Anxiety among Adolescents

Measurement, Clinical Characteristics, and Influences of Parenting and Genetics

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Abstract


Anxiety is the most commonly reported mental health problem among adolescents. Still, many adolescents in need of treatment are not detected and the clinical characteristics and etiological pathways of adolescent anxiety are under-researched topics. This thesis examined the clinical utility of the Swedish versions of the Spence Children’s Anxiety Scale (SCAS) and the clinical characteristics of multiple anxiety disorders among psychiatrically referred adolescents, and the influence of parenting and oxytocin gene (OXT) variants on anxiety among adolescents in the general population. Studies employed cross-sectional and longitudinal designs and were based on questionnaire, interview, and genotype data.

Support for the reliability and validity of both SCAS and SCAS-P was obtained. The overall ability to predict anxiety among referred adolescents ranged from fair to excellent for both scales.

Among adolescents psychiatrically referred for any reason, the prevalence of any anxiety disorder was 46%. Homotypic comorbidity was observed in 43%, and heterotypic comorbidity in 91%.

Early adolescent anxiety influenced homotypic anxiety in late adolescence independent of parental rejection and control. The mediating role of parenting was small with indirect effect sizes no larger than one-tenth the size of direct effects, irrespective of the informant on parenting behavior.

Significant interaction effects with positive and negative parenting were observed for OXT variants rs4813625 and rs2770378 in relation to social anxiety. The nature of the interactions was in line with the differential susceptibility framework for rs4813625, whereas for rs2770378, results indicated a diathesis–stress type of interaction.

The findings suggest that psychiatrically referred adolescents with anxiety disorders are best characterized as a highly complex patient group and call attention to the necessity of structured assessment. For this purpose, this thesis provides evidence for the clinical utility of the SCAS; routine utilization of this questionnaire can improve detection of adolescents in need of anxiety treatment. Findings of this theses further suggest that the influence of positive and negative parenting behaviors on anxiety may be of greater importance among some adolescents than others, depending on individual differences in sensitivity to parenting. The etiology of anxiety among adolescents may therefore involve differential susceptibility effects of the interplay between genes and parenting behaviors.

Keywords: Adolescent, anxiety, assessment, prevalence, comorbidity, parenting, oxytocin, gene–environment interaction, differential susceptibility

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“Those people who are imaginative see many more dangers than perhaps exist; certainly many more than will happen; but then they must also pray to be given that extra courage to carry this far-reaching imagination. But for everyone, surely, [...] this is the lesson: Never give in, never give in, never, never, never, never – in nothing, great or small, large or petty – never give in except to convictions of honour and good sense.”

Winston Churchill

To Thomas, Alexander, and Johann
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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    Spence Ångestskala självrapport (Swedish self-report version)
    Spence Ångestskala föräldraversion (Swedish parent report version)
  Parents As Social Context Questionnaire (PASCQ)
    Items in Swedish adolescent and parent versions, by subscale
Abbreviations

CBT  Cognitive behavioral therapy
CNS  Central nervous system
DNA  Deoxyribonucleic acid
DSM  Diagnostic and Statistical Manual of Mental Disorders
EPIQ  Electronic Psychiatric Intake Questionnaire
GAD  Generalized anxiety disorder
GWAS  Genome-wide association study
G × E  Gene–environment interaction
ICD  International Classification of Diseases
inOT  Intra-nasally administered oxytocin
K-SADS  Schedule for Affective Disorders and Schizophrenia for School-Age Children
LEAD  Longitudinal Expert All Data
LR  Likelihood ratio
MAF  Minor allele frequency
NPV  Negative predictive value
OCD  Obsessive compulsive disorder
OXT  Oxytocin gene
OXTR  Oxytocin receptor gene
PA  Proportion affected
PASCQ  Parents as Social Context Questionnaire
PoI  Proportion of the interaction
PPV  Positive predictive value
ROC  Receiver operating characteristics
RoS  Regions of significance
SCAS  Spence Children´s Anxiety Scale – self-report version
SCAS-P  Spence Children´s Anxiety Scale – parent report version
SDI  Structured diagnostic interview
SNP  Single Nucleotide Polymorphism
UDI  Unstructured diagnostic interview
For children, adolescents, and adults alike, in modern society there is always something to worry and feel anxious about, although events or situations that one person perceives as stressful may not be a concern at all for another. Because we do not experience and respond to events in identical ways, we all have individual levels of anxiety.

Anxiety and fear are adaptive emotional and behavioral responses to threatening stimuli, present from infancy and essential for survival. The subjective experience of anxiety includes physiological (e.g., muscle tension, increased heart rate, sweating), cognitive (e.g., thinking about suspected dangers, often in the form of “what-if’s”), and behavioral (e.g., avoiding anxiety-provoking situations) reactions. When these reactions are out of proportion to the actual danger posed, persistent, and negatively affect normal everyday functioning, they are considered maladaptive and, depending on the triggering stimuli, characterized as different types of anxiety disorders. The shift from adaptive to maladaptive anxiety is thought to be caused by multiple extrinsic and intrinsic factors in a complex interplay.

Although publication trends show increasing research since the 1980s, anxiety during childhood and adolescence has historically been considered a normal and transient manifestation of typical developmental challenges and fears; it has therefore been considered of less clinical and research relevance than the study of anxiety in adults [1]. Another factor believed to have hampered research has been the slow development of clinically useful instruments for assessing anxiety in youths. While anxiety disorders are now known to be the most common psychiatric disorders among adolescents, with a lifetime prevalence of approximately 30% and a chronic course into adulthood if not treated, adolescent anxiety is still an under-researched topic [2-6]. Despite reports showing that anxiety disorders are among the leading causes of disability and associated with high societal costs, they frequently remain undetected and untreated in primary and mental health care [7-15].
Classification of anxiety disorders

The two major systems for classifying mental disorders, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and the *International Classification of Diseases* (ICD) have organized anxiety disorders in a similar way in their current and forthcoming editions, the DSM-5 \[16\] and ICD-11 \[17\], respectively. In both systems, the chapter on anxiety disorders includes seven major diagnostic categories, six of which are typically considered in investigations of anxiety among children and adolescents (*Table 1*). The seventh diagnostic category of selective mutism, historically classified in other sections of the DSM and ICD systems, is a relatively rare disorder and is not usually included in epidemiological studies of anxiety. Other changes related to classification include the removal of obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) from the anxiety section and the uncoupling of panic disorder and agoraphobia into two separate categories. Special cases of anxiety are secondary anxiety, such as substance-induced anxiety disorder and anxiety due to another medical condition, which are typically not handled in the same way as other anxiety disorders, and other specified or unspecified anxiety disorder, which are two categories used when symptoms of anxiety cause impairment or distress but do not meet the full criteria for a disorder. The need for the last two categories, included in almost all psychiatric disorders, highlights problems with diagnostic boundaries and heterogeneity within disorders; individuals classified as falling just below or above a diagnostic border can be more similar in terms of symptom severity and functional impairment than individuals who meet the full criteria. While acknowledging the shortcomings with psychiatric nosology, diagnostic classifications of anxiety disorders, like other psychiatric disorders, are essential clinical tools that facilitate communication and research and are often a prerequisite for treatment.
Table 1. Anxiety disorders commonly included in anxiety research among children and adolescents. Typical onset period and core features.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Typical onset period</th>
<th>Core features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Separation anxiety disorder</td>
<td>Early childhood</td>
<td>Anxiety concerning personal or parental harm. Refusal to go to school, leave home alone, leave parents, attend school trips, or sleep at friends’ homes. Anxiety exceeds that expected for developmental stage.</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>Early childhood</td>
<td>Intense fear and avoidance of specific situations or objects, e.g., spiders, heights, or injections.</td>
</tr>
<tr>
<td>Social anxiety disorder (social phobia)</td>
<td>Late childhood to early adolescence</td>
<td>Intense fear and anxiety of negative evaluations in social situations, e.g., being judged as stupid, anxious, crazy, or boring, leading to avoidance or endurance of social situations with intense anxiety.</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>Late childhood to early adolescence</td>
<td>Excessive anxiety and worry about possible negative outcomes in several activities or events. The worry is difficult to control and out of proportion to the likelihood or impact of the feared outcome, e.g., worry about school performances and negative impact on adult life, or worry about social competence and keeping friends. Frequently associated symptoms are muscle tension or aches, difficulty concentrating, sleep disturbance, and irritability.</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>Late adolescence to early adulthood</td>
<td>Recurring and unexpected panic attacks with physical symptoms, such as palpitations, shaking, shortness of breath, or nausea, and fear of going crazy or dying, followed by avoidance of situations thought to trigger panic attacks.</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>Late adolescence to early adulthood</td>
<td>Intense fear and anxiety of situations where bad things are anticipated to happen and where escape might be difficult, such as vomiting in the school bus, getting lost in shops, or panic attacks when standing in a crowd, leading to avoidance of these situations or endurance with intense anxiety.</td>
</tr>
</tbody>
</table>
Measurement

The utilization of validated and structured instruments in routine clinical practice has been proposed as an important factor for increasing the detection and treatment of anxiety among young people [13, 18-19]. Two main types of instruments are typically considered in evidence-based assessments of anxiety, and they are often administered in two stages: questionnaires, followed by structured diagnostic interviews (SDI) if ratings show elevated levels of anxiety.

A specific assessment challenge entails the integration of multiple informants’ reports as adolescence, internalizing problems, and different perceptions of symptoms have been associated with lower parent–child agreement [20]. It is considered best practice to combine all available information from multiple informants and from SDIs, questionnaires, psychological assessments, medical records, observations, and clinical expert opinion for final decisions on diagnoses, a procedure generally referred to as best-estimate diagnosis or Longitudinal, Expert, All Data (LEAD) diagnosis [21-22].

Questionnaires

Self- and parent ratings obtained through questionnaires are a time- and cost-effective method of gathering information on the symptoms of anxiety, and can be helpful both in the detection of clinically anxious youths and for monitoring of treatment effects. Typically, an anxiety questionnaire consists of items in the form of questions or statements regarding feelings of anxiety, worry, and fear in different situations, and respondents are asked to rate how often they experience these feelings or the degree to which they agree on statements. The ratings are then summed into a score, which can be used as a continuous, dimensional measure of anxiety. However, for clinical decision making, a criterion-based transformation of the score into a categorical or dichotomous measure of anxiety is often more helpful for differentiating “cases” from “noncases”. In other words, depending on whether questionnaire scores fall above or under a specified threshold (i.e., a cutoff), individuals may be considered as clinically anxious or nonanxious, pending additional information to confirm the diagnostic status. Evidence for the consistency and accuracy of a questionnaire is often reported by examinations of psychometric
properties, such as internal consistency, test–retest reliability, and concurrent, discriminant, and diagnostic validity (i.e., association with diagnostic classification criteria). Ultimately, information on the clinical relevance and utility of anxiety questionnaires are dependent on evaluations of their performance in settings that permit generalization to equivalent clinical populations.

Three questionnaires are typically mentioned in the literature and designed specifically for the assessment of multiple diagnostic-like categories of anxiety in children and adolescents through both self- and parent reports: the Spence Children’s Anxiety Scale (SCAS) [23], the Screen for Child Anxiety Related Emotional Disorders (SCARED) [24], and the Multidimensional Anxiety Scale for Children (MASC) [25]. Of these, the SCAS has the advantages of covering more anxiety disorders, having a broader answer range, and is free of charge.

The six-factor structure and psychometric properties of the SCAS and its parent version SCAS-P have been examined in Australia where it was originally developed [23, 26-28] and across multiple cultures in Europe [27, 29-36], Asia [37-41], Africa [42] and South and North America [43-47]. In Sweden, the SCAS has been evaluated in an adolescent community sample in Stockholm where results showed good internal reliability, and overall support for the six-factor structure, except for two items, one related to panic/agoraphobia and the other to social phobia. Both of these showed low loadings on their respective factor [35]. Although these studies have all strongly supported the reliability and validity of the SCAS [48], their generalizability is restricted because they have been conducted in community samples, anxiety-specialized clinics, or in a two-stage procedure where participants have been included only if they meet the criteria for an anxiety disorder. None of these samples, settings, and procedures mirror the conditions of general child and adolescent psychiatry clinics, where anxiety is often not a clear or agreed primary cause for help-seeking [11, 49].

Evaluations of the clinical utility of the SCARED and the MASC among Swedish child- and adolescent psychiatric patients are scarce; only the SCARED has been evaluated. The report, published in 2017, showed that the overall ability of the SCARED to predict the presence of anxiety disorders among psychiatrically referred youth was low-to-moderate [50].

Structured diagnostic interviews

Although SDI procedures are considered the gold standard in psychiatric research, they are seldom incorporated into clinical routine practice. Instead, clinical evaluations or clinician-generated diagnoses, such as unstructured diagnostic interviews (UDI), are more commonly used [51]. Studies of agreement between SDI- and UDI-derived diagnoses in clinical youth samples
have shown generally poor agreement for all disorders \cite{51}, and particularly for anxiety disorders. Only 2\% agreement between the two procedures on the presence of anxiety was observed in an American child- and adolescent psychiatric sample, with poor agreement mainly due to UDI-missed diagnoses; UDI procedures identified only 8\% of SDI-derived anxiety \cite{52}. Several causes for the low sensitivity of UDIs have been suggested, including premature termination of information gathering and clinicians’ attitudes toward psychiatric diagnoses \cite{52-54}.

SDIs can be either fully-structured or semi-structured. Fully-structured interviews focus on specified questions to be asked verbatim by the interviewer and in a fixed order. This type of interview is called respondent-based, i.e., it is the respondent who decides whether a symptom is present or not, typically by answering yes or no to each question. Because minimal clinical judgement is required, the use of a fully-structured interview increases the risk of both over- and misdiagnosis of psychiatric disorders. A semi-structured interview is interviewer-based and requires clinical skills and training in order to question respondents in a flexible but systematic manner until the interviewer has gathered sufficient information to decide whether a symptom is present or not. Because this procedure gives respondents the opportunity to describe behaviors and functioning in detail, semi-structured interviews can contribute to individualized treatment planning.

Among several semi-structured diagnostic interviews available for clinicians, one that is widely used especially in psychiatric research is the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) \cite{55}, which guides clinicians in gathering evidence for over 30 psychiatric diagnoses. High agreement between major child and adolescent psychiatric diagnoses derived from a LEAD-procedure and the K-SADS has been reported \cite{56}. For anxiety specifically, the most widely used interview is the Anxiety Disorders Interview Schedule for Children (ADIS-C/P) \cite{57}. Although the ADIS-C/P examines diagnostic criteria for some common co-occurring disorders and symptoms of additional less common disorders, the coverage is narrower than that of the K-SADS and other general SDIs, which makes decisions pertaining to differential diagnostics more precarious and restricts reports of comorbidity.
Epidemiology

Current knowledge on the epidemiology of anxiety disorders in youths is largely based on community surveys with broad age-range samples. In contrast, clinical studies are relatively few in number, and typically include samples referred to specialized anxiety clinics and are limited by the number of disorders investigated. On a national level, epidemiological studies of anxiety among adolescents in Sweden are scarce and influenced by differences in methodological approach and populations, such as single-disorder self-reports of community samples [58], retrospective medical chart reviews [59], or patient administrative systems [60]. In 2013, the Swedish National Board of Health and Welfare published data on self-reported mental health among adolescents and young adults during 1994–2006, showing a period prevalence of 15.2% for mild anxiety and 3.1% for severe anxiety in 16–19-year-olds [61]. Data from community sample surveys more recently conducted in Sweden show that, between the years of 2008/2009 and 2016, the highest increase in the prevalence of troublesome worry and anxiety was found among respondents aged 16–24 years; the prevalence increased from 14.1% to 26.6% among males and from 27.4% to 38.2% among females [62].

Prevalence and onset

Epidemiological community studies consistently show that anxiety disorders are the most prevalent psychiatric disorders during childhood and adolescence, with a global point prevalence of any anxiety of 6–7% and 20–30% having met criteria for an anxiety disorder at some point by early adulthood [2-3, 5, 63-64]. Across the lifespan, anxiety is approximately twice as common among females as among males [63, 65]. Congruent with the observations of high-risk developmental periods for first onset of different anxiety disorders presented in Table 1 [2], reports on individual anxiety disorders show that prevalence estimates vary with age such that separation anxiety disorder is common among children and rare among adolescents, with the opposite being true for social anxiety, panic disorder, and agoraphobia [66-67]. Similarly, the transition from adolescence to early adulthood is a core incidence period for panic disorder, agoraphobia, and generalized anxiety disorder (GAD) whereas first onsets for social anxiety, specific phobias, and separation anxiety rarely occur after adolescence [2-3]. These developmental-specific frequencies of individual anxiety disorders are thought to drive a U-
shaped prevalence curve of any anxiety with a drop in prevalence from early to middle childhood and an increase from early adolescence to young adulthood [3].

While reports consistently describe anxiety as the most common psychiatric disorder in young people, prevalence estimates vary considerably among studies. Meta-analyses of variability sources in community studies reveal that moderating factors partly parallel essential epidemiological characteristics of anxiety, but methodological aspects such as diagnostic method and the categories and number of anxiety disorders included are also important to consider in understanding the differences in prevalence between studies [63-64].

Only three studies on the prevalence of multiple anxiety disorders in nonspecialized child and adolescent psychiatry clinics have been reported, including broad age-range samples of children and adolescents referred for multiple causes [13-14, 68]. Highly disparate estimates were found, ranging from 5.3% to 57%, with a higher prevalence observed when diagnoses were based on structured diagnostic interviews, and a lower prevalence of ~5% reported when diagnoses were based on patient administrative registers rather than on a single structured assessment method. There are no reports of the adolescent-specific anxiety prevalence in nonspecialized child and adolescent psychiatry.

Comorbidity

Among all psychiatric disorders and especially in psychiatrically referred samples, comorbidity is the rule rather than the exception, and this is also true for anxiety disorders. A special case has been made of concurrent anxiety disorders, so-called homotypic comorbidity, because this type of comorbidity is a regular observation in both community and clinical studies of anxiety and has generated specific research concerning the diagnostic and discriminant validity of separate anxiety disorders and the impact of homotypic comorbidity on treatment effect. In the presence of concurrent disorders, the most impairing diagnosis is often assigned as the primary diagnosis whereas less impairing diagnoses are considered as secondary. Anxiety studies often require primary diagnostic status of the target disorder for participant inclusion, however, findings of equal symptomatology, impairment, and comorbidity in referred youth diagnosed with primary and secondary GAD suggest that the distinction between primary versus secondary anxiety diagnosis may not be meaningful in clinical and research settings [69]. Longitudinal observations of childhood anxiety have shown that each anxiety disorder is associated with specific psychiatric outcomes in adulthood, thus arguing for the need to investigate the epidemiology and etiology of individual anxiety disorders in young people rather than treat anxiety as a unidimensional construct [3]. The most commonly co-occurring nonanxiety disorder
(heterotypic comorbidity) is depression, which has been shown to be associated with both general and specific anxiety categories and more impairment \[^2\]. A general finding in studies conducted in nonanxiety-specific clinics, such as general child and adolescent psychiatry, is that heterotypic comorbidity is more prevalent than homotypic comorbidity among anxious youths \[^13-14, 68\].

