Chapter 1

General introduction
This PhD thesis focuses on the associations of several candidate genes, environmental factors, and their interaction (i.e., gene-environment [GxE] interactions) with the course of Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms from early into late adolescence. While ADHD symptoms often persist throughout adolescence and even adulthood, relatively little is known about determinants of the course of ADHD symptoms across adolescence. This PhD thesis aims to advance our understanding why ADHD symptoms persist into late adolescence in some individuals but not in others. Furthermore, in this PhD thesis it will be analyzed whether the contribution of genes, environments, and GxE’s on ADHD symptoms may differ across various stages of adolescence.

This chapter begins with an introduction of the clinical features and course of ADHD. In the following sections I will discuss what is currently known about the role of genetic and environmental influences as well as gene-environment interactions on the course of ADHD symptoms. Then I will emphasize why it is important to examine the influence of genes, environments, and their interaction on ADHD symptoms across adolescent development. Finally, the chapter ends with an overview of the aims and an outline of this PhD thesis.

**Attention-Deficit/Hyperactivity Disorder**

Attention Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that affects individuals across the life span and is characterized by symptoms of inattention, impulsivity, and hyperactivity (American Psychiatric Association [APA], 2000). An ADHD diagnosis requires that six or more symptoms of inattention or hyperactivity-impulsivity should be present in multiple settings of which some symptoms were present before the age of 7 and are associated and with clinically significant impairment (DSM-IV-TR; APA, 2000). Based on the symptoms, three types of ADHD are distinguished: predominantly inattentive, predominantly hyperactive-impulsive, or a combined type of both inattention and hyperactive-impulsive symptoms (DSM-IV-TR; APA, 2000). Importantly, in 2013 the DSM-IV-TR was replaced by the DSM-V (APA, 2013); although the diagnostic criteria remained similar between the two DSM versions, some minor changes have been made. For example, the onset criterion has been changed from 7 to 12 years of age and a reduction from six to five in the minimum number of symptoms in either symptom domain required for older adolescents and adults (DSM-V, 2013). For the present thesis I stuck to the DSM-IV-TR to maximize comparability to previous studies.

The worldwide prevalence of ADHD in childhood is 5.3% (Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007). The estimated prevalence of ADHD in adulthood lies in the range of 2.5%-4.4% (Kessler et al., 2006; Simon, Czobor, Balint, Meszaros, & Bitter, 2009). Moreover, recent longitudinal studies have shown that 15% of patients diagnosed with ADHD in childhood will have full syndromic persistence into adolescence and adult-
hood (Faraone, Biederman, & Mick, 2006; Faraone et al., 2015). Notably, the prevalence of ADHD is higher in boys than in girls in both clinical (9:1; Biederman et al., 2002; Gaub & Carlson, 1997) and community samples of children and adolescents (3:1; Barkley, 2006; Nøvik et al., 2006).

Clinical Features of ADHD

Individuals with ADHD vary widely in their clinical profile and course of the disorder. The distinction of ADHD types is still under debate since it has been suggested that ADHD types may not be stable over time (Coghill & Seth, 2011). Another point of discussion in the ADHD literature is whether ADHD should be better viewed as a distinct entity or as the extreme negative end of a continuous distribution of ADHD symptoms in the population (Asherson & Trzaskowski, 2015; Larsson, Anckarsater, Rastam, Chang, & Lichtenstein, 2012). The last point of view is supported by twin studies showing a substantial overlap between the genetic factors for a clinical diagnosis of ADHD and continuous measures of ADHD symptoms in the general population (Larsson et al., 2012; Levy, Hay, McStephen, Wood, & Waldman, 1997). Therefore, the focus in this PhD thesis lies on the dimensional nature of ADHD, rather than on the distinction between ADHD and individuals without the disorder.

ADHD is a heterogeneous disorder that is associated with tremendous financial burden for both the individual (Swensen et al., 2003) and the society (Le et al., 2014), stress on families (Johnston & Mash, 2011), social impairments (Das, Cherbuin, Butterworth, Anestey, & Easteal, 2012; Wehmeier, Schacht, & Barkley, 2010), and adverse academic and vocational outcomes (Loe & Feldman, 2007; Polderman, Boomsma, Bartels, Verhulst, & Huizink, 2010) on the long term. Another worrisome issue is that individuals with ADHD may develop high comorbidity with substance use disorders (Van Emmerik-Van Ootmerssen et al., 2012), antisocial behaviors, and depression (Secnik, Swensen, & Lage, 2005) and anxiety (Michielsen, et al., 2013) into adulthood. Recent studies suggest that functional outcomes differ between participants with persisting versus decreasing ADHD symptoms (Barkley, Murphy, & Fisher, 2008; Swanson, Owens, & Hinshaw, 2014). Therefore, it is important to know what determines the course of ADHD symptoms across adolescence since ADHD symptoms can have severe long-term consequences on many domains of an individual’s life.

