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## **SUMMARY AND GENERAL DISCUSSION**

## SUMMARY

This thesis contributed to knowledge on the causes of individual differences between children in educational achievement by looking at the influence of genetic effects and of twinning, teachers and other environmental factors on educational achievement, as measured by teachers' reports and objective standardized tests. The teacher reports included ratings on arithmetic, language, reading and physical education. The standardized tests included pupil monitoring tests on arithmetic, reading, reading comprehension and spelling for primary school grades (Cito, 2014a; Vlug, 1997) and a national educational achievement test (Cito, 2002) administered in the final grade of primary school, at about 12 years of age, with questions on arithmetic, language, study skills and science and social studies. In addition, we extended the study of individual differences in educational achievement by also looking at their association with problem behaviors, as rated by teachers and mothers. The teacher and mother ratings of problem behavior focused on the presence of symptoms of Oppositional Defiant Disorder (ODD) and Attention Deficit Hyperactivity Disorder (ADHD) and were assessed by the short versions of the Conners' Teacher Rating Scale - Revised and the Conners' Parent Rating Scale - Revised (Conners et al., 1998; Conners, 2001). The data were collected at age 7, 9 and 12 years from mothers and teachers of twins and teachers of non-twin siblings of the twins registered with the Netherlands Twin Register (NTR). I will present a summary of the main findings of each chapter of this thesis and discuss the results, some practical implications and future research.

In the first part of this thesis, several predictors of school performance, educational achievement and problem behavior were examined. **Chapter 2** focused on pre- and perinatal risk factors, more prevalent in twins, for educational achievement. It was established that low birth weight and being small for gestational age were risk factors for lower school performance. These results were robust even after correcting for socioeconomic status (SES). The effects of these risk factors were small, especially when compared to the effect of gender of the child, which had a larger influence. Other pre- and perinatal risk factors that are more prevalent in twins are assisted conception, cesarean section, incubator time and birth complications. With the exception of mode of delivery, these risk factors negatively affected performance in physical education, but they had no other effects on educational achievement. The twin-specific risk factor zygosity had no effect. To test the assumption that twins are not different from singletons, the school performance of twins was compared to that of their non-twin siblings in a within-family design, thereby taking into account confounding of multiple demographic characteristics. There were small differences between twins and singletons in school performance when

comparing the twins to their older siblings, but not when comparing them to their younger siblings. Thus, birth order within the family partly explains the small differences that are often suggested to exist between twins and singletons.

Another potential factor influencing educational achievement is having a teacher of opposite gender, i.e. for boys it is suggested to be detrimental for their performance at school to have a female teacher and girls would benefit from being taught by a female teacher. In **chapter 3**, a contribution is made to the ongoing discussion in society as to whether boys might be disadvantaged by the feminization of primary education. This was done by selecting a subgroup of 12-year old monozygotic and dizygotic of opposite-sex twin pairs where one twin was taught by a male teacher whereas the other twin was taught by a female teacher. As (part of) their genotype, family background, social economic status and multiple other characteristics are more or less similar, differences within the twin pairs may be ascribed to the influence of the gender of the teacher. Boys outperformed girls in arithmetic, while girls scored higher on language and reading. Boys also demonstrated more ADHD related behavior, but these findings were independent of teachers' gender. Therefore, increasing the number of male teachers in primary education or implementing single-gender education may not be as effective to close a possible gender gap in educational achievement or ADHD behavior as suggested by some.

