General introduction

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INTRODUCTION

Anxiety is a basic human emotion with expressions falling on a continuum from mild to severe (Pine et al., 2009). The studies presented in this thesis extend the knowledge on the role of stress physiology as a cause, correlate, and predictor of pediatric anxiety.

Of fraidy-cats

Anxiety is not typically pathologic but commonly adaptive when it facilitates anticipation of threat or danger. The organisms' responses to danger and the underlying brain circuitry engaged by threats reflect these adaptive aspects of anxiety (Pine et al., 2009). Pure anxiety problems have a low prevalence at toddler age, but become more prevalent during later childhood (Gilliom, Shaw, 2004; Basten et al., 2016). To some extent, many fears and anxieties in pre-school aged children are age-appropriate and in keeping with normal development (Egger, Angold, 2006). This has made it difficult to discern age-appropriate behavior, reflecting normal development, from persistent anxiety problems and underlines the need to identify early risk factors for deviant developmental pathways.

Maladaptive and pathologic anxiety is characterized by persisting or extensive degrees of anxiety and avoidance associated with subjective distress or impairment (American Psychiatric Association, 2000).

It can be hypothesized that children with an anxiety disorder function under conditions of persistent stress, with an excessive and prolonged stress system activation. Variations in the activity of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), two major physiological stress systems, have been implicated as possible biological markers of pathological anxiety in children (Feder et al., 2004; Dietrich et al., 2007). Normally, activation of these stress systems leads to behavioral and physical adaptive changes that improve the ability to survive. However, children with an anxiety disorder may perceive the world as full of stressors that demand endless vigilance and coping, with no possibility to relax and to regard their living environment as safe (Sapolsky, 2002). The developing stress systems of children and adolescents may be especially vulnerable to stress-induced changes. For instance, permanent HPA-axis dysfunctioning in early life has repeatedly been linked to chronicity and recurrence of affective disorders and affective symptoms (Flory et al., 2009; Nicolson et al., 2010).

The hypothalamic-pituitary-adrenal axis and the autonomic nervous system

Humans have different stress systems, two of which have been mostly studied: the ANS and the HPA-axis. The ANS has two branches: the sympathetic nervous system and the parasympathetic nervous system. The autonomic nervous system regulates critical life functions on a moment-to-moment basis through its sympathetic and parasympathetic branches. The sympathetic branch of the ANS is engaged within seconds of stressor presentation, which
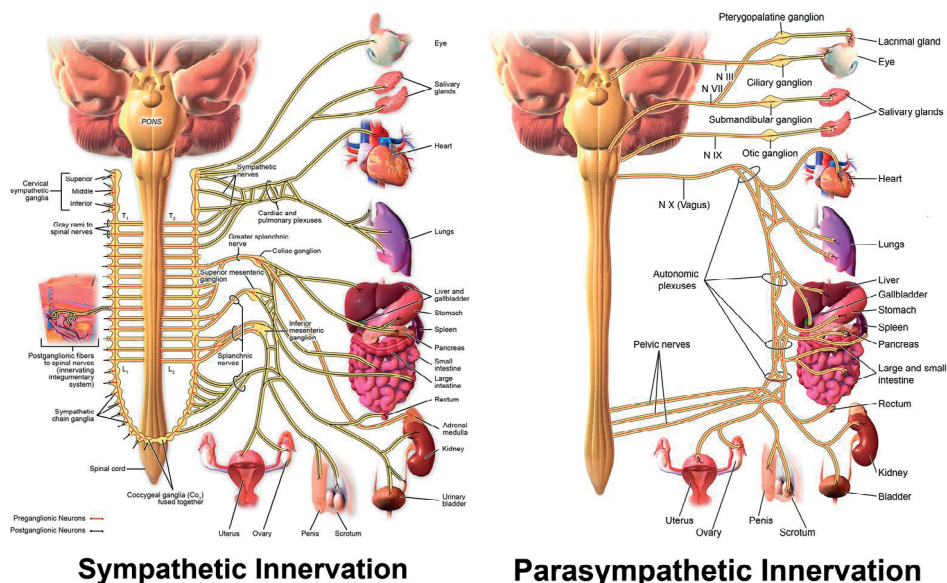
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Sympathetic Innervation **Parasympathetic Innervation**