The Course of ADHD Symptoms across Adolescence

In general, ADHD symptoms tend to decrease during adolescence (Biederman, Mick, & Faraone, 2000), but the course of symptoms differs between individuals. Studies showed that of all children with ADHD, 45% to 85% are still symptomatic in adolescence and 50% to 60% continue to show symptoms in adulthood (Faraone et al., 2006). Thus, the rate of persistence of ADHD is especially high when persistence is defined as functional
impairment or the persistence of subthreshold (three or fewer) impairing symptoms (Faraone et al., 2015). Various ADHD symptom trajectories have been described across adolescence, in both clinical and population samples, and most studies reported a low stable and a high persistent ADHD symptom trajectory (e.g., Döpfner et al., 2015; Muss-er, Karalunas, Dieckman, Peris, & Nigg, 2016; Sasser, Kalvin, & Bierman, 2016; Tandon, Tillmann, Argrawal, & Luby, 2016). However, some studies also described an increasing ADHD symptom trajectory (Döpfner et al., 2015; Riglin et al., 2016; Van Lier, Van der Ende, Koot, & Verhulst, 2007). The rate of adolescents following a high persistent ADHD symptom trajectory is 2.8%-5% in population-based samples (Döpfner et al., 2015; Van Lier et al., 2005) and 17.5%-22% in clinical samples (Musser et al., 2016; Tandon et al., 2016). Overall, there is large heterogeneity in the course of ADHD symptoms, highlight-ing the need to find the causes of this heterogeneity.

Determinants of the Course of ADHD Symptoms

Relatively little is known about determinants of the course of ADHD symptoms in adolescents in the transition towards adulthood. As mentioned above, it is important to understand why symptoms persist in some individuals but not in others, since ADHD symptoms may lead to impairments in functioning in several domains. Moreover, it is possible that determinants may operate through time-sensitive windows during development, playing a role at one time but not another. Thereby it is important to recognize that the same risk factors that influence the onset of ADHD may be involved in the course of the disorder, but it may also be that a different set of risk and protective factors influence the course of ADHD, with varying influences over time (Thapar, Langley, Asherson, & Gill, 2007b). For example, in a twin study with individuals of whom symptoms were obtained from the ages 8 to 20 it was found that genetic effects operating in childhood explained less of the total variance in early adulthood than during childhood, thus pointing to decreasing genetic influences over time (Chang, Lichtenstein, Asherson, & Larsson, 2013). Yet, new sets of genetic risk factors emerged at different stages across adolescence in this study.

In this PhD thesis, I made a selection of genes and environments which have been implicated in the etiology of ADHD, but which might also be relevant determinants for the course of ADHD symptoms across adolescence. In the following, I will also discuss a number of G×E interactions that may be related to the course of ADHD symptoms.

Genetic Factors

It has been suggested that 70 to 90% of the ADHD symptoms can be accounted for by genetic factors (Faraone & Mick, 2010; Nikolas & Burt, 2010). ADHD symptoms are likely to be caused by multiple genes of small effects (Asherson, Kuntsi, & Taylor, 2005), as well as rare genetic variants of large effects (Elia et al., 2010). Nearly 180 candidate
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genes for the etiology of ADHD have been implicated (Li, Chang, Zhang, Gao, & Wang, 2014), which mainly involve genes in the functioning and synthesis of neurotransmitters in the dopaminergic and serotonergic systems, and the degradation of these enzymes (Brookes et al., 2006; Gizer, Ficks, & Waldman, 2009). The dopamine system has been implicated in ADHD because of its central role of planning and initiation of motor responses, activation, switching, reaction to novelty, and processing of rewards (Faraone et al., 2015). Genes involved in the serotonin system are plausible candidates for ADHD studies since experimentally manipulated serotonin levels lead to ADHD-like behaviors such as impulsive choices, increased motor activity, and delay aversion in both humans and animal models (Brewer & Potenza, 2008). Therefore, based on meta-analyses investigating the etiology of ADHD (Brookes et al., 2006; Gizer, Ficks, & Waldman, 2009), the five selected relevant candidate genes for ADHD that were available in our dataset were the dopamine receptor D4 (DRD4), dopamine D2 receptor (DRD2), serotonin transporter (5-HTTLPR), catechol-O-methyl transferase (COMT), and monoamine oxidase A (MAOA). The 7-repeat of the DRD4 (Gizer et al., 2009; Li, Sham, Owen, & He, 2006) and the long version of the 5-HTTLPR genotype (Brookes et al., 2006; Gizer et al., 2009) have been repeatedly associated with ADHD; less robust associations have been suggested for the A1 allele of the DRD2 (Kopečková et al., 2008), the Val-allele of the COMT, (Gizer et al., 2009; Sun, Yuan, Shen, Xiong, & Wu, 2014) and high-activity of the MAOA genotype with ADHD (Gizer et al., 2009). Still, definite conclusions on which genes influence ADHD will have to await further research, given the large heterogeneity across genetic studies and the complex genetic architecture of neuropsychiatric disorders, which requires large samples (Li et al., 2014).

