Syndromes versus Symptoms

Towards Validation of a Dimensional Approach of Depression and Anxiety

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Table of Contents

Chapter 1: Introduction

1.1 The epidemiology of depression and anxiety

Both depressive and anxiety disorders are very common. Major depressive disorder (MDD) alone has a lifetime prevalence of 19.0% in the general population (Bijl et al., 1998). Anxiety disorders are a more heterogeneous group and can be divided into different diagnoses: social phobia, generalised anxiety disorder (GAD), panic disorder, agoraphobia, specific phobia, obsessive compulsive disorder and post-traumatic stress disorder. The lifetime prevalence of these diagnoses is also high and ranges up to 19.3% in the general population (Bijl et al., 1998). The World Health Organization (WHO) reported that MDD is the leading cause of years lost to disability (WHO, 2004). Moreover, in the year 2000, MDD was ranked as the fourth largest contributor to the global burden of disease and it is projected to rank second by the year 2020 for all ages and both sexes, leaving only cardiovascular disease above it as the largest global cause of disability (Murray & Lopez, 1996; WHO, 2004).

Depressive disorders exert a long lasting influence on many aspects of a person's life, including social, personal and productive functioning (Ormel et al., 2008). Role-disability has been found to be larger for psychiatric disorders than for many somatic disorders (Alonso et al., 2004). Therefore, MDD constitutes a considerable economic burden on society (Sobocki et al., 2006).

Both MDD and anxiety follow a chronic-intermittent course. MDD is characterised by an episodic course with interchanging periods of remission and recurrence of depressive episodes; some MDD patients only experience a few episodes throughout their lives, while others experience an episode every year or even chronic depression (Keller & Baker, 1992; Spijker et al., 2002; Ormel et al., 1993; Piccinelli & Wilkinson, 1994). Anxiety disorders tend to follow a more chronic course trajectory with less remission than single MDD (Ormel et al., 1993; Keller & Hanks, 1993; Pollack & Otto, 1997; Keller, 2006; Tiemens et al., 1996; Penninx et al., 2011). When depression and anxiety occur together, prognosis is especially unfavourable with less remission and more chronicity (e.g. Penninx et al., 2011).

1.2 The etiology of depression and anxiety

Much research has focussed on the underlying mechanisms that determine the onset and course of depression and anxiety, addressing biological, social and psychological etiological mechanisms. Over the past decades, research has become more focussed on biological mechanisms (Kendler, 2005).

Genetic studies in particular have garnered much attention during the past decade. Many early studies have focussed on candidate genes of depression (reviews: Charney & Manji, 2004; Levinson, 2006) and anxiety (review: Hamilton, 2009). More recently, large genome-wide association (GWA) studies have yielded possible genetic loci involved in the etiology of depression (Sullivan et al., 2009; Lewis et al., 2010; Liu et al.,

2011). However, although much was expected from these GWA studies, replicability of many initial results has been limited (e.g. Bosker et al., 2010; Breen et al., 2011). Moreover, other GWA studies have found no associations at all (Muglia et al., 2008).

Other lines of research have focussed more upstream on the different biological pathways that could play a role in the pathophysiology of depression and anxiety. For instance, the hypothalamo-pituitary-adrenal (HPA) axis, which regulates the secretion of the stress hormone cortisol, has for long been hypothesized to play an important role in depression (Holsboer, 2000). Several studies have found dysregulated patterns of cortisol secretion in depressed patients (Pruessner et al., 2003; Bhagwagar et al, 2005; Vreeburg et al., 2009; Holsboer & Ising, 2010). However, these effects have been invariably small and other studies have found no differences between patients and controls or even the reversed effect (Stetler & Miller, 2005; Huber et al., 2006; Veen et al., 2011), leaving an inconsistent and inconclusive body of results. Moreover, it is still unclear whether these effects are the effect rather than the cause of depression and anxiety. Numerous lines of research have focussed on a variety of other possible underlying mechanisms, including: monoamines (review: Heninger et al., 1996), neuroplasticity (review: Duman & Monteggia, 2006) the autonomic nervous system (Licht et al., 2008; Kemp et al., 2010) and neuroimaging (review: Drevets et al., 2008). Many of these factors seem to play a role in the etiology of depression and/or anxiety, but the extent and consistency of their distinct and interactive roles have been hard to establish. Like biological research, studies that have focussed more on psychosocial factors, such as life events (Kessler, 1997), social support and coping styles (Coyne & Downey, 1991; Paykel, 1994) have yielded similarly varied results.

Another broad and relevant field of research is that of the interactions between psychiatric problems and indicators of somatic health. For instance, a large body of psychosomatic work has shown that depression is associated with a larger risk of cardiovascular disease (CVD) and vice versa (e.g. Musselman, 1998; Vogelzangs et al., 2010; Ormel & De Jonge, 2011). Increased prevalence of the metabolic syndrome (components) and autonomic nervous system dysregulations have been hypothesized to underlie both depression and CVD (Vogelzangs et al., 2009). This would explain the observed bi-directional link between these disorders in the population.

In addition to biological factors, several environmental factors have been shown to play a role in the etiology of both depression and anxiety. A well-known example is childhood trauma, which has been shown to be associated with an increased risk of psychopathology and chronicity in later life (e.g. Wiersma et al., 2009; Hovens et al., 2010). Other environmental factors that have garnered much attention as potential etiological factors of depression are adverse life events (extensively reviewed by Kessler, 1997). However, the findings with regard to adult life events have been less consistent than for childhood events and traumata, with many studies reporting no associations between life events and depression or anxiety (e.g. Spinhoven et al., 2010). This could be due to methodological differences across studies, but it is also likely that the effects of life

events are mediated by buffering factors, such as coping (Billings & Moos, 1981), social support (Cohen & Wills, 1985) and vulnerability factors, such as previous childhood trauma (Heim & Nemeroff, 2001). A more recent line of research has started to focus on the impact of daily hassles/stressors on day-to-day emotional variations and has shown that the magnitude of these variations is related to important clinical characteristics, including clinical course (Wichers et al., 2010) and treatment response (Geschwind et al., 2011).

In conclusion, there seem to be sufficient promising leads for further research into the etiology of depression and anxiety, but no general and consistent findings that could be regarded as undisputable textbook truisms.

1.2.1 Lack of scientific progress

Given the abovementioned inconclusive results, one would be tempted to think that we have been looking for the wrong causes of psychopathology. Should we try harder and expand our search for possible mechanisms? The answer is likely to be no. Given the large range of already investigated mechanisms with small and inconsistent effects, it is not very plausible that much will be gained by simply adding ever more new mechanisms to the list of possible candidate pathways, each of which is still poorly understood on an individual level. In fact, it seems that until now, every new and promising direction of research has only yielded small reward in terms of understanding the etiology of depression or anxiety.

A more plausible hypothesis is that depression and anxiety are caused by many interacting mechanisms, each with a very small effect on its own but with a larger combined effect (Caspi & Moffit, 2006; Jaffee & Price, 2007). From this perspective, it seems only reasonable that conflicting results are found when only a single mechanism is investigated. Indeed, results from studies of interactions between genes and environmental factors have indicated that important effects can be missed if genetic and environmental factors are each studied in isolation (e.g. Caspi et al., 2003). However, these interactive effects are much more complex to investigate and have so far been hard to replicate (Risch et al., 2009).

Another plausible reason for lack of progress in understanding the etiology of depression and anxiety could be that we have been searching for the causes of the wrong disorders or, alternatively, of the wrong mental states. Although the DSM diagnoses of depression and anxiety have become accepted as real medical diagnoses, the DSM clearly states that its classification is only based on clinical consensus and does not assume that its categories represent distinct clinical entities with absolute borders (American Psychiatric Association, 2000). Moreover, no DSM diagnosis has thus far been found to be associated with a biological or laboratory marker (Kupfer et al., 2002; Widiger & Samuel, 2005). Consequently, there is no reason to expect that DSM-syndromes are naturally occurring endpoints of biological pathways. Summarizing this point with regard to genetics, Stefanis (2006) wrote: “genes do not read the DSM”.

The DSM has without doubt helped the clinical field of psychiatry grow into a professional medical discipline with a globally accepted standardized diagnostic classification system and has improved the communication between health-care professionals worldwide (First, 2005). However, despite its obvious clinical utility, the DSM should primarily be judged on its validity when it comes to its use in scientific research (Kendell & Jablensky, 2002). In fact, it is doubtful whether DSM diagnoses could be considered valid and suitable for this use (e.g. Kendell, 1989; Kendell & Jablensky, 2002; Widiger & Clark, 2000; Widiger & Samuel, 2005). Taking this point even further, the widespread adaptation of DSM diagnoses as outcome variables in research could be argued to be one of the main reasons why scientific progress in psychiatry has been very slow during the last three decades (Shorter & Tyrer, 2003). Although this point is tentative and impossible to prove, the practice of pursuing the underlying mechanisms of a DSM-diagnosis does not seem very useful to gain more understanding of psychiatric problems, when we know that DSM-diagnoses were merely intended as clinical tools (Kendell & Jablensky, 2002).

With regard to depression and anxiety, several important issues of the DSM have been raised that are problematic for clinical and scientific purposes and could explain why so far scientific breakthroughs have been scarce and results inconsistent. These issues form the background to the research that is described in this dissertation and three of the most important issues will be discussed: comorbidity of depression and anxiety (see 1.3), heterogeneity of diagnoses (see 1.4) and discontinuity between health and disease (see 1.5)

1.3 Comorbidity of depression and anxiety

Depressive and anxiety disorders frequently co-occur. Comorbidity between the two diagnostic groups has been investigated in large-scale epidemiological studies and reported prevalence rates range from around 40 to 60%, depending on the population and diagnoses studied (Kaufman & Charney, 2000; Bijl et al., 1998). The rate of comorbidity seems to be even higher in clinical samples, probably because comorbid patients are more severely ill and more prone to seek help (Clark et al., 1995). The high rates of comorbidity of MDD and anxiety disorders have important clinical implications and have also given rise to a heated theoretical debate about the appropriateness of the division between anxiety and depression as separate entities (Mineka et al., 1998; Widiger & Clark, 2000; Clark et al., 1995). Below, both implications will be discussed.

1.3.1 Clinical implications of comorbidity

From a clinical perspective, comorbidity between depression and anxiety is very interesting because it is associated with a heavier burden of disease compared to single cases. In comorbid cases, prognosis is worse (Shankman & Klein, 2002; Merikangas, 2003; van Beljouw et al., 2010; Fichter et al., 2010; Patten et al., 2010; Penninx et al., 2011), severity is higher (Roy-Byrne et al., 2000), overall functioning is poorer (Roy-Byrne et al.,

2000), response to treatment is lower (Brown et al., 1996; Kornstein & Schneider, 2001), and there is a higher probability of attempted and committed suicide (Beautrais et al., 1996; Roy-Byrne et al., 2000) than in single cases. Longitudinal studies have shown that the course of comorbid MDD and anxiety is chronic (56.8%) much more often than the course of single MDD (24.5%) or single anxiety disorders (41.9%; Penninx et al., 2011). Unfortunately, research on the etiology and pharmacological treatment of comorbid patients is scarce. Despite its high prevalence, comorbidity is often an exclusion criterion for research because it is regarded as an anomaly that blurs the depression- or anxiety-specific effects that researchers are usually looking for (Shorter & Tyner, 2003). Although comorbid patients have gained more attention in research in recent years, it seems that the group is still under-investigated.

1.3.2 Theoretical implications of comorbidity

The formal distinction between depression and anxiety was introduced in the first drafts that lead to the eventual DSM in the beginning of the 1980's (Widiger & Clark, 2000). Depression and anxiety have since become widely accepted as separate clinical entities, which has lead clinicians and pharmacologists to organise separate lines of care for depression and anxiety. This has lead researchers to search for distinct etiological mechanisms underlying these different classes of disorders (Kendell & Jablensky, 2002). Indeed there seems to be some face-validity and clinical utility to the distinction between depression and anxiety. Semantically, the terms clearly have different meanings and some symptoms can easily be characterized as either depressive (e.g. 'lack of interest') or anxious (e.g. 'feeling jumpy'). However, although some patients fit the diagnostic moulds nicely, real world epidemiological studies have shown that the majority of patients do not fit neatly into one well-defined diagnostic class, because boundaries between diagnoses are blurry (Kendell, 1989). From this perspective, the separation between depression and anxiety as separate disorders looks rather forced and artificial. In fact, one could argue that if a model is designed to optimally describe and organize the nosology of psychopathology, the boundaries should be drawn such that the resulting groups explain as much information as possible (Kendell, 1989). Thus, the system should be able to classify all patients in the simplest and most consistent way possible (Kendell, 1989; Kendell & Jablensky, 2002). Unfortunately, in the majority of cases, more than one diagnostic label is needed to diagnose the patient, which indicates that the underlying categorical model of the DSM is inefficient in describing reality, adding more complexity instead of one simple and reliable diagnostic solution for each individual (e.g. Clark, 1995; Widiger & Clark, 2000; Kendell & Jablensky, 2002; Widiger & Samuel, 2005).

It has been proposed that the frequent co-occurrence and shared etiology of depression and anxiety show that the diagnostic categories are not valid: they are neither distinct on the observed level nor on the etiological level (Kendell & Jablensky, 2002). So, although DSM disorders seem to have clinical utility, boundary disputes and comorbidity should encourage researchers to use different approaches to describe clinical symptoms

that account more elegantly for the blurry boundaries between individual patients (Kendell & Jablensky, 2002)

1.4 Heterogeneity

An important issue that is inherent to the way the DSM works is within-diagnosis heterogeneity (Frances et al., 1990). DSM-diagnoses are made using a syndrome-approach, in which a fixed number of criteria has to be met in order to get a diagnosis. An inevitable side effect of this approach is that patients with a similar DSM diagnosis do not necessarily have similar symptoms; there is considerable *within-diagnosis heterogeneity* (Clark et al., 1995; Widiger & Samuel, 2005). For instance, if two patients both meet five out of nine criterion symptoms for MDD, they both meet the criteria but only have to share one symptom. Understandably, this leads to a lot of symptom variation across MDD patients, who might be assumed to be very similar judged by their common diagnosis. Within-diagnosis heterogeneity has several important practical and theoretical implications.

1.4.1 Clinical Implications of diagnostic heterogeneity

In clinical practice, large diagnostic heterogeneity means that a diagnosis of MDD does not automatically entail one clear treatment indication. On the contrary, no two MDD patients respond equally to the same treatment and it is the rule rather than the exception that treatment has to be tailor-fitted for each individual patient's symptoms. This often requires experimenting with different types of medication and/or psychosocial interventions. In this way, the DSM leaves a lot of additional effort to be made by the clinician. Therefore, attempts have been made to decrease heterogeneity in MDD and to reach a better correspondence between diagnosis and indicated treatment, by introducing MDD subtypes (Goldberg et al., 2011). Of these, the subtypes of *melancholic* and *atypical* depression have received most attention in the literature and indeed there seems to be some evidence that patients with an atypical MDD differ from patients with a melancholic MDD in terms of biological mechanisms, treatment response and other aspects of disease (reviewed by: Stewart et al., 2007; Brown, 2007). For instance, some studies have shown that patients with atypical MDD respond better to MAO-inhibitors compared to general MDD and other subtypes (Liebovitz et al., 1988). However, there are also studies that have found less support for the validity and usefulness of subtypes (Parker et al., 2002). In fact, subtypes of depression have also been found to constitute quite heterogeneous diagnostic classes themselves (Stewart et al., 2007) and it seems that they do not solve the essential problem of heterogeneity, but merely break the disorder up into a range of smaller subcategories. Although valid subtypes could decrease diagnostic heterogeneity to a certain extent, they are not likely to completely solve it. Each added subtype will apply to a limited group of patients, which could eventually lead to an unwieldy system of infrequently used subtypes (Clark et al., 1995).

The problem of heterogeneity also applies to the widely used severity ratings of depression, which assume that all symptoms of depression contribute equally to the same broad underlying dimensions of severity. Such measures include the widely used Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI). Indeed, many factor-analytical studies have shown that simply adding up symptom ratings to acquire a simple and broad severity score does not do justice to the heterogeneity of the assessed symptoms. Instead, factor analyses have repeatedly shown that sets of items that assess similar symptom domains cluster together on distinct factors, across which scores can vary independently (Shafer, 2006). So, where a one-construct structure is often assumed, a two-, three or more-construct structure often fits better to the actual data. This suggests that a more complex model is needed to measure the several coexisting spectra of severity that play a role in depression and anxiety (Goekoop et al., 2007). Indeed, for many depression severity measures, well validated subscales that measure these spectra have been developed to assess more specific symptom domains (e.g. for the HRSD: Bagby et al., 2004; for the BDI: Endler et al., 1999). In the current dissertation this pragmatic approach to decrease the heterogeneity of psychiatric assessment is also explored. Chapter 3 describes the development and validation of a dimensional model and corresponding subscales for the widely used Inventory of Depressive Symptomatology Self Report (IDS-SR).

1.4.2 Theoretical implications of heterogeneity

Diagnostic heterogeneity is a particular problem for scientific research. As stated above, many etiological effects are expected to be very small because - especially in psychiatry - the etiology of disorders is hypothesized to depend on interacting biological, psychological and social factors in a so called *biopsychosocial* model (Engel, 1979). To detect these small individual effects, a great deal of statistical power is needed. In other words, the signal-to-noise ratio should be as high as possible and outcome measures should be internally consistent and not overly sensitive to measurement error (or random variations). If the measurement error is large, statistical power will remain relatively low, even when the sample size is increased (MacCallum et al., 2002). This is exactly the effect of diagnostic heterogeneity when patients with the same diagnosis are put together in an experimental group and made part a dichotomous variable for use in statistical analyses. The patients undoubtedly have something in common, but as illustrated above they also differ in many respects. In addition, the control group can be heterogeneous as well. Consequently, there is so much error-variation or 'noise' within the groups, that when the patient group is compared with the control group, 'noise' can obscure the true 'signal'. For instance, when comparing gene frequencies, a difference in frequency can go undetected because the within-group variation in frequency ('noise') is almost equally as large as the between-group variation in frequency (the 'signal' or 'effect'). Heterogeneity thus introduces two strongly related issues: (1) categories are too heterogeneous to have a clear and simple genetic basis, and (2) because of this heterogeneity, it is very hard to

find out how the complex underlying mechanisms work, since there is a severe lack of statistical power. These issues revolve around each other and constitute a circular problem, which is not limited to genetic research: regardless of the etiological factor, diagnostic heterogeneity will be a problem when the expected effect or difference is small.

The lack of power in psychiatric research has certainly received attention, especially in genetic research, but the focus has been mainly on decreasing the relative influence of within-group noise by increasing sample size (e.g. Wray et al., 2009). Especially in the field of psychiatric genetics, experts have been stating that collecting enormous samples, in the order of tens- or hundreds-of-thousands of subjects is the only way to gain the power that will be needed to detect meaningful and replicable results from genetic studies and genome wide screens (discussed in: Abbott, 2008). In a similar vein, power could be increased by performing repeated measurements within the same group of people (Vickers et al., 2003). Although these methods of increasing measurement quantity should be considered as one viable option, the abovementioned issues should also encourage researchers to do something about the heterogeneity of their studied phenotypes, since this is one of the reasons why enormous power – and thus vast samples and multiple measurements - are needed in the first place.

In conclusion, diagnostic heterogeneity leads to a lack of clinical specificity and loss of power in scientific research. Therefore, researchers should find better ways to account for this.

1.5 Discontinuity

The DSM uses a syndrome approach, which intrinsically assumes that a dichotomy, or "point of rarity", exists between psychiatrically ill and healthy individuals (Kendell, 1989). Although this makes the DSM classification conveniently similar to the systems used in other medical fields, there is no reason to suspect that such a dichotomy is actually valid for psychiatric disorders (Kendell & Jablensky, 2003). In the case of MDD, there is actually no clear cut-off in the population between those that are depressed and those that are healthy (Flett et al., 1997; Ruscio, 2000). Rather, there is a gradual transition along a continuum from psychiatrically healthy to subclinical depression to a full-blown MDD, with each stage differing quantitatively, but not qualitatively from the other (Akiskal et al., 1997; Judd et al., 1998; Cox et al., 2000). Following this continuum, severe MDD could eventually be seen as the end-point on a depression continuum of increasing severity that runs through the population (Flett et al., 1997). Importantly, continuity is not only evident in the distribution of depression in the population (between subjects) but also in the development of symptoms within individuals (e.g. Rao et al., 1999). Similar continuous distributions have been proposed for other forms of psychopathology, such as psychosis (van Os et al., 2000) and autism (Wing, 1988).

1.5.1 Clinical implications of discontinuity

The actual continuity of psychopathology in the population is not incorporated in our current diagnostic system. However, there exists a considerable group of individuals that could be characterized as patients with subclinical illness: they do not (yet) meet the full criteria for a diagnosis. It has been found that even in these subclinical cases, increases in severity are associated with increased disability (e.g. Martin et al., 1996; Lewinsohn et al., 2000; Cuijpers et al., 2004). Thus, these individuals could very well be in need of care or preventive measures. Indeed, it has been shown that preventive psychosocial treatment decreases the incidence of MDD, disease severity, the level of disability (Clarke et al., 1995; 2001; Willemse et al., 2004), and the subsequent use of care in individuals with subclinical depression (Wells et al., 2005). However, no evidence has been found for the efficacy of antidepressants in sub-threshold depressive individuals (Barbui et al., 2011). Indeed, in a meta-analysis these were shown to be mainly effective in patients with severe MDD (Kirsch et al., 2008). Thus, using a strict dichotomous model to divide care among individuals seems to lead to a situation in which a proportion of those needing care are ignored. This is unfortunate, because if treatment is only started after a DSM diagnosis is made, the developmental end-stage of the disorder is already reached and the disabling effects are much harder to stop and reverse than when interventions are made in an earlier developmental stage (McGorry et al., 2006; McGorry; 2007).

1.5.2 Theoretical implications of discontinuity

As discussed above, most researchers divide their subjects into DSM-defined healthy and diseased groups. However, the continuous distribution of disease severity in the population causes both groups in these so called case-control studies to include subjects with varying levels of psychopathology, decreasing the contrast between the mean psychopathology levels of the two groups and thus decreasing the potential to detect a difference on an etiological variable. In fact, the methodology literature advises clearly against dichotomising variables that are actually continuously distributed, because it leads to a decrease in statistical power that is equal to the decrease that would be seen after reducing sample size by a third (Altman & Royston, 2006). In other words, if we choose to dichotomise depression rather than to approach it as a continuous variable, we need to collect 50% more data to reach the same amount of statistical power. Dichotomising can be seen as effectively throwing away valuable information about possible effects and it has been shown to lead to biased results (Royston et al., 2006). Therefore, phenomena with a continuous distribution throughout the population should ideally be analysed with continuous variables (MacCallum et al, 2002; Royston et al., 2006).

1.5.3 Patching up the DSM

The issues, summarized above are all broadly acknowledged, and through the years, many proposals have been made to improve the diagnostic system. Easiest would be if

the issues could be solved with relatively minor adjustments or additions to the existing system as has been the practice for all previous editions of the DSM. Comorbidity could be tackled by introducing an ad hoc "mixed depression-anxiety" diagnosis in the DSM (Katon & Roy-Byrne, 1991; Zinbarg et al., 1994; Shorter & Tyrer, 2003). This would mould comorbidity into one official diagnosis, albeit without any direct consequence for treatment other than the already known consequences of comorbidity itself. Diagnostic heterogeneity could be reduced by assigning individuals to increasingly numerous and specific diagnostic subcategories (e.g. Carragher et al., 2009). However, for reasons listed above, subtypes within diagnoses have so far proven to be limited in their validity and usefulness (Clark et al., 1995; Stewart et al., 2007). Discontinuity could partly be accounted for by including a threshold for subclinical depression (e.g. Hybels et al., 2001) and/or anxiety to better enable staged diagnostics (Fava & Kellner, 1993; McGorry et al., 2006). However, introduction of such a diagnosis would automatically create new subclinical diagnoses with limited specificity: many subtreshold cases do not need treatment or will not respond to it (Lyness et al., 2007). In addition, it is unclear where cut-offs should be defined between different preclinical stages. If natural points of rarity do not exist between different clinical entities (Kendell & Jablensky, 2002), it remains to be seen if they exist between different clinical stages.

1.6 Solution of issues: a dimensional approach

The problems with each of the abovementioned proposals are that they tackle specific issues in an ad hoc fashion and act as specific add-ons that bear no relation to the functioning of the system as a whole. Moreover, rather than to suggest that some small adjustments are needed to the system, the issues with the DSM go deeper and imply that something much more elemental is wrong with its categorical approach. Therefore, it would be overly optimistic to expect that the problems can simply be patched up until a next revision is due.

Completely different approaches to psychopathology have been proposed that aim to better describe the actual characteristics of psychiatric symptoms in a more integrated fashion. Of the proposed approaches, the dimensional approach has been shown to be one of the most promising contenders. This approach is the main focus of this dissertation.

1.6.1 A dimensional approach to psychopathology

The most important assumption of dimensional models of psychopathology is that symptom severity follows a continuum, rather than a dichotomy, which, as described above, is more in line with observations in the general population (Goldberg, 2000). In addition, most dimensional models assume that psychiatric symptomatology consists of several co-existing symptom-domains, each varying along its own severity continuum. In other words: they account for heterogeneity across patients by assuming multidimensionality (e.g. Goekoop et al., 2007). Also, particularly in the case of

depression and anxiety, dimensional models circumvent and explain comorbidity, by assuming common and specific symptom dimensions instead of a fixed set of categories (Clark & Watson, 1991). For depressive and anxiety disorders, promising dimensional models have been developed that have been shown to be very useful in describing the clinical state of any individual, irrespective of his or her DSM diagnosis.

1.6.2 A dimensional approach to depression and anxiety

The starting point for the development of a dimensional approach of depression and anxiety was the observed high rate of comorbidity between the two disorders, as this highlighted an elemental flaw in the descriptive model of the DSM (Mineka et al., 1998). As described above, comorbid patients often have a less favourable prognosis and respond poorly to treatment. The obvious reason for this is that comorbidity occurs more often in patients that have more (severe) symptoms. Therefore, authors argued that it is these patients' relatively high position on an underlying severity dimension that accounts for their worse prognosis and not merely the fact that they have two or more diagnoses (Clark et al., 1995). This assumption was central to the emergence of a series of dimensional models of depression and anxiety during the past two decades.

The first question that the developers of these dimensional models sought to answer was how the general underlying severity dimension could be defined. Researchers that aimed to explain the relationship between depression and anxiety observed that patients with depression and anxiety show considerable overlap in their experienced symptoms irrespective of severity or demographics. These shared symptoms were mainly characterised by general psychological distress, and together they were labelled as '*Negative Affect*' (Watson & Clark, 1984; Watson et al, 1988). In this form, increased Negative Affect was found to be associated with the occurrence and persistence of both depression and anxiety and worse prognosis (Watson et al., 1988; Clark et al., 1994). This led researchers to assume that Negative Affect is indeed a central or common symptom domain that explains the overlap between DSM-defined depression and anxiety and their comorbidity (Watson et al., 1988; Clark et al, 1995).

1.6.3 The tripartite model

In 1991, Clark and Watson published an influential dimensional model that was aimed to describe symptoms of depression and anxiety, while circumventing the problem of comorbidity: the *tripartite model*. The model had a Negative Affect dimension as its central pillar, which included the symptoms that are shared by depression and anxiety, such as: feelings of worthlessness, guilt and pessimism. In addition, the model included two specific dimensions that described symptom domains that were more characteristic for either depression or anxiety. The dimension of '*Positive Affect*' covers lack of positive emotions and energy. The addition of this dimension in the model was in line with earlier research that had shown that increased Negative Affect is necessary but not sufficient to describe the clinical picture of a depressed state. Rather, increased Negative Affect

together with decreased Positive Affect, were found to specifically characterize those individual with mood-related problems, such as anhedonia (Watson & Clark, 1984; Watson et al., 1988). Importantly, the dimensional nature of both Negative and Positive Affect allows a large range of combinations of both common and specific symptom severity to be described, and models the heterogeneity across different individuals. The third dimension of '*Somatic Arousal*' included symptoms of somatic hyper arousal, such as sweating, trembling, palpitations and other sympathetic symptoms. This specific dimension was added to the model to account for panic and anxiety symptoms (Mineka et al., 1998; Joiner et al., 1996).

The tripartite model was initially meant to explain comorbidity between depression and anxiety, and at the same time to acknowledge the specific features on which individuals can differ from each other. Although the tripartite approach is simple and far from complete in explaining all aspects of depressive and anxious symptomatology, this seems to have advantages. The model is easy to operationalize with a simple measurement scale, called the mood and anxiety symptoms questionnaire (MASQ, Watson et al., 1995a; 1995b). Using data collected with the MASQ and other instruments, the hypothesized 3-dimensional structure was proven to be generalizable across many populations. The 3-dimensional structure has been replicated in school children (Chorpita et al., 2000; 2002; Cannon & Weems, 2006), healthy college students (Watson et al., 1995a; Keogh & Reidy, 2000), veterans (Watson et al., 1995a), adult psychiatric outpatients (de Beurs et al., 2007), adolescent psychiatric patients (Joiner et al., 2000), the elderly (Cook et al, 2004), and patients with somatic problems (e.g. Geisser et al., 2006).

However, issues with the tripartite model have also been raised and that these need to be resolved. A considerable number of studies did not find a 3-dimensional structure to underlie the data collected with the MASQ and other instruments (e.g. Burns & Eidelson, 1998; Marshall et al., 2003; Buckby et al., 2008; Bedford et al., 2010; Boschen et al., 2006; Greaves-Lord et al., 2007). Some have interpreted this to indicate that the tripartite model is not applicable to all populations (Buckby et al., 2008; Marshall et al., 2003). However, others have suggested that the MASQ is not an optimal measure of the tripartite model, because it includes too many items that do not clearly belong to one dimension (unclear items). This increases the measurement error of the MASQ scales, which in turn decreases the reliability of the scales and thus the replicability of the model it aims to measure. In addition, the inclusion of unclear items causes the MASQ scales to be highly correlated, which makes it harder to distinguish the independent dimensions each time the model is tested in another population (Boschen et al., 2006; Keogh & Reidy, 2000). Thus, although the model seems structurally valid, measurement could be improved. This is the first point that will be addressed in this dissertation: the development of an improved version of the MASQ is described in Chapter 2. Another limitation of the tripartite model is that heterogeneity is still present; within the Negative Affect dimension in particular, many seemingly unrelated symptoms are lumped together, which implies that two similar Negative Affect scores do not mean that similar

symptoms are present. Therefore, it has been proposed that Negative Affect should be subdivided into more homogenous subdimensions (Mineka et al., 1998; Den Hollander-Gijsman et al., 2010).

Interestingly, parallel to the tripartite model, other models have also been proposed in the literature from a more neurobiological perspective (Shankman & Klein, 2003). The best known of these are the *approach-withdrawal* model and the *valence-arousal* model (Murphy & Lawrence, 2003), which make predictions about patterns of activation of different emotional response systems for negative (withdrawal related) and positive (approach related) emotions in the brain (Murphy & Lawrence, 2003). These emotional systems roughly correspond to Negative Affect, Positive Affect and Somatic Arousal. The valence-arousal model adds an extra anxiety-specific domain, called Anxious Apprehension (Shankman & Klein, 2003). These models make similar assumptions about the way affect is structured in depression and anxiety, but operationalize the framework in terms of brain-activation patterns in reaction to stimuli instead of questionnaire scores.

1.6.4 The hierarchical model

The realisation that Negative Affect is a very broad severity-defining construct with many underlying specific dimensions that account for the variation across patients has led researchers to take the tripartite model a step further. Several authors (Zinbarg & Barlow, 1996; Brown et al. 1998; Mineka et al. 1998; Krueger & Finger, 2001; Kotov, 2011) proposed that rather than to coexist, the dimensions of the tripartite model should be seen in a hierarchical structure: Negative Affect was defined as a general distress factor with several underlying specific dimensions, including positive affect and somatic arousal, but also other dimensions that capture the specific features of different anxiety disorders. This hierarchical model has been proven very successful in explaining how different DSM diagnoses are interrelated in the general population (Watson et al., 2005). Depression and GAD on one hand and anxiety disorders on the other hand can be grouped in separate factors under the umbrella of one broad negative affect factor (Krueger, 1999; Vollebergh et al., 2001; Watson, 2005). The disorders that can be grouped under negative affect are often referred to as '*internalising*' disorders, as opposed to '*externalising'* disorders, such as substance abuse and antisocial behaviour, which fall under their own factor (Krueger, 1999). All internalising disorders are thought to have a largely shared aetiology, which explains why they co-occur so often (Watson et al., 2005). The same rationale applies to the externalising disorders.

Recently, researchers have focussed on defining the sub-dimensions that are necessary to cover all internalising disorders. Watson et al (2007), not straying too far away from the structure of the DSM classification, developed the inventory of depressive and anxiety symptoms (IDAS) to measure smultiple sub-dimensions: suicidality, lassitude, insomnia, appetite loss, appetite gain, ill temper, well-being, panic, social anxiety, traumatic intrusions, general depression and dysphoria, each of which are associated with specific internalising disorders (Watson et al., 2008). Indeed, it was found that data

collected with this instrument had a hierarchical structure, operationalized in a bifactor factor model with one general latent factor, explaining variation in all assessed symptoms, and several specific latent factors explaining variation in subsets of symptoms (Simms et al., 2008). Importantly, the hierarchical, bifactor model was also found to fit well on data collected with other instruments (Simms et al., 2011; Den Hollander-Gijsman et al., 2011).

1.6.5 The hierarchical model versus the tripartite model

What distinguishes the hierarchical model from the tripartite model is that the former defines negative affect as a latent factor that loads on all lower level dimensions. Negative Affect is thus solely represented in the high covariances between the lower level dimensions. Measures that aim to assess these lower level dimensions consequently do not include a common Negative Affect scale (e.g. the IDAS). In contrast, the tripartite model defines negative affect as a part of a symptom profile that can be measured alongside other, more specific dimensions. The hierarchical model has the advantage that it works elegantly to explain the structure of psychopathology. The tripartite model has the advantage that all of its dimensions, including Negative Affect, can be easily measured and used as variables in etiological research. Thus, although the hierarchical model may be superior in describing how disorders co-occur within the DSM in the way they do, the tripartite model is a more descriptive model that can be used to describe an individual's clinical state with a dimensional profile, irrespective of DSM-diagnosis. Both approaches have potential clinical and scientific use.

1.7 Towards the use of dimensions in the DSM

Dimensional approaches have gained a lot of attention as potential alternatives or additions to the DSM. Several dimensional models – especially for depression and anxiety - have proven to be structurally valid and effective in describing patients' clinical states.

Some work groups have investigated whether it is possible to implement a paradigm shift and add dimensions to the existing system or to completely replace some categories with dimensions in the DSM-V (Helzer et al., 2008). The latter has, for instance, been proposed for Axis-II personality disorders and there is a fair chance that Axis II will become largely dimensional in the DSM-V, mainly because widely accepted dimensional operationalisations of personality have been around for decades (e.g. the MMPI; the Big Five) and have already become a trusted part of the working clinicians' vocabulary. However, especially for those, who work in a strictly medical environment, the transition from Axis-II disorders to dimensions will be less natural and it will probably take time before the new approach will be completely trusted and accepted within the field.

Unfortunately, the debate has been much more complex with regard to Axis-I disorders. Several dimensional approaches have been developed for depression and anxiety, autism and psychosis. However, most find it premature to introduce dimensions into the DSM and have plausible objections against it, some of which are discussed below.

1.7.1 Coverage and integration

The most general objection to introducing dimensions into the DSM-V is that there is currently no dimensional model that is ready to be implemented as *the* clinical standard. Most published dimensional models cover a limited range of disorders (e.g. depression or autism or psychosis), each offering strong *proof of concept* but not a readily usable clinical approach. Although recent attempts to integrate a broader range of symptoms in a single model have been quite successful (e.g. Watson, 2005), no well-validated model covers all clinically relevant symptoms that would be needed for daily diagnostic practice.

1.7.2 Acceptability of dimensions

The current psychiatric system has been designed around the DSM. Clinicians, scientists, insurance companies and drug administration bodies such as the Federal Drug Administration have all become used to thinking in terms of categorical diagnoses. Describing patients with DSM-diagnoses has become second nature within the field, making any alternative approach seem unintuitive.

