bremmer et al., 2008). Also, HPA axis overactivation could lead to altered lipid patterns, which could lead to other symptoms, such as overweight, abdominal obesity, and hypertriglyceridemia (Vogelzangs et al., 2009). In addition, prolonged activation of the sympathetic nervous system and deactivation of the parasympathetic nervous system could lead to hypertension and, thus, feelings of hyperarousal (Lambert et al., 2011). From the other direction, metabolic dysregulations could cause (somatic) symptoms of depression and anxiety (Alexopoulos et al., 1997; Mast et al., 2008). Alternatively, the link between psychopathology and metabolic dysregulation could be explained by external factors, such as a depression-related unhealthy life-style (Reedt-Dortland et al 2010b). Because of the observational design of the current study, the mechanisms and their causal directions could not be uncovered. However, the results clearly illustrated how breaking down heterogeneous syndromes into more specific parts is a feasible way to close in on specific underlying mechanisms.

9.4.3   Dimensions and other biological factors

Dimensions have also been shown to be very useful in other lines of biological research, not covered in this dissertation. Moreover, other research has also shown dimensions to be useful and valid.

Given the paucity of any or replicable results for DSM-diagnoses, the potential use of dimensional concepts in genetic research is particularly interesting. Research has been

relatively successful in showing that depression and anxiety are heritable and that this heritability is driven by different components (e.g. Mineka et al., 1998; Hettema et al., 2006). Interestingly, the structure of these heritability components was found to be quite similar to the tripartite and hierarchical models do (e.g. Hettema et al., 2006), suggesting that the heritability components correspond to phenotypic symptom-dimensions. However, to prove that dimensions (e.g. the tripartite model) really have a well-defined genetic basis, their variation should be shown to be (partly) heritable. Indeed, twin-research has shown that increased genetic load for psychiatric problems (an affected sibling), was associated with more variation in negative affect (Wichers et al., 2007). Thus, there seems to be preliminary evidence supporting the heritability of dimensions.

In contrast to heritability research, genetic localization studies have yielded limited or poorly replicable results (Bosker et al., 2010; Breen et al., 2011). Therefore, many have argued that studies have been too small to reliably detect the small effects of individual genetic loci (Wray et al., 2009; Abbott, 2008). However, as summarized in the introduction, the arbitrariness, discontinuity and heterogeneity of the used DSM-definitions are important contributors to the lack of power and lack of associations between genes and psychopathology. Using more homogeneous, empirically defined dimensional phenotypes could increase statistical power, forgoing the need to increase sample-size. Surprisingly, only few studies have tried to do this. Van Veen et al. (submitted) investigated the associations between the tripartite dimensions and several pathway-related gene-sets. They found that different dimensions showed associations with different gene-sets and thus are likely to have different underlying etiologies. Importantly, the effect-sizes were substantial in this study with R-squares ranging from 3.3 to 6.4. Although they need replication, these results indicate that the search for genetic loci underlying psychopathology does not have to be in vain if researchers are prepared to look outside the realm of DSM-defined diagnoses.

9.5   Dimensions and environmental factors

Adverse life-events have often been identified as risk factors for the development of depression and anxiety. However, the associated risk varies greatly across individuals (Kessler, 1997) and some life events are more strongly related with depression (e.g. Brown et al., 1995; Brilman & Ormel, 2001) or anxiety (Kendler et al., 1998; Goodyer et al., 1985) than others. Like for other etiological mechanisms, there seem to be no consistently identifiable associations between life-events and depression and anxiety. Instead, it is has been suggested that different life-events lead to changes in different symptom-domains (Keller et al., 2007; Keller & Nesse, 2005; 2006; Tiet et al., 2001). In addition, several factors have been proposed to affect or mediate the relation between life-events and psychopathology, such as social support (Cohen & Wills, 1985), coping (Billings & Moos, 1981), habituation and scarring (Kendler et al., 2000). Thus, the relations between life-events and psychopathology are very complex and are unlikely to be unraveled by simply comparing their occurrence-rates between groups of patients and

controls. In chapter 6, we investigated the associations between different life-events and specific symptom-dimensions. We used a longitudinal approach to model the change over time of dimensional scores induced by both negative and positive life-events that occurred between repeated measurements. The results showed that general distress increased in response to negative life-events and that anhedonic depression decreased in response to positive life-events. The life-event induced changes on dimensions were seen across groups with different course-trajectories (i.e. early remission, late remission/recurrent, chronic). Thus, life events induced similar dimensional changes in, for instance, chronically diseased and in people who were healthy and stable. 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. Taken together, our results had several implications.

