Summary and General Discussion
In this chapter the studies presented in this thesis are summarized and discussed. In addition, clinical implications and suggestions for future research are provided.

**Introduction**

ADHD is a common psychiatric disorder characterized by inattention, impulsivity, and hyperactivity. Impairments in social functioning are an important and common associated feature in children with ADHD. Despite this, there is a paucity of knowledge about the etiology of social problems in children with ADHD, and about the relation of these problems with other disorders that are characterized by problems in social functioning, especially ASD. In their apparent lack of social understanding (Cantwell, 1996), children with ADHD seem to be similar to children with ASD, which suggests a certain degree of symptom overlap between ADHD and ASD. This thesis presents studies into the nature and genetic causes of the occurrence of ASD symptoms in children with ADHD, which is introduced by a chapter on the social problems of children with ADHD.

**Study results**

**ADHD and social functioning**

Most children with ADHD do show an interest in connecting with other people, but they often fail to properly attune their behavior to other people and the social context. As a consequence, children with ADHD frequently have conflicts, suffer from unpopularity, and have little or no close friends. Specific socially inadequate behaviors displayed by children with ADHD that are associated with peer rejection are negative, aggressive behaviors (including being bossy, argumentative, explosive and violating rules), as well as typical ADHD behaviors (e.g., loud, fidgety, inattentive, and intrusive behavior). Multiple studies have focussed on comorbid disorders, especially oppositional defiant disorder and conduct disorder, as sources for social problems in children with ADHD. Although comorbid disorders are important predictors of severe problems in social functioning, it also seems evident that ADHD as such brings along important limitations in acquiring and performing social skills. All three ADHD core dimensions impair the adjustment of behavior to a continuously changing (social) environment. Therefore, problems in social interaction may at least in some children be a direct consequence of the core dimensions of ADHD. Indeed, many children with ADHD have appropriate knowledge of adequate social behavior, but difficulties to apply this in real world settings (Barkley, 1997).
The importance of social problems is reflected in the fact that these are long-term problems with negative long-term effects. Social problems are a significant risk factor for disorders other than ADHD, such as mood disorders and antisocial behavior. Medication and behavior therapy may have favorable effects on social functioning, but thus far, no treatment has been proven to normalize the social behavior of children with ADHD. Treatment with medication, in particular stimulants, is the most effective treatment available to date for problems in social functioning in children with ADHD. Whereas the relation between conduct problems and social functioning in children with ADHD has received quite some attention, the role of ASD symptoms is relatively understudied. Partly, this is due to the fact that both DSM-IV and ICD-10 do not allow for a diagnosis of ADHD in the presence of an ASD. Still, several studies report the occurrence of clinically relevant symptoms from all three ASD symptom domains in children with ADHD, especially in those with ADHD of the combined type, and more frequently than in children with other psychiatric disorders. Interestingly, Santosh and Mijovic (2004) discerned two types of social impairment, with one confirming the importance of comorbid ODD/CD in the social dysfunctioning of ADHD, and the other suggesting that ASD symptoms in children with ADHD may be associated with a separate type of social dysfunctioning. Research that has appeared in the past few years (dated after the review presented in Chapter 2) seems to confirm this finding (Gadow, DeVincent, & Drabick, 2008; Gadow, DeVincent, & Schneider, 2009; Guttmann-Steinmetz, Gadow, & DeVincent, 2009). For instance, Guttmann-Steinmetz et al. (2009) replicate previous studies in finding an association between both ADHD and ASD and oppositional behavior. They also find that in children with ASD or a combination of ADHD and ASD, ODD behaviors that require more social cognition (such as deliberately annoying others or blaming others for own mistakes) are no more frequent than in controls. This implies that the social defects in ASD and oppositional behavior are in different areas, with difficulties in reciprocal interaction and communication being essential in ASD, and aggression being a core feature in oppositional behavior. These findings also suggest that comorbid neurodevelopmental disorders (such as ASD in combination with ADHD) alter generally accepted features of other disorders (such as ODD).

ADHD and ASD do not only share symptoms, but also share similar deficits in executive functioning, suggesting common underlying brain deficits. Studies on the etiology of ADHD and ASD in community twin samples have shown that a substantial part of genetic influences are shared between ADHD and ASD. Moreover, genetic overlap is suggested by genetic linkage studies for ADHD and ASD, in which overlapping sets of suggestive disease loci have been identified. Nevertheless, although clinical, neuropsychological and linkage studies may have shown that many children display both ADHD and ASD symptoms, it is still unknown whether this association represents a true overlap in causal mechanisms. The studies presented in
this thesis investigates the genetic causes for the occurrence of ASD symptoms in children with ADHD, and includes the first results on possible molecular genetic mechanisms.