Even if an all-encompassing, completely valid and intuitively acceptable dimensional approach existed, introduction into the DSM would have many undesirable side effects. For instance, additional dimensional ratings could increase the workload for already busy clinicians (Frances, 2009). More generally, a shift to a dimensional paradigm would have severe consequences for the *continuity* within the field: mental health care administration systems would all need to be reformed and previous DSM-based scientific findings would become hard to interpret (First, 2005). Although realistic and relevant, these objections would be rendered obsolete if a dimensional approach was proven to have significant clinical and scientific benefits. However, as long as dimensional models remain in the realm of theory and have not been operationalized for actual practical applications, these objections stand firmly. As Frances (2009) aptly stated: *"…introducing a botched dimensional system prematurely into DSM–V may have the negative effect of poisoning the well for their future acceptance by clinicians … "*.

1.8 The validity of dimensions

It is fair to state that if DSM categories were to be replaced because they lack validity, the dimensional alternative should at least be superior in this aspect. Although many factor-analytical studies have yielded strong support for the *internal validity* of dimensional models for depression and anxiety, this does not mean that the dimensions that make up these models automatically have any biological or clinical significance. In fact, factor-analytical models only explain the structure of variables that they were designed to explain: the symptom-assessments that formed the input-data for the model. Dimensional models should also explain something more and should thus be associated with other variables, such as different etiological factors and, ideally, different clinical consequences: they should have *external validity*.

The external validity of current dimensional models is far from established and has received far less attention than their internal validity. With regard to the tripartite model, some etiological studies have been conducted showing that Negative Affect and Positive Affect are associated with biological factors, such as the HPA-axis (e.g. Veen et al., 2011). Also, studies of the course and outcome of psychopathology have shown that NA and PA predict the outcome of depression and anxiety in certain settings (e.g. Joiner & Lonigan, 2000; Lonigan et al., 2003; Clark et al., 2003). However, these studies have been limited in relative size and scope, when compared to studies of internal validity, summarized in paragraph 1.6.3.

Meaningful associations between dimensions and etiological factors, such as genetic, biological and environmental factors could be established where DSM diagnoses show inconsistent or very small associations. If dimensions really add something on top of DSM diagnoses in terms of explanatory power and are shown to have their own underlying mechanisms, this would be strong evidence that dimensions are not just psychometric constructs, but naturally occurring phenomena (Kendell & Jablensky, 2002). The value of dimensions can only be established if they are shown to represent endpoints of different etiological mechanisms. Ideally, factor analytical and etiological research should thus be combined for the validation of dimensional psychopathology.

1.9 The current project

The aim of this dissertation was (1) to further improve measurement of dimensions of depression and anxiety by improving the validity of the measurement scales and (2) to investigate the added value of the measured dimensions in etiological and clinical psychiatric research.

The first step was to find optimal ways to measure dimensions across different settings. In Chapter 2, the development and validation of an instrument that can be used to efficiently measure the three dimensions of the tripartite model is described. In Chapter 3, a pragmatic approach is described to optimally measure specific symptom dimensions, extracted from an already widely used self-report questionnaire.

The second step of the project was dedicated to the investigation of associations between dimensions and a range of potential etiological factors and to establish whether the dimensions did show more specific associations. In Chapter 4, a study of the association between dimensions and the HPA-axis is described. In Chapter 5, a study of the associations between dimensions and different metabolic factors is described. Chapters 6 describes studies of the dynamic associations between dimensions and different types of life events.

The third step of the project was aimed to explore the added value of dimensions in clinical research. In Chapter 7 and Chapter 8 investigations of the utility of different dimensional approaches to predict the course and outcome of psychopathology over a 2 year period are described.

Chapter 2:

Development and Validation of a 30 Item Short Adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ)

Abstract

The original Mood and Anxiety Symptoms Questionnaire (MASQ) is a 90 item self report, designed to measure the dimensions of Clark and Watson's tripartite model. We developed and validated a 30-item short adaptation of the MASQ: the MASQ-D30, which is more suitable for large scale psychopathology research and has a clearer factor structure. The MASQ-D30 was developed through a process of item reduction and grouping of the appropriate subscales in a sample of 489 psychiatric outpatients, using a validated Dutch translation, based on the original English MASQ, as a starting point. Validation was done in 2 other large samples of respectively 1461 and 2471 subjects with an anxiety, somatoform and/or depression diagnosis or no psychiatric diagnosis. Psychometric properties were investigated and compared between the MASQ-D30 and the full (adapted) MASQ. A 3-dimensional model (negative affect, positive affect and somatic arousal) was found to represent the data well, indicating good construct validity. The scales of the MASQ-D30 showed good internal consistency (all alphas > 0.87) in patient-samples. Correlations of the subscales with other instruments indicated acceptable convergent validity. Psychometric properties were similar for the MASQ-D30 and the full questionnaire. In conclusion, the MASQ-D30 is a valid instrument to assess dimensional aspects of depression and anxiety and can easily be implemented in psychopathology studies.

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2.1 Introduction

The validity of the traditional conceptual distinction between anxiety and depression has often been challenged. Anxiety and depressive moods often co-occur, and their key symptoms show substantial overlap (Mineka et al., 1998). As a result, self report instruments that assess symptoms of anxiety and depression are often highly correlated, indicating only modest discriminant validity (Clark and Watson, 1991). With their tripartite model, Clark and Watson (1991) proposed a way to model and assess both the shared and distinct symptoms of anxiety and depression and to circumvent the problem of comorbidity. The model is based on the assumption that mood can be dissected into two components: Negative Affect (NA) and Positive Affect (PA) (Tellegen et al., 1999). Clark and Watson (1991) added a third dimension of Somatic Arousal (SA). Whereas NA is characterized by aversive emotional states such as fear, anger and guilt that are associated with both anxiety and depression, PA represents positive emotional states such as feeling active, excited, delighted, enthusiastic and interested. A lack of PA is described as feeling 'tired and sluggish' and is associated with depressive moods (Clark and Watson, 1991). The SA dimension represents symptoms of physiological hyperarousal such as trembling, shaking, dizziness, sweating and heart racing. These symptoms appeared to better differentiate anxiety (especially panic disorder) from depression than symptoms of subjective fear (Joiner et al., 1999). The tripartite model has found broad acceptance and is supported by several studies in psychiatric patients (Joiner et al., 1996; Keogh and Reidy, 2000; Chorpita and Daleiden, 2002; Marshall et al., 2003; De Beurs et al., 2007). To measure the dimensions of the tripartite model, Watson et al. (1995a, 1995b) developed the Mood and Anxiety Symptoms Questionnaire (MASQ). The MASQ is a 90 item self-report questionnaire that consists of five symptom scales. The Anhedonic Depression (AD) scale measures a lack of PA and the Anxious Arousal (AA) scale measures symptoms of SA. The General Distress (GD) scale measures non-specific symptoms of General Distress or NA, the General Distress-Depression (GD-D) scale measures NA symptoms that are traditionally considered depressive and the General Distress Anxiety (GD-A) scale measures NA symptoms that are traditionally viewed as anxious. Watson et al. (1995a, 1995b) found the MASQ scales to have acceptable psychometric properties. This was replicated later (Reidy and Keogh, 1997; Keogh and Reidy, 2000). Although the MASQ was found to be a good representation of the tripartite model by De Beurs et al. (2007), other authors found that a 3-dimensional model did not adequately fit the MASQ, when tested with confirmatory factor analysis (CFA) (Burns and Eidelson, 1998; Boschen and Oei, 2006; Buckby et al., 2008). In addition, about a third of the items appeared to show weak or complex loadings on the three factors of the tripartite model (Bedford, 1997; Keogh and Reidy, 2000; De Beurs et al, 2007). Removal of these items could improve the validity of the MASQ (Boschen and Oei, 2007). In addition, the questionnaire is rather lengthy, which hampers inclusion in a comprehensive assessment. The administration is time-consuming and therefore expensive. The aim of the present study was to develop a substantially shorter version with a clear tripartite factor structure that

can be used in large scale prospective cohort studies and trials, taking the Dutch translation of the MASQ that is based on the original English MASQ, as starting point. Use of short and self-report questionnaires is the most effective method to decrease respondent burden, increase response rates and to reduce possible bias due to selective loss (Dillman et al., 1993). Therefore, we developed a 30 item short adaptation of the MASQ (MASQ-D30) to use in large scale research into shared and distinctive features of anxiety and depression. We aimed for the psychometric qualities to be as close as possible to the full questionnaire. To evaluate this, a number of analyses were conducted. First, we assessed indices of internal consistency and evaluated the inter-correlations of the AD, AA and GD scales. Second, we investigated convergent validity by comparison of the 3 scale scores with other psychometric instruments. Third, we compared these psychometric results between the MASQ-D30 and the full questionnaire. Fourth, we investigated the dimensional structure of the MASQ-D30 with confirmatory factor analysis. The initial development of the short-form was done by use of data from a large sample of psychiatric outpatients (*n* = 489): the Routine Outcome Monitoring (ROM). We carried out subsequent analyses with more data from ROM (*n* = 1461) and with data from a large sample of psychiatric patients: the Netherlands Study of Depression and Anxiety (NESDA *n*=2471).

2. 2 Methods

Participants and procedures

Routine outcome monitoring participants

The sample in which the MASQ-D30 was developed (sample 1) and the evaluation sample (sample 2) both consisted of participants in a Routine Outcome Monitoring (ROM) programme (De Beurs and Zitman, 2007). These samples were composed of outpatients who were referred by General Practices to different clinics of the Rivierduinen Psychiatric Hospital with an anxiety, mood or somatoform disorder between January 2002 and December 2003 (sample1) and between July 2006 and May 2007 (sample2). About 80% of all referred patients participated in the ROM project. Patients were excluded when they refused to participate, they withheld their consent for use of their data for research, the assessment was deemed too invasive or their mastery of the Dutch language was insufficient. All participants were administered a standardized diagnostic interview and several rating scales (for both somatic and/or mental complaints) during an assessment session with a trained research nurse. A computer program was used to administer various self report questionnaires. In sample 1 (*n*=489), there were 297 women (60.7%) and 192 men (39.3%) and the mean age was 37.5 years (SD=11.7, range 18-65). In sample 2 (*n*=1461), there were 941 women (64.4 %) and 520 men (35.6%) and the mean age was 38.7 years (SD=13.1, range 18-65).

NESDA participants

Sample 3 was composed of participants in the NESDA study (Penninx et al., 2008). NESDA is a large scale longitudinal research project, in which 2981 participants with an anxiety disorder, depressive disorder and no psychiatric diagnosis are included from different locations in the Netherlands and in different settings (community, primary care and mental health care organizations). The baseline assessment consisted of a blood draw, a cognitive task, a medical exam, a psychiatric interview and administration of several self report questionnaires. Of all participants, 82.9% completed all questionnaires that were used for the present analyses (*n*=2471). In sample 3 there were 1652 women (66.9 %) and 819 men (33.1%) and the mean age was 42.1 years (SD=13.1, range 18-65).

For subgroup analyses, three subsamples were drawn from sample 3, based on mental health care setting. A *primary care group* (*n*=909) was composed of patients who received care in general practices (for general, somatic and/or mental complaints), a *mental health care group* (*n*=621) was composed of patients who were referred to mental health care organizations and a *healthy control group* (*n*=577) was composed of subjects without any lifetime psychiatric diagnosis. The protocol of the NESDA study was approved centrally by the Ethical Review Board of the Leiden University Medical Centre and by local review boards of participating centres. All subjects signed informed consent before assessment.

Instruments

Dutch translation based on the MASQ

All participants in sample 1 and sample 2 filled out the Dutch translation that was based on the original MASQ. The translation process and psychometric evaluation of this adapted MASQ were described by De Beurs et al. (2007). Like in the original English version of the MASQ, on this adapted MASQ individuals are asked to rate how much in the past week they have experienced “feelings, sensations, problems and experiences that people sometimes have” on a 5-point Likert scale, with 1 being “not at all” and 5 being “extremely”. Sum scores were computed, using the items described by De Beurs et al. (2007) with a GD scale of 20 items, an AD scale of 22 items and an AA scale of 18 items.

Short adaptation of the MASQ (MASQ-D30)

For the development of the short-form, the methodological steps for short-form development described by Smith et al. (2000) were followed. In short, the items of the MASQ-D30 with their loadings on the dimensions of the tripartite model are shown in Table 2.1. A principle components analysis with varimax rotation was conducted in sample 2 using the SPSS 14.0 statistical package (SPSS Inc. Chicago, Illinois, USA). Inspection of a scree-plot suggested that three factors could be extracted that corresponded to the three scales of the MASQ. After this, the 10 highest loading items (all

factor loadings >0.50) with sufficient ability to differentiate (difference of at least 0.20 between loadings on different factors) were selected from each of the three extracted factors to construct short scales. Next, the content of the selected items was evaluated by clinical experts and several redundant and overlapping items were replaced by items with a lower factor loading (none <0.50) that contributed to better content coverage.

Other instruments in sample 1 and 2 (ROM)

The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998; Van Vliet and De Beurs, 2007: Dutch version), a standardized diagnostic interview with 23 modules that assess the presence of DSM criteria for the main Axis I psychiatric disorders (mood, anxiety, psychotic, somatoform and eating disorders) was used to assess diagnostic status. The Brief Symptom Inventory (BSI) (Derogatis, 1975: De Beurs and Zitman, 2006: Dutch version), a list of 53 symptoms, was administered to all patients. A 5-point Likert scale (0 =“not at all”, 4=“extremely”) was used to assess to what extent respondents experienced each of these symptoms in the past week. The BSI, with subscales for somatic complaints, depression, anxiety, phobic avoidance and interpersonal sensitivity was completed by all respondents. The total BSI score was used as an index of general psychopathology. The Beck Depression Inventory II (BDI) (Beck and Steer, 1987; Beck et al., 2002: Dutch version) was completed by patients with a current major depression or dysthymia diagnosis. The psychopathology of the patients was also rated by the research nurse, using two subscales from a shortened version of the Comprehensive Psychiatric Rating Scale (CPRS), a scale of 25 items (Goekoop et al., 1991: Dutch version). The used subscales were the Brief Anxiety Scale (BAS, 10 items) and the Montgomery-Åsberg Depression Rating scale (MADRS, 10 items). Different response options for each of the items of the CPRS were rated on a 7 point scale anchored at 4 points (1, 3, 5 and 7).

Other instruments in sample 3 (NESDA)

The Composite International Diagnostic Interview (CIDI, WHO version 2.1) was used to assess the presence of DSM-IV criteria for depressive disorders (i.e. major depressive disorder and dysthymia) and anxiety disorders (i.e. panic disorder, social phobia, generalized anxiety disorder and agoraphobia). The Beck Anxiety Inventory (BAI) (Beck et al., 1988), a self report of 21 items rated on a 4-point severity scale was used to assess affective and somatic symptoms of anxiety. The Inventory of Depressive Symptomatology (IDS) (Rush et al., 1996; Nolen and Dingemans, 2004: Dutch translation), a self report of 30 items rated on a 4-point severity scale (1=“not at all”; 5=“extremely”) was used to assess symptoms of depression. The Distress scale of the Four Dimensional Symptoms Questionnaire (4DSQ-distress) (Terluin et al., 2006), a self report of 16 items, rated on a 5-point scale (1=”no”, 2=”sometimes”, 3=”regularly”, 4=”often”, 5=”very often or continuously”) was used to assess general psychological distress. The 4-DSQ was originally developed in Dutch. All other instruments were Dutch translations of the original English versions.

Statistical Analyses

Analyses were conducted using the SPSS 14.0 and EQS 6.1 (Multivariate Software Inc., Encino, California, USA) software packages. First, the internal consistency coefficients (Cronbach's alpha) of the scales were computed. Second, the bivariate correlations between the MASQ-D30 subscales were computed to assess whether the subscales measure distinct constructs. Third, bivariate correlations between the MASQ-D30 subscales with other instruments were calculated to investigate convergent validity. Fourth, internal consistency and validity were compared between the MASQ-D30 and the full MASQ. Fifth, the analyses were repeated in sample 3 and the subsamples to obtain independent replications. Sixth, confirmatory factor analysis (CFA) was used in sample 3 and the subsamples to evaluate the fit of a 3-dimensional model to the data, based on a maximum likelihood estimation method. To assess the fit of the model to the data with CFA, several approaches can be used. Model fit can be assessed with a χ^2 statistic or a robust Satorra-Bentler (S-B) χ^2 statistic, which is less impacted by deviations from normality. In this test, a non significant result indicates good fit. However, in large samples the χ^2 statistic is oversensitive to minor derivations from perfect model fit, which makes it practically not useful for this study. Thus, the fit of the model was assessed with fit-indices that are less affected by sample size (Byrne, 2006). The used fit indices were: the comparative fit index (CFI), the normed fit index (NFI), the non-normed fit index (NNFI) and the root mean square error of approximation (RMSEA). A CFI, NFI and NNFI of at least 0.90 indicate satisfactory fit and a RMSEA, lower than 0.06 indicates that the model is a good descriptor of the data (Byrne, 2006).

Missing Data

In samples 1 and 2, no data were missing. In sample 3, 2624 (90.8%) of 2891 subjects completed the MASQ-D30; 357 subjects (9.2%) did not return the MASQ-D30 questionnaire they received to complete at home. This group of non-responders had a higher percentage of males, a lower mean age and fewer years of education than the group of responders, which could have made our sample slightly less representative.

Of the 2624 subjects that completed the MASQ-D30, 153 (5.8%) subjects had one or more missing responses. All items were categorical with a strongly skewed distribution. Therefore, we decided not to impute the missing values, because each method could introduce new sources of bias into our data. Thus, subjects with missing values were excluded from the analyses. This resulted in a sample size of 2471 subjects. We checked whether the psychometric results of the MASQ-D30 differed between this sample and the original sample of 2624 subjects and found that the psychometric results were largely similar. This makes it unlikely that exclusion of incomplete cases has biased our results.

2.3 Results

Throughout the results section and in the tables, the name MASQ refers to the full Dutch translation based on the MASQ, as described above.

Diagnoses and demographic variables

The demographic information and the lifetime diagnoses of depressive, anxiety, somatoform and comorbid diagnoses for each of the three studied samples are shown in Table 2.2. From the table it can be seen that there is a considerable amount of comorbidity between anxiety and depression in each of the samples. However, the percentages of subjects with anxiety, depressive or both disorders differ significantly between the samples. Somatoform disorders were only diagnosed in samples 1 and 2; the percentages of these disorders (single and together with anxiety and/or depression) did not differ significantly between the samples.

The observed differences between the developmental and validation samples make it possible to evaluate the consistency of the characteristics of the MASQ-D30 across different patient groups.

Internal Consistency

Internal consistency coefficients (Cronbach's alpha) for each of the three scales are presented in Table 2.3. These ranged from 0.93 to 0.96 for the full MASQ and from 0.87 to 0.93 for the MASQ-D30. We used the Spearman-Brown formula (Nunnally and Bernstein, 1994, pp. 262-264) to assess whether the lower alphas of the MASQ-D30 scales could be attributed to the reduced number of items. Using this formula we computed the estimated alpha coefficients of the MASQ-D30 scales when expanded back to original length. These estimated alpha coefficients ranged from 0.91 to 0.96, indicating that the internal consistency was preserved with item reduction.

In sample 3, we found a similar pattern of Cronbach's alpha coefficients (0.85 to 0.95) for the MASQ-D30. In the subgroups, the alpha coefficients ranged from 0.81 to 0.94 in the primary care group and from 0.85 to 0.94 in the mental health care group. In the healthy control group, the alphas of the GD and AD scale were 0.84 and 0.93 respectively. However, for the AA scale, alpha was considerably lower (0.70), which indicated only moderate internal consistency. These results indicate that the MASQ-D30 scale reliability, estimated by internal consistency, is good and stable over different patient subsamples and only less for the AA scale in non-patients.

Subscale inter-correlations

Table 2.3 shows the correlations between the subscales of the MASQ-D30 and the full MASQ. In sample 2 the AD and AA scales showed low inter-correlations (MASQ: r=0.35; MASQ-D30: r=0.30), while both scales showed considerable correlations with GD (MASQ: r=0.62, r=0.59; MASQ-D30: r=0.56, r=0.57). These results were largely similar for the MASQ and the MASQ-D30, indicating that the scale inter-correlations were maintained in the MASQ-D30. Comparable patterns of scale inter-correlations were found in sample 3 and the sub-samples. Together, these results implicate that the AD and AA scales assess

fairly distinct symptom domains, while GD is related to both AD and AA. This is in line with the tripartite model.

Table 2.1: Factor loadings on the dimensions of the tripartite model for the MASQ-D30 in 489 subjects

Items		General Distress	Anhedonic Depression	Anxious Arousal
1	Felt confused	**0.59**	0.12	0.35
4	Felt worthless	**0.76**	0.29	0.05
7	Felt irritable	**0.54**	0.19	0.34
10	Felt hopeless	**0.76**	0.28	0.23
12	Blamed myself for a lot of things	**0.70**	0.10	0.10
13	Felt dissatisfied with everything	**0.67**	0.35	0.20
17	Felt pessimistic about the future	**0.65**	0.23	0.10
23	Felt inferior to others	**0.70**	0.17	0.08
25	Had trouble making decisions	**0.62**	0.19	0.19
28	Worried a lot about things	**0.62**	0.19	0.24
3	Felt successful	0.18	**0.67**	0.13
6	Felt really happy	0.35	**0.62**	0.13
9	Felt optimistic	0.27	**0.71**	0.02
11	Felt like I was having a lot of fun	0.23	**0.75**	0.14
14	Felt like I accomplished a lot	0.17	**0.73**	0.06
16	Felt like I had a lot to look forward to	0.15	**0.71**	0.04
19	Felt really talkative	0.16	**0.58**	0.02
22	Felt really ‘up’ or lively	0.27	**0.73**	0.13
26	Felt like I had a lot of energy	0.21	**0.69**	0.07
29	Felt really good about myself	0.39	**0.68**	0.09
2	Startled easily	0.35	-0.06	**0.57**
5	Felt nauseous	0.17	0.09	**0.58**
8	Felt dizzy or light-headed	0.14	0.14	**0.66**
15	Was trembling or shaking	0.18	0.10	**0.72**
18	Had pain in my chest	0.01	0.04	**0.61**
20	Had hot or cold spells	0.18	0.14	**0.65**
21	Was short of breath	0.12	0.04	**0.57**
24	Muscles were tense or sore	0.05	0.12	**0.65**
27	Heart was racing or pounding	0.20	0.08	**0.61**
30	Had trouble swallowing	0.14	-0.04	**0.61**

Results from factor analysis in sample 1. Only the factor loadings for the short form items are presented, the remaining 60 MASQ items are not included. The highest factor loading for each item is printed in bold font; the Item numbers for MASQ-D30.

Table 2.2: Demographic and diagnostic information for samples 1, 2 and 3

	Sample 1	Sample 2	Sample 3	P value[1]
Source study	ROM	ROM	NESDA	
N	489	1461	2471	
Male	192 (39.3%)	520 (35.6%)	819 (33.1%)	0.03
Female	297 (60.7%)	941 (64.4%)	1652 (66.9%)	
Age mean (SD)	37.5 (11.7)	38.7 (13.1)	42.1 (13.1)	<0.001
Age range	18-65	18-65	18-65	
Lifetime psychiatric diagnoses:				
Diagnostic instrument	MINI	MINI	CIDI	
Only depressive disorder	76 (15%)	302 (21%)	478 (19%)	0.05
Only anxiety disorder	103 (21%)	371 (25%)	294 (12%)	<0.001
Only somatoform disorder	28 (6%)	70 (5%)	-	0.48
Comorbidity: depression and anxiety	105 (22%)	294 (20%)	1122 (46%)	<0.001
Comorbidity: depression and/or anxiety and Somatoform disorder	42 (8%)	128 (9%)	-	0.91
No lifetime diagnosis	135 (28%)	296 (20%)	577 (23%)	0.002

[1])Tests of significance using ANOVAs or χ^2-tests. ROM = Routine Outcome Monitoring; NESDA = Netherlands Study of Depression and Anxiety; MINI = Mini International Neuropsychiatric Interview; CIDI = Composite International Diagnostic Interview.

Convergent validity

Table 2.4 shows the correlation coefficients between the scales of the MASQ-D30 and the MASQ (Dutch adaptation) and other instruments. The GD scale of the MASQ-D30 was highly correlated with the BSI-total scale (*r*=0.83) and the 4DSQ-distress scale (*r*=0.83). In addition, correlations of GD with more specific scales ranged from 0.53 with the BSI-somatisation scale to 0.85 with the BSI-depression scale. These results indicate that the GD is associated with general psychological distress, depression, anxiety andsomatisation. The AD scale of the MASQ-D30 showed robust but modest correlations with the MADRS (*r*=0.61), the BDI-total (*r*=0.56), the BDI-affective (*r*=0.57), the BSI-depression (*r* = 0.60) and the IDS (*r* =0.67). Conversely, AD showed lower correlations with measures of anxiety and somatisation (correlation coefficients ranged from 0.31 with BSI-somatic to 0.49 with the BAI). These results indicate that the AD scale is moderately specific to depression and less to anxiety and somatisation. The AA scale of the MASQ-D30 showed considerable correlations with measures of anxiety and somatisation (BSI-somatic: *r*=0.89, BAI: *r* =0.76, BSI-anxiety: *r*=0.70 and BAS: *r*=0.60) and lower correlations with measures of depression (MADRS: *r*=0.52, BSI-depression: *r*=0.51, BDI-affect: *r*=0.44). This suggests that AA is

mostly specific to anxiety and somatisation and less to depressed state. Remarkably, the correlation of the IDS with AD (*r*=0.67) was similar to that with AA (*r*=0.66), while the IDS is intended as a measure of depression. This could be caused by the fact that the IDS is heterogeneous and also measures somatic and anxious symptoms along with symptoms of depression. Table 2.4 reveals that the correlations are largely similar for the MASQ-D30 and MASQ scales. This indicates that the convergent validity of the MASQ is preserved in the MASQ-D30. The correlations of the MASQ-D30 scales with the BAI, IDS and the 4DSQ-distress scale were similar in the 3 healthcare subgroups of sample 3. Thus, convergent validity was consistent across different health care settings.

Table 2.3: Reliability and inter correlations of the MASQ-D30 scales and the full MASQ scales

Scale:		General Distress		Anhedonic Depression		Anxious Arousal	
		MASQ	MASQ-D30	MASQ	MASQ-D30	MASQ	MASQ-D30
Item number		20[a]	10	22[a]	10	18[a]	10
Sample 2	GD	0.95	0.91 (0.95)[b]	-	-	-	-
(n=1461)	AD	0.62	0.57	0.96	0.93 (0.96)[b]	-	-
	AA	0.59	0.56	0.35	0.30	0.93	0.87 (0.92)[b]
Sample 3	GD	-	0.92	-	-	-	-
(n=2471)	AD	-	0.68	-	0.95	-	-
	AA	-	0.63	-	0.48	-	0.85
HC	GD	-	0.84	-	-	-	-
(n=577)	AD	-	0.48	-	0.93	-	-
	AA	-	0.45	-	0.26	-	0.70
PC	GD	-	0.91	-	-	-	-
(n=909)	AD	-	0.62	-	0.94	-	-
	AA	-	0.54	-	0.39	-	0.81
MHC	GD	-	0.90	-	-	-	-
(n=621)	AD	-	0.62	-	0.94	-	-
	AA	-	0.53	-	0.33	-	0.85

Cronbach's alpha coefficients are underlined; MASQ = Dutch Adaptation of the Mood and Anxiety Symptoms Questionnaire; MASQ-D30 = Short Form of the Dutch adaptation of the MASQ; GD =General Distress; AD = Anhedonic Depression; AA = Anxious Arousal; HC = healthy control group; PC = primary care group; MHC = mental health care group (all correlations $p < 0.01$).

[a]Computation of GD, AD and AA scales following de Beurs et al. (2007).

[b]Numbers between parentheses are estimated reliabilities, using Spearman-Brown formula computations

Construct validity

We conducted CFA to assess the fit of a 3 factor model to the MASQ-D30 data of several samples, with items 1, 4, 7, 10, 12, 13, 17, 23, 25 and 28 loading on a GD factor, items 3, 6, 9, 11, 14, 16, 19, 22, 26, and 29 loading on an AD factor and items 2, 5, 8, 15, 18, 20, 21, 24, 27, and 30 loading on an AA factors. The 3 factors were left free to inter-correlate. Table 2.5 shows the χ^2 statistics and indices. The 3 factor model showed acceptable fit to the MASQ-D30 data of sample 3, with fit indices that all exceeded their respective critical cut-off values (NNFI, NFI and CFI > 0.90 and RMSEA < 0.06). Similar results of acceptable model fit were found in the primary care group, mental health care group, healthy control group and the male and female subpopulations of sample 3. These results indicate that the MASQ-D30 represents the 3 dimensions it was designed to measure and that the underlying structure is invariant over different subpopulations, which supports the construct validity of the instrument.

2.4 Discussion

We present a shortened 30 item adaptation of the MASQ: the MASQ-D30, which we constructed by use of factor analysis and the additional judgement of clinical experts. The MASQ-D30 questionnaire was constructed to represent the dimensions of the tripartite model and we demonstrated its scales to have acceptable internal consistency and convergent validity that were comparable with the full MASQ. In addition, we found support for the construct validity of the MASQ-D30.

The MASQ-D30 has two major advantages. First, problematic items with weak or complex loadings in the MASQ are not present in the MASQ-D30, which is likely to make it a more stable representation of the tripartite model. Second, administration of the MASQ-D30 takes less time, which makes the application less expensive.

The MASQ-D30 represents an underlying tripartite structure, analogue to the model that has been found in earlier studies with the MASQ (Keogh and Reidy, 2000; De Beurs et al., 2007). Research on the tripartite model has mostly relied on the study of associations between self report measures, structured interviews and observer ratings (Watson et al., 1995a, b; Keogh and Reidy, 2000; De Beurs et al., 2007) and has regularly used instruments that were not primarily designed to measure the dimensions of the tripartite model (De Beurs et al., 2005). Because of its improved applicability, the MASQ-D30 can help to study the tripartite model more thoroughly and to compare this dimensional approach to the categorical DSM-IV method. In addition, the MASQ-D30 can be used in epidemiological studies and trials to study the relation between the tripartite model and biological markers and psychosocial determinants.

The MASQ-D30 could eventually be used to place the tripartite model in a broad dimensional framework of anxiety and depression together with aspects of other models, like the approach-withdrawal model and the valence-arousal model. These models have a comparable theoretical approach but a different perspective and make assumptions

about the neural substrates of distinct behavioural dimensions that could underlie symptoms of depression and anxiety (Shankman and Klein, 2003).

Table 2.4: The bivariate correlation coefficients of the MASQ-D30 and full MASQ scales with rating scales and self-report measures in sample 2 (n =1461), sample 3 (n = 2471), the healthy control group (HC), the primary care group (PC) and the mental health care group (MHC)

Scale:			General Distress (GD)		Anhedonic Depression (AD)		Anxious Arousal (AA)	
			MASQ	MASQ-D30	MASQ	MASQ-D30	MASQ	MASQ-D30
MADRS		1416	0.72	0.70	0.64	0.61	0.53	0.52
BAS		1416	0.57	0.56	0.45	0.42	0.60	0.60
BDI-aff[a]		961	0.73	0.71	0.61	0.57	0.49	0.47
BDI-som[a]		961	0.64	0.63	0.52	0.48	0.58	0.55
BDI-cog[a]		961	0.71	0.72	0.47	0.44	0.42	0.40
BDI-tot[a]		961	0.79	0.78	0.60	0.56	0.57	0.55
BSI-dep		1456	0.87	0.85	0.63	0.60	0.52	0.51
BSI-anx		1456	0.67	0.66	0.40	0.36	0.70	0.70
BSI-pho		1456	0.58	0.57	0.39	0.34	0.59	0.58
BSI-som		1456	0.54	0.53	0.35	0.31	0.88	0.89
BSI-int		1456	0.70	0.71	0.44	0.40	0.42	0.42
BSI-tot		1456	0.84	0.83	0.53	0.49	0.72	0.71
IDS		2471	-	0.75	-	0.67	-	0.66
BAI		2471	-	0.60	-	0.49	-	0.76
4DQSd		2471	-	0.83	-	0.67	-	0.65
HC	IDS	577	-	0.60	-	0.50	-	0.55
	BAI	577	-	0.50	-	0.37	-	0.61
	4DQSd	577	-	0.65	-	0.41	-	0.40
PC	IDS	909	-	0.67	-	0.59	-	0.56
	BAI	909	-	0.48	-	0.37	-	0.68
	4DQSd	909	-	0.79	-	0.61	-	0.59
MHC	IDS	621	-	0.65	-	0.57	-	0.56
	BAI	621	-	0.45	-	0.28	-	0.72
	4DQSd	621	-	0.78	-	0.62	-	0.56

Table 4 (continued). Legend: MASQ = Dutch Adaptation of the Mood and Anxiety Symptoms Questionnaire; MASQ-D30 = Short Form of the Dutch adaptation of the MASQ; MADRS = Montgomery Åsberg Depression Rating Scale; BAS = Brief Anxiety Scale; BDI = Beck Depression Inventory II: aff = affectivity, som = somatisation, cog = cognition, tot = total score; BSI = Brief Symptom Inventory: dep = depression, anx =anxiety, pho = phobic anxiety, som = somatic complaints, int = interpersonal sensitivity, tot = total score; IDS = Inventory of Depressive Symptoms; BAI = Beck Anxiety Inventory; 4DSQd = 4-Dimensional Symptoms Questionnaire Distress scale; HC = healthy control group; PC = primary care group; MHC = mental health care group (all correlations p<*0.01* two-tailed)

[a] The BDI was only administered to patients who met criteria for a mood disorder.

Table 2.5: Results of confirmatory factor analysis with a 3-dimensional model of the MASQ-D30 in sample 3, the healthy control group (HC), the primary care group (PC) and the mental health care group (MHC) and separately for males and females in sample 3.

Sample	N	S-Bχ^{2} [a]	NFI	NNFI	CFI	RMSEA (90% CI)
Sample 3	2471	2375.46	0.94	0.94	0.95	0.045 (0.043-0.046)
PC	909	1149.93	0.91	0.94	0.94	0.045 (0.042-0.048)
MHC	621	979.35	0.90	0.94	0.94	0.048 (0.044-0.052)
HC	577	671.60	0.82	0.91	0.92	0.034 (0.030-0.039)
Male	819	1102.24	0.92	0.94	0.95	0.046 (0.043-0.049)
Female	1652	1770.30	0.93	0.94	0.94	0.045 (0.043-0.048)

MASQ-D30 = Short Form of the Dutch Adaptation of the Mood and Anxiety Symptoms Questionnaire; NFI = Normed fit index; NNFI = non-normed fit index; CFI = comparative fit index; RMSEA = root mean-square error of approximation; 90% CI = 90% confidence interval

[a)] All Satorra-Bentler χ^{2} statistics with 402 degrees of freedom; all p-values <0.001

In spite of broad scientific support, some aspects of the tripartite model and the MASQ have remained subject of debate. An important point of disagreement in the literature is the assumption that elevated SA is specific to anxiety in general. Several studies have shown that SA is mostly specific to panic disorder and that other aspects of anxiety are underrepresented by the model (Mineka et al., 1998; Joiner et al., 1999; Chorpita, 2002). Some authors thus suggest that the tripartite model and the MASQ should be extended to grant a more complete representation of anxiety symptoms. Mineka et al. (1998), for instance proposed an integrated hierarchical model in which each anxiety syndrome is hypothesized to contain a common (NA) and a unique component. In this model, SA is

defined as a specific component for panic disorder and all other anxiety disorders have other unique components. This model was further extended and modified by Watson (2005), based on a review of results about the underlying structure of the DSM categories. In addition, a symptom level, dimensional approach was described by Watson et al. (2005).

A second issue is that the PA scale largely consists of high-PA reverse-key items (for instance, 'I felt optimistic'). Consequently, the loadings of all high-PA items on one factor could be due to methodological artefact rather than a shared underlying construct (Brown, 2006). However, a high-PA scale and a low-PA scale were found to be interrelated (Watson et al., 1995b), indicating that high and low PA items both represent a PA construct.

The present study has several strengths. First, we developed the MASQ-D30 using a systematic method that is firmly based in the psychometric literature (Smith et al., 2000). Second, large samples from the general population, primary care and mental health care were used, which gives our findings about the MASQ-D30 a high degree of external validity for the intended fields of use. Third, we used confirmatory factor analysis in addition to exploratory factor analysis, which enabled us evaluate and statistically confirm the fit of the underlying dimensional structure (Fabrigar et al., 1999).

