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Rhebergen, D.

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Chapter

1

General Introduction

On the 5th of April 1722, Jacob Roggeveen discovered a small island in the South Pacific. He named it Paasch Eyland (Easter Island), because it was discovered on Easter Day. Today the island is known as Rapa Nui. In the ship's log Roggeveen reported on menlike sculptures, the Moai, overlooking the land. The cover of this thesis shows some beautiful examples of these Moai. Since their discovery, several scientific expeditions have tried to unravel the mysteries of the Moai's (Bahn and Flenley, 1992). It was shown, that most statues are buried in greater or lesser degree. What appears on the outside as a complete sculpture, turns out to be only part of the full image after thorough inspection. Furthermore, most Moai are positioned in a row. In the archeological world this fuelled debate on whether the Moai should be regarded as individual statues or as a collectivity. Their collective name *aringa ora* (living faces) may be an indication that they are generalized rather than individualized portraits (Bahn and Flenley, 1992). However, to date, many mysteries remain unsolved. Or as Father Sebastian Englert (1888-1969), a missionary priest on Rapa Nui, stated: "When the subject is enigmatic Easter Island no man's knowledge is either complete or secure" (Bahn and Flenley, 1992).

Depressive disorders

Like knowledge on the origin and meaning of the Moai, knowledge on depressive disorders is continuously evolving, with many issues unsettled yet and sometimes resulting in fierce scientific debates: Should depressive disorders be regarded as one broad spectrum disorder, in which symptomatology waxes and wanes (Judd and Akiskal, 2000), or should they be divided into categories such as Major Depressive Disorder (MDD), Dysthymic Disorder, Minor Depression, Subthreshold Depression and Mixed Anxiety and Depression Disorder.

At present, the Diagnostic and Statistical Manual (DSM)-IV-TR (APA, 2000), the world's leading diagnostic classification system of mental disorders, classifies depression into i) Major Depressive Disorder (MDD), characterized by the presence of a depressed mood or loss of interest that persists for at least two weeks, ii) Dysthymic Disorder, characterized by a depressed mood, less severe than MDD, but with a duration of at least two years, and iii) Depressive Disorder- not otherwise specified, a residual category for persons with depressive symptomatology, not fulfilling the criteria of MDD, Dysthymic Disorder or any adjustment disorder. MDD is further characterized along specifiers, such as severity (e.g. remission, mild, moderate, severe), course characteristics (e.g. single episode, recurrent, chronic) and the presence of psychotic, catatonic, melancholic or atypical features. Dysthymic Disorder can be further specified as early versus late onset and according to the presence of atypical features. New concepts that are listed as proposed categories for DSM-V, scheduled to be released in May 2013, include Prodromal Depression, Subsyndromal Depression and Mixed Subsyndromal Anxiety-Depressive Disorder (see also <http://www.dsm5.org/ProposedRevisions>).

Part I. Depressive categories: carving nature at its joints?

The current classification of depressive disorders has been topic of debate. In particular, the concept of Dysthymic Disorder that was introduced into the DSM in 1980 is heavily criticized. Robert Spitzer, who was at the cradle of Dysthymia, now reckons it is “the least homogeneous disorder of all” (personal communication-2006). Demarcation from other mood disorders, such as (chronic) Major Depressive Disorder, on a range of demographic, clinical, psychosocial, family history and treatment response variables (McCullough et al., 2000, 2003; Klein et al., 2004) has been proven difficult and comorbidity rates between Dysthymic Disorder and Major Depressive Disorder are as high as 90% (Klein et al., 2000), questioning its discriminant validity. It was argued that Dysthymia is a highly heterogeneous group, and that it does not constitute for a clearly defined disease entity (Serretti et al., 1999). Judd and Akiskal (2000) suggested that Dysthymic Disorder is just an integral component of the longitudinal structure of MDD, with each symptom level representing a different phase of illness intensity, activity and severity. On the other hand, there is evidence to support the existence of Chronic Depression as a specific diagnostic subtype within the larger group of affective disorders (McCullough et al., 2000, 2003). The latter findings have resulted in the proposal for DSM-V to merge the concept of Dysthymic Disorder and Chronic Depression into one broad category ‘Chronic Depression’, hence marking a clear distinction between chronic and non-chronic depressions (see also <http://www.dsm5.org/ProposedRevisions>).

