The long-term course of anxiety disorders

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Chapter 1

General introduction

BACKGROUND AND HISTORY

Fear and anxiety are normal and essential warning signals, natural vital reactions to threats [1]. We all experience these emotions in daily life in challenging situations, such as applying for a job or defending a PhD thesis, in case of threats such as a near car accident, or when the lights are low and shadows are misinterpreted. Fear and anxiety allow us to respond appropriately to these threatening situations. Although fear and anxiety resemble each other and their symptoms overlap, the two concepts are not interchangeable [2]. Whereas fear is the response to a real, imminent threat, the result of the inborn fight-flight-response, anxiety is the anticipation of future threats, the perception of possible danger of which the cause can be unknown [3,4]. Feelings of anxiety may be equally adaptive, but may also become excessive, overwhelming, uncontrollable, do not subside, and interfere with daily life. In cases where anxiety becomes problematic in normal daily life, the diagnostic criteria for an anxiety disorder may be met. Anxiety disorders belong to the most common mental disorders with lifetime prevalence rates of 5% to 31% [5]. This means that, on average, one out of four people will have to deal with an anxiety disorder in their lifetime. Women are almost twice as likely to suffer from anxiety disorders than men, supposedly because of genetic vulnerabilities and physiological differences, although psychosocial and cultural factors such as living circumstances and responsibilities may also play a role [6–10]. Anxiety disorders can influence various aspects of life, such as health, personal well-being, physical functioning, social life, and employment [11–13]. As a result, anxiety disorders diminish the quality of life and can be very disabling. Besides the impact on individuals, anxiety disorders have large societal consequences. The direct health care costs and indirect costs due to reduced productivity, work absenteeism and suicide, are immense and constitute more than 30% of all costs for mental disorders, estimated at $63 billion in the United States and €74 billion in Europe [14–16].

The onset of anxiety disorders is typically at a young age, in childhood or adolescence, or early adulthood, with considerable psychosocial and developmental consequences, such as failure at school, problems at work or in relationships [17,18]. Anxiety disorders often have a persistent nature and individuals can suffer from it for a lifetime [9,19]. The physiological and psychological anxiety symptoms might be understood as an episode of acute stress getting out of control. Anxiety disorders are characterized by excessive and long-lasting fear or anxiety of perceived threats, an elevated stress response, and avoidance behaviour (see review [17]). Symptoms may encompass panic, increased nervousness, and fear, but also physical symptoms like increased heart rate, hyperventilation, nausea, diarrhea, loss of appetite, dizziness, and muscle tension [20].

The recognition that anxiety is stress response related, especially when the stress is frequent or chronic, and that anxiety can cause impairment in functioning has a long history that goes back to 5000 BC. Ancient Indian literature described symptoms reminiscent of current post-traumatic stress disorder and generalized anxiety disorder [21]. In classical antiquity, the ancient Greeks and Romans (approximately between the 8th century BC and the 6th century AD) identified anxiety as a negative affect and described clinical features and certain forms of cognitive treatment [22]. However, in subsequent centuries, anxiety was no longer recognized as a separate construct or disorder. In the Middle Ages (600-1500) the concept of anxiety changed and a surplus of anxiety - just as other mental disorders - was seen as the result of a demonic presence.

The ideas about mental disorders, and therefore also about the concept of anxiety, evolved substantially between the Renaissance (1350-1600) and the Industrial Revolution (1750-1900). The demonological view [23,24] was gradually replaced by a medical view, namely that anxiety had a neurological aetiology, with a focus on physical symptoms [25,26]. Whereas the mentally ill were seen as a domestic problem in the Middle Ages, the institutionalization of individuals with mental problems became more and more common practice from the 17th century onwards [27,28]. The treatment of these 'lunatics', as these patients were named, was often cruel and patients were sometimes chained to restrain them [27]. Pinel (1745-1826) reformed the attitude towards mentally ill patients and advocated a more humane approach characterized by kindness and sensitivity. Pinel was the first who was credited for literally freeing patients from their chains. But although the beliefs about mental disorders changed, anxiety was not yet considered to be a separate disorder. Instead, other terms were used to designate anxiety-related diagnoses, such as neurasthenia, melancholia, hypochondriasis, and hysteria [25]. In the late 19th and early 20th centuries the concept of anxiety evolved further under the influence of, among others, the scholars Kraepelin, Pavlov, Freud, and Cannon. The fight-flight response was described, the first classifications of mental disorders emerged, and the term anxiety neurosis was introduced [22,29–31]. Contrary to the then usual tradition of considering psychiatry from a biological point of view, Kraepelin introduced a clinical classification of mental disorders [32]. Yet, he did not want diagnoses to be taken too seriously, as is illustrated by a cartoon he drew for the Heidelberg Beer Zeitung in 1896 [33] (Figure 1).