**Correlates and outcome**

Untreated, anxiety disorders among adolescents are considered chronic, persisting into adulthood, and are associated with functional impairment and negative outcomes in several areas \[^2-3, 70-72\]. Impaired social functioning, including rejection by peers, difficulties making or keeping friends, and not participating in group activities, has been identified both as a predictor and an outcome of anxiety \[^3, 73-74\]. Functional impairment in school is often related to anxiety-triggering situations such as speaking in class, exams, school sports, or a lack of friends to socialize with between lesson breaks \[^58\]. These situations are often completely avoided or endured with marked distress and may lead to short- and long-term academic underachievement and school dropout \[^3, 75-76\]. Aches and pain are included in the diagnostic criteria for some anxiety disorders, they commonly co-occur with anxiety in individuals seeking help primarily because of their physical symptoms, and have been associated with more chronic anxiety \[^77-81\]. Associations between anxiety and poor health outcomes are frequently observed in adults, including increased risk of coronary heart disease and hypertension \[^3, 72, 82-84\].

Follow-up studies have shown that family characteristics play an important role in the course and outcome of anxiety in young people. Living in a family with below-average living standards, low socioeconomic status, experiences of physical or sexual abuse, and parental alcohol problems are family characteristics that have been associated with higher rates of anxiety disorders during adolescence, however this association may be non-specific to anxiety disorders \[^70\]. Childhood traumas such as emotional neglect and psychological and physical abuse have also been associated with more comorbidity and chronicity in adults with anxiety and depression \[^85\].

Regarding treatment outcomes, results from follow-up studies of children and adolescents treated with cognitive-behavioral therapy (CBT), medication, or their combination, suggest that baseline characteristics such as lower levels of anxiety, not having a diagnosis of social phobia, and less caregiver strain are associated with more favorable outcomes directly after treatment \[^86\]. Conversely, being male, having better family functioning, higher socioeconomic status, absence of comorbid externalizing disorders, and fewer negative life events are factors associated with symptom reduction and better functioning at long-term follow-up \[^87\].
Historically, there has been a debate about whether human behaviors are inherited or determined by the environment; the so-called nature versus nurture debate. It is now widely accepted that both environmental and genetic influences are important to consider in the development of complex traits such as anxiety disorders. Recognizing the dynamic interplay between multiple influencing factors and their likely differential impact at different ages, the research field of developmental psychopathology is concerned with adaptive and maladaptive behaviors across the lifespan and factors that contribute to changes in normal and pathological development [88-90]. It is important to note that there are multiple pathways that can result in the development of anxiety disorders (the principle of equifinality) and that a single etiological factor can have an impact on multiple outcomes, not just anxiety (the principle of multifinality) [91-92].

Parenting behavior is often highlighted as an important extrinsic influence in etiological models of anxiety and is singled out as the environmental etiological factor of interest in this thesis alongside genetic influences on anxiety.

Parenting influences

The broad dimensions of rejection and control are commonly regarded as the most relevant parenting characteristics in etiological models of anxiety [4, 93-96]. Several other parental factors are also considered to contribute to the development and maintenance of anxiety disorders in childhood and adolescence. These include parental psychopathology, especially parental anxiety, which increases the risk of their children having an anxiety disorder and predicts worse treatment outcome [97-98], and aspects of parenting behaviors such as modeling and reinforcement of anxious behavior and accommodation, i.e., changes in parental behaviors in order to reduce children’s distress [99-100]. Parenting behaviors across the dimensions of rejection and control were investigated in this thesis and thus will be described in detail below.
Parental rejection and control

Parental rejection involves hostility, withdrawal, negativity, disapproving, and critical behavior as well as lack of warmth, acceptance, and emotional support [101]. Parental control can be conceptualized as either behavioral or psychological in nature. Adequate behavioral control is hypothesized to support children’s sense of competence whereas inadequate behavioral control, e.g., lax control, unpredictability, and unclear and inconsistent rules, has been associated with externalizing disorders [92, 101]. Psychological control refers to restrictive, excessively regulating, and over-controlling behavior and lack of autonomy granting and is considered to contribute more to the development of anxiety in youths compared to behavioral control [93, 98, 102].

The hypothesized mechanisms linking parental rejection and control to anxiety are the negative effects of these parental behaviors on children’s emotion regulation, safety perceptions, and opportunities to explore the environment and learn to cope on their own which in turn diminish children’s sense of mastery and lead to increased anxiety [92, 95, 103]. Conversely, parenting behaviors characterized by warmth, responsiveness, autonomy granting, and firmness are considered important contributors to healthy development with a positive impact on mental health and adaptive behaviors in children and adolescents [104-106].

Paradoxically, given the prominent role that parenting behaviors of rejection and control have in models of anxiety, recent meta-analyses have shown mixed support for a relationship and suggest that these behaviors jointly explain only 4% of the variance in childhood anxiety [4, 95]. Outlined below, theoretical, demographic, and methodological factors have been considered to explain the weak and inconsistent relationships.

Parental rejection and control are commonly conceptualized as bipolar dimensions with positive behaviors (e.g., warmth) at one end of the continuum and negative behaviors (e.g., rejection) at the other end. However, these opposite ends may in fact reflect quite different constructs. Whereas rejection and control have been found to explain 4% and 6% of the variance in childhood anxiety, respectively, analyses of sub-dimensions within these constructs have shown a substantially broader range of explained variance, ranging from <1% to 18% with the smallest effect observed for warmth and the largest for autonomy granting [95]. Thus, current understanding of the parenting–anxiety relationship may be facilitated by investigating sub-dimensions of parenting rather than the broad constructs of rejection and control.

Comparisons between reviews including either samples of broad age ranges or samples of only adolescents have found some dissimilarities. In relation to findings in broader age groups, weaker relationships between anxiety and parental control and stronger relationships between anxiety and parental rejection were found when adolescents were investigated as a
separate group [4, 95, 107]. This may reflect a differential impact and perception of parenting behaviors depending on the age of the child, which are important to consider in the etiology and treatment of anxiety [92, 94, 108].

In general, studies of the parenting–anxiety relationship have focused either on only mothers or on both parents as a unit, without considering the potential differential impact of maternal and paternal behaviors on this relationship [109]. A significant association between adolescent anxiety and paternal control, but not maternal control, has been reported [110]. Likewise, differential impacts of maternal and paternal behaviors on girls’ and boys’ anxiety and depression levels have been found [111]. However, meta-analysis findings are inconsistent regarding differential impacts of mothers and fathers [95, 112]. Relatedly, compensating effects that the behavior of one parent can have on the other parent can also affect the parenting–anxiety relationship [109].

Perceptions of normative parenting and childrearing goals may vary across cultures with implications for the parenting–anxiety relationship. For example, whereas American mothers promote autonomy in their children, Japanese mothers promote interdependence in theirs [113]. Likewise, a study of parents’ self-reported levels of acceptance and rejection across diverse cultures showed that, compared to the overall mean levels, parents in China, Jordan, and Kenya rated themselves as less accepting, whereas parents in Colombia, Italy, Sweden, and the United States rated themselves as more accepting [114].

How anxiety is modeled and how parenting is measured affect the strength of the rejection/control–anxiety relationship. Compared to self- and parent reports of anxiety and parenting through questionnaires, stronger relationships have been observed with clinical diagnoses of anxiety and when parenting behaviors have been rated by an observer [4, 95]. However, it has been argued that analyses of adolescents’ subjective reports of how they perceive their parents’ behaviors can facilitate further understanding of the processes by which parenting behaviors are related to adolescent outcomes [115]. The extent to which findings of the parenting–anxiety relationship obtained in community samples can be generalized to clinical samples remains unclear.

A major limitation in the literature is the dearth of data on the direction of effects—is the relationship between parenting and anxiety best described as parenting predicting child anxiety (parent effect model), or child anxiety eliciting parenting responses (child effect model), or is it reciprocal with children and parents influencing each other’s behavior (bidirectional effect model)? The paucity of data on this topic is often noted in reviews as it hampers further understanding of the parents’ role in evidence-based interventions [4, 92-94, 98, 107]. Results from available prospective studies have provided some support for bi-directional effects, however observations of stronger child than parent effects have also been reported [102, 116-121].

The literature on rejection and control is also limited regarding the spectrum of anxiety disorders as the majority of studies have focused on
general anxiety symptoms rather than diagnostic classifications \cite{4, 95}. Hence, little is known about the specificity in the relationship between parental control and rejection and specific phobia, panic disorder, and agoraphobia.

Finally, parenting behaviors do not affect all children and adolescents to the same degree. The conventional way of understanding differences in effects of parenting is from the perspective of the diatheses–stress framework. According to this, some individuals, due to their personal characteristics, are more likely than others to be negatively affected by negative parenting, whereas all individuals are equally affected by positive parenting. However, this perspective has been challenged by the evolutionary-inspired framework of differential susceptibility, which proposes that children and adolescents differ in their sensitivity to both positive and negative parenting, in a “for better and for worse” manner \cite{122-124}. In the presence of differential susceptibility to parenting, which can be genetically driven \cite{125-126}, positive and negative effects across the continuums of parental rejection and control will be observable only among sensitive individuals, leading to lower or higher levels of anxiety in those individuals compared to non-sensitive individuals.

To summarize, although parenting behaviors of rejection and control are given a prominent role in traditional etiological models of anxiety, meta-analyses have found mixed support for a relationship with small to medium effect sizes. Several issues need to be addressed to further understand the mechanisms by which parenting and anxiety may be linked.

**Genetic influences**

Relative to environmental influences, genetic influences on complex behaviors typically increase across the adolescent period, likely due to increased autonomy and opportunities to choose environments during this developmental stage and changes in brain structure \cite{127-128}. Complex behaviors and traits such as anxiety are influenced by multiple gene variants of small effects and gene–environment interactions (G × E). Furthermore, genetic risk factors are probabilistic rather than deterministic in nature. As an introduction to the chapter on the genetics of anxiety, a brief primer on basic genetics and G × E interaction is first provided.
Basic genetics

Deoxyribonucleic acid (DNA)

DNA is a large molecule that contains the genetic instructions for development and functioning in humans and all other living organisms (Figure 1). The structural units and building blocks of DNA are nucleotides.

![DNA Structure](image)

Figure 1. DNA structure. Image credit: For the National Cancer Institute © 2015 Terese Winslow LLC, U.S. Govt. has certain rights.

A single nucleotide is composed of three units: a sugar molecule, a phosphate-group, and one of the four nitrogenous bases of adenine (A), guanine (G), cytosine (C), and thymine (T). The sequence of the nitrogenous bases determines the amino acid sequence of a protein molecule. The DNA consists of two long nucleotide chains or strands and the nitrogenous bases of each strand form base pairs (bp) according to base pairing rules: A always pairs with T and C always pairs with G.

In human cells, DNA is organized in 23 pairs of chromosomes with one chromosome of each pair inherited maternally and one paternally. A gene is a small section of DNA affecting observable characteristics of an organism (i.e., the phenotype). Each gene has a specific position, a locus, on the chromosome, and typically consists of three types of nucleotide sequence. These are coding regions (exons), non-coding regions (introns), and regulatory sequences which control the expression of the gene. Protein-coding
sequences account for only a small fraction of the human genome (< 2%). Previously considered as abundant “junk DNA”, recent findings of genome-wide association studies (GWAS) indicate that a majority of loci that are associated with phenotypic traits lie outside protein-coding regions, suggesting that noncoding regions of the human genome include important functional elements [129].

**Genetic variation**

The human genome has a total length of ~3 billion bp and is ~99.9% identical between humans, leaving only 0.1% for individual genetic variability. Mutations are the ultimate source of genetic variation. The most common mutation is nucleotide sequence variation which is termed a polymorphism when it is present in more than 1% of the population. Another characteristic of polymorphisms is that they confer weak effects on the phenotype. Different types of polymorphisms include single-base nucleotide substitutions (single nucleotide polymorphisms; SNPs) and structural variations, including deletions, insertions, and repeat variations. A typical human genome differs from the reference human genome at 4–5 million sites, and >99.9% of the variants consist of SNPs and short insertions [130]. All SNPs are assigned a unique reference SNP (rs) number in the Database of Single Nucleotide Polymorphisms (dbSNP) at the National Center for Biotechnology Information [131].

A variant of a nucleotide sequence on a specific locus on a specific chromosome is called an allele. Referred to as a genotype, an individual has two alleles for every locus, one inherited maternally and the other paternally. An individual is said to be homozygous at a locus if the alleles are identical, and heterozygous at that locus if they differ. A SNP with two alleles results in three possible genotypes, e.g., GG, GC and CC. The least common allele in a genotype is called the minor allele. SNPs are classified as common if minor allele frequencies (MAF) are at least 5% and rare when the MAF are below 1%. Polymorphisms may be functional, for example, affecting protein production or gene regulation, and ultimately affect traits such as behaviors or disease susceptibility, either by being protective or by increasing risk. However, polymorphisms may also be silent, not affecting the phenotype at all. In most cases where SNPs have been associated with a phenotype, the function of the polymorphism has not been identified [132].

**Methodological approaches in behavioral and psychiatric genetics**

Different methodological approaches are used to investigate the genetic influences on human behaviors and psychiatric disorders. In family, twin, and adoption studies, there are no direct measurement of the genotype of each individual; instead, the heritability of a trait, i.e., the influence of genetic variation on a trait, is estimated based on known genetic relationships (e.g., dizygotic and monozygotic twins). In molecular studies, genetic variants are
directly measured. Two common approaches in molecular studies of complex traits are candidate gene association studies, which require a priori knowledge or theory regarding which genes are involved in a phenotype, and genome-wide association studies (GWAS), which is a largely atheoretical approach in which polymorphisms across the entire genome are scanned to test associations with a phenotype. In order to fully understand how specific genes contribute to a phenotype, studies of gene expression and function must follow after initial findings of associations between a phenotype and gene variants.

**Gene × environment interaction**

Gene expression is a highly regulated process that is responsive to environmental factors. Some genetic variants may also be modifiers of environmental effects on a phenotype. Thus, studies that investigate only environmental factors or only genetic factors, i.e., main effect studies, may be unable to detect associations with a phenotype. This is the basis of gene–environment interaction (G × E) studies [133]. In the statistical sense, this means that the effect of genotype depends on the environment, and the effect of the environment depends on the genotype; the effect of neither variable is independent [134]. In the biological sense, epigenetic processes, such as DNA methylation and histone modification, provide one mechanism by which environmental and genetic factors affect a phenotype [134-135].

**Nature of G × E interactions**

Traditionally, psychiatric G × E association studies have searched for vulnerability genes and risk alleles. The central idea has been that, depending on genotype, some individuals are more vulnerable to environmental adversities and are thus more likely to develop maladaptive behaviors in response to that exposure, whereas other individuals are more resistant to the same environment and will not develop maladaptive behaviors [136]. This perspective, labeled the diathesis–stress/dual-risk framework [137-138], was adopted in the landmark G × E studies of Caspi and colleagues in which interaction effects between functional polymorphisms and negative life events in relation to antisocial behavior and depression were observed [136, 139]. In turn, this work resulted in a dramatic increase in dual-risk G × E studies of complex behavioral outcomes [134, 140]. Implicit in the diathesis–stress/dual-risk framework is the assumption that vulnerable and non-vulnerable individuals will be equally affected and respond in a similar manner to a nonadverse or supportive environment and thus the dual-risk approach is predictive of a fan-shaped G × E interaction effect (*Figure 2A*) [141]. As a consequence of this assumption, many G × E studies have not measured the full range of environment and outcome, but have instead included, for example, only negative aspects of parenting and only negative outcomes [142]. An evolutionary-based challenge to the dual-risk approach is the differential
susceptibility framework, a perspective predictive of a crossover form of interaction (Figure 2B) [122, 141]. This perspective argues that i) natural selection has shaped humans to respond adaptively to both negative and positive environments, and ii) individual variability in responsiveness to the environment can be genetically driven [126].

**Figure 2.** The nature of a G × E interaction effect. A) The diathesis-stress/dual-risk framework is predictive of a fan-shaped form of interaction. B) The differential susceptibility framework is predictive of a cross-over form of interaction.

Hence, within the G × E research field, the differential susceptibility theory proposes that certain gene variants may be conceptualized as susceptibility alleles rather than vulnerability alleles, and that carriers of susceptible alleles are more susceptible and responsive to both positive and negative environments, in a “for better and for worse” manner [143]. Thus, in the presence of differential susceptibility G × E interaction effects, carriers of susceptible gene variants would be more likely to experience negative outcomes in negative contexts and to benefit more from positive contexts, compared to carriers of non-susceptible gene variants who will be unaffected by the environment. A growing body of G × E studies support a proposal of differential susceptibility effects of interactions including monoaminergic, oxytocinergic and cholinergic gene variants [144].

Regardless of how G × E interactions are conceptualized, difficulties in replicating the findings of G × E studies have raised concerns about the quality and validity of this research field and several recommendations for improving G × E studies have been suggested [140, 145]. Among others, these recommendations include: a theory-driven selection of environment; consideration of the distribution of the environmental factor in the study group; empirical support for selection of genes; presentation of power calculations for the detection of reasonable effect sizes; and tests of the robustness of the interaction [145-146].
Genetics of anxiety

Heritability

Family and twin studies have shown that the risk of having anxiety among first-degree relatives of anxiety-disordered individuals is approximately 5 times higher than among those without an affected relative [147]. Across all anxiety disorders, heritability estimates of 30-50% have been reported, implying that 50-70% of the variance in anxiety may be due to environmental influence [148]. Age, sex, and informant differences in heritability of anxiety have been found, with higher estimates observed for children and adolescents than for adults [149], for girls than for boys, and for fathers’ ratings of their daughters compared to mothers’ ratings and vice versa for their sons [150]. Results from twin studies suggest that the genetic influences on panic disorder, agoraphobia, social phobia, GAD, and specific phobia are best explained by one or two shared genetic factors [151-152].

Molecular studies

Association studies of main genetic effects

The majority of genetic association studies of the anxiety disorders are candidate gene studies conducted among adults, focusing on main effects of genes involved in monoaminergic neurotransmitter systems, neuropeptides, and hypothalamic–pituitary–adrenal (HPA) axis function; neurochemicals implicated in human behavior, cognition, emotion, and arousal [147-148]. A systematic review of candidate gene studies of anxiety, restricted to sample sizes of at least 200 cases, revealed that 56 different genes had been investigated and that a majority of the studies focused on panic disorder (46%) and grouped anxiety disorders or anxiety symptoms (45%) whereas there was only one study on social anxiety and no studies of separation anxiety disorder [153]. The three most commonly studied genes were catechol-O-methyltransferase (COMT), the serotonin transporter (SLC6A4) and brain-derived neurotrophic factor (BDNF). Out of the thirteen genes that had been studied in more than one independent report, no replicated associations were found [153]. A recent meta-analysis of the association of 23 gene variants with panic disorder observed significant associations for only three variants in two genes: the transmembrane protein 132D gene (TMEM132D) and COMT [154]. Among an adult clinical sample, significant main associations with several anxiety disorders were found for 10 polymorphisms linked to four candidate genes: GAD and panic/agoraphobia with SLC6A4; social anxiety with COMT; and panic/agoraphobia with the glutamic acid decarboxylase 1 gene (GAD1) [155].

A meta-analysis of GWAS of multiple anxiety categories and dimensions identified a larger number of associated SNPs for quantitative compared to categorical anxiety [156]. The strongest association with categorical anxiety was
found for a SNP located on chromosome 3, and for quantitative anxiety, loci in three genes located on chromosome 2 exceeded genome-wide significance: the prolyl endopeptidase-like gene (*PREPL*), the calmodulin-lysine N-methyltransferase gene (*CAMKMT*), and the solute carrier family 3 member 1 gene (*SLC3A1*) [156]. The first meta-analysis of GWAS of social anxiety, reported in 2017, found two associated SNPs, located on chromosome 1 and 6 [157]. Also reported in 2017, the largest GWAS of quantitative generalized anxiety found one associated SNP linked to the thrombospondin 2 gene (*THBS2*) on chromosome 6, however this finding was not replicated in three independent samples [158]. A GWAS of phobic anxiety found no genome-wide associations, and a risk score based on SNPs in 31 candidate genes was also unrelated to phobic anxiety [159]. A GWAS including only younger children found no significant SNP associations with parent-rated quantitative anxiety and anxiety-related traits [160].

