Genetic Overlap between ADHD Symptoms and Reading is largely Driven by Inattentiveness rather than Hyperactivity-Impulsivity

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Abstract

Objective: To assess the genetic and environmental etiology of the co-occurrence of ADHD symptoms and reading difficulties using the largest sample to date, distinguishing two dimensions of ADHD and two of reading. Method: Data were obtained from 6428 12-year old twin pairs drawn from the population-based Twins Early Development Study. ADHD symptoms (combined ADHD, inattentiveness and hyperactivity-impulsivity) were assessed using parent ratings. Reading was assessed using a battery of reading comprehension and word decoding tests. Results: Heritabilities were high, around 70% for ADHD symptoms and 45-65% for the reading measures. Some of the same genes affected combined ADHD and reading with a genetic correlation of -0.31. The most notable finding was that the genetic correlation with reading was significantly greater for inattentiveness (-0.31) than for hyperactivity-impulsivity (-0.16), suggesting that genetic overlap between combined ADHD and reading is largely driven by inattentiveness. Moreover results showed that it is word decoding rather than reading comprehension that is differentially related to the ADHD dimensions (lower genetic correlation to hyperactivity-impulsivity than to inattentiveness). Conclusions: Genetic overlap between ADHD and reading is largely driven by inattentiveness rather than hyperactivity-impulsivity.

Résumé

Objectif: Étudier l’étiologie génétique et environnementale de la concomitance des symptômes du TDAH et des difficultés de lecture dans le plus vaste échantillon étudié à ce jour, en distinguant deux dimensions dans le TDAH et dans la lecture. Méthodologie: Analyse des données tirées de l’étude populationnelle Twins Early Development Study portant sur 6 428 paires de jumeaux âgés de 12 ans. Les symptômes du TDAH (type mixte, type inattentif et type hyperactif/impulsif) ont été consignés à partir les notes des parents. La lecture a été évaluée au moyen d’une batterie de tests de compréhension et de décodage. Résultats: L’héritabilité est élevée: elle est d’environ 70 % pour les symptômes du TDAH et de 45 à 65 % pour la lecture. Certains gènes identiques aident le TDAH de type mixte et la lecture, avec une corrélation génétique de—0,31. La constatation la plus notable a été que la corrélation génétique-lecture était significativement plus élevée dans le type inattentif (-0,31) que dans le type hyperactif-impulsif (-0,16), ce qui permet de penser que le recouplement génétique entre le TDAH mixte et la lecture est surtout motivé par l’inattention. En outre, les résultats montrent que le décodage, et non la compréhension, est relié, de manière différentielle, au TDAH (corrélation génétique moins marquée avec le TDAH de type hyperactif-impulsif qu’avec le type inattentif). Conclusion: Le recoulement génétique entre le TDAH et la lecture est davantage motivé par l’inattention que par l’hyperactivité-impulsivité.

Mots clés: étude de jumeaux, TDAH, lecture, compréhension, décodage
Attention-deficit hyperactivity disorder (ADHD) is one of the most highly heritable childhood psychiatric disorders, with a mean heritability of around 75% (Faraone et al., 2005). Besides developmentally inappropriate levels of inattention, hyperactivity and impulsivity, children with ADHD often present with reading disability. Up to 40% of children with ADHD or reading disability also meet criteria for the other disorder (Maughan & Carroll, 2006). Whether defined categorically or continuously, reading disability is also highly heritable with a heritability of around 40-70% (Harlaar et al., submitted; Olson, 2006). Given that both ADHD and reading disability are so highly heritable individually, it is not surprising that genetic factors have been implicated in their overlap. Twin studies, by comparing relative similarities of monozygotic (MZ) and dizygotic (DZ) twins, have shown that ADHD and reading disability share some of the same genes and that these shared genes are primarily responsible for the comorbidity of the disorders (Light et al., 1995; Willcutt, Pennington, & DeFries, 2000; Willcutt et al., 2007).

According to DSM-IV, ADHD is characterized by two core symptom dimensions: hyperactivity-impulsivity and inattentiveness (American Psychiatric Association, 1994). Interestingly, the two ADHD dimensions relate differentially to reading disability, as reading disability is more strongly associated phenotypically (i.e. at the level of observation) with inattentiveness than hyperactivity-impulsivity (Willcutt & Pennington, 2000). Given these differential relationships, some twin studies have investigated the two ADHD dimensions separately in relation to reading disability (Martin et al., 2006; Paloyelis et al., in press; Willcutt, Pennington, & DeFries, 2000; Willcutt et al., 2007). They concluded that genetics mediates the greater association of reading disability with inattentiveness than with hyperactivity-impulsivity.