1) Our results showed that general and symptom specific effects of life-events on symptomatology could both be captured by using multiple separate symptom-dimensions.

2) Our results indicated that different classes of life-events induced longitudinal change in one or more symptom-dimensions. Making a distinction between negative and positive life-events, we found on the one hand that negative life-events led to increases in general distress. On the other hand, we found a more specific effect of positive life-events on anhedonic depression.

3) Our results further supported the validity of anhedonic depression (lack of positive affect) as a distinct clinical entity, which responds independently to particular environmental triggers. In contrast, general distress was shown to respond to both negative (mainly) and positive life-events, which was in line with its supposed role as a general severity indicator (Clark & Watson, 1991).

4) We found that life-events have detectable effects on within subject change in mental state. Importantly, life-events explained variance in mental state that was not captured by traditional diagnostic methods, because change on dimensional scales better captured the dynamic of psychiatric problems over time. This dynamic has been shown previously to play an important role in the susceptibility to psychopathology (e.g. Wichers et al., 2007, Peeters et al, 2003) and in the outcome (Wichers et al., 2009) and treatment-response of depression and anxiety (Wichers et al., 2009; Geschwind et al, 2010), so could be a promising subject for further research.

Taken together, the presented results illustrate how dimensions can be used to uncover the specific and subtle associations between life events and depression and anxiety and support their role as independent clinical entities. Moreover, the results illustrated the added value of looking at within subject symptom change as an outcome measure of mental wellbeing.

9.6   Dimensions and the course of depression and anxiety

The currently known predictive factors for the course and outcome of depression and anxiety are very general, and patients with similar diagnoses and clinical characteristics (e.g. severity, age-at-onset) can still have different course trajectories. To enable more specific estimates of prognoses, more specific predictors should be identified. In chapters 7 and 8 we aimed to find out whether dimensions could be used as such specific predictors of the course of depression and anxiety. In chapter 7, we showed that different dimensions were associated with different diagnoses after 2 years and that mainly general distress was predictive of an unfavorable course trajectory (i.e. more chronicity). In chapter 8, we took a different approach and used the IDS-SR dimensions as predictors and showed that different dimensions predicted different diagnoses at follow-up. Mood/cognition predicted depression at follow-up and the course of depressive symptomatology, and anxiety/arousal predicted anxiety at follow-up and the course of anxiety symptomatology. Importantly, in both studies, we found that the dimensions yielded predictive information on top of DSM-IV diagnoses and other well-known prognostic factors, such as severity and duration of disease. We found somewhat different results for chapters 7 and 8 because we used different dimensions (tripartite model versus IDS-SR dimensions). However, the general conclusions regarding the added specific predictive information by each symptom-dimension were similar.

As expected, we found dimensions that included somatic- and anxiety-related symptomatology (anxious arousal in chapter 7 and anxiety/arousal in chapter 8) to be predictive of anxiety disorders at follow-up, either on itself or comorbid with a depressive disorder. Closer scrutiny of the results showed that in chapter 7 the anxious arousal dimension, which only covers somatic hyperarousal, was mainly predictive of panic disorder and generalized anxiety disorder (GAD), in line with the idea that more dimensions are needed to cover all anxiety disorders (Mineka et al., 1998). It was similar for the IDS-SR analyses in chapter 8, where we found anxiety/arousal to be predictive of panic disorder at follow-up. In addition, both mood/cognition and anxiety/arousal were predictive of GAD and social phobia. These findings were also in line with the idea that depression is closely related to GAD and social phobia (e.g. Van Ameringen et al., 1991; Kessler et al., 2000).