Although there might be some differences between groups of children, e.g. boys and girls, even children attending the same school and taught by the same teacher differ greatly in their performance and behavior at school. In the second part of this thesis, we tried to get a better understanding of why children differ in their educational achievement and problem behavior by exploring the interaction between genetic effects and the environment on educational achievement and problem behavior. The moderating influence of several (environmental) factors on the heritability of educational achievement and problem behavior was explored (Purcell, 2002). Moderation of heritability of educational achievement was investigated for gender and country of the student and moderation of the heritability of ODD and ADHD behavior was investigated for classroom sharing, gender of the student and gender of the teacher. In **chapter 4**, the heritability of educational achievement across several educational domains, i.e. arithmetic, reading, reading comprehension and spelling, across grade 1 to 6 (age 6 to 13), was estimated. Genes explained most of the individual differences in educational achievement across all grades for arithmetic (60-74%), reading (72-82%) and reading comprehension (54-63%). In contrast, the heritability of spelling was smaller in the first grade (33%) compared to later ages (58-70%). The heritability of general educational achievement in the final grade of primary school was high (74%). The common

environmental effects had only a small influence on the individual differences in educational achievement. Boys and girls for some educational domains differed in the average test results, but there were no differences between boys and girls in the heritability of educational achievement. This implies that the extent to which genes and the environment influence educational achievement is similar across gender (no quantitative gender differences) and that the genes that have an influence on educational achievement are the same for boys and girls (no qualitative gender differences).

In **chapter 5**, the heritability of educational achievement in the Netherlands is put into perspective by a review of the existing literature on twin studies from different countries estimating heritability of educational achievement in primary school. A PubMed search retrieved 61 studies describing studies from 6 different, mostly English speaking, countries and including subjects from 11 different cohorts. Heritability estimates varied considerably across studies as did the influence of the environmental effects. The small sample sizes, different age groups and the variety of measurement instruments are probably the main reasons for this variability. Meta-analyses of the twin correlations was done to obtain a heritability estimate in the largest sample and test for differences in the heritability between countries. The estimated mean heritability for the educational domains reading (69%), reading comprehension (49%), mathematics (57%) and spelling (44%) and for general educational achievement (66%) was moderate to high. The importance of genetic effects for educational achievement differed between the USA, UK and the Netherlands. The heritability estimates for reading, reading comprehension and mathematics were consistently high in the Netherlands whereas this was not true for the USA and UK, suggesting moderation of the heritability by country. Heritability of reading was equally high across countries (USA: 70%; UK: 69%; NL: 66%), but heritability of reading comprehension was larger in the Netherlands (64%) and the USA (67%) compared to the UK (38%) and heritability of mathematics was low in the USA (26%), moderate in the UK (46%) and high in the Netherlands (71%).

In **chapter 6**, the heritability of ODD and ADHD behavior was estimated at the ages of 7, 9 and 12 years. To this end, it was first tested whether the scales of the short CTRS-R measured the same underlying construct across groups, in other words, whether the scales were measurement invariant (MI) (Millsap & Yun-Tein, 2004). There were two grouping variables, i.e. gender of the teacher and gender of the student, and MI was confirmed for three of the four scales measuring ODD and ADHD behavior, namely oppositional behavior (OPP), hyperactivity (HYP) and ADHD index (ADHD). In contrast, measurement invariance did not hold for the inattention/cognitive problems (ATT) scale.

Even without constraints on the factor structure the model fit was not acceptable for ATT and increasing MI levels resulted in a worsening of the model fit. This strongly questions the reliability of this scale and its use in clinical practice. After having established MI for three scales of the CTRS-R we looked at the extent to which individual differences in ODD and ADHD behavior, as measured by these scales, could be explained by genes and the environment. There were some gender differences in the etiology of ODD behavior. Heritability was higher for boys (OPP - ST: 62-80%; DT: 12-57%) than girls (OPP - ST: 33-46%; DT: 25-55). The ratio between the contribution of additive and non-additive genetic effects resulted in gender differences for the hyperactive component of ADHD behavior (boys - ST: 76-84%; DT: 48-51%; girls - ST: 66-75%; DT: 43-51%). The heritability for ODD and ADHD behavior at school depended in some cases on the gender of the teacher. However, the direction of the effects of gender of the teacher was not consistent across ages and within scales which makes interpreting the findings difficult. Heritability of ODD and ADHD behavior was substantially larger in children who shared a classroom (ST) compared to those who did not (DT) (boys: OPP - ST: 62-80%; DT: 12-57%; girls OPP - ST: 33-46%; DT: 25-55%; boys: HYP - ST: 76-84%; DT: 48-51%; girls: HYP - ST: 66-75%; DT: 43-51%; boys and girls: ADHD - ST: 78-88%; DT: 46-61%). The results excluded teacher bias as an explanation and indicated that the heritability of ODD and ADHD behavior is moderated by the classroom. Apparently the difference in behavior is elicited by different classroom environments, teachers and peers.