Although the ADHD dimensions share most of their genes (genetic correlations are about 0.60), there is also substantial genetic specificity (the remaining 0.40; Greven et al., in press; McLoughlin et al., 2007). A similar finding has emerged for two major components of the reading process—word decoding (the ability to accurately recognize printed words) and reading comprehension (the ability to understand the meaning of text). Genetic correlations between them are about 0.65 (Harlaar et al., submitted). Because these two reading dimensions are genetically differentiable, we can ask the extent to which the two ADHD components relate differentially to these two components of reading.

**The present study**

The aim of the present study is to examine the genetic and environmental etiologies of the ADHD-reading disability comorbidity in a genetically sensitive design. However, whereas the majority of previous twin studies have been based on selected samples (Gilger et al., 1992; Light et al., 1995; Willcutt, Pennington, & DeFries, 2000; Willcutt et al., 2007) or on subtype analysis of ADHD (Martin et al., 2006), the present study will examine this comorbidity based on quantitative measures of ADHD symptoms (combined ADHD, inattentiveness and hyperactivity-impulsivity) and reading in a community-based twin sample. A focus on the entire distribution follows from a core aspect the quantitative trait locus hypothesis (Plomin et al., 2009), which is that the abnormal is a quantitative extreme of the normal. By using population-based data we can also eliminate possible biases associated with sample selection as well as collect data from a large number of participants (>12,000 twins). This makes our findings more generalizable to the general population and provides increased power for quantitative genetic analyses.

Moreover, this is the first study to focus on the genetic relations between the ADHD dimensions and two reading dimensions recently identified to be genetically distinct: reading comprehension and word decoding. Reading comprehension deficits are particularly prominent in ADHD (Samuelsson et al., 2004), possibly because reading comprehension makes strong demands on higher-order cognitive processes such as working memory, attention control, motivation and state regulation. These processes are impaired in many children with ADHD (Willcutt et al., 2005). However, such higher-order processes appear to be less critical for word decoding. Thus, we hypothesize that the ADHD dimensions are less strongly related to word decoding than to reading comprehension, and that this difference is a result of differences in the underlying genetic relationship.

**Method**

**Participants**

The sampling frame for this study was the Twins Early Development Study (TEDS), a community sample of twins identified from birth records of all twins born in England and Wales between 1994 and 1996 (Oliver & Plomin, 2007). TEDS families have been shown to be representative of families in the United Kingdom in terms of key demographic indices (Oliver et al., 2007). For the present study, families were excluded with extreme pregnancy or perinatal difficulties (e.g., low birth weight, short gestational age) or if one or both twins had a severe medical condition (e.g., cerebral palsy, Down’s syndrome, autism). After exclusions, the sample consisted of 6428 twin pairs: 1044 MZ male, 1264 MZ female, 967 DZ male, 1116 DZ female and 2037 DZ opposite-sex twin pairs. Twins in this study had a mean age of 11.54 years (SD= 0.63).
Informed parental consent was obtained prior to data collection.

**ADHD symptoms**

ADHD symptoms were rated by postal questionnaire using the DSM-IV based Revised Conners’ Parent Rating Scale (CPRS-R; Conners et al., 1998). The Conners’ assesses combined ADHD based on 18 items, 9 of which assess hyperactivity-impulsivity, and 9 assess inattentiveness. Parents rated each child’s behavior on a 4-point Likert scale from (0) “not true at all” to (3) “very much true”. Cronbach’s alphas were high (.90 for inattentiveness and .83 for hyperactivity-impulsivity).

**Reading, reading comprehension and word decoding**

Reading comprehension was assessed using web-based tests which have been validated against in-person testing (Haworth et al., 2007). The two reading comprehension tests were the Reading Comprehension Subtest of the Peabody Individual Achievement Test (PIAT; Markwardt, 1997) and the GOAL Formative Assessment in Literacy (GOAL, 2002). A reading comprehension composite was created by taking the mean of standardized scores from the two tests.

Word decoding was assessed using the Test of Word Reading Efficiency (TOWRE; Torgesen et al., 1999), administered by telephone, and a web-based adaptation of the Woodcock-Johnson III Reading Fluency Test (Woodcock et al., 2001). A word decoding composite was created by taking the mean of standardized scores from the two tests.

A general reading ability (hereafter referred to as reading) composite was created by taking the mean of the standardized PIAT, GOAL, TOWRE and Fluency scores. Further details on the administration and validity of the reading tests are available elsewhere (Haworth et al., 2007; Davis et al., 2009).