**Familiality and genetic background of ASD symptoms in children with ADHD**

The familiality and genetic causes of ASD symptoms in children with ADHD were investigated in a large, extensively phenotyped group of children with combined type ADHD and their siblings, from whom DNA was collected as well. In the studies presented in this thesis, ASD symptoms were assessed using the CSBQ (Hartman, Luteijn, Serra, & Minderaa, 2006) or the SCQ (Berument, Rutter, Lord, Pickles, & Bailey, 1999). In chapter 3, 4, and 6, we studied the Dutch participants of the IMAGE study using the CSBQ, whereas in chapter 5, the SCQ was used to investigate the larger IMAGE sample.

In chapter 3 we reported that subtle ASD traits as covered by the CSBQ were elevated in children with ADHD compared to their siblings, with sibling scores still well above those of healthy control children. The elevations in ASD symptoms were not restricted to a specific subset of ASD symptoms, but covered the whole ASD spectrum. We found positive associations between ADHD and ASD symptoms, and found no indication that either attention problems or hyperactivity-impulsivity alone could explain these associations. Our results did suggest, however, that withdrawn behavior as assessed by the ‘social’ scale occurred more frequently in children with relatively severe attention problems. Our findings furthermore implied that ASD symptoms in the context of ADHD were familial, but that the correspondence between siblings’ ASD scores was mostly independent from siblings’ similarity in ADHD symptom scores. IQ and comorbid anxiety were found to be unlikely confounding factors. Interestingly, girls with ADHD had higher gender and age specific ASD symptom scores, and showed somewhat stronger sibling correlations than boys. Furthermore, the ‘social’ subscale showed stronger sibling correlations in elder than in younger sibling pairs. As ASD familiality is largely explained by genetic rather than shared environmental factors, the familiality we found most likely reflects heritability. The most familial CSBQ subscale was the stereotyped scale.

Our findings add to previous research that calls into question the exclusionary clause in DSM-IV that prohibits a combined diagnosis of ADHD and ASD, and stress the importance of assessing symptoms of both disorders in children with (presumed) ADHD. In agreement with this notion, the clause is omitted in the proposed criteria for ADHD in DSM-V (see www.dsm5.org). None of the cases included in this study fulfilled PACS (Taylor, Schachar, Thorley, & Wieselberg, 1986) criteria for classical or atypical autism, so our findings should be seen as reflecting ASD symptoms in children with a primary diagnosis of ADHD.
This study furthermore showed that many children with ADHD display social problems that are typical for ASD. We found that compared to their siblings and control children, children with ADHD show significantly higher levels of impaired spontaneous sharing, reciprocity, and use of nonverbal communication. This was particularly the case in children with relatively severe inattention symptoms. An interaction between ADHD and ASD traits may play a role here: perhaps a child who has ASD symptoms in addition to extreme inattentiveness may have little motivation to pay attention to social cues. No research published to date has addressed this possibility. Other typical ASD symptoms that we found to be increased in children with ADHD were communication problems as assessed with the ‘understanding’ subscale, insistence on sameness as measured by the ‘change’ subscale, and stereotyped behavior. The fact that we found low correlations between ADHD and ASD scores strengthens the ASD specificity of our results.

Although we found that the subtle ASD symptoms, and stereotyped behavior in particular, were familial, we found no evidence that the occurrence of ASD symptoms in sibling pairs with ADHD is substantially influenced by familial influences shared between the two disorders. This challenges the hypothesis that ADHD and ASD share genetic risk factors as postulated in the introduction of this thesis. Our findings leave the fact that children with ADHD show higher levels of ASD symptoms than children with other disorders unexplained, and does not correspond with findings reported in other studies (Reiersen, Constantino, Grimmer, Martin, & Todd, 2008; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008). A restriction of range of ADHD symptom scores in the ADHD probands may be one explanation for the fact that we could not replicate the shared familiality of ADHD and ASD. However, the fact that we also found very weak and non-significant correlations between sibling ADHD and proband CSBQ scores strengthens our finding, as siblings were not selected for ADHD affection status. Obviously, however, our findings are in need of replication in independent, preferably general population, samples.