Several dimensions included mood-related symptoms and cognitions. General distress and anhedonic depression (chapter 7) and mood/cognition (chapter 8), the latter of which could be seen as a slightly more heterogeneous mix of the symptoms covered by two of the tripartite dimensions. As expected, we found anhedonic depression to specifically predict a single depressive disorder at follow-up and general distress to predict a comorbid depressive and anxiety disorder at follow-up. In line with its mixed content, mood/cognition predicted both a single depressive disorder and comorbid depressive and anxiety disorders at follow-up. Together our findings show that symptom dimensions can be used on top of other predictors to achieve more prognostic specificity,

with different dimensions being associated with the course and outcome of different (combinations of) disorders

In addition to our main findings, the IDS-SR results in chapter 8 clearly illustrated the issue with generic scale-scores (e.g. IDS-SR total score, CES-D, HAM-D) as prognostic factors. Because all of these scales assume unidimensionality where in fact they are not (review: Shafer, 2006). On these instruments, individuals with the same total-score may have different symptomatology. For instance, the same score can either consist of mainly increased somatic symptoms or of mainly increased mood/cognition symptoms. Both of these domains have distinct prognostic value and thus, the generic severity scale only gives an indication of overall severity and outcome but is not helpful in formulating specific prognoses.

9.7   Synthesis: the use of dimensions

The presented results provides a broader view on the validity and potential applications of symptom-dimensions in psychiatric research. Based on the results, several conclusions can be drawn..

1   In both the etiological (chapters 4-6) and clinical (chapters 7 and 8) studies, it was found that dimensions capture more variation within and across subjects than is captured by DSM-diagnoses. The results confirmed the expectation that, because of their specific and continuous nature, dimensions detected more variation in the underlying mechanisms.

2   Across various studies on the metabolic syndrome (chapter 4), life-events (chapter 7) and disease-course (chapters 7 and 8), dimensions were found to enable the detection of symptom-specific associations. Thus, using more homogenous clinical descriptions in scientific research clearly brings us closer to the specific mechanisms that underlie depression and anxiety.

3   The used continuous dimensions were shown to have two general advantages in addition to increased power. (A) Non-linear associations could be investigated, where appropriate, allowing for the investigation of more complex underlying processes that would be impossible to uncover with dichotomous or categorical variables (chapter 4). (B) Approaching psychopathology as continuous phenomena often enabled the inclusion of participants from the whole population (irrespective of DSM-diagnosis) in psychopathology research. This increased the generalizability to the population as a whole and adhered to the idea that psychopathology is continuously distributed in the population: associations between dimensions and etiological factors occurred independently of DSM-diagnosis.

4   The results from chapter 6 show that dimensions can be used to capture subtle changes of affect and emotions over time. Such responsivity could be regarded as a new kind of psychiatric outcome-measure, which is sensitive to variations in etiological factors (e.g. life-events).

5   From a more practical perspective, the presented work showed that including dimensions in depression and anxiety research can have notable added value without being overly cumbersome or expensive. In fact, based on the current dissertation, it would be fair to state that the ratio between investment and scientific return could in many cases be fruitful.

9.8   Study limitations

Although the presented studies had several strong characteristics, including thoroughly validated dimensional measurements, large sample sizes, high generalizability, careful adjustment for confounders/mediators and a high response at follow-up, all results should be interpreted in the light of some overall limitations (in random order):

1   All results applied to participants with no or low to medium-high psychopathology severity. Therefore, results cannot be generalized to more severely affected psychiatric (in)patients.

2   The studied dimensions are an obvious oversimplification of reality. Although the tripartite model and the more general distinction between somatic and mood/cognitive symptoms has found widespread support, many more specific subdimensions are thought to exist (see below). In addition, the studied dimensions were limited to the phenomenology of depression and anxiety; whereas many additional dimensions will exist that cover other symptomatology (e.g. psychotic experiences, impulsivity, apathy, somatoform symptoms etc.).

3   As in virtually all psychiatric research, the presented associations had relatively small effect-sizes, indicating that many additional factors play a role. It will be a big challenge to identify as many as possible of these factors and study their combined roles in psychopathology. In addition, measures should be improved in such a way to allow minimal random error.