In the third part of this thesis the association between ODD and ADHD behavior and educational achievement was investigated by two genetic approaches, namely polygenic score analyses, and causality models. The association of ODD and ADHD with educational achievement is usually negative; children with these problems perform less well in school, and it is an important question what the etiology of this association might be. In **chapter 7** the effect sizes from a large genome wide association (GWA) meta-analysis of educational attainment (Rietveld et al., 2013) were used to calculate polygenic scores in an independent sample of 12-year-old children. This cohort had data on school performance, educational achievement and ADHD symptoms as well as on genome wide single nucleotide polymorphisms (SNPs) available. The polygenic scores explained up to 4, 3 and 2 per cent of the variance in school performance, educational achievement and ADHD behavior, respectively. Clearly, some of the genetic variants that influence educational attainment in adults also have an effect on school performance and educational achievement in children. Moreover, the genetic variants also had a significant effect on

ADHD behavior. This confirms at the measured genotype level a genetic association between educational achievement and ADHD.

The question that remains is whether this genetic correlation is due to genetic pleiotropy, where the same genetic variants influence multiple (brain) phenotypes, or due to a causal effect of ADHD on educational achievement. The genetic variants causing ADHD will then indirectly also cause low educational achievement. The causal hypothesis of a detrimental effect of ODD and ADHD behavior on educational achievement has high face validity: being genetically predisposed to ADHD, for instance, could make it harder to concentrate at school, leading to lower educational achievement. In **chapter 8** the hypothesis of a causal effect was tested against the null hypothesis of genetic pleiotropy in a large genetically sensitive sample. Children who displayed more ODD or ADHD behavior scored lower on educational achievement and this was true for ODD and ADHD behavior measured at the same age as well as 5 years earlier. The results suggest a causal effect as most likely explanation for the association between ADHD and educational achievement. First, in genetically identical twins, the child who shows more ADHD behavior than his co-twin also performs worse at school. Thus within genetically identical twin pairs, a design correcting for possible genetic confounding, there was a negative association between ADHD behavior and educational achievement. Second, both the cross-sectional and longitudinal genetic and environmental correlation between ADHD and educational achievement were significant. The genetic as well as the environmental effects with an influence on ADHD behavior also affected educational achievement, supporting the causal effect hypothesis. The results for ODD behavior and educational achievement were less consistent, due to a lack of power, and only partly supported a causal effect. Thus, the causal effect for ODD behavior on educational achievement could not be falsified.

## GENERAL DISCUSSION

In the last decade (2003-2013) the number of twin births in the Netherlands decreased from 18.3 to 16.5 per 1,000 births (Wobma & Garssen, 2014). This decline in twin births is, in general, seen as a positive trend since twin births are often associated with a higher prevalence of risk factors during pregnancy and birth (Glasner et al., 2012). These risk factors include prematurity, low birth weight and birth complications and have a higher prevalence in twins than in singleton births. They all tend to be associated with negative health outcomes and possibly also with a negative influence on educational achievement (Khadem & Khadivzadeh, 2010; Lundgren & Tuvemo, 2008; Wagenaar et al., 2008). In this thesis we describe that low birth weight and being small for

gestational age were indeed relevant risk factors for educational achievement, but in comparison to the effects of socioeconomic status (SES) and gender, their effects were rather small.