Another interesting finding that emerged from this study is the apparent differential familiality of the different ASD dimensions as measured with the CSBQ. This finding appears to be in line with findings of the genetic independence of the different ASD symptom domains (Happé & Ronald, 2008). Only stereotyped behavior ratings showed significant between-sibling correlations that in addition survived corrections for covariates. As far as we know, our study was the first publication that analyzed the familiality of ASD subdimensions in children with ADHD, thus it remains to be investigated whether indeed stereotyped behavior is the most heritable component of the ASD spectrum in the context of combined type ADHD. Although the genetic independence of the ASD dimensions has been reported in other studies, it is an intriguing question why this would be the case, since, as far as we know, all ASD dimensions have been shown to be highly heritable.
The gender differences we found in CSBQ scores and sibling correlation strengths suggest that the genetic underpinnings of the co-occurrence of ASD and ADHD symptoms may vary depending on gender, although, obviously, these findings are in need of replication in samples enriched with females. Also, our results (for withdrawn behavior in particular) suggest that developmental changes may affect the relation between ASD and ADHD symptoms over time. Some evidence for an increased genetic contribution to (pro-)social behavior with increasing age has been reported previously (Knafo & Plomin, 2006; Scourfield, John, Martin, & McGuffin, 2004), but never before in the context of ADHD.

Chapter 4 describes a study into the association of two polymorphisms in two candidate genes for both ADHD and ASD (i.e., the catechol O-methyltransferase [COMT] Val158Met polymorphism and the serotonin transporter [SLC6A4/SERT/5-HTT] 5-HTTLPR insertion/deletion polymorphism), with ASD symptoms (measured with the CSBQ) in children with ADHD, and the interaction of these polymorphisms with pre- and perinatal risk factors, i.e., maternal smoking during pregnancy and low birth weight. Two independent samples of children with ADHD, i.e. participants from the IMAGE study and TRAILS, respectively, were analyzed. We found no significant main effects of COMT Val158Met, 5-HTTLPR, maternal smoking during pregnancy and low birth weight on ASD symptoms. However, the COMT Val/Val genotype interacted with maternal smoking during pregnancy in increasing stereotyped behavior in both samples. Furthermore, the 5-HTTLPR S/S genotype interacted with maternal smoking during pregnancy, increasing problems in social interaction, and also interacted with low birth weight, increasing rigid behavior. Findings for 5-HTTLPR in the TRAILS sample were similar, albeit for related CSBQ subscales.

Although the genes as such do not convey an increased risk for ASD symptoms, these findings suggest modifying effects of gene environment (GxE) interaction on ASD symptoms in children with ADHD. The significant GxE interactions in the IMAGE sample and the interaction between COMT and maternal smoking during pregnancy in the TRAILS sample were robust against correction for potential confounders (including anxiety, shyness, ADHD severity, gender, and SES), which underlines the ASD-specificity of these results. As only a small number of children in the IMAGE sample had a birth weight below 2500 grams, caution in interpreting the interaction we found between 5-HTTLPR and birth weight is needed.

All findings in this study were for specific CSBQ subscales rather than for an overall measure of ASD. This is (again) in line with evidence of distinct genetic influences for the different ASD symptom domains (Happé et al., 2008). With regard to the 5-HTTLPR interaction with maternal smoking during pregnancy, we found influences in the social interaction domain. This corresponds to previous studies that reported specific effects of the 5-HTTLPR S-allele on social and communication problems (Brune et al.,
Likewise, a study by Sutcliffe et al. (2005) suggested that allelic heterogeneity at the SLC6A4 locus confers a risk for autism and rigid compulsive behavior in particular, which fits well with the interaction effects between the 5-HTTLPR S/S genotype and low birth weight for rigid behavior observed in the current study. Interestingly, in our study the specific domain affected appeared to depend on what environmental factor was at play.

Notably, all significant interactions we found indicated that children with the high risk genotypes (i.e., COMT Val/Val or 5-HTTLPR S/S) were not only the most likely children to have increased levels of ASD symptoms when exposed to maternal smoking during pregnancy or when they had a low birth weight, but were also the children who had the lowest levels of ASD symptoms when not exposed to maternal smoking during pregnancy or low birth weight. These findings are consistent with Belsky’s differential-susceptibility hypothesis (Belsky et al., 2009), and suggest that COMT Val158Met and 5-HTTLPR may be regarded as “plasticity genes” rather than “vulnerability genes”.