Epigenetic studies have shown associations between panic disorder and methylation changes in multiple genes, e.g., glutamate decarboxylase 1 (*GAD1*), monoamine oxidase A (*MAOA*) and corticotropin releasing hormone receptor 1 (*CRHRI*) [161-164].

**Association studies of G × E effects**

G × E studies of anxiety have generally focused on the same candidate genes studied in main effect analyses [147-148] and, similar to main effect studies, few have been replicated. A majority of studies have adopted the dual-risk perspective. Variants in two genes have been suggested as robustly associated with anxiety in G × E studies: the *SLC6A4* polymorphism 5HTTLPR and the *BDNF* polymorphism Val66Met [165]. Interactions between childhood maltreatment and 5HTTLPR in relation to anxiety sensitivity have been reported [166-169]. Findings from case-control studies of 5HTTLPR suggest interaction effects with low support and separation experiences in relation to social anxiety [170] and panic disorder [171]. Interaction between the Val66Met-polymorphism in the *BDNF* gene and exposure to early life stress and mothers’ warmth reasoning has been reported, with the Val allele related to increased gray matter of the amygdala and medial prefrontal cortex and higher anxiety [172-173].

“Therapygenetics” is a new approach aimed at identifying genes associated with treatment response. A GWAS investigated genetic influences on CBT treatment response among children and adolescents diagnosed with an anxiety disorder and found no variants to be independently associated with treatment outcome [174]. However, a G × E GWAS of CBT treatment response found that a polygenetic score of environmental sensitivity (i.e., the combination of several genetic variants associated with increased sensitivity to the environment) was related to response to treatment format: individuals with high environmental sensitivity responded best to individual CBT and poorly
to parent-led CBT, whereas low-sensitive individuals responded equally well to all formats [175].

To summarize, efforts to identify the genetic contribution to anxiety disorders have had limited success, compared with other major psychiatric disorders [176]. The reasons for this may be the phenotypic complexity of these disorders, unclear boundaries between normal and pathological anxiety, the likely involvement of thousands of genetic variants of small effect, and the under-utilization of a G × E approach [177].

A growing body of literature suggests that oxytocin and genetic variability in oxytocin pathway genes may play a role in anxiety, especially social anxiety [178-181]. Due to the relevance of this thesis, the last section will focus on oxytocin.

**Oxytocin’s role in social behavior and anxiety**

Oxytocin is an evolutionary ancient neuropeptide hormone dating back more than 600 million years [182]. Oxytocin is long known to affect lactation and parturition, but recent research has focused more on its role in the regulation of human social behavior and mental disorders, especially disorders characterized by social impairment [178].

Oxytocin is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and acts as a neurotransmitter in the central nervous system (CNS), as well as a peripheral hormone in the body [178]. Oxytocin is released during sexual and parenting behaviors and in response to affiliative touch and social stress and interacts with other hormonal and neurotransmitter systems [183-184]. Compared to classical neurotransmitters, neuropeptides degrade much slower and lack spatial specificity, enabling them to dilute throughout the brain [183]. Oxytocin has a key role in the regulation of human social behavior and the response to stress through its projections in a number of brain regions related to social-, emotional-, threat-, and reward-processing, including the basal ganglia, the amygdala, the prefrontal cortex, and the hypothalamus [185-188]. In rodents, administration of oxytocin or oxytocin receptor antagonists in the brain has consistently shown effects on anxiety-related and social behaviors [189].

Several theories about the mechanisms by which oxytocin influences social behavior have been proposed, including the anxiolytic account, which proposes that the anxiolytic effect of oxytocin facilitates prosocial behavior [190-191]; the social salience account, which proposes that oxytocin increases attention to safety and threat signals in the social context, which in turn affects prosocial behavior and anxiety levels [192-195]; the reward sensitivity account, which proposes that the oxytocin–dopamine and oxytocin–opioid pathways influences social reward sensitivity, which in turn affects social behavior [196]; and the in-group/out-group account which
proposes that oxytocin regulates human behavior in the context of intergroup relations [197-198].

Empirical studies of the effects of oxytocin on social behaviors and psychiatric disorders commonly include measurement of peripheral levels of oxytocin (e.g., blood plasma, saliva, urine) as markers of oxytocin levels in the CNS. Consistent with the assumption that central and peripheral levels of oxytocin are correlated, a significant and positive correlation between blood plasma and cerebrospinal fluid (CSF) oxytocin concentrations has been observed among both children and adults, and negative relationships between anxiety ratings and saliva, plasma, and CSF concentrations have been found among children, adolescents, and men [199-201]. However, a recent meta-analysis of the relationship between central and peripheral oxytocin found positive associations only after experimental stress induction and intranasally administered oxytocin (inOT), but not under basal conditions [202].

Reports of inOT effects on anxiety are inconsistent. In a study of healthy men exposed to a social stress test, inOT decreased anxiety levels, and the combination of inOT and social support yielded the lowest cortisol concentrations [203]. In another study of healthy volunteers exposed to stress, inOT reduced anticipatory anxiety prior to a public speaking test, but did not affect anxiety levels during public speaking [204]. In a treatment study of spider phobia, inOT prior to spider exposure negatively affected treatment response as well as ratings of therapeutic alliance and confidence in the treatment [205]. A neuro-imaging study found that the initial reduced amygdala–frontal cortex connectivity observed among social anxiety patients was normalized relative to healthy controls after inOT [206]. Among patients with social anxiety exposed to facial expressions, brain hyper-reactivity in the amygdala, prefrontal cortex, and anterior cingulate cortex were reduced to the same levels as in the placebo groups following inOT [207-208], but, among healthy women, inOT increased amygdala reactivity to threatening pictures [209]. These mixed findings of inOT effects on anxiety mirror findings from studies of inOT effects on prosocial behaviors that suggest that both situational and individual factors moderate inOT effects, which can be negative [192, 210].

Oxytocin pathway genes: involvement in social behavior and psychopathology

Studies of individual genetic variability in the oxytocin system in relation to social behavior and psychiatric disorders have primarily focused on SNPs located in the oxytocin receptor gene (OXTR) [181, 211-216]. The most widely studied OXTR SNPs are rs53576 and rs2254298, but a meta-analysis of research related to main effects of these polymorphisms found that they failed to explain individual differences in personality, psychopathology, social behavior, or autism, and moderator analyses for sex, age, and clinical status did not alter the null findings [217]. Among available G × E studies including OXTR, interaction effects of attachment style and family relationships with
rs53576 in relation to social anxiety \cite{218} and borderline symptoms \cite{219} have been observed. Interaction effects between rs53576 and parenting predicted the student–teacher relationship among Norwegian children in a manner consistent with the differential susceptibility framework, but this finding was not replicated among American children \cite{220}. Among adolescent girls, exposure to maternal depression was found to interact with rs2254298 to predict social anxiety and depression \cite{221}. In contrast, the relationship between childhood trauma and anxiety was not moderated by \textit{OXTR} SNPs rs53576, rs2254298, and rs2268498 in a large Dutch clinical sample \cite{222}. For the latter SNP, rs2268498, genotype-dependent differences in gene expression has been found \cite{223}. \textit{OXTR} hypomethylation has been observed among adults with social anxiety disorder \cite{179}. Differential \textit{OXTR} methylation, conditional on rs53576 genotype, has been observed in older women with anxiety \cite{224}.

Although limited in number, findings of studies that have investigated the structural gene for oxytocin (\textit{OXT}) in relation to social behavior and psychiatric disorders implicate a role for \textit{OXT}-related gene variants \cite{216}. In a positron emission tomography study, the \textit{OXT} SNP rs4813625 was associated with greater stress-induced dopamine responses in female C allele carriers relative to G homozygotes, and the C allele was also related to lower emotional well-being and higher trait and attachment anxiety \cite{225}. Significant associations between the rs4813625 C allele and social withdrawal scores and whole-blood serotonin levels have been observed in autistic children \cite{226}. In a Swedish twin study that investigated associations between four \textit{OXT} SNPs and autistic-like behavior, a significant association with rs2770378 was observed among girls, with more autistic behaviors observed among homozygote major allele carriers than among minor allele carriers \cite{227}. \textit{OXT} SNPs rs274010, rs2770378, and rs4813627 were related to childhood-onset mood disorders in a family-based study, but associations did not remain significant after correction for multiple testing \cite{228}. Associations between \textit{OXT} SNPs rs274010 and rs4813627 and differences in mothers’ vocalization to their infants have been reported, and these SNPs did also interact with mothers’ early life quality of care in predicting instrumental care of their infants and postpartum depression \cite{229}. Results of functional and structural neuroimaging and behavioral and self-report measures suggest that greater \textit{OXT} methylation is associated with un-secure attachment, reduced ability to recognize emotional facial expression, and reduced brain activity and gray matter volume within regions associated with social information processing \cite{230}.

As outlined above, a limited body of research support the role of oxytocin pathway genes in regulating social behavior, anxiety, and stress response. However, the majority of studies have conducted analyses either of the main effects of gene variants or from a risk perspective, without considering contextual factors or differential sensitivity to the environment.
Aims

The overall aim of the present thesis was to examine different aspects of anxiety among psychiatrically referred and community samples of Swedish adolescents.

The specific objectives were to investigate:

- the psychometric properties and diagnostic accuracy of the Swedish versions of the Spence Children’s Anxiety Scale, self- and parent-report versions, among adolescents referred to child and adolescent psychiatric services (Paper I);
- the clinical characteristics of seven anxiety disorders among Swedish adolescents referred to child and adolescent psychiatric services (Paper II);
- the extent to which different parenting behaviors are mediators of the relationship between early and late adolescent levels of anxiety in a Swedish community sample (Paper III);
- the potential interplay between aspects of parenting behavior and polymorphic variations in the OXT gene in association with social anxiety symptoms in a community sample of Swedish adolescents (Paper IV);
- the nature of the OXT × parenting interactions from the perspectives of the differential susceptibility and diathesis–stress frameworks (Paper IV).
Method

This work is a compilation of four papers within a thesis frame. Two of the papers (I and II) were also included in the licentiate thesis titled *Anxiety disorders among adolescents in child and adolescent psychiatry: assessment and characteristics* presented by the author in 2016. Therefore, there are inevitably some similarities between the licentiate thesis and the current doctoral thesis regarding the thesis frame and descriptions of the methods, results, and conclusions. An overview of the methods used in this thesis is presented in Table 2.

Study designs and settings

The cross-sectional design of Papers I and II involved prospective data collection conducted over 63 predefined weeks between August 2011 and June 2013 at two child and adolescent outpatient psychiatry units in the county of Västmanland, Sweden. The units provide services to children and adolescents under 18 years ($N = 37,494$) living within the catchment area and the average number of new referrals is approximately 470 per year. Referrals to the service are made by parents, school health services, primary care units, social services, and hospital departments. The longitudinal design of Paper III and cross-sectional design of Paper IV involved data from the first two waves of an ongoing cohort study, the SALVe cohort (the Survey of Adolescent Life in Vestmanland), with three years between the data collection waves. The SALVe cohort started in 2012 and consists of two birth cohorts (birth years 1997 and 1999; $N = 5,233$) in the county of Västmanland, Sweden. Västmanland is a medium-sized county located in the southwest of Sweden with approximately 264,000 inhabitants. The county is representative of the larger Swedish society with regard to the distribution of educational, income, and employment levels, urban and rural areas, and ethnic backgrounds.
Table 2. Overview of methods.

<table>
<thead>
<tr>
<th>Design</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Child and adolescent psychiatry units in the county of Västmanland, Sweden, between August 2011 and June 2013.</td>
<td>104 adolescents, aged 12–18 years, and their parents.</td>
<td>125 adolescents, aged 12–18 years, and their parents.</td>
<td>1350 adolescents, aged 14 years (2012) and 17 years (2015), and their parents.</td>
</tr>
<tr>
<td>Data collection</td>
<td>Adolescent and parent ratings of anxiety symptoms were assessed by the questionnaires SCAS and SCAS-P (index test). Presence of anxiety disorders was assessed by the diagnostic interview K-SADS (reference standard).</td>
<td>Prevalence of seven anxiety disorders and associated clinical presentation and comorbidity were assessed by the K-SADS, SCAS, and EPIQ.</td>
<td>Adolescent ratings of anxiety symptoms were assessed by the SCAS. Adolescent and parent ratings of parenting behaviors were assessed by the PASCQ.</td>
<td>Adolescent ratings of anxiety symptoms and parenting behaviors were assessed by the SCAS and PASCQ. Two SNPs linked to the OXT gene, rs4813625 and rs2770378, were genotyped using saliva-derived DNA.</td>
</tr>
<tr>
<td>Anxiety disorders/ dimensions</td>
<td>Social anxiety disorder (social phobia) Generalized anxiety disorder Specific phobia Panic disorder with/without agoraphobia Separation anxiety disorder Obsessive compulsive disorder Unspecified anxiety Any anxiety</td>
<td>Social anxiety disorder (social phobia) Generalized anxiety disorder Specific phobia Panic disorder Agoraphobia Separation anxiety disorder Unspecified anxiety Any anxiety</td>
<td>Social anxiety (social phobia) Generalized anxiety Specific phobia Panic/agoraphobia Separation anxiety Total anxiety</td>
<td>Social anxiety (social phobia)</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Psychometric properties of the SCAS and SCAS-P were examined with Cronbach’s alpha and Spearman’s rho statistics. Diagnostic accuracy and predictive power of prior and new cut-off scores was examined by methods of receiver operator characteristics analyses, sensitivity, specificity, positive and negative predictive values and likelihood ratios.</td>
<td>Descriptive statistics. Binomial logistic regression models were used to examine variables associated with anxiety and comorbidity.</td>
<td>Linear regression and path analysis for multiple mediator models were used to examine the influence of baseline anxiety on anxiety at follow-up through six adolescent-rated parenting dimensions. General and specific indirect effects were examined. Informant effects were investigated by replacing adolescent-rated parental behavior with parents’ ratings.</td>
<td>Multiple linear regression models were used to test interaction effects between OXT SNPs and positive and negative parenting in relation to social anxiety. Methods recommended for distinguishing between differential-susceptibility and diathesis-stress models were adopted in the evaluation of the nature of G × E interaction effects.</td>
</tr>
</tbody>
</table>
Participants

In Papers I and II, participants were consecutively enrolled at initial visits and deemed eligible if they met age criteria (minimum age 13 years old during the calendar year of assessment, maximum age 17 years old at recruitment), irrespective of presenting symptoms or referral reason. Exclusion criteria were insufficient Swedish-speaking skills of either child or parent, and a prior diagnosis of intellectual disability. Of the 202 participants eligible for inclusion, 73 were excluded (Figure 3). Informed written consent to participate was obtained from a total of 129 adolescents and their parents. Four did not show up for the interview, leaving 125 participants for final inclusion. A combination of exceeded time frame between intake visit and interview and questionnaire technical problems excluded 21 adolescents from Paper I, leaving a subsample of 104 participants (included in Paper II) for final analysis. Participants’ average age was 16 years and more girls than boys were included. The most frequent causes for seeking help were symptoms of attention-deficit hyperactivity disorder and depression, followed by anxiety. Four adolescents were referred for anxiety only.

Participants in Papers III and IV were from the SALVe cohort. Participants and their parents were recruited by regular mail, and informed written consents, saliva samples and behavioral questionnaires were collected by mail in reply envelopes. Exclusion criteria were insufficient Swedish-speaking skills of either child or parent, a prior diagnosis of intellectual disability or severe mental illness, having lived in Sweden for less than 5 years, and having moved out of the county of Västmanland. Of the 4,712 participants initially eligible for inclusion, a total of 3,127 were excluded after first and second wave data collection, leaving 1,585 with questionnaire data and 1,456 with both questionnaire and genotype data for inclusion (Figure 4). A complete case analysis strategy was adopted and 1,350 adolescents and their parents (85% of eligible participants) in Paper III and 1,359 adolescents (93% of eligible participants) in Paper IV were retained for final analyses. Participants’ average ages at first and second data collection waves were 14 and 17 years, respectively. More girls than boys were included.
Figure 3. Participant recruitment for Papers I and II.
Eligible participants
\( n = 4712 \)

Consented to participate at first wave (2012)
\( n = 1877 \)

Remaining participants at second wave (2015)
\( n = 1585 \)

Participants with questionnaire + genotype data
\( n = 1456 \)

Included in Paper III
\( n = 1350 \)
(781 girls, 57.9%; 569 boys, 42.1%)

Included in Paper IV
\( n = 1359 \)
(807 girls, 59.4%; 552 boys, 40.6%)

Excluded \( n = 2825 \)
Reasons for exclusion:
Declined participation \( n = 1396 \)
Nonresponders \( n = 1429 \)

Excluded \( n = 235 \)
Reasons for exclusion:
Missing items on:
- SCAS social anxiety W2: 1%
- PASCQ: 5%
- rs4813625: 2%
- rs2770378: 1%

Consented to participate at first wave (2012)
\( n = 1877 \)

Non-responders \( n = 292 \)

Excluded \( n = 97 \)
Reasons for exclusion:
Missing items/data on:
- SCAS social anxiety W2: 1%
- PASCQ: 5%
- rs4813625: 2%
- rs2770378: 1%
Measures

Behavioral questionnaires

Anxiety symptoms
In Papers I–IV, symptoms of anxiety were measured by the self- and parent report versions of the Spence Children’s Anxiety Scale (SCAS; SCAS-P) [26-27]. The SCAS and SCAS-P are 44-item (38 score-generating items in both versions and 6 positive filler items in the self-report version to reduce negative bias), Likert-type (0 = “never”, 3 = “always”) questionnaires designed to assess anxiety symptoms in children and adolescents (see an overview of score-generating items in Table 3). The SCAS and SCAS-P provide a total score (range 0–114) as well as scores on six subscales: social phobia (range 0–18), generalized anxiety (range 0–18), separation anxiety (range 0–18), panic/agoraphobia (range 0–27), obsessive compulsive (range 0–18), and physical injury fears (i.e., animal, natural environment, and blood-injection-injury type specific phobias; range 0–15). The SCAS has been examined across multiple cultures and support for its six-factor structure and high internal consistency has been found in the majority of studies [48]. The English versions of the SCAS and SCAS-P were adapted and translated to Swedish using the guidelines recommended by the International Test Commission (see the Swedish versions in the Appendix) [231]. A clinical expert committee reviewed the translated versions to ensure appropriate cultural and linguistic adaptation. Clinical pilot applications before data collection verified the current Swedish versions.

Functional impairment and negative life events
In Paper II, self-reports of functional impairment and negative life events were collected from adolescents during their initial visits through the intake questionnaire, the Electronic Psychiatric Intake Questionnaire (EPIQ), which is routinely used in all child and adolescent psychiatry units in the county of Västmanland [232]. Data obtained from the EPIQ concerned experiences of problems in the five functional domains of family, school, interpersonal, somatic, and sleep. Functional impairment and negative life events were coded as present if adolescents reported any problems in these domains. Items in the family domain concerned any occurrence of child physical abuse, violence between parents, and alcohol or drug problems. Items in the school domain concerned current extra help and current failed courses. Items in the interpersonal domain concerned school-related bullying during the last school-year and difficulty making new friends. Items covering somatic and sleep concerns were headache, stomachache, pain in the neck, shoulders, back, or legs during the last three months and difficulties with sleep during the last three months, and were coded as present if answered with “often” or “always”.
Table 3. Overview of the SCAS, self-report. Score-generating items grouped by subscale.