Nevertheless, the clinical classification of Kraepelin was increasingly accepted, resulting in a new nosology and classification developed by the American Psychiatric Association (APA) [32]. In 1952, the Diagnostic and Statistical Manual of Mental Disorders first edition (DSM-I) was published [34]. In this manual anxiety was defined as a characteristic of psychoneurotic disorders. In the subsequent DSM-II, an overarching term 'neuroses' was mentioned of which anxiety was the main characteristic [22,35]. It was not until 1980, in the DSM-III, that anxiety

was recognized as a separate mental disorder and the currently dominant classification of anxiety disorders was introduced [22,36]. Anxiety disorders were conceptualized as heterogeneous constructs, combining a set of mental and physiological symptoms resulting from feelings and thoughts about experienced or possible future threats [37,38]. Several updates resulted via the DSM-IV, DSM-IV-TR, in 2013 in the DSM-5 [20,39,40]. Under the umbrella of anxiety disorders, the DSM-5 classifies several different anxiety disorder diagnoses. Anxiety disorders have many symptoms in common, but each individual anxiety disorder also has its own specific characteristics and symptoms. An overview of currently distinguished anxiety disorders is given in Table 1.

Figure 1. *"Psychiater Europas! Wahret Eure heiligsten Diagnosen!" ("Psychiatrists of Europe! Protect your sanctified diagnoses!").* With this satirizing cartoon in the Heidelberg Beer Zeitung in1896, Emil Kraepelin indicated that although he had introduced a classification of mental disorders, these diagnoses should not be taken too seriously.

In this PhD thesis the following anxiety disorders, listed in the DSM-5, were studied: agoraphobia, generalized anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder, and specific phobia. Substance/medication-induced disorder, anxiety disorder due to another medical condition, other specified and unspecified anxiety disorders were not studied because of lack of consensus on diagnostic criteria, or because of the very specific causal factors that are implicated in the diagnosis [20].

Table 1. DSM-5 anxiety disorder diagnoses and characteristics (according to American Psychiatric Association)

Anxiety Disorder	**Short description of characteristics***
Specific Phobia	Marked fear or anxiety about a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood). The fear or anxiety is out of proportion to the actual perceived danger.
Social Anxiety Disorder (Social Phobia)	Marked fear or anxiety about one or more social situations in which the individual is the center of attention and is exposed to possible scrutiny by others. Examples include social interactions (e.g., having a conversation, meeting unfamiliar people), being observed (e.g., eating or drinking), and performing in front of others (e.g., giving a speech).
Panic Disorder	Recurrent unexpected panic attacks that reaches a peak within minutes, and during which time symptoms of anxiety occur, such as palpitations, sweating, trembling or shaking, sensations of shortness of breath, feelings of choking, chest pain, nausea, feeling dizzy, paresthesia, derealization or depersonalization, fear of losing control or "going crazy", fear of dying.
Agoraphobia	Marked fear or anxiety about the following situations: using public transportation, being in open spaces (e.g., parking lots, marketplaces, bridges), being in enclosed places (e.g., shops, theaters, cinemas), being in a crowd, being outside of the home alone.
Generalized Anxiety Disorder	Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least six months, about a number of events or activities (such as work or school performance). The individual finds it difficult to control the worry. Symptoms are e.g., restlessness, easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance.
Separation Anxiety Disorder	Inappropriate and excessive fear or anxiety concerning separation from those to whom the individual is attached.
Selective Mutism	Consistent failure to speak in specific social situations in which there is an expectation for speaking (e.g., at school) despite speaking in other situations.
Substance/Medication-Induced Anxiety Disorder	Panic attacks or anxiety is predominant in the clinical picture, while it is evident from the history, physical examination, or laboratory findings that the symptoms developed during or soon after substance intoxication or withdrawal or after exposure to a medication.
Anxiety Disorder Due to Another Medical Condition	Panic attacks or anxiety is predominant in the clinical picture, while it is evident from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition.