Based on the present study, one can speculate about the way the GxE interactions we found increase ASD symptoms in children with ADHD. For instance, the interaction of COMT Val158Met and 5-HTTLPR with maternal smoking during pregnancy may be mediated by the effects of nicotine on both dopamine (COMT) and serotonin (5-HTTLPR) metabolism. From animal studies it is known that nicotine influences several neurotransmitter systems, including dopamine and serotonin systems, by its effect on brain nicotinic acetylcholine receptors, and thus could influence behavior (Ernst, Moolchan, & Robinson, 2001; Slotkin, Ryde, Tate, & Seidler, 2007). The effects of low birth weight in interaction with the 5-HTTLPR polymorphism could be mediated by the effects of intra-uterine growth retardation (which is one of the causes of low birth weight) on serotonin metabolism. This is suggested by studies in rats which have shown that intrauterine growth retardation accelerates brain 5-HT synthesis and neuronal activity, thereby modifying for instance cerebral cortical sensory responses (Hernandez-Rodriguez, Meneses, Herrera, & Manjarrez, 2009; Manjarrez et al., 2005). Clearly, further research is needed to investigate whether these changes in serotonin and dopamine metabolism are influenced by the polymorphisms we investigated, and whether indeed they relate to ASD symptoms in children with ADHD.

In chapter 5 and 6, two whole genome quantitative trait linkage (QTL) studies are presented. In chapter 5, the total and subscale scores of the SCQ were analyzed as quantitative traits in the larger IMAGE sample. Analyses without ADHD symptom scores as covariates resulted in 3 suggestive linkage signals, i.e., on chromosomes 15q24, 16p13, and 18p11. Inclusion of ADHD symptom scores as covariates resulted in additional suggestive loci on chromosomes 7q36 and 12q24, whereas the LOD score of the locus on chromosome 15q decreased below the threshold for suggestive
linkage. The loci on 7q, 16p, and 18p were found for the SCQ restricted & repetitive subscale, the locus on 15q was found for the SCQ communication subscale, and the locus on 12q for the SCQ total score. The QTL on chromosome 15q could have pleiotropic effects on ADHD and ASD, given that its LOD score decreased below the threshold for suggestive linkage after including ADHD symptom scores in the analyses. The other suggestive QTLs (i.e., on chromosome 7q, 12q, 16p, and 18p) appear to be primarily associated with ASD symptoms, independent of ADHD symptom scores, as LOD scores did not change substantially, and in the case of chromosome 12q24 even appeared, after inclusion of ADHD symptom scores as covariates.

Our results for 7q, 18p, 15q and 16p show overlap with previous studies for ASD, which suggests that these findings may not be confined to ASD symptoms within the context of ADHD. Furthermore, our results for 12q and 16p correspond to previous ADHD findings. From the QTLs identified in this study, those on 12q, 16p, and 18p may be the most likely regions to explain the ASD comorbidity in ADHD, given their identification in previous ADHD studies (Fischer, Barkley, Smallish, & Fletcher, 2002; Hebebrand et al., 2006; Jain et al., 2007; Nicot, Otto, Brabet, & Dicicco-Bloom, 2004; Ogdie et al., 2004; Smalley et al., 2002; Tanaka et al., 2006), and given their possible role in ASD symptoms as found in the current study and in previous autism linkage studies (16p and 18p; International Molecular Genetic Study of Autism Consortium, 2001; Lauritsen et al., 2006; Philippe et al., 1999; Ylisaukko-Oja et al., 2004).

Our findings suggest that linkage studies regarding the occurrence of ASD symptoms in children with ADHD may assist in teasing apart the genetics underlying ADHD and ASD. Furthermore, they support the assumption that ASD traits lie along a continuum of severity, as loci potentially underlying ASD symptoms in children with ADHD were identified that correspond with identified loci or genes for clinical ASD, even though autistic cases had been excluded from the IMAGE sample. Additionally, our findings appear to confirm the hypothesis that the different ASD symptom domains have partially different genetic origins (Happé & Ronald, 2008).

Chapter 6 describes a study that combines QTL genome-wide linkage and association analysis, using the CSBQ total and subscale scores and the Conners DSM-IV total score as quantitative traits in Dutch participants of the IMAGE study. Significant and suggestive linkage regions were fine-mapped using locus wide association testing. We identified a genome-wide significant locus on chromosome 7q11.23 for the CSBQ subscale addressing social interaction, as well as eight suggestive loci for the CSBQ total scale and individual subscales. Potentially pleiotropic loci were found on 4q35, 7p12, and 18q21, 22q11, given that their LOD scores decreased after including the Conners’ score as a covariate in the analyses. Nevertheless, their pleiotropy could not be confirmed when we analysed ADHD symptom severity as a QTL, which resulted in no linkage signals at all. Suggestive loci that appeared to be primarily associated with ASD symptoms were found on 1q42, 2q37, 3p24, 8p21, and 16q12. LOD scores for
these regions did not change substantially, or even appeared after inclusion of the Conners’ score as covariates. Fine mapping resulted in locus-wide significant association for rs9935845 on chromosome 16 for the understanding scale, and suggestive association for SNPs in the carboxylesterase 7 isoform 1 gene (CES7) and the huntingtin-interacting protein 1 gene (HIP1).