The average difference in birth weight between twins and singletons is more than 1000 grams (De Geus et al., 2001) and the gestational age of twins is on average 3-4 weeks shorter than that of singletons (Gielen et al., 2010). This raises the question whether these pre- and perinatal risk factors, which are more prevalent in twins, might explain the differences between twins and their non-twin siblings that often have been suggested for general cognitive ability and educational achievement. The results of **chapter 2** indicate that, in 7-year-olds, there are small differences in educational achievement between twins and their non-twin siblings. However, when taking into account the birth order within the family, the differences between twins and siblings disappear. Because twins often are the last born children in a family, not taking into account birth order - even when using an optimal design that compares twins to their own siblings - might lead to the wrong conclusion that 'being a twin' is a risk factor for lower educational achievement. This is an important finding, also suggesting that pre- and perinatal risk factors that are more prevalent in twins do not lead to long term twin-sibling differences and it is supported by observations that the small observed differences due to birth order dissipate when the twins grow older. From research in other domains, such as general cognitive ability (Webbink et al., 2008), body composition (Estourgie-van Burk et al., 2010) and development of ADHD symptoms (Robbers et al., 2011), it is known that the differences between twins and singletons disappeared at later ages and that twins do not seem to differ from singletons in educational achievement, behavior or health (Petersen et al., 2011) and twin data are a valuable resource to draw conclusions about heritability that may be generalized to the population at large.

A further consideration is whether the twin pairs in the study sample from the NTR were representative of the general population of twins in the Netherlands. Exclusion criteria for analyses of phenotypes reported on in this thesis by teachers were a disease or handicap that interfered severely with daily functioning, and attendance of specialized education. In the Dutch educational system, special schools are available for children who need extra care due to learning problems, physical and/or mental disabilities or behavioral disorders. This means that the lower end of the distribution was not represented in the teacher sample for both twins and singletons. A bias would be present when more twins are referred to specialized education compared to non-twin singleton children. To our knowledge, there are no national statistics available on the percentage of multiples attending specialized education. As indicated before a large percentage of children are part of a multiple (Wobma & Garssen,

2014) and it is astonishing that no data are available on the total number of twins in specialized education. In our sample, parents reported for approximately 4 per cent (age 7: 2.9%; age 9: 5.2%; age 12: 5.3%) of the twins that they attended specialized education while in the Netherlands around 5 per cent of all school aged children attend some type of specialized education (CBS Statistics Nederland, 2014). However, this lower percentage in NTR twins may not accurately reflect the percentage of Dutch twins in specialized education. Parents might have more often decided to refrain from participating in research of the NTR when one of their children is a child with special needs.

With a unique design of identical twin pairs discordant for the gender of their teacher and dizygotic twins of opposite-sex concordant for the gender of their teacher, we made a contribution to the ongoing debate in the media and society about the declining number of male teachers in the educational system and its negative effect on the performance and behavior of boys in school. Some people argue that a same-gender teacher enhances the performance of a child at school because students identify themselves more with a same-gender teacher (Carrington, Tymms & Merrell, 2008), teachers feel more competent with a same-gender student (Powell & Downey, 1997) or by the effects of stereotype threat (Steele, 1997). However, we found no evidence for an effect of a same-gender teacher on educational achievement or ADHD behavior.

An underlying issue in this debate is whether boys are actually underperforming at school compared to girls ('boys problem') (Ailwood, 2003; Carrington, Tymms & Merrell, 2008; van Langen & Driessen, 2006). The existence of an overall lower performance for boys compared to girls has not been found in our primary school sample. However, substantial traditional gender differences were observed with boys scoring higher on numeracy domains and girls performing better on literacy domains. Boys received higher teacher ratings for arithmetic and performed much better on the standardized tests for arithmetic whereas girls received higher teacher ratings for language and reading and performed somewhat better on the standardized tests for language and reading comprehension. These gender differences are also present in the recent national cohorts of Dutch primary school children participating in the educational achievement test administered in the final grade (Cito, 2014b). The percentage of boys, in the NTR data, scoring in the highest category of the total score of the educational achievement test was somewhat higher than the percentage of girls. It should be noted that boys are more likely to have to repeat a grade and are more often attending specialized education with a ratio for boys and girls of approximately 2.5:1 (CBS Statistics Nederland, 2014). This suggests that boys are overrepresented among the underperformers as well as the high performers.