Table 1. Continued

Anxiety Disorder	Short description of characteristics*
Other Specified Anxiety Disorder	Symptoms characteristic of an anxiety disorder that cause clinically significant distress or impairment in important areas of functioning predominate but do not meet the full criteria for any of the disorders in the anxiety disorders diagnostic class.
Unspecified Anxiety Disorder	Symptoms characteristic of an anxiety disorder that cause clinically significant distress or impairment in important areas of functioning predominate but do not meet the full criteria for any of the disorders in the anxiety disorders diagnostic class.

Notes: DSM = Diagnostic and Statistical Manual of Mental Disorders (DSM-5); * For complete description see the DSM-5 [20]

OVERVIEW OF RESEARCH INTO ANXIETY DISORDERS AS OF 1980

Research

When the DSM-III was introduced in 1980, the new anxiety disorder classification resulted in an abundance of research on the aetiology, nature, course, and treatment of anxiety disorders. Large epidemiological studies revealed that anxiety disorders are among the most common mental health disorders, are very disabling, commonly have an early age of onset (i.e. in childhood or adolescence), are highly comorbid with each other as well as with depressive disorders, and are very heterogeneous with respect to symptomatology and course [41,42]. A range of variables were found which were associated with prevalence and which predicted onset of anxiety disorders, such as genetic, neurobiological, environmental, as well as several behavioural, personality, and cognitive factors [3,43–50].

Theoretical models

On the basis of this research, various theoretical models have been formulated to describe the onset and development of anxiety disorders. These models were constructed from different viewpoints, whether or not in relation to depressive disorders. For instance, Clark and Watson [51] concluded that anxiety and depressive disorders can best be described by a tripartite model. Both disorders share a nonspecific component of general affective distress but can be distinguished by the factors specific for these disorders, that is physiological arousal for anxiety and absence of positive affect for depression. Chorpita and Barlow [44] proposed a model of the environmental influences on the development of anxiety disorders. They highlighted the importance of a perceived diminished control as a vulnerability for anxiety. The importance of associative learning processes as diatheses for anxiety and the way these learning processes can be incorporated in etiological models of anxiety disorders

were reviewed by Mineka and Oehlberg [52]. Furthermore, a model showing the influence of cognitive vulnerabilities on the development and maintenance of anxiety disorders was presented by Ouimet et al. [53]. However, these different approaches hamper comparison of the models and the identified vulnerabilities, making it difficult to get a comprehensive overview of the processes defining anxiety disorders.

Categorical or dimensional

Other factors complicating a better understanding of onset, development, and course were that studies found high rates of comorbidity between anxiety disorders, with unclear boundaries between the categories. In addition, there were questions on the stability of specific anxiety disorders over time [54–57]. As with other domains in the DSM, there was debate whether anxiety disorders should be grouped together and considered as one disorder or should be divided into different diagnostic categories [58]. Similarly to this discussion about lumping or splitting of anxiety disorders, discussion arose as to whether the classification should be categorical or dimensional. More and more researchers have pleaded for a more dimensional approach [54,55,57,59–61], a plea that is reflected in the recent changes in DSM-5 towards a more dimensional classification. This discussion was prompted by the doubts that arose by the categorical classification [57]. This classification has definitely contributed to a better international communication about psychiatric disorders, it enabled the development of precise diagnostic criteria and research on efficacy of different treatments and is also easy to use in clinical settings. Yet, the system also has some limitations. The categorical classification does not take into account subthreshold symptoms and symptom severity, nor the fact that diagnostic boundaries are generally fuzzy, and that several anxiety symptoms are found in a broad range of disorders [54,57]. Anxiety symptoms are not restricted to anxiety disorders, but are common in other psychiatric disorders as well, which is now reflected in the formulation of a transdiagnostic anxious distress specifier in the DSM-5 [20]. Nowadays, most scholars and clinicians agree that the current categorical diagnostic classification is suitable and useful, especially in the clinic, but also that it has clear disadvantages [61–63].