**Analyses**

**The twin method**

The twin method capitalizes on the fact that similarities between siblings growing up in the same family can be attributed to shared genetic or shared environmental factors (Plomin et al., 2008). MZ (identical) twins, who are genetic clones of each other, share 100% of their additive genes, whereas DZ (fraternal) twins on average share only 50% of their additive genes, just like any other siblings. The twin model assumes that shared environmental influences, which make children in the same family more alike, are equally similar for MZ and DZ twins. In contrast, non-shared environmental influences, which contribute to differences between children in the same family, are specific to each child. Based on this twin model, it is possible to construct models of the covariation between twins which can then be fitted to the data using the structural equation modeling software Mx (Neale et al., 2006).

**Genetic analyses**

The present paper utilizes the Correlated Factors Model, which partitions variance in each trait into underlying latent genetic (called heritability, A), shared environmental (C) and non-shared environmental (E) factors. In the Correlated Factors Model A, C and E influences on different traits may correlate, and these correlations are known as genetic and environmental correlations. Genetic correlations indicate the extent to which two traits are influenced by the same genes independent of their heritabilities, and can range from -1 to 1. The same logic applies to shared and non-shared environmental correlations. The Correlated Factors Model also estimates bivariate heritabilities and environmentalities, which indicate the proportion of the phenotypic correlation between two traits attributable to genetic or environmental factors.

Standard regression-based corrections for sex and age were applied to raw scores on all measures (McGue & Bouchard, 1984) and residual scores were then analyzed. The ADHD measures were transformed using the optimized minimal skew command ‘lnskew0’ in STATA, which minimizes the skew. The reading measures were normally distributed. Genetic and environmental estimates were obtained using full-information maximum likelihood (FIML) estimation, which allows for the inclusion of missing data with minimum bias. The significance of obtained estimates was assessed using likelihood-based 95% confidence intervals (the inclusion of zero indicates non-significance).

Based on previous results from the present sample (Greven et al. in press; Harlaar et al., submitted), we fitted models incorporating shared environment rather than genetic dominance (the interaction between genes at the same locus). Data from boys and girls were combined as we had previously found no evidence for qualitative sex differences (differences in the genes that influence the ADHD and reading measures in boys and girls), or quantitative sex differences (sex differences in the relative importance of genes and environments). However, ADHD variances were modeled separately for boys and girls, as boys demonstrated higher variability on ADHD symptoms than girls.

**Model fit**

With very large samples, the likelihood ratio $\chi^2$ test of goodness-of-fit is sensitive to even minor deviations in fit.
especially in multivariate analyses. Thus, indices of approximate fit such as Akaike’s Information Criterion (AIC) and the Bayesian Information Criterion (BIC) are often used (see figure captions). Negative values on the AIC or BIC are indicative of good fit. The BIC favors parsimonious models more heavily than the AIC.

Results
Phenotypic correlations, presented in the top portion of Table 1, revealed that reading correlated moderately with combined ADHD (-0.26). Moreover reading showed significantly stronger correlations with inattentiveness (-0.27) than hyperactivity-impulsivity (-0.19) in that their confidence intervals do not overlap. Likewise, word decoding correlated significantly more highly with inattentiveness (-0.23) than with hyperactivity-impulsivity (-0.13). However, the association with reading comprehension was not significantly different for inattentiveness (-0.22) and hyperactivity-impulsivity (-0.20).

Twin and cross-twin cross-trait correlations
To obtain a preliminary impression of the extent to which ADHD symptoms and reading were influenced by genes and environments, twin correlations were calculated (Table 2). MZ twin correlations were high and DZ twin correlations were roughly half the MZ correlation for each measure, thus implicating substantial additive genetic influences on the ADHD and reading measures. DZ correlations that were somewhat greater than half the MZ correlation suggested that shared environmental influences also played a modest role. As MZ twin correlations were less than unity, moderate non-shared environmental influences on the ADHD and reading measures were also implicated.

Table 2 also includes cross-twin cross-trait correlations (CTCTs), which are correlations between a twin’s score on a first trait (e.g. inattentiveness) and the co-twin’s score on a second trait (e.g. reading). MZ CTCTs were similar to the phenotypic correlations (Table 1) which implicated only modest non-shared environmental contributions to the correlations between the ADHD and reading measures. DZ CTCTs were roughly half the MZ CTCTs, suggesting that additive genetic factors played a substantial role in the covariation of the ADHD and reading measures. Where DZ CTCTs were more than half the MZ CTCTs, shared environmental mediation was also implicated. The impressions obtained from the twin and CTCTs are tested more formally below using structural equation modeling.