Mean differences between boys and girls explain part of the variance in educational achievement between children, but even after taking these gender differences into account, there are large differences between children in their educational achievement. The underlying causes, genes or the environment, of these individual differences in educational achievement between children are the same for boys and girls as was shown in **chapter 4**. Heritability of educational achievement is substantial and relatively stable across all grades of primary school in the Netherlands in both genders. Genes are the most important cause of individual differences between children in their educational achievement for the core educational domains, i.e. arithmetic, reading (comprehension) and spelling. This contrasts with general cognitive ability where, in children, the environment explains the largest part of the individual differences (Van Soelen et al., 2011). The heritability of general cognitive ability increases significantly and linearly from 41% in childhood (9 years) to 55% in adolescence (12 years) and to 66% in young adulthood (17 years), as demonstrated in a sample of 11,000 pairs of twins from four countries (Haworth et al., 2010). In the NTR, the heritability of general cognitive ability at younger ages is estimated even lower (Bartels et al., 2002).

Often general cognitive ability is thought to be an ‘innate’ ability while educational achievement is seen as the result of several factors, including but not limited to general cognitive ability. Hence, it seems counterintuitive that the heritability of educational achievement is higher than the heritability of general cognitive ability. One hypothesis for this difference is that the homogeneity of education reduces differences in the environment and, as a result, individual differences between children in educational achievement can to a greater extent be explained by genes (Heath et al., 1985). Studies in preschool children report a much larger influence of the common environment, shared by all children in a family, on, for example, reading (Byrne et al., 2009; Oliver, Dale & Plomin, 2005), than has been found for school going children (Kovas et al., 2013). It could be that the common environment for educational achievement mainly consists of the educational system and school environment, whereas the common environment that influences general cognitive ability has many more aspects. Obviously, ‘common environment’ for twins and siblings can only be ‘common’ when twins go to the same class or school and common environment for siblings of different ages also will be less, as they nearly always attend different classes. Homogeneity of the school environment and educational system would reduce the impact of the common environment on educational achievement but not necessarily on general cognitive ability. The influence of the common environment on general cognitive ability clearly decreases when children grow up (Bartels et al., 2002; Haworth et al., 2011). An influential

hypothesis states that one reason is that children increasingly have the opportunity to select their own unique environments when they grow up (Deary et al., 2012; Molenaar et al., 2013).

Although heritability of educational achievement is high in most Western societies, which is reflected in the overview presented in **chapter 5**, there are some differences between countries. In the Netherlands, heritability was consistently high across different educational domains whereas the variability in estimates was larger across different educational domains for the USA and UK. This is an indication of moderation of the heritability by country. An explanation might be that the equality in income and circumstances under which children grow up, but importantly also the heterogeneity in educational opportunity, is larger in the Netherlands compared to the USA and the UK.

The consequence of the homogeneity in an educational system is that it will highlight the innate individual differences between children as reflected in the high heritability (Harlaar et al., 2012; Kovas et al., 2013). What must be kept in mind is that heritability does not equal determinism. The variance between children may be heritable, but the mean of a population or a group can be positively influenced by a good quality school environment. High heritability in a homogeneous school environment can imply that children with a predisposition for lower educational achievement will have to struggle while children with a genetic advantage can excel at school without ever tapping their full potential. High heritability therefore supports the importance of differentiation in teaching. The double challenge for primary school teachers is to make sure that children, who have more difficulty at school, will learn reading, writing and arithmetic, but that those who have it easy are still sufficiently challenged. Classroom teaching might not be the best method to achieve this goal and a more personalized approach to learning may be warranted. Unfortunately, the increasing number of children per teacher and the demand on teachers with regard to administrative duties might preclude teachers from customizing their lessons to the needs of each child.