In contrast to the wealth of genetic studies on the etiology of ADHD, there is far less literature on the genetic influences on the course of ADHD symptoms; only a handful of candidate gene studies is currently available. For example, the DRD4 7-repeat was found to be associated with a more persistent course of ADHD symptom severity over time by two studies (Biederman et al., 2009; Langley et al., 2009), whereas the presence of the long version of the 5-HTTLPR was not associated with the course of ADHD (Langley et al., 2009). Furthermore, the low activity MAOA genotype was associated with stable attention problems during adolescence (Zohsel et al, 2015), rather than with the high activity MAOA that has been related to the onset of ADHD (Gizer et al., 2009). Moreover, as mentioned above, it is important to be aware that genetic influences on the course of ADHD symptoms may change over time (Chang et al., 2013). For example, the dopamine active transporter 1 gene (DAT1), although not available in our dataset, was found to be differentially associated with ADHD in children and in adults, suggesting that the DAT1 gene interacts with developmental factors (Franke et al., 2008; 2009). By focusing on genetic underpinnings of changes in ADHD symptoms across adolescence, there might
be new insights into neurobiological mechanisms that underlie the course of ADHD symptoms.

**Environmental Factors**

Just as genetic factors are involved in the etiology and likely also in the course of ADHD, non-genetic factors may play a role in its onset and course. Indeed, it has been suggested that change over time of ADHD symptoms is markedly influenced by environmental factors (Kan et al., 2013). More specifically, in a twin study with 8-9 year old children who were examined four years later it was found that change in symptoms between childhood and early adolescence was partly due to new nonshared environmental effects that became important during adolescence (Larsson, Larsson, & Lichtenstein, 2004). Yet our current knowledge of developmental processes is much more limited compared to the wider literature that has focused on a variety of environmental factors in relation to ADHD (e.g., Banerjee, Middleton, & Faraone, 2007; Kim & Yoo, 2013; Sagiv, Epstein, Bellinger, & Korrick, 2013; Wirth et al., 2017). Well replicated environmental risk factors of ADHD involve, for instance, pre- and perinatal adversities (Banerjee et al., 2007; Gustafsson & Källén, 2011; Silva, Colvin, Hagemann, & Bower, 2014); these are theoretically attractive as a causal factor for neuropsychiatric disorders such as ADHD because of their potential influence on the developing brain (Marsh, Gerber, & Peterson, 2008). In particular, prenatal exposure to maternal smoking, alcohol or cannabis use have been linked to behavioral characteristics of ADHD (Huizink & Mulder, 2006). However, it should be noted that this effect of the environment might be caused by underlying causal genetic factors that have elicited the exposure to these environmental factors. Although these events occur before birth, the effects of pre- and perinatal adversities should be considered in the light of postnatal environment conditions, since neurodevelopment continues into young adulthood (Toga, Thompson, & Sowell, 2006). While these pre- and perinatal adversities seem risk factors for ADHD during the early stages of life with possible prolonged effects in later life, still little is known about their role on the course of ADHD symptoms (Galéra et al., 2011; Halmøy et al., 2012).