More advanced models

To explicate the underlying structure and to do justice to the dimensional nature of anxiety disorders, more advanced structural models have been developed that describe the symptoms, diagnoses, and their interrelations, often with use of hierarchical designs. These hierarchical models consist of multiple levels, usually with one overarching factor at the top and one or more branching levels below. Such an overarching class is sometimes labelled emotional disorders or emotional distress. This overarching class is then divided into two or three dimensions (e.g., [49,64–68]; for an example, see Figure 2). It is often suggested to place generalized anxiety disorder together with depressive disorders in one dimension, while the other anxiety disorders (panic disorder, agoraphobia, social phobia/social anxiety disorder, specific phobia) are grouped

together in the fear dimension. Kotov et al. [69] took it a step further and developed the Hierarchical Taxonomy Of Psychopathology (HiTOP) model, which addresses the aforementioned shortcomings of the traditional categorical classification. The HiTOP model presents mental disorders as a spectrum in which psychopathological syndromes and symptoms are grouped based on their similarities. In this way, comorbidity, boundary issues, and diagnostic instability are less of a problem. Another alternative approach to classifying mental disorders is the Research Domain Criteria (RDoC) project [70,71]. This classification system is not primarily developed for clinical practice but is especially aimed at research on possible underlying pathophysiological mechanisms and how they are related to specific domains of psychopathology. Just like the hierarchical models, the RDoC model is intended to incorporate the dimensional nature of mental disorders, such as anxiety disorders, into the classification.

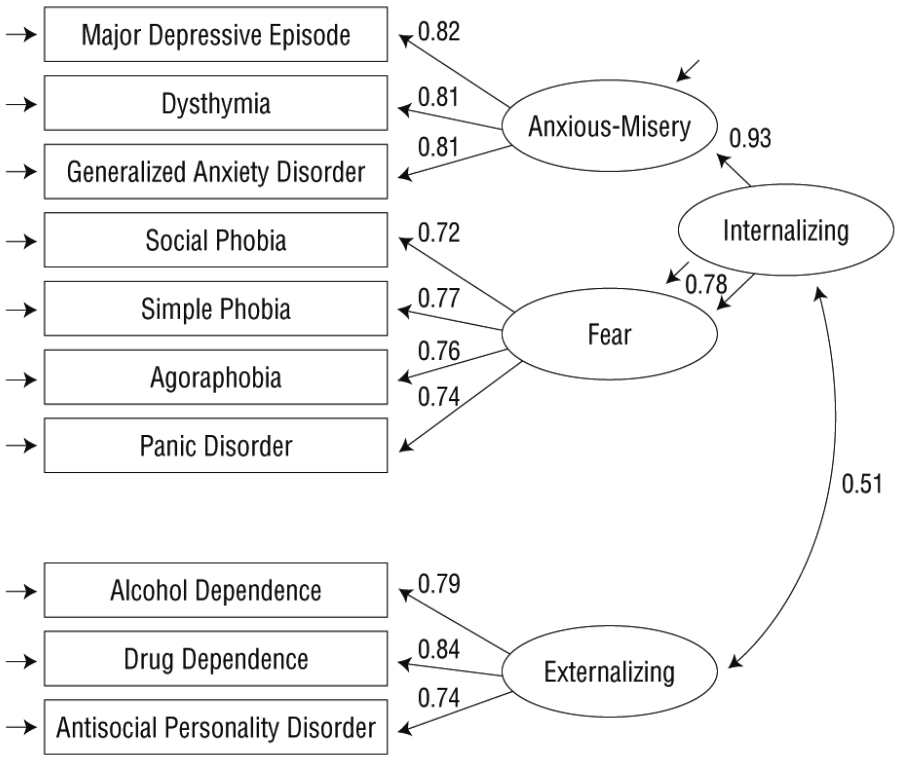

Figure 2. Three-factor model of Krueger, based on National Comorbidity Survey (NCS) data. This model is a variant of the two-factor internalizing-externalizing model. The higher order internalizing factor is subdivided into two subfactors, i.e. anxious-misery and fear. Each subfactor and the externalizing factor encompasses a number of mental disorders. The numerical values represent standardized parameter estimates (factor loadings) of confirmatory factor analysis. (The figure is adapted from Krueger et al. [68])