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Item</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalized anxiety</strong></td>
<td>1</td>
<td>I worry about things.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>When I have a problem, I get a funny feeling in my stomach.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>I feel afraid.</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>When I have a problem, my heart beats really fast.</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>I worry that something bad will happen to me.</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>When I have a problem, I feel shaky.</td>
</tr>
<tr>
<td><strong>Physical injury fears</strong></td>
<td>2</td>
<td>I am scared of the dark.</td>
</tr>
<tr>
<td>(specific phobia)</td>
<td>18</td>
<td>I am scared of dogs.</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>I am scared of going to the doctors or dentists.</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>I am scared of being in high places or lifts (elevators).</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>I am scared of insects or spiders.</td>
</tr>
<tr>
<td><strong>Separation anxiety</strong></td>
<td>5</td>
<td>I would feel afraid of being on my own at home.</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>I worry about being away from my parents.</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>I worry that something awful will happen to someone in my family.</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>I feel scared if I have to sleep on my own.</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>I have trouble going to school in the mornings because I feel nervous or afraid.</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>I would feel scared if I had to stay away from home overnight.</td>
</tr>
<tr>
<td><strong>Social phobia</strong></td>
<td>6</td>
<td>I feel scared when I have to take a test.</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>I feel afraid if I have to use public toilets or bathrooms.</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>I feel afraid that I will make a fool of myself in front of people.</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>I worry that I will do badly at my school work.</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>I worry what other people think of me.</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>I feel afraid if I have to talk in front of my class.</td>
</tr>
<tr>
<td><strong>Panic/agoraphobia</strong></td>
<td>13</td>
<td>I suddenly feel as if I can’t breathe when there is no reason for this.</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>I suddenly start to tremble or shake when there is no reason for this.</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>I feel scared if I have to travel in the car, or on a bus or a train.</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>I am afraid of being in crowded places (like shopping centres, the movies, buses, busy playgrounds).</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>All of a sudden I feel really scared for no reason at all.</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>I suddenly become dizzy or faint when there is no reason for this.</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>My heart suddenly starts to beat too quickly for no reason.</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>I worry that I will suddenly get a scared feeling when there is nothing to be afraid of.</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>I am afraid of being in small closed places, like tunnels or small rooms.</td>
</tr>
<tr>
<td><strong>Obsessive compulsive</strong></td>
<td>14</td>
<td>I have to keep checking that I have done things right (like the switch is off, or the door is locked).</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>I can’t seem to get bad or silly thoughts out of my head.</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>I have to think of special thoughts to stop bad things from happening (like numbers or words).</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>I have to do some things over and over again (like washing my hands, cleaning or putting things in a certain order).</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>I get bothered by bad or silly thoughts or pictures in my mind.</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>I have to do some things in just the right way to stop bad things happening.</td>
</tr>
</tbody>
</table>
Parenting behaviors
In Papers III and IV, aspects of parenting behavior were measured by the Parents as Social Context Questionnaire (PASCQ), a 24-item (adolescent report) and 30-item (parent report), Likert-type (0 = “not at all true”, 3 = “very true”) questionnaire designed to measure parenting behaviors [101, 233] (see the Appendix for the Swedish versions of the items). The PASCQ assesses parenting behaviors in six dimensions, corresponding to six subscales: warmth, rejection, structure, chaos, autonomy support, and coercion. Subscale scores range from 0 to 12 for the adolescent version and 0 to 15 for the parent version. Psychometric evaluations of the PASCQ have provided support for its six-factor structure as well as its reliability and construct validity as an instrument to assess parenting behavior [101, 234]. Support for a six-factor structure of the Swedish adolescent version of the PASCQ has been reported [235]. The six parenting dimensions of the PASCQ were investigated individually in Paper III. In Paper IV, positive and negative aspects of parenting were captured by combining the subscales of warmth/structure/autonomy support and rejection/chaos/coercion into two composite variables, PASCQPOS and PASCQNEG, computed by the summation of individual participant subscale scores corresponding to each composite variable [101].

Diagnostic assessment
In Papers I and II the semi-structured diagnostic interview Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version 2009 (K-SADS) [55], Swedish version [236], was conducted to obtain data on psychiatric disorders. The K-SADS is designed to guide clinicians in the assessment of over 30 separate DSM-IV psychiatric disorders in children and adolescents aged 6–17 years. The interview is widely used as a diagnostic tool in child and adolescent mental health research [68, 237-238]. The predictive validity of the K-SADS in a Swedish child and adolescent psychiatric outpatient setting has been examined and showed excellent validity for most major child psychiatric disorders [56]. Good-to-excellent agreement with LEAD diagnoses as measured by Cohen’s kappa (k) was observed for any anxiety disorder (k = 0.94), with kappas for separate anxiety disorders ranging from k = 0.75 for unspecified anxiety disorder to k = 0.98 for specific phobia.

Prior to data collection for Papers I and II, five experienced clinicians were trained by a K-SADS teacher. Adolescents and parents were interviewed together. Interviewers determined the presence of diagnoses based on full DSM-IV criteria and information collected during the interview, without knowledge of results from the SCAS, SCAS-P or EPIQ. For calibration purposes and to prevent interviewer drift, interviewers watched video
recordings of randomly selected interviews monthly throughout the study. Interrater reliability was calculated with a free-marginal multirater kappa (multirater $\kappa_{\text{free}}$) \(^{239-240}\). Average multirater $\kappa_{\text{free}}$ during data collection was for all diagnoses: $\kappa_{\text{free}} = 0.94$; any anxiety (including OCD): $\kappa_{\text{free}} = 0.92$; separation anxiety: $\kappa_{\text{free}} = 0.83$; social phobia: $\kappa_{\text{free}} = 0.92$; specific phobia: $\kappa_{\text{free}} = 0.94$; OCD: $\kappa_{\text{free}} = 1.00$; GAD: $\kappa_{\text{free}} = 1.00$; and panic/agoraphobia: $\kappa_{\text{free}} = 0.94$.

Genotyping

The process of genotyping typically starts with DNA amplification and proceeds with allele discrimination and identification. The polymerase chain reaction (PCR) is a common method to amplify target DNA sequences. PCR works by using heat to separate a double-stranded DNA molecule into two single-stranded molecules and then copying each single strand with DNA polymerase and a predesigned primer, yielding new double-stranded DNA molecules \(^{241}\). The process can be repeated 30-40 times with each round doubling the amount of target DNA sequence.

In Paper IV, DNA was extracted according to the manufacturer’s guidelines from saliva samples collected using a DNA Self Collection Kit (Oragene®, Ottawa, Canada). Genotyping was performed using a fluorescence-based competitive allele-specific PCR (KASPar™) assay (KBioscience®, Teddington, UK). In the KASPar™ protocol, genotype-specific primers are used in a PCR to produce an allele-specific fluorescent signal that increases with each PCR round. After completion of PCR cycles, the genotype can be determined by reading the fluorescent signal \(^{242}\). Allele discrimination was performed using SNPviewer2®, Teddington, UK.

If no evolutionary mechanisms are present, the genotype and allele frequencies of a population will remain constant from one generation to another and the population is said to be in Hardy–Weinberg equilibrium (HWE). This is typically assessed with a chi-squared test, with a nonsignificant result indicating HWE. Although deviations from HWE may reflect the presence of evolutionary pressure, genotyping errors are a more common cause. Thus, testing of HWE is considered a type of genotyping quality control in genetic association studies \(^{133}\).

OXT gene variants

In Paper IV, two SNPs, rs4813625 and rs2770378, mapped to chromosome 20p13 and located in noncoding regions upstream and downstream of the OXT gene were genotyped (Figure 5 and Table 4) \(^{243-244}\). Participants’ genotypic assignment was performed blind to psychosocial data. The genotypes were in HWE. Genotypes were coded assuming an additive function and based on minor allele count: 0) homozygous for the major allele; 1) heterozygous; and 2) homozygous for the minor allele.
Table 4. Descriptive statistics of oxytocin gene polymorphisms included in Paper IV

<table>
<thead>
<tr>
<th>OXT SNPs</th>
<th>Location</th>
<th>Genotype frequencies N (%)</th>
<th>Minor allele frequency</th>
<th>HWE p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs4813625</td>
<td>chr20:3069074</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>non-coding</td>
<td>386 (28.4)</td>
<td>C: 0.47</td>
<td>0.84</td>
</tr>
<tr>
<td>GC</td>
<td></td>
<td>680 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td></td>
<td>293 (21.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs2770378</td>
<td>chr20:3072868</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>downstream</td>
<td>535 (39.4)</td>
<td>A: 0.37</td>
<td>0.64</td>
</tr>
<tr>
<td>GA</td>
<td></td>
<td>629 (46.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td></td>
<td>195 (14.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: OXT = oxytocin gene; SNP = single nucleotide polymorphism; chr20 = chromosome 20; HWE = Hardy–Weinberg equilibrium.

Statistical analysis

Descriptive statistics

Descriptive statistics, including measures of sample size (n), central tendency (mean, median), dispersion (standard deviation; SD, interquartile range), frequency and percentage were used to describe basic features of the data in Papers I–IV.

Measurement reliability and validity

Reliability and validity are key indicators of the quality of the instruments used in a study. In general terms, the validity of an instrument refers to the degree to which it measures what it is intended to measure. Reliability refers to how consistently a certain characteristic is measured.
Interrater reliability
Interrater reliability (IRR) refers to the degree of agreement between two or more raters. When these raters classify the same subjects into nominal categories, e.g., diagnostic categories, the kappa ($\kappa$) statistic is commonly used as a measure of IRR. A $\kappa$ value of 0.80 or more is considered to be a strong level of agreement. In Papers I and II, a free-marginal multirater kappa (multirater $\kappa_{\text{free}}$) was chosen to calculate the IRR. This kappa statistic differs from the commonly used Cohen’s kappa in that it allows for multiple raters and free marginals (Cohen’s kappa is appropriate for studies with two raters and fixed marginals, i.e., when raters know the quantity of cases that should be distributed into each category).

Internal consistency
The internal consistency of an instrument is an estimate of the degree to which items that propose to measure the same construct yield similar scores and is usually measured with Cronbach’s alpha ($\alpha$). In general, an internal consistency of 0.7 is considered acceptable, although some authors suggest that higher values of 0.90–0.95 should be the norm. The internal consistencies of measures included in this thesis were calculated for the SCAS in Papers I, III, and IV; for SCAS-P in Paper I; for the PASCQ self-report version in Papers III and IV; and for the PASCQ parent report version in Paper III.

Concurrent validity
Concurrent validity is demonstrated when an instrument correlates to a high degree with another measure that has been validated. In Paper I, concurrent validity was examined by calculating Spearman’s rho correlations between the SCAS and SCAS-P scores and interviewer ratings on anxiety items in the K-SADS screening interview. Correlation coefficients can vary from $-1$ (perfect negative correlation) through 0 (no correlation) to $+1$ (perfect positive correlation).

Discriminant validity
Discriminant validity or known-groups validity, is a subtype of construct validity, and here referred to as the ability of an instrument to discriminate between individuals on a certain characteristic. The discriminant validity of the SCAS and SCAS-P was examined in Paper I by analyzing group mean score differences between anxious and nonanxious adolescents.

Diagnostic accuracy
In studies of diagnostic accuracy, an instrument is evaluated in terms of how well it can predict or detect a condition of interest. The instrument being evaluated is called the index test, and the results obtained with the index test
are compared with results of a reference standard, obtained from the same participants. In the framework of diagnostic accuracy studies, the reference standard is the best available method for establishing the presence or absence of a condition and accuracy refers to the amount of agreement between the index test and the reference standard. In Paper I, the diagnostic accuracy of the SCAS and SCAS-P was evaluated in several ways, as presented below.

**Receiver operating characteristics (ROC) analyses**

ROC analyses can be used to examine the criterion validity of an index test, i.e., how well the index test predicts the outcome of the reference standard. The ROC curve is a plot showing the sensitivity for all possible cutoff values of the index test as a function of the false positive rate \((1 - \text{specificity})\). A ROC curve of a perfectly discriminating index test will reach the top left corner in the graph, whereas a position close to the diagonal line represents chance performance.

From the ROC curve, the area under the curve (AUC) can be derived. The AUC is a measure of the overall performance of an index test and is not influenced by a specific cutoff value. The AUC of an index test represents the proportion of individuals with a condition who have higher index test scores than individuals without the condition and can be interpreted as the average sensitivity of the index test. AUC values close to 1 represents better overall predictive diagnostic performance, whereas values close to 0.5 represent chance performance.

Cutoff scores can be derived from ROC analyses, and chosen depending on how the index test is intended to be used. If the objective is to use the test as a screening tool, high sensitivity is more important than high specificity, whereas if the test is intended to be used as a diagnostic tool, high specificity is more important. For all possible cutoff scores provided by ROC analysis in Paper I, the highest cutoff scores with a minimum sensitivity of 0.90 were identified for screening purposes for the SCAS and SCAS-P total scores and all subscales. Likewise, the lowest cutoff scores with a minimum specificity of 0.90 were identified for diagnostic purposes for the SCAS and SCAS-P.

**Sensitivity, specificity, and efficiency**

Using the reference standard as the criterion, the sensitivity of the index test refers to the probability that individuals with a condition are correctly identified by the test, whereas the specificity of the test refers to the probability that individuals without the condition are correctly identified. Efficiency refers to the proportion of individuals correctly classified as either having or not having the condition. The sensitivity, specificity and efficiency of an index test are functions of the chosen cutoff level, e.g., the score that represents the boundary between normal and diagnostic levels of an outcome. In Paper I, the sensitivity, specificity, and efficiency of previous cutoff scores, referred to as \(T60\) and derived from an Australian community sample using the normal
distribution method, and new cutoff scores obtained from ROC analyses were examined.

**Posterior probabilities**
The diagnostic utility of a test can be evaluated in terms of how the probability of having a condition of interest changes after administration of the index test, i.e., did the patient’s test score fall above or below the chosen cutoff score and how does the result change the probability of the condition compared with the probability prior to the administration of the test? In Paper I, the posterior probabilities were examined for the SCAS and SCAS-P in two ways (presented below), using previous cutoff scores and new cutoff scores obtained from ROC-analyses.

Positive and negative predictive values (PPV and NPV, respectively) are the proportions of results above or below a chosen cutoff score that are true positives and true negatives. High PPVs and NPVs indicate high accuracy. PPVs and NPVs are dependent on the prevalence in the reference group where they were first calculated, and thus they are only transferrable to similar settings and prevalence rates.

Positive and negative likelihood ratios (LR+ and LR−, respectively) indicate how many more times likely a test result is in individuals with a condition than in those without, and range from 0 to infinity. LRs greater than 1 indicate a higher likelihood of the presence of the condition, LRs smaller than 1 indicate that the condition is less likely and LRs equal to 1 lack diagnostic value. LRs are calculated from the sensitivity and specificity of the index test, and therefore are not driven by the prevalence of the condition. To interpret LRs in terms of posttest probabilities, a graphical conversion tool, such as a nomogram, can be used [245].

**Inferential statistics**
Statistical inference is the process whereby certain characteristics or properties of a population are estimated using data obtained from a sample of the population. Statistical significance, the probability of observing an effect or difference given that the null hypothesis of no relationship/difference is true, was set at p < .05 in all papers. Statistical power, the probability of correctly rejecting the null hypothesis when a true association exists, was calculated in Papers III and IV.

**Between-group differences**
Between-group differences were investigated by chi-squared tests for categorical data and t tests for continuous and ordinal data in all papers. The results of the t tests were validated by the nonparametric Mann–Whitney U test.
Regression analyses and linear models

Linear regression

In linear regression analysis, data obtained from a study is used to create a mathematical model—an equation—that estimates a continuous outcome variable from a single predictor or a set of predictor variables. Each predictor in the model is given a regression weight that quantifies the expected change in the outcome variable for every one-unit change in the predictor, holding constant other predictors in the model. The regression equation can be graphed in a scatterplot, where the resulting regression line shows the straight line that best represents the data.

Research questions such as how, for whom, and under what circumstances require additional variables to explain the relationship between a predictor and an outcome. Mediation and moderation analyses are two examples of “third variable” analyses. Ordinary least squares (OLS) regression was used to estimate mediation and moderation models in Papers III and IV. In OLS regression, the most common method for estimating a linear regression model, the regression equation is constructed so that the sum of the squared distance between the observed values of the outcome and the predicted values is minimized.

Mediation

Mediation analysis is a statistical method for investigating mechanisms and quantifying pathways of influence by which a predictor influences an outcome variable. A simple mediation model (Figure 6, model A) assumes directions of effects through two pathways. One pathway, the direct effect $c'$, leads from the predictor to the outcome variable without passing through a mediator. A second pathway, the indirect effect $ab$ (i.e., the product of pathways $a$ and $b$ in Figure 6, model A), goes from the predictor through a mediator to the outcome variable. The direct and indirect effects partition the total effect, which estimates the effect of the predictor on the outcome variable without the mediator in the model. The regression coefficients of the total, direct, and indirect effects can be estimated by conducting OLS regression analyses. In Paper III, parallel multiple mediation was modeled to simultaneously examine the extent to which six parenting behaviors, measured by the PASCQ, are mediators of the relationship between early and late adolescent levels of anxiety as measured by the SCAS.

Moderation

The goal of moderation analyses is to establish the boundary conditions for an association between a predictor and an outcome variable. If the effect of the predictor on the outcome depends on a second variable, a moderator, the predictor and the moderator are said to interact in influencing the outcome. A simple moderation model (Figure 6, model B) can be represented by an
equation with a predictor, a moderator, and a cross-product term defined as the product of the predictor and the moderator. This equation allows the effect of the predictor on the outcome to be a linear function of the moderator. **Paper IV**, a G × E study, aimed to investigate the interaction between parenting behaviors, which was measured by the two composite variables, PASCQ^{POS} and PASCQ^{NEG}, and oxytocin gene variants in association with social anxiety, measured by the SCAS.

![Conceptual diagrams for two methods to investigate how a third variable can explain the relationship between a predictor and an outcome variable. A) A simple mediation model. B) A simple moderation model.](image)

**Figure 6.**

**Nature of the interaction**

Interpretations of G × E interactions differ depending on the form. Whereas early research lacked formal criteria for discriminating between fan-shaped and crossover types of interaction, more rigorous methods have now been developed to help researchers identify evidence for the two types of interaction. In **Paper IV**, a series of critical tests was conducted to examine whether significant interactions conformed to a crossover pattern [246]. All tests were conducted within a conventional range of ±2 SD from the mean on the PASCQ^{POS} and PASCQ^{NEG}.

The first critical test is called the regions of significance (RoS) test. This test defines the values of the environmental variables at which the relationship between gene variants and the outcome moves from nonsignificance to significance. The RoS test is deemed consistent with differential susceptibility if it demonstrates that oxytocin gene variants are associated with social anxiety at both low and high levels of the PASCQ^{POS} and/or PASCQ^{NEG} (Figure 7) [246].

The second critical test, the proportion of the interaction (PoI), is based on the shape of the interaction. The PoI is a measure of the proportion of the total area between the regression lines in an interaction plot that is on the qualitatively positive side of the crossover point (Figure 7). A PoI value between 0.20 and 0.80 is considered evidence for differential susceptibility [247].