Adolescence is a unique period that might influence the course of ADHD symptoms. Adolescence represents a particularly sensitive period of life, characterized by increasing peer influences and social relations, self-awareness, sensitivity to social environmental cues (particularly social acceptance), inter-personal conflicts, and mental health problems, resulting from personal experiences, maturation, and neurobiological changes (Arnett, 1999; Schriber & Guyer, 2016). It is important to acknowledge that, when examining the course of ADHD symptoms, the impact of environmental factors may change during development. For example, parents’ contribution to ADHD symptoms might be different in childhood than in adolescence as youths strive to gain independence from their families and become more engaged with their peers (Rubin, Bukowski, & Parker,
To conclude, the influence of the pre- and perinatal environment (‘Chapter 2’), parenting environment (see ‘Chapter 3’ and ‘Chapter 5’), stressful environment (‘Chapter 4’), and school environment (‘Chapter 5’) across adolescence will be examined in relation to the course of ADHD symptoms in my studies.

**Gene-Environment Interactions**

Individuals differ in the extent to which they are influenced by the environment. More specifically, the impact of the environment may vary depending on the individual’s genetic make-up. GxE interactions can be defined as genetically modulated sensitivity to environmental factors (e.g., Bakermans-Kranenburg & Van IJzendoorn, 2011; Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Pluess & Belsky, 2010). GxE interactions are crucial to understand the mechanisms underlying ADHD symptoms (Buitelaar, 2005; Nikolas, Klump, & Burt, 2012). More specifically, through examining GxE interactions it is possible to get a more accurate estimate of the importance of both the genetic and environmental risk factors involved, and identify those individuals most susceptible to environmental influences (Moffitt, Caspi, & Rutter, 2005).

The interplay between genes and environmental factors is thought to play a pivotal role in both the etiology (Thapar, Cooper, Jefferies, & Stergiakouli, 2012) and also the course of ADHD symptoms (Nigg, Nikolas, & Burt, 2010; Thapar, Harold, Rice, Langley, & O’Donovan, 2007a), although still few studies have examined GxE in relation to the course. One of the first GxE studies in ADHD looked into possible interactions of DRD4 with prenatal exposure to alcohol or smoking (Neuman et al., 2007). Neuman and colleagues found evidence that individuals with the 7-repeat DRD4 genotype and whose mother smoked during pregnancy had higher odds of having ADHD. However, this association was not replicated in other studies (Altink et al., 2008; Langley et al., 2008).

A well-replicated GxE interaction concerns the interaction between 5-HTTLPR and psychosocial stress. Individuals carrying the S-allele have been found to be more sensitive to the negative effects of long-term stress exposure for a range of psychiatric disorders such as depression (e.g., Caspi et al., 2003), substance use (e.g., Covault et al., 2007), and also ADHD (Müller et al., 2008; Retz et al., 2008; Van der Meer et al., 2014).

The differential susceptibility theory posits that individuals are more susceptible to both positive and negative influences of the environment depending on their genetic background (Belsky & Pluess, 2009, 2013; Ellis, Boyce, Belsky, Bakermans-Kranenburg, Van IJzendoorn, 2011). Several studies have indicated that the DRD4 genotype may render children susceptible to environmental influences ‘for better and for worse’ (Bakermans-Kranenburg & Van IJzendoorn, 2006). That is, children carrying the 7-repeat allele of the DRD4 genotype were susceptible to the effects of both maternal sensitivity and maternal insensitivity: these children showed the highest levels of externalizing behavior when their mothers were insensitive, and the lowest levels of externalizing
behavior when their mothers were sensitive. Also serotonergic genes have been found to contribute to individual differences in response to environmental influences. For example, for S-allele homozygotes of the *5-HTTLPR* genotype, family conflict predicted increased inattention scores, while family cohesion predicted decreased inattention scores (Elmore, Nigg, Friderici, Jernigan, & Nikolas, 2016).

In sum, the majority of the existing studies that examined G×E interactions in relation to ADHD are cross-sectional in nature and focused on the onset of ADHD symptoms rather than the course over time (e.g., Elmore et al., 2016; Van der Meer et al., 2014; Nikitopoulos et al., 2014). Longitudinal designs examining G×E interactions are important for two reasons. First, the relative contribution of genes and environment on ADHD symptoms may differ across age (Chang et al., 2013; Larsson et al., 2004; Pingault et al., 2015), suggesting that G×E interactions are not always stable over time (Belsky & Pluess, 2013; Berry, Deater-Deckard, McCartney, Wang, & Petrill, 2013), pointing to the importance to consider change over time. Second, the expression of ADHD symptoms of adolescents is present within a complex and changing social context (we will discuss this in more detail below). In this PhD thesis I examined whether G×E interactions that have been implicated in the etiology of ADHD are also relevant to the course of ADHD symptoms across adolescence focusing on G×Pre- and perinatal adversities, G×Parenting, G×Stress, and G×Family and School climate.