GAPS IN THE CURRENT KNOWLEDGE

From the aforementioned research it has repeatedly been concluded that anxiety disorders are likely to have a chronic course [19,72]. Nevertheless, research on the longitudinal aspects of anxiety disorders has been relatively neglected. Studies were typically designed cross-sectionally, disregarding the often persistent nature of anxiety disorders. The need for more prospective longitudinal research has however been pointed out in various studies [73–78]. It was for example stated that variables may change over time with concurrent changing influences on the course of anxiety disorders. In addition, the fact that retrospective studies have dominated so far, a study design with a higher chance of recall bias, has led to a call for prospective studies. Similarly, cross-sectional studies are insufficient to investigate patterns of comorbidity that may develop over time between anxiety disorders and other psychiatric disorders, especially depression. Cross-sectional studies can also not be used to investigate transitions from anxiety to depressive disorders. Consequently, there is a lack of knowledge about different aspects of the course of anxiety disorders over time. A complicating factor here is the fact that current literature is mostly restricted to one aspect of anxiety disorders, for instance focusing on a specific age group (children, adolescents, students, elderly), or only on one or a few anxiety disorders rather than anxiety disorders in general (e.g., [79–83]). To provide patients and clinicians with more reliable estimations of prognosis, it is important to get more insight into the processes underlying the longitudinal course of anxiety disorders, of the different course types and the factors associated with these course types. Such knowledge may contribute to prevention and help to adjust treatments according to prognosis.

AIMS AND OUTLINE OF THIS THESIS

To obtain a deeper insight into these longitudinal trajectories of anxiety it is important to know who is at risk of an unfavourable prognosis and what contributes to such an untoward outcome. The aim of the research presented in this thesis is to expand the knowledge of the longitudinal course of anxiety disorders.

Important in this context is that longitudinal research designs on anxiety are complicated by the high comorbidity rates and diagnostic instability of anxiety disorders. These constraints can at least partly be addressed by not focusing on one particular anxiety disorder, but on anxiety disorders in general. Another option is bypassing the specific categorical diagnoses and instead investigating the course of severity of anxiety symptoms, as anxiety symptoms play a key role in determining the nature, severity and course of anxiety disorders. Furthermore, a focus on anxiety symptoms fits in with the dimensional viewpoint [84]. In my thesis I therefore conducted both: studies on severity of anxiety symptoms and on categorical anxiety disorders.

Studies on severity of anxiety symptoms

Previous studies found a clear relationship between personality traits and other related psychological factors and the manifestation of anxiety symptoms (see for instance [85]). My focus pertains the relationships of two key psychological factors related to anxiety disorders, anxiety sensitivity and locus of control, with severity of anxiety symptoms. Anxiety sensitivity can be defined as the fear of anxiety-related symptoms and is also known as 'fear of fear' [86–88]. A high level of anxiety sensitivity can cause a misinterpretation of anxiety symptoms and see these symptoms as harmful or catastrophic. Locus of control refers to the extent to which individuals believe they can control the events that influence their lives [89,90]. Those who feel little control over their fate (external locus of control) experience more stress and are more vulnerable to develop an anxiety disorder [3,44]. High anxiety sensitivity and an external locus of control are both considered to be key risk factors in the development of anxiety disorders [91–94], but their stability over time and the association with changes in anxiety symptom severity still needs to be investigated. Moreover, previous cross-sectional studies showed that chronotype, that is the internal circadian clock especially with respect to preferred timing of sleep and activity [95], is associated with severity of anxiety (and depressive) symptoms [96,97]. To analyse whether chronotype is a vulnerability factor for persistent anxiety disorders, this thesis also covers an examination of the longitudinal association between change in chronotype and changing severity of anxiety symptoms.