The third critical test, the proportion affected (PA), concerns the proportion of the sample that falls on the positive side of the crossover point. Interactions are deemed consistent with differential susceptibility if the PA is above 16% [246].
The fourth test is a test of nonlinearity. This test must show that the interaction terms remain significant in models including quadratic terms of PASCQ\textsuperscript{POS} and PASCQ\textsuperscript{NEG}\textsuperscript{[246]}. 

![Diagram](image)

*Figure 7. Example of a G × E interaction plot with critical tests of differential susceptibility superimposed.*

**Logistic regression**

Logistic regression is a special case of the generalized linear model where the outcome variable is categorical. It is used to predict a dependent variable that can take only one of two values, i.e., a binary categorical variable. The regression weight estimated in logistic regression is often transformed to an odds ratio (OR) prior to interpretation. The OR represents the factor change in odds of an event as the predictor variable increases by one unit. In **Paper II**, logistic regression analyses were conducted to examine variables associated with anxiety and comorbidity.

**Effect sizes**

Besides reporting that a relationship is statistically significant, it is also important to report effect sizes, which are measures of the strength of a relationship or the magnitude of a difference between groups. There are multiple measures of effect size, and they are commonly divided into three families: the correlation family (based on variance explained), the difference family (based on differences between means), and the categorical family (based on associations between categorical variables). For all measures of effect size, a larger absolute value indicates a stronger effect.

The following effect size measures from the correlation family were reported: Spearman’s correlation coefficient, \( r \) (**Papers I, III, and IV**), the coefficient of determination, \( R^2 \) (**Paper III**), and \( R^2 \) change due to interaction, \( \Delta R^2 \) (**Paper IV**). One effect size measure from the difference family was reported: Cohen’s \( d \) (**Papers I and III**). One effect size measure from the categorical family was reported: odds ratio, OR (**Paper II**). In addition, in **Paper III**, the partially standardized (\( ps \)) effect size was calculated. This
effect size estimated how much individuals that differed by one point in raw SCAS-scores at baseline were estimated to differ in standard deviations on the SCAS at follow-up.

Statistical programs
Statistical analyses were conducted using SPSS versions 20, 22, and 24 running on Windows 7. Additional statistical software and online calculators were used to obtain estimates not provided by SPSS procedures. Online calculators were used in Paper I to obtain multirater $\kappa$ \cite{248} and significance tests for the difference between dependent correlations \cite{249}, and in Paper II to obtain confidence intervals for proportions \cite{250}. The MedCalc for Windows software was used to obtain likelihood ratios with confidence intervals and to test the statistical significance of the difference between dependent ROC curves in Paper I \cite{251}. The PROCESS macro version 2.16 for SPSS was used in Paper III to model and analyze parallel multiple mediation and in Paper IV to test and visualize interaction effects \cite{252}. Power calculations were made with an online Java applet \cite{253} in Paper III, and with the Quanto software \cite{254} in Paper IV.

Ethical statement and considerations
Papers I and II were approved by the Regional Ethical Review Board in Uppsala (approval number 2008:214). Participants were enrolled by clinical staff when they visited the psychiatric units and thus had the opportunity to ask questions about the project before they gave their consent to participate. After data collection, which included extensive problem-focused assessment through questionnaires and interviews, participants were asked to provide a confidential evaluation of how they perceived the usefulness and adequacy of all assessments as well as their treatment as a participant during data collection. Results showed that, on average, participants felt well treated and assessments were perceived as useful, leading to an increased understanding of presenting symptoms. Papers III and IV were approved by the Regional Ethical Review Board in Uppsala (approval number 2012:187). Data collection for both papers was home-based. Participants were informed in writing and were also provided with links to videotaped information, available on the Center for Clinical Research Västerås website, and telephone numbers to the principal investigator for further questions regarding participation and the purpose and content of the project. All studies included in this thesis were conducted in accordance with the Declaration of Helsinki \cite{255}.
Results and brief discussion

A summary of the aims, findings, and conclusions of studies in the thesis is presented at the end of this chapter in Table 7, (page 60).

Paper I

Assessing adolescent anxiety in general psychiatric care: diagnostic accuracy of the Swedish self-report and parent versions of the Spence Children’s Anxiety Scale

This study addressed the lack of data on the diagnostic utility of the SCAS and SCAS-P in nonanxiety-specific clinical settings. Using the diagnostic interview K-SADS \[55\] as the reference standard, the objectives were to investigate the psychometric properties of the Swedish translations of the SCAS and SCAS-P, to determine empirical cutoff scores for screening and diagnostic purposes, and to evaluate the diagnostic accuracy of the SCAS and SCAS-P among Swedish adolescents referred to a general psychiatric outpatient clinic.

Evaluation of the psychometric properties of the SCAS-and SCAS-P showed that the internal consistency coefficients $\alpha$ fell in the good to excellent range. In the total sample, $\alpha$ for the total score was 0.94 for the SCAS and 0.91 for SCAS-P. For the subscales, $\alpha$ values were generally lower than for the total scores. Evaluation of concurrent validity showed that both the SCAS and SCAS-P total and subscale scores were significantly and positively correlated with the K-SADS anxiety screening scores. The strength of the associations ranged from $r = 0.22$ to $r = 0.74$ with no differences in the strength of the relationship between the SCAS and SCAS-P, except for the total score and the separation anxiety subscale, where stronger relationships between the SCAS and the K-SADS than between the SCAS-P and the K-SADS were observed. Examination of the discriminant validity showed that the SCAS and SCAS-P scores of anxious adolescents were significantly higher than the scores of nonanxious adolescents with effect sizes in the medium-to-large range ($d = 0.69–1.75$) as determined by Cohen’s $d^{256}$.

The overall ability of the SCAS and SCAS-P to predict any anxiety as well as the specific diagnoses of social phobia, GAD, specific phobia, panic/agoraphobia, OCD, and separation anxiety disorder was significant for
both the total score and all subscales and fell in the fair-to-excellent range (AUC range = 0.70–0.94) (see example ROC curve for total scores in Figure 8).

**Figure 8.** ROC curve and AUC estimates for SCAS and SCAS-P total scores to predict any K-SADS-derived anxiety disorder.

![ROC Curve Image](image)

<table>
<thead>
<tr>
<th>Index test</th>
<th>Area under the curve (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCAS total score</td>
<td>.89</td>
</tr>
<tr>
<td>SCAS-P total score</td>
<td>.86</td>
</tr>
</tbody>
</table>

The diagnostic accuracy of previous (T60) and new (screening and diagnostic) cutoff scores was evaluated. For all subscales of the SCAS, the diagnostic (i.e., high specificity) cutoff was the best cutoff for overall correct classification, and scores above this threshold yielded the largest increase in pre-to-posttest probability of an anxiety disorder with an average increase of 40 percentage points. For the SCAS total score, the screening (i.e., high sensitivity) cutoff yielded the highest efficiency and the T60 cutoff the largest increase in probability of anxiety. For both the total score and all subscales, scores under the screening cutoff yielded the largest decrease of the probability of anxiety with an average decrease of 17 percentage points. For the SCAS-P, no previous cutoff scores were available. For both the total score and all subscales, the diagnostic cutoff was the best for overall efficiency and yielded the highest pre-to-posttest probability increase. Overall, posttest increases and decreases of probabilities of anxiety disorders were smaller for cutoff scores of the SCAS-P than for the SCAS.

**Paper 1** represents the first evaluation of the SCAS and SCAS-P in a nonanxiety-specific psychiatric setting where participants were included irrespective of anxiety status or referral cause. Results showed support for the reliability and validity of the Swedish translations of the SCAS and SCAS-P.
and demonstrated that these measures can distinguish between adolescents with and without an anxiety disorder. Evaluations of the diagnostic accuracy of new and previous cutoff scores showed that the new cutoff scores performed better in terms of correct classification and changes of the pretest probabilities of anxiety. General implementation of the SCAS and SCAS-P and utilization of the new empirical cutoff scores, available at https://www.scaswebsite.com/, can facilitate detection and identification of adolescents in need of anxiety treatment.

Paper II

Anxiety disorders among adolescents referred to general psychiatry for multiple causes: clinical presentation, prevalence, and comorbidity

There is a general paucity of data regarding the prevalence and clinical correlates of multiple anxiety disorders in nonspecialized psychiatric outpatient settings, where anxiety may not be a recognized or primary cause for help-seeking \[11, 49\]. There are no diagnostic interview-based reports of the specific characteristics among adolescents referred to psychiatry clinics for any cause \[13-14, 66, 68\]. The aim of this study was to examine the clinical characteristics of anxiety among adolescents psychiatrically referred for any cause, using the K-SADS diagnostic interview \[24\] and an intake questionnaire \[232\]. Anxiety disorders were characterized by prevalence, clinical presentation and patterns of comorbidity, including both homotypic and heterotypic comorbidity.

At least one anxiety disorder was found in 46.4% of adolescents, with girls diagnosed more than three times more often than boys. The prevalence of the individual anxiety disorders was as follows: social anxiety disorder, 27.2%; GAD, 17.6%; specific phobia, 16.8%; panic disorder, 9.6%; agoraphobia, 9.6%; separation anxiety disorder, 4.0%; and unspecified anxiety disorder, 1.6%. A referral for anxiety symptoms was not related to any K-SADS-defined anxiety disorder. Only 21% of adolescents diagnosed with an anxiety disorder were referred for symptoms of anxiety.

Significant differences in clinical presentation, functional impairment, and experiences of negative life events between anxious and nonanxious adolescents were found for SCAS mean total scores, prior admission to the units, referral cause, difficulties making friends, and body aches (Table 5). There were no significant differences with regard to referral source, family problems, school functioning, or sleep concerns. However, the total number of problems related to impairment or negative life events was significantly higher among anxious than nonanxious adolescents.

Of those diagnosed with an anxiety disorder, 5.2% had no comorbidity, 43.1% had homotypic comorbidity (i.e., concurrent anxiety disorders), and
91.4% had heterotypic comorbidity (i.e., concurrent nonanxiety psychiatric disorders).

Table 5. Differences in clinical presentation between K-SADS-defined anxious and nonanxious adolescents.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Anxious (n = 58)</th>
<th>Nonanxious (n = 67)</th>
<th>t/χ²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCAS scores, mean (SD)</td>
<td>40.2 (18.3)</td>
<td>20.2 (14.2)</td>
<td>6.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prior admission, n (%)</td>
<td>24 (41.4)</td>
<td>13 (19.4)</td>
<td>7.2</td>
<td>0.007</td>
</tr>
<tr>
<td>ADHD</td>
<td>11 (19.0)</td>
<td>28 (41.8)</td>
<td>7.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Depression</td>
<td>23 (39.7)</td>
<td>15 (22.4)</td>
<td>4.4</td>
<td>0.036</td>
</tr>
<tr>
<td>Difficulties making friends, n (%)</td>
<td>21 (36.2)</td>
<td>7 (10.4)</td>
<td>11.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Body aches, n (%)</td>
<td>46 (79.3)</td>
<td>25 (37.3)</td>
<td>22.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of problems a, mean (SD)</td>
<td>3.5 (1.7)</td>
<td>2.5 (1.6)</td>
<td>3.6</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Note: ADHD = attention deficit hyperactivity disorder; SCAS = Spence Children’s Anxiety Scale.

The most frequent overlaps between anxiety disorders were social anxiety with concurrent GAD (20.7%) and social anxiety with concurrent specific phobia (20.7%). Among anxious adolescents, the diagnoses of GAD, specific phobia, and panic disorder were significantly associated with homotypic comorbidity. Significantly higher rates of trauma-related disorders were observed among adolescents with anxiety than in those without (Table 6). There were no other significant differences in the prevalence of heterotypic comorbid categories between anxious and nonanxious adolescents. Significant associations were observed between trauma and panic disorder, trauma and social anxiety, depression and GAD, and between conduct disorder and agoraphobia.

Table 6. K-SADS-defined homotypic and heterotypic comorbidity among psychiatrically referred adolescents, by anxiety status.

<table>
<thead>
<tr>
<th>Comorbid category</th>
<th>Anxious (n = 58)</th>
<th>Nonanxious (n = 67)</th>
<th>χ²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homotypic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>53.4 (40.8–65.7)</td>
<td>37.3 (26.7–49.3)</td>
<td>3.3</td>
<td>0.070</td>
</tr>
<tr>
<td>Neurodevelopmental</td>
<td>51.7 (39.2–64.1)</td>
<td>59.7 (47.7–70.6)</td>
<td>0.8</td>
<td>0.370</td>
</tr>
<tr>
<td>Trauma</td>
<td>15.5 (8.4–26.9)</td>
<td>4.5 (1.5–12.4)</td>
<td>4.4</td>
<td>0.037</td>
</tr>
<tr>
<td>Conduct</td>
<td>13.8 (7.2–24.9)</td>
<td>14.9 (8.3–25.3)</td>
<td>0.0</td>
<td>0.857</td>
</tr>
<tr>
<td>Eating</td>
<td>8.6 (3.7–18.6)</td>
<td>4.5 (1.5–12.4)</td>
<td>0.9</td>
<td>0.470</td>
</tr>
<tr>
<td>Obsessive</td>
<td>6.9 (2.7–16.4)</td>
<td>7.5 (3.2–16.3)</td>
<td>0.0</td>
<td>1.000</td>
</tr>
<tr>
<td>Psychotic</td>
<td>3.4 (1.0–11.7)</td>
<td>3.0 (0.8–10.2)</td>
<td>0.0</td>
<td>1.000</td>
</tr>
<tr>
<td>Bipolar</td>
<td>1.7 (0.3–9.1)</td>
<td>1.5 (0.3–8.0)</td>
<td>0.0</td>
<td>1.000</td>
</tr>
<tr>
<td>Substance</td>
<td>0 (0.0–6.2)</td>
<td>3.0 (0.8–10.2)</td>
<td>1.8</td>
<td>0.499</td>
</tr>
</tbody>
</table>

Note: a Presence of ≥1 non-anxiety psychiatric disorder
Paper II represents the first structured interview-based examination of the specific characteristics of anxiety among adolescents referred to a psychiatric clinic for any cause. The prevalence of any anxiety disorder observed in this study is akin to the two previously reported prevalence studies based on diagnostic interviews conducted in a nonanxiety specific setting, although those studies included samples with a broader age range or only younger children. The finding that only 21% of adolescents diagnosed with anxiety disorders were referred because of anxiety symptoms further supports the importance of routine use of standardized and structured instruments, irrespective of referral reason, to improve detection rates in the clinical setting. The clinical correlates of anxiety disorders observed in this study have been associated with more chronicity and negative outcomes, and highlight the necessity of comprehensive assessment and individualized treatment to attend to the complexity of symptoms in this patient group.

Paper III

The mediating role of parenting behaviors in the relationship between early and late adolescent levels of anxiety: specificity and informant effects

The role of parenting behavior is often highlighted in the development of anxiety in children and adolescents [2, 257-258]. Previous reports are limited in terms of the specificity of the relationship between different types of anxiety and parenting behaviors and informant effects on these relationships. The aim of this study was to examine the extent to which parenting behaviors across the continuums of behavioral and psychological control and rejection, as measured by the PASCQ, are mediators of the relationship between early and late adolescent levels of anxiety, measured by the SCAS. Specific and general mediation effects were examined by analyzing the influence of adolescent-reported anxiety in early adolescence on homotypic (i.e., same-type) anxiety at 3-year follow-up through six parenting behaviors. Informant effects were investigated by replacing adolescent-rated parental behavior with parents’ own ratings.

Parallel multiple mediation models were used to simultaneously examine the extent to which baseline anxiety influenced anxiety at follow-up both directly and indirectly through six adolescent-rated parenting dimensions. Holding sex, baseline age, all parenting dimensions, and baseline levels of all anxiety dimensions other than the focal dimension constant, significant direct effects of baseline anxiety on anxiety at follow-up were observed for all anxiety dimensions. On average and with statistical control for all variables in the models as described above, for every one-point increase in raw SCAS scores at baseline, the direct effect on anxiety at follow-up was an increase of 0.5 points, corresponding to $\leq 0.2$ SD on the dependent variable.
Analyses of general mediating mechanisms through all parenting dimensions simultaneously showed significant and positive total indirect effects for social anxiety, panic disorder/agoraphobia, and total anxiety (Figure 9). All significant total indirect effects, measured with partially standardized effect sizes, were small, with individuals differing by one point in baseline SCAS scores estimated to differ by 0.004–0.015 SD on the corresponding SCAS subscale at follow-up as a result of the influence of all parenting dimensions simultaneously.

Analyses of mediation mechanisms through each parenting dimension separately and with statistical control for competing parenting behaviors showed significant and positive specific indirect effects for generalized anxiety through structure and chaos, and for panic/agoraphobia and total anxiety through rejection and chaos (Figure 10). Again, all significant specific indirect effects were small, as measured with partially standardized effect sizes, with individuals differing by one point in baseline SCAS scores estimated to differ by 0.001–0.012 SD on the corresponding SCAS subscale at follow-up as a result of the influence of parenting.

Compared with models with adolescent-reported parenting, general mediating effects remained significant only for total anxiety when parents rated their own behavior. Specific indirect effects remained significant only for panic/agoraphobia and total anxiety through the parenting dimension of rejection when parents rated their own behavior. Partially standardized effect sizes were comparable with those obtained from models with adolescent-reported parenting.

The results of Paper III demonstrated that early adolescent anxiety influences homotypic anxiety in late adolescence independent of parenting behaviors. Overall, the results suggest that parenting behaviors play a very minor role as unconditional mediators in the relationship between early and late adolescent levels of anxiety, irrespective of the informant on parenting behaviors. Evidence of specificity was the exception rather than the rule when competing parenting behaviors were held constant.
Figure 9. Summary of the general mediating role of adolescent-reported parenting behaviors in the relationship between early and late adolescent levels of anxiety. Significant and positive total indirect effects simultaneously through six dimensions of parenting behaviors were observed for total anxiety, panic/agoraphobia, and social anxiety.

Figure 10. Summary of the specificity of the mediating role of adolescent-reported parenting behaviors in the relationship between early and late adolescent levels of anxiety. Significant and positive specific indirect effects of total anxiety, generalized anxiety, and panic/agoraphobia through chaos, structure, and rejection were observed.
Paper IV

Differential susceptibility effects of oxytocin gene (OXT) polymorphisms and perceived parenting on social anxiety among adolescents

Social anxiety is one of the most commonly reported mental health problems among adolescents, and it has been suggested that parenting style influences an adolescent’s level of social anxiety \cite{105, 259}. A limited body of research provides preliminary support for associations between variants in the OXT gene and the stress response, anxiety, and social withdrawal \cite{225-229}. The majority of studies in these two lines of research have conducted analyses either on the main effects of gene variants and parental behavior on anxiety or from a risk perspective, without considering moderating factors or differential sensitivity to the environment. The primary aim of this study was to investigate the potential interactions between positive and negative aspects of parenting behaviors, as measured by the PASCQ, and polymorphic variations in the OXT gene in association with social anxiety symptoms, as measured by the SCAS social anxiety subscale. A secondary aim was to explore whether the nature of G x E interactions conformed to the differential susceptibility framework.