There are also some limitations in the present study. First, our results apply to a Dutch adaptation of the MASQ. However, we expect that the results from this translation are generalizable to English language (and other Western) populations, because the Dutch translation of the MASQ was shown to have good psychometric properties that were comparable to the original English MASQ (de Beurs et al., 2007). In addition, there are no striking cultural differences in the assessment and definition of mental illness between the US and the Netherlands as illustrated by the fact that in both countries the DSM-IV is used to define mental illness and the fact that other Dutch have not been problematic (e.g. Dutch BDI-II, Beck et al., 2002). Second, we only tested the fit of one model with CFA, which does not completely rule out the possibility of another, unknown better fitting model. Previous studies (Burns and Eidelson, 1998; Boschen and Oei, 2006) tested more models (2, 3 and 5 dimensional) based on five original MASQ subscales (Watson et al., 1995a, b). However, this structure of 5 subscales was not preserved in the MASQ-D30, because it was constructed to be truly 3-dimensional. This made it impossible to test the fit of the alternative models from the literature. Third, the used samples consist of subjects with a broad range of DSM-IV diagnoses as well as healthy subjects, which could conceal differences in factor structure between clinical conditions. However, we think that the 3 dimensional structure of the MASQ-D30 should be consistent across individuals irrespective of categorical diagnosis. This should be further investigated.

An important point that should be addressed in future research is comparison of the MASQ-D30 to the Mini-MASQ, a short form of the original MASQ (Casillas and Clark, 2000). The Mini-MASQ consists of 26 items and was developed in the US in healthy community samples of (low income African American adults and college students), to be

used as a measure of psychological wellbeing in a community study of lower income families (e.g. Cutrona et al., 2000). The MASQ-D30 and the Mini-MASQ share little overlap and are thus expected to have different psychometric characteristics, possibly due to differences in development sample (psychiatric patients versus community dwelling adults) and/or chance effects. These issues should be investigated in subsequent research.

In conclusion, the MASQ-D30 is a reliable and valid instrument with the advantage of being compact and therefore broadly applicable. The questionnaire provides a promising basic framework for the study of dimensional psychopathology. Therefore we have included the MASQ-D30 in NESDA to investigate the tripartite model in relation to biological measures and other external criteria. Large scale efforts like these could eventually provide the knowledge that is needed to establish the dimensional approach to psychopathology as a credible clinical and scientific supplement for the mainstream categorical thinking of the DSM-IV and the ICD-10.

Chapter 3:

The Structure and Dimensionality of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in Patients with Depressive Disorders and Healthy Controls

Abstract

Background: The inventory of depressive symptomatology self report (IDS-SR) is a widely used but heterogeneous measure of depression severity. Insight in its factor structure and dimensionality could help to develop more homogeneous IDS-SR subscales. However previous factoranalytical studies have found mixed results. Therefore, the present study tested which factor structure underlies the IDS-SR and, in addition, if the factors can be used as unidimensional subscales. *Methods:* Confirmatory factor analysis (CFA) was done to identify the best fitting factor structure. The study sample consisted of 2600 individuals (mean age 40.5 ± 12.1). We assessed model fit in 4 groups: 957 Major Depressive Disorder (MDD) patients, 450 remitted MDD patients, 570 patients with an anxiety disorder and 623 healthy controls to test the consistency of model fit. Rasch analyses in the full sample were used to evaluate and optimize the unidimensionality and psychometric quality of the factors.

Results: CFA indicated that a 3-factor model fits the IDS-SR data best and is consistent across groups, with a 'mood/cognition' factor, an 'anxiety/ arousal' factor and a 'sleep' factor. In addition, Rasch analyses indicated that the 'mood/cognition' and 'anxiety/arousal' factors could be optimized to be used as unidimensional subscales.

Limitations: The fit of only 4 models was tested, ranging from a 1- to 4-factor model.

Conclusions: The IDS-SR is a heterogeneous instrument with a multifactorial underlying structure. It is possible to measure more homogenous symptomatology with IDS-SR subscales, which could be useful in clinical practice and scientific research.

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3.1 Introduction

Major Depressive Disorder (MDD) is a heterogeneous disease; patients vary in terms of severity, age of onset, duration, recurrence and symptom profiles (Kendler, 1999). Consequently, the 'depression' label provides limited information about the particular problems experienced by a patient. The description of a patient's condition in terms of symptom dimensions creates possibilities for more specific diagnosis, treatment evaluation and research (Shafer, 2006; Andrews et al., 2007). Therefore, in the present study we evaluated which factor structure underlies the widely used Inventory of Depressive Symptomatology self report (IDS-SR) and whether the identified factors could be used as unidimensional subscales.

The IDS-SR is a self report questionnaire that was introduced by Rush et al (1986; 1996) as a measure of depression severity. The IDS-SR comprises all symptoms of depression, as defined by the DSM-III-R / IV-TR, including melancholic, atypical and anxious symptoms. The questionnaire has been shown to have adequate reliability, acceptable validity, good responsiveness and good discriminative ability (Rush et al., 1996, 2003; Corruble et al., 1999; Trivedi et al., 2004).

The IDS was aimed to measure a unitary construct of depressive symptom severity (Rush et al., 1996; Trivedi et al., 2004). However, different underlying factor structures have been described for the IDS-SR, with solutions of two factors (Bernstein, 2006), three factors (Rush et al., 1996) and four factors (Rush et al., 1986). Although the numbers of factors are different, the models show conceptual overlap: all the multifactorial models make some distinction between a 'depression/mood' and an 'anxiety/somatic' dimension (Bernstein, 2006; Rush et al., 1986; 1996). In addition, the 3-dimensional model contains a 'sleeping problems' factor and the 4-dimensional model contains an 'atypical' and an 'endogenous' factor.

Differences between the presented structures may be attributed to differences in characteristics of the analyzed samples and analytic approaches (Fabrigar et al., 1999). One study (Bernstein, 2006) used principal components analysis (PCA) to explore the underlying structure of the IDS-SR. Two studies used PCA with a predefined number of components to be extracted (Rush et al., 1986, 1996). Yet, confirmatory factor analysis (CFA) would provide valuable information about the appropriateness of hypothesized factor structures. Trivedi et al (2004) used CFA to test the fit of a 1-factor model to a large set of items, including the IDS-SR, and found it to fit well. However, CFA should ideally be used to investigate and compare the fit of several hypothesized structural models (Brown et al., 2006).

A stable factor model for the IDS-SR would have a potential utility in patient care and to address specific research questions. It could help uncover clusters of symptoms that are systematically related to each other, which could potentially be used as IDS-SR subscales. However, before a set of items is used as an additive interval scale, it should be determined if it is really unidimensional. This can be investigated with Rasch modelling methods. The Rasch model is an Item Response Theory (IRT) model that models the

probability of endorsement of each item in an instrument as a function of its location on the underlying symptom-severity dimension. If all items fit adequately to the Rasch model, this indicates that the items are ordered along one dimension and that the added up raw, ordinal item-responses can be interpreted as a true interval scale (Wright & Masters, 1982). In addition, Rasch analyses can be used to investigate the discriminative ability of a measure, and whether items function consistently across different person characteristics. Importantly, if the factor structure and the fit to the Rasch model are consistent across healthy subjects and patients, this would indicate that each subscale measures the same underlying severity dimension, irrespective of an individual's categorical diagnosis.

We aimed to find the best-fitting, most consistent factor structure for the IDS-SR and to investigate the usability of the factors as subscales. To this end, we tested and compared the fit of four factor models from the literature using CFA in patients with current MDD (n=957). Next, we investigated the consistency of the best-fitting model across patients with a remitted MDD (n=450), patients with a lifetime anxiety disorder (n=570) and healthy control subjects (n=623). Rasch analyses were conducted to evaluate unidimensionality of the factors and to investigate whether the added up, raw responses on each factor could be used as subscales with sufficient discriminative ability and stability across different person characteristics. We conducted these analyses on data from the Netherlands Study of Depression and Anxiety (NESDA; N = 2981).

3.2 Methods

Sample and procedures

Participants came from the NESDA study, a large scale longitudinal study conducted among 2981 adult subjects (mean age 41.9, age range: 18-65; 1002 men and 1979 women) (Penninx et al., 2008). The NESDA sample consists of 2329 subjects with a lifetime diagnosis of depressive or anxiety disorder and 652 subjects without a lifetime psychiatric diagnosis. These were recruited from three different settings: community, primary care and mental health care organizations. All participants were interviewed and assessed during a visit to a research location.

For the CFA analyses, subjects that completed the IDS-SR without missing values (n=2600) were included in one of 4 non-overlapping groups. Group 1 consisted of all subjects with a current MDD diagnosis (within last 6 months; with or without MDD in the past; n=957). Group 2 consisted of subjects with MDD in remission during the past 6 months; n=450). Group 3 (n=570) consisted of patients with a lifetime anxiety disorder and no lifetime depression. Group 4 (n=623) consisted of all mentally healthy control subjects. The protocol of the NESDA study was approved centrally by the Ethical Review Board of the Leiden University Medical Center and by local review boards of participating centres. All subjects signed informed consent.

Instruments

All participants completed the Dutch translation of the IDS-SR (Rush et al., 1996) that consists of 30 equally weighed items, rated on a four-point scale (range 0-3). 28 of the 30 items are summed to a standard total score, ranging from 0 to 84 (as only appetite and weight increase or decrease is scored). For the analyses of the 1, 2 and 3-factor models and the Rasch analyses, items 11 and 12 and items 13 and 14 were rescored into a single 'change of appetite' (item 11/12) variable and a 'weight change' variable (item 13/14). Only for the analysis of the 4-factor model, items 11, 12, 13 and 14 were treated as separate variables. The Composite International Diagnostic Interview (CIDI, WHO version 2.1) was used to assess the DSM-IV criteria for depressive disorders (MDD and dysthymia) and anxiety disorders (panic disorder, social phobia, generalized anxiety disorder and agoraphobia).

Statistical analyses

Principal Component Analysis

To gain some preliminary insight into the number of components that could be expected to underlie the IDS-SR, an initial PCA was conducted in all subjects that completed the IDS-SR (n=2600). Parallel analysis was used for factor extraction. With this method, the eigenvalues generated with PCA in the real data are compared with the (95^{th} percentile of) eigenvalues that are generated in 1000 random datasets with the same number of variables and observations. Only the components are retained for which the eigenvalues in the real data exceed the randomly generated eigenvalues, and thus are higher than expected by chance. This method has been shown to be superior to traditionally used extraction techniques like Kaiser's criterion (O'Connor, 2000). PROMAX was used for oblique component rotation. The analyses were conducted with SPSS (version 16).

Confirmatory factor Analysis (CFA)

To investigate and compare the fit of four factor-models from the literature, CFA was conducted in current MDD patients (group 1), because all four hypothesized models were developed in comparable samples of depressed (out)patients. To test model-fit with CFA, the models were first defined based on the (PCA) factor loadings reported in each publication (Rush et al., 1986, 1996; Trivedi et al., 2004; Bernstein, 2006). For each item it was evaluated on which factor it had its highest (primary) loading in the PCA results. In the CFA model, this primary loading was set to be freely estimated and the factor loadings on other factors were fixed to zero. Items with high loadings on more than one factor (differing <0.15) were set to load freely on both factors. To scale the estimated factors, on each factor the loading of one item was fixed to 1 (Brown, 2006). In the multi-factorial models, factor covariances were set to be freely estimated.

In the *1-factor model* all items loaded on one 'depression' factor (Trivedi et al., 2004). In the *2-factor model* (Bernstein, 2006) there was a 'depression' factor (all items)

and a 'somatic' factor (items 25, 26 and 28). In the *3-factor model* (Rush et al., 1996), there was a 'mood/cognition' factor (items 5, 8, 10, 11-14 and 17-22), an 'anxiety/ arousal' factor (items 6, 7, 23-27 and 30) and a 'sleep' factor (items 1-4). Items 9, 15, 20 and 29 loaded on the 'mood/cognition' and 'somatic' factors and item 24 loaded on the 'somatic' and 'sleep' factors. In the *4-factor model* (Rush et al., 1986; 28 item version) there was a mood/cognition factor (items 5-8 and 15-22), an 'anxious/hypochondria' factor (items 24-28), an 'endogenous' factor (items 2, 3, 9, 11 and 13) and an 'atypical' factor (items 4, 12 and 14). Item 23 loaded on the first two factors, item 1 loaded on the second and third factor.

Because the IDS-SR items were categorical and had a non-normal distribution, estimation of model fit with maximum likelihood (ML) would likely lead to an underestimation of model-fit (Byrne, 2006). Therefore, we used an adapted approach for categorical data (Bentler, 2006). First, a matrix of polychoric correlations between the items was generated. Second, ML was used to estimate model fit-statistics. Third, the ML-based statistics were corrected using an appropriate weight-matrix to obtain *robust* fit-statistics (Satorra and Bentler, 1988), which have been shown to perform well for categorical and non-normal data (Byrne, 2006). Model-fit was evaluated with fit-indices, in stead of the traditional χ^2-test, which is oversensitive to minor deviations from perfect fit in large samples and with complex models (Brown, 2006). The following fit-indices were used: the Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA) and the Akaike Information Criterion (AIC). A CFI of at least 0.95 indicates good fit and a RMSEA smaller than 0.06 indicates good fit (Hu and Bentler, 1999). The AIC can be used to compare different models, balancing statistical goodness-of-fit and the number of model parameters. The model with the lowest AIC can be regarded as potentially most useful (Bentler, 2006). In addition to the CFA in group 1, CFA was performed in groups 2, 3 and 4 with the best fitting model from group 1 to investigate the consistency of model-fit across different groups. The EQS statistical package (Multivariate Software Inc., Encino, California, USA) was used to conduct the analyses.

Rasch Analyses

To test if the identified factors were unidimensional measurement scales, fit to the Rasch model was investigated. The Rasch model assumes that the probability of a person's response on an item is described by a *logistic* function of the distance between the location of the person and the location of the item on the underlying linear *severity dimension*. Thus, if a person is located higher on the dimension than the item, the probability of responding with the highest response option is high. Conversely, if the person is located lower than the item, the probability of responding with the lowest response option is high. If all items fit adequately to the Rasch model, this indicates that all items are lined up along one underlying dimension in order of increasing severity. In addition, fit to the Rasch model indicates that the ordinal responses on the items can be

added up to a linear interval-scale that is a *sufficient statistic* for the underlying severity dimension.

The unrestricted partial credit model was used for fit-estimation. To estimate the fit to the Rasch model, the unweighted mean square standardized residual (outfit) was calculated for each item (formulas from: Wright & Masters, 1982, p100). Outfit was used in the current study because it is essentially a χ^2 statistic divided by its degrees of freedom (n), and thus less affected by the large sample size than traditional significance-tests of (mis)fit. An outfit close to 1 (within the range of 0.7 to 1.3) was considered to indicate adequate fit to the Rasch model (Wright & Stone, 1979). Persons with extreme scores (with a total score of 0 or with fit-residuals>|2.5|) were excluded from model-fit calculations because they do not behave in line with model expectations.

For each factor, the same analytic procedure was followed to assess and improve fit to the Rasch model. First, the fit of the items to the Rasch model was assessed. Second, the thresholds between adjacent response categories were inspected for ordering problems. If the response scale was disordered, for instance, if a category was never most probable to be endorsed (redundant), adjacent categories were collapsed. Third, the fit of the items was assessed again to see if fit had improved. Items with inadequate fit were removed to arrive at a unidimensional subscale with optimal fit to the Rasch model. The locations were inspected to see how the items were distributed along the underlying dimension. Fourth, all items in the final subscale were tested for differential item functioning (DIF) across person characteristics (Age group (young: 18-42 versus old: 43-65), gender and lifetime depression). An ANOVA was used to compare scores between levels of each person characteristic (uniform DIF) and across different classes of severity (non-uniform DIF). To investigate the actual extent and implications of DIF, the location and outfit were assessed for the different levels of the person characteristic (e.g. men vs. women). Because the ANOVA was likely to pick up less relevant DIF due to the large sample size (statistical power), a large difference in location (we chose >0.5 logits as cut-off) and model fit between two characteristic subgroups (e.g. men and women) was taken to indicate that the generalizability of item functioning is potentially problematic. Fifth, unidimensionality was additionally checked with a PCA of the residuals. Two subsets of items with respectively positive and negative loadings on the first component of this PCA were selected and person estimates were calculated for these subsets of items. If these estimates differed significantly from the full-scale estimates (as indicated by t>|1.96| in more than 5% of individuals), this indicated that the responses on the subsets were interdependent (when controlled for the primary underlying dimension) and that there was still some multidimensionality present in the measure (Smith, 2004). Sixth, to evaluate clinical usefulness of each subscale, the person-separation index was calculated and the number of severity strata that could be discriminated was derived from the separation-ratio (G). Additionally, to evaluate the (multi)dimensionality of the complete IDS-SR, its fit to the Rasch model was also investigated. Calculations were done with RUMM2020 (RUMM Laboratory, Perth, WA, Australia).

Missing Data

In group 1, 139 of 1096 subjects (12.7%) were excluded because they had one or more missing responses on the IDS-SR, resulting in a group of 957 subjects. In groups 2, 3 and 4, respectively 50 (10%), 48 (7.2%) and 58 (9.2%) subjects were excluded because of missing responses. The subjects with missing values were found to be younger and have less years of education than the subject with complete data (data not shown). However, it was decided not to impute missing items because to our knowledge there is no widely supported method to impute non-normal, categorical data without introducing new and unknown sources of bias.

Table 3.1: Demographic and diagnostic information of the studied subgroups in the NESDA data (n=2600)

Sample Diagnostic Status	Group 1 current MDD (<6 months)	Group 2 Remitted MDD (>6 months)	Group 3 Only anxiety (Lifetime)	Group 4 Healthy Controls
N	957	450	570	623
Women (%)	639 (66.8%)	319 (70.9%)	377 (66.1%)	382 (61.3%)
Men (%)	318 (33.2%)	131 (29.1%)	193 (33.9%)	241 (38.7%)
Mean age (SD)	40.5 (12.1)	43.8 (12.6)	41.7 (13.0)	40.8 (14.8)
Age range	18–64	18-65	18-65	18-65
Mean Yrs of Ed (SD)	11.7 (3.2)	12.5 (3.2)	12.3 (3.2)	12.9 (3.2)
DSM-IV diagnoses[a]				
Only current MDD[b]	331 (34.6%)	0	0	0
Only current anxiety	0	0	490 (86.0%)	0
Current comorbidity	626 (65.4%)	0	0	0
Only remitted MDD	0	301 (66.9%)	0	0
Only remitted anxiety	0	0	80 (14.0%)	0
Remitted comorbidity	0	149 (33.1%)	0	0

MDD = Major Depressive Disorder, Mean Yrs of Ed = mean years of education

[a] DSM-IV diagnoses assessed with the CIDI

[b] Also includes cases of current MDD + dythymia

3.3 Results

Diagnoses and demographic variables

The demographic and diagnostic information for the four non-overlapping study groups are shown in Table 3.1. The distribution of gender as well as mean age and mean years of education were largely comparable across the 4 groups. In group 1 (Current MDD), the majority (65.4%) of current MDD patients had a comorbid anxiety disorder. In group 2 (Remitted MDD), the majority (33.1%) of subjects had a comorbid remitted anxiety disorder. In group 3 (Lifetime anxiety disorders, no MDD), the majority (86.0%) of subjects had a current anxiety diagnosis. In group 4, by definition nobody had a psychiatric diagnosis.

Principal Component Analysis

The results of the initial PCA are shown in Table 3.2. Parallel analysis indicated that 3 components should be extracted. After rotation, items that covered symptoms of (depressed) mood, affect and cognitions loaded on the first component ('mood/cognition'), items that covered anxiety and somatic arousal and somatic complaints loaded on the second component ('anxiety/arousal') and items that covered sleep symptoms loaded on the third component ('sleep'). The extracted components were largely similar to the 3 components reported by Rush et al. (1996): only 7 of the 28 items had a completely different primary loading in the present study (items 6, 7, 15, 11/12, 13/14, 23 and 29). These results indicate that a 3-factor structure is likely to underlie the IDS-SR across a wide variety of subjects.

Confirmatory Factor Analysis

To test and compare the fit of the 4 models of the IDS-SR (1, 2, 3 and 4-facor), CFA was conducted in group 1 (Current MDD). The results are shown in Table 3.3. For the 3-factor model, the CFI was highest (CFI=0.95) and the RMSEA was lowest (RMSEA=0.056), which both indicated better fit than the 1, 2 and 4-factor models (all: CFI≤0.93; RMSEA≥0.065). In addition, the AIC was lowest for the 3-factor model (AIC=684.70), which indicates that this model is potentially most useful, taking into account both model-fit and the number of model-parameters. These results indicate that the 3-factor model proposed by Rush et al. (1996) best represents the underlying structure of the IDS-SR.

Confirmatory Factor Analysis in different groups

To investigate the consistency of model-fit of the 3-factor model, CFA was conducted in groups 2, 3 and 4. Results are shown in Table 3.4. The indices-of-fit indicated good model-fit in all groups (CFI≥0.95; RMSEA≤0.049), which indicated that the fit of the 3-factor model is consistent across subjects with remitted MDD, subjects with a lifetime anxiety disorder and healthy controls.

Table 3.2 Results of a Principal Components Analysis in the complete dataset (n=2600): factor loadings and eigenvalues

IDS-SR items	Component			Factor in Rush et al. (1996)[1]
	1. Mood/ Cognition	2. Anxiety/ Somatic	3. Sleep	
21. Pleasure or enjoyment (not sex)	**0.92**	-0.17	0.04	*1*
5. Feeling sad	**0.89**	-0.09	0.02	*1*
8. Reactivity of mood	**0.86**	-0.26	0.06	*1*
19. Interest in people/activities	**0.84**	-0.10	0.01	*1*
17. Future pessimism	**0.78**	-0.06	0.03	*1*
10. Quality of mood	**0.72**	-0.01	-0.03	*1*
16. Self criticism and blame	**0.66**	0.02	-0.10	*1*
15. Concentration/decision making	**0.64**	0.14	0.01	*2*
18. Suicidal thoughts	**0.60**	-0.07	0.01	*1*
6. Feeling irritable	**0.59**	0.14	0.01	*2*
23. Psychomotor retardation	**0.57**	0.10	0.04	*2*
20. Energy/fatiguability	**0.57**	0.27	-0.05	*1*
22. Interest in Sex	**0.53**	0.05	0.08	*1*
29. Interpersonal sensitivity	**0.51**	0.20	-0.16	*2*
7. Feeling anxious or tense	**0.50**	0.32	0.03	*2*
30. Leaden paralysis/physical energy	**0.46**	**0.39**	-0.04	*2*
28. Constipation/diarrhoea	-0.22	**0.79**	-0.03	*2*
25. Aches and pains	-0.06	**0.69**	0.14	*2*
26. Sympathetic arousal	0.08	**0.58**	0.13	*2*
27. Panic/phobic symptoms	0.08	**0.56**	-0.04	*2*
13/14. Weight disturbance	-0.13	**0.53**	0.01	*1*
11/12. Appetite disturbance	0.23	**0.43**	-0.09	*1*
24. Psychomotor agitation	**0.25**	**0.29**	0.10	*2*
3. Early morning awakening	0.12	0.00	**0.69**	*3*
2. Middle insomnia	-0.06	0.19	**0.68**	*3*
4. Sleeping too much	0.15	0.31	**-0.56**	*3*
1. Initial insomnia	0.16	0.19	**0.42**	*3*
9. Diurnal variation of mood	0.16	0.16	-0.04	-
Eigenvalue (in real data)	9.97	1.47	1.26	
Eigenvalue (randomly generated)	1.22	1.18	1.16	

Table 3.2 (continued). Legend: IDS-SR = Inventory of Depressive Symptomatology Self Report; communalities after extraction ranged from 0.21 to 0.70; the components were rotated with PROMAX; the primary loading for each item is printed in bold font
[1)] Components on which each item had its highest loading in PCA results by Rush et al. (1996): 1 = 'mood/cognition', 2= 'anxiety/arousal', 3 = 'sleep'; an underlined number indicates that the item loads on a different component in the present study

Table 3.3: Confirmatory factor analysis of four factor-models of the IDS-SR in group 1 (Current MDD; n = 957)

Input model	Source	Df	Satorra-Bentler χ^2	CFI	RMSEA (90% CI)	AIC
1-factor	Trivedi et al. (2004)	350	2043.23	0.92	0.071 (0.068 – 0.074)	1343.23
2-factor	Bernstein (2006)	347	1845.39	0.93	0.067 (0.064 -0.070)	1151.39
3-factor	Rush et al. (1996)	343	**1370.70**	**0.95**	**0.056 (0.053 – 0.059)**	**684.70**
4-factor[a]	Rush et al. (1986)	291	1466.78	0.93	0.065 (0.061 - 0.068)	880.78

IDS-SR = Inventory of Depressive Symptomatology Self Report; Df = Degrees of freedom; CFI = Comparative fit index; Standardized root mean-square residual; RMSEA = Root mean square error of approximation; 90% CI (RMSEA) = 90% confidence interval of the RMSEA; AIC = Akaike Information criterion
CFA based on polychoric correlation matrix with robust Satorra-Bentler correction
[a]The 4-factor input model included 26 of the 28 IDS-SR items: of the 4 appetite/weight items, only item 11 (decreased appetite) and item 14 (increased weight) were included because the polychoric correlations between item 11 and item 12 (increased appetite) and between item 13 and item 14 (decreased weight) both approached -1.0, resulting in a non-positive definite correlation matrix, which can not be used to estimate model-fit. By including only one item of each pair in the model, this problem was solved and the proposed distinction between an atypical and endogenous factor was still expressed in the model

Rasch Analyses

The full IDS-SR

Of the 28 items in the IDS-SR, 10 items showed poor fit to the Rasch model, which is further evidence for the multidimensionality of the IDS-SR.

The IDS-SR 'Mood/Cognition' subscale

All 15 items that were set to load on the 'Mood/Cognition' factor in the CFA were investigated for fit to the Rasch model. Items 9, 13/14, 19 and 21 did have an outfit statistic outside the acceptable range. Inspection of the threshold-ordering revealed that seven items (9, 11/12, 14-17 and 29) had disordered thresholds, which resulted from category 1 or 2 to be redundant in each of these items. Therefore, it was decided to collapse category 1 and 2, resulting in a 3-point response scale (0=0, 1=1, 2=1 and 3=2). For ease of use all items were rescored accordingly. The thresholds, locations and outfit after rescoring are shown in Table 3.5. All thresholds were now ordered correctly and item-fit had mostly increased after rescoring. However, the same four items still fit poorly and were therefore removed. This resulted in a final 11-item subscale with item-locations ordered as follows (in ascending order): 29, 16, 17, 10, 15, 20, 5, 22, 11/12, 8 and 18.
Thus, interpersonal sensitivity (item 29), problematic self view (item 16) and pessimism about the future (item 17) were at the low end of the 'mood/cognition' dimension and decreased reactivity of mood (item 8) and suicidal thoughts (item 18) were at the severe end.

Several items displayed DIF (significant DIF and difference between locations>0.5). Item 5 displayed DIF between depressed (location=-0.24) and non-depressed subjects (location=0.51) but had adequate outfit in both subgroups (0.7<outfit<1.3). Item 8 displayed DIF between men (location=0.66) and women (location=1.37) but showed adequate outfit in both groups. Item 29 displayed DIF between men (location=-0.55) and women (location=-1.09) and between young (location=-1.23) and old subjects (location=-0.60) but had adequate outfit in all subgroups. Inspection of the location-ordering indicated that the items were generally ordered in the same way in the different person-factor groups, with items 29, 16 and 17 at the lowest and items 8 and 18 at the highest end of the severity dimension. Thus, although items 5, 8 and 29 show some DIF, the consistent adequate outfit and threshold ordering across subgroups indicates this does not severely affect the generalizability of measurement.

Comparing the person estimates between the PCA item-subsets and the final 11 item 'mood/cognition' subscale indicated no significant difference for any person (all t-values <|1.96|), which forms further evidence for unidimensionality.

The 11-item 'mood/cognition' subscale had a person-separation-index of 0.88, which indicates that the scale can be used to discriminate around 4 severity strata (G≈3; Wright & Masters, 1982). The removal of 4 items from the initial 15-item subscale only

led to a 0.01 reduction of the person-separation-index, indicating that these items did not contribute substantially to the discriminative ability of the subscale.

Table 3.4: Confirmatory factor analysis of the 3-factor model of the IDS-SR in group 2 (remitted MDD), group 3 (Lifetime anxiety) and group 4 (Healthy controls)

Model	Group	Df	Satorra-Bentler χ^2	CFI	RMSEA (90% CI)
3-factor	2 (remitted MDD), n = 450	343	670.34	0.96	0.046 (0.041 – 0.051)
	3 (Anxiety), n = 570	343	821.17	0.95	0.049 (0.045 – 0.054)
	4 (healthy Controls), n = 623	343	752.14	0.96	0.044 (0.040 – 0.048)

IDS-SR = Inventory of Depressive Symptomatology Self Report ; MDD = Major Depressive Disorder; Df = Degrees of freedom; CFI = Comparative fit index; Standardized root mean-square residual; RMSEA = Root mean square error of approximation; 90% CI (RMSEA) = 90% confidence interval of the RMSEA
CFA based on polychoric correlation matrix with robust Satorra-Bentler correction.

The IDS-SR 'Anxiety/Arousal' subscale

All nine items that were set to load on the 'anxiety/arousal' factor in the CFA were investigated for fit to the Rasch model. Only item 7 fit poorly (outfit=0.63). Inspection of the threshold-ordering again revealed redundancy of category 1 or 2 in some items (items 23, 24 and 30). Therefore, the items in the 'anxiety/arousal' subscale were also rescored to a 3-point scale (0=0, 1=1, 2=1 and 3=2). The thresholds, locations and outfit statistics are shown in table 3.5. All thresholds were now ordered correctly and item fit had mostly increased after rescoring. However, item 7 still fit poorly and was removed. This resulted in an 8-item subscale with item-locations ordered as follows: 30, 25, 6, 27, 28, 24, 26 and 23. Thus, symptoms such as leaden paralysis (item 30), aches and pains (item 25) and feeling irritable (item 6) were at the lower end of the severity dimension and psychomotor agitation (item 24), sympathetic symptoms (e.g. arrhythmic or pounding heartbeat, blurred vision, sweating; item 26) and psychomotor retardation (item 23) were on the severe end.

Items 24 and 25 displayed DIF between men (location=-0.03 and -0.23) and women (location=0.58 and -0.77) but both had adequate fit in both subgroups (0.7<outfit<1.3). Item 6 displayed DIF between young (location=-0.53) and old (location=-0.05) but had adequate fit in both groups. Item 27 displayed DIF between depressed (location=0.34) and non-depressed (location=-0.20) and showed poorer fit in the depressed (outfit=0.69) than in the non-depressed subgroup (outfit=0.86). Inspection of

the location-ordering indicated that the items were generally ordered in the same way in the different person-factor groups, with items 30, 25 and 6 at the lowest and items 24, 26 and 23 at the highest end of the dimension. The results indicate that items 24 and 25 showed some DIF that was not likely to severely affect the generalizability of measurement. The DIF for item 27 was more serious, although its outfit statistic of 0.69 in depressed subjects was only just below the cut-off of 0.70, the function of this item could be less consistent.

3.4 Discussion

The present study used CFA to identify the best fitting structural model of the IDS-SR. An initial PCA indicated that 3 factors were expected to underlie the IDS-SR and when the fit of four models from the literature was tested with CFA, the 3-factor model (Rush et al., 1996) was indeed found to fit best to the data. This model consisted of a 'mood/cognition', 'anxiety/arousal' and 'sleep' factor and was found to fit well across different groups of patients and healthy controls. To evaluate if they could be used as subscales, the factors were tested and fine-tuned using Rasch analyses: items were rescored to a more optimal 3-point scale (0, 1, 1, 2) and items that fit the model poorly were removed. This resulted in two unidimensional IDS-SR subscales: the 11-item 'mood/cognition' subscale and the 8-item 'anxiety/arousal' subscale. The adequate fit to the Rasch model indicated that the sum scores on these subscales can be regarded as *sufficient statistic* for their underlying symptom dimensions. An additional PCA of the residuals indicated that the scales were unidimensional. DIF analyses showed that some items functioned differently across groups, though measurement characteristics generally seemed consistent. Finally, the subscales were found to have adequate discriminative ability. Importantly, Rasch analyses with the total IDS-SR indicated that it is multidimensional, underlining the need for more homogeneous symptom measures.

The IDS-SR subscales could be helpful for both clinicians and researchers who seek less heterogeneous symptom-severity measures. Using the subscales could have added value because: (1) they function well as 'measurement scales' (as shown by the Rasch results), (2) they assess severity for more specific symptom-domains and (3) different patterns of subscale scores could indicate different treatment indications and/or disease prognosis. In addition, the finding of two symptom dimensions could indicate (partly) distinct underlying etiological mechanisms.The present results have some additional general implications. First, the traditionally used total sum score on the IDS-SR does not seem to be a unidimensional measure of depression-severity. This is a general problem that is also observed for other widely used instruments like the Hamilton Depression Rating Scale (HDRS; Gibbons et al, 1993) the Beck Depression Inventory (BDI; Gibbons et al., 1985) and the Centre for Epidemiological Studies Depression Scale (CES-D; Stansbury et al., 2006). Second, the finding that a 3-dimensional model fit the IDS-SR better than the 4-dimensional model (Rush et al., 1986), does contradict the traditional idea of distinct 'atypical' and 'melancholic/endogenous' symptom domains.

Table 3.5: The location and outfit statistic for each of the items in the IDS-SR 'Mood/Cognition' subscale and 'Anxiety/Arousal' subscale

	IDS-SR 'Mood/Cognition' subscale Threshold				IDS-SR 'Anxiety Arousal' subscale Threshold			
	1	2	Location	Outfit	1	2	Location	Outfit
5. Feeling sad	-2.38	2.09	-0.15	**0.72**	-	-	-	-
6. Feeling irritable	-	-	-	-	-2.56	1.99	-0.28	**0.84**
7. Feeling anxious or tense	-	-	-	-	-2.61	2.13	-0.24	0.67
8. Reactivity of Mood	-0.56	2.50	-0.97	**1.01**	-	-	-	-
9. Diurnal variation of mood	-0.50	0.60	0.05	2.26	-	-	-	-
10. Quality of mood	-1.36	0.56	-0.40	**0.79**	-	-	-	-
11/12. Appetite disturbance	-1.15	1.01	-0.07	**1.04**	-	-	-	-
13/14. Weight disturbance	-1.42	0.89	-0.26	2.31	-	-	-	-
15. Concentration/decision making	-2.37	1.79	-0.29	**0.82**	-	-	-	-
16. Self criticism and blame	-1.07	-0.46	-0.76	**0.96**	-	-	-	-
17. Future pessimism	-2.90	2.06	-0.42	**0.82**	-	-	-	-
18. Suicidal thoughts	-3.42	2.92	0.29	**1.01**	-	-	-	-
19. Interest in people/ activities	-1.04	1.59	0.27	0.62	-	-	-	-
20. Energy/fatiguability	-2.26	1.96	-0.15	**0.82**	-	-	-	-
21. Pleasure or enjoyment	-1.17	3.08	0.96	0.60	-	-	-	-
22. Interest in sex	-1.37	1.19	-0.09	**1.26**	-	-		-
23. Psychomotor retardation	-	-	-	-	-0.34	2.36	1.01	**0.72**
24. Psychomotor agitation	-	-	-	-	-1.36	2.03	0.33	**1.01**
25. Aches and pains	-	-	-	-	-3.07	1.91	-0.58	**0.96**
26. Sympathetic arousal	-	-	-	-	-2.52	3.81	-0.65	**0.85**
27. Panic/phobic symptoms	-	-	-	-	-1.66	1.92	0.13	**0.96**
28. Constipation/diarrhoea	-	-	-	-	-1.45	1.78	0.16	**1.19**
29. Interpersonal Sensitivity	-2.45	0.55	-0.95	**1.01**	-	-	-	-
30. Leaden Paralysis	-	-	-	-	-2.85	0.49	-1.18	**0.76**

IDS-SR = Inventory of Depressive Symptomatology Self Report. Items 1 to 4 are omitted from the table. Threshold 1= location of threshold between response option 0 and 1; threshold 2=location of threshold between response option 1 and 2; Location = value between threshold 1 and 2. Items with an outfit in bold font were retained in the subscale

Evidence of heterogeneity has been found for many widely used depression scales (e.g. the HDRS, BDI and CES-D), and many shorter, unidimensional versions and/or subscales have been proposed. For the HDRS, subsets of items have been proposed to measure only

'core symptoms' of depression (Bech et al, 1981; Maier and Philipp, 1985; Santor et al., 2008). These 'subscales' were indeed shown to function as unidimensional measures with IRT analyses (e.g. Bech et al., 1981; Gibbons et al., 1993; Santor et al, 2008). Recently, the same was found for the self rated HDRS version (Bech et al., 2009). For the BDI, several revisions and subscales have been proposed. For instance, Gibbons et al (1985) found the BDI to be more unidimensional without vegetative symptoms. Bouman & Kok (1987) further subdivided the BDI into three unidimensional subscales using Rasch analyses: 'mood/inhibition', 'guilt/failure' and 'vegetative'. This subdivision is in line with the most commonly found factor structure for the BDI (review: Beck et al., 1988; Shafer, 2006). Also for the CES-D shorter (IRT derived) unidimensional subscales have been developed (e.g. Cole et al., 2004; Stansbury et al., 2006). The current IDS-SR 'mood/cognition' subscale can be regarded as conceptually similar to the abovementioned attempts to create a more homogenous depression measure. However, coverage seems to vary somewhat across the different subscales, most likely because each original instrument has a slightly different focus and item-pool to select from. The IDS-SR 'anxiety/arousal' subscale mostly resembles the item-sets that have been found to load on one 'anxiety-agitation' factor or two distinct 'somatic anxiety' and 'psychic anxiety' factors in the HDRS (Bagby et al., 2004; Shafer et al., 2006). However, these factors have received less attention, which is not surprising given that the instrument is mainly used as a depression measure in antidepressant trials. Both the BDI and CES-D mainly focus on depressed mood and/or cognitions and cover only a few somatic/vegetative symptoms, which is not enough to construct a reliable subscale (Gibbons et al., 1985). The present finding of a 'sleep' factor is in line with other studies that found sleeping problems to load on a separate 'insomnia' factor (HDRS) or on a 'neurovegetative' factor (BDI; CES-D) (Shafer, 2006).