Figure 1. Schematic presentation of the autonomic nervous system. From: Blausen.com staff. "Blausen gallery 2014". Wikiversity Journal of Medicine. DOI:10.15347/wjm/2014.010. ISSN 20018762

ensures an immediate response, which rapidly subsides as the result of the reflex activation of the parasympathetic branch (McKlveen et al., 2016). To be able to respond to a threatening situation, the body prepares itself for fight or flight. This autonomic activation leads to an increase in heart rate, blood pressure, sweat gland activity, and respiration. Subjectively, the individual feels tense and flushed, has palpitations, shortness of breath and increased perspiration. In many cases, both of these systems have opposite actions where one system activates a physiological response and the other inhibits it. Heart rate is controlled by the sympathetic and parasympathetic branches of the autonomic nervous system, skin conductance is controlled by the sympathetic branches of the ANS, and high frequency variations in heart rate (heart rate variability) is a proxy for the parasympathetic component of autonomic cardiac control.
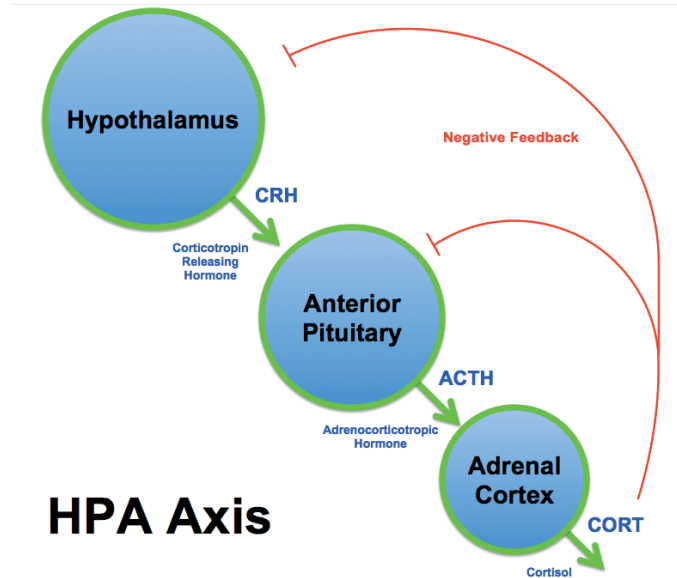
Figure 2. Basic hypothalamic–pituitary–adrenal axis summary (corticotropin-releasing hormone=CRH, adrenocorticotropic hormone=ACTH). Original work from Jessica Malisch and Theodore Garland Feb. 25, 2004.

Besides the ANS, the HPA axis is the major physiological stress response system. Cortisol is the end product of the adrenal axis in humans. During non-stress conditions the HPA-axis shows a diurnal pattern of cortisol secretion, with peak levels approximately 30 minutes after waking up and a subsequent decline during the day (Wust et al., 2000). The HPA-axis stress response occurs on a slower time scale than the ANS response (Ulrich-Lai, Herman, 2009). Upon stressor initiation, corticotropin-releasing hormone (CRH) is released and travels to the anterior pituitary. In turn, CRH triggers the release of adrenocorticotropic hormone (ACTH). By way of systemic circulation, ACTH acts at the adrenal cortex to induce the release of cortisol. Glucocorticoids are then able to spread via systematic circulation to peripheral targets as well as central targets in the brain. Glucocorticoids can act both to augment and suppress sympathetically mediated changes in e.g. cardiovascular function, metabolism, and immune function. Glucocorticoids exert their effects through binding to mineralocorticoid (MR) and glucocorticoid receptors (GR). The MR is indicated to be important for perceiving resting levels of glucocorticoids for circadian regulation of the HPA-axis, whereas the GR is thought to be important for perceiving stress-induced levels of glucocorticoids. The MR and GR are expressed in key stress-regulatory regions, such as the medial prefrontal cortex, hippocampus, amygdala, hypothalamus, and hindbrain, with MR expression being more limited than that of GR (McKlveen et al., 2016).

