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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 subthreshold 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.