The present study has several strong characteristics. First, CFA was conducted in large and representative samples of healthy subjects and psychiatric patients, which makes the results generalizable to a broad range of settings and patients. Second, CFA was used to test the fit of multiple hypothesized models, which allowed both for assessment of model fit and selection of a best-fitting model from among several plausible models. Third, a CFA approach was used that minimized bias due to the categorical and non-normal nature of the IDS-SR data, increasing the validity of the results. Fourth, the Rasch analyses resulted in subscales that can really be regarded as unidimensional measurement scales; something that would not have been achieved with classical psychometric analyses. The results should be interpreted in the light of some limitations. First, only the fit of four models from the literature was tested, which does not rule out that an unknown model with a different structure (e.g. more factors) might fit better. However, the initial PCA in the present study did not suggest that this was the case. Second, the current analyses were conducted in a group of subjects with relatively mild psychopathology. Future research should point out whether our findings can also be generalized to more severely ill and/or institutionalized patients. Finally, although DIF did

not seem to be very problematic for general use, researchers that are specifically interested in score differences between groups (e.g. men and women) should be aware of DIF that could reduce subscale-score comparability. They could leave DIF items out of the subscale calculations.

In conclusion, the IDS-SR has three underlying factors, of which two can be adapted for use as specific subscales in both clinical practice and scientific research.

Chapter 4:

Dimensions of Depression and Anxiety and the Hypothalamo-Pituitary-Adrenal Axis

Abstract

Background: Results on the association between depression and the HPA-axis have been inconsistent, possibly due to heterogeneity of the DSM-IV category of depression. Specific symptom-dimensions could be used as a more homogenous phenotype in HPA-axis research.

Methods: 1029 subjects with a lifetime depression and/or anxiety disorder from the NESDA study (mean age: 43.0±12.7; 67.4% female) provided 7 saliva samples to yield the cortisol awakening response (CAR), evening cortisol and dexamethasone suppression data. The dimensions of the tripartite model (General Distress, Anhedonic Depression and Anxious Arousal) were measured with the 30-item adapted Mood and Anxiety Symptoms Questionnaire (MASQ-D30) and analyzed in association with the cortisol measures using linear and non-linear regression.

Results: Median (interquartile range) scores of General Distress, Anhedonic Depression and Anxious Arousal were respectively 20 (14-27), 36 (28-44) and 15 (12-19), indicating large variability. Non-linear associations with the shape of an inverted U were found between General Distress, Anhedonic Depression and Anxious Arousal on one hand and total morning secretion and the dynamic of the CAR on the other hand. Both high and low severity levels were associated with a lower CAR, compared to intermediate levels of severity. Most of the associations remained significant when adjusted for covariates and the presence of DSM-IV diagnoses.

Conclusions: Non-linear associations were found between the CAR and the dimensions of the tripartite model. This could explain previous inconsistent findings regarding HPA-axis activity in depressed patients and illustrates the added value of symptom-dimensions for HPA-axis research.

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4.1 Introduction

Dysregulation of the Hypothalamo-Pituitary-Adrenal (HPA) axis may play a role in the etiology of depression (Holsboer & Barden, 1996; De Kloet, 2005). A hyperactive HPA-axis has indeed been found in severely depressed patients and, to a lesser extent, in outpatients and mildly depressed patients, measured through e.g. increased evening cortisol levels, a higher cortisol awakening response (CAR), an altered dexamethasone suppression test (DST) or a decreased response on the 'Dexamethasone Suppression Test' and the more sensitive 'Dexamethasone Corticotrophin Releasing Hormone (CRH) Suppression Test' (Bhagwaghar et al., 2005; Pruessner et al., 2003; Holsboer & Ising, 2010). Our group found a slightly higher CAR in subjects with a current or lifetime MDD and higher evening cortisol in subjects with a current MDD but found no differences in suppression on the DST (Vreeburg et al., 2009a). However, others have found no or other HPA-axis dysregulations in MDD outpatients (Stetler & Miller, 2005; Huber et al., 2006).

A possible explanation for these modest and inconsistent findings could be that the DSM-IV category of MDD is not an optimal clinical phenotype for HPA-axis research. Patients may even receive the same MDD diagnosis if they only overlap on one of nine criterion symptoms, resulting in a heterogeneous patient group. When comparing these patients to healthy controls, specific associations between symptoms and cortisol levels can easily go undetected. Similar problems arise with overall measures of 'depression severity', because persons with the same severity score can still have very different symptom patterns. There is much overlap in clinical features between MDD and anxiety disorders, leading to high comorbidity (Hasin et al., 2005), and both groups of disorders respond to similar treatments. This indicates that research should not be limited to MDD only, because a lot of underlying pathophysiology is likely to be shared with anxiety. Indeed, an altered HPA-axis has also been observed in anxious patients versus healthy controls (Schreiber et al, 1996; Erhardt et al., 2006, Abelson et al., 2007) and our research group found increased morning cortisol in current anxiety patients, mainly in current panic disorder with agoraphobia (Vreeburg et al., 2010). Research on the HPA-axis should thus address both specific and shared symptom domains of depression and anxiety.

A way to investigate symptom-specific associations with the HPA-axis can be through the use of s*ymptom-dimensions* as clinical determinants. A symptom dimension represents a continuum of increasing severity on a symptom-domain (Goldberg, 2000). Each dimension covers specific symptomatology, which can help to distinguish symptom-specific pathophysiological effects. In addition, dimensions are continuous, providing more statistical power to detect small -but potentially relevant- effects (MacCallum et al., 2002). Additionally, using continuous dimensions, non-linear (curved) associations can be effectively investigated. This is useful given the observations that both hypo-and hyperactivity of the HPA-axis are associated with higher risk of depression, indicating a non-linear, U-shaped association between HPA-axis activity and depression (Bremmer et al., 2007; Penninx et al., 2007).

A well-known dimensional model of anxiety and depression is the 'tripartite model' (Clark & Watson, 1991). In this model, a *'General Distress'* dimension covers symptoms of general psychological distress (e.g. pessimism and feelings of guilt), common to both depression and anxiety. In addition, a specific *'Anhedonic Depression'* dimension covers anhedonic symptoms (i.e. lack of positive affect and emotionality), associated with depression. An *'Anxious Arousal'* dimension covers symptoms of somatic hyperarousal (e.g. sweating, trembling and palpitations), associated rather specifically with anxiety/panic disorder. Several studies have found this model to work well in different patient populations (Keogh & Reidy, 2000; Marshall et al., 2003; de Beurs et al., 2007; Wardenaar et al., 2010). The association between the tripartite dimensions and the HPA-axis was investigated by our group (Veen et al., 2011). We recently found that General Distress and Anhedonic Depression were both associated with morning cortisol. These associations had an "inverted U-shape": low and high dimensional scores were associated with decreased morning cortisol. This observation can explain why low and high HPA-axis activity is observed in depressed patients depending on their specific profile of symptomatology, which could cause the inconsistencies in the literature so far. Using the dimensions of the tripartite model can thus have added value for HPA-axis research.

Therefore, the present study aimed to answer several questions. First, we investigated whether the dimensions of the tripartite model were associated with the HPA-axis in a large sample of lifetime depression and/or anxiety patients (n=1029). Second, we investigated the shape of these associations. Third, we investigated whether the dimensional associations were generalizable across different DSM-IV groups (e.g. current versus lifetime patients) and whether they provided additional information about HPA-axis variability on top of the DSM-IV diagnoses that were previously found to be associated with the HPA-axis (e.g. lifetime/current MDD, current anxiety).

4.2 Methods and Materials

Subjects

Subjects came from the NESDA study, a large longitudinal study to investigate the course of depressive and anxiety disorders. The NESDA sample consists of 2.981 subjects (mean age 41.9; 1.002 men and 1.979 women), who were recruited from community, primary care and specialized mental health care organizations. The sample consists of 2.329 subjects with a lifetime diagnosis of depressive or anxiety disorder and 652 subjects without a lifetime psychiatric diagnosis. Detailed objectives and rationales can be found elsewhere (Penninx et al., 2008). The protocol of the NESDA study was approved centrally by the Ethical Review Board of the Leiden University Medical Center and by local review boards of the participating centres. All participants signed informed consent.

Of the 2981 subjects in NESDA, 2167 (72.6%) returned saliva samples. These subjects were older ($p<0.001$) and had more years of education ($p<0.001$) than the subjects who did not return the saliva samples. 130 subjects were excluded because they

used corticosteroids, 19 because they were pregnant or breastfeeding and 50 subjects using tricyclic antidepressants (TCA; WHO Anatomical Therapeutic Chemical classification N06AA) because TCA's were shown to affect the HPA-axis in previous research (6). Users of selective serotonin reuptake inhibitors (SSRIs; N06AB) and other antidepressants (N06AF, N06AG and N06AX) were *not* excluded. Of the remaining 1968 subjects, 1782 subjects returned the required questionnaires. These were significantly younger ($p=0.03$) and had more years of education ($p<0.001$) than subjects who did not return all questionnaires. During data cleaning (described below), 278 subjects were excluded, resulting in a group of 1378 subjects with usable cortisol samples. Of these, 1029 subjects had a lifetime depression and/or anxiety disorder and were used as study group for the main analyses.

Salivary Cortisol Measurements

An extensive description of the cortisol measurement and analysis was presented previously (6). Participants were instructed to collect saliva samples at home on a regular working day. Saliva was collected with Salivettes® (Starstedt AG, Germany) at seven sampling points. The CAR was assessed with four time points: at awakening (T1), 30 (T2), 45 (T3) and 60 minutes later (T4). Two samples were collected at 22h00 (T5) and 23h00 (T6) to assess the (basal) evening cortisol level. Directly after T6, participants ingested 0.5 mg of dexamethasone and the next morning saliva was collected at awakening (T7). Samples were centrifuged at 2000g (for 10 min), aliquoted and stored at -80°C. The analysis of cortisol was done with competitive electrochemiluminescence immunoassay (E170, Roche, Switzerland) (van Aken et al., 2003). The functional detection limit was 2.0 nmol/l and the intra- and interassay variability coefficients were less than 10% in the measurement range.

During data cleaning, 149 subjects who collected their cortisol samples more than five minutes before or after the right protocol time were excluded. Also, 129 subjects were excluded because they had cortisol samples with values higher than two standard deviations above the mean. These values exceeded the realistic range for saliva cortisol and were likely to be a result of measurement factors (e.g. bleedings of the gums after tooth brushing or as a result of gingivitis). Three cortisol indicators were computed: the CAR, the evening cortisol level and the DST. The CAR was assessed by calculation of the area under the curve with respect to the ground (AUCg) and with respect to the increase (AUCi), by use of a trapezoid formula (Pruessner et al., 2003). The AUCg estimates the total body exposure to cortisol and predicts mean saliva cortisol exposure throughout the day. The AUCi is a measure of the dynamic of the CAR, related to the sensitivity of the system and change in cortisol exposure over time (Pruessner et al., 2003; Edwards et al., 2001). The mean of cortisol levels at T5 and T6 was calculated as a measure of evening cortisol. The DST was assessed using the samples at T1 and T7. The percentage of suppression by dexamethasone was calculated by taking the ratio of T1/T7, with higher values indicating more post-dexamethasone suppression.

Psychopathology

All participants completed the shortened, 30-item, Dutch adaptation of the MASQ (Watson et al., 1995a,b: the MASQ-D30 (Wardenaar et al., 2010). In the MASQ-D30, individuals rate how much in the past week they have experienced "feelings, sensations, problems and experiences that people sometimes have" on a 5-point scale, with 1 being "not at all" and 5 being "extremely". The MASQ-D30 consists of three 10-item subscales that measure General Distress, Anhedonic Depression and Anxious Arousal and has good psychometric characteristics (Wardenaar et al., 2010). The Composite International Diagnostic Interview (CIDI, WHO version 2.1) was used to assess the DSM-IV criteria for depressive disorders (i.e. MDD and dysthymia) and anxiety disorders (i.e. panic disorder, social phobia, generalized anxiety disorder and agoraphobia).

Covariates

Sociodemographic variables (gender, age), sampling factors (time of awakening, working status, seasonality and sleep duration) and physical health indicators (smoking, alcohol use/dependence, physical activity, cardiovascular disease [CVD]) have been found to be associated with salivary cortisol levels in previous research using the NESDA data (Vreeburg et al., 2009b). These determinants were treated as covariates in the present analyses. Each participant reported time of awakening and working status. The month of cortisol collection was dichotomized into months with less (October – February) versus more (March – September) daylight. Sleep duration was dichotomized as more or less than 6 hours/night. Smoking was dichotomized into current and non-smokers. The International Physical Activity Questionnaire (IPAQ) was used to assess physical activity, expressed in 100 MET-minutes (metabolic equivalent of number of calories spent per minute) per week (Craig et al., 2003). Prevalent CVD was established using an algorithm based on self-report and medication use. The Alcohol Use Disorder Identification Test (Saunders et al., 1993) was used to assess the number of daily ingested alcoholic beverages and the presence of alcohol dependence (a score >14 for males and >12 for females).

Statistical Analyses

The AUCs and the DST (T1/T7) were log-transformed to improve normality. Inspection of the plotted standardized residuals and normal (P-P) plots of all univariate and multivariate models revealed that the residuals were normally distributed.

To investigate the associations of the dimensions with cortisol exposure, several regression analyses were conducted. In each analysis, one of the dimensions was the continuous predictor variable and a cortisol indicator the outcome variable. Next, to test if the association had the shape of a curve instead of a straight line, a quadratic term of the scale was added as predictor variable (e.g. both General Distress and [General Distress]^2); If the regression coefficients were significant for both the linear and quadratic

term, the association with cortisol would have a curved shape. All analyses were conducted without (Crude) and with covariates (Model 1). Finally, lifetime MDD, current (6-month) MDD, and current anxiety were added as dichotomous covariates (Model 2). If the regression coefficients of the dimension did not change in this incremental model, this would indicate that the dimension explained variation in the cortisol indicator, independently from DSM-IV status. For each model, the proportion of explained variance was calculated (R^2). The variance inflation factor (VIF) was calculated to check for collinearity. Only in the non-linear models, the VIF indicated collinearity between the dimension and its quadratic term, which is a well-documented phenomenon for polynomial regression models (33). This collinearity was not likely to affect the reliability of our results, since the collinear variables are mathematically related to each other and not intended as independent predictors. Moreover, eliminating the collinearity by centering the linear and non-linear terms (Brauner & Shacham, 1998; data not shown) did not lead to large changes in the observed results, which further indicated that collinearity did not affect our findings. Durbin-Watson coefficients were calculated to test for auto-correlated residuals. For all models, the coefficients (range: 1.96-2.03) suggested to reject the hypothesis of auto-correlated residuals (Savin & White, 1977). P-values <0.05 were considered significant. Because we tested only a priori hypothesized associations and for confounding, we did not correct for multiple testing.

Additional analyses were conducted to evaluate to what extent the associations were generalizable across different diagnostic groups (healthy, remitted patients and current patients). To investigate whether the inclusion of remitted patients in the main research group, all analyses were rerun in a group of current patients only (n=729). To investigate whether the associations could be generalized across the complete spectrum of diagnostic severity (from healthy to ill), all analyses were rerun in a group including lifetime patients and healthy subjects (n=1378). All analyses were done with SPSS 16.0.

4.3 Results

Demographic information and diagnoses

The demographic and diagnostic information of the study group is shown in Table 4.1. The mean age was 43.0 years (SD=12.7) and the percentage of women was 67.4%. Of the subjects, 45.6% had a current and 24.7% had a remitted MDD diagnosis with or without a comorbid anxiety disorder. In addition, 25.3% had a current and 4.4% had a remitted anxiety diagnosis without MDD. Of the subjects 19.8% used SSRIs and 8.0% used other antidepressants.

General Distress had a median of 20 (interquartile range [IQR]: 14-26; Anhedonic Depression had a median of 36 (IQR: 29-43); and Anxious Arousal had a median of 15 (IQR: 12-18), which indicated that there was considerable variability on each of the dimensions.

The cortisol awakening response: AUCg and AUCi

None of the AUC's showed a linear association with any of the symptom-dimensions (Table 4.2). The results of the regression analyses with the added quadratic terms are shown in Table 4.3. The AUCg showed a significant curved association with Anhedonic Depression. The AUCi showed significant curved associations with General Distress, Anhedonic Depression and Anxious Arousal. All associations remained statistically significant when covariates were added (Model 1 in Table 4.3). In addition, when lifetime MDD, current MDD and current anxiety disorders were added as covariates (Model 2 in Table 4.3), all associations remained significant and regression coefficients barely changed (1.6 to 6.0%). This indicated that the curve-shaped associations explain variation in the AUC's, independently from lifetime and current DSM-IV diagnoses.

R^2-statistics indicated that 6.7 to 10.6% of the variance in the AUCs was explained by the different multivariate regression models. The dimensions alone explained 0.8 to 1.0% of the variance in the AUCs, which indicated a small effect size, but these percentages were considerably more substantial for each individual dimension than for lifetime MDD, current MDD and Current Anxiety together, which only added 0.2-0.6% of explained variance in the AUCs (Model 2 compared to Model 1 in Table 4.3). For all analyzed associations, the regression coefficient was positive for the linear term and negative for the quadratic term of the dimension. In other words, the associations had an inverted U-shape. The AUC first increased with increasing dimensional score, then slowly flattened and eventually decreased at the severe end of the dimension (see Figure 4.1; to aid interpretation of the figure, categorized dimensions are depicted on the x-axis).

When the non-linear associations between each dimension and the AUCs were additionally adjusted for the other two dimensions, the results remained the same (data not shown). This indicates that the observation of similarly shaped associations between each of the dimensions and the AUCs were not merely an artefact of (linear) correlations between the dimensions (ρ=0.44-0.66 in the current research group).

In the research group with only current patients (n=729; see Supplementary Table 4.4 [S1]), the AUCi showed significant curved associations with General Distress, Anhedonic Depression and Anxious Arousal. The AUCg showed a borderline significant curved association with Anhedonic Depression. These results were largely similar to the main results; they hardly changed after excluding remitted patients. In the research group with lifetime patients and healthy subjects (n=1378; Supplementary Table 4.5 [S2]), the AUCi also showed curved associations with General Distress, Anhedonic Depression and Anxious Arousal. The AUCg showed a curved association with General Distress and Anhedonic Depression. These results hardly differed from the main results. The curved associations thus seem to be generalizable across the complete spectrum of healthy subjects and current and remitted patients.

Table 4.1: Characteristics of the study group

Characteristic	Total
N	1029
% female	67.4%
Age (Mean, SD)	43.0 (12.7)
% working on sampling day	60.4%
% sampling in light month	57.6%
% < 6 hours of sleep	30.5%
% smoking	33.9%
Physical activity (mean 1000 MET-min/week; SD)	3.5 (3.0)
Current (6-month) MDD and/or dysthymia	178 (17.3%)
Current (6-month) anxiety disorder	260 (25.3%)
Current (6-month) MDD and/or dysthymia with comorbid anxiety disorder	291 (28.3%)
Remitted (6-month) MDD and/or dysthymia	172 (16.7%)
Remitted (6-month) anxiety disorder	45 (4.4%)
Remitted (6-month) MDD and/or dysthymia with comorbid anxiety disorder	83 (8.0%)
Medication use	
SSRI	19.8%
Other antidepressants	8.0%
Median MASQ scale scores (median and interquartile range)	
- General Distress	20 (14-26)
- Anhedonic Depression	36 (29-43)
- Anxious Arousal	15 (12-18)
Cortisol measurements, mean (SD)	
Cortisol T1, at awakening (nmol/l)	16.4 (6.0)
Cortisol T2, + 30 min (nmol/l)	21.0 (8.7)
Cortisol T3, + 45 min (nmol/l)	19.6 (9.4)
Cortisol T4, + 60 min (nmol/l)	17.1 (8.2)
AUCg (nmol/l/h)[1]	17.8 (17.4-18.2)
AUCi (nmol/l/h)[1]	2.4 (2.0-2.8)
Cortisol T5, at 10pm (nmol/l)	5.2 (2.9)
Cortisol T6, at 11pm (nmol/l)	5.1 (3.0)
Evening cortisol (T5+T6 / 2)	5.1 (2.6)
Cortisol T7, at awakening the next day (nmol/l)	6.9 (3.5)
mean Cortisol Suppression Ratio[1,2]	2.46 (2.39-2.54)

Table 4.1 (continued). Legend: AUCg = area under the curve with respect to the ground; AUCi = area under the curve with respect to the increase; MDD = major depressive disorder; MET-min = metabolic equivalent of number of calories spent per minute; SSRI = selective serotonin reuptake inhibitor; T1 to T7 = 7 time points of salivary cortisol collection;
[1] Because of their skewed distributions, back-transformed geometric mean and 95% confidence intervals are presented.
[2] Cortisol suppression ratio = log (salivary cortisol level at T1/salivary cortisol level at T7)

Evening cortisol levels and the DST

General Distress showed a linear association with the DST, which remained significant after addition of covariates (Model 1), and current and lifetime MDD and current anxiety (Model 2). However, when remitted MDD patients were excluded from the study group, the association was no longer significant, indicating that the association between general distress and the DST was partly explained by diagnostic status. Anhedonic Depression and Anxious Arousal were not associated with the DST. None of the dimensions was associated with evening cortisol.

4.4 Discussion

The present study investigated the associations between several HPA-axis indicators and the dimensions of the tripartite model in a large group of psychiatric outpatients with a lifetime depression and/or anxiety disorder. Analyses with the AUCg and AUCi showed the dimension Anhedonic Depression to be associated with both total cortisol exposure and the dynamic of the CAR. The dimensions General Distress and Anxious Arousal were only associated with the dynamic of the CAR. Notably, the associations had the curved shape of an inverted U: both low and high dimensional scores were associated with a lower morning cortisol exposure, compared to intermediate dimension scores. Importantly, each individual dimension explained more variation in morning cortisol exposure than was explained by lifetime MDD, current MDD, and current anxiety disorders together. Interestingly, largely similar associations were found when only patients with a current diagnosis were included in the analyses and when lifetime patients and healthy subjects were analysed together. This indicates that the identified associations are not limited to (current) psychiatric patients only, but can be generalized to a broader group, including remitted patients and healthy subjects. Evening cortisol and the DST did not show any consistent associations with the tripartite dimensions.

Table 4.2: Linear associations between the MASQ-D30 dimensions and cortisol indices in 1029 subjects with lifetime psychopathology.

Dimension		Log AUCg	R^2	Log AUCi	R^2	Evening cortisol	R^2	DST	R^2
General Distress (GD)	Crude	0.03 (0.28)	0.001	0.05 (0.14)	0.002	-0.02 (0.62)	0.000	0.05 (0.10)	0.003*
	Model 1	0.05 (0.08)	0.101	0.04 (0.17)	0.057	-0.03 (0.24)	0.176	0.06 (0.04)	0.046*
	Model 2	0.04 (0.16)	0.107	0.04 (0.23)	0.060	-0.05 (0.13)	0.182	0.07 (0.026)	0.049*
Anhedonic Depression (AD)	Crude	0.04 (0.26)	0.001	0.03 (0.42)	0.001	0.03 (0.29)	0.001	0.00 (0.97)	0.000
	Model 1	0.03 (0.30)	0.099	0.03 (0.36)	0.056	0.00 (0.99)	0.174	0.03 (0.36)	0.043
	Model 2	0.02 (0.45)	0.106	0.02 (0.51)	0.059	-0.01 (0.77)	0.180	0.04 (0.28)	0.045
Anxious Arousal (AA)	Crude	0.02 (0.45)	0.001	0.03 (0.34)	0.001	0.02 (0.53)	0.000	0.01 (0.75)	0.000
	Model 1	0.03 (0.26)	0.100	0.03 (0.37)	0.056	0.00 (0.91)	0.174	0.03 (0.38)	0.043
	Model 2	0.02 (0.45)	0.106	0.02 (0.48)	0.059	0.00 (0.94)	0.180	0.04 (0.27)	0.045

Data are β-coefficients (p-value); AUCg = area under the curve with respect to the ground; AUCi = area under the curve with respect to the increase; DST = dexamethasone suppression test

Model 1 is adjusted for sociodemographic factors (sex, age and Northern European ancestry), sampling factors (working, time of awakening, sleep duration and months with more or less daylight), and health indicators (smoking, alcohol use (# of daily beverages), alcohol dependence, physical activity, cardiovascular disease). Model 2 is additionally adjusted for current major depressive disorder and current anxiety disorder.

*) When remitted MDD patients were removed, these associations were no longer significant

Table 4.3: Non-linear associations between the MASQ-D30 dimensions and cortisol indices in 1029 subjects with lifetime psychopathology.

Scale		Term	Log AUCg	R^2	Log AUCi	R^2	Evening cortisol	R^2	DST	R^2
General Distress (GD)	Crude	Linear (GD)	0.29 (0.09)	0.003	0.51 (0.003)	0.010	-0.15 (0.36)	0.00	0.08 (0.64)	0.003
		Quadratic (GD^2)	-0.26 (0.13)		-0.47 (0.005)		0.14 (0.41)	1	-0.02 (0.84)	
	Model 1	Linear (GD)	0.34 (0.03)	0.104	0.50 (0.003)	0.064	-0.17 (0.28)	0.17	0.09 (0.57)	0.046
		Quadratic (GD^2)	-0.29 (0.07)		-0.46 (0.006)		0.13 (0.39)	6	-0.03 (0.86)	
	Model 2	Linear (GD)	0.37 (0.03)	0.111	0.47 (0.005)	0.066	-0.15 (0.35)	0.18	0.12 (0.49)	0.049
		Quadratic (GD^2)	-0.32 (0.06)		-0.44 (0.008)		0.10 (0.51)	2	-0.05 (0.78)	
Anhedonic Depression (AD)	Crude	Linear (AD)	0.73 (0.002)	0.010	0.66 (0.005)	0.008	-0.06 (0.82)	0.00	0.03 (0.91)	0.000
		Quadratic (AD^2)	-0.70 (0.003)		-0.64 (0.007)		0.09 (0.71)	1	-0.03 (0.90)	
	Model 1	Linear (AD)	0.63 (0.006)	0.106	0.59 (0.011)	0.062	-0.18 (0.41)	0.17	0.10 (0.67)	0.043
		Quadratic (AD^2)	-0.60 (0.008)		-0.57 (0.014)		0.18 (0.40)	5	-0.07 (0.76)	
	Model 2	Linear (AD)	0.62 (0.006)	0.112	0.57 (0.016)	0.064	-0.13 (0.56)	0.18	0.13 (0.57)	0.045
		Quadratic (AD^2)	-0.61 (0.008)		-0.55 (0.019)		0.12 (0.58)	0	-0.10 (0.67)	
Anxious Arousal (AA)	Crude	Linear (AA)	0.27 (0.12)	0.003	0.51 (0.003)	0.009	0.04 (0.83)	0.00	0.09 (0.59)	0.000
		Quadratic (AA^2)	-0.25 (0.14)		-0.49 (0.004)		-0.02 (0.91)	0	-0.08 (0.63)	
	Model 1	Linear (AA)	0.28 (0.09)	0.102	0.51 (0.003)	0.064	-0.12 (0.46)	0.17	0.18 (0.29)	0.043
		Quadratic (AA^2)	-0.25 (0.13)		-0.48 (0.004)		0.12 (0.46)	5	-0.16 (0.36)	
	Model 2	Linear (AA)	0.26 (0.13)	0.108	0.48 (0.005)	0.066	-0.10 (0.55)	0.18	0.22 (0.21)	0.046
		Quadratic (AA^2)	-0.24 (0.16)		-0.46 (0.007)		0.09 (0.56)	0	-0.19 (0.28)	

Data are β-coefficients (p-value); AUCg = area under the curve with respect to the ground; AUCi = area under the curve with respect to the increase; DST = dexamethasone suppression test. Model 1 is adjusted for sociodemographic factors (sex, age and Northern European ancestry), sampling factors (working, time of awakening, sleep duration and months with more or less daylight), and health indicators (smoking, alcohol use (# of daily beverages), alcohol dependence, physical activity, cardiovascular disease). Model 2 is additionally adjusted for lifetime and current major depressive disorder and current anxiety.

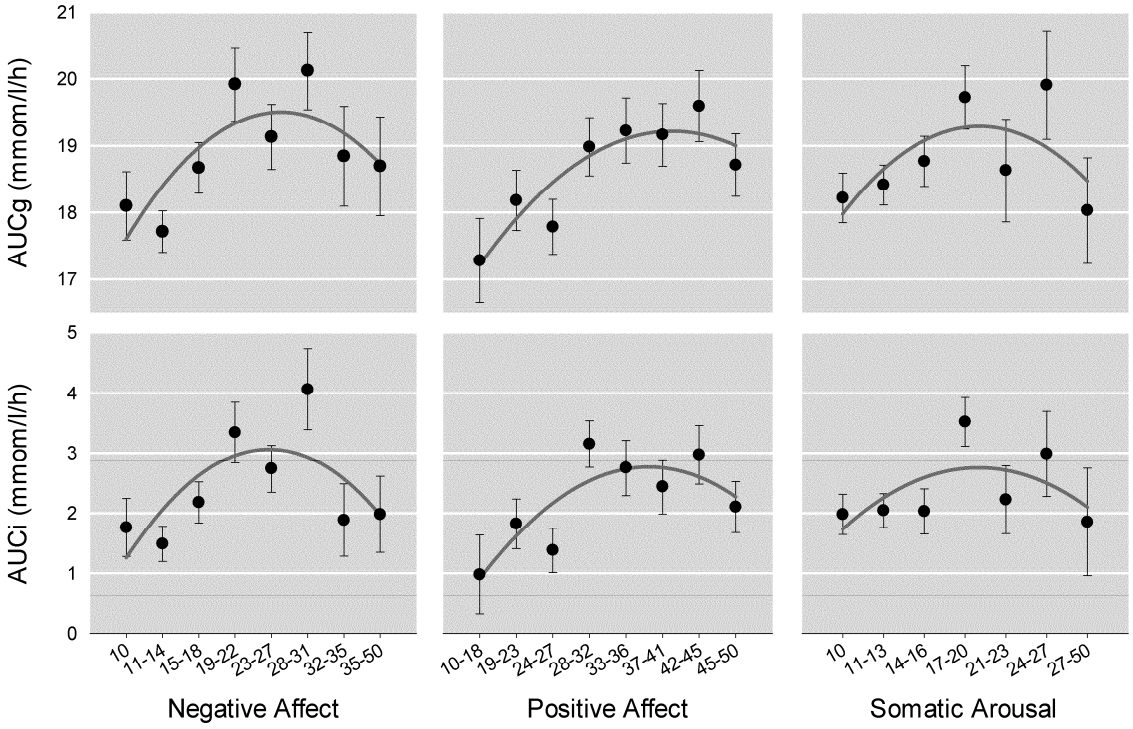

Figure 4.1: Plots of the association between each tripartite model dimension (x-axis) and the area under the curve with respect to the ground (AUCg, upper plots y-axis) and the area under the curve with respect to the increase (AUCi, lower plots y-axis) of the cortisol morning response. Both AUCs had a slightly skewed distribution and were log-transformed before analysis; displayed are the back-transformed means and standard errors. Categorized dimensions are depicted on the x-axis to aid interpretability. The categorized dimensions on the x-axis were only used to aid clearer interpretability of the figure; the tripartite dimensions were actually treated as continuous variables in all analyses.

These results have some interesting implications. Change in HPA-axis activity seems not to be exclusively linked to DSM-IV diagnosis, but also to specific symptom patterns and severity. For instance, the association of morning cortisol exposure with Anhedonic Depression across subjects with lifetime MDD, current MDD and/or current anxiety (treated as covariates), indicates that it is not merely the presence of a diagnosis, but also the amount of, for instance, associated Anhedonic Depression that predicts the height and shape of cortisol exposure during the CAR. Thus, etiological research with the HPA-axis ought not to be limited to the specific group of MDD patients, because the HPA-axis is very likely to play a broader role, for instance in the etiology of subtreshold depression and anxiety. From this perspective, the present results can be regarded as an elaboration

on previous findings of increased morning cortisol in lifetime MDD and anxiety (Vreeburg et al., 2009a; 2010).

Our use of a dimensional approach enabled us to detect non-linear associations that would have gone undetected, had we only used DSM-IV diagnoses. The observed 'inversed U'-shaped associations between the CAR indicators and the dimensions replicates earlier findings by our group in another, smaller sample (Veen et al., 2011) and indicates that, depending on his/her dimensional symptom profile, a patient is more likely to have higher or lower exposure to cortisol during the morning. This could explain why both hypo- and hypercortisolemia are observed in depressed (elderly) patients (Bremmer et al., 2007; Penninx et al., 2007). A possible explanation for the inverted U-shape of the observed associations is that cortisol levels increase with dimensional symptom severity until a critical threshold is reached and the HPA-axis is down-regulated or exhausted (Veen et al., 2011). There are several potential underlying mechanisms for such "hypocortisolism" (Heim et al., 2000). It could be related to a down-regulation of CRH receptors in the pituitary, following a longer period of stress-induced hypothalamic CRH secretion, resulting in lower adrenocorticotropic hormone (ACTH) and reduced cortisol levels. Other possible mechanisms that have found some support from studies in both humans and animals could be a reduced biosynthesis or depletion of CRH, ACTH, cortisol (Heim et al., 2000) or increased sensitivity of the HPA-axis to negative feedback (Holsboer et al., 1985). Although some studies found that especially patients with severe (psychotic) major depression showed a higher cortisol exposure during the CAR versus healthy controls (Belanoff et al., 2001; Posener et al., 2000), other studies in humans and animals have found the HPA-axis to be down-regulated in response to prolonged severe stress, leading to a blunted CAR (Oldehinkel et al., 2001; Meinlschmidt et al., 2005). Our results fit in with both lines of evidence and suggest that they are not necessarily inconsistent.

The association between General Distress and Anhedonic Depression on the one hand and the HPA-axis on the other hand, has been investigated in previous studies outside the tripartite framework (using various different questionnaires). Several studies found an association between measures of General Distress (also called 'Negative Affect') and increased HPA-axis activity in healthy adults (van Eck et al., 1996; Smyth et al., 1998; Buchanan et al., 1999; Jacobs et al., 2007; Polk et al., 2005). Our findings are in line with this, since we also found an increase of the CAR when scores increased within the lower (healthy) spectrum of General Distress. Previous studies mainly investigated the association between the HPA-axis and the opposite pole of Anhedonic Depression, called 'Positive Affect'. These studies generally found decreasing cortisol levels with increasing Positive Affect (Smyth et al., 1998; Polk et al., 2005; La et al., 2005; Steptoe et al., 2008). Our findings are in line with this, because we found an increase in cortisol exposure during the CAR with increasing Anhedonic Depression (i.e. *lack of* Positive Affect). The only previous study to investigate the association between Anxious Arousal and (morning) cortisol (n=36) did not find an association (Veen et al., 2011). However, larger statistical power due to the much larger sample size in the present study (n=1029) could explain

why we did find an association between Anxious Arousal and the dynamic of morning cortisol exposure. Interestingly, our observed U-shaped associations were not found by any of the abovementioned studies, possibly because they used healthy subjects with relatively low symptom severity and were thus unable to detect a decrease in subjects with severe symptomatology, or because only linear associations were explored.