Notably, our results appear to underline both the existence of a general autism factor and the genetic independence of the different autism symptom domains. The QTL on chromosome 7q11 may be considered support for a general autism factor, as it was found for subscales related to different ASD domains. The eight other loci showed suggestive linkage to individual traits, which may support findings of the independent heritability of distinct ASD subdomains. An important limitation of the study lies in the fact that we did not investigate the most severe end of the ASD spectrum, and therefore cannot be sure whether our findings pertain to narrowly defined autism as well. Furthermore, our modest linkage analysis’ results for ADHD symptoms as a quantitative trait may be a consequence of the restriction of range in ADHD scores, inherent to the clinical ADHD sample we used, or to the relatively small sample size. This renders our interpretation of the loci we found as being specific for ASD or potentially pleiotropic interesting, but preliminary.

In general, the results of this study are promising, in that a combination of linkage and association appears to be a fruitful approach to study the genetics of complex phenotypes, ASD symptoms in children with ADHD in particular. Linkage studies in ADHD and ASD thus far have shown inconsistent results, most likely as a consequence of the polygenic and multifactorial nature of these disorders. Genome-wide association study (GWAS) is an alternative (to linkage), hypothesis-free approach to search the whole genome, with the power to detect genetic variants of small effect size. A drawback of GWAS is the need for large samples it involves due to the large number of statistical tests that are performed. We tried to circumvent this problem by selecting chromosome areas that seemed promising based on our linkage results, explicitly including suggestive results. Even though our sample size was relatively modest, we found a significant SNP and several interesting candidate genes through this method.

Limitations
The findings presented in this thesis should be considered in light of their limitations. First, our results are based on parent reports of ASD symptoms, as formulated in the CSQB (chapter 3, 4, 6) and the SCQ (chapter 5). The CSQB has been shown to have a good inter-rater reliability and both CSQB and SCQ have good sensitivity and specificity for ASD diagnoses (Berument et al., 1999, Chandler et al., 2007, Hartman et al., 2006). Nevertheless, it will be important to confirm our findings in samples where ASD symptoms are assessed by other raters than children’s parents (e.g., teachers, clinicians), ideally including observations in naturalistic settings.
Second, our sample consisted of clinically referred children with a diagnosis of combined type ADHD and their siblings. On one hand, the precise ADHD phenotyping of our sample facilitates replication of our findings. On the other hand, our sample may have been influenced by referral and selection bias, which necessitates investigation of whether our findings apply to ADHD in the general population. Notably, although the genetic etiology of ADHD has been reported to be the same independent of symptom severity (Levy, Hay, McStephen, Wood, & Waldman, 1997; Stevenson, 1992), other studies have suggested that the genetic underpinnings of the most severe end of the ADHD spectrum may be different from those that influence ADHD symptoms in the general population (Zhou et al., 2008a). If the latter proves true, this also has an impact on genetic studies on the overlap between ADHD and ASD.

Third, children with classical and atypical autism were excluded from the IMAGE study, which limits our findings to ADHD with relatively mild ASD symptoms. However, since ASD-symptoms are generally considered to represent a continuous trait (Constantino & Todd, 2003, Constantino & Todd, 2005; Spiker, Lotspeich, Dimiceli, Myers, & Risch, 2002), this is not likely to be a serious shortcoming. Our linkage findings appear to confirm this, given the fact that we did find overlap with previous linkage studies for ASD affection status, even though autistic cases were excluded from our sample. Nevertheless, further studies are needed to investigate whether indeed our findings pertain to narrowly defined autism as well.

Fourth, we did not determine whether the CSBQ and SCQ subscales that we used for the molecular genetic studies were heritable, although the heritability of the ASD symptoms as such has been extensively documented (Freitag, 2007). Moreover, we did establish familiality for the CSBQ total and subscale scores, and given that shared environmental effects are considered to contribute little to ASD risk, familiality most likely reflects genetic effects.