**Exploring ADHD Symptoms across Adolescence**

**Adolescents as a Unique Developmental Period in Examining ADHD Symptoms**

Although the severity of ADHD symptoms peaks during early elementary school (Schmidt & Petermann, 2009), adolescence is an important developmental period to study G×E interactions in relation to ADHD symptoms. Adolescence differs fundamentally from childhood. With increasing age, both the individual and its environment change and it is, therefore, key to acknowledge that predictors (genes, environment, and gene-environment interactions) of ADHD symptoms may differ across the life course. Adolescence is a core developmental period setting the stage for the course of ADHD symptoms in later life for several reasons. First, in adolescence the ability to focus and regulate behavior are put increasingly into practice in order to meet progressing demands of the environment. For example, in secondary education individuals have to make their homework, which might overwhelm and frustrate students with ADHD who often struggle with executive functions, focus, and organization. Indeed, individuals with ADHD frequently lose homework assignments or fail to turn them in on-time, misplace school materials such as books, pencils, and classwork, and procrastinate and fail to adequately prepare for tests (Evans et al., 2009; Langberg et al., 2011). But more importantly, in adolescence social skills are strongly put to the test since peers become more important than parents and become the main domain of social interaction of adolescents (Véronneau, Trempe,
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& Paiva, 2014). However, symptoms of hyperactivity and impulsivity of individuals with ADHD may result in more irritating, socially inappropriate, and aversive behaviors when they are interacting with peers (Whalen & Henker, 1985). As a result, adolescents with high levels of ADHD symptoms may be rejected and are then more likely to be excluded from social activities with peers (Buhs & Ladd, 2001). This may lead to social isolation and deprivation of important socialization experiences, of opportunities to develop and refine social skills, and of important sources of social support (Parker, Rubin, Erath, Wojslawowicz, & Buskirk, 2006). Over time this may ultimately lead to continuation or exacerbation of ADHD symptoms.

Second, recent research has drawn attention to the development of the adolescent brain (Giedd, 2008; Giedd & Rapoport, 2008). While there is evidence that ADHD is associated with a different brain structure (Hoogman et al., 2017), adolescence is a period of time where brain maturation is dynamic. This might possibly explain the significant change in ADHD symptoms that take place in a proportion of patients during this time window. On the other hand, this developmental plasticity may also make the adolescent brain amenable to interventions that help mitigate environmental adversities of emotional and/or physical nature (Andersen, 2003).

Third, current treatment strategies for ADHD are not optimally attuned to the needs and vulnerabilities of adolescents (Buitelaar, 2017). Many adolescents with ADHD have poor medication adherence or even stop medication treatment, and use of behavioral interventions is also suboptimal. This is related to characteristics related to adolescence: poor decision making, poor insight into one’s own functioning, and peer pressure (for a more elaborated overview, see Chan, Fogler, & Hammerness, 2009). Examining how genes, environments and their interactions are related to the course of ADHD symptoms in adolescence might help targeting treatment strategies to those who need it most.

Longitudinal GxE Research Designs in Examining the Course of ADHD Symptoms

As I have outlined above, it is important to include a developmental aspect in GxE research. Nonetheless, most studies tested the interplay between genes and the environment cross-sectionally or on a single or one combined outcome measure over time. When examining the longitudinal course of ADHD symptoms across adolescence it is desirable to include multiple measures across time. Many research designs can be chosen when examining GxE interactions longitudinally and it is important to think about their implications in defining the course of ADHD symptoms. For example, pre- and perinatal adversities (see ‘Chapter 2’), which are low-prevalent, might have long-term effects on ADHD symptoms that may vary over the course of adolescence. This requires a large sample size and justifies estimating the course of ADHD symptoms as a single curve over time. On the other hand, the family and school climate (see ‘Chapter 5’) might be different at the age of 11 than at 16 years and then it is important to include each
outcome measure separately, providing the possibility to estimate bidirectional relationships between different ages. It is also possible to define the course of ADHD symptoms by creating homogenous groups (i.e., individuals within these groups are more alike compared to individuals from another group) over time based on the outcome measure; these so-called ‘trajectories’ allow for studying symptom persistence, remission, and stability (see ‘Chapter 3’). In sum, it is of great importance to include a developmental perspective when studying the role of GxE interactions on ADHD symptoms over time, while different research designs will address different aspects across the studies in this PhD thesis.