Our findings could be regarded as further (external) validation of the dimensions of the tripartite model and the MASQ-D30. The associations of the MASQ-D30 scales with different aspects of the CAR indicate that they are not merely psychometric constructs, but also have a biological substrate. The tripartite dimensions (as measured with the MASQ-D30) could thus be a promising clinical phenotype for future etiological research.

The present study has some strong characteristics. First, the studied group was one of the largest to date, which increased the reliability of our results. Second, we were able to test the associations across groups including current and remitted MDD patients, anxiety patients and healthy subjects, making our results broadly generalizable. Third, a wide range of determinants of the HPA-axis (Vreeburg et al., 2009b) were considered as possible confounders. Fourth, we studied multiple cortisol indicators that were all indicative of different aspects of the HPA-axis across the day. The present results should also be interpreted in the light of some limitations. First, our results are cross-sectional and cannot indicate change over time or causality. Second, the saliva samples were collected by the participants themselves at home and compliance with the sampling protocol was not monitored. This may have resulted in some measurement error (Vreeburg et al., 2009a). Third, we only measured cortisol during one day, possibly missing day-to-day variations in cortisol levels, which could have further increased measurement error. Fourth, systematic differences between those that did and did not return saliva samples may have biased our results somewhat towards an older and higher educated population. Fifth, our results apply to outpatients with relatively low levels of symptom severity, which limits generalizability of our results to severely ill psychiatric inpatients. Sixth, we only used three, quite broad symptom-dimensions, whereas in reality more (sub)dimensions may exist (Hollander-Gijsman et al., 2010). Finally, the effect sizes suggest that many more factors play a role in symptom dimensions of depression and anxiety on top of cortisol, which, for now, prevents the use of cortisol measurements as clinical marker for psychopathology in individual patients.

In future research, a prospective design should be used to investigate the association between symptom-dimensions and cortisol indicators across a large range of clinical patients (from subtreshold to inpatient), using a broad range of symptom dimensions.

In conclusion, the dimensions of the tripartite model were found to be associated with morning cortisol exposure. Because the dimensions were continuous, non-linear associations could be detected, demonstrating the added value of symptom-dimensions when investigating the role of small and/or complex neuroendocrine mechanisms, underlying psychiatric disease.

Supplementary Table 4.4 (S1): Non-linear associations between the MASQ-D30 dimensions and cortisol indices in 729 subjects with a current major depressive disorder and/or an anxiety disorder.

Scale		Term	AUCg	R^2	AUCi	R^2	Evening cortisol	R^2	DST	R^2
General Distress (GD)	Crude	Linear (GD)	0.39 (0.06)	0.006	0.60 (0.003)	0.012	-0.10 (0.63)	0.001	-0.05 (0.83)	0.001
		Quadratic (GD^2)	-0.35 (0.09)		-0.58 (0.005)		0.12 (0.58)		0.08 (0.69)	
	Model 1	Linear (GD)	0.39 (0.05)	0.105	0.59 (0.003)	0.065	-0.20 (0.30)	0.189	-0.04 (0.87)	0.040
		Quadratic (GD^2)	-0.34 (0.09)		-0.56 (0.006)		0.18 (0.34)		0.08 (0.89)	
	Model 2	Linear (GD)	0.38 (0.06)	0.110	0.59 (0.004)	0.069	-0.23 (0.23)	0.196	-0.03 (0.89)	0.050
		Quadratic (GD^2)	-0.34 (0.08)		-0.55 (0.006)		0.19 (0.32)		0.07 (0.73)	
Anhedonic Depression (AD)	Crude	Linear (AD)	0.68 (0.020)	0.008	0.70 (0.016)	0.008	-0.04 (0.89)	0.002	-0.07 (0.82)	0.000
		Quadratic (AD^2)	-0.65 (0.027)		-0.70 (0.017)		0.08 (0.78)		0.07 (0.80)	
	Model 1	Linear (AD)	0.50 (0.08)	0.103	0.59 (0.042)	0.059	-0.19 (0.49)	0.188	0.00 (0.99)	0.039
		Quadratic (AD^2)	-0.50 (0.08)		-0.59 (0.044)		0.19 (0.49)		0.03 (0.93)	
	Model 2	Linear (AD)	0.54 (0.06)	0.110	0.58 (0.045)	0.063	-0.15 (0.59)	0.194	0.02 (0.94)	0.048
		Quadratic (AD^2)	-0.55 (0.06)		-0.58 (0.048)		0.13 (0.64)		0.00 (0.99)	
Anxious Arousal (AA)	Crude	Linear (AA)	0.44 (0.04)	0.007	0.53 (0.011)	0.009	0.08 (0.72)	0.002	0.10 (0.65)	0.000
		Quadratic (AA^2)	-0.40 (0.06)		-0.53 (0.012)		-0.03 (0.88)		-0.09 (0.68)	
	Model 1	Linear (AA)	0.45 (0.03)	0.106	0.54 (0.010)	0.062	-0.07 (0.73)	0.189	0.18 (0.40)	0.039
		Quadratic (AA^2)	-0.40 (0.05)		-0.54 (0.010)		0.09 (0.64)		-0.16 (0.46)	
	Model 2	Linear (AA)	0.40 (0.06)	0.110	0.55 (0.010)	0.066	-0.06 (0.76)	0.194	0.21 (0.33)	0.050
		Quadratic (AA^2)	-0.36 (0.08)		-0.54 (0.011)		0.08 (0.67)		-0.19 (0.38)	

Data are β-coefficients (p-value); AUCg = area under the curve with respect to the ground; AUCi = area under the curve with respect to the increase; DST = dexamethasone suppression testModel 1 is adjusted for sociodemographic factors (sex, age and Northern European ancestry), sampling factors (working, time of awakening, sleep duration and months with more or less daylight), and health indicators (smoking, alcohol use (# of daily beverages), alcohol dependence, physical activity, cardiovascular disease). Model 2 is additionally adjusted for lifetime and current major depressive disorder and current anxiety disorder.

Supplementary Table 4.5 (S2): Non-linear associations between the MASQ-D30 dimensions and cortisol indices in 1378 subjects with and without lifetime psychopathology

Scale		Term	AUCg	R^2	AUCi	R^2	Evening cortisol	R^2	DST	R^2
General Distress (GD)	Crude	Linear (GD)	0.40 (0.005)	0.009	0.47 (0.001)	0.011	0.01 (0.95)	0.000	0.13 (0.38)	0.003
		Quadratic (GD^2)	-0.33 (0.02)		-0.41 (0.004)		0.01 (0.92)		-0.08 (0.58)	
	Model 1	Linear (GD)	0.44 (0.001)	0.100	0.43 (0.002)	0.067	-0.04 (0.78)	0.165	0.13 (0.36)	0.043
		Quadratic (GD^2)	-0.36 (0.009)		-0.37 (0.008)		0.03 (0.85)		-0.07 (0.63)	
	Model 2	Linear (GD)	0.40 (0.005)	0.105	0.37 (0.011)	0.068	-0.06 (0.66)	0.170	0.20 (0.18)	0.045
		Quadratic (GD^2)	-0.34 (0.015)		-0.33 (0.021)		0.03 (0.84)		-0.12 (0.43)	
Anhedonic Depression (AD)	Crude	Linear (AD)	0.55 (0.004)	0.008	0.56 (0.004)	0.008	-0.04 (0.85)	0.003	0.18 (0.37)	0.001
		Quadratic (AD^2)	-0.50 (0.010)		-0.51 (0.009)		0.09 (0.65)		-0.16 (0.41)	
	Model 1	Linear (AD)	0.43 (0.022)	0.094	0.47 (0.013)	0.064	-0.20 (0.27)	0.165	0.23 (0.23)	0.042
		Quadratic (AD^2)	-0.38 (0.043)		-0.43 (0.025)		0.20 (0.28)		-0.18 (0.35)	
	Model 2	Linear (AD)	0.39 (0.038)	0.102	0.45 (0.043)	0.067	-0.18 (0.32)	0.170	0.27 (0.17)	0.044
		Quadratic (AD^2)	-0.37 (0.050)		-0.41(0.041)		0.16 (0.38)		-0.21 (0.29)	
Anxious Arousal (AA)	Crude	Linear (AA)	0.36 (0.015)	0.006	0.48 (0.001)	0.009	0.19 (0.19)	0.003	0.15 (0.31)	0.001
		Quadratic (AA^2)	-0.31 (0.034)		-0.44 (0.003)		-0.15 (0.32)		-0.14 (0.34)	
	Model 1	Linear (AA)	0.35 (0.014)	0.095	0.45 (0.002)	0.066	0.02 (0.89)	0.165	0.21 (0.15)	0.041
		Quadratic (AA^2)	-0.30 (0.036)		-0.42 (0.004)		-0.01 (0.96)		-0.19 (0.20)	
	Model 2	Linear (AA)	0.27 (0.06)	0.102	0.45 (0.002)	0.066	0.01 (0.94)	0.169	0.26 (0.08)	0.042
		Quadratic (AA^2)	-0.24 (0.09)		-0.42 (0.004)		-0.01 (0.97)		-0.22 (0.13)	

Data are β -coefficients (p-value); AUCg = area under the curve with respect to the ground; AUCi = area under the curve with respect to the increase; DST = dexamethasone suppression test. Model 1 is adjusted for sociodemographic factors (sex, age and Northern European ancestry), sampling factors (working, time of awakening, sleep duration and months with more or less daylight), and health indicators (smoking, alcohol use (# of daily beverages), alcohol dependence, physical activity, cardiovascular disease). Model 2 is additionally adjusted for lifetime and current major depressive disorder and current anxiety disorder.

Chapter 5:

Dimensions of Depression and Anxiety and the Metabolic Syndrome: Somatic Arousal is Associated with Somatic Symptoms of the Metabolic Syndrome

Abstract

Objective: To investigate the association between depression and anxiety symptoms and the metabolic syndrome (MetSyn), using a dimensional approach. The association between depression and anxiety, on the one hand, and the MetSyn as a cluster or its individual components, on the other hand, is equivocal. The categorical nature of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* might partly explain the inconsistent findings. *Methods:* In 2,433 Netherlands Study of Depression and Anxiety participants (mean age, 42.3 years; 33.1% male), three symptoms dimensions—lack of positive affect (PA, depression specific); negative affect (NA, aspecific); and somatic arousal (SA, anxiety specific)—were assessed by a shortened adaptation of the Mood and Anxiety Symptom Questionnaire. The association between symptom dimensions and MetSyn components (waist circumference, triglycerides, high-density lipoprotein cholesterol, glucose, and mean blood pressure) was analyzed, using linear regression analysis. *Results:* The occurrence rate of the MetSyn was 20.1% (*n*=490). SA, but not PA and NA, was strongly associated with four out of five MetSyn components, especially waist circumference, triglycerides, and blood pressure (β=0.046, *p*<.01; β=0.077, *p*<.001; and β=0.069, *p*<.001, respectively), and with the total number of MetSyn components (β=0.098, *p*<.001). *Conclusions:* Our results demonstrate a strong association of most of the MetSyn components with the SA dimension, but not with the NA and PA scales.

Previously published as:

Luppino, FS, van Reedt-Dortland, AKB, Wardenaar, KJ, Bouvy, PF, Giltay, EJ, Zitman, FG, Penninx, BWJH (2011). Somatic arousal is associated with somatic symptoms of the metabolic syndrome. *Psychosomatic Medicine* 73: 257-264.

Note: *Troughout the literature, different interchangeable names are used for the measured dimensions of the tripartite model. In this published chapter, the names that were used to describe the dimensions differ from the names that were used in the other chapters. In this chapter, the name negative affect (NA) is used in stead of general distress, the name positive affect (PA) is used in stead of anhedonic depression, and the name somatic arousal (SA) is used in stead of anxious arousal. This difference of terminology is purely circumstantial and does not reflect any difference in the used theoretical framework.*

5.1 Introcuction

Mood and anxiety disorders are related to an increased risk of cardiovascular morbidity and mortality (Penninx et al., 2001; Barth et al., 2004). The metabolic syndrome (MetSyn) is a cluster of cardiovascular risk factors (i.e., elevated waist circumference, triglycerides, blood pressure, and fasting glucose, and reduced high-density lipoprotein [HDL]) cholesterol) (Grundy et al., 2005) and is thought to mediate partly this relationship (Bjorntorp, 2001). The association between depression and anxiety and the MetSyn has been extensively investigated. Most studies (Heiskanen et al., 2007) focused on the association between depression and the cluster of the MetSyn and its individual components. Other studies (Skilton et al., 2007; Carroll et al., 2009), however less numerous, investigated the association between anxiety and both the MetSyn cluster and its individual components. In addition, in a recent publication (Reedt Dortland et al., 2010), we examined whether disorder status and symptom severity were associated with the MetSyn. No significant difference was found between subjects with and without psychopathology (both depression and/or anxiety). Only the subgroups of the most severely depressed or anxious subjects had increased occurrence rates of the MetSyn, an association predominantly driven by abdominal obesity and dyslipidemia. Despite these observations, the question remains whether a complete mood disorder diagnosis or rather only specific symptom dimensions are related to the MetSyn and whether the dichotomous MetSyn diagnosis or only some
of its components are related to psychopathology dimensions.

There are three major reasons that could explain why this question has so far remained unanswered. First, the studies have been conducted in widely differing samples, which limit the possibilities to formulate a broadly generalizable model. For instance, there have been differences in the settings (e.g., clinical population or the general population) (Ierodiakonou & Iacovides, 1987), age of the subjects (an elderly population or young adult patients) (Almeida et al., 2009; Franko et al., 2005), and the assessment of psychopathology (questionnaires versus clinical diagnoses) (Koponen et al., 2010; Goldbacher et al., 2009). Second, the categorical diagnostic approach (using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV]) for depressive and anxiety disorders, lumping together disparate symptom clusters, may have limited the power to detect subtle associations (Goldberg, 1996). Patients with the

same diagnosis can be very different in terms of their symptom profiles, whereas other individuals with important mental health problems fail to meet the diagnostic criteria due to symptom heterogeneity. Third, like the DSM-IV diagnosis, the MetSyn concept is also heterogeneous, and is the subject of substantial debate (Kahn et al., 2005; Reaven, 2005). Because at least three of five components are needed to fulfil the criteria of the MetSyn, there are numerous combinations of components possible that all lead to the same MetSyn diagnosis. Studies (Tolker & Shirom, 2008) have shown that sometimes only specific components of the MetSyn are associated with depression, which cast doubt over the usability of the total MetSyn concept in psychopathology research. It is possible that, in the large variety of depression/anxiety symptoms, some are "specifically" associated with a distinct MetSyn component (e.g., energy loss, often leading to decreased physical activity, might lead to elevated waist circumference [WC]). Based on the criticized definition of the MetSyn and the possible specific associations between diagnostic and MetSyn symptoms, it would thus be informative to investigate the association between specific depression/anxiety symptoms, on the one hand, and the MetSyn, both defined as a cluster of symptoms and as individual components, on the other hand.

So far, research on the association between depression and anxiety and the MetSyn has mainly focused on categorical and heterogeneous assessments of affective disorders symptomatology or anxiety and depression severity scales (Barefoot & Schroll, 1996; Frasure-Smith & Lesperance, 2005). In addition, diagnoses show overlapping criteria and comorbidity rates are high (Kessler et al., 2005; Brown et al., 2001). To overcome these problems, diagnoses should be more homogeneous and not dichotomous. A feasible alternative for categorical diagnoses is the use of a dimensional approach. Within a dimensional approach, a patient is described in terms of coexisting different symptom domains or dimensions, and not in terms of presence or absence of psychopathology. Each dimension provides specific information on the level of a specific symptom domain, running from absent or healthy to severe. Importantly, dimensions are continuous by principle. Along a continuous scale, changes from one level to another are subtle, whereas in a dichotomous scale, changes are rough and restricted (e.g., depressed versus non-depressed). This makes continuous variables more sensible for detection of (small) differentiating factors (Veen et al., 2011), thus increasing statistical power (MacCallum et al., 2002).

A well-known dimensional model is the tripartite model for depression and anxiety (Clark & Watson, 1991), which distinguishes three symptom dimensions. The broad "negative affect" (NA) dimension describes general symptoms of psychological distress (e.g., lack of concentration or pessimism) that are seen both in depression and anxiety and could account for their high comorbidity. The (lack of) "positive affect" (PA) dimension (also called anhedonic depression), covers anhedonic symptoms, which are mainly specific to depression. The "somatic arousal" (SA) dimension covers symptoms of hyperarousal (e.g., palpitations, shortness of breath, and dizziness), which are specific for anxiety, especially panic disorder. The dimensional model was not developed for

detection of DSM-IV diagnoses, but rather to provide a descriptive alternative for the presence or absence of psychopathological symptoms in a subject. The tripartite model was developed to circumvent the lack of diagnostic specificity due to the high levels of comorbidity observed in depression and anxiety, one of the major problems of the DSM-IV "golden standard." Typifying patients in terms of their NA, PA, and SA scores has two advantages: first, comorbidity is circumvented; and second, based on the profile of the scores, patients can be described in more specific terms of symptomatology. Several studies (de Beurs et al., 2007, Watson et al., 1995a) have shown these specific dimensions to be specifically increased in depression (PA) and anxiety (mainly panic disorder, SA) and that NA was more indicative for overall severity across patients.

The aim of the present study was to investigate the relationship between the symptom dimensions of depression and anxiety of the tripartite model, and the MetSyn and its individual components within the Netherlands Study of Depression and Anxiety (NESDA), as a dimensional approach makes it possible to look more specifically into these associations.

5.2 Methods and Materials

Subjects

Subjects selected for these analyses were baseline participants of NESDA, a cohort study among 2,981 individuals aged 18 years through 65 years. Respondents were recruited in the community, in primary care, and in specialized mental healthcare settings from September 2004 through February 2007, throughout The Netherlands. All subjects completed a medical examination, a face-to-face interview, and self-report questionnaires. A detailed description of NESDA is reported elsewhere (Penninx et al., 2008). The study protocol was approved by the Ethical Review Board of each participating centre and all subjects signed an informed consent.

In the same study sample, tricyclic antidepressant (TCA) users were found to have a significantly increased prevalence of the MetSyn (Reedt Dortland et al., 2010). This association was not found for users of other types of antidepressants, such as selective serotonin reuptake inhibitors (Reedt Dortland et al., 2010). Therefore, the relatively small group of TCA users (n = 80) was excluded from our analyses, so that the results would not be affected by the potential confounding influence of TCAs. Subjects with missing MetSyn or Mood and Anxiety Symptom Questionnaire (MASQ) values (n = 468) were excluded as well, resulting in a sample of 2,433 (81.6%) subjects. An important number of the included subjects comprised healthy controls or remitted patients (n=1449), whereas other subjects had a current diagnosis of pure depression (n=222), pure anxiety (n=226), or comorbid disorder (n=536). No inpatients were included. The included subjects did not differ from the excluded group in sex distribution, presence of cardiovascular disease (CVD), and physical activity. Included subjects were older (42.3 years versus 40.0 years, p<.001), were more educated (12.3 versus 11.3 years, p <.001), were less often smokers

(35.8% current smokers versus 50.9%, p<.001), and consumed more alcohol (16.4% consumed >2 glasses/day versus 15.3%, p<.001) compared with the excluded subjects.

Measurements

MASQ dimensions

The three dimensions of the tripartite model were measured with the 30-item adaptation (MASQ-D30) of the MASQ (Watson et al., 1995a; 1995b). The MASQ-D30 was previously validated and showed reliability and validity within the NESDA study (de Beurs et al., 2007; Chorpita & Daleiden, 2002; Wardenaar et al., 2010). The MASQ-D30 consists of three ten-item scales, representing NA, PA, and SA (Table 1). On each item, participants were asked to rate how much in the past week they have experienced "feelings, sensations, problems and experiences that people sometimes have" on a 5 point scale, 1 being "not at all" and 5 being "extremely." Higher scores indicate more severe symptom levels for that specific dimension.

MetSyn

The MetSyn and its components, when expressed as dichotomous variables (i.e., elevated WC, triglycerides, blood pressure, and fasting glucose, and reduced HDL cholesterol), were exactly defined according to the revised criteria of the National Cholesterol Education Program-Adult Treatment Panel III (Grundy et al., 2005). WC was measured with a measuring tape at the central point between the lowest rib and the highest point of the iliac crest, on light clothing. Triglycerides, HDL cholesterol, and glucose levels were determined by standardized routine laboratory assays, and diastolic and systolic blood pressures were measured during supine rest (OMRON M4 IntelliSense Digital Blood Pressure Monitor, HEM-752A, Omron Healthcare, Inc., Bannockburn, Illinois). Use of triglyceride or HDL cholesterol-influencing medication and use of antihypertensive or glucose reducing drug were registered. In addition, we used continuous variables for the MetSyn components (which is preferable when aiming for more statistical power) (MacCallum et al., 2002). In these analyses, we "adjusted" the values for those subjects, using a MetSyn component influencing medication. This was done following the methods described in several previous publications (Bays et al., 2003; Grundy et al., 2005). For the use of fibrates, 0.10 mmol/L (3.8 mg/dL) was subtracted from HDL cholesterol, and 0.67 mmol/L (60 mg/dL) was added to the triglycerides. For the use of nicotinic acid, 0.15 mmol/L (5.8 mg/dL) was subtracted from HDL cholesterol, and 0.19 mmol/L (17 mg/dL) was added to the triglycerides. For the use of antidiabetic medication and a glucose level of < 7 mmol/L (126 mg/dL), a value of 7 mmol/L (126 mg/dL) was given to glucose, as was done previously (33). Mean blood pressure (MBP) was expressed as the arithmetic mean of systolic and diastolic blood pressures, which were both measured twice during supine rest on the right arm (OMRON M4 IntelliSense Digital Blood Pressure Monitor, HEM-752A, Omron Healthcare, Inc.) and averaged over the two measurements. For persons using

antihypertensive medication, 10 mm Hg was added to systolic blood pressure, and 5 mm Hg was added to diastolic blood pressure, in line with earlier studies (Vogelzangs et al., 2007). These values represent the average decline in blood pressure in antihypertensive medication trials (SHEP, 1991; Tannen et al., 2006).

Table 5.1: This table lists all the symptoms incorporated in the three symptom dimensions of the MASQ-D30.

Negative Affect	Positive Affect	Somatic Arousal
Felt confused	Felt successful	Startled easily
Felt worthless	Felt really happy	Felt nauseous
Felt irritable	Felt optimistic	Felt dizzy or light-headed
Felt hopeless	Felt like I was having a lot of fun	Was trembling or shaking
Blamed myself for a lot of things	Felt like I accomplished a lot	Had pain in my chest
Felt dissatisfied with everything	Felt like I had a lot to look forward to	Had hot or cold spells
Felt pessimistic about the future	Felt really talkative	Was short of breath
Felt inferior to others	Felt really 'up' or lively	Muscles were tense or sore
Had trouble making decisions	Felt like I had a lot of energy	Heart was racing or pounding
Worried a lot about things	Felt really good about myself	Had trouble swallowing

Severity scales

Information on depression and anxiety severity was collected during the baseline measurement of the NESDA study (Penninx et al., 2008), using the Beck Anxiety Inventory (BAI) (Beck et al., 1988) and the Inventory of Depressive Symptoms self-report (IDS-SR;

www.ids-qids.org), in which the most severe groups were defined as “severe anxiety symptoms” with a score of ≥ 29 on the BAI and “very severe depressive symptoms” with a score of ≥ 49 on the IDS-SD. Previous NESDA research (Reedt Dortland et al., 2010) indicated that the prevalence rates of the MetSyn were increased in those with severe anxiety symptoms (*n*=185) in crude models and independently increased in those with very severe depressive symptoms (*n*=102) after fully adjusted models. Because information on the BAI and IDS-SR scores was available for our sample, we decided to investigate whether the previous found associations in the same cohort between the highest scores of the BAI and IDS severity scales and metabolic derangements would be driven by symptom dimensions.

Covariates

Covariates were grouped into two types of variables: sociodemographic and life-style variables. Sociodemographic variables included age, sex, and years of education. Life-style characteristics included smoking status (never/ former/current), alcohol use (<1/1–2/>2 drinks per day), both assessed by standardized questionnaires, and physical activity, which was assessed by the International Physical Activity Questionnaire (Booth, 2000) and expressed in 1000 Metabolic Equivalent-minutes in the past week. Metabolic Equivalent-minutes reflects the ratio of the associated metabolic rate for specific activities divided by the resting metabolic rate multiplied by the minutes performed activity. CVD was considered to be present when participants self-reported a diagnosis of coronary heart disease, cardiac arrhythmia, angina, heart failure, or myocardial infarction, confirmed with the use of cardiovascular medication. Medication use of any kind within the past month was registered by observation of drug containers brought in and coded according to the Anatomical Therapeutic Chemical Classification System (World Health organization, 2009).

Statistical Analyses

Sample characteristics were summarized, using means and standard deviations (SD) for quantitative variables and by percentages for categorical variables. Multivariate linear regression analyses were conducted to assess the association between each MASQ-D30 dimensions (i.e., PA, NA, and SA) and the individual continuous MetSyn components and the total number of MetSyn components. Analyses for each dimension were performed separately. To normalize residuals, non-normally distributed dependent variables were naturally log-transformed. After running crude models, we adjusted for basic covariates (i.e., age, sex, and years of education) in model 1, and for additional life-style-related covariates (i.e., smoking status, alcohol use, and physical activity) in model 2. Because sex differences in the association between anxiety, depression, and the MetSyn have previously been observed (Token et al., 2008; Kinder et al., 2004), appropriate interaction terms with sex were explored. To evaluate the influence of prevalent CVD, participants diagnosed with CVD were excluded in a sensitivity analysis.

To evaluate whether the earlier described association between severity of depressive and anxious symptoms and MetSyn abnormalities were driven by symptom dimensions, additional regression analyses were performed. We analyzed the association of BAI and IDS-SR severity categories with the individual MetSyn components and the total number of components by performing linear regression analyses, adjusting for models 1 and 2 covariates, and additionally adjusting for those symptom dimensions that demonstrated to be associated significantly with the MetSyn components in the main analyses.

Multivariate logistic regression analyses were performed to assess the association between the SDs of continuous scores of the three symptom dimensions and the MetSyn diagnosis. All assumptions for linearity were tested and fulfilled. All tests were two-tailed with $p < .05$ denoting statistical significance. Statistical analyses were done with SPSS 16.0 (SPSS Inc., Chicago, Illinois).

5.3 Results

General Characteristics

Sample characteristics are shown in Table 5.2. The mean age was 42.3 years (SD=13.1), 33.1% were men, and mean number of years of education was 12.3 years (SD=3.3). The criteria for the MetSyn were fulfilled by 20.1% (*n*=490). The reported means and SDs for each dimension are calculated from the continuous values of all subjects included (*n*=2433) for that dimension.

Symptom dimensions and MetSyn components

Outcomes of the linear regression analyses between MASQ-D30 dimensions and MetSyn components are shown in Table 5.3. PA showed a significant association with every MetSyn component in the crude model. Adjustments in model 1 led to a decrease of the β with >10% and to nonsignificant associations with WC, fasting glucose levels, and MBP. Analyses with the separate covariates of model 1 showed age to be the most important confounder. Associations of PA with triglycerides and HDL cholesterol became statistically nonsignificant after adjustment for life-style factors (model 2). No significant associations were found for NA with any of the MetSyn components, in the unadjusted and fully adjusted models.

On the contrary, in the crude unadjusted model, SA showed a significant association with all MetSyn components except for fasting glucose. The associations for SA remained significant in both adjusted models with regard to WC (WC_{crude}: β=0.061, p=.003; $WC_{model\ 2}$: β=0.046, p=.01), triglycerides ($Trig_{crude}$: β=0.077, p<.001; $Trig_{model\ 2}$: β=0.046, p=.02) and MBP (MBP_{crude}: β=0.069, p<.001; $MBP_{model\ 2}$: β=0.068, p <.001).

Table 5.2. Sample characteristics (n=2433)

General characteristics	
Age	42.3 (13.1)
Sex (% men)	33.1
Years of education	12.3 (3.3)
Cardiovascular disease	5.8
Smoking	
Never	29.3
Former	34.9
Current	35.8
Alcohol consumption	
< 1 glasses/day	61.0
1-2 glasses/day	22.4
> 2 glasses/day	16.4
Physical activity (1000 MET minutes)	3.7 (3.06)
Metabolic syndrome components	
Waist circumference total (cm)	88.7 (13.8)
HDL- cholesterol (mmol/l)	1.6 (0.4)
Triglycerides (mmol/l)	1.3 (0.8)
Glucose (mmol/l)	5.2 (0.9)
Systolic blood pressure (mmHg)	136.2 (19.7)
Diastolic blood pressure (mmHg)	81.5 (11.1)
Mean blood pressure (mmHg)	108.9 (14.7)
Number MetSyn components	1.45 (1.3)
Metabolic syndrome (%)	20.1
Symptom dimensions (mean scores)	
MASQ Positive affect	33.4 (9.7)
MASQ Negative affect	20.0 (8.6)
MASQ Somatic arousal	15.7 (6.1)

Means and standard deviations (SD) are given for age, years of education, physical activity, number of metabolic syndrome components and the three symptom dimensions. Percentages are given for sex, smoking status, alcohol consumption, and presence of metabolic syndrome.
HDL: High Density Lipoprotein; MET: Metabolic Equivalent.

Table 5.3: Linear regression for association between MASQ dimensions and metabolic syndrome components in 2433 subjects.

	Waist Circumference		Triglycerides		HDL Cholesterol		Glucose		Blood Pressure		Number of MetSyn Components	
	B	p-value	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
Negative Affect												
Crude	.070	.001	.097	< .001	- .063	.002	.079	< .001	.076	< .001	.107	< .001
Model 1	- .001	.94	.044	.02	- .039	.04	.027	.15	.008	.64	.036	.05
Model 2	- .009	.60	.021	.29	- .012	.52	.026	.17	.009	.63	.019	.29
Postive Affect												
Crude	- .002	.93	.031	.12	- .036	.08	.008	.68	- .028	.17	.018	.37
Model 1	.016	.34	.042	.03	- .017	.36	.036	.05	- .001	.94	.033	.07
Model 2	.011	.51	.022	.25	.001	.08	.037	.05	- .002	.90	.020	.27
Somatic Arousal												
Crude	.061	.003	.077	< .001	- .056	.01	.025	.22	.069	< .001	.098	< .001
Model 1	.050	.01	.064	.001	- .045	.02	.023	.21	.062	< .001	.074	< .001
Model 2	.046	.01	.046	.02	- .018	.32	.023	.22	.068	< .001	.062	.001

β, standardised β by linear regression analyses.

Abbreviations: HDL, high density lipoprotein.

Model 1: adjusted for age, sex and years of education (sociodemographic factors)

Model 2: additionally adjusted for smoking status, alcohol use and physical activity (life style factors).

The significant crude association of SA with HDL cholesterol weakened after adjustment in model 1, and further in model 2 to a nonsignificant level. Also, the association of SA with the number of metabolic syndrome components (Nr.) remained highly statistically significant throughout all models ($Nr._{crude}$: β=0.098, *p*<.001; $Nr._{model\ 2}$: β=0.062, *p*<.001). The graded, positive association between SA and the number of MetSyn components, and SA and quartiles of the individual fully adjusted MetSyn components are shown in Figure 5.1. In sensitivity analyses in which 141 subjects with CVD were excluded excluded, results did not change (data not shown). None of the interaction terms between dimensions with sex were statistically significant, which suggests that associations were largely similar for men and women.

To evaluate whether another measure for somatic symptoms would give comparable results, we repeated the linear regression model analyses with the validated BAI somatic subscale (36). These analyses confirmed an association for the somatic BAI subscale and a much less consistent association for the nonsomatic BAI subscale. The associations with the BAI somatic scale score remained significant in the fully adjusted models for the number of MetSyn components (Nr. MetSyn: β =0.072, *p*<.001), and all MetSyn components, except for HDL cholesterol, which showed a trend toward significance with a β=-0.033, *p*=.08 (WC: β=0.056, *p*<.001; Trig: β=0.083, *p*<.001; Gluc: β=0.038, p=.04; MBP: β=0.046, *p*=.01). There was a strong Intercorrelation between the somatic symptom dimension of the MASQ (SA) and the subscale of the BAI (r_{sBAI}=0.73, *p*<.001). We did not analyze associations with subscales of the IDS-SR because earlier work by Wardenaar et al. (2010) did identify three subscales but none of these was a clear somatic subscale (in factor analyses, the rather restricted somatic items were attributed to all three subscales). So, no valid somatic IDS subscale exists. Therefore, it is not appropriate to use a subscale in a comparative analysis. To explore whether results would also be consistent for the nonsomatic symptom subscale, we also conducted linear regression analyses with the nonsomatic BAI subscale (BAI subjective scale score). We expected that associations for the subjective BAI subscale would be similar to those for the PA and NA dimensions of the MASQ-30, which was confirmed. None of the associations with the BAI subjective scale score were statistically significant in the fully adjusted models, with exception of the number of MetSyn components (β=0.041, *p* =.02).
Regression analyses performed to investigate whether previously found positive associations between MetSyn abnormalities and symptom severity were driven by symptom dimensions, in particular, the SA dimension, showed the following: Initial significant outcomes (in which the number of MetSyn components was the dependent variable and BAI and IDS-SR severity categories were the independent variables) lost statistical significance after adjustment with the SA dimension. This means that the earlier described associations between the high severe groups according to the BAI and IDS-SR with the MetSyn were largely attributable to a high SA score.

Table 5.4: Logistic regression for the association between standard deviations (SDs) of continuous scores on MASQ dimensions and the odds of metabolic syndrome in 2433 subjects

	OR of MetSyn per SD increase of MASQ-D30 dimension	95% CI	*P*-value
Positive Affect			
Crude	1.16	1.05-1.28	.004
Model 1	1.02	0.92-1.14	.67
Model 2	0.99	0.88-1.10	.99
Negative Affect			
Crude	1.01	0.92-1.12	.78
Model 1	1.01	0.99-1.02	.28
Model 2	1.04	0.93-1.16	.51
Somatic Arousal			
Crude	1.19	1.08-1.31	< .001
Model 1	1.18	1.06-1.30	.002
Model 2	1.15	1.04-1.28	.008

Abbreviations: OR, odds ratio per SD increase, by logistic regression analysis; CI, confidence interval
Model 1: adjusted for age, sex, years of education.
Model 2: additionally adjusted for lifestyle factors: smoking status, alcohol use and physical activity.

Symptom dimensions and cluster of the MetSyn

Logistic regression analyses of the symptom dimension with the MetSyn showed a small but significant crude relationship between PA and the MetSyn. NA was not significantly associated with the MetSyn. The initial significant crude relationship between SA and the MetSyn remained statistically significant throughout multivariable adjustment (odds ratio per SD increase, 1.15; 95% confidence interval, 1.04–1.28; *p*=.008) (Table 5.4). Analyses, in which the associations of BAI or IDS severity categories with the MetSyn were adjusted for SA, showed that the severity category indicator lost statistical significance after adjustment.

5.4 Discussion

The main finding of this study is that only SA symptom dimension is strongly and independently associated with most of the MetSyn components (especially WC,

triglycerides, and MBP) and shows a graded association with the number of MetSyn components. Using a dimensional approach, SA was thus associated with an increased metabolic risk. No independent associations between MetSyn with NA and PA were observed. These results are supported by our finding that the somatic scale of the BAI is associated with the MetSyn components, whereas the non-somatic scales are not. Approaching depression and anxiety dimensionally, the aspecific NA dimension and the depression specific PA dimension did not show any association with the MetSyn. We only found a strong and consistent relationship between the somatic arousal dimension and multiple MetSyn components. This is in line with previous research on symptom dimensions of especially depression in relation to somatic outcomes, in which the somatic/affective sub-dimension, rather than other important dimensions (e.g., cognitive/affective and appetitive), was most strongly associated with cardiovascular risk and outcome (De Jonge et al., 2006; Bosch et al., 2009). It seems we are looking at a specific sub-dimension: the “somatic depression/anxiety” sub-dimension. On the one hand, this subtype could be reflective of underlying dysregulated homeostasis mechanisms due to anxious or depressed mood states, such as inflammation (Howren et al., 2009), impaired hypothalamus-pituitary-adrenal axis function (Brown et al., 2004; Vreeburg et al., 2009a), or a higher sympathetic and lower parasympathetic autonomic tone (Licht et al., 2010).