Studies on anxiety disorders

Stability of diagnosis was listed as an important predictive validator for maintaining separate diagnostic classifications in DSM-5 [98]. In previous NESDA studies it was established that there is a considerable degree of diagnostic instability in recurring anxiety disorders [99,100]. Nevertheless, many questions about the longitudinal diagnostic stability remain. My research is aimed at the investigation of the diagnostic stability of anxiety disorder diagnoses over a period of six years. Another point of attention is the often persistent nature of anxiety disorders [19,101]. This is a major issue for the affected individuals and for professionals, but also from a public health perspective. Although studies have been done on factors that predict such an untoward course, a thorough and comprehensive review of the literature is lacking. I performed a systematic review to provide an overview of all known predictors of anxiety disorder persistence across the lifespan.

In this thesis I aim to expand the knowledge of the longitudinal naturalistic course of anxiety disorders by:

- examine the association of specific factors, in particular anxiety sensitivity, locus of control, and chronotype, with changes in severity of anxiety symptoms over time;
- examine the stability of anxiety disorder diagnoses over time;
- review predictors of a persistent course of anxiety disorders across the lifespan.

The studies in this thesis, with an exception for the systematic review in Chapter 6, were part of the Netherlands Study of Depression and Anxiety (NESDA). A detailed description of the NESDA study and data collection is given elsewhere [102]. In short, NESDA is an ongoing large naturalistic cohort study, designed to investigate the long-term course of depressive and anxiety disorders, the predictors of this course and the consequences. The longitudinal design of the study, covering an extensive time period with repeated assessment waves, make the NESDA study eminently suitable to study the longitudinal course of anxiety disorders. At baseline, NESDA included 2981 subjects, aged 18 to 65 years, consisting of individuals with a history of a depressive or anxiety disorder, a current depressive or anxiety disorder, and healthy controls. Recruitment took place in the general community, and primary and secondary care. Baseline data collection was from 2004-2007. In this thesis data from the baseline, 2-year, 4-year, 6-year, and 9-year follow-up assessments were used.

Chapter 2 describes the role of anxiety sensitivity in the development of anxiety symptoms. Elevated anxiety sensitivity is found to be a risk factor for the onset of anxiety symptoms, anxiety and depressive disorders, as well as other diagnoses previously known as DSM-Axis I disorders. However, there are uncertainties about the stability of this construct over time and the association between changing anxiety sensitivity levels and changes in severity of anxiety symptoms over time remains unclear. Using data from the NESDA study, the longitudinal stability of anxiety sensitivity is examined in a sample of subjects with and without an anxiety, a depressive, or a comorbid anxiety-depressive disorder. Subsequently, the association of the change in anxiety sensitivity with the change in anxiety symptom severity is analysed.

In *Chapter 3* the role of the cognitive vulnerability factor locus of control in anxiety pathology is investigated. First, the longitudinal stability of locus of control is established. Then, the bidirectional relationships between locus of control and symptom severity of anxiety and depression over a period of nine years are investigated. In addition, the influence of intermediate positive and negative life-events on these associations are analysed.

Chapter 4 was aimed to analyse the effect of chronotype on anxiety and depressive symptom severity. Chronotype is the individual's preferred timing of sleep and activity and the preferences range from extreme early (morning types) to extreme late (evening types). According to the literature, individuals with an evening preference would be more vulnerable for anxiety and depressive disorders. To examine the accuracy of this statement, the stability of chronotype over a period of seven years is tested and the longitudinal association of change in chronotype with change in anxiety and depressive symptom severity is analysed.

In *Chapter 5* the stability of anxiety disorder diagnoses is investigated. Diagnostic stability has been one of the factors on which the classification of anxiety disorders in the DSM-5 was based. The question is put forward whether this diagnostic stability really exists and to what extent these diagnoses are stable over time.

Chapter 6 provides a comprehensive systematic review that evaluates and synthesizes the predictors of a persistent course of anxiety disorders across the lifespan and across diagnoses including agoraphobia, generalized anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder, and specific phobia. Predictors of a persistent course are identified and compared to predictors of a non-persistent course.

Finally, in *Chapter 7* the main findings of this thesis are summarized and put in the context of the broader literature. A reflection on the methodologies of the studies is given, in addition to the potential impact of the findings for clinical practice and recommendations for future research.

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