Some parts of a child's environment that we regard as 'common', or shared by children from the same family, like parental educational level, are influenced by parental genotype (Rietveld et al., 2013; Vinkhuyzen et al., 2010). Because the children share genes with their parents, the genes of a child can become correlated with its environment, i.e. passive gene-environment (GxE) correlation. The common environment did not seem to have much of an influence on educational achievement in children when correcting for this genetic confounding. However, there are several mechanisms through which the common environment, e.g. SES and parental upbringing, can still influence educational achievement. The common environment can have an influence

through gene-environment interaction, thereby having a different influence on siblings who have different genotypes. Also, the influence of the environment may not be uniform across the entire distribution, for example, the influence of the environment appears to be larger in so called high-risk home environments (low SES) while it has no influence in more advantaged homes (Scarr-Salapatek, 1971; Turkheimer et al., 2003). It could also be that the impact of the common environment on a child's educational achievement may be at a child-specific level rather than at a family-wide level (McGue & Bouchard Jr, 1998). The interaction with the teacher at school, for example, may be experienced rather differently by children from the same family, transforming these common environmental factors into unique environmental effects (Somersalo, Solantaus & Almqvist, 2002).

A favorable role for factors like SES and parental upbringing has been shown in adoption studies where children grow up in the same environment with parents that they are not genetically related to. Adoptive families mostly have a SES above average while the opposite is true for the biological families. Adoption studies found that general cognitive ability and educational achievement of adopted children was higher than of their non-adopted biological siblings, who were raised by their birth parents (Maughan, Collishaw & Pickles, 1998; Scarr & Weinberg, 1983; Van IJzendoorn, Juffer & Poelhuis, 2005). However, the scores for the adopted children were lower than those for the biological children of their adoptive parents and individual differences among them were more related to differences among their biological than adoptive parents, whether they lived together or not. Young siblings were found to be quite similar, whether genetically related or not, but adolescents' general cognitive ability scores were similar to those of their parents and siblings only if they were biologically related (Scarr & Weinberg, 1983).

Educational achievement is known to relate to childhood problem behaviors, including ODD and ADHD. Expression of these behaviors appears to be sensitive to the classroom setting. The heritability estimates of both ODD and ADHD behavior were much larger in children sharing a classroom compared to children in different classrooms. Different classrooms with different peers, teachers and classroom settings trigger different behavior in children depending on their genotype (Eaves, 1984). A teacher might be a very important factor in the expression of the problem behavior in a child with a predisposition for ODD or ADHD. Teachers differ in, for example, the structure of their teaching and the rules children have to comply with in the classroom. When a child displays, for example, ADHD behavior in the classroom, which is to a large extent genetically influenced, a teacher will respond to the behavior of this child in his or her own way. As a consequence the behavior of the teacher changes the

environment which can then have an influence on the child's expression of the genes associated with ADHD behavior. These findings are clinically relevant as it implies the possibility for the school to implement teacher based interventions to buffer against the genetic vulnerability of developing ODD or ADHD (Reinke & Herman, 2002).

Raters can have their own perception on behavior which makes ratings by the same person of multiple children more similar. Although this type of rater bias was ruled out as an explanation, the lower heritability of ODD and ADHD behavior for children in different classrooms may be the result of other rater effects. It has been demonstrated that, when rater specific factors are genetically influenced, heritability estimates depend on whether children are assessed by the same rater or by two different raters (Kan et al., 2014). When heritability estimates for ADHD behavior are based on ratings from different teachers only the component of the phenotype that they both agree on, the common component, is estimated while the rater specific component ends up in the environmental effects (McLoughlin et al., 2011; Merwood et al., 2013). When the same teacher rates both members of a twin pair the component that only the teacher observes, the rater specific component, will contribute to the genetic effects which results in a higher estimated heritability.

The interpretation of the heritability in the presence of rater specific genetic factors requires caution, but the existence of rater specific factors is not inconsistent with GxE interaction. The more environments differ the less genetic variance tends to be shared between raters observing a child in the different classroom environments. This also explains the finding that the genetic overlap between mother and father ratings is larger than between parent and teacher ratings (Merwood et al., 2013). In primary school, children are sometimes taught by two teachers, for example when teachers do not work fulltime, as is increasingly common in the Netherlands. Ratings from two teachers each rating both children from a twin pair sharing a classroom could improve our understanding of GxE interaction and the contribution of rater specific genetic factors to ODD and ADHD behavior.