Since Thomas Sydenham (1624-1689), an English physician who is widely recognized as the founder of clinical medicine and epidemiology, the importance of longitudinal observation to validate clinical entities is widely known. Sydenham studied fevers by detailed longitudinal observations, which enabled him to distinguish measles and scarlet fever. Likewise, Emile Kraepelin reckoned the importance of course for classifying mental disorders: when naturalistic course differs across disorders, their distinction could be useful in clinical practice and psychiatric nosology (Kraepelin, 1899). However, longitudinal studies on Dysthymic Disorder, with sufficient numbers of respondents, are sparse. In addition outpatient studies far outnumber general population studies, thus limiting generalizability into the general population (for an overview: see Hölzel et al., 2010). Finally, most studies merge Dysthymia and Double Depression (defined as Dysthymic Disorder with a superimposed episode of MDD (Keller and Shapiro, 1982)) into one broad category of chronic depression (e.g. Riso et al., 2003; McCullough et al., 2000, 2003), hence limiting insight into pure Dysthymia. The first part of this thesis extends existing literature in three respects. First, we implement cross-sectional as well as longitudinal approaches. Second, we distinguish between persons with MDD, pure Dysthymia and Double Depression and examine differences between these groups on a wide range of putative risk factors. Third, data were derived from both general population and outpatients cohorts, providing insight into the full range of depressive disorders.

Part II. Alternative models for depressive subtypes

Traditional approaches, centered around DSM-categories, have greatly increased our understanding of mood disorders and identified a range of risk factors for onset, recurrence and chronicity. However, failing to account for heterogeneity in the clinical presentations comes at a cost. If, for example, a specific risk factor is only associated with a particular subtype of a disorder, this may be overlooked in an analysis based on traditional DSM-classification. Incomplete understanding results, with important implications for treatment and clinical management. Facilitated by data-driven methods such as Latent Class Analysis, a growing body of epidemiologic research has attempted to disentangle phenotypic heterogeneity of mood disorders by identifying clusters of symptoms (see Nandi et al., 2009).

Free from any a priori assumptions, data-driven techniques like Latent Class (Growth) Analysis (LC(G)A), that cluster persons based on (their trajectories of) a given outcome, may thus result in a more empirically based classification. For example, previous studies, that implemented data-driven methods, have provided evidence for the existence of depressive subtypes such as atypical depression (Sullivan et al., 1998; Lamers et al., 2010). Most studies so far implemented Latent Class Analysis. An extension of the cross-sectional LCA model is the Latent Class Growth Analysis (LCGA), which can be used to examine course trajectories in longitudinal data. Another extension is the Latent Transition Analysis (LTA), which can be used to examine the transition patterns among depressive subtypes in longitudinal data.

To date a number of studies employed LCGA to assess course trajectories in depressive disorders. However, study populations were limited to adolescents (Stoolmiller et al., 2005; Olino et al., 2010), mothers throughout the childrearing phase (Skipstein et al., 2010; Campbell et al., 2009) and bereaved caregivers (Li, 2005; Taylor et al., 2008). Colman et al. (2007) examined course trajectories of depressive and anxiety symptoms over the life course among the general population (Colman et al. 2007). However, inclusion of anxiety symptoms blurs comparisons of the identified latent course trajectories with current DSM-categories for depression. In this thesis, we conduct Latent Class Growth Analyses to empirically examine the broad concept of depression and we compare identified classes with current DSM-diagnostic categories of MDD, Dysthymic Disorder and Double Depression. Furthermore, we apply Latent Transition Analysis to examine the stability of depressive subtypes. To our knowledge, no previous study has applied transition models to examine the stability and transitions of depressive subtypes over time. In addition, evaluation of the correlates of depression among those with specific subtypes or course trajectories enables us to define more homogeneous subgroups of depression. Results on alternative models of depression are presented in part II of this thesis.