Of fraidy-cats, wild tigers and feeling blue

Anxiety disorders are among the most prevalent psychiatric disorders in children and adolescents (Verhulst et al., 1997; Bittner et al., 2007), with separation anxiety disorder, specific phobia, and social phobia being the most frequent childhood anxiety disorders (Beesdo-Baum, Knappe, 2012). High comorbidity rates between anxiety disorders have been reported (e.g. Beesdo, Knappe, Pine, 2009), which will be addressed in *Chapter 2*. The high degree of comorbidity amongst anxiety disorders in children and adolescents seems to point in the direction of one taxonomic construct, instead of a number of separate disorders. However, previous research supports the idea of specific phobia as a distinct taxonomic entity: in a twin study two genetic factors were identified that exclusively predispose to two broad groups of anxiety disorders dichotomized as generalized and panic anxiety plus agoraphobia versus the specific phobias. Social phobia was influenced by both genetic factors (Hettema et al., 2005). Few studies have compared the endocrine and autonomic profiles between different pediatric anxiety disorders, and if so the focus was on one specific anxiety disorder with a disorder-specific stimulus to elicit stress reactions. At present, it is still unclear as to what extent ANS or HPA-axis activity relates to anxiety in general, or whether they are specific correlates of certain types of anxiety disorders. This will be addressed in *Chapter 5*.

Anxiety and depressive symptoms in children and adolescents are often comorbid, with comorbidity rates ranging from 21 to 54% in population-based studies (e.g. Essau, Conradt, Petermann, 2000; Costello et al., 2003; Ferdinand et al., 2005). Childhood anxiety and depression might be two different disorders that often co-occur, or they could be different manifestations of the same underlying vulnerability. Furthermore, internalizing and externalizing problems in childhood often co-occur (Fanti, Henrich, 2010) and show heterotypic stability, i.e. there is lack of measurement invariance in profiles across ages suggesting that children are very likely to show different patterns of problems across the preschool period (Basten et al., 2016). Given the above, comorbid externalizing problems and depressive symptoms need to be considered when studying risk factors and (bio)markers in anxious children, as described in *Chapters 3, 4 and 5*.

The need to treat

Childhood anxiety has been associated with a range of negative outcomes, including academic underachievement, drug dependency, and an increased risk for developing other psychiatric disorders (Woodward, Fergusson, 2001; Bittner et al., 2007). After the onset of the first anxiety disorder in childhood, a pattern with multiple anxiety disorders often develops by adolescence or early adulthood (Wittchen et al., 2003). The development of these secondary negative outcomes seems to increase with the 'load' of anxiety, i.e. the number of anxiety disorders (Woodward, Fergusson, 2001). Given the differences in outcome, one could argue that the causes and correlates of a high anxiety 'load' may differ from those of a low anxiety 'load' (described in *Chapter 5*).

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The chronic and pathological anxiety experienced by children and adolescents in a clinical population is on average more severe than the reported anxiety reported by children and adolescents from the general population, hence it may have a greater impact on the stress systems and influence its future functioning. In addition, children and adolescents in the general population who experience chronic anxiety, but remain untreated, have a significantly poorer prognosis and high persistence (Ferdinand, Verhulst, 1995; Ferdinand, Verhulst, Wiznitzer, 1995).

Cognitive behavioral therapy (CBT) is the treatment of choice for children with an anxiety disorder, with a remission rate of 59% following treatment (James et al., 2013). A 7- to 19-years follow-up study of the long-term outcomes of treated childhood anxiety disorders showed that patients with a poorer response to CBT, had higher rates of panic disorder, substance abuse and dependency in adulthood than the successfully treated patients (Benjamin et al., 2013). It is, therefore, important to identify predictors of symptom improvement in treated children with an anxiety disorder, which will be discussed in *Chapter 7*.