4   In all studies, participants were excluded from analyses because of missing values on the MASQ-D30 or IDS-SR, which could have led to some *selection bias*. Unfortunately, the categorical and non-normal nature of self-report data did not allow for reliable imputation of missing items.

5   The studies showed that different dimensional approaches can be used (e.g. IDS-SR dimensions versus MASQ-D30 dimensions). However, in order to build up a consistent knowledge base about the added value of dimensions, standardization across studies should ideally be implemented. However, it is still too early to make recommendations about such standardization, based on the current results.

9.9   Future directions

The presented findings have given a thorough insight in the way dimensions can be used and how they can contribute to different fields of investigation. Still, more questions arise from the presented work. Most importantly, the presented findings need independent replication in similar and different populations. Dimensions could be used in other lines of etiological (e.g. neuro imaging) and/or clinical research (e.g. medication trials) to provide further information about their external validity. Furthermore, there seems to be ample opportunity to elaborate on and integrate the etiological findings from this dissertation.

   With regard to etiological research the role of different dimensions in the link between depression, the HPA-axis and metabolic risk could be investigated. Also, the association between trauma, life-events, social support, coping and other risk/buffering-factors could be further disentangled, using dimensions as highly sensitive outcome measures. In addition, it could be evaluated how the biological factors (e.g. HPA-axis) interact with environmental factors (life-events) in acting on different symptom-dimensions. From a methodological perspective, it would be very interesting to address symptom variations over time within subjects, when evaluating the effects of biological and environmental factors and interventions. For instance, studies have monitored variations in positive and negative affect during the day, using an ambulatory self-report system, to see how persons respond emotionally to daily hassles. These studies have shown that this emotional responsivity among others determined by biological factors, such as heritability (Wichers et al., 2007). On a larger month-to-month scale, such an approach could also be used to uncover the factors that determine the way individuals react to high-impact life events.

   With regard to clinical research, a next step would be to evaluate whether dimensional patterns have the ability to predict more specific and informative clinical parameters than only course-trajectories and DSM-outcome. Such factors could be: response to pharmacological or psychotherapeutic treatment, psychosocial functioning and/or suicidality. Pharmacological research could focus on symptom dimensions as more specific treatment targets for medication. For instance, it has been suggested that patients, who experience a pronounced reduction of positive affect, respond better to medication that acts on noradrenergic and dopaminergic activity (e.g. bupropion) than to serotonergic antidepressants (reviewed by: Nutt et al., 2007).

   A more general aim should be to further investigate the internal validity of dimensions and to extend existing models to do more justice to the complexity that is

seen in reality. Several of such extensions have been proposed (e.g. Watson, 2007, 2008; Simms et al., 2008, 2011; Den Hollander-Gijsman et al., 2010, 2011).

9.10 Concluding remarks

This dissertation was aimed to find out whether dimensions of depression and anxiety are valid and are of added value in research and, potentially, clinical settings. The different chapters provided many useful insights in the way dimensions are ideally constructed and measured and how they can be used in etiological and clinical research. From all chosen perspectives in this dissertation, dimensions were seen to have clear added value on top of categorical diagnoses, when it came to uncovering symptom-specific, non-linear and population-wide associations with etiological and clinical factors. In addition, both the internal and external validity of dimensions was thoroughly investigated and confirmed. Taken together, this leads to the conclusion that dimensions of depression and anxiety are valid and have clear added value compared to categorical DSM-diagnoses. The use of symptom dimensions could eventually bring us closer to disentangling all the complex specific associations that underlie psychopathology and that determine how psychiatric problems develop over time. Given the accumulating proof for the added value of dimensions and the current lack of progress in the field, researchers should embrace such new possibilities and include dimensions in their design.

Currently, many scientists and professionals are held back from using dimensions by a healthy skepticism, but also by the habits and conventions that they have grown attached to and that prevent them from thinking along alternative lines. However, if dimensions will prove themselves useful and valid across many research-areas, these will no longer be defensible reasons to oppose the shift to a formal dimensional approach to psychopathology. Eventually, such a paradigm-shift could stimulate progress in the field of psychiatry.