Part III. Depression and Anxiety: different or same side of the coin?

Anxiety has traditionally been considered a core symptom of depression. For example, Emile Kraepelin specified “anxious tension” as a typical symptom of depressive illness (Wakefield, 2012). However, starting with DSM-III, the attempt to sharply distinguish depressive and anxiety syndromes led to elimination of anxiety as a symptom of Major Depression. Subsequently, psychiatry “discovered” a mysteriously high comorbidity between depression and anxiety (Wakefield, 2012), ranging from 30% through 60% (Kessler et al., 1994; De Graaf et al., 2002). The issue became more urgent as studies showed that depression with comorbid anxiety has an increased risk of various negative outcomes. Comorbid anxiety and depression have found to be more severe, carry more disability, are associated with higher health care utilization and are less likely to respond to treatment than pure anxiety or depression (Bijl and Ravelli, 2000; Hecht et al., 1990; Roy-Byrne et al., 2000; Bruce et al., 2005). In addition, it was consistently demonstrated that comorbidity was associated with poorer course trajectories than either depression or anxiety alone (Keller et al., 1992; Bruce et al., 2005). However, most studies on course trajectories focused on respectively depressed or anxious patients and were not able to directly compare the prognosis of pure depression, pure anxiety and a comorbid depression/anxiety in one study. The few existing long-term naturalistic studies in community settings, with a focus on both depressive and anxiety disorders, have provided inconsistent results on the course of depression and anxiety, as well as on the predictors of course (Fichter et al., 2010; Merikangas et al., 2003). In this thesis, we present the results of a 7-year follow-up study, comparing pure depression, pure anxiety and their composite state.

In DSM-V the great comorbidity between anxiety and depression, and the prognostic value of anxiety, is partly reckoned by its proposal to dimensionally rate panic attacks across all mental disorders (Craske et al., 2010). However, a more thorough understanding of the impact of panic attacks is needed to test this proposal. Since the majority of studies to date did not stratify their analyses to compare panic attacks versus Panic Disorder, findings cannot always be attributed to panic attacks outside the realm of Panic Disorder. The impact of comorbid full-blown mental disorders such as Panic Disorder on other mental disorders is known, and would be no reason to specify panic attacks alongside mental disorders. In this thesis, we examine the impact of panic attacks on prevalence and onset, course and functioning of mental disorders.

The recognition of great comorbidity between depression and anxiety not only resulted in DSM-V’s proposal to rate panic attacks as a dimension across all disorders, it also questioned the validity of a categorical distinction between specific depressive and anxiety categories (Goldberg, 1996). In particular a great overlap between Generalized Anxiety Disorder (GAD) and MDD and/or Dysthymia was noted. Andrews et al. (2002) found that the associations between GAD and MDD (odds ratio (OR) 10.2) and GAD and Dysthymic Disorder (OR 12.6) were similar in magnitude to the ORs within diagnostic groupings, such as between panic

and social phobia (OR 8.6). Hence, it was suggested that GAD and depression might belong to one diagnostic category. This line of thought was supported by results from the Nottingham Study of Neurotic Disorders. Tyrer et al. (2004) demonstrated the poor temporal stability of Generalized Anxiety Disorder (GAD), Panic Disorder, MDD and Dysthymia, conditions once collectively described as neurotic disorders. In addition, analyses on the structure of psychopathology identified a two-dimensional model that distinguished an externalizing domain as well as an internalizing domain, in which depression and anxiety-including GAD- are grouped together (Krueger, 1999; Vollebergh et al., 2001; Olino et al., 2012). However, to our knowledge, no previous study has applied data-driven models to examine the nosological status of GAD versus Dysthymic Disorder. In this thesis we present the results of a Latent Class Analysis, examining symptom profiles of GAD and Dysthymic Disorder.