Several studies investigated possible clinical predictors of treatment outcome in children with anxiety disorders. Some studies reported that higher anxiety severity predicts a less favorable outcome (Last, Hansen, Franco, 1998; Liber et al., 2010; Hudson et al., 2013; Compton et al., 2014). A few studies showed that children with comorbid mood disorders are more likely to remit to their primary anxiety disorder following treatment (Liber et al., 2010; Hudson et al., 2013). Various studies examined the role of parental characteristics as predictors of treatment outcome in children, but an inconsistent pattern of findings resulted (Legerstee et al., 2008; Hudson et al., 2013; Compton et al., 2014). Because clinical characteristics are weak or inconsistent indicators of response to CBT, there is an increasing interest in identifying biomarkers to predict differential treatment response (Lester, Eley, 2013). Despite the evidence of altered pre-treatment HPA axis and autonomic functioning in anxiety-disordered children, studies that have assessed the concomitant changes in stress physiology during treatment or that have investigated stress physiology as a predictor of therapy outcome are lacking. This will be addressed in *Chapter 6*.

AIM OF THIS THESIS

The main aim of the present thesis is to extend the knowledge on the role of stress physiology as a cause, correlate, and predictor of pediatric anxiety disorders with the ultimate goal to improve treatment and prognosis. More specifically, the aim is to examine the specificity of the association of stress physiology with child anxiety problems and its subtypes, given the high co-occurrence with other anxiety disorders, externalizing and depressive problems. In addition, we examine the trajectory of an anxiety disorder and the concomitant change in stress physiology, and stress physiology as a predictor of therapy outcome.

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Study samples

The studies described in this thesis were embedded in four study samples.

General population samples

The first study population is the TRacking Adolescents' Individual Lives Survey (TRAILS). **TRAILS** is a prospective cohort study of Dutch early adolescents aged 10-12 years, who are followed biennially. The present study used data from the first (2001-2002; T1 mean age 11.09 years, SD 0.55) and second (2003-2004; T2 mean age 13.56 years, SD 0.53) assessment wave. The TRAILS target sample consisted of young adolescents from five municipalities in the North of the Netherlands, including both urban and rural areas.

The second study population is the **Generation R Study** ("R" for Rotterdam). This study is a longitudinal, population-based cohort in which children are followed up from fetal life forward. The initial cohort comprised 9,778 pregnant women with a delivery date between April 2002 and January 2006, living in Rotterdam, the Netherlands. The aim of Generation R Study is to identify early environmental and genetic determinants of growth, development, and health. Generation R focuses on a wide range of issues relating to physical development, childhood diseases, use of health care, and behavior and cognition. The study in this thesis was conducted within the Focus cohort of the Generation R Study, a population-based prospective cohort from fetal life onwards (Tiemeier et al., 2012). All children were born between February 2003 and August 2005. The cohort consists of Dutch children and their parents and is ethnically homogeneous, to rule out confounding and effect modification by ethnicity. Measurements of infant autonomic indices were added to the protocol of the examination round at age 14 months, while assessment was already ongoing. We obtained physiological measurements for 528 infants.

Patient sample and control group

The third study population is a **clinical sample** of 184 children and adolescents aged 8 to 16 years with a primary diagnosis of generalized anxiety disorder, separation anxiety disorder, social phobia or specific phobia. Eligible for participation were children and adolescents consecutively referred between September 2002 and May 2007 to the outpatient clinic of the department of Child and Adolescent Psychiatry of either the Erasmus Medical Center in Rotterdam or Leiden University Medical Center – Curium. All consecutive referrals to these departments were assessed with the Anxiety Disorders Interview Schedule for DSM-IV-Child Version (ADIS-C). All children and adolescents participated in a standardized stepped-care CBT program for childhood anxiety disorders, consisting of two phases (Van der Leeden et al., 2011). In the first phase, children were treated with the FRIENDS program, an evidence-based treatment program for anxiety disorders (Barrett, Lowry-Webster, Turner, 2000), which encompassed 10 child sessions and 4 separate parent sessions. The FRIENDS program comprised psychoeducation, relaxation and breathing exercises, exposure, problem-

solving skills training, social support training and cognitive restructuring exercises (Shortt, Barrett, Fox, 2001; Liber et al., 2008). Parent sessions comprised mainly psychoeducation. All children that were not successfully treated in the first phase, as determined by ADIS-C at three months follow-up, received supplementary CBT. The second phase consisted of 10 manualized sessions, in which parents and child participated together in each session.