**Study Design**

We used data from the first three measurement waves (mean ages from about 10 to 18 years) of the Dutch ‘TRacking Adolescents’ Individual Lives Survey’ (TRAILS; e.g., De Winter et al., 2005; Huisman et al., 2008; Oldehinkel et al., 2015). TRAILS aims to contribute to the understanding of the course of ADHD symptoms across adolescence following 10-12 year-old Dutch children biennially into adulthood. Data from both the general-population cohort and the parallel clinic referred cohort were pooled to obtain results reflecting the entire spectrum of ADHD symptom levels. In brief, for the population-based cohort TRAILS approached 135 primary schools in five municipalities in the Northern Netherlands. Of these schools, 90.4% agreed to participate. TRAILS contacted eligible students \((n = 3,145)\) and their parents, enrolling 76% \((n = 2,230)\) of those contacted in the study. The three data waves included in this study ran from March 2001 to July 2002 (T1), September 2003 to December 2004 (T2), and September 2005 to August 2007 (T3), with response rates consistently above 80%. The clinic-referred sample \((n = 543)\) consisted of pre-adolescents who had been referred to a child and adolescent psychiatric outpatient clinic in the northern of the Netherlands at any point in their life \((20.8 \% \leq 5 \text{ years}, 66.1 \% 6-9 \text{ years}, 13.1 \% 10-12 \text{ years})\) for consultation or treatment. The first three data waves in the clinic-referred cohort ran two years behind those of the population cohort: From September 2004 to December 2005 (T1), September 2006 to November 2007 (T2), and September 2009 to February 2011 (T3). The measurement instruments and design for the clinic-referred cohort were the same as those of the population cohort. Of the 1264 eligible pre-adolescents, 543 were enrolled in the study and finished baseline measurements (T1). Further details of the included measurements across the different time points, sampling procedures, and response rates of both cohorts are well-documented elsewhere (e.g., De Winter et al., 2005; Huisman et al., 2008; Oldehinkel et al., 2015).
**Aims and Outline of this Thesis**

The overall aim of this PhD thesis is to elucidate the role of genetic and environmental influences as well as their interplay in the course of ADHD symptoms across adolescence. For that purpose, different environmental contexts were examined to obtain a more comprehensive picture of how ADHD candidate genes, environment, and their interaction may be involved in adolescent development in the transition into adulthood. The general hypothesis of this PhD thesis was that G×E interactions (partly) explain the course of ADHD symptoms across adolescence.

In *Chapter 2*, I examined whether candidate genes (*DRD4*, *5-HTTLPR*, *DRD2*, *COMT*, and *MAOA*), a set of pre- and perinatal factors (i.e., index measure of various pregnancy and delivery complications, maternal smoking, maternal drinking, and low birth weight), and their interactions were associated during the course of ADHD symptoms from early to late adolescence, using Linear Mixed Models (LMM). While these factors have been implicated in the etiology of ADHD, it is currently unknown whether they have an enduring effect on the course of ADHD symptoms across adolescence.

*Chapter 3* explored whether perceived parenting styles, both independent and dependent of candidate genes (i.e., *DRD4*, *5-HTTLPR*, and *MAOA*), predicted different ADHD symptom trajectories across adolescence, using Growth Mixture Modeling (GMM). This might serve as a starting point for treatment to prevent adolescents following at-risk (persistent) ADHD symptom trajectories.

In *Chapter 4*, I investigated whether the *5-HTTLPR* genotype moderated associations between two types of life stressors (i.e., environment-related and person-related life stressors) and ADHD symptoms between early, mid, and late adolescence. Using a bidirectional longitudinal design with Structural Equation Modeling [SEM] helps to determine whether exposure to life stressors contributed to adolescents’ ADHD symptoms and vice versa, all in the context of the *5-HTTLPR* genotype. This elucidates the directionality (ADHD <-> life stressors), specificity (independent vs. dependent life stressors), and time dependency of the associations.

In *Chapter 5*, by using an innovative analysis method (Random Intercept Cross Lagged Path Model [RI-CLPM]), genetic moderation by the *DRD4* and *5-HTTLPR* genotypes were examined on longitudinal bidirectional associations of the family climate and school climate with ADHD symptoms across adolescence. The importance of the family and school context changes across adolescence and since adolescents may be differently affected by the environment because of their genetic make-up, it would be interesting to see how susceptibility genes, the family and school environment, and their interaction are related to ADHD symptoms across adolescence.

Finally, in *Chapter 6* I will discuss the main findings and integrate these within current research, concluding with directions for future research.
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