Public health significance of Depressive Disorders

Greater insight into the heterogeneity of depressive disorders is of great public relevance. Worldwide, depressive disorders are highly prevalent. In the Netherlands, about 6% of the adult population suffers from a mood disorder per year and during lifetime around 20% of the adult population fulfils the criteria of a Major Depressive Disorder, Dysthymic Disorder or Bipolar Disorder (De Graaf et al., 2010a). In actual numbers, around 650 thousand persons (aged 18 to 64 years) suffered from a mood disorder in 2011 in the Netherlands. In addition, depressive disorders have a large impact on well-being and daily functioning (Rapaport et al., 2005) similar to or even exceeding the impact noted in common medical illnesses (Merikangas et al., 2007). According to the World Health Organization (www.who.int), depression is the leading cause of disability as measured by Years Lived with Disability (YLDs)¹ and the 4th leading contributor to the global burden of disease (Disability Adjusted Life Years, DALYs)¹ in 2000. It is calculated that by the year 2020, depression will reach second place of the ranking of DALYs (World Health Organization, 2012).

General aim

As Barney Carroll, the Sydney born psychiatrist, wrote “to know depression, is to know psychiatry” (Carroll, 1989). This thesis aims to contribute to the current knowledge on the heterogeneity of depressive disorders. It is divided into three parts. The first part examines the nosological status of Dysthymic Disorder, including its demarcation from its twin brother, Major Depression, and their composite ‘Double Depression’, on socio-demographic, biological and psychological parameters and differences in course trajectories. The second

¹ YLDs= Years Lived with Disability; DALYs= Disability Adjusted Life Years= Sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability.

part aims to explore alternative classifications of depressive disorders, derived from data-driven techniques such as Latent Class Growth Analysis and Latent Transition Analysis. The third part investigates the relation between depression and anxiety disorders. We aim to gain insight into the influence of anxiety on the 7-year course of depression, and the impact of panic as a specifier across mental disorders is studied. Finally, we aim to gain insight into differences in symptom profiles of Dysthymic Disorder and Generalized Anxiety Disorder, and hence their nosological status.

Knowledge to be gained by this thesis could help to critically evaluate the current classification of depressive disorders, which is of great importance with the DSM-V forthcoming. Is a separate diagnostic category of Dysthymic Disorder warranted? How should we position anxiety versus depressive disorders? And do data-driven techniques provide us with more homogeneous depressive categories? More clearly defined, homogeneous depressive categories have important implications for the translation of research into effective treatment and clinical management. Clinical guidelines are based on diagnostic categories. Hence, if the validity of diagnostic categories is at stake, clinical decisions like the use of antidepressants or more psychological oriented strategies like Cognitive Behavioral Therapy, become flawed, with great risks for the patients involved.

METHODS

Studies used in this thesis

This thesis is based on several large surveys and an outpatient sample of the Black Dog Institute, Sydney, Australia.

The *Netherlands Study of Depression and Anxiety (NESDA)* is designed to investigate depressive and anxiety disorders (Penninx et al., 2008). It is a multi-site naturalistic cohort study of adults (aged 18 to 65 years) recruited from the general population, general practices, and mental health organizations. The total sample consisted of 2981 persons. Psychopathology was assessed using the Composite Interview Diagnostic Instrument (CIDI) version 2.1, generating diagnoses according to DSM-IV criteria (World Health Organization, 1998). Baseline and 2-year follow-up data were available for the present thesis. Chapter 2, 6, 7, 8 and 10 are based on NESDA-data.

The *Netherlands Mental Health Survey and Incidence Study (NEMESIS)-1* and *-2* are naturalistic, prospective, epidemiological cohort surveys among the general adult population (aged 18 to 64 years) in the Netherlands (Bijl et al., 1998; De Graaf et al., 2010a, b). The sampling procedure consisted of a multistage, stratified, random sample. The total sample of NEMESIS-1 consisted of 7076 persons. Data were recorded in three waves: at baseline in 1996, after 12-month follow-up (1997) and after 3 years (1999). Psychopathology was assessed using the CIDI version 1.1, generating diagnoses according to DSM-III-R criteria

(World Health Organization, 1990). Chapter 3, 4, 8 and 9 are based on NEMESIS-1-data. The total sample of NEMESIS-2, conducted more than ten years after NEMESIS-1, consisted of 6646 persons. Psychopathology was assessed using the CIDI version 3.0 (Kessler and Ustün, 2004), generating diagnoses according to DSM-IV criteria. Baseline data were available for this thesis. Chapter 10 is based on NEMESIS-2-data.