In regression models adjusted for sex, significant interaction effects were observed for both rs4813625 and rs2770378 with the PASCQ\textsuperscript{POS} but only for rs2770378 with PASCQ\textsuperscript{NEG}. Negative associations with social anxiety were observed for both variants with the PASCQ\textsuperscript{POS} with marginal $R^2$ changes due to the interaction of 1\% for rs4813625 and 0.3\% for rs2770378. The interaction of the PASCQ\textsuperscript{NEG} with rs2770378 was positively associated with social anxiety with a marginal $R^2$ change of 0.3\%. Two interaction terms remained significant after tests of nonlinearity: rs4813625 $\times$ PASCQ\textsuperscript{POS} and rs2770378 $\times$ PASCQ\textsuperscript{NEG}. Consistent with a differential susceptibility prediction of a crossover type of interaction, the RoS test showed that rs4813625 was associated with social anxiety at both low and high levels of positive parenting behavior, with lower and upper boundaries of the RoS within $\pm 1$ SD from the mean score of the PASCQ\textsuperscript{POS} (Figure 11.). Carriers of the C allele reported higher levels of social anxiety under low parental support and lower levels of anxiety under high parental support than G homozygote carriers, who were close to unaffected by parenting. The rs4813625 $\times$ PASCQ\textsuperscript{POS} interaction also passed the PoI and PA critical tests of a differential susceptibility type of interaction. Consistent with the diathesis–stress framework, the RoS test showed that rs2770378 was associated with social anxiety only at higher levels of negative parenting behavior, corresponding to 1.8 SD above the mean score on the PASCQ\textsuperscript{NEG}, with A allele carriers reporting higher levels of social anxiety than GG carriers (Figure 12).

Paper IV is the first study of joint associations of OXT variants and aspects of parenting behaviors with social anxiety among healthy adolescents. The results contribute to research relating to the etiology of social anxiety.
Figure 11. Interaction effect of OXT SNP rs4813625 and PASCQ^POS on social anxiety scores. Shadowed areas represent RoS within ±2 SD from the mean score of the PASCQ^POS.

Figure 12. Interaction effect of OXT SNP rs2770348 and PASCQ^NEG on social anxiety scores. Shadowed area represent RoS within ±2 SD from the mean score of the PASCQ^NEG.
Table 7. Summary of aims, findings, and conclusions of studies in the thesis.

<table>
<thead>
<tr>
<th>Paper I</th>
<th>Aims</th>
<th>Main findings</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Investigate the psychometric properties and diagnostic accuracy of the Swedish versions of the SCAS and SCAS-P in a nonanxiety-specialized psychiatric setting. Determine empirical cutoff scores for screening and diagnostic purposes.</td>
<td>Support for reliability and validity of both scales was obtained. The overall ability to predict anxiety ranged from fair to excellent for both scales. The percentage of correctly classified anxiety was consistently higher for new cutoff scores compared to previous cutoff scores. The SCAS and SCAS-P can differentiate adolescents with an anxiety disorder from those without an anxiety disorder in a nonanxiety-specialized psychiatric setting. Detection of anxiety can be improved by using new cutoff scores for screening purposes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Characterize seven anxiety disorders among psychiatrically referred adolescents by prevalence, clinical presentation, and comorbidity.</td>
<td>The prevalence of any anxiety was 46%. Homotypic comorbidity was observed in 43%, and heterotypic comorbidity in 91%. Trauma, body aches, and difficulties making friends were more common among anxious than in nonanxious adolescents. Only 21% of adolescents diagnosed with an anxiety disorder had anxiety as a referral reason. Referral cause is an inadequate method for detection of anxiety. Proficient treatment planning based on comprehensive assessment is important to address fully the complexity of symptoms in this patient group.</td>
<td></td>
</tr>
<tr>
<td>Paper II</td>
<td>Examine the extent to which six dimensions of parenting behaviors are mediators of the relationship between early and late adolescent levels of anxiety. Investigate if mediating mechanisms change as a function of informant on parenting behaviors.</td>
<td>General mediating effects were more common when adolescents reported on parenting than parent reports of parenting. Specific mediated effects were observed only for total anxiety, panic/agoraphobia, and generalized anxiety through three dimensions of parenting. Mediated effects were small with indirect effect sizes no larger than 1/10th the size of direct effects. Parenting behaviors play a minor role as unconditional mediators in the relationship between early and late adolescent levels of anxiety, irrespective of the informant on parenting behaviors. Studies on the influence of parenting conditional on other etiological factors in relation to adolescent anxiety appear warranted.</td>
<td></td>
</tr>
<tr>
<td>Paper III</td>
<td>Investigate the interaction between parenting and polymorphic variations in the OXT gene in association with social anxiety symptoms. Explore the nature of G × E interactions.</td>
<td>In interaction models adjusted for sex, significant interaction effects with parenting style were observed for both variants in relation to social anxiety. The nature of the interactions was in line with the differential susceptibility framework for rs4813625, whereas for rs2770378, results indicated a diathesis–stress type of interaction. Results provide preliminary evidence for interaction effects between aspects of parenting and OXT variants in relation to social anxiety symptoms among adolescents. The results warrant replication. Further studies are needed on the function of rs4813625 and rs2770378, and whether the function is context dependent in relation to social outcomes other than social anxiety.</td>
<td></td>
</tr>
</tbody>
</table>
General discussion

The four studies that comprise this thesis examined the clinical utility and psychometric properties of the Swedish versions of the Spence Children’s Anxiety Scale (SCAS and SCAS-P) in a general child and adolescent psychiatry setting, the clinical characteristics of multiple anxiety disorders among psychiatrically referred adolescents, and parenting and genetic influences on anxiety among adolescents in the general population. The findings suggest that referred adolescents with anxiety disorders are best characterized as a highly complex patient group where heterotypic comorbidity may impede the detection of anxiety if standardized assessment tools are not used. Both the SCAS and SCAS-P were useful clinical instruments for the assessment and detection of anxiety disorders among Swedish adolescents. Finally, whereas the influence of parenting behaviors on anxiety independent of other etiological factors was minimal, the joint effects of oxytocin gene variants and parenting behaviors on social anxiety showed that adolescents can differ in their susceptibility to parenting depending on whether or not they are carriers of susceptible gene variants.

Clinical utility of the Spence Children’s Anxiety Scale

**Paper I** represents the first evaluation of the SCAS—one of the most widely used measures for assessing multiple dimensions of anxiety among children and adolescents—within a nonanxiety-specific clinical setting. Moreover, the inclusion of participants, irrespective of referral cause or anxiety status as defined by questionnaire results and diagnostic interview, increased the generalizability of the results to general psychiatric settings for adolescents. Overall, the results supported the reliability and validity of the Swedish translations of the SCAS and SCAS-P and demonstrated that these scales can differentiate between adolescents with an anxiety disorder and those without in a general psychiatric outpatient clinical sample. The mean total scores of the SCAS observed among anxious adolescents were consistent with findings in one comparable study of adolescents conducted in an anxiety-specific clinic [66]. However, the observed mean total SCAS-P scores were lower, which may reflect the extent to which psychiatrically referred adolescents and their parents have a shared understanding of the reasons for help-seeking in a nonspecialized psychiatric setting. Overall, and congruent with previous
studies of the SCAS and SCAS-P, agreement between self- and parent report was high when symptoms were measured in a continuous rather than dichotomous manner. Similarly, comparisons of the overall ability to predict anxiety showed no differences between the SCAS and SCAS-P. The fact that adolescents and parents were interviewed together may have facilitated a shared view of symptoms, consequently affecting the level of agreement, the latter noticeable among 34% of participants who completed the questionnaire after the interview.

One important aim of this study was to examine and compare the diagnostic accuracy of the SCAS using three different cutoff levels: (1) “T60”, obtained from a community sample in Australia and equivalent to a sex- and age-group-specific $t$ score of 60 in that sample; (2) “screening”, optimized for screening purposes, with a minimum sensitivity of 0.90; and (3) “diagnostic”, with a minimum specificity of 0.90. The two latter levels were empirically obtained from the ROC analyses in Paper I and were the only cutoff levels used for accuracy analyses of the SCAS-P. Results showed that the T60, a level suggested for the detection of elevated levels of anxiety, was not optimal for screening purposes in a Swedish adolescent clinical population, and was generally outperformed by the empirical screening and diagnostic cutoff levels. Determining a cutoff level, such as the T60, by the normal distribution method has an advantage over empirically derived cutoff levels in that it does not require a resource-intensive reference test. However, a disadvantage of this method is that it precludes determination of cutoff levels based on predefined criteria for the sensitivity and specificity. Thus, this method can yield highly variable sensitivities and specificities of the multiple cutoff levels that must be established in questionnaires measuring multiple dimensions such as the SCAS and SCAS-P. Varying sensitivities and specificities of the T60 were indeed observed in this study, which is consistent with findings of a previous evaluation of the utility of the SCAS and SCAS-P in an anxiety-specialized clinic where cutoff scores were determined by the normal distribution method [45]. A common criterion for determining empirical cutoff levels is the “optimal” criterion, which aims to maximize the sensitivity and specificity in one single cutoff level [260-261]. This criterion was used in a validation study of the SCAS and SCAS-P obsessive-compulsive subscale where examination of the sensitivities and specificities of the “optimal” cutoff levels showed considerably lower sensitivities for the SCAS than for SCAS-P [46]. Thus, by using the “optimal” criterion for choosing one single cutoff level, informant effects on detection rates and posttest alterations of the probability of OCD were introduced. To summarize, in determining clinically useful cutoff levels, careful consideration of how and where a questionnaire is intended to be used is of the utmost importance, and one single, “optimal” cutoff may not be the best alternative for achieving both high detection rates and precision.
While sensitivity and specificity are properties of a chosen cutoff level, these estimates do not help clinicians in interpreting test results of individual patients, for example, in determining the probability of diagnosis given a certain test score. Posttest probabilities were calculated by two methods: LRs have the advantage over PPVs and NPVs in that they are not driven by disorder prevalence and are therefore transferable to settings with a different prevalence. Comparisons of the different cutoff levels in terms of their ability to change the pretest probability showed that for both the SCAS and SCAS-P, scores above the diagnostic cutoffs and under the screening cutoffs yielded the largest changes in the probability of an anxiety disorder except for the SCAS total score where the sex-specific $T_{60}$ showed the strongest performance. Overall, posttest absolute changes of probabilities were smaller for the SCAS-P than for the SCAS. Furthermore, for SCAS-P, scores under the diagnostic cutoffs lacked to a high degree clinical value; these results did not change the probability of anxiety.

Clinical characteristics

In Paper II, at least one of the anxiety disorders of social anxiety, GAD, specific phobia, separation anxiety disorder, panic disorder, agoraphobia, and unspecified anxiety disorder was found in 46.4% of adolescents psychiatrically referred for any reason, with girls diagnosed more than three times more often than boys. The most frequent anxiety disorder was social anxiety (27.2%), and the least frequent were separation anxiety (4.0%) and unspecified anxiety disorder (1.6%), which is consistent with previous findings of separation anxiety disorder as an uncommon disorder among adolescents [66-67]. Nearly all anxious adolescents had concurrent disorders; heterotypic comorbidity was twice as common as homotypic comorbidity. Prior admission to the clinic, depression as referral cause, difficulties making friends, and frequent body aches were characteristics that were at least twice as common in anxious compared with nonanxious adolescents.

There are no fully comparable reports of the prevalence of anxiety among adolescents referred to a nonanxiety-specific psychiatric clinic. In relation to three available clinical reports of multiple anxiety disorders among children and adolescents [13-14, 68], the sample characteristics of the current study differed in terms of having a higher proportion of girls, age range, and categories and number of studied anxiety disorders. These differences may explain the observation that no previous study has reported estimates within the 95% CI of 37.9–55.1 for the observed prevalence of any anxiety in the current study. It is worth noting that the differences in sample characteristics mentioned above are analogous with findings from a meta-analysis of sources of anxiety prevalence variability in community studies where sex explained the greatest proportion of variance and no effect of diagnostic instrument was
found once the number of anxiety disorders was considered [63]. The observed prevalence in the current study was consistent with previous findings in one way, in that a standardized diagnostic method yielded a substantially higher prevalence than the prevalence derived from unstandardized methods.

The observed homotypic and heterotypic comorbidity also differed from previous studies, although observations of heterotypic comorbidity as the more prevalent type were alike. Moreover, the absolute difference in proportions between heterotypic and homotypic comorbidity observed in the current study (0.5) was similar to that observed in other Scandinavian countries [13-14]. This suggests that this comorbidity pattern is a clinical characteristic that can be expected among anxious youths within nonanxiety-specialized Scandinavian child and adolescent psychiatry. Observations of high heterotypic comorbidity may explain the low anxiety prevalence obtained from patient administrative systems in previous studies (~5%) [13-14] and in Paper II prior to data collection (10%), if in fact the heterotypic comorbidity was the primary cause for help seeking and diagnostic procedures inadequately assessed the presence of concurrent anxiety disorders. Further, and in line with findings reported by Hansen et al. [14], the study reported in Paper II found that referral reason (i.e., a referral because of anxiety) is an inadequate method with a detection rate of only 21% (0% of boys with anxiety detected; 27% of girls). This finding further supports the routine use of standardized and structured instruments—irrespective of referral cause—to improve both precision and detection rates within general child and adolescent psychiatric settings.

Consistent with the literature, self-reports of family, interpersonal, school, sleep, and somatic functioning among anxious adolescents revealed problems in all areas. On average, the number of self-reported problems was higher among anxious than nonanxious adolescents. Overall, the clinical characteristics of anxiety disorders observed in this study have been associated with more chronicity and negative outcomes and call attention to the necessity of comprehensive assessment, individualized treatment, and adequate follow-up to attend fully to the complexity of symptoms in this patient group [75, 80, 85-87, 262-265].

Influence of parenting

In Paper III, the mediating role of parenting behaviors in the relationship between early and late adolescent levels of anxiety was examined. By including multiple dimensions of parenting and anxiety, the specific relationships between some of these dimensions were investigated for the first time.

Overall, the findings suggest that early adolescent anxiety influences homotypic anxiety in late adolescence independent of parenting behaviors. A
general mediating role of all parenting behaviors simultaneously was observed in the relationship between early and late adolescent levels of social anxiety, panic disorder/agoraphobia, and total anxiety when adolescents reported on parenting. When parents rated their own parenting, a general mediating mechanism through parenting behaviors was observed only for total anxiety. Evidence of specific mediation mechanisms through any of the six included parenting dimensions was the exception rather than the rule when competing parenting behaviors were held constant. The overall mediating role of parenting was small with indirect effect sizes no larger than one-tenth the size of direct effects, irrespective of the informant on parenting behavior.

In particular, the two broad bipolar dimensions of rejection (warmth–rejection) and psychological control (autonomy support–coercion) are commonly highlighted in etiological models of anxiety. In Paper III, results showed that adolescent- and parent-reported rejection was a mediator only of the effects of baseline levels of panic disorder/agoraphobia and total anxiety on homotypic anxiety at follow-up. Results showed no support for a mediating role of warmth, autonomy support, or coercion in any anxiety dimension. The latter findings are in contrast to previous research which has shown quite consistent support for an association between psychological control and generalized anxiety, social anxiety, and separation anxiety with small-to-medium effect sizes. This raises the question of how the parenting–anxiety relationship is best modeled. In the current study, the specificity of relationships was investigated by controlling for competing parenting behaviors as well as competing anxiety dimensions. By controlling for multiple correlated mediators in one single model, spurious associations may be disentangled from true associations. Moreover, the separation of conventionally used bipolar dimensions of parenting behaviors into unipolar constructs has potential for increasing the current understanding of the parenting–anxiety relationship.

Compared to psychological control, behavior control has been studied to a much lesser degree in relation to anxiety. The results showed a mediating role across the dimension of behavior control in the relationship between baseline and follow-up levels of generalized anxiety, with positive specific indirect effects observed through adolescent-reported structure and chaos. Commonly associated features among children and adolescents with generalized anxiety disorder are excessive worry about future events and possible negative outcomes of these events. This may lead to frequent reassurance-seeking from parents, which in turn elicits parental accommodation and stress-reducing behaviors, with higher levels of accommodation associated with increased levels of anxiety and impairment. Thus, in relation to generalized anxiety, and based on the findings of this study, one interpretation of the role of parental structure among adolescents is that of parental accommodation. Alternatively, adolescents with higher generalized anxiety may perceive their parents as more inconsistent and unpredictable, suggesting
that adjusting behavior control to appropriate levels can be particularly challenging for parents of adolescents with this type of anxiety.

Because the direct effect of any mediation model essentially estimates the influence of the independent variable on the outcome through mechanisms that have not been included in the model, findings of substantially larger direct than indirect effects in this study can be interpreted in several ways. The first, straightforward interpretation is that parenting behaviors, divided into the dimensions of rejection, behavioral control, and psychological control, play a minor role as mechanisms by which anxiety in early adolescence influences anxiety in late adolescence. This interpretation is supported by meta-analyses of independent effects that show that parenting explains ~4 % of the variance in anxiety among children 2–19 years of age and that there is no additional benefit of adding parental components to individual treatment [95, 266-267]. A second interpretation concerns the direction of effects in the parenting–anxiety relationship and the analytic method of mediation, which, by definition, assumes specified directions of effects. In Paper III, reciprocal effects between adolescent anxiety and parenting were implicit in the model; adolescent anxiety elicits parenting responses, which in turn influence adolescent anxiety. Although this assumption is supported by previous research [4], support for unidirectional child effect models has also been reported with adolescent anxiety and shyness predicting later parental control and rejection [102, 116, 120]. In analyses of the separate pathways of the mediation models in this study, child effects were indeed more frequently observed than parent effects, irrespective of informant. Previous research has suggested that observations of child effects may be due to parents actually changing their behaviors in response to their children’s anxiety levels or to cognitive biases among individuals with anxiety, which make them perceive their parents more negatively [92, 102]. Although this study did not aim to explore the direction of effects, the findings of significant child effects independent of informant do not support cognitive bias among adolescents as an explanation for these effects. Finally, a third interpretation of larger direct than indirect effects concerns questions such as for whom and under what circumstances may the influence of parenting behavior be of greater importance. The results of the current study and the majority of previous studies are based on investigations of the unconditional relationship between anxiety and parenting without considering interactions between parenting behavior and other factors related to the development of anxiety [2]. As exemplified in Paper IV, parenting behaviors may be more influential among some individuals than others, both for better and for worse outcomes of adolescent anxiety, depending on the characteristics of these individuals (e.g., genetic makeup, temperament and life experiences) [2, 257, 268].
Interaction effects of OXT variants and perceived parenting on social anxiety

**Paper IV** provides preliminary evidence for interaction effects between positive and negative aspects of parenting and OXT variants in relation to social anxiety symptoms among adolescents, independent of sex. Several theories about the mechanisms by which oxytocin influences social behavior have been proposed; they include: the anxiolytic account which proposes that the anxiolytic effect of oxytocin facilitates prosocial behavior[^196-191]; the social salience hypothesis, which proposes that oxytocin increases attention to safety and threat signals in the social context, which in turn affects prosocial behavior and anxiety levels[^192-194]; the reward sensitivity account, which proposes that the oxytocin-dopamine and oxytocin-opioid pathways influence social reward sensitivity, which in turn affects social behavior[^196]; and the in-group/out-group account, which proposes that oxytocin regulates human behavior in the context of intergroup relations[^197-198]. A growing body of literature also suggests that both individual characteristics and context moderate the effects of oxytocin which can be negative[^192]. The findings of this study further support a contextual dependency of oxytocin where the OXT variant rs4813625 was related to social anxiety at high and low levels of positive parenting but not at average levels. Similarly, rs2770378 was related to social anxiety only at high levels of negative parenting. These findings further highlight how the use of subcategories of parenting behaviors other than the conventional bipolar dimensions of rejection and control can expand current understanding of the parenting–anxiety relationship among adolescents[^4].