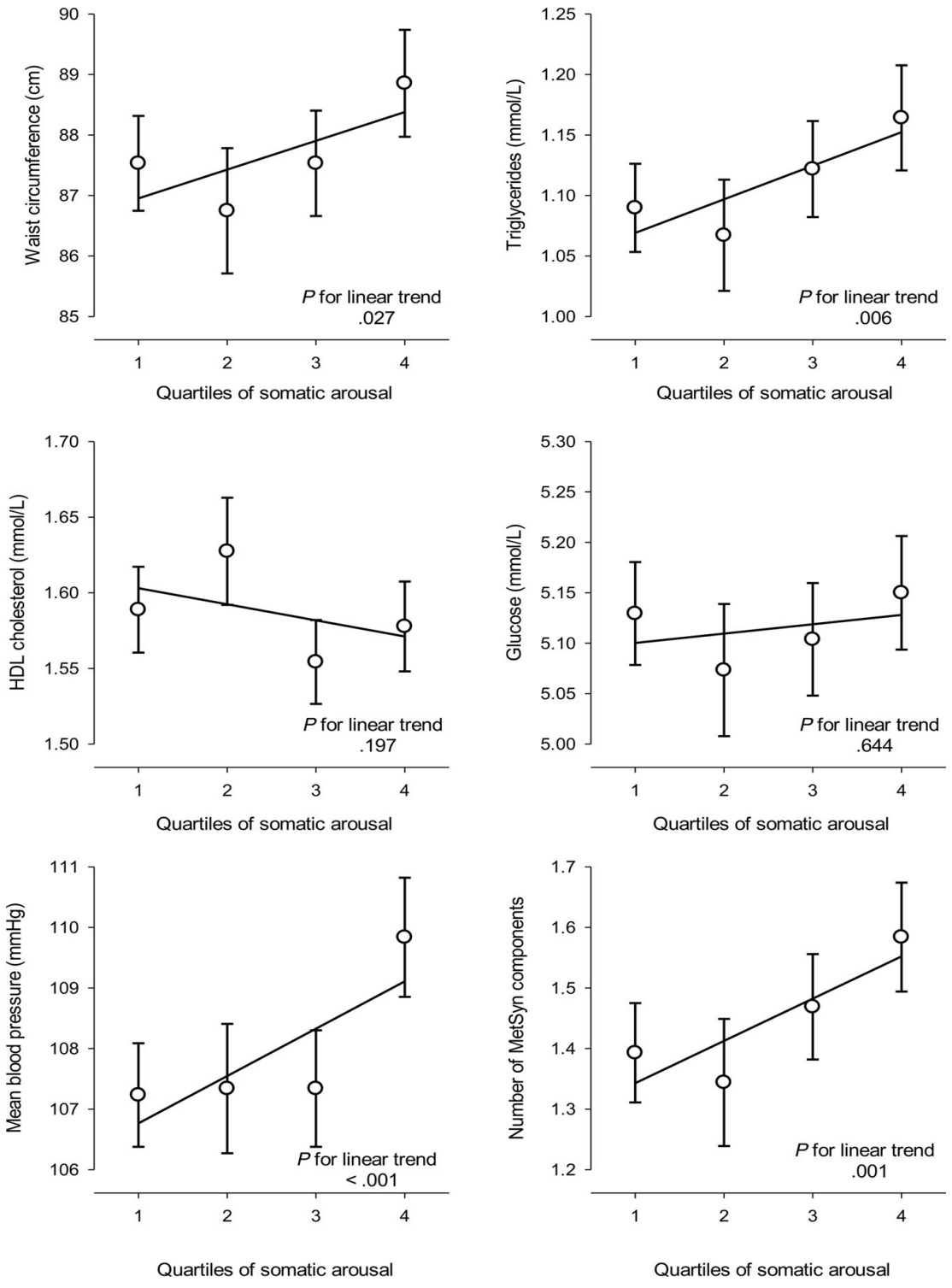

Figure 5.1: Adjusted (geometric) means across quartiles of somatic arousal on the MASQ-D30, for the individual MetSyn components and the total number of MetSyn components. Data are adjusted for age, sex, educational level, alcohol consumption, smoking status and physical activity. Error bars indicate 95% confidence intervals of the mean, and regression lines are shown. $N_{quartile\ 1}$ =744; $N_{quartile\ 2}$ =436; $N_{quartile\ 3}$ =652; $N_{quartile\ 4}$ =601.

Elevated levels of inflammatory markers could induce a depressive episode (48); altered lipid patterns caused by high levels of cortisol (Bjorntorp, 2001; Chrousos, 2000) could lead to other lipid-related symptoms (overweight, abdominal obesity, and hypertriglyceridemia) (Veen et al 2011; Vogelzangs et al., 2009); and activation of sympathetic nervous system leads to increased blood pressure (Shibao et al., 2007) and, thus, to hypertension (Bjorntorp, 2001; Lambert et al., 2010). This network of pathways can, thus, result in an increased metabolic or cardiovascular risk and cardiovascular disease. On the other hand, the reverse mechanism could be active. Ongoing metabolic dysregulations could be causing (especially SA) symptoms of depression and anxiety (Mast et al., 2008l Alexopoulos et al., 1997; Steffens et al., 2002; Ajilore et al., 2007; Huber, 2008). Regardless of the underlying mechanisms and the direction of causality, the dose-response gradient between the number of MetSyn components and levels of SA indicates that, when more SA symptoms are present, more MetSyn abnormalities are present. Apart from biological mechanisms, other processes may be involved during a depressive episode as a consequence of anhedonia, such as altered life-style patterns (poor diet and decreased physical activity) (LaMonte et al., 2005; Hu & Willett, 2002), which might induce metabolic changes and cardiovascular risk factors.

Previous research based on NESDA data (8) showed that the prevalence rates of the MetSyn were increased in those with the highest levels of depressive symptoms based on the BAI and the IDS-SR. After adjustment for the MASQ SA dimension, the earlier described associations lost statistical significance. These results indicate that the earlier described association between MetSyn and the most severe depression and anxiety symptom scales can be explained by the fact that these persons had high scores on the SA dimension.

In terms of metabolic risk evaluation and detection, a dimensional approach has more differentiating capacities compared with the widely used diagnostic DSM-IV categories. The somatic symptom dimension could, therefore, be the key feature in the association between depression/anxiety and somatic outcomes.

Using a dimensional approach, the level of a symptom dimension varies differentially between diagnostic groups (e.g., singular depression, singular anxiety, or comorbid state). At the same time, all symptom dimensions can be present at a significant level within every diagnostic group. This means that the clinical presentation of a subject is dependent on the symptom dimension(s) with the highest scores. Our results demonstrate that the SA dimension is associated with several MetSyn components. The fact that SA levels are not equally high for every depressed and/or anxious subject might explain the inconsistent findings in literature on the association with the MetSyn.

Our study has several strengths. This is, to our knowledge, the first study describing the relationship between depression and anxiety dimensions in relation to the MetSyn. We not only approached the MetSyn and its components as continua, in line with the idea that MetSyn components have a natural continuous distribution (Ingram, 2009), but also depression and anxiety symptom dimensions (Ingram, 2009). Because we

chose this approach, we were able to show a dose-response gradient with SA levels. Furthermore, the results are based on a large sample, making results reliable. Finally, in the analyses, we adjusted for a substantial number of covariates, minimizing the chance that the findings can be explained by confounding.

This study presents some limitations. First, the tripartite model is a rather simple dimensional model. Probably, there are more relevant subdimensions present (Hollander-Gijsman et al., 2010). Second, the sample includes both healthy controls and subjects with (remitted) psychopathology, who were recruited from the community as well as mental healthcare settings. As inpatients were excluded, our results cannot be generalized to this group. Third, the concept of the MetSyn has been criticized (Kahn et al., 2005; Reaven, 2005), and our findings support the idea that it may be worthwhile to study (the number of) individual metabolic components in addition to a dichotomous MetSyn variable. Finally, due to the cross-sectional design, our results cannot be used to make any causal inferences. Prospective studies, especially across more heterogeneous populations, would help to understand the direction of the potential causal relationship.

In this sample, in which previously the association between a categorical diagnosis, on the one hand, and the MetSyn components, on the other hand, was found only for the most severe depressive symptoms (Reedt Dortland et al., 2010), we demonstrate a strong association between the SA symptom dimension and the metabolic syndrome and its individual components, especially WC, triglycerides, and blood pressure, and the number of MetSyn components. Not every depressed subject is at increased metabolic risk. But our findings suggest that those with an elevated SA level are. Those with elevated non-somatic dimensions scores (i.e., PA and NA) did not show an increased metabolic risk. This indicates the additional value of a dimensional approach in terms of metabolic risk evaluation. In addition, we found that the association between depression severity (BAI severity categories) and the MetSyn is, in part, driven by the SA dimension. Although our results need to be replicated, the discriminating ability of a dimensional approach could facilitate the identification of those with a higher metabolic risk within a clinical population with apparently the same diagnoses.

Chapter 6:

Change in Symptom Dimensions of Depression and Anxiety in Response to Life Events

Abstract

Background: Results on the association between life-events and depression and anxiety have been inconsistent. This could be due to heterogeneity of DSM diagnoses, which does not allow the detection of symptom-specific effects of life events. Therefore, the current longitudinal study was aimed to close in on more specific associations between different types of life-events and change in different symptom dimensions over time.

Methods: Data from 2267 participants with or without psychiatric diagnoses were included. Dimensions of the tripartite model (general distress, anhedonic depression and anxious arousal) were assessed at three times (baseline, 1-year, 2-year), to model change over time. The positive and negative life-events that occurred between the measurement points were assessed retrospectively at 1-year and 2-year follow-up. The data were analysed with linear mixed models to adjust for repeated measures and several covariates.

Results: Negative life-events (e.g. financial problems, getting ill or wounded) were associated with increased general distress and anxious arousal. Positive life events (e.g. making new friends, going on holiday) were associated with decreased anhedonic depression. These associations were independent for both types of life-events and persisted when adjusted for demographic covariates and DSM-based course-trajectories.

Conclusions: Different types of life-events lead to specific symptomatology. Negative life events affect both general distress and anxiety symptomatology, whereas positive life events specifically affected depression-specific symptomatology. These findings illustrated the added value of using specific symptom dimensions in etiological research.

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6.1 Introduction

Many authors have suggested a relationship between life events and the onset (e.g. Kendler et al., 1995; 2000; Kessler, 1997) and course of depression (e.g. Mundt et al., 2000; Friis et al., 2002) and anxiety (e.g. Lteif & Mavissakalian, 1985; Roy-Byrne, 1986; Blazer et al., 1987). Unfortunately, findings on the association between life events and psychopathology have been inconsistent with studies that reported varying (reviewed by Mundt et al., 2000) or no associations between life events and depression and/or anxiety (e.g. Spinhoven et al., 2010). These inconsistent results could be explained by the use of different samples, definitions, instruments, and analyses across studies (reviewed by Mundt et al., 2000; Kessler, 1997). However, the heterogeneity and arbitrary boundaries of the used DSM-diagnoses are also likely contributors to the inconsistent results found so far (Widiger & Samuel, 2005). From this perspective, it could pay off to use better-specified and more homogeneous outcome measures in life event research.

Several studies have shown that different types of life-events are associated with specific types of symptoms. Keller and Nesse (2005; 2006) showed that in healthy participants, social loss (e.g. death of a loved one, romantic breakup) led to increased crying, desire for social support, and decreased appetite, and that chronic stress and failure led to increased feelings of guilt, hopelessness, and fatigue. In a later longitudinal study in participants with previous depressive symptoms, Keller et al (2007) showed that social loss was followed by symptom patterns with increased sadness, anhedonia and decreased appetite, and that chronic stress and failure were followed by symptom patterns with increased fatigue and hypersomnia. Although they did not include all types of life events (e.g. positive events) and symptoms (e.g. anxiety symptoms), the results of these studies strongly suggest that life events affect specific symptoms rather than complete syndromes.

A good way to define and measure symptoms more specifically, is through the assessment of symptom dimensions with reliable psychometric instruments. Dimensions cover distinct symptom domains and follow a severity-continuum from healthy to severely pathological (Goldberg, 2000). In addition to being homogeneous, dimensions conveniently circumvent the DSM-related problems of comorbidity and arbitrary dichotomous boundaries between ill and non-ill (Widiger & Clark, 2000; Widiger & Samuel, 2005). Moreover, dimensions provide more statistical power in etiological research because they are continuous, which makes them more sensitive to variation between and within patients (MacCallum et al., 2005).

The *tripartite model* is a well-known dimensional approach, which assumes the existence of three basic symptom dimensions of depressive and anxiety symptomatology (Clark & Watson, 1991). The dimension of *general distress* covers symptoms of psychological distress (e.g. feeling guilty, worry), which are common in both depression and anxiety. The more specific dimension of *anhedonic depression* covers symptoms that involve decreased positive affect and energy, which are specific features of a depressed state. The dimension of *anxious arousal* covers symptoms of somatic hyperarousal, which

are specific for anxiety, and panic disorder in particular. The tripartite model has been thoroughly validated through the years; studies have shown its structure to be valid (e.g. Watson et al., 1995; Keogh & Reidy, 2000) and its dimensions to be associated with different biological mechanisms, such as the stress system (Wardenaar et al., 2011) and metabolic factors (Luppino et al., 2010). In line with this, studies in healthy subjects have shown the tripartite dimensions to be associated with different life events: negative life-events were associated with increased general distress and positive life events with increased positive affect/decreased anhedonic depression (e.g. Reich *&* Zautra, 1981; Zautra & Reich, 1988; Suh et al., 1996). However, these studies were limited to healthy subjects and did not include anxious arousal. Therefore, it is still unclear to what extent the tripartite dimensions can help to clarify the link between life events and symptomatology when looking at a broader spectrum of symptoms. Also, previous studies have been cross-sectional, comparing dimensional scores between those that did and those that did not experience a certain event. However, to optimally benefit from the dimensions' sensitivity to change, a prospective design should be used to evaluate the effects of life-events on the development of symptoms *within* individuals. Previous work has shown that such change is clearly detected in response to daily hassles on a day-to-day 'micro' timescale (e.g. Peeters et al., 2003; Gable et al., 2000; Suls et al., 1998). So far, this approach has not been used to investigate the associations between major life-events and symptom-dimensions on a 'macro' time-scale of months or years.

A final issue is that studies should ideally address whether the employed dimensions actually help to uncover associations that would go undetected when only using categorical measures of psychopathology. Research could do this by checking whether dimensional results hold when adjusted for DSM-based clinical features. Likewise, analyses of longitudinal course of dimensional scores could be adjusted for DSM-based course trajectories to see if and how much variation in symptomatology is uniquely captured by the dimensions.

We aimed to investigate the associations between, on the one hand, negative and positive life-events, and on the other hand, change on the tripartite dimensions in a large group of subjects from the Netherlands Study of Depression and Anxiety (NESDA; n=2981). We used a 2-year longitudinal design with three measurements (baseline, 1 year, 2 years) and we analysed the data with multilevel regression analyses to account for repeated measures. These analyses were adjusted for demographic covariates, but also for DSM-based course trajectories to evaluate whether the dimensions captured unique temporal variation in symptomatology.

6.2 Methods

Participants

Participants came from the NESDA study, a large longitudinal study to investigate the course of depressive and anxiety disorders (N=2981), who were recruited from

community, primary care and specialized mental health care organizations. At baseline, the mean age was 41.9 years (range 18-65), there were 1002 men and 1979 women, and 2329 participants had a lifetime diagnosis of major depressive disorder (MDD) and/or an anxiety disorder. Six hundred fifty two participants had no lifetime psychiatric diagnosis. Exclusion criteria were not being fluent in Dutch and a primary diagnosis of psychotic, obsessive-compulsive, bipolar or severe addiction disorder because these latter low prevalent disorders would largely affect the course trajectories in NESDA. Detailed objectives and rationales of NESDA can be found elsewhere (Penninx et al., 2008). The Ethical Review Boards of all participating universities approved the research protocol. All participants signed informed consent.

All participants were seen for a baseline assessment (T0), which consisted of a face-to-face structured psychiatric interview by a trained research-assistant, administration of self-report questionnaires, biological measurements and a blood-draw. After 1 year (T1), all participants were sent a booklet of self-report questionnaires to complete at home and return by post. Two years after baseline (T2), participants were assessed again in a face-to face session, similar to the one at baseline. The used dimensional scores were collected at T0, T1 and T2 and all participants were included, who provided all dimensional scores on these time-points and information about life-event occurrence (independent variable) for at least one of the two covered years. In total, 2267 participants (76.0%) provided sufficient data to be included in the study. The included participants were older ($t=-5.8$; $p<0.001$), had more years of education ($t=-7.5$; $p<0.001$), and were less probable to be male ($\chi^2=5.58$; $p=0.02$) than excluded subjects.

Study design

The study design is illustrated in Figure 6.1. To investigate if change on symptom-dimensions was associated with the occurrence of life-events, change in dimensional score between T0 and T1 was associated with life-events between T0 and T1 and change between T1 and T2 was associated with life-events between T1 and T2 and T0 and T1. By clustering repeated measurements within persons in LMM analyses, an effect-estimation (β) could be calculated, while accounting for interdependence between repeated measures. To evaluate whether the dimensions actually captured unique specific symptom variation in response to life events, very strict multivariable adjustment was used: all variation that was also explained by DSM-based course-trajectory variables (confounding) and their interactions with life events (effect-modification), was covaried out.

The main analyses were done with negative and positive life events clustered in two respective variables. Additional exploratory analyses were done to investigate the patterns of more specific effects of individual life events.

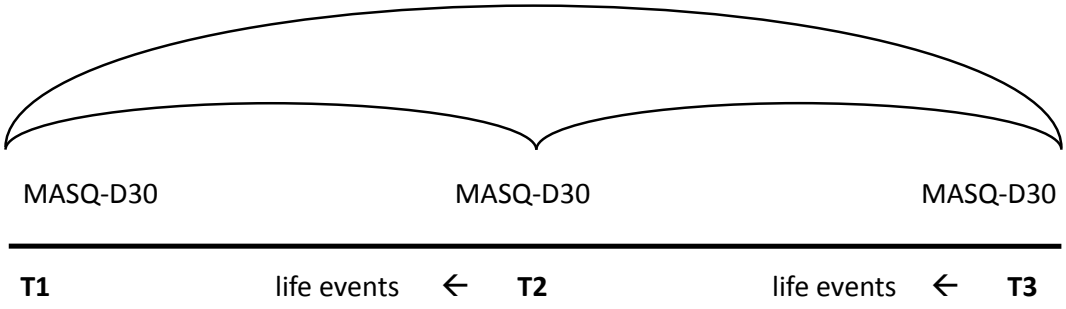

Figure 6.1: the used study design: change in the dimensions of the Dutch 30-item adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ-D30) was modelled over 2 years. Life events that occurred in the meantime were assessed retrospectively at T1 and T2.

Instruments

Dimensions: MASQ-D30

To measure the tripartite dimensions at T0, T1 and T2, the 30-item Dutch adaptation of the Mood and Anxiety Symptoms Questionnaire: the MASQ-D30 was used (Wardenaar et al., 2010; original MASQ by Watson et al., 1995a, 1995b). On the MASQ-D30, participants are asked to rate to what extent in the past week they have experienced "feelings, sensations, problems and experiences that people sometimes have" on a 5-point scale, with 1 being "not at all" and 5 being "extremely". The MASQ-D30 consists of three 10-item subscales: 'general distress', 'anhedonic depression' and 'anxious arousal'. The anhedonic depression scale items are reverse-keyed and are rescored before subscale computation. The MASQ-D30 scales have been shown to have adequate psychometric characteristics (Wardenaar et al., 2010).

Life-events

To assess the occurrence of negative life-events between respectively T0 and T1 and T1 and T2, the List of Threatening Events Questionnaire (LTE-Q; Brugha et al., 1985) was (retrospectively) administered at T1 and T2. The LTE-Q has been shown to have good test–retest reliability, high agreement between participant and informant ratings and good agreement with interview-based ratings (Brugha and Cragg, 1990). Examples of the assessed negative life events were: 'financial problems', 'the death of a close friend or family-member', and 'getting fired'. Positive life-events were also assessed at T1 and T2 with an additional list of seven positive life-events. Examples of the assessed positive life events were: 'making new friends', 'getting a new job or an important promotion', and 'finding a new partner'. For each listed event, participants were asked to indicate if it

happened in the period before the assessment and - if yes – when the event occurred or started (in case of long-lasting events). The complete lists of assessed individual life events are displayed in Figure 6.2. Positive and negative life-events were clustered to investigate the effects of the *occurrence* of any (yes/no) and the *number* of negative or positive life-events. As outlined above, the individual life events were also used in additional analyses.

Course-trajectory variables

The DSM-based course-trajectory variables were computed on the basis of two data-sources. At To and T2, the presence of DSM-IV diagnoses (MDD, Dysthymia, Panic disorder, Social Phobia, GAD, and Agoraphobia) was established with the Composite Interview Diagnostic Instrument (CIDI, WHO version 2.1). The organic exclusion rules were used and diagnoses were hierarchy-free. If at T2 participants met the criteria for any diagnosis since T0, the Life Chart Interview (LCI) was also administered to assess the course of this disorder. The presence (yes/no) of symptoms was evaluated for each month during follow-up by use of a calendar method (Lyketsos et al., 1994). Participants rated the symptom-severity for each symptomatic month on a 5-point scale (no/minimal, mild, moderate, severe, very severe). Symptomatology was only considered to be present if at least mildly severe. Remission was considered present after at least 3 consecutive months without symptoms.

The CIDI and LCI data were combined to define three course-trajectory groups: (a) the *stable healthy* group (no disorder between T0 and T2), (b) the *stable chronic* group (persistent disorder between T0 and T2), and (c) the *unstable course* group (onset of a new disorder/remission from a disorder/remission and recurrence of a disorder). Membership of each group (0=no, 1=yes) was used as a dummy variable in the analyses.

Statistical Analyses

Both the dependent variables (dimensions) and the independent variables (life events) were standardized to enable effect-size comparisons across different event types and dimensions. Several LMM analyses were conducted, each with a MASQ-D30 scale as dependent variable and one of the investigated life-event-variables as independent variable. 'Time' was used as a repeated measures factor in all analyses and an *unstructured* covariance structure was used to account for the dependence between repeated measures. The T0 value of the MASQ-D30 dimension under investigation was always added as a covariate to model all dimensional change across T0, T1 and T2. The main analyses were run with two different independent variables: between change on dimensions and (1) the *occurrence* of any negative or positive life-event, and between dimensions and (2) the *number* of negative and/or positive life-events. The analyses were adjusted for several covariates. Age and gender were added as covariates in Model 1 to adjust for potential confounding and to increase the general precision of model-estimations. In model 2, the course-group membership dummies and their interactions

with life events (e.g. positive life event occurrence*stable chronic) were added to covary out all dimensional variation that was explained by the course-trajectory groups. Additional exploratory LMM analyses, each with an individual life event as independent variable and one of the dimensions as dependent variable, were done to explore the patterns of effects of the individual life-events on symptomatology. All analyses were done with SPSS 17.0 and $p<0.05$ was taken to indicate statistical significance.

6.3 Results

Demographic and psychiatric characteristics

The sample characteristics are listed in Table 6.1. In the complete sample, there were 1531 (67.5%) women and the mean age at baseline was 42.6 years (SD=13.1). Of the group, 949 (41.9%) had a stable healthy course, 431 (19.0%) had a stable chronic course, and 887 (39.1%) had an unstable course between T0 and T2. Anhedonic depression and anxious arousal were only moderately correlated ($\rho=0.43$), in line with their distinct symptom coverage. General distress was moderate-strongly correlated with anhedonic depression ($\rho=0.60$) and anxious arousal ($\rho=0.61$), in line with its general role in the tripartite model.

The occurrence of life events

The results of the LMM analyses of the association between the occurrence of any (1,0) negative or positive life-event and the MASQ-D30 scores are shown in Table 6.2. In model 1, negative life-event occurrence was associated with increased general distress ($\beta=0.19$) and with increased anxious arousal ($\beta=0.12$). Negative life-events were not associated with change in anhedonic depression. The significant effects both increased after additional adjustment for course trajectories in model 2. Positive life-event occurrence was most strongly associated with decreases in anhedonic depression ($\beta=-0.22$), but also with anxious arousal ($\beta=-0.18$), and general distress ($\beta=-0.15$). When adjusted for course-trajectories in model 2, the effect on anhedonic depression was much less decreased ($\Delta\beta=0.01$ [4.5%]), compared to general distress ($\Delta\beta=0.04$ [26.7%]) and anxious arousal ($\Delta\beta=0.06$ [33.3%]).

These results indicated that general distress and anxious arousal showed the strongest and most consistent increase in reaction to the occurrence of a negative life event, and that anhedonic depression consistently decreased in reaction to the occurrence of a positive life event.

Table 6.1: Baseline descriptive characteristics of the used study samples

N	2267
Mean Age at baseline (SD)	42.6 (13.1)
Number of women (%)	1531 (67.5%)
Mean years of education (SD)	12.4 (3.2)
MASQ-D30 scores, mean (SD)	
General Distress	19.8 (8.4)
Anhedonic Depression	33.2 (9.6)
Anxious Arousal	15.5 (5.8)
DSM-IV diagnoses	
No disorder	1240 (54.7%)
Depressive disorders	225 (9.9%)
Anxiety disorders	418 (18.4%)
Depression and Anxiety	384 (16.9%)
Course-trajectory groups	
Stable Healthy	949 (41.9%)
Stable Chronic	431 (19.0%)
Unstable course	887 (39.1%)

MASQ-D30 = Dutch short adaptation of the Mood and Anxiety Symptoms Questionnaire; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders Fourth Edition

Table 6.2: Multivariate longitudinal Linear Mixed Models analyses of the change in the tripartite model dimensions in reaction to the occurrence any life-event

N=2267	Model	General Distress	Anhedonic Depression	Anxious Arousal
		β (p-value)	β (p-value)	β (p-value)
Negative life event	Model 1	0.19 (<0.001)	0.05 (0.12)	0.12 (<0.001)
(yes/no)	Model 2	0.20 (<0.001)	0.01 (0.84)	0.18 (<0.001)
Positive life event	Model 1	-0.15 (0.001)	-0.22 (<0.001)	-0.18 (<0.001)
(yes/no)	Model 2	-0.11 (0.04)	-0.21 (<0.001)	-0.12 (0.03)

Data based on Linear Mixed Models analyses: an unstructured covariance matrix was used to account for repeated measures

Model 1: adjusted for age, gender and MASQ scale-score at T1.

Model 2: additional variables: stable chronic (1,0); stable healthy course (1,0) unstable course (1,0), and six interactions between the course variables and life event variables.

Table 6.3: Multivariate longitudinal Linear Mixed Models analyses of the change in the tripartite model dimensions in reaction to the number of life-events

N=2267		General Distress β (p-value)	Anhedonic Depression β (p-value)	Anxious Arousal β (p-value)
Number of Negative life events	Model 1	0.11 (<0.001)	0.05 (<0.001)	0.08 (<0.001)
	Model 2	0.11 (<0.001)	0.03 (0.07)	0.10 (<0.001)
Number of Positive life events	Model 1	-0.06 (<0.001)	-0.12 (<0.001)	-0.05 (<0.001)
	Model 2	-0.04 (0.05)	-0.11 (<0.001)	-0.04 (0.10)

Data based on Linear Mixed Models analyses: an unstructured covariance matrix was used to account for repeated measures
Model 1: adjusted for age, gender and MASQ scale-score at T1.
Model 2: additional variables: stable chronic (1,0); stable healthy course (1,0) unstable course (1,0), and six interactions between the course variables and life event variables.

The number of life events

The results of the LMM analyses of the association between the number of negative and positive life events and MASQ-D30 scores are shown in Table 6.3. In model 1, the number of negative life-events was associated with increased anhedonic depression (β=0.05), but more strongly with general distress (β=0.11) and anxious arousal (β=0.08). When adjusted for course trajectories in model 2, the associations remained significant and unchanged with general distress (Δβ=0) and increased with anxious arousal (Δβ=0.2). The association with anhedonic depression was no longer significant in model 2. The number of positive life-events was associated with general distress (β=-0.06) and Anxious Arousal (β =-0.05), but most strongly with anhedonic depression (β=-0.12). When adjusted for the course trajectories in model 2, the associations with general distress and anxious arousal decreased and were no longer significant (p=0.05-0.10). The association with anhedonic depression only decreased with 8.3% (Δβ=0.01).

These results indicated that general distress and anxious arousal were consistently associated with the number of negative life events, and that anhedonic depression was associated with the number of positive life events.

Individual life-events

The associations of the individual life-events with each of the tripartite dimensions are illustrated in Figure 6.2. The results showed that most life events had effects on one or

more dimensions. Only four events were not associated with any dimension (e.g. 'contact with police or justice system' and 'completion of education').

Figure 6.2 clearly shows that negative life events were primarily associated with general distress and/or anxious arousal. 'Financial problems', 'being seriously ill or wounded' and 'becoming unemployed' led to increases in all dimensions, but strongest in general distress. This indicated that events with a broad and long-lasting impact on quality of life had a general effect on symptomatology. 'Death of a parent, child, brother or sister' and 'death of a friend or other family member' specifically led to increased general distress, 'Getting fired' led to increased anxious arousal, and 'a serious problem with a friend, family member or neighbour', 'the ending of a friendship with a friend, family member or neighbour' and 'a close family member getting ill or wounded' led to increases on both dimensions. Only 'separation from a partner' was associated with increased general distress and anhedonic depression. These results indicated that general distress was mainly affected by events that involved social loss. Figure 6.2 clearly illustrates that positive life events had most effect on anhedonic depression. 'Making new friends' and 'going on holiday' led to decreases on all dimensions, but most strongly on anhedonic depression. 'Meeting a new partner', 'being better off financially', and 'a new job or promotion' specifically decreased anhedonic depression.

6.4 Discussion

The current longitudinal study investigated the association between life-events and change on the dimensions of the tripartite model over a 2-year period. The results showed that different types of life-events led to change in different symptom dimensions. Negative life-events led to increases in general distress and anxious arousal and positive life-events led to a decrease in anhedonic depression. These associations were not affected by the adjustment for (confounding and effect-modification by) DSM-based course trajectories, indicating that the dimensions captured unique symptom variation in response to life events. Additional analyses of the individual life events showed that some life events had larger effects than others. Several high-impact events (e.g. 'financial problems', 'being seriously ill or wounded') led to increases on all dimensions. However, most negative life events (e.g. 'death of a parent, child, brother or sister') primarily led to increases in general distress and/or anxious arousal. Positive life events (e.g. 'making new friends') primarily led to decreased anhedonic depression. Taken together, these findings indicated that dimensions can be used to detect specific effects of life events on psychiatric symptomatology.

The current results had several interesting implications. The findings of consistent effects of negative and positive life-events on respectively general distress and anhedonic depression, was in line with previous research in healthy subjects (e.g. Reich & Zautra, 1981; Zautra & Reich, 1988; Suh et al., 1996). The present findings suggested that the specificity of the effects of negative and positive life events to different symptom-dimensions is a phenomenon that is generalizable across both healthy and diseased

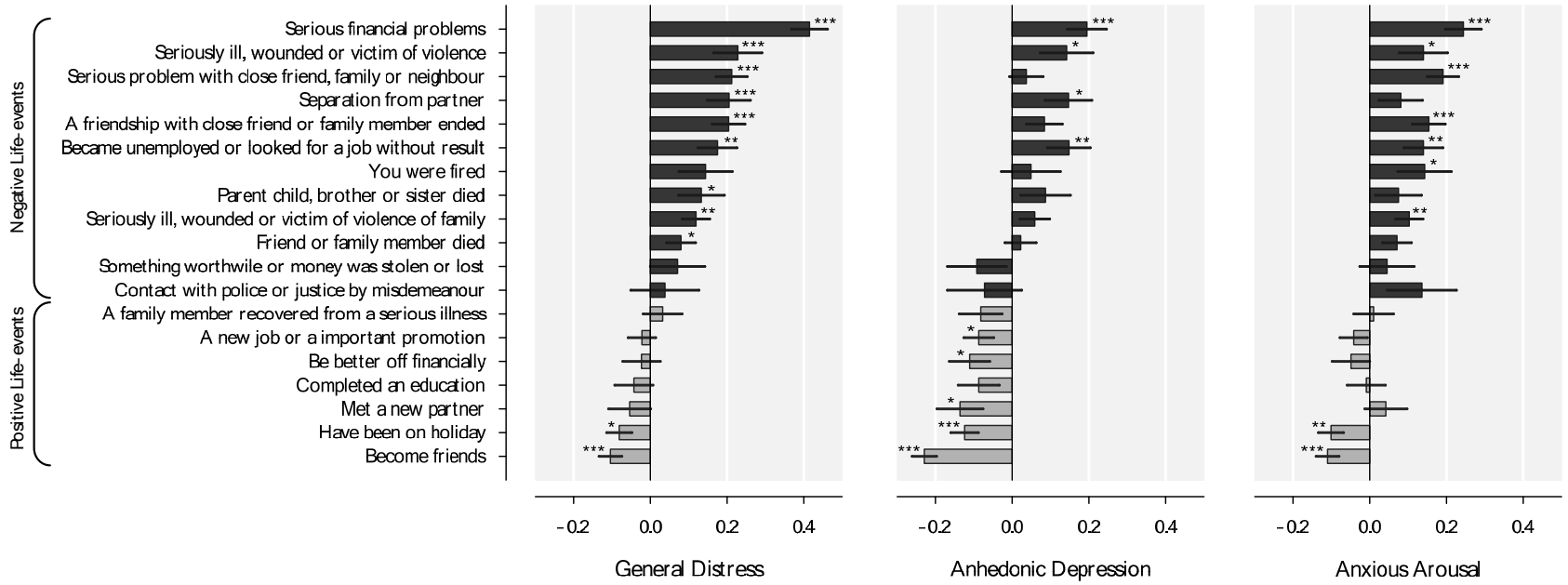

Figure 6.2: β 's (on x-axis) and standard errors for the associations between individual negative and positive life-events (on y-axis) and change on the three dimensions of the tripartite model over time (T1, T2 and T3) in a large group of subjects with or without depression and/or anxiety (n=2267). Results based on Linear Mixed Models analyses with an unstructured covariance matrix to account for repeated measures. All associations adjusted for age, gender, MASQ scale-score at T1 and time (as repeated measures factor).

*) p<0.05; **) p<0.01; ***) p<0.001

individuals. Also, the results were largely in line with the expectation of the tripartite model that the dimensions of general distress and anhedonic depression represent separate constructs with separate etiology. In line with their previously reported moderate interrelatedness (e.g. Wardenaar et al., 2010), some life events (e.g. 'serious financial problems', 'being seriously ill or wounded' or 'making new friends') were found to significantly affect both general distress and anhedonic depression. However, in all cases the effects of these events were still stronger on one of the two dimensions. Thus, on the one hand, these results indicated that some etiological mechanisms are shared between the dimensions (based on significance alone). On the other hand, the results also showed that there is still differentiation between the dimensions (based on effect-sizes), supporting the validity of the tripartite model assumptions.

Change in anxious arousal was primarily associated with negative life-events, although the effects were slightly smaller than for general distress. In addition, analyses of the individual events showed anxious arousal was associated with several negative life events and specifically with 'being fired' and 'becoming unemployed'. Although not previously investigated in a similar fashion, these findings were in line with the idea that negative life events play a role in the onset of anxiety and panic disorders in particular (Klauke et al., 2010). The above described findings that anhedonic depression changed in response to positive life events is also in line with previous work, which showed that positive life events predicted future depressive disorders and do not predict anxiety disorders (Spinhoven et al., in press).

The current results illustrate the ability of dimensions to detect temporal variations in mental state in reaction to external triggers. Even within groups of patients with a supposedly stable course (e.g. chronic over 2 years), there was notable variation in dimensional scores. The pattern of symptoms could differ across persons but the development of each symptom dimension could also change within each person over time. All this variation is not captured by categorical classifications and likely to reflect the complex effects of many etiological mechanisms. In the current study, part of the variation turned out to be explained by the occurrence of particular types of life-events. This was in line with previous work on a much smaller time-scale, which found that emotional responsivity to particular daily hassles was also captured very effectively with repeated dimensional assessments (Peeters et al., 2003; Gable et al., 2000; Suls et al., 1998). Expanding this previous work, our results indicate that dimensions can be used in a comparable fashion to detect emotional reactivity across a much larger time-span.