In addition to NEMESIS-2-data, Chapter 10 also involves data from two other surveys. The *National Survey of Mental Health and Wellbeing-2007* (NSMHWB-2007) is a nationwide household survey of adults (aged 16 to 85 years) (Slade et al., 2009). The survey was conducted in 2007 by the Australian Bureau of Statistics, under the Census and Statistics Act, 1905. Respondents were selected at random from a stratified, multistage area probability sample of private dwellings. Psychopathology was assessed using the CIDI version 3.0 (Kessler and Ustün, 2004). The total sample consisted of 8841 respondents. The *National Comorbidity Survey-Replication study* (NCS-R) is a nationally representative household survey of adults (aged 18 years and older) in the United States (Kessler et al., 2004). The respondents were selected from a multistage clustered area probability sample of households. The total sample consisted of 9282 persons for diagnostic assessment. Psychopathology was assessed using the CIDI version 3.0 (Kessler and Ustün, 2004). With the courtesy of the NCS-R, we downloaded the public use version of NCS-R data-part 1 (<http://www.icpsr.umich.edu/CPES>).

Finally, a sample of 318 depressed outpatients was recruited through the Depression Clinic at the Black Dog Institute (BDI), Sydney, Australia. This Institute provides a state-wide service, offering diagnostic and management advice to patients referred by general practitioners or mental health professionals. Psychopathology was assessed using the Mini-International Neuropsychiatric Interview (MINI) (Lecrubier et al., 1997). Elements of the assessment process have been detailed elsewhere (see Parker et al., 2006). Chapter 5 is based on BDI-data.

OUTLINE

The outline of this thesis is as follows. The first part investigates the current DSM-classification of depressive disorders into MDD, Dysthymic Disorder and their composite state: Double Depression. **Chapter 2** examines the distinction between MDD, Dysthymic Disorder and Double Depression on a broad range of both biological and psychological parameters. In **Chapter 3**, the 3-year course, assessed by the Composite Interview Diagnostic Instrument (CIDI)-diagnostic status, and in **Chapter 4**, the 3-year course of social and physical functioning of persons with MDD, Dysthymia and Double Depression and the most important determinants for course are examined. **Chapter 5** examines the concept of Dysthymia in an outpatient sample, and explores whether Latent Class Analysis and Latent

Profile Analysis can detect meaningful constituents. In addition, DSM-categories are compared with clinician's appraisal.

The second part explores alternative classification models for depressive subtypes. **Chapter 6** employs Latent Class Growth Analysis to examine the broad concept of depression and compares identified classes with current DSM-diagnostic categories of MDD, Dysthymic Disorder and Double Depression. **Chapter 7** concerns the diagnostic stability of previously empirically identified subtypes of depressive disorders, implementing Latent Transition Analysis.

The third part of this thesis focuses on the relation between depression and anxiety. **Chapter 8** describes the 7-year course trajectories of persons with depression, with or without anxiety. In **Chapter 9** anxiety is less broad defined and the impact of (a history of) panic attacks on prevalence and onset, course and functioning of mental disorders is examined. In **Chapter 10**, differences in symptom profiles of Generalized Anxiety Disorder and Dysthymic Disorder are investigated. A Latent Class Analysis is conducted on an aggregated general population sample, derived from NSMHWB-2007, NCS-R, and NEMESIS-2, as well as a multi-site sample derived from NESDA. Finally, the results of Chapter 2 to 10 are summarized, discussed and integrated into current scientific debates in **Chapter 11**.

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