Can we confirm previous findings of genetic overlap between combined ADHD and reading?
The bivariate Correlated Factors Solution revealed that combined ADHD and reading showed high heritabilities (74% and 63% respectively), whereas shared and non-shared environmental influences were modest (between 12% and 23%; Figure 1). The genetic correlation between combined ADHD and reading was moderate (-0.31), suggesting moderate sharing of genetic influences on the two traits. The genetic overlap between ADHD Symptoms and Reading is largely Driven by Inattentiveness rather than Hyperactivity-Impulsivity
correlation was negative because the phenotypic correlation was negative (see Table 1).

Bivariate heritability was estimated at 0.80, suggesting that 80% of the phenotypic association between combined ADHD and reading was attributable to genes (Table 1). Bivariate heritability is estimated by multiplying the paths connecting the variables. For example, from Figure 1 bivariate heritability can be estimated as $0.74 \times -0.31 \times 0.63$ divided by the phenotypic correlation ($-0.21/ -0.26 \approx 0.80$).

**Does reading show larger genetic overlap with inattentiveness than with hyperactivity-impulsivity?**

Inattentiveness and hyperactivity-impulsivity were both substantially heritable (68% and 73%) and showed a genetic correlation of 0.56 (Figure 2). The most notable finding was that the genetic correlation with reading was significantly and substantially larger for inattentiveness ($-0.31$) than for hyperactivity-impulsivity ($-0.15$). Thus the genetic overlap between reading and ADHD appears to be largely driven by inattentiveness rather than by hyperactivity-impulsivity.

Phenotypically, reading correlated significantly more highly with inattentiveness than hyperactivity-impulsivity, but the proportion of this correlation due to genes was not significantly larger for inattentiveness (74%) than hyperactivity-impulsivity (52%; Table 1). The phenotypic correlation with reading was also significantly mediated by shared environment for hyperactivity-impulsivity (47%), but not for inattentiveness (10%).

**What is the genetic relationship of the ADHD dimensions with reading comprehension and word decoding?**

Reading comprehension and word decoding showed heritabilities of 44% and 65%, respectively and their genetic correlation was 0.59 (Figure 3). Genetic correlations with reading comprehension and word decoding were moderate for inattentiveness ($-0.28$ and $-0.26$, respectively), and modest for hyperactivity-impulsivity ($-0.18$ and $-0.08$, respectively). The most interesting finding concerning the reading dimensions was that the genetic correlation with word decoding was significantly lower for hyperactivity-impulsivity ($-0.08$) than for inattentiveness ($-0.26$). Thus, the finding that

<table>
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<tr>
<th>Trait</th>
<th>MZ twin correlation</th>
<th>N(pairs)</th>
<th>DZ twin correlation</th>
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<td>.48</td>
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<td>2012</td>
<td>.37</td>
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<td>2013</td>
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<td>.42</td>
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<table>
<thead>
<tr>
<th>Trait</th>
<th>MZ cross-twin cross-trait correlation</th>
<th>N(pairs)</th>
<th>DZ cross-twin cross-trait correlation</th>
<th>N(pairs)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1670</td>
<td>-.11</td>
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<tr>
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<td>-.07</td>
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<td>2012</td>
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<td>Inattentiveness t1—reading comprehension t2</td>
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<td>1666</td>
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<tr>
<td>Inattentiveness t1—word decoding t2</td>
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<tr>
<td>Word decoding t1—reading comprehension t2</td>
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<td>1868</td>
<td>.28</td>
<td>3218</td>
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</table>

Note. MZ = monozygotic; DZ = dizygotic twins
genetic overlap with reading is lower for hyperactivity-impulsivity than inattentiveness can largely be attributed to word decoding rather than reading comprehension. Finally, phenotypic associations between the ADHD dimensions and reading components were all substantially mediated genetically (48-77%; Table 1).

Discussion
This study confirmed that the association between ADHD symptoms and reading has important genetic underpinnings: more than half of this association could be attributed to shared genes. The most notable findings were, first, that the genetic correlation with reading was significantly larger for inattentiveness (-0.31) than for hyperactivity-impulsivity (-0.16), suggesting that genetic overlap between combined ADHD and reading (-0.31) is largely driven by inattentiveness. The second notable finding was that the genetic correlations with the two reading components were also larger for inattentiveness (-0.26 to -0.28) than for hyperactivity-impulsivity (-0.08 to -0.18), but only for word decoding was the genetic correlation significantly larger with inattentiveness than with hyperactivity-impulsivity. Thus, this study provided tentative evidence that the lower genetic correlation between reading and hyperactivity-impulsivity (as compared to reading and inattentiveness) may largely be driven by word decoding rather than reading comprehension.