The effects of life events on change in symptom dimensions were only minimally affected by the inclusion of DSM-based course trajectories and their interactions with life events. This indicated that the dimensions picked up life event-induced changes in mental state that were not also explained by the more traditionally defined course trajectories. The fact that dimensions are specific and continuous probably made them sensitive to

specific effects of life-events that cannot be picked up by changes in heterogeneous syndrome classifications. The reason that life-events have often been observed not to cause the onset of full-fledged depression might be due to the fact that all individuals, irrespective of diagnosis, react differently to environmental stimuli. These differences in emotional reactivity might reflect the widely observed variation in susceptibility to depression in reaction to life-events (e.g. Kessler, 1997). The mechanisms underlying this variation are still unclear, but might involve coping mechanisms (Billings & Moos, 1981; Kraaij et al., 2003), the amount and quality of social support (Cohen & Wills, 1985) but also genetic predisposition (Wichers et al., 2007) and early life adversity (Heim & Nemeroff, 2001).

Different life events were found to be associated with different dimensions. As described above, the most consistent differential associations were found between negative and positive life event types. However, the additional analyses of the individual life events also provided some further hints about more event-specific effects. For instance, life events that lead to deterioration on all dimensions seemed to mainly deal with the loss of aspects like good health and a steady income, which are first requirements for a good quality of life. Events that specifically affected general distress all involved some amount of social loss, ranging from 'losing a friend' to 'the death of a close family member'. Although we should be careful not to overinterpret these explorative results, which involved a large number of statistical tests, the observed associations at least indicate that it is likely that specific types of psychopathology can be linked to specific types of life events, in line with previous findings (Keller et al., 2007; Keller & Nesse, 2005; 2006).

Although the current study had several strong characteristics, including large sample-size, a longitudinal approach, sophisticated statistical analyses and the possibility to look at both patients and healthy participants, some study-limitations should be kept in mind. First, the results apply to a mixed group of healthy persons and psychiatric outpatients, but cannot be directly generalized to more severely affected inpatients. Second, only three dimensions were used as outcome variables, whereas in reality much more relevant symptom-dimensions will exist (e.g. Den Hollander-Gijsman et al., 2011). Third, the LMM analyses of the individual events could not be used to account for clustering of events because this resulted in an overly complex (19 independent variables, without covariates) and unstable model. Fourth, it is known that pre-existent psychopathology increases the chance of life-event occurrence, which often leads to an overestimation of the causal effect of life-events that precede measured psychopathology (e.g. Kessler, 1997). Although we adjusted for the severity of baseline symptomatology in our longitudinal analyses, it is possible that the incidence of certain events was associated with preexistent psychopathology not included in our models. This should be kept in mind when interpreting our results. Future studies could investigate the mediating roles of protective factors (e.g. coping, social support) and susceptibility factors (e.g. genetic predisposition) in the association between life-events and symptoms over time.

In conclusion, the current study showed that dimensions capture life-event induced changes in mood/emotionality. Moreover, the results indicated that these changes transcended the traditional DSM-based course-trajectory distinctions and might thus be useful as alternative or additional outcome characteristic in the etiological research of psychopathology.

Chapter 7:

Symptom Dimensions as Predictors of the Two-Year Course of Depressive and Anxiety Disorders

Abstract

Background, Because of the heterogeneity of known predictive factors, course-predictions for depression and anxiety are often unspecific. Therefore, it was investigated whether symptom-dimensions could be used as more specific course-predictors, on top of already known predictors, such as diagnosis and overall severity. *Methods,* A sample of 992 subjects with depressive and/or anxiety disorders was followed in a 2-year prospective cohort study. Dimensions of the *tripartite model* (general distress, anhedonic depression and anxious arousal) were assessed at baseline. Diagnostic and course information were assessed at baseline and 2-year follow-up. *Results,* Dimensional scores at baseline predicted diagnosis after two years and course-trajectories during follow-up. Increased general distress at baseline was associated with comorbid depression-anxiety at follow-up, increased anhedonic depression was associated with single depression and anxious arousal was associated with (comorbid) panic disorders at follow-up. Baseline general distress was associated with an unfavourable course in all patients. All associations were independent and added prognostic information on top of diagnosis and other predictive factors at baseline.
Limitations, Only prevalent patients were included at baseline and only three dimensions were measured. *Conclusions,* Symptom dimensions predict the future 2-year course of depression and anxiety. Importantly, the dimensions yield predictive information on top of diagnosis and other prognostic factors at baseline.

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7.1 Introduction

Although several predictive factors are known, course predictions for depression and anxiety are usually unspecific. Depression is known to be episodic and sometimes chronic (±20%) (e.g. Keller & Baker, 1992; Ormel et al., 1993; Piccinelli & Wilkinson, 1994), anxiety disorders are known to remit less often (e.g. Keller & Hanks, 1993; Pollack & Otto, 1997; Tiemens et al., 1996), and comorbid depression-anxiety are known to have a particularly unfavourable course (e.g. Shankman & Klein, 2002; Merikangas, 2003; Patten et al., 2010; Penninx et al., 2011). Other predictors of poor prognosis include old age (Penninx et al., 2011), young age-of-onset (Karlsson et al. 2008, Penninx et al. 2011), high severity (van Beljouw et al., 2010, Penninx et al. 2011) and long disorder duration (Conradi et al., 2008).

Still, prognosis varies between individuals with seemingly similar characteristics. To account for this heterogeneity, *symptom-dimensions* could be used as additional predictors, increasing homogeneity, circumventing comorbidity (Widiger & Samuel, 2005) and increasing statistical power (MacCallum et al., 2002). The tripartite model (Clark & Watson, 1991) describes well-validated common and specific dimensions for depression and anxiety (e.g. Keogh & Reidy, 2000; de Beurs et al., 2007). The common dimension of *'General distress (GD)'* covers psychological distress seen in both depression and anxiety and accounts for their comorbidity. The specific dimension of *'Anhedonic depression (AD)'* covers depression-specific anhedonia/energy loss and *'Anxious arousal (AA)'* covers anxiety/panic-specific somatic arousal. Each tripartite dimension was hypothesized to have specific prognostic value (Clark et al., 1995). Indeed, GD and AD were found to predict outcome of depression (Joiner et al., 2000; Lonigan et al., 2003) and generalized anxiety disorder (Chambers et al., 2004) and related dimensions made similar predictions (Geerts & Bouhuys, 1998; Clark et al., 2003). However, there were large methodological differences across studies and the AA-dimension was not often investigated. Moreover, anxiety and comorbid depression-anxiety patients were not accounted for in these studies, hampering the differentiation between the predictive abilities of GD, AD and AA. Importantly, the added value of dimensions on top of known predictors was not evaluated.

Therefore, we investigated the ability and added value of the tripartite dimensions in predicting the 2-year course and outcome of depression, anxiety and comorbid depression-anxiety in a large outpatient cohort (n=992).

7.2 Methods

Participants

Participants came from the Netherlands Study of Depression and Anxiety (NESDA), a large longitudinal cohort study (N=2981) of participants with (n=2329) or without (n=652) a lifetime depressive/anxiety disorder (see Penninx et al. (2008) for details). Exclusion criteria were: not being fluent in Dutch or a psychotic, obsessive-compulsive, bipolar or

severe addiction disorder. Ethical Review Boards of all participating universities approved the study-protocol. All participants signed informed consent.

At baseline, a face-to-face assessment was conducted (demographic/personal information, psychiatric interview, questionnaires) and 2596 (87.1%) participants were followed-up after 2-years. For this study, only current patients were included: 1495 participants had a 1-month diagnosis at baseline or had a 6-month diagnosis and were symptomatic in the month prior to baseline. Of these, 1209 (80.9%) completed the follow-up. Dropouts were younger and lower educated (Lamers et al., 2011). Of these patients, 992 (82.1%) provided all required data to compute dimensional scores and covariates. Incomplete data were associated with fewer years of education ($p<0.001$) but not with age or gender.

Instruments

The adapted Mood and Anxiety Symptoms Questionnaire

To measure the tripartite dimensions at baseline, participants completed the 30-item adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ-D30; Wardenaar et al., 2010; original: Watson et al., 1995) MASQ-D30-items were rated on a 5-point scale and added up to three subscales (GD, AD and AA). The MASQ-D30 was previously shown valid and reliable (Wardenaar et al., 2010).

The course of depression and anxiety

DSM-IV depressive disorders (MDD, Dysthymia) and anxiety disorders (Panic disorder, Social Phobia, GAD, and Agoraphobia) were diagnosed at baseline and follow-up with the Composite Interview Diagnostic Instrument (CIDI, WHO version 2.1; hierarchy-free diagnoses with organic exclusion rules). If participants reported any diagnosis during follow-up on the CIDI, the Life Chart Interview (LCI) was administered: using a calendar method, the presence and severity of depressive or anxiety symptoms was determined for each month during follow-up, using recalled life-events as memory-aids (Lyketsos et al., 1994). Symptom-severity was rated on a 5-point scale (no/minimal, mild, moderate, severe, very severe). The baseline LCI was used to determine the presence of symptoms in the month prior to baseline. The follow-up LCI was used to calculate course-indicators. Symptomatology was only considered present if at least mildly severe and remission was considered present after ≥3 symptom-free months.

Two course indicators were created. The *1-month CIDI diagnosis at follow-up* was defined as follows: (1) being healthy at follow-up, (2) MDD or dysthymia at follow-up, (3) anxiety at follow-up and (4) comorbid MDD and anxiety at follow-up. Additional dichotomous variables were created to test the specific prediction of social phobia, panic disorder, agoraphobia and GAD. The *course trajectory* was defined as follows: (1) early sustained remission (<6 months after baseline), (2) late remission (>6 months after baseline) or recurrence following remission, and (3) chronic course.

Covariates

Following Penninx et al (2011), sociodemographic covariates were age, gender and years of education. Clinical covariates at baseline were: the percentage of symptomatic months during the four years before baseline (based on LCI), the CIDI-based age-at-onset of the baseline disorder (youngest age for comorbid cases). Treatment was not included because a previous study in the same sample found no treatment effects of either antidepressant use or the receipt of psychological interventions on course in multivariate analyses (Penninx et al., 2011).

Statistical analyses

Multinomial regression analyses were used to investigate the associations between the dimensions at baseline on the one hand and diagnosis at follow-up (using 'no diagnosis' as reference) and course trajectory (using 'early-sustained remission' as reference) on the other hand. Additional anxiety-disorder specific associations were tested with logistic regression. Different models were used to investigate if dimensions predicted course independently from diagnosis and demographics. In *model 1*, baseline DSM-IV dummies were added (depression, anxiety and comorbidity). In *model 2*, demographic and clinical covariates were added. $P<0.05$ was considered significant. Analyses were done with SPSS-17 for Windows.

7.3 Results

Baseline characteristics

Of the sample, 66.2% was female and the mean age was 42.5 years (s.d.=12.3, see Table 7.1). Of the participants 227 (22.9%) had a single depressive disorder, 400 (40.3%) had single anxiety, and 365 (36.8%) had comorbid depression-anxiety. At baseline, mean age-at-onset was 20.9 (s.d.=12.5), the mean percentage of months with symptomatology prior to baseline was 31.6 (s.d.=20.1) and 384 participants (38.7%) used antidepressants. AD and AA were weakly correlated (r=0.31) and GD was moderately correlated with both AD (r=0.58) and AA (r=0.48).

Diagnoses at follow-up

At follow-up, 118 participants (11.9%) had single depression, 224 (22.6%) had single anxiety, 178 (17.9%) had comorbid depression-anxiety and 472 (47.6%) had no disorder (see Table 7.2). Only increased baseline AD was associated with increased odds of single depression at follow-up (OR=1.24). Both increased baseline GD and AA were associated with increased odds of comorbid depression-anxiety at follow-up after adjustment (OR=1.25 and OR=1.37). Only increased baseline AA was associated with increased odds of single anxiety after adjustment (OR=1.32). In the analyses with separate anxiety disorders at follow-up (see Table 7.1 for frequencies), baseline AA was only associated with the risk of a panic disorder at follow-up, even when adjusted for panic disorder at baseline (OR=1.66 [95% CI, 1.37-2.02]). In addition, associations between AA and other

anxiety disorders (OR=1.11 to 1.28), overall single anxiety (OR=1.12 [95% CI, 0.93-1.36]) and comorbid depression-anxiety (OR=1.13 [95% CI, 0.92-1.39]) all disappeared when panic-patients were excluded (n=842), indicating that the initially observed predictions of anxiety (and comorbidity) by AA were all driven by AA's specific predictive value for panic disorder.

Course trajectories during follow-up

During follow-up, 252 participants (25.4%) went into early-sustained remission, 324 participants (32.7%) went into late remission or into remission followed by recurrence, and 416 participants (41.9%) had a chronic course (see Table 7.2). Only increased GD was associated with increased odds of unfavorable course.

7.4 Discussion

The current study showed that common and specific dimensions of depression and anxiety, each add specific prognostic information on top of baseline DSM-diagnosis and other prognostic factors. Increased baseline GD was associated with increased odds of comorbid depression-anxiety at follow-up. Increased AD was associated with increased odds of single depression and increased AA was associated with increased odds of anxiety. In addition, increased GD predicted unfavourable course trajectories. These results showed the added value of using three (common GD; specific AD and AA) instead of two (depression and anxiety) dimensions, because each of the former had different implications for prognosis, which would go unnoticed when looking solely at depression and anxiety severity, without accounting for their heterogeneity and overlap. Thus, the results further empirically supported the tripartite model assumptions.

As in previous studies (e.g. Joiner et al., 2000; Lonigan et al., 2003; Clark et al., 2003) AD predicted risk of future depression. Also, AA predicted risk of future anxiety, particularly panic disorder. All associations of AA with other anxiety disorders, but also with comorbid depression-anxiety at follow-up disappeared when participants with a panic disorder were excluded. These results suggest that the prognostic value of AA is limited to panic disorders. Thus, more dimensions are needed to cover all anxiety disorders (e.g. Mineka et al., 1998).

In line with its presumed common role, increased GD only predicted increased risk of future comorbid depression-anxiety. Previously, general distress was also found to be associated with later comorbidity (Chamber et al., 2004). Thus, other findings of associations between GD and depression (Joiner et al., 2000; Lonigan et al., 2003; Clark et al., 2003) were most likely driven by both depression and anxiety in these groups. These findings confirm the idea that comorbidity is mostly accounted for by overlapping symptoms of depression and anxiety, and not by disorder-specific symptom-domains, showing the added value of the tripartite dimensions to increase prognostic differentiation. GD also was the only dimension to predict unfavourable course trajectories; probably because the trajectories were pooled across depressive, anxious and comorbid cases to limit the number of specific trajectory subgroups (5 instead of 12).

Table 7.1: Baseline characteristics of the study group

Baseline variable	Study Group
N	992
% female	66.2%
Mean years of age (s.d.)	42.5 (12.3)
Age range	18-65
Level of education (years), mean (s.d.)	11.9 (3.3)
MASQ-D30 scales: median (Interquartile range)	
General distress	24 (18-32)
Anhedonic depression	40 (34-46)
Anxious arousal	17 (13-21)
Psychiatric Characteristics	
Only depressive disorder (MDD or dysthymia), n (%)	227 (22.9%)
Only anxiety disorder, n (%)*	400 (40.3%)
Panic Disorder, n (%)	170 (42.5%)
Social Anxiety, n (%)	187 (46.8%)
Generalized Anxiety Disorder, n (%)	78 (19.5%)
Agoraphobia (without panic)	65 (16.2%)
Comorbid MDD, dysthymia and anxiety disorders, n (%)	365 (36.8%)
Antidepressant use at baseline, n (%)	384 (38.7%)
Percentage of months with symptoms in past 4 years, mean (s.d.)	31.6 (20.1)
Age of onset of index episode, mean (s.d.)	20.9 (12.5)
Care setting, n (%)	
Primary care	443 (44.7%)
Specialized mental health care	458 (46.2%)
General population	91 (9.2%)

SD, standard deviation; MASQ-D30, Mood and Anxiety Symptoms Questionnaire Dutch short adaptation; IDS-SR, Inventory of Depressive Symptomatology Self Report; FQ, Fear Questionnaire.
*) 63 patient with single Social phobia, 46 with Panic disorder, 33 with Agoraphobia, 15 with GAD, 5 with Panic disorder + GAD, 18 with panic disorder + social phobia, 3 with GAD + Agoraphobia, 8 with GAD + Social phobia, 12 with Social phobia + Agoraphobia, 9 with >2 anxiety diagnoses.

GD is often described as a general indicator of depression and anxiety severity (Clark & Watson, 1991; Mineka et al., 1998). Thus, its general predictive value for course trajectories was in line with expectations. However, it also pointed out that depression or anxiety-specific symptoms had no overall prognostic value.

From a clinical perspective, the current findings indicate that within a group of patients with the same diagnosis, *dimensions* capture inter-individual differences in symptomatology, which account for differences in prognosis. For instance, varying levels of AA in a depressed group could reflect varying risk of future (comorbid) panic disorder and varying levels of AD in a panic disorder group could reflect varying risk of future (comorbid) depression. Eventually, symptom dimensions could become part of routine risk assessment, which may for instance be useful to judge the potential efficacy of therapy (Sotsky et al., 1991).

The present study had several strengths, including a large sample size, systematic course assessments and thorough statistical adjustment. However, there were also study-limitations. (1) Sample attrition may have caused selection and/or attrition bias. (2) Only three symptom dimensions were used, whereas much more dimensions may exist (Den Hollander-Gijsman et al., 2010; 2011). (3) Only prevalent cases were included at baseline, excluding incident cases during the follow-up period. (4) Not all anxiety disorders (e.g. post-traumatic stress disorder) were assessed at baseline. Future research could focus on a broader range of more specific sub-dimensions and multiple dimensional assessments over time.

Table 7.2: Associations of the tripartite dimensions at baseline with the 1-month diagnosis at follow-up and the 2-year course trajectories of depression and/or anxiety in 992 psychiatric outpatients.

MASQ-D30 Dimension & Model	Diagnosis at follow-up				Course-trajectory during follow-up		
	Healthy (n=438)	Depression (n=115) OR (95% CI)	Anxiety (n=211) OR (95% CI)	Depression and anxiety (n=177) OR (95% CI)	Early remission (n=252)	Late remission/ recurrence & remission (n=324) OR (95% CI)	Chronic Course (n=416) OR (95% CI)
GeneralDistress:							
Crude	Ref.	1.16 (0.99-1.35)	1.06 (0.93-1.20)	1.30 (1.13-1.50)***	Ref.	1.24 (1.08-1.43)**	1.29 (1.13-1.47)***
Model 1	Ref.	1.11 (0.94-1.30)	1.09 (0.95-1.24)	1.27 (1.09-1.47)**	Ref.	1.24 (1.08-1.43)**	1.27 (1.10-1.45)***
Model 2	Ref.	1.12 (0.94-1.33)	1.01 (0.88-1.17)	1.25 (1.07-1.45)**	Ref.	1.21 (1.05-1.41)**	1.21 (1.04-1.39)*
Anhedonic Depression:							
Crude	Ref.	1.36 (1.15-1.59)***	1.00 (0.89-1.12)	1.19 (1.03-1.38)*	Ref.	1.05 (0.93-1.18)	1.09 (0.97-1.22)
Model 1	Ref.	1.27 (1.08-1.50)**	1.05 (0.93-1.18)	1.18 (1.02-1.37)*	Ref.	1.05 (0.93-1.18)	1.10 (0.98-1.24)
Model 2	Ref.	1.24 (1.05-1.46)*	1.05 (0.92-1.19)	1.14 (0.98-1.33)	Ref.	1.06 (0.94-1.20)	1.10 (0.97-1.24)
AnxiousArousal:							
Crude	Ref.	0.99 (0.82-1.20)	1.35 (1.16-1.56)***	1.43 (1.22-1.67)***	Ref.	1.05 (0.89-1.21)	1.19 (1.02-1.39)**
Model 1	Ref.	0.97 (0.80-1.18)	1.28 (1.10-1.49)**	1.35 (1.15-1.59)***	Ref.	1.03 (0.88-1.21)	1.11 (0.95-1.29)
Model 2	Ref.	0.97 (0.80-1.19)	1.32 (1.12-1.55)**	1.37 (1.16-1.62)***	Ref.	1.02 (0.87-1.21)	1.13 (0.96-1.32)

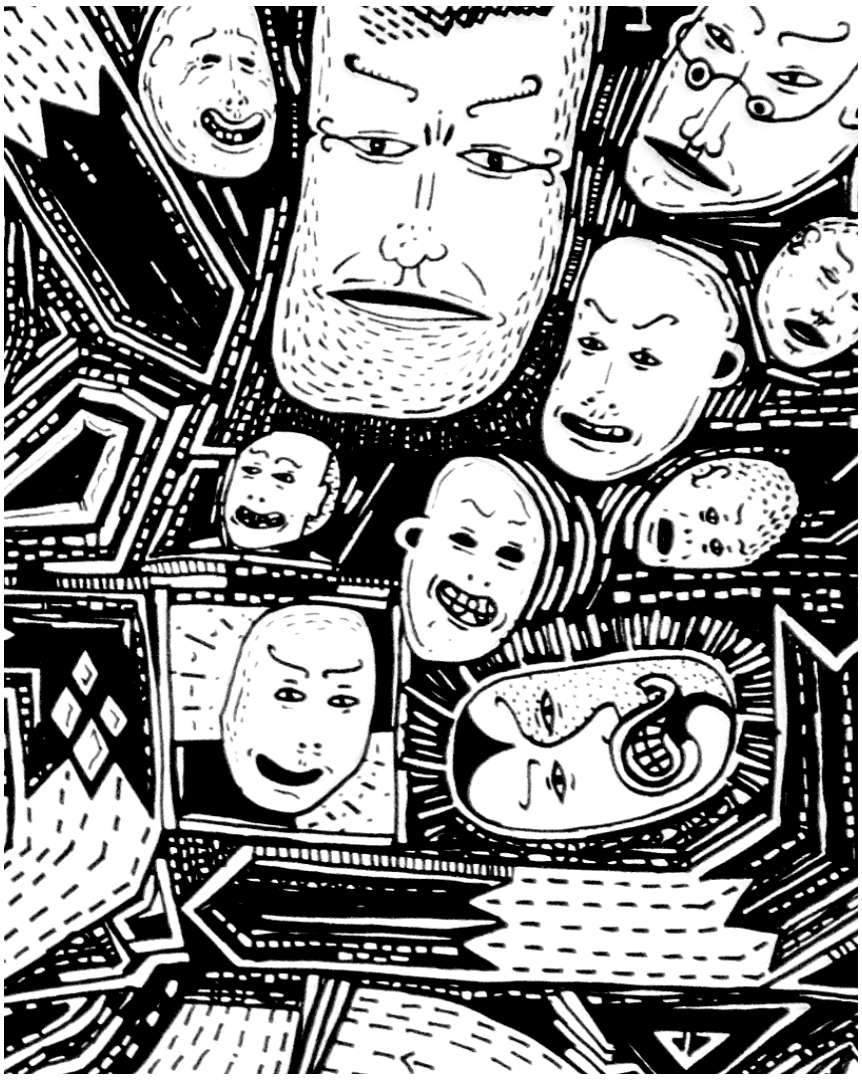
Results of multinomial regression analyses: Odds Ratio's (OR) are given for 5-point increments on each dimension with 95% Confidence intervals (CI). MASQ-D30=Mood and Anxiety Symptoms Questionnaire Dutch 30-item adaptation.

Crude: dimensions adjusted for each other; Model 1: adjusted for DSM-IV diagnosis; Model 2: additionally adjusted for age, gender, years of education, duration of disorder at baseline, age of onset of the disorder at baseline.

*p<0.05, **p<0.01, ***p<0.001.

Chapter 8:

Dimensions of the Inventory of Depressive Symptomatology as Predictors of the Course of Depressive and Anxiety Disorders



Abstract

Objective: For depressive and/or anxiety disorders general course characteristics are known. However, prognosis varies among patients with the same diagnosis. The current study investigated whether the use of the more homogeneous symptom dimensions of mood/cognition and anxiety/arousal, would yield more specific prognoses than overall severity and course-categories. Method: 1053 subjects with a depressive and/or anxiety disorder from the Netherlands Study of Depression and Anxiety (NESDA) were assessed at baseline and at 2-year follow-up. Dimensions of *mood/cognition* and *anxiety/arousal* were extracted from the Self Report Inventory of Depressive Symptomatology (IDS-SR). Diagnoses at baseline and follow-up were assessed with a standardized psychiatric interview. Course trajectories were assessed with a life chart interview. Results: Increased mood/cognition scores predicted single depression (OR=1.80) and comorbid depression-anxiety (OR=2.00) at follow-up and unfavourable course trajectories of depressive symptomatology (OR=1.94-2.08). Increased anxiety/arousal predicted single panic disorder) at follow-up (OR=2.24) and unfavourable course trajectories of anxiety symptomatology (OR=1.38-1.42). All associations remained significant when adjusted for diagnosis and prognostic factors, including baseline diagnosis. Conclusion: The widely used IDS-SR can be used to measure two dimensions, with specific prognostic value on top of other, previously known prognostic factors.

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8.1 Introduction

Both depressive and anxiety disorders are characterized by a chronic-intermittent course and a high disease burden and both have a continuous impact on well-being functioning and productivity throughout the lifecycle (Ormel et al., 2008). Given their large impact, understanding of the factors that contribute to the course of depression and anxiety is essential. Several course characteristics have been described previously. Depression is characterized by periods of remission and recurrence and becomes chronic in circa 20% of patients (Keller & Baker, 1992; Spijker et al., 2002; Ormel et al., 1993; Piccinelli & Wilkinson, 1994) Anxiety disorders show more chronicity and recurrence after remission (Ormel et al., 1993; Keller & Hanks, 1993; Pollack & Otto, 1997; Keller, 2006; Tiemens et al., 1996; Penninx et al., 2011). When depression and anxiety co-occur, prognosis is especially poor (Shankman & Klein, 2002; Merikangas, 2003; van Beljouw et al., 2010; Fichter et al., 2010; Patten et al., 2010; Penninx et al., 2011) Other clinical predictors of poor prognosis include: older age (Mueller et al., 2004; Penninx et al., 2011), younger age-of-onset (Karlsson et al. 2008; Penninx et al., 2011), higher severity (Conradi et al., 2008; van Beljouw et al., 2010; Penninx et al., 2011) and longer duration of the disorder (Conradi et al., 2008; Penninx et al., 2011).

Although general course characteristics have been described for each disorder, the prognosis can vary widely between patients with similar diagnoses. To account for these variations, *symptom-dimensions* could be used in addition to DSM-IV diagnoses. With this approach, an individual's clinical state is described by a specific pattern of dimensional scores on spectra that range from healthy to pathological (Goldberg, 2000). Importantly, continuous dimensions provide more statistical power to detect etiological or prognostic associations than categorical diagnoses (MacCallum et al., 2002). Because of these potential advantages, the inclusion of dimensions in addition to categorical diagnoses in the new DSM-V is currently under consideration. However, as of yet only limited information is available on which dimensions could have most use in predicting a patients' prognosis.

A well-known dimensional model of depression and anxiety, with clear clinical implications, is the *tripartite model* (Clark & Watson, 1991), which consists of 3 dimensions. (1) 'General distress' (also called 'negative affect') covers symptoms of general psychological distress (e.g. pessimism, feelings of guilt), which are usually increased in all patients with depression and/or anxiety and could account for the high observed rates of comorbidity between depression and anxiety. (2) 'Anhedonic depression' (or 'lack of positive affect') covers depression specific symptoms of anhedonia and energy loss (e.g. lack of enthusiasm). (3) 'Anxious arousal' (or 'somatic arousal') covers anxiety/panic specific symptoms of somatic hyper-arousal (e.g. palpitations, sweating). According to the tripartite model, an individual's clinical picture and prognosis depend on his/her specific scores on the three dimensions of the model.

Several studies have investigated the structural validity of the tripartite model and the 3-dimensional structure has repeatedly been found to fit well on data from different populations (e.g. Keogh & Reidy, 2000; Marshall et al., 2003; de Beurs et al., 2007).

About the prognostic role of the tripartite dimensions, several hypotheses have been formulated. Clark et al (1994) hypothesized that increased general distress and anhedonic depression predict increased chronicity and poorer prognosis of depression. Indeed, increased general distress and anhedonic depression predicted an increase of depressive symptoms in youth psychiatric patients (n=58; Joiner et al., 2000) and in healthy children (n=270; Lonigan et al., 2003) as well as increased comorbidity in patients with generalized anxiety disorder (n=83; Chambers et al., 2004). Increases on constructs related to general distress and anhedonic depression were also associated with an unfavourable course of depression (Geerts & Bouhuys, 1998; Clark et al., 2003) However, these studies showed large methodological differences and investigated limited aspects of psychopathology course. For instance, several studies were focussed on children and adolescents (Joiner et al., 2000; Lonigan et al., 2003), whereas others focussed on adults (Geerts & Bouhuys, 1998; Clark et al., 2003; Chambers et al., 2004). Also, follow-up time varied and ranged from only 6 weeks (Geerts & Bouhuys, 1998) to 7 months (Lonigan et al., 2003), sample sizes ranged from 26 (Geerts & Bouhuys, 1998) to 270 (Lonigan et al., 2003). Further, follow-up was limited to a single depression measurement, anxiety and comorbid depression-anxiety were mostly omitted, course during follow-up was not investigated and the anxious arousal dimension was not included in any of the studies (Geerts & Bouhuys, 1998; Joiner et al., 2000; Lonigan et al., 2003; Clark et al., 2003; Chambers et al., 2004). Importantly, it was not investigated how much prognostic information the dimension add on top of traditional predictors, by statistically accounting for diagnosis and prognostic factors at baseline.

In the present study, we aimed to gain more insight into the added value of symptom-dimensions in predicting the course of psychopathology, and thus in their potential clinical use. We investigated the ability of the tripartite dimensions to predict the course and outcome of psychopathology over a 2-year period in a large cohort of 992 outpatients with a depressive and/or anxiety disorder at baseline. Specifically, we evaluated whether the dimensions added extra information on top of the DSM-IV diagnosis and other important prognostic factors at baseline. The analyses were conducted on data from the Netherlands Study of Depression and Anxiety (NESDA).

8.2 Method

Participants

Participants came from the NESDA, a large longitudinal study to investigate the course of depressive and anxiety disorders. The NESDA sample consists of 2981 participants with a mean age of 41.9 (range 18-65), who were recruited from community, primary care and specialized mental health care organizations. At baseline, there were 1002 men and 1979

women and 2329 participants had a lifetime diagnosis of major depressive disorder (MDD) and/or an anxiety disorder. Six hundred fifty two participants had no lifetime psychiatric diagnosis. Exclusion criteria were not being fluent in Dutch and a primary diagnosis of psychotic, obsessive-compulsive, bipolar or severe addiction disorder because these latter low prevalent disorders would largely affect the course trajectories, found in NESDA (Penninx et al., 2008). Detailed objectives and rationales of NESDA can be found elsewhere (Penninx et al., 2008). The research protocol was approved by the Ethical Review Boards of all participating universities and all participants signed an informed consent form.

The baseline assessment was conducted face-to-face by trained research staff at one of seven research locations and consisted of an extensive assessment of demographic and personal characteristics, a standardized psychiatric interview, a medical assessment and the administration of self-report questionnaires. After 2 years, the assessments were repeated in a follow-up session. The mean duration until follow-up was 24.0 months (s.d.=1.5) and this duration did not differ across gender (p=0.30) or across different disorder groups at baseline (depressive, anxious, comorbid) (p=0.30). Of the 2981 participants that were included at baseline, 2596 (87.1%) were assessed again at follow-up. Persons that did not participate in the follow-up assessments were younger, lower educated and more often had a MDD (Lamers et al., 2011). Of the 2596 participants with baseline and follow-up data, 2253 (86.8%) completed the questionnaire that we needed to compute the dimensional scores for this study. Here, non-response was associated with older age (t=-1.98; df=2594; p=0.05), less years of education (t=4.93; df=2594; p<0.001) and the presence of baseline psychopathology (χ^2=15.0; df=3; p=0.002). Because we wanted to investigate the added value of dimensions to predict the course of disease in participants with an established DSM-IV diagnosis, we only selected the participants with a diagnosis at baseline that were symptomatic in the month prior to baseline (n=1018; 56.3%). This was confirmed with either the CIDI recency question or the Life Chart Interview (see below). Of these 1018 participants, 992 (97.4%) provided all needed psychopathology-course information and covariates and were included in the presented analyses.

Instruments

Dimensional measures at baseline

All participants completed the short, 30-item Dutch adaptation of the Mood and Anxiety Symptoms Questionnaire: the MASQ-D30 (Wardenaar et al., 2010; original MASQ by Watson et al., 1995a, 1995b). On the MASQ-D30, individuals rate to what extent in the past week they have experienced “feelings, sensations, problems and experiences that people sometimes have” on a 5-point scale, with 1 being “not at all” and 5 being “extremely”. The MASQ-D30 consists of three 10-item subscales that cover the tripartite model dimensions: ‘general distress’, ‘anhedonic depression’ and ‘anxious arousal’. The

items that are included in each scale are listed in Table 8.1. The anhedonic depression scale consists wholly of negatively keyed items that assess the presence of positive affect, which are rescored before computation of the anhedonic depression scale score. The MASQ-D30 scales were found to have adequate internal consistency (Cronbach's alpha ranged from 0.87-0.93), construct validity and convergent validity (Wardenaar et al., 2010).

Measurement of the course of depression and anxiety

The course of psychopathology was assessed in two ways. At baseline and at follow-up the presence of DSM-IV depressive disorders (MDD, Dysthymia) and/or a selection of anxiety disorders (Panic disorder, Social Phobia, GAD, and Agoraphobia) were established using the DSM-IV based Composite Interview Diagnostic Instrument (CIDI, WHO version 2.1). The organic exclusion rules were used and hierarchy-free diagnoses were determined.

If participants met the criteria of MDD or an anxiety diagnosis on the CIDI, the Life Chart Interview (LCI) was also administered. With the LCI, using a calendar method, life events were recalled to refresh memory and the presence of depressive or anxiety symptoms were separately determined for each month during the follow-up period (Lyketsos et al., 1994). For each month with symptoms, participants rated the severity of the symptoms on a scale ranging from no/minimal severity, mild, moderate, severe to very severe severity. The LCI data collected at baseline were used to check whether participants were symptomatic in the month prior to baseline and to calculate the amount of time with symptoms prior to baseline (for use as a covariate). The data collected at follow-up were used to calculate indicators of the course of the participants' disorders during the follow-up period. In determining course indicators, symptomatology on the LCI was only considered to be present if a participant reported at least mild severity. Remission was considered present if at least 3 months without symptoms were reported.

Several course indicators were created based on the CIDI and/or the LCI. The 1-month diagnosis at follow-up was defined with the CIDI. A categorical variable was created with the categories: (1) being healthy at follow-up, (2) MDD or dysthymia at follow-up, (3) anxiety disorder at follow-up and (4) comorbid MDD and anxiety disorder at follow-up. For analyses with each of the specific anxiety disorders, dichotomous variables were created for social phobia, panic disorder (with and without agoraphobia), agoraphobia (without panic) and GAD (disorder present at follow-up vs. no disorder at follow-up). The course trajectory (for all disorders combined) was divided into three categories: (1) early sustained remission (<6 months after baseline), (2) late remission (>6 months after baseline) or recurrence following remission, and (3) chronic course (no remission and enduring presence of symptoms with at least mild severity).

Covariates

Several previously described prognostic variables (Penninx et al., 2011) were selected as covariates in the analyses. Sociodemographic covariates were age, gender and mean years of education. Clinical characteristics at baseline that were used as additional covariates: (1) The percentage of time the patient spent with depressive and/or anxiety symptoms in the four years prior to baseline, derived from the LCI. (2) The age at onset of the index disorder was assessed in the CIDI interview (the earliest age for comorbid cases). (3) Antidepressant-use during the month before baseline (yes/no) was assessed during the interview.

Statistical analyses

To evaluate the interrelatedness between the tripartite dimensions, we calculated Pearson correlation coefficients. We used multinomial regression analysis to investigate the associations between the dimensions at baseline (independent variables) and the categorical (dependent) variable: diagnosis at follow-up (categories: no diagnosis [reference], MDD, anxiety disorder, and comorbid MDD-anxiety disorder). We used logistic regression analyses to investigate specific associations between the dimensions (independent variables) and different anxiety disorders at follow-up (dichotomous). We used multinomial regression analysis to investigate the associations between the dimensions at baseline (independent variables) and the categorical (dependent) variable: course trajectory (categories: early-sustained remission [reference], late remission/remission with recurrence, and chronic course). The three dimensions were entered simultaneously in each analysis to investigate their independent effects. Each regression model was run three times: crude and twice with covariates. In *model 1*, DSM-IV dummy-variables were added for single MDD, single anxiety disorder and comorbid MDD and anxiety disorders. In *model 2*, demographic and disease characteristics were added. These models were intended to evaluate if the dimensions predicted the course of psychopathology independently from diagnosis and demographics. Two sided p-values of less than 0.05 were considered to indicate statistical significance. All analyses were done with SPSS 17 for Windows.