**Paper IV** is the first study of joint associations of OXT variants and aspects of parenting style with social anxiety among healthy adolescents. The sample size provided adequate power (96%) for the detection of a 1% interaction effect on social anxiety outcome. However, the power to detect the observed effect of 0.3% for the interaction terms including rs2770378 was inadequate (52%), which reduces the likelihood that statistically significant findings reflect a true effect[^269]. The effect of rs4813625 and rs2770378 on oxytocin levels is still unknown, which precludes any interpretation of the results in terms of higher or lower levels of central or peripheral oxytocin among minor allele carriers compared with homozygote major allele carriers. Further investigations of the function of rs4813625, rs2770378, and co-localized OXT SNPs in other samples are warranted, as are studies of the influence of different types of contextual factors and the interplay between OXT SNPs and context in relation to social outcomes other than social anxiety.
Differential susceptibility to parenting behaviors

Two models of G × E interaction remained significant after recommended tests of nonlinearity: rs4813625 × PASCQ<sup>POS</sup> and rs2770378 × PASCQ<sup>NEG</sup>. Examination of the nature of these interactions revealed inconsistencies in form. When positive parenting behavior was perceived as low, carriers of the minor C allele of rs4813625 reported higher-than-average levels of social anxiety than homozygote G allele carriers, whose levels of social anxiety were close to average. Likewise, at high perceived levels of supportive parental behavior, C allele carriers reported lower-than-average levels of social anxiety, again with homozygote G allele carriers remaining almost unaffected by parenting style. At average levels of parental support, rs4813625 was not associated with social anxiety. Thus, the nature of the rs4813625 × PASCQ<sup>POS</sup> effect was in line with the differential susceptibility theory, which proposes that individuals differ in their sensitivity to both favorable and unfavorable environments, leading to a better- or worse-than-average outcome for carriers of susceptibility gene variants depending on the environment. Further support for a differential susceptibility effect was provided by results from a series of recommended tests. By contrast, the rs2770378 × PASCQ<sup>NEG</sup> effect was consistent with the diatheses–stress model as indicated by the RoS test which showed that rs2770378 was related to social anxiety only at higher levels of negative parenting, just within the conventional range of 2 SD from the mean. Explanations for inconsistencies in the form of interaction for rs4813625 compared with rs2770378 may be inadequate power, a restricted range of negative parenting behaviors in the sample, or a difference in functionality between these variants. The inclusion of only two <i>OXT</i> SNPs in this study precluded further analyses of their respective loci.

In line with the observed differential susceptibility effect of rs4813625 and positive parenting on social anxiety, the social salience hypothesis of oxytocin specifies that oxytocin increases attention to safety and threat signals and that prosocial behavior can be enhanced in positive, safe contexts, whereas negative or unsafe situations decrease prosocial behavior and increase anxiety<sup>[193]</sup>. Hence, by interpreting the results from the social salience perspective, the influence of rs4813625 can be thought of as salience-enhancing: parenting behaviors that deviate upward or downward from a presumed normal level, will be more salient to carriers of the susceptible allele, consequently affecting the general perception of safety as well as social anxiety levels to a higher degree among those individuals than among homozygote carriers of the non-susceptible allele. Other theories about how oxytocin influences human social behaviors, such as the anxiolytic account, fail to explain the observed crossover effect of the interaction term including rs4813625.
Methodological considerations

The major strengths of Papers I - II are the consecutive inclusion of participants, irrespective of presenting symptoms or referral cause, the use of a semistructured diagnostic interview to investigate diagnostic criteria for psychiatric disorders, and prospective data collection in a nonanxiety-specialized setting likely to be generalizable to standard clinical care settings. The major limitations are the small sample sizes and the small number of boys diagnosed with an anxiety disorder, precluding further analyses of sex differences and sex-specific cutoff scores. The major strengths of Papers III – IV are the sample sizes, which were sufficient to detect small effects, and the sample characteristics, which were representative of adolescents in the wider Swedish society.

Diagnostic procedures

In Papers I and II, all diagnoses were determined by the individual clinician solely on the basis of information collected from adolescents and parents during joint interviews with the K-SADS, and excluding other information sources considered in best-estimate diagnostic procedures [21-22]. Consequently, the diagnostic procedure required a high level of participant ability to adequately recognize and verbalize their feelings and behaviors, skills that for various reasons can be impaired in psychiatrically referred youths. Although comparisons of diagnoses derived from structured interviews alone and diagnoses from full LEAD procedures generally show high agreement, some psychiatric disorders need further assessment and monitoring of symptoms over time to be correctly identified [270] [56]. The implication of the diagnostic procedure in Paper II is missed comorbidity, which is likely to have been detected with best-estimate or LEAD diagnostic procedures. The diagnostic procedure may also have influenced both the inclination of adolescents and parents to describe symptoms of anxiety, and a shared view of symptoms, thus affecting both the prevalence of all disorders as well as parent–child agreement. Interview procedure effects on agreement were indeed observed in Paper I where the relationships between the SCAS and SCAS-P were significantly stronger among the one-third of participants who completed the questionnaires after the interview than among participants who completed the questionnaires before the interview.

The use of the former (DSM-IV) and current (DSM-5) versions of the Diagnostic and Statistical Manual of Mental Disorders in this thesis requires some clarification. Because a DSM-IV-based Swedish version of the K-SADS was used [236], diagnostic decisions on the presence of all psychiatric disorders investigated in Papers I and II were based on DSM-IV diagnostic criteria [271]. Although the core features of anxiety disorders remain the same for children and adolescents in the DSM-5 [116], some organizational and criteria changes
may have implications for the generalizability of the findings in Papers I and II. The major changes in the DSM-5 that are relevant to this thesis are the exclusion of OCD and trauma- and stress disorders from the chapter on anxiety disorders, and the uncoupling of the diagnoses of panic disorder and agoraphobia, leading to the coding of two diagnoses if they co-occur. To evaluate fully the SCAS, OCD was included in the category of any anxiety in Paper I, but not in Papers II–IV where the included anxiety disorders and dimensions were consistent with the organization of the DSM-5 (see Table 2 on page 35 for an overview of included anxiety disorders in Papers I–IV).

Data-driven cutoff scores

Data-driven selection of cutoff levels has been found to produce inflated estimates of both sensitivity and specificity, with the amount of bias increasing with smaller sample sizes [272]. A prevalence of 50% has been proposed to be the most efficient prevalence for reducing uncertainty when cutoff levels are data-driven [273]. Because a prevalence of 53% for any anxiety was observed in Paper I, the diagnostic accuracy estimates of the “screening” and “diagnostic” cutoff levels for the SCAS and SCAS-P total scores could be considered more robust than estimates of cutoff scores for the subscales. To provide further evidence for the validity of the proposed cutoff scores, future research would have to include larger samples.

Mediation analysis

In Paper III, the mediating role of parenting was investigated under the assumption of reciprocal effects between adolescent anxiety and parenting behaviors. This assumption is supported by previous research [4], but unidirectional child effects have also been reported [102, 116, 120]. Moreover, parenting behaviors were only assessed at a single point in time, which precluded statistical control for baseline levels of parenting behaviors in the models. Thus, it is possible that the temporal stability of parental behavior in the current sample was high with the observed levels of different parenting behaviors present before data collection.

In Paper III, the general mediating role of parenting was examined by the total indirect effects, which quantified how differences in baseline levels of anxiety relate to differences in anxiety at follow-up through all parenting behaviors at once. Evidence that a total indirect effect is different from zero supports a claim of mediation mechanisms through one or more of the mediators in the model, but because the total indirect effect is the sum of all specific indirect effects of the model, some paradoxical results are possible. One possibility is that several specific indirect effects are different from zero, but the total indirect effect is not. This can occur when the specific indirect effects differ in sign but are of a similar magnitude. Specifically, by including
both positive and negative parenting behaviors in the same model, this scenario was introduced and paradoxical results for total and specific indirect effects were observed in the generalized anxiety dimension.

**Gene × environment interaction**

**Paper IV** is the first study of joint associations of OXT variants and aspects of parenting style with social anxiety among adolescents. The results must be interpreted in light of important limitations.

The entire OXT gene cannot be said to be represented because only two OXT-related SNPs were genotyped with unknown functions, precluding any interpretation of the results in terms of function (i.e., differences in levels of central or peripheral oxytocin between genotypes).

The observed marginal interaction effects of 0.5–1% were of a magnitude typically seen in observational studies and, although the power to detect small effects was high, the winner’s curse phenomenon of inflated effects is plausible until the findings have been replicated in well-powered studies [269].

A common critique of genetic association studies is the multiple testing problem, where the risk of Type I errors increases with each additional test. Different statistical correction methods for this problem exist [274], but reducing the risk of Type I errors comes at the expense of lower power and increased probability of a Type II error [275-276]. A thorough description and explanation of what has been done has been proposed as a better approach to multiple testing correction, and this approach was chosen in **Paper IV** [277]. However, a standard Bonferroni correction for eight primary tests (four main effects models and four interaction models) would yield an adjusted significance level of 0.006 and thus retain significance for rs4813625 × PASCQPOS but not for rs2770378 × PASCQNEG.

Recommendations for testing the robustness of the observed interaction effects were followed. These included additional models with statistical control for gene-by-sex interaction and quadratic interaction terms with mean-centered parenting variables [145, 246]. The interactions between rs4813625 and PASCQPOS and rs2770378 and PASCQNEG remained significant in these models, suggesting that the findings of the current study are robust.

The risk of misrepresentation of the nature of the interaction was increased by using an additive genetic model and a cross-product term to model interaction [278]. It has been suggested that a more accurate way to represent the interaction is the use of dummy-coded variables for the genotypes [278]. Using this procedure, interaction plots based on dummy-coded genotype variables revealed changes from the original model primarily for the rs4813625 × PASCQPOS interaction and the GC genotype, which differed from the original model in terms of slope differences between adjacent genotype groups and cross-over point. The interaction form for homozygote genotype groups did not differ from original models. Tests of regions of significance with dummy-
coded genotype variables yielded broader significance regions for \( \text{rs4813625} \times \text{PASCQ}^{\text{POS}} \) but no significant regions for \( \text{rs2770378} \times \text{PASCQ}^{\text{NEG}} \).

Finally, the study design of Paper IV may raise concerns of biased associations due to the use of a common method and a single respondent to assess social anxiety and parenting. However, because common method variance deflates rather than inflates interaction effects, findings of significant effects in the presence of shared variance should be taken as strong evidence that an interaction effect exists \[^{[279]}\].

**Future research**

In the general population, and across the life span, anxiety disorders are twice as commonly observed among females compared to males \[^{[2, 63]}\]. Similar female to male ratios have also been observed in clinical samples including adolescents \[^{[13, 66]}\] but inverted proportions, with anxiety being more common among boys, have been observed in clinical samples with mostly younger children where parents commonly are the primary informant \[^{[14, 68]}\]. In this thesis, the prevalence of any anxiety disorder among referred adolescents was nearly four times more common among girls than boys, and the female to male ratio was even higher for the separate anxiety disorders. In relation to previous reports, this finding raises questions regarding “true” sex differences in anxiety prevalence. Can it be that observed differences are in part related to how anxiety is operationally defined in questionnaires and interviews? It has been shown that depressed men experience symptoms that differ from the diagnostic criteria of depression, and instead report more anger and substance abuse \[^{[280]}\]. It would be of great importance to investigate whether males experience other symptoms than those specified in the diagnostic criteria for various anxiety disorders, and if wordings to describe reactions to anxiety-provoking situations differ between males and females.

The findings of this thesis and previous research indicate that the influence of parental rejection and control on adolescent anxiety is very small. However, nearly all studies on this relationship have investigated independent associations in community samples. It is therefore important to investigate the specific characteristics of the parenting–anxiety relationship among clinically referred adolescents. In general, further understanding of the parenting–anxiety relationship may require a more complex modeling approach, where questions of how parents and anxious adolescents influence each other are combined with questions of for whom and under what circumstances effects are observed, so-called moderated mediation analysis. Relatedly, it would be highly interesting to further examine interaction effects of oxytocin pathway polymorphisms and environmental variables in relation to the presence and treatment of anxiety and other psychiatric disorders among referred adolescents and children.
Conclusions

Anxiety disorders are known to be the most common psychiatric disorders among adolescents, with a lifetime prevalence of approximately 30%. Despite reports showing that anxiety disorders are i) chronic if not treated; ii) among the leading causes of disability; and iii) associated with high societal costs, they frequently remain undetected and untreated.

Parenting behaviors of rejection and control are often highlighted as important contributing factors in the development of anxiety. The findings of this thesis suggest that the influence of these parenting behaviors on adolescent anxiety is minimal, but may be of greater importance among some adolescents, depending on genetically driven individual differences in sensitivity to parenting. These findings thus suggest that the etiology of anxiety among adolescents may involve differential susceptibility effects of the interplay between genes and parenting behaviors. In the presence of such “for better and for worse”-effects, carriers of susceptible gene variants would be more likely to experience elevated anxiety in un-supportive parenting contexts and to benefit more from supportive parenting, compared to carriers of non-susceptible gene variants. The results have implications for parental involvement in the treatment of childhood anxiety, where meta-analytic findings suggest that there is no additional benefit of parental components.

Anxiety disorders are very common among adolescents psychiatrically referred for any reason. Despite high prevalence, anxiety may go undetected among referred adolescents if non-anxiety concurrent disorders are the primary reason for seeking help and structured assessment tools are not used. For this purpose, this thesis provides evidence for the clinical utility of the SCAS, self- and parent report. Routine utilization of the SCAS and suggested thresholds for screening purposes can increase detection rates and direct limited clinical resources more efficiently. Importantly, the clinical characteristics of anxiety disorders observed in this thesis have been associated with more chronicity and negative outcomes, and call attention to the necessity of treatment planning based on comprehensive assessment to attend fully to the complexity of symptoms in this patient group.
Svensk sammanfattning
(Summary in Swedish)


Avhandlingen består av fyra studier med det övergripande syftet att:

I) utvärdera den kliniska nyttan av frågeformuläret Spence Ångestskala, självrapport och föräldraversion, bland tonåringar som remitterats till barn- och ungdomspsykiatrin (BUP)

II) undersöka förekomst av ångest och samtidiga andra problem bland tonåringar som remitterats till BUP, oavsett skäl för remiss

III) bland tonåringar i den allmänna befolkningen undersöka om relationen mellan ångest under de tidiga och sena tonåren medieras av föräldrabeteenden

IV) undersöka om genetisk variation i oxytocin-genen modifierar relationen mellan föräldrabeteenden och social ångest bland tonåringar i den allmänna befolkningen

Metod
tonåringar och deras föräldrar vid en baslinjemätning och uppföljning efter 3 år. Studie IV är baserad på genotyp- och enkätdata från 1359 tonåringar.

Studie I
Den kliniska nyttan av det frekvent använda frågeformuläret Spence Ångestskala (SCAS) har tidigare inte undersökts bland tonåringar som remitterats till en icke-ångestspecialiserad psykiatrisk mottagning. Syftet med studie I var att adressera denna kunskapslucka. Den semi-strukturerade diagnostiska intervjun K-SADS \[55\] användes som referens-standard för att i) utvärdera de psykometriska egenskaperna hos den svenska versionen av självrapport (SCAS) och föräldraversion (SCAS-P), ii) ta fram empiriska gränsvärden för upptäckt (screening) och identivering (diagnostik), och iii) utvärdera den diagnostiska tillförlitligheten hos SCAS bland tonåringar som remitterats till BUP, oavsett sökorsak.

Sammantaget visade utvärderingen god reliabilitet och validitet hos de svenska versionerna av SCAS och SCAS-P. Resultaten visade även att såväl självrapport som föräldraversion kan differentiera mellan tonåringar med respektive utan en ångeststörning. Utvärderingar av tidigare och nya gränsvärden visade att de nya gränsvärdena presterade bättre vad gäller korrekt klassificering och förändringar av sannolikheten för en ångestdiagnos. En generell implementering av SCAS och SCAS-P med de nya gränsvärdena (nedladdningsbara från https://www.scaswebsite.com) kan förenkla upptäckt och identifikation av tonåringar i behov av ångestbehandling.

Studie II
Det råder en brist på kunskap gällande ångeststörningarnas förekomst och kliniska karaktäristika på BUP, där ångest kanske inte är en uttalad eller primär anledning till att man söker hjälp \[11, 49\]. Uppgifter hämtade från patientadministrativa system på BUP i Norge och Danmark samt i Västmanland visar anmärkningsvärt låg prevalens bland barn och tonåringar (5-10 %) \[13-14\], vilket antas bero på otillräcklig användning av strukturerade diagnostiska instrument. Det saknas rapporter baserade på strukturerade diagnostiska intervjuer som berör de specifika korrelaten för ångest bland tonåringar som oavsett orsak remitterats till BUP \[13-14, 66, 68\]. I studie II användes den diagnostiska intervjun K-SADS \[24\] och nybesöks-enkäten EPIQ \[232\] för att undersöka förekomst av sju olika ångeststörningar samt klinisk presentation och samsjuklighetsmönster vid ångest bland tonåringar som remitterats till BUP, oavsett skäl till remiss.

Knappt hälften (46.4 %) av tonåringarna diagnosticerades med minst en ångeststörning enligt K-SADS, och ångest var mer än tre gånger vanligare bland flickor än bland pojkar. Den vanligaste ångestdiagnosen var social ångest (27.2 %) och de minst vanliga var separationsångest (4.0 %) följt av
ospecificerad ångest (1.6 %). Bland tonåringar med ångest hade 95 % någon form av psykiatrisk samsjuklighet: 43.1 % hade ytterligare ångeststörningar och 91.4 % hade ytterligare övriga psykiatriska diagnoser. Tidigare kontakt med BUP, depression som remissorsak, svårigheter att få nya vänner och frekvent kroppslig värk var dubbelt så vanligt bland tonåringar med ångest än bland dem utan ångest. Endast 21 % av tonåringarna som enligt K-SADS hade en ångeststörning hade remitterats på grund av ångest, vilket belyser vitkan av en systematisk användning av strukturerade instrument för att upptäcka tonåringar med ångest i vården, oavsett skäl för remiss. De kliniska karaktäristika som observerades i studie II har associerats med mer kronicitet och negativa konsekvenser och understryker vitken av en bred initial bedömning och individualiserad behandling för att till fullo adressera denna patientgrupps komplexa symtombild.

Studie III
Olika föräldrabeteenden såsom att vara avvisande och överdrivet kontrollerande lyfts ofta fram som bidragande faktorer till ångest bland barn och ungdomar [2, 257-258]. Tidigare forskning är begränsad vad gäller det specifika sambandet mellan olika typer av ångest och föräldrabeteenden och huruvida rapportör av föräldrabeteende (tonåring eller förälder) har betydelse för sambandet. I populationsbaserade studie III undersöktes i vilken utsträckning positiva och negativa föräldrabeteenden medierade sambandet mellan ångest i tidiga och sena tonåren. Medierande (indirekta) mekanismer undersöktes genom att analysera om en viss typ av ångest under de tidiga tonåren påverkade graden av samma typ av ångest i de sena tonåren via sex olika föräldrabeteenden. Informanteffekter undersöktes genom att ersätta tonåringarnas skattningar av föräldrabeteenden med föräldrarnas egna skattnings.