Fifth, our study sample encompassed a broad age range and was primarily male. Our findings in chapter 3 suggest that the familiality of ASD symptoms may differ according to age and gender. Although we covaried our subsequent analyses for age and gender, we think age effects deserve further study in a longitudinal design, and gender effects need to be considered in samples enriched with females.

Suggestions for future research
Our studies provide pointers for further investigation. First, although we confirmed the presence of ASD symptoms in children with ADHD, the meaning of these symptoms in terms of everyday functioning, prognosis, and treatment response needs clarification. Problems in social functioning in children with ADHD are associated with an increased risk of psychiatric disorders other than ADHD, but whether this is the case for social interaction problems as seen in ASD is unknown, as are the consequences
of stereotyped behaviors and communication problems in children with ADHD. Furthermore, if identifying ASD symptoms in children with ADHD proves clinically relevant, i.e., if it can be distinguished from ‘pure’ ADHD for instance in terms of prognosis, this would support the idea that ADHD combined with ASD symptoms represents an ADHD subtype, which potentially is more homogeneous than the broader ADHD phenotype. The significance of this subtype for genetic studies, i.e., investigating whether it represents a more heritable subtype, needs additional attention as well, in studies applying both twin- and multi-generational family designs.

Second, in tandem with the research proposed in the former paragraph, future research should address what uniquely characterizes ADHD and ASD, respectively, especially with regard to social functioning. Using the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the way symptoms of social dysfunctioning are interpreted in children who also portray ADHD characteristics (i.e., interpreted as being a part of ADHD, or as representing ASD symptomatology) is to some extent in the eye of the beholder. Furthermore, there is ongoing discussion on whether ADHD symptoms in children with ASD represent ‘true’ ADHD, or are a derivate of ASD symptomatology. To learn the possible differences between ADHD and ASD, we need to go beyond DSM descriptions, and in the case of social interaction problems for instance address ‘aloofness’, and ‘active but odd’ social behavior. Longitudinal research may in addition help to disentangle if, and how ADHD and ASD symptoms may influence one another over time.

Furthermore, the underlying deficits that give rise to ADHD and ASD symptoms as well as their co-occurrence need to be studied further, e.g., with the help of neuropsychological tasks and imaging techniques. For example, comparison of executive functioning measures and magnetic resonance imaging (MRI) results of children with ADHD, ASD, and children with different levels of both disorders could perhaps shed a light on what brain systems are affected in ADHD, ASD, and the combination of the two. Our candidate gene study results provide an indication that dopaminergic (COMT) and serotonergic (5-HTT) systems in the brain and their interaction with prenatal exposure to maternal smoking and (causes for) low birth weight may be interesting targets in this respect. Specific measures for executive functioning and event related potentials could be useful in this line of research, as well as structural and functional MRI, including resting state and diffusion MRI. Also, the linkage peaks we found harbor some interesting candidate genes that deserve further study in relation to the overlap between ADHD and ASD. A compelling study that addresses several of the aforementioned issues is on its way, in which phenotypic, neuropsychological, and imaging data are collected for a large number of ADHD and ASD families.
**Clinical implications**

This thesis highlights the need to look beyond diagnostic boundaries. Classification of psychiatric disorders is useful because it provides a tool to explain behavior to patients and their families, and a tool for communication between professionals. However, as it is, classification systems for psychiatric diseases are a-theoretical, and largely descriptive. We know far too little about these disorders to strictly adhere to the perhaps artificial divisions between them. It is widely acknowledged that ADHD comes with a high incidence of comorbid disorders, but ASD is generally not considered to be one of these. Although we do not know the exact course and consequences of ASD symptoms in children with ADHD, we should be aware that they are often present and may need to be addressed with specific treatments.

Furthermore, our linkage findings indicate potentially pleiotropic disease loci that lend (albeit preliminary) support to the existence of shared genetic risk factors between ADHD and ASD. This emphasizes the value of evaluating family members of children with ADHD, not only for the presence of ADHD, but also of ASD symptoms. Another clinically important finding from this thesis is the confirmation of the detrimental effects of maternal smoking during pregnancy in our gene-environment interaction study. Smoking cessation services for pregnant women are warranted for multiple reasons, and our study appears to once more support their relevance.

It is too early to formulate clinical implications based on our genetic findings. Nonetheless, our findings provide some clues about the genes and chromosomal loci that may be involved in ASD symptoms in children with ADHD. Hopefully, future research will learn us if, and how, we can translate genetic and environmental risk profiles into diagnostic strategies and tailored treatments for individual patients.
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