8.3 Results

Baseline characteristics

The characteristics of the study-group (n=992) are shown in Table 8.2. Of the sample, 66.2% was female and the mean age was 42.5 (s.d.=12.3). Of the participants 227 (22.9%) had a single MDD, 400 (40.3%) only had an anxiety disorder, and 365 (36.8%) had a comorbid MDD and anxiety disorder. Mean age at onset was 20.9 (s.d.=12.5) and the mean percentage of months with at least mild symptoms during the 4 years prior to baseline was 31.6 (s.d.=20.1). Three hundred eighty four participants (38.7%) used antidepressants at baseline.

The correlations between the tripartite dimensions were weak to moderate. In line with their specific roles in the tripartite model, anhedonic depression and anxious arousal were only weakly correlated (Pearson r=0.31; p<0.001). General distress was correlated moderately with both anhedonic depression (r=0.58; p<0.001) and anxious arousal (r=0.48; p<0.001), in line with its common role in the model.

Diagnoses at follow-up

At follow-up, 118 participants (11.9%) had a MDD, 224 (22.6%) had an anxiety disorder, 178 (17.9%) had a comorbid MDD and anxiety disorder and 472 (47.6%) had no disorder. The results of the analyses are shown in Table 8.3. When adjusted for the other dimensions, diagnosis and other covariates, only increased baseline anhedonic depression was independently associated with increased risk of a depressive disorder at follow-up (OR=1.24), which indicated that this dimension provided independent prognostic information on top of other predictive factors.

Both increased general distress and increased anxious arousal were associated with an increased risk of comorbid depression and anxiety at follow-up, even when adjusted for baseline diagnosis and other covariates (respectively OR=1.25 and OR=1.38). Anhedonic depression also showed an association with comorbidity at follow-up (OR=1.18), but after adjustment for covariates (model 2) this was only borderline significant (OR=1.14). This indicated that dimensions provided prognostic information on top of other predictive factors.

Only increased baseline anxious arousal was independently associated with increased risk of an anxiety disorder at follow-up, when adjusted for baseline diagnosis and other covariates (OR=1.31). We conducted additional analyses with the separate anxiety disorders at follow-up. Of the participants, 63 had only social phobia, 46 had only a panic disorder, 33 had agoraphobia and 15 had GAD. Seventy participants had more than 1 anxiety diagnosis: 5 participants had panic disorder and GAD, 18 had panic disorder and social phobia, 3 had GAD and agoraphobia, 8 had GAD and social phobia and 12 had social phobia and agoraphobia. Nine participants had 3 anxiety diagnoses. The analyses with the separate anxiety disorders showed that baseline anxious arousal was associated with the risk of a panic disorder at follow-up (OR=1.56 [95% CI: 1.18-2.05]). Even when specifically adjusted for the presence of a panic disorder at baseline, this association remained significant (OR=1.47 [95% CI: 1.16-1.87]). For social phobia, agoraphobia and GAD, the associations were not statistically significant when participants with (comorbid) panic disorder were excluded (n=842; OR=1.03 to 1.33). Using the same sample without panic disorder at follow-up (n=842), we also found that the association of anxious arousal with anxiety disorders at follow-up (OR=1.12 [95% CI: 0.93-1.36]) and with comorbid depressive and anxiety disorders (OR=1.13 [95% CI: 0.92-1.39]) were both no longer significant. This indicated that the initially observed associations between anxious arousal and anxiety or comorbidity at follow-up in the complete sample were driven by the participants who turned out with a (comorbid) panic disorder at follow-up. This confirmed

that anxious arousal is a specific prognostic factor for both single and comorbid panic disorder. Together, these results indicate that anxious arousal added prognostic information about the risk of future anxiety/panic disorder, on top of DSM-IV diagnosis at baseline and other covariates.

Course trajectories during follow-up

During follow-up, 252 participants (25.4%) went into early-sustained remission, 324 participants (32.7%) went into late remission or into remission followed by recurrence, and 416 participants (41.9%) had a chronic course. The results of the analyses are shown in Table 8.4. Only increased general distress was associated with an increased risk of late/temporary remission (OR=1.20) and chronic course (OR=1.21) and these associations remained significant when adjusted for diagnosis and other prognostic factors at baseline. This indicated that general distress provided independent prognostic information on top of other known prognostic factors.

8.4 Discussion

The present study evaluated whether two dimensions derived from the widely used IDS-SR had added value as predictors of the course and outcome of depressive and/or anxiety disorders. The results showed that increased severity on the 'mood/cognition' dimension at baseline predicted increased risk of single depression at follow-up, and that increased severity on the 'anxiety/arousal' dimension at baseline predicted increased risk of single anxiety (mainly panic disorder) at follow-up. Increases on both dimensions predicted increased risk of comorbid depression and anxiety at 2-year follow-up. The IDS-SR total scale-score was associated with all three diagnoses at follow-up, indicating a less specific prognostic ability than its two separate subdimensions. Increased mood/cognition predicted a higher probability of unfavourable course-trajectories of depressive symptomatology. Increased anxiety/arousal predicted a higher probability of unfavourable course-trajectories of depressive symptomatology. Increases on the IDS-SR total scale score also predicted an increased probability of worse course-trajectories for depressive symptomatology and anxious symptomatology. However, both for depressive- and anxious symptomatology the predictive effects of the IDS-SR total scale were similar to that of mood/cognition or anxiety/arousal.

Mood/cognition predicted the risk of single depression (with or without comorbid anxiety) after 2 years and also predicted the risk of an unfavourable course of depressive symptomatology, independently of anxiety/arousal and all other included prognostic factors. These results showed the particular prognostic importance of the mood/cognition-domain for depression, in line with previous work (e.g. Lux & Kendler, 2010). Anxiety-arousal was shown to mainly have added value as a predictor of panic disorder at follow-up. GAD and Social Phobia were predicted by anxiety/arousal, but also by mood/cognition. This observation was in line with previous work, which has shown that anxiety disorders are heterogeneous and determined by multiple dimensions (e.g.

Mineka et al., 1998). The predictive role of mood/cognition in GAD and Social Phobia was in line with the oft-observed overlap between GAD/Social Phobia and depressive disorders (e.g. van Ameringen et al., 1991). In addition, anxiety/arousal predicted course trajectories of anxious symptomatology. Here also, mood/cognition had a predictive effect. This was likely due to the same reasons as discussed above.

Table 8.1: Baseline characteristics of the study group

Baseline variable	Study Group
N	1053
% female	692 (65.7%)
Mean years of age (SD)	42.2 (12.1)
Age range	18-65
Level of education (years), mean (SD)	11.8 (3.3)
IDS-SR Subdimensions: mean (SD)	
Mood/Cognition, *mean (SD)*	9.3 (3.7)
Mood/Cognition, *range*	0-21
Anxiety/Arousal, *mean (SD)*	6.4 (2.2)
Anxiety/Arousal, range	0-16
Psychiatric Characteristics	
Only depressive disorder: n (%)	243 (23.1%)
Only anxiety disorder: n (%)	396 (37.6%)
Panic Disorder	367 (34.9)
Social Anxiety	405 (38.5%)
Generalized Anxiety Disorder	276 (26.2%)
Agoraphobia (without panic)	103 (9.8%)
Comorbid depression and anxiety: n (%)	414 (39.3%)
Antidepressant use at baseline: n (%)	379 (36.0%)
Months with symptoms in past 4 years, mean % (SD)	32.0 (20.0)
Age of onset of index episode: mean (SD)	37.2 (11.9)
Care setting n (%)	
Primary care	456 (43.3%)
Specialized mental health care	510 (48.4%)
General population	87 (8.3%)

SD=standard deviation; MASQ-D30= Mood and Anxiety Symptoms Questionnaire Dutch short adaptation; IDS-SR=Inventory of Depressive Symptomatology Self Report; BAI=Beck anxiety inventory;

We compared the standardized predictive effects of the two dimensions with the effects of the IDS-SR total score. The prediction of diagnoses after two years became more specific if the IDS-SR was broken up into mood/cognition and anxiety/arousal. Also,

mood/cognition dimension was an equally effective predictor of the course of depressive symptomatology as the IDS-SR total scale and the anxiety/arousal dimension was an equally effective predictor of the course of anxious symptomatology as the IDS-SR total scale. These observations indicate that mood-cognition would be a more efficient and cost-effective choice than the IDS-SR total scale when the aim is to specifically predict the course of depression. In addition, the IDS-SR was shown not only to predict depression; the IDS-SR anxiety/arousal dimension even specifically predicted future panic disorder and the course of anxiety symptomatology. The IDS-SR dimensions can thus be used to increase specificity when using the IDS-SR to formulate prognoses of depression and/or anxiety.

The predictive associations of the dimensions persisted after multivariable adjustment. This indicates that within a group of individuals with similar DSM-IV diagnoses, the dimensions provide unique prognostic information. This is in line with previous work by our group, where we showed the added value of the dimensions of the tripartite model (Clark & Watson et al., 1991; General Distress, Anhedonic Depression and Anxious Arousal) in predicting the course and outcome of depression and anxiety (Wardenaar et al., 2011).

Table 8.2: Symptom dimensions as predictors of DSM-IV diagnosis at 2 year follow-up in 1053 subjects with a depressive and/or anxiety disorder at baseline.

			Current (6-month) diagnosis at 2-year follow-up		
	model	healthy at follow-up (n=484)	Depression (n=124)	Anxiety (n=237)	Depression and anxiety (n=208)
		Reference	OR (95% CI)	OR (95% CI)	OR (95% CI)
IDS-SR Total	Crude	-	1.95 (1.52-2.51)***	1.58 (1.29-1.92)***	3.09 (2.47-3.85)***
	1	-	1.58 (1.19-2.10)**	1.89 (1.50-1.39)***	2.86 (2.22-3.67)***
	2	-	1.57 (1.18-2.10)**	1.81 (1.43-2.30)***	2.73 (2.11-3.52)***
IDS-SR M/C	crude	-	2.11 (1.54-2.89)***	1.05 (0.83-1.35)	2.12 (1.61-2.80)***
	1	-	1.70 (1.21-2.38)**	1.27 (0.97-1.67)	2.00 (1.49-2.68)***
	2	-	1.80 (1.28-2.54)**	1.25 (0.95-1.64)	2.00 (1.48-2.69)***
IDS-SR A/A	crude	-	0.98 (0.71-1.35)	1.69 (1.31-2.19)***	1.79 (1.36-2.35)***
	1	-	0.97 (0.70-1.34)	1.61 (1.22-2.11)**	1.63 (1.23-2.15)**
	2	-	0.92 (0.66-1.27)	1.57 (1.19-2.07)**	1.55 (1.16-2.06)**

Results of multinomial regression analyses: OR (Odds Ratio's) are given for 1 SD increments on each dimension. IDS-SR= Inventory of Depressive Symptomatology Self Report; M/C=Mood/Cognition; A/A=Anxiety/Arousal. Crude: dimensions adjusted for each other; Model 1: adjusted for DSM-IV diagnosis; Model 2: additionally adjusted for age, duration of disorder at baseline, age of onset of the disorder at baseline.
*) p<0.05; **) p<0.01; ***) p<0.001

In addition, our findings confirmed the hypothesis of Lux and Kendler (2010) that different symptom-domains of within the same diagnosis are related to different clinical variables.

The current study had several strengths, including large sample size, thorough assessment of course and diagnoses and consideration of several covariates. However, some limitations should also be considered. The study included prevalent DSM-IV outpatients, and the results are not directly generalizable to incident cases and inpatients with more severe disorders. Also, the follow-up period was only 2-years; predictions about the course and outcome beyond this duration could not be evaluated.

In conclusion, the current results showed that the IDS-SR dimensions had clear added prognostic value. They increased the specificity of prognoses and are easy to apply, which makes them very useful for clinical and research applications. These results can also be seen as an encouragement to decrease the heterogeneity of diagnostic instruments and to include more specific dimensional aspects in future diagnostic classifications.

Table 8.3: Associations between specific symptom dimensions and course-trajectories of depressive symptomatology during follow-up

		No symptoms or early sustained remission	Late remission or recurrence after remission	Chronic Course
		(n=434)	(n=335)	(n=284)
N=1053	model	Reference	OR (95% CI)	OR (95% CI)
IDS-SR	crude	-	2.29 (1.88-2.80)***	3.81 (3.08-4.80)***
Total	1	-	2.05 (1.66-2.54)***	2.47 (1.94-3.15)***
	2	-	2.03 (1.63-2.52)***	2.39 (1.87-3.05)***
IDS-SR	crude	-	2.32 (1.83-2.95)***	2.92 (2.24-3.81)***
Mood/	1	-	2.07 (1.61-2.66)***	1.93 (1.45-2.56)***
Cognition	2	-	2.08 (1.61-2.68)***	1.94 (1.45-2.58)***
IDS-SR	crude	-	1.06 (0.82-1.33)	1.51 (1.16-1.93)**
Anxiety/	1	-	1.07 (0.84-1.36)	1.36 (1.04-1.79)*
Arousal	2	-	1.05 (0.82-1.34)	1.30 (0.98-1.71)

Results of multinomial regression analyses with standardized scales (z-values): OR (Odds Ratio's) are given for 1 SD increments on each dimension. IDS-SR=Inventory of Depressive Symptomatology Self Report. Crude: dimensions adjusted for each other; Model 1: adjusted for presence of a single depressive disorder, single anxiety disorder or comorbid depressive and anxiety disorders at baseline; Model 2: additionally adjusted for age, duration of disorder at baseline, age of onset of the disorder at baseline.

*) $p<0.05$; **) $p<0.01$; ***) $p<0.001$

Table 8.4: Associations between specific symptom dimensions and course-trajectories of anxiety symptomatology during follow-up

		No symptoms or early sustained remission	Late remission or recurrence after remission	Chronic Course
		(n=411)	(n=221)	(n=421)
N=1053	model	Reference	OR (95% CI)	OR (95% CI)
IDS-SR Total score	crude	-	1.23 (1.00-1.50)*	1.70 (1.43-2.01)***
	1	-	1.53 (1.20-1.95)**	1.96 (1.59-2.42)***
	2	-	1.49 (1.17-1.90)**	1.84 (1.48-2.28)***
IDS-SR Mood/ Cognition	crude	-	0.94 (0.73-1.20)	1.18 (0.95-1.46)
	1	-	1.23 (0.93-1.63)	1.44 (1.12-1.83)**
	2	-	1.20 (0.90-1.59)	1.38 (1.07-1.77)*
IDS-SR Anxiety/ Arousal	crude	-	1.50 (1.15-1.95)**	1.66 (1.32-2.08)***
	1	-	1.38 (1.04-1.83)*	1.44 (1.12-1.83)**
	2	-	1.38 (1.03-1.84)*	1.42 (1.11-1.83)*

Results of multinomial regression analyses with standardized scales (z-values): OR (Odds Ratio's) are given for 1 SD increments on each dimension. IDS-SR= Inventory of Depressive Symptomatology Self Report. Crude: dimensions adjusted for each other; Model 1: adjusted for presence of a single depressive disorder, single anxiety disorder or comorbid depressive and anxiety disorders at baseline; Model 2: additionally adjusted for age, duration of disorder at baseline, age of onset of the disorder at baseline.

*) p<0.05; **) p<0.01; ***) p<0.001

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.

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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.

Samenvatting

Depressieve- en angststoornissen komen veel voor in de algemene bevolking en veroorzaken veel invaliditeit en medische kosten. De stoornissen hebben vaak een chronisch beloop met afwisselende periodes van remissie en recidive. Depressie en angst zijn vaak langdurig en moeilijk te behandelen, wat hun ziektelast en invloed op het leven vergroot. Helaas is er slechts beperkte kennis over de etiologische mechanismen die aan het ontstaan en beloop van depressie en angst ten grondslag liggen. Bovendien berust de behandeling, ondanks het bestaan van richtlijnen, vaak op 'trial-and-error', want goed gedefinieerde één-op-één behandelindicaties zijn er niet.

Er is veel onderzoek gedaan naar de oorzakelijke mechanismen van depressie en angst. In het afgelopen decennium is dat onderzoek zich steeds meer gaan richten op biologische mechanismen, zoals bijvoorbeeld het stress-systeem, genetica en beeldvormende technieken, zoals MRI. Daarnaast is er ook gekeken naar de rol van omgevings factoren, zoals bijvoorbeeld jeugdtrauma's en ingrijpende levensgebeurtenissen. Ook zijn psychologische mechanismen, zoals coping-mechanismen en het ervaren van sociale steun, uitgebreid onderzocht. Meer recentelijk is er in onderzoek ook meer gekeken naar de interacties tussen deze verschillende factoren. Zo interacteren omgevings- en genetische factoren in het ontstaan van psychopathologie. Ondanks deze veelheid aan wetenschappelijk werk, zijn er maar weinig resultaten repliceerbaar gebleken. Daarnaast zijn de gevonden effecten statistisch gezien erg klein. Bij elkaar beschouwd is er dus maar beperkt vooruitgang geboekt in het doorgronden van de oorzaken van depressie en angst.

Er zijn verschillende aanwijsbare redenen voor het gebrek aan wetenschappelijke vooruitgang. Het zou door een systematisch gebrek aan statistische power kunnen komen en als gevolg van te kleine onderzoeksgroepen. Ook zou men naar de verkeerde mechanismen gekeken kunnen hebben. Wat echter ook steeds duidelijker is geworden, is dat de aard van de momenteel gebruikte Diagnostic and Statistical Manual (DSM) diagnoses leidt tot problemen die het doen van goed wetenschappelijk onderzoek bemoeilijken. Het **eerste probleem** is dat DSM-diagnoses veel samen voorkomen: er is dus sprake van overvloedige comorbiditeit. Depressieve- en angststoornissen komen bijvoorbeeld veel vaker samen voor dan je zou verwachten op basis van hun strikte scheiding in de DSM. In de realiteit tonen depressie en angst inderdaad grote overlap in hun symptomatologie en het is waarschijnlijk dat ze, gelet op hun frequente samen voorkomen, een aanzienlijk deel van hun etiologie delen. Dit wordt verder ondersteund door de vergelijkbare behandel-indicaties voor depressie en angst (meestal selectieve serotonine heropname remmers en/of cognitieve therapie). Veel onderzoek kijkt echter alleen naar depressie of angst en mist daardoor dus de belangrijke gedeelde mechanismen van de twee stoornissen. Door meer rekening te houden met overlap tussen depressie en angst, zou een veel completer beeld kunnen worden verkregen van de etiologie van affectieve stoornissen als geheel. Een **tweede probleem** met DSM-diagnoses, is hun grote *binnen-diagnose heterogeniteit*: geen twee patienten met

dezelfde diagnose zijn hetzelfde. Dit heeft belangrijke implicaties voor onderzoek en de klinische praktijk. Etiologisch onderzoek wordt belemmerd door diagnostische heterogeniteit, want de variatie binnen een diagnosegroep kan de verschillen tussen patient- en controlegroep overschaduwen. Met andere woorden: de statistische power om kleine verschillen tussen groepen te vinden is klein. Daarnaast suggereren de grote verschillen in symptomatologie tussen patienten met dezelfde diagnose dat verschillende mechanismen er een rol spelen. Om deze symptoom-specifieke effecten te kunnen vangen in onderzoek moet de specificiteit van de klinische beschrijving worden verhoogd. Naast de problemen voor onderzoek, leidt binnen-diagnose heterogeniteit ook tot aspecifieke behandel-indicaties. Omdat patienten zo sterk van elkaar kunnen verschillen, moeten hulpverleners vaak vertrouwen op hun klinische ervaring en 'trial-and-error'. Het **derde probleem** van de DSM-diagnoses is de veronderstelde discontinuïteit tussen ziekte en gezondheid. In werkelijkheid volgen symptomen van depressie en angst een continue verdeling in de algemene populatie zonder een duidelijk afkappunt tussen gezond en ziek. Het plaatsen van een afkappunt op deze continue verdeling in de vorm van een dichotome diagnose, heeft als gevolg dat de statistische power om (bijvoorbeeld etiologische) effecten te detecteren sterk wordt gereduceerd. Daarnaast is er een grote groep van subklinische patiënten, die niet voldoen aan de DSM-criteria, maar wel zeer relevante psychische problemen hebben. In het huidige DSM-systeem hebben deze mensen geen formele status. Bovendien, worden zij vaak van deelname aan onderzoek uitgesloten of in de gezonde controlegroep geplaatst, waardoor de verschillen tussen patiënten en gezonde controlepersonen weer verder verwateren.

Er zijn verschillende voorstellen gedaan om de hierboven genoemde problemen in nieuwe versies van de DSM op te lossen. Er zijn bijvoorbeeld subtypen van depressie voorgesteld om de diagnostische heterogeniteit te verminderen. Ook is er een nieuwe diagnose voor 'gemengde depressie-angst' voorgesteld om recht te doen aan de overlap en comorbiditeit tussen de twee stoornissen. Ten slotte zijn er ook sub-klinische categorieën voorgesteld om de mensen te kunnen vatten die niet voldoen aan de volledige diagnose-criteria. Echter, deze maatregelen doen niets aan de meer elementaire problemen van de DSM, maar pakken alleen specifieke problemen aan. Om de bovengenoemde problemen echt te overwinnen, zou de DSM op een meer elementair niveau moeten worden veranderd. Een alternatief is een *dimensionele benadering*, waarmee meer individuele symptoom-patronen kunnen worden beschreven. Dimensies hebben twee belangrijke kenmerken. Ten eerste zijn ze continu zonder vast afkappunt tussen gezond en ziek. Ten tweede, dekken zij specifieke symptoom-domeinen. Een dimensionele benadering gaat ervan uit dat er meerdere dimensies naast elkaar bestaan en dat iemands klinische toestand kan worden beschreven door het patroon van scores op deze dimensies. Op deze manier gebruikt, kunnen dimensies de problemen van comorbiditeit, heterogeniteit en discontinuiteit oplossen of omzeilen.

Een bekend en eenvoudig dimensioneel model van de symptomen van depressie en angst is het *tripartite model,* ontwikkeld door Clark & Watson in 1991. Dit model is

ontwikkeld om de gemeenschappelijke en specifieke symptoom-domeinen van depressie en angst te beschrijven met drie dimensies. Een algemene dimensie *General Distress (GD)* bestaat uit symptomen van negatief affect en algemeen psychologisch onwelbevinden, die vaak voorkomen bij zowel depressie als angst en verantwoordelijk zijn voor hun overlap en comorbiditeit. Daarnaast zijn er twee specifieke dimensies waarop patiënten meer van elkaar kunnen worden onderscheiden. De dimensie *Anhedonic Depression (AD)* bestaat uit symptomen van gebrek aan positief affect en energie, die specifiek zijn voor depressie. De dimensie *Anxious Arousal (AA)* bestaat uit symptomen van somatische opwinding en/of geprikkeldheid, die specifiek is voor angst (en met name paniek). Door veel studies is aangetoond dat drie-dimensionele structuur van het tripartite model inderdaad een goed, zij het vereenvoudigd, model voor de symptomatologie van depressie en angst vormt. Het tripartite model werd gevolgd door een reeks modellen die erop voortbouwden (bijv. het hiërarchische model). Deze modellen zijn met succes gebruikt om de eigenlijke onderliggende structuur van de DSM-stoornissen te beschrijven en de gemeenschappelijke basis van depressie en angst bloot te leggen. Zo is in veel onderzoek aangetoond dat het tripartite model en haar opvolgers intern valide zijn en dat ze potentiële aanknopingspunten bieden voor het oplossen van de problemen van de DSM.

Eén van de duidelijkste problemen van de huidige DSM-diagnoses is het ontbreken van overeenstemming tussen de diagnoses en onderliggende etiologische mechanismen en tussen de diagnoses en klinische implicaties; met andere woorden: de diagnoses zijn niet extern valide. Als van dimensies werd aangetoond dat ze wel consistent geassocieerd zijn met etiologische mechanismen en klinische kenmerken, dan zou dat erop wijzen dat zij wel *extern valide* zijn en een betere reflectie vormen van de dynamische manier waarop symptomen in de werkelijkheid voorkomen. Hoewel er veel ondersteuning is voor de interne validiteit van de dimensionale benaderingen, is de externe validiteit van dimensies niet grondig onderzocht. Om dimensies als serieus alternatief voor categoriële DSM-diagnoses te kunnen presenteren, moet eerst worden aangetoond dat ze zowel intern als extern valide zijn en dat ze hierin superieur zijn aan DSM-diagnoses. Dit is zeker van belang gezien de terughoudendheid die veel hulpverleners nog steeds voelen jegens het gebruik van dimensies in de praktijk.

Daarom was het doel van dit proefschrift om de interne en externe validiteit van een dimensionale benadering van depressie en angst grondig te evalueren. Er werden hiervoor verschillende benaderingen genomen: de optimale meting van de dimensies werd onderzocht (hoofdstukken 2 en 3), de associaties tussen dimensies en etiologische factoren werden onderzocht (hoofdstukken 4-6) en de associaties tussen dimensies en het klinisch beloop van depressie en/of angst werden onderzocht (hoofdstukken 7 en 8) .

De eerste twee hoofdstukken gingen over het optimaliseren van de meting van dimensies. In **hoofdstuk 2**, werd de ontwikkeling en validatie beschreven van een instrument om de dimensies van het tripartite model te meten: de verkorte Nederlandse versie van de 'Mood and Anxiety Symptoms Questionnaire (MASQ-D30)'. Het werd

aangetoond dat de schalen een goede interne consistentie hadden in zowel gezonde als zieke groepen deelnemers. Ook bleken de construct validiteit en de convergente validiteit van de schalen adequaat. Omdat de MASQ-D30 een goed instrument bleek te zijn, werd deze in meerdere hoofdstukken van dit proefschrift gebruikt om de tripartite dimensies te meten. Voor **hoofdstuk 3**, werd een andere insteek gekozen om dimensionele meetinstrumenten te ontwikkelen en te valideren op basis van de items van de reeds veel gebruikte 'Inventory of Depressive Symptomatology (IDS)'. Eerst werd de best passende factor-structuur van de IDS geïdentificeerd met confirmatieve factor analyses. Deze analyses lieten zien dat een 3-factor-structuur het beste op de data paste. Van deze 3 factoren, werd met item-response (Rasch) analyses vastgesteld dat er twee geschikt waren voor gebruik als één-dimensionele subschalen: een 'mood/cognition' schaal en een 'anxiety/arousal' schaal. Het belangrijke van deze resultaten is dat ze aantoonden dat specifieke dimensies niet uitsluitend kunnen worden gemeten met gespecialiseerde instrumenten, maar ook met een bestaand en veel gebruikt instrument als de IDS.

In de volgende drie hoofdstukken werden de associaties tussen de dimensies en biologische en omgevingsfactoren onderzocht. In **hoofdstuk 4,** werd de associatie tussen de tripartite dimensies en de activiteit van de hypothalamus-hypofyse-bijnier (HPA)-as onderzocht. De HPA-as-activiteit werd gemeten met een reeks van speekselmonsters, genomen over de dag (bij het ontwaken en na 30, 45 en 60 minuten, om 22.00 uur en om 23.00 uur) en de volgende ochtend na het ontwaken volgend op dexamethason-inname de avond ervoor. Met deze gegevens konden de 'cortisol awakening rise (CAR)' curve, het 'basale cortisol niveau' en 'dexamethason suppressie' worden onderzocht. De resultaten lieten zien dat de tripartite dimensies alleen waren geassocieerd met de CAR en dat deze associatie de vorm had van een omgekeerde U. Deze associaties bleven staan na correctie voor demografische, psychiatrische (waaronder DSM-diagnoses) en sampling-factoren. De resultaten lieten zien dat de CAR aanvankelijk steeg met toenemende ernst op de dimensies, maar vanaf een bepaald punt weer begon te dalen, wat wijst op een 'negatief terugkoppelingssysteem'. Deze bevindingen kunnen verklaren waarom in eerder onderzoek zowel verhoogde en verlaagde HPA-as activiteit werd waargenomen bij depressieve patiënten, afhankelijk van de ernst van de klachten in de gebruikte onderzoeksgroepen. Bovendien toonden de resultaten ook de non-lineaire en complexe associatie tussen de HPA-as en psychopathologie. In **hoofdstuk 5** werden de associaties tussen de tripartite dimensies en het metabool syndroom en de onderdelen ervan onderzocht. Er lijkt sprake te zijn van een tweezijdige link tussen depressie en het metabool syndroom. De huidige studie was bedoeld om te zien welke symptoom-specifieke associaties aan deze deze globale associatie ten grondslag liggen. Het metabool syndroom (verhoogde taille omtrek, verhoogde triglyceriden, verhoogde bloeddruk, verhoogd nuchter bloedglucose, en minder high-density lipoprotein [HDL] cholesterol) was aanwezig bij 20.1% van de deelnemers. Alleen verhogingen op de AA dimensie waren geassocieerd met een verhoogde kans op het metabool syndroom. Daarnaast was AA alleen significant geassocieerd met drie van de vijf afzonderlijke metabool syndroom-

componenten (tailleomtrek, triglyceriden en bloeddruk). Dit wijst erop dat de vaak geobserveerde associatie tussen depressie en het metabool syndroom waarschijnlijk gedreven wordt door AA symptomen en een aantal specifieke metabole componenten. Deze resultaten toonden hoe het verminderen van de heterogeniteit van zowel de onderzochte psychopathologische als de metabolische concepten hielp om de schijnbaar algemene associatie tussen depressie en metabool syndroom uit elkaar te trekken.

Hoofdstuk 6 was gericht op omgevingsfactoren. Al lang wordt vermoed dat levensgebeurtenissen een rol spelen bij het ontstaan en het beloop van depressie en angst. Een longitudinale benadering werd gebruikt om te kijken hoe verschillende levensgebeurtenissen (gedurende de volwassenheid) leiden tot veranderingen in dimensionele scores over tijd. De resultaten toonden aan dat GD steeg in reactie op negatieve levensgebeurtenissen en dat AD daalde in reactie op positieve levensgebeurtenissen. Dezelfde associaties werden gezien in groepen patiënten met verschillend beloopstrajecten (vroege remissie, late remissie/recidive, chronisch beloop). Dit wijst erop dat door verandering binnen personen te modelleren, specifieke effecten van levensgebeurtenissen werden opgemerkt, die niet werden gevat door eenmalige dimensionele metingen en DSM-gedefinieerde beloopstrajecten. Verdere analyses van individuele levensgebeurtenissen liet zien dat sommige een algemeen effect op alle dimensies hadden en dat sommigen een meer dimensie-specifiek effect hadden. Deze resultaten vormden een goede illustratie van de manier waarop dimensies kunnen worden gebruikt om complexe etiologische mechanismen bloot te leggen.

De volgende hoofdstukken gingen over het voorspellen van het beloop van depressie en angst. Twee patiënten met dezelfde DSM-diagnose hebben vaak verschillende prognoses als gevolg van de grote binnen-diagnose heterogeniteit. Dimensies zouden kunnen worden gebruikt om het klinisch beeld van patiënten meer specifiek te beschrijven, en daarmee ook de prognose specifieker te maken. Of dimensies die toegevoegde prognostische waarde daadwerkelijk hebben werd geëvalueerd in hoofdstukken 7 en 8. In **hoofdstuk 7,** werd de toegevoegde waarde onderzocht van de tripartite dimensies voor het voorspellen van het beloop en de uitkomst van depressie en/of angst over een periode van 2 jaar. De dimensionele scores werden bij aanvang gemeten en het beloop over de daarop volgende 2 jaar werd gemeten met gestandaardiseerde diagnostische interviews en een life-chart methode. Op basis hiervan werden twee uitkomstvariabelen gemaakt: (1) de diagnose na twee jaar (gezond, alleen depressie, alleen angst, of comorbide depressie-angst) en (2) het beloops-traject (vroege remissie, late remissie/recidive, of chronisch beloop). De resultaten lieten zien dat AD specifiek een grotere kans op alleen depressie na twee jaar voorspelde. AA voorspelde alleen een hogere kans op angst (vooral paniekstoornis) na twee jaar en GD voorspelde een hogere kans op comorbide depressie-angst na twee jaar. Daarnaast voorspelde alleen GD een grotere kans op minder gunstige beloops-trajecten (late remissie of een chronisch beloop). Deze resultaten bleven overeind na correctie voor de traditioneel gebruikte prognostische factoren, zoals DSM-diagnose. Bij elkaar lieten deze resultaten zien dat

specifieke symptoom dimensies toegevoegde waarde hadden als prognostische factoren bovenop meer traditionele voorspellers, zoals DSM-diagnose. In **hoofdstuk 8** werd een vergelijkbare aanpak gebruikt, maar hier werden de IDS dimensies mood/cognition en anxiety/arousal gebruikt. De resultaten lieten zien dat waar de totale IDS-schaal depressie, angst en comorbide depressie-angst na twee jaar voorspelde, de dimensies meer specifieke associaties lieten zien. Mood/cognition was geassocieerd met een verhoogde kans op depressie na twee jaar en met een minder gunstig beloop van depressieve klachten. Anxiety/arousal was geassocieerd met angst na twee jaar (paniek in het bijzonder) en met een minder gunstig beloop van angstklachten. Beide dimensies voorspelden comorbide depressie en angst na twee jaar. Net als in hoofdstuk 7, bleven alle associaties overeind na correctie voor andere bekende prognostische factoren. Deze resultaten toonden de toegevoegde waarde van het opbreken van een generiek instrument in afzonderlijke dimensies, om meer specifieke prognoses te formuleren.

Samen waren de hoofdstukken van dit proefschrift bedoeld om een dimensionele benadering van depressie en angst te valideren. Hoofdstukken 2 en 3 lieten duidelijk zien dat het mogelijk is om dimensies relatief eenvoudig, maar op valide wijze te meten met geoptimaliseerde instrumenten. Hoofdstukken 4 en 5 lieten zien dat dimensies konden worden gebruikt om complexe (niet-lineaire) biologische associaties bloot te leggen en symptoom-specifieke biologische associaties te detecteren. Uit hoofdstuk 6 bleek dat de dimensies konden worden gebruikt om de generieke en specifieke effecten van levensgebeurtenissen te detecteren. Daarnaast, toonde hoofdstuk 6 de meerwaarde van het modelleren van verandering op dimensies binnen personen. Hoofdstukken 7 en 8 lieten zien dat dimensies kunnen worden gebruikt om het beloop van depressieve en angststoornissen meer specifiek te voorspellen.

Dit onderzoek had een aantal sterke punten (bijv. gevalideerd dimensionele metingen, grote steekproeven en zorgvuldige correctie voor vertekenende factoren). Toch moeten de resultaten ook worden geïnterpreteerd in het licht van een aantal beperkingen, waaronder beperkte generaliseerbaarheid buiten de poliklinische populatie, het gebruik van vereenvoudigde dimensionele modellen en de uitval van deelnemers over tijd.

Als conclusie kan gesteld worden dat resultaten van dit proefschrift de validiteit en toegevoegde waarde van een dimensionele benadering in depressie en angst onderzoek ondersteunen. Dimensies zijn niet alleen intern, maar ook extern valide en kunnen zonder dat het veel tijd en moeite kost worden gemeten.

Curriculum Vitae

On the 20th of February 1983 Klaas Wardenaar was born in Heerhugowaard, the Netherlands. He finished his secondary education at the Stedelijk Gymnasium Arnhem in 2000 and in the same year, he started his study of psychology at the Radboud University Nijmegen. In the process of obtaining his master's degree in neuro- and rehabilitation psychology, Klaas did an internship at the department of psychiatry of the University Medical Centre in Utrecht in 2004. Here, he conducted neuropsychological assessments and psychiatric screenings with schizophrenia patients. In the following year, he did his research internship at the Clinical Neuroscience Lab of the University of California Los Angeles (UCLA) in Los Angeles, California. In 2006, Klaas graduated and worked as a neuropsychologist at GGZ Meerkanten in Ermelo.

From the beginning of 2007 until the end of 2011, Klaas has worked on the research, presented in this dissertation. During this period, he earned a post-doctoral master's degree in epidemiology from the Vrije Universiteit in Amsterdam.

Currently, Klaas works as a postdoctoral researcher at the Interdisciplinary Centre of Psychopathology and Emotion regulation (ICPE) of the department of psychiatry at the University Medical Centre in Groningen. In his research, he focusses on ways to deconstruct heterogeneous psychopathological constructs into more homogeneous entities, in order to increase the specificity of psychiatric diagnostics.

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