Resultatet visade att ångest under de tidiga tonåren påverkade ångest i de sena tonåren oberoende av föräldrabeteenden. De indirekta effekterna på ångest i sena tonåren via föräldrabeteenden var mycket små och som högst en tiondel så stora som de direkta, icke-medierade, effekterna, oavsett vem som skattade föräldrabeteenden. Endast undantagsvis observerades specifika samband mellan olika typer av föräldrabeteenden och ångest när den statistiska analysen kontrollerades för konkurrerande föräldrabeteenden. En viktig begränsning i denna studie, liksom i tidigare studier är att ett oberoende samband undersöktes; ett potentiellt interagerande mellan föräldrabeteenden och andra faktorer som bidrar till ångest undersöktes inte.

Studie IV
Tidigare forskning ger visst stöd för ett samband mellan vanliga varianter i oxytokingen och ångest och socialt beteende [225-229] och mellan
föräldrabeteende och social ångest \cite{259}. Majoriteten av studierna i dessa båda forskningslinjer har undersökt antingen huvudeffekter av genetiska varianter och föräldrabeteenden på social ångest, eller utifrån ett risk-perspektiv, utan att överväga modererande faktorer eller differentiell känslighet för föräldrabeteenden. Det primära syftet med studie IV var att undersöka ett potentiellt interagerande mellan positiva (PASCQ\textsuperscript{POS}) och negativa (PASCQ\textsuperscript{NEG}) föräldrabeteenden och två polymorfier i oxytocingenen, rs4813625 och rs2770378, i relation till social ångest bland tonåringar i den allmänna populationen. Det sekundära syftet var att undersöka om gen-miljö interaktioner var i linje med teorin om differentiell känslighet. För det senare syftet genomfördes flera rekommenderade test efter vilka två signifikanta interaktioner kvarstod: \text{rs4813625 × PASCQ\textsuperscript{POS}} och \text{rs2770378 × PASCQ\textsuperscript{NEG}}.

Resultaten visade att interaktionen \text{rs4813625 × PASCQ\textsuperscript{POS}} var i linje med teorin om differentiell känslighet: rs4813625 var associerad med social ångest både vid höga och låga nivåer av positivt föräldrabeteende. Interaktionen \text{rs2770378 × PASCQ\textsuperscript{NEG}} var i linje med stress-sårbarhetsmodellen, med ett signifikant samband mellan social ångest och rs2770378 endast vid höga nivåer av negativt föräldrabeteende. Studie IV är den första publicerade studien av interaktioner mellan polymorfier i oxytocingenen och föräldrabeteende i relation till social ångest bland tonåringar och utgör ett bidrag till forskningen rörande etiologin vid social ångest.

**Slutsatser**

Spence Ångestskala är ett kliniskt användbart instrument för att mäta ångest hos tonåringar. En viktig slutsats är att såväl själv- som föräldrarapport kan användas för att upptäcka tonåringar med förhöjda nivåer av ångest.

Tonåringar som remitterats till BUP och som har ångest är en komplex patientgrupp där förekomsten av samtliga andra psykiatriska tillstånd kan försvåra upptäckten av ångest om inte strukturerade och standardiserade bedömningsinstrument används. Remissorsak är en otillräcklig metod för att upptäcka ångest hos tonåringar på BUP. En generell implementering av Spence Ångestskala med föreslagna nya gränsvärden kan öka graden av upptäckt och optimera användandet av begränsade kliniska resurser.

Olika föräldrabeteenden lyfts ofta fram i etiologin vid ångest. Denna avhandling visar att föräldrabeteenden har minimalt inflytande på ångest hos tonåringar, men kan vara av större betydelse för vissa, beroende på individuella, genetiskt drivna skillnader i känslighet för föräldrabeteenden. Dessa fynd antyder således att etiologin rörande ångest kan innefatta differentiella känslighets-effekter i interaktionen mellan gen-varianger och föräldrabeteenden. I närvaro av sådana effekter är det mer troligt att ångestnivåerna hos individer med känslighets-genvarianger påverkas i såväl negativ som positiv riktning av föräldrabeteenden, jämfört med individer utan dessa genvarianger.
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Sofia, my brilliant, unique, and inspirational friend and colleague—thank you for all your support and encouraging words. You have enriched these years in so many ways! Karin, together, we have accomplished demanding projects, during which the sunniest of smiles—yours!—often eased my strain. Cecilia, thank you very much for detailed and insightful comments on manuscripts and helpful advice on general PhD matters. Mattias, you have been invaluable for everything concerning data management, but I have also much appreciated our methodological discussions. My past and present room-mates Sara and Rebecka, thank you for your kindness, and for sharing thoughts on life and moments of anxiety! Lotta, thank you for cheering me on and for wise and honest comments on present and future research projects.

To old friends comprising The Girls—Åsa, Kerstin, Anneli, Mona, and Lotta—life happened during these years, and we have shared both happy and dark moments. Thank you for your supportive friendship and much-needed non-research and hilarious conversations!

My parents Sven-Olov and Barbro, my sister Anna, and my brother Sven-Åke, have in different ways contributed to the three major phases of doing a PhD: to start, to persist, and to finish! Thank you!

My sons Alexander and Johann, you have been so supportive of my doctoral studies, but your greatest gift to me has been, and still is, your self-knowledge-based pursuits in your lives! I am so proud of you!

Thomas, my love, you are my rock. I can never thank you enough for your loving support, encouragement, and patience, and for bringing balance into my life during these years.

Finally, I would like to thank all the participating adolescents and their parents for their contribution to this thesis!
References


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presented at the Joensuu University Learning and Instruction Symposium 2005, Joensuu, Finland.


Environmental Influences. *Current Directions in Psychological Science, 16*(6), 300-304.


Appendix

Spence Children’s Anxiety Scale (SCAS)
  Spence Ångestskala självrapport (Swedish self-report version)
  Spence Ångestskala föräldraversion (Swedish parent report version)

Parents As Social Context Questionnaire (PASCQ)
  Items in Swedish adolescent and parent versions, by subscale
<table>
<thead>
<tr>
<th>Förfrågning</th>
<th>Aldrig</th>
<th>Ibländ</th>
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<tbody>
<tr>
<td>Jag oroar mig över saker.</td>
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<td>Jag är rädd för mörkret.</td>
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<td>När jag har problem, får jag en konstig känsla i magen.</td>
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<td>Jag känner mig rädd.</td>
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<td>Jag skulle känna mig rädd om jag var ensam hemma.</td>
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<td>Jag känner mig rädd när jag måste göra ett prov.</td>
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<td>Jag känner mig rädd när jag måste använda offentliga toaletter eller badrum.</td>
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<td>Jag oroar mig för att vara borta från mina föräldrar.</td>
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<td>Jag är rädd för att göra bort mig framför andra människor.</td>
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<td>Jag oroar mig över att jag ska misslyckas i skolan.</td>
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<td>Jag är populär bland andra barn i min ålder.</td>
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<td>Jag oroar mig över att något hemskt ska hända någon i min familj.</td>
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<td>Jag kan plötsligt känna att jag inte kan andas, fast det inte finns någon anledning till det.</td>
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<td>Jag måste kontrollera om och om igen att jag har gjort saker rätt (som att släcka ljuset eller låsa dörren).</td>
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<td>Jag känner mig rädd om jag måste sova ensam.</td>
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<tr>
<td>Jag har problem med att gå till skolan på morgonen, eftersom jag känner mig nervös eller rädd.</td>
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<td>Jag är bra på idrott.</td>
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<td>Jag är rädd för hundar.</td>
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<td>Jag kan inte få hemskas eller dumma tankar ur mitt huvud.</td>
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<td>När jag har problem, slår mitt hjärta väldigt fort.</td>
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<td>Jag börjar plötsligt skaka eller darra utan att det finns någon anledning.</td>
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<td>Jag oroar mig över att något hemskt ska hånda mig.</td>
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<td>Jag är rädd för att gå till doktorn eller tandläkaren.</td>
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<td>När jag har problem känner jag mig darrig eller svag.</td>
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<tr>
<td>Jag är rädd för att vara på höga höjder eller i hissar.</td>
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<tr>
<td>Jag är en bra person.</td>
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<td>Jag måste tänka speciella tankar för att hindra att hemskasaker händer (så som nummer eller ord).</td>
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**SPENCE ÅNGESTSKALA**

*Självrapport*

<table>
<thead>
<tr>
<th>Hur bra stämmer frågorna in på dig?</th>
<th>Aldrig</th>
<th>Ibland</th>
<th>Ofta</th>
<th>Alltid</th>
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<tbody>
<tr>
<td>29. Jag oroar mig över vad andra människor tänker om mig.</td>
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<tr>
<td>30. Jag är rädd för att vara på platser med mycket folk (t.ex. affärscentrum, på bio, bussar eller lekplatser med mycket människor).</td>
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<td>31. Jag känner mig glad.</td>
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<td>32. Plötsligt kan jag känna mig väldigt rädd utan någon anledning.</td>
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<td>33. Jag är rädd för insekter eller spindlar.</td>
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<td>34. Jag blir plötsligt yr eller svag utan att det finns någon anledning.</td>
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<tr>
<td>35. Jag känner mig rädd om jag måste prata framför klassen.</td>
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<tr>
<td>36. Mitt hjärta kan plötsligt börja slå väldigt snabbt utan någon anledning.</td>
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<td>37. Jag oroar mig över att jag plötsligt ska få en känsla av att vara rädd, när det inte finns något att vara rädd för.</td>
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<td>38. Jag gillar mig själv.</td>
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<td>40. Jag måste göra vissa saker om och om igen (så som tvätta händerna, städa, eller lägga saker i en bestämd ordning).</td>
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<td>41. Jag blir störd av hemska eller dumma tankar eller bilder i mitt huvud.</td>
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<td>42. Jag måste göra vissa saker på precis rätt sätt för atthindra hemska saker från att hända.</td>
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<td>43. Jag är stolt över mitt skolarbete.</td>
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<td>44. Jag skulle känna mig rädd om jag var tvungen att vara borta hemifrån över natten.</td>
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<td>45. Finns det något annat du är väldigt rädd för?</td>
<td>Ja</td>
<td>Nej</td>
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Skriv ner vad det är:

<table>
<thead>
<tr>
<th>Hur ofta är du rädd för det?</th>
<th>Aldrig</th>
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### SPENCE ÅNGESTSKALA
#### Föräldraversion

#### Hur bra stämmer frågorna in på ditt barn?
Kryssa i den ruta som stämmer bäst.

<table>
<thead>
<tr>
<th>Fråga</th>
<th>Aldrig</th>
<th>Ibland</th>
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<tr>
<td>1. Mitt barn oroar sig över saker.</td>
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<tr>
<td>2. Mitt barn är rädd för mörkret.</td>
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<td>3. När mitt barn har problem, får han/hon en konstig känsla i magen.</td>
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<td>4. Mitt barn klagar över att känna sig rädd.</td>
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<td>5. Mitt barn skulle känna rädsla över att vara ensam hemma.</td>
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<tr>
<td>7. Mitt barn känner sig rädd när han/hon måste använda offentliga toaletter eller badrum.</td>
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<tr>
<td>9. Mitt barn är rädd för att göra bort sig framför andra människor.</td>
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<tr>
<td>10. Mitt barn oroar sig över att han/hon ska misslyckas i skolan.</td>
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<tr>
<td>11. Mitt barn oroar sig över att något hemskt ska hända någon i vår familj.</td>
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<tr>
<td>12. Mitt barn kan plötsligt känna att han/hon inte kan andas, fast det inte finns någon anledning till det.</td>
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<td>13. Mitt barn måste kontrollera om och om igen att han/hon har gjort saker rätt (som att släcka ljuset eller låsa dörr).</td>
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<td>14. Mitt barn känner rädsla om han/hon måste sova ensam.</td>
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<td>15. Mitt barn har problem med att gå till skolan på morgonen, eftersom han/hon känner sig nervös eller rädd.</td>
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<td>16. Mitt barn är rädd för hundar.</td>
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<td>17. Mitt barn verkar inte kunna få dåliga eller dumma tankar ur sitt huvud.</td>
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<tr>
<td>18. När mitt barn har problem, klagar han/hon på att hjärtat slår väldigt fort.</td>
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<td>19. Mitt barn kan plötsligt börja skaka eller darra utan att det finns någon anledning.</td>
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<tr>
<td>20. Mitt barn oroar sig över att något hemskt ska hända honom/henne.</td>
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<tr>
<td>21. Mitt barn är rädd för att gå till doktorn eller tandläkaren.</td>
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<tr>
<td>22. När mitt barn har problem känner han/hon sig svag och darrig.</td>
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<td>23. Mitt barn är rädd för höjder (t.ex. att stå uppe på ett berg).</td>
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<tr>
<td>24. Mitt barn måste tänka speciella tankar (t.ex. nummer eller ord) för att förhindra att hemskasaker ska hända.</td>
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<td>25. Mitt barn känner rädsla om han/hon måste åka i en bil, eller på buss eller tåg.</td>
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### Spence Ångestskala

**Föräldraversion**

**Hur bra stämmer frågorna in på ditt barn?**

Kryssa i den ruta som stämmer bäst.

<table>
<thead>
<tr>
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<th>Aldrig</th>
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<tr>
<td>27. Mitt barn är rädd för att vara på platser med mycket folk (t.ex. affärscenrum, på bio, bussar eller lekplatser med mycket folk).</td>
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<td>28. Helt plötsligt kan mitt barn känna sig väldigt rädd utan någon anledning.</td>
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<td>29. Mitt barn är rädd för insekter eller spindlar.</td>
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<tr>
<td>30. Mitt barn klagar över att plötsligt känna sig yr eller svag utan att det finns någon anledning.</td>
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<td>31. Mitt barn känner rädsla när han/hon måste prata framför klassen.</td>
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<td>32. Mitt barn klagar över att hans/hennes hjärta plötsligt börjar slå för snabbt utan någon anledning.</td>
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<td>33. Mitt barn oroar sig över att han/hon plötsligt får en känsla av att vara rädd, när det inte finns något att vara rädd för.</td>
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<td>34. Mitt barn är rädd för att vara i små, stängda utrymmen, som tunnlar eller små rum.</td>
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<td>35. Mitt barn måste göra vissa saker om och om igen (som tvätta sina händer, städa, eller lägga saker i en bestämd ordning).</td>
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<td>36. Mitt barn blir stört av hemska eller dumma tankar eller bilder i sitt huvud.</td>
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<tr>
<td>37. Mitt barn måste göra vissa saker på precis rätt sätt för att hindra hemska saker från att hända.</td>
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<tr>
<td>38. Mitt barn skulle känna sig rädd om han/hon var tvungen att vara borta hemifrån över natten.</td>
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<tr>
<td>39. Finns det något annat som ditt barn är väldigt rädd för?</td>
<td>Ja</td>
<td>Nej</td>
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Skriv ner vad det är:

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**Hur ofta är han/hon rädd för det?**

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<td>Subscale</td>
<td>Adolescent version</td>
<td>Parent version</td>
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<tr>
<td>Warmth</td>
<td>Mina föräldrar visar att de älskar mig.</td>
<td>Jag känner väl till vad som händer i mitt barns liv/var-dag.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Mina föräldrar tycker om att vara med mig.</td>
<td>Jag vet verkligen hur mitt barn känner för olika saker.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mina föräldrar är alltid glada att se mig.</td>
<td>Jag gör speciella saker tillsammans med mitt barn (utöver vardagen).</td>
<td></td>
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<tr>
<td></td>
<td>Mina föräldrar tycker att jag är speciell.</td>
<td>Jag avsätter tid för att prata med mitt barn om sådant som är viktigt för honom/henne.</td>
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<td></td>
<td></td>
<td>Jag visar eller säger till mitt barn att jag älskar honom/henne.</td>
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<tr>
<td>Rejection</td>
<td>Ibland undrar jag om mina föräldrar tycker om mig.</td>
<td>Jag förstår mig inte på mitt barn särskilt bra.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Mina föräldrar tycker att jag alltid är i vägen.</td>
<td>Ibland är mitt barn svårt att tycka om.</td>
<td></td>
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<tr>
<td></td>
<td>Mina föräldrar får mig att känna som att jag inte är önskad.</td>
<td>Ibland kräver mitt barn så mycket att det känns som en böra</td>
<td></td>
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<tr>
<td></td>
<td>Ingenting jag gör är tillräckligt bra för mina föräldrar.</td>
<td>Mitt barn behöver mer än vad jag hinner ge honom/henne.</td>
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<tr>
<td></td>
<td></td>
<td>Ibland känner jag att jag inte kan vara där för mitt barn när han/hon behöver mig</td>
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<tr>
<td>Structure</td>
<td>När jag vill göra något, visar mina föräldrar hur.</td>
<td>Jag är tydlig med vad som händer om mitt barn inte följer våra regler.</td>
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<td></td>
<td>När jag vill förstå hur något fungerar, förklarar mina föräldrar det för mig.</td>
<td>Jag gör det tydligt för mitt barn vad jag förväntar mig av honom/henne.</td>
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<td></td>
<td>Om jag har ett problem, hjälper mina föräldrar mig att komma på hur jag ska lösa det.</td>
<td>Jag förväntar mig att mitt barn följer våra familjeregler.</td>
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<td></td>
<td>Mina föräldrar förklarar varför vi har våra familjeregler.</td>
<td>När jag säger till mitt barn att jag ska göra något, så gör jag det.</td>
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<td></td>
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<td>Om mitt barn har ett problem, så hjälper jag honom/henne att komma på hur han/hon ska lösa det.</td>
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<tr>
<td>Chaos</td>
<td>När mina föräldrar lovär något, vet jag aldrig om de kommer att hålla det.</td>
<td>Kunst att bekämpa ett problem som jag inte kan förvarna.</td>
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<tr>
<td></td>
<td>När mina föräldrar säger att de ska göra något, händer det att de inte alls gör det.</td>
<td>Kunst att bekämpa ett problem som jag inte kan förvarna.</td>
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<td></td>
<td>Mina föräldrar blir arga på mig utan förvarning.</td>
<td>Kunst att bekämpa ett problem som jag inte kan förvarna.</td>
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<tr>
<td>Autonomy</td>
<td>Mina föräldrar litar på mig.</td>
<td>Jag uppmuntrar mitt barn att utrycka sina känslor även när de är svåra eller jobbiga att höra.</td>
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<td></td>
<td>Mina föräldrar låter mig göra de saker som jag tycker är viktiga.</td>
<td>Jag litar på mitt barn.</td>
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<td></td>
<td>Mina föräldrar försöker förstå min synvinkel.</td>
<td>Jag uppmuntrar mitt barn att vara sann mot sig själv.</td>
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<td>Jag förväntar mig att mitt barn säger vad han/hon verkliga tycker.</td>
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<tr>
<td>Coercion</td>
<td>Mina föräldrar säger alltid åt mig vad jag ska göra.</td>
<td>Mitt barn bräkar jämt med mig.</td>
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<tr>
<td></td>
<td>Mina föräldrar bestämmer jämt över mig.</td>
<td>För att få mitt barn att göra något, måste jag skrika åt honom/henne.</td>
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<td></td>
<td>Mina föräldrar tycker att det finns ettenda sätt att göra saker på – deras sätt.</td>
<td>Jag kan inte tillåta att mitt barn bestämmer för många saker på egen hand.</td>
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<td></td>
<td>Mina föräldrar säger “nej” till allting.</td>
<td>Ibland känns det som att jag måste pressa mitt barn för att få honom/henne att göra saker.</td>
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<td></td>
<td></td>
<td>Jag märker att jag hamnar i maktbakarna med mitt barn.</td>
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