**Chapter 6** reports that for ADHD, additive as well as non-additive (dominant) genetic effects were relevant for the differences between children. ADHD seems to be influenced by interactions between genes and is not just a summation of the effects of the different genes. Such strong evidence for the influence of interacting genes is hardly ever seen for other behavioral traits or disorders (Burt, 2009). This is somewhat surprising given the large comorbidity between ADHD and other disorders, e.g. externalizing behavior (Angold, Costello & Erkanli, 1999). To examine this difference in genetic architecture between

ADHD behavior and other childhood psychopathologies is an important future research step.

A clinically relevant finding from **chapter 8** is that the negative association between ADHD behavior and educational achievement is likely to be due to a causal effect of ADHD behavior on educational achievement instead of genetic pleiotropy, where the same genetic variants have an effect on both ADHD behavior and educational achievement. This indicates that a behavioral intervention or medication prescription, leading to a reduction in symptoms of ADHD (King et al., 2006; Schachter et al., 2001), will also indirectly, through the causal chain, improve the educational achievement of children. The effects of prescription of medication for ADHD on the performance at school have been investigated in earlier research. When medication use resulted in a decrease in symptoms of ADHD, children were indeed better able to stay focused and completed more of their school work (Brown et al., 2005; Prasad et al., 2013). The influence on the actual educational achievement was only modest and evidence was less convincing.

This outcome is independent of the current discussion on whether children are nowadays too often diagnosed with ADHD and prescribed medication. It is well recognized that an ADHD diagnosis can be considered the extreme end of the normal distribution of inattentive and hyperactive symptoms in the population (Groen-Blokhuis et al., 2014; Lubke et al., 2009). However, it seems that the perception of what is normal for a child of a certain age has changed over the years. Data from the NTR indicate that the number of symptoms associated with ADHD, as reported by parents, has remained very similar over a period of 25 years. If more children have received an ADHD diagnosis and are prescribed medication, there are other reasons beyond the number of symptoms that contribute to such an increase.

A next important next step towards understanding the underlying causes for individual differences between children in behavior and educational achievement would be to investigate the causes of continuity and change. There are two main hypotheses with regard to the underlying mechanisms of development (Rowe & Britt, 1991). A transmission model assumes that educational achievement at different grades is causally linked and preceding experiences are transmitted to later time points. A liability model assumes a stable underlying liability which explains the association between educational achievement in different grades. In a longitudinal twin study across all grades of primary school, these models can be studied at the genetic and environmental level. Genetic and environmental effects might exert their influence on educational achievement through the same or different developmental models. The mechanisms underlying continuity are especially important as the longer a

child is performing below average at school, the more difficult it will be to prevent that child from falling behind. The same is true for ODD and ADHD behavior since the longer a child deviates from normal development, the more difficult it will be to successfully intervene and put it back on a normal developmental trajectory (Sroufe, 1990).

Earlier research towards continuity and change in behavioral problems has found that genetic effects are partly transmitted to later ages with some new genes coming into play at each age, whereas the influence of common environmental effects remains the same across development and unique environmental effects are important but specific to a certain age (Bartels et al., 2004). Apparently, for internalizing and externalizing problems, the unique environment is mainly specific to a certain age and has no long-term effect whereas the common environmental effects persist over time. Studies towards developmental trajectories and underlying causes of stability and change are still lacking for educational achievement. NTR started to collect teacher surveys at the ages 7, 9 and 12 years. The longitudinal data collection is now providing a unique opportunity to investigate the stability of ODD and ADHD behavior and educational achievement without the bias of a constant rater, since the longitudinal data on the behavior and school performance of a child come from different teachers at different ages and from objective tests.