Our prediction that the ADHD dimensions would relate less strongly to word decoding than reading comprehension was confirmed with respect to hyperactivity-impulsivity: the phenotypic correlation between hyperactivity-impulsivity and word decoding was significantly lower than the one between hyperactivity-impulsivity and reading comprehension. In addition, hyperactivity-impulsivity and word decoding showed a significantly lower genetic correlation than inattentiveness and word decoding. However, finding that inattentiveness demonstrated genetic correlations of similar magnitude with each reading dimension was somewhat counterintuitive. Word decoding skills are usually largely automatic by age 12, and therefore should be less affected by inattentiveness. On the other hand, word decoding skills were normally distributed, so automaticity in word decoding may not have been achieved by all children. Findings may have been driven by children with significant word decoding difficulties and co-occurring inattentiveness. Another explanation is that the word decoding tests in the present study were timed, whereas the reading comprehension tests were not. Inattentiveness may have had more devastating consequences for word decoding skills as a result. Lastly, our findings may be specific to behavioral inattentiveness—attention as assessed by cognitive tests might have demonstrated the lower phenotypic and genetic associations with word decoding we had predicted.

Limitations and future studies
Limitations of this study include standard assumptions of the twin method (Plomin et al., 2008). In addition, although our findings are consistent with the idea of pleiotropic gene effects, i.e. shared genes that influence the development of both ADHD symptoms and reading difficulties, this study was unable to account for the possibility of direct phenotypic effects of one phenotype on the other, which could have mimicked pleiotropic effects even in the absence of a shared etiology (Willcutt, Pennington, & DeFries, 2000). Longitudinal effects of one phenotype on the other, including phenotypic ones, merit further investigation in full multivariate designs in which all measures are obtained at all ages.

Another limitation is that ADHD (in particular inattentiveness) and reading both correlate genetically with IQ (Davis et al., 2009; Harlaar et al., 2005; Haworth et al., 2009; Kuntsi et al., 2004). Thus, genetic overlap between ADHD symptoms and reading could be attributable to genetic influences shared
with general cognitive ability. However, previous studies concluded that the etiology of the co-occurrence of ADHD symptoms and reading disability does not differ significantly as a function of IQ (Light et al., 1995; Paloyelis et al., in press; Willcutt, Pennington, & DeFries, 2000). In addition, in supplementary analyses, we regressed our ADHD and reading measures on general cognitive ability and findings remained similar.

Recent findings by Willcutt et al. (2010) suggest that the comorbidity between ADHD and reading disability has at its core a genetic link between inattention and word decoding, with an endophenotype of processing speed being primarily responsible. It is a plausible hypothesis that processing speed is more important for word decoding than for reading comprehension (while acknowledging that there is also a direct phenotypic effect of decoding on comprehension). This is because good word decoding involves first, the ability to recognize the individual letters, and then to convert these letters quickly and automatically to word units, either individually or in larger chunks. In contrast, reading comprehension is much more influenced by general language and world knowledge, that is fewer but larger acts. Future studies should examine whether the results by Willcutt et al. will differ for reading comprehension. Examining this issue may help explain our unexpected finding that word decoding rather than reading comprehension is differentially related genetically to the ADHD dimensions. Willcutt et al. did not include reading comprehension measures in their study, and
processing speed measures were not included in the present study, so this possibility is only speculative at present.

**Implications**

The present findings suggest that molecular genetic studies should be able to identify a larger number of genetic markers that are simultaneously associated with inattentiveness and reading, and comparatively fewer genetic markers that are simultaneously associated with hyperactivity-impulsivity and reading (in particular word decoding).

This study also has implications for diagnosis. Finding genetic heterogeneity in the relations between the ADHD dimensions and reading suggests that there is need to distinguish between subtypes of ADHD. However, there is also need for a combined diagnosis supported by the high genetic correlations between the two ADHD dimensions.

Moreover, this study highlights the importance of careful, multidimensional monitoring of reading abilities in children with ADHD. We found that ADHD symptoms and reading largely co-occur for genetic reasons; however, this does not mean that environmental interventions will be ineffective. Even monogenetic disorders, which are 100% genetic, can be treated effectively by 100% environmental interventions. An example for this is phenylketonuria, which can be successfully treated by a change in diet. If we can identify the genes involved in this comorbidity, it may allow us to identify, at an
early stage, children who are likely to develop this comorbidity, and to alleviate these difficulties before they develop.

Acknowledgements / Conflicts of Interest

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