The fourth study population, which acts as a control group for children aged 8 to 12 years from the patient sample, is a general population sample drawn from a larger general population sample from the Dutch province of Zuid-Holland (see "2003 sample" in Tick, Van der Ende, Verhulst, 2007), the **Zuid-Holland study**. Of the 2,286 eligible respondents, 1,710 (74.8%) parents of children aged 6-18-year olds participated in this study of Tick, Van der Ende and Verhulst (2007). A subsample of 508 8-12-year-olds living in municipalities relatively close to the city of Rotterdam was selected to participate in a study investigating stress physiology. All 8-12-year-olds with scores above the borderline or the clinical cut-off on the internalizing and/or externalizing problem scales on the Child Behavior Checklist (CBCL; Achenbach, Rescorla, 2001) were invited. This resulted in a selection of 140 children. Furthermore, 156 children aged 8-12 were randomly selected from the remaining 368 children with scores below the borderline cut-off, evenly distributed with regard to degree of urbanization, age and sex. From this subsample three children were excluded because their parents did not speak the Dutch language. Of the remaining 293 eligible respondents, 231 (78.8%) participated.

Methylphenidate treatment in children with ADHD was discontinued the day before and on the day of measurements (clinical sample N=7, general population N=6) because methylphenidate treatment can increase heart rate and blood pressure (Ballard et al., 1976).

Outline

First, given the high degree of comorbidity amongst anxiety disorders in children and adolescents, it is important to extend the knowledge about the taxonomy of anxiety disorders. The main focus of ***Chapter 2*** is the investigation of homotypic and heterotypic longitudinal patterns of symptoms of different anxiety disorders in TRAILS, a large population-based sample of young adolescents.

Second, there is a need to establish the specificity of the association of stress physiology with child anxiety problems, given the high co-occurrence with externalizing and depressive problems. In ***Chapter 3***, we study the tripartite model, in which symptoms of anxiety and depression are viewed along three dimensions. This model groups symptoms of depression and anxiety into three subtypes: negative affectivity, positive affectivity, and physiological hyperarousal. In the Zuid-Holland study, a general population sample of children, we examined whether basal and reactive HPA-axis functioning, as a proxy for physiological hyperarousal, and perceived arousal before, during and after stress differentiate anxious from depressive children. ***Chapter 4*** discusses the longitudinal associations between infant

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autonomic functioning and early childhood internalizing and externalizing problems simultaneously in the Generation R Study, a large general population sample. Establishing the specificity in a longitudinal design reduces the risk of reverse causation.

Third, despite a large body of literature detailing an association with stress physiology and anxiety, gaps in our knowledge remain. At present, it is still unclear as to what extent stress physiology relates to anxiety in general, or whether it is a specific correlate of certain types of anxiety disorders. Few studies have compared the stress physiology between different pediatric anxiety disorders, and if so the focus was on one specific anxiety disorder with a disorder-specific stimulus. ***Chapter 5*** discusses whether HPA-axis, ANS and perceived arousal measures can distinguish children with different primary diagnoses of clinical anxiety disorders (the clinical sample), and from a general population reference group (the Zuid-Holland study). In addition, we explore the association of between stress physiology and the number of clinical disorders.

Fourth, despite the evidence of altered pre-treatment HPA axis and autonomic functioning in anxiety-disordered children, studies that have assessed the trajectory of an anxiety disorders and concomitant change in stress physiology, or stress physiology as a predictor of therapy outcome in childhood anxiety disorders are lacking. In ***Chapter 6***, we study the relation between the trajectory of an anxiety disorder during treatment and the concomitant change in cortisol levels in a clinical sample of children and adolescents with an anxiety disorder. Finally, in ***Chapter 7***, we investigate the longitudinal association of stress physiology at pre-treatment baseline with anxiety and depressive symptoms at one-year follow-up in a clinical sample of children with an anxiety disorder treated with cognitive behavioral therapy. In addition, we explore the longitudinal association of stress physiology with depressive symptoms.

The concluding chapter of this thesis, ***Chapter 8***, discusses the main findings of the studies described in this thesis, including methodological considerations and implications for research and clinical practice.

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