Another important next step towards understanding the underlying causes for individual differences between children in behavior and educational achievement would be to identify genetic variants, and their biological mechanisms, related to educational achievement and ODD and ADHD behavior. Knowledge of these causes could lead to more effective interventions and the development of preventions. Heritability of educational achievement and of ODD and ADHD behavior is relatively high, but the identification of genetic variants associated with educational achievement or with a risk for ODD or ADHD has turned out to be much harder than expected. Genome wide association (GWA) studies have been less successful for phenotypes, such as ADHD (Neale et al., 2010) and educational achievement (Rietveld et al., 2013), than for physical phenotypes, such as height (Wood et al., 2014). One of the explanations is that behavioral phenotypes are highly complex and caused by many genetic variants with only small effects (Flint & Munafò, 2013). Other explanations are that it is more difficult to obtain large sample sizes for behavioral phenotypes and that different definitions or assessments of the phenotype might lead to heterogeneity which makes gene finding also more difficult (Wray & Maier, 2014).

Polygenic scores established that a large number of common genetic variants are contributing to variance in the phenotype of interest (Purcell et al., 2009).

The effects of these variants are not significant if tested against genome-wide significance thresholds, but polygenic score analysis allows for an exploration of the underlying etiology of an association between two phenotypes at the measured genotype level, because the information from genome-wide studies is combined into a weighted score across a large number of variants. In **chapter 7**, polygenic scores indicated that genetic variants associated with educational attainment in adults also had an influence on ADHD behavior in children. This demonstrates that even though only a few genetic variants are associated with a phenotype at the genome-wide significance threshold, the information from GWA studies can be used to further our understanding of the causes of the association between two phenotypes.

Single measured genetic variants will likely not be used in the near future to predict a predisposition for ODD or ADHD or for lower educational achievement. However, the authors of the GWA meta-analysis of educational attainment in adults calculated the power of polygenic scores as a prediction variable to make decisions regarding which children to target for interventions, e.g. pre-school programs, when sample sizes will continue to increase. A sample size of 500,000 individuals will be large enough to obtain polygenic scores that can explain 12 per cent of the variance in educational achievement, when other predictors already explain 10 per cent of the variance. This can result in a reduction of 13 per cent in sample size for an intervention and, as the costs of genotyping continue to drop, reducing the number of children to be included in costly interventions could result in substantial savings (Rietveld et al., 2013).

Identification of environmental factors does not seem to be much easier than finding genetic variants responsible for the variance between children in educational achievement and behavior. The unique environmental factors investigated so far do not account for a substantial proportion of the individual differences between children. Nonetheless, in a meta-analysis the proportion of the total variance in, amongst others, behavioral problems and general cognitive ability, explained by differences in peer interaction and student-teacher interaction, reached up to 5 per cent, which is considerably larger than the effect sizes found for genetic variants (Turkheimer & Waldron, 2000). Common environmental factors might explain larger proportions of variance and may therefore be easier to identify, but suffer as indicated earlier, from the difficulty that what we conceive of as common environment, reflects parental genotype (e.g. SES and parental education).

The co-twin control design is an attractive research design to find an association between an environmental factor and a phenotype and to test for causality of this association. This method corrects for several confounding factors, including genetic effects and several other environmental effects, such as shared SES. For

example, a study including discordant twins revealed that the negative association between low birth weight and attention problems was probably due to a causal effect (Groen-Blokhuis et al., 2011). Another discordant twin study, disproved anesthesia as an environmental factor with a negative effect on educational achievement and general cognitive ability (Bartels, Althoff & Boomsma, 2009). Similarly, a study on differences between monozygotic twins in their perception of the classroom environment identified the perception of a student of the relationship with the teacher as a unique environmental factor that differed between the genetically identical twins and was linked to hyperactivity as rated by the teacher (Somersalo, Solantaus & Almqvist, 2002).

Further exploration of genetic variants, in larger sample sizes, and of environmental factors, using the methods that control for the possible confounding by genetic effects, will hopefully point to genuine causal associations making it possible to develop new prevention programs and interventions to ensure that each child masters the basic skills at school necessary to succeed in society.

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