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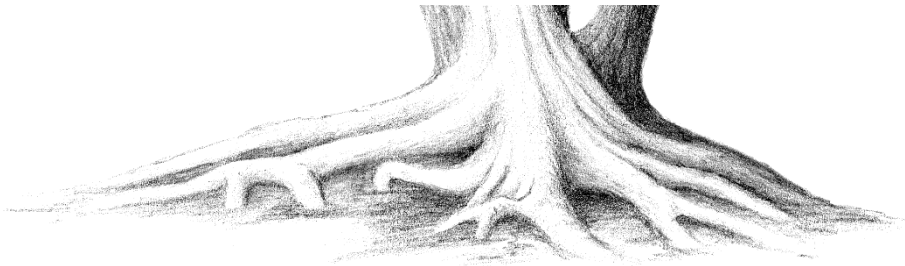
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Chapter 4

Genetic transmission of reading ability

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Introduction

Dyslexia, usually conceptualized as the lower tail of the word reading-ability distribution, tends to run in families. Children of dyslexic parents, as well as siblings of dyslexic children, have a higher chance of developing dyslexia themselves (Snowling, Gallagher, & Frith, 2003; Torppa, Lyytinen, Erskine, Eklund, & Lyytinen, 2010; van Bergen, van der Leij, & de Jong, 2014; Vogler, Defries, & Decker, 1985). Their heightened risk is utilized in studies seeking neuro-anatomical, neuro-functional, cognitive, and environmental precursors of dyslexia. For instance, it has been found that children with familial risk have altered structural brain networks in language areas (Hosseini et al., 2013) and impaired auditory processing (Lyytinen et al., 2005; van der Leij et al., 2013). Despite the ubiquitous use of this familial-risk design in reading and language research, what remains to be resolved is the nature of the transmitted risk (van Bergen et al., 2014). A mainly genetic cause for reading ability and disability implies that parents with reading problems pass on less advantageous genes, whereas a mainly environmental explanation would mean that these parents create a less advantageous home-literacy environment. Which of these two is the main driver has consequences for the interpretation of dyslexia precursors seen in at-risk children.

Evidence for the genetic explanation comes from twin and family studies, which indicate that genetic factors explain a large part of individual differences in children's word-level reading ability (henceforth called 'reading ability'). Reading ability (or decoding) is typically assessed by asking participants to read a list of words, and measuring accuracy or a combination of accuracy and speed (called fluency). The heritability of dyslexia and reading ability is high (60-70%) from a young age onwards (Hawke, Wadsworth, & Defries, 2006; Kovas et al., 2013). The heritability might be higher for timed compared to untimed tasks (Petrill et al., 2012). The current study was conducted in a large Dutch twin-family sample. The Dutch orthography (writing system) is less complex compared to English (Seymour et al., 2003). Hence, accuracy is close to ceiling and reading ability in Dutch is typically measured using fluency tasks (Patel, Snowling, & de Jong, 2004). This might be related to the even higher heritability found for reading ability in Dutch children (around 80%, van Leeuwen, van den Berg, Peper, Hulshoff Pol, & Boomsma, 2009). However, Samuelsson et al., (2008) did not find differences in heritability between orthographies. Alternatively, the high heritability found in the Netherlands may be due to the egalitarian educational system, which reduces environmental variance. Besides children, our study also includes adults. In adults, the heritability of reading has hardly been studied.

One study in adult men found somewhat lower though still robust heritability estimates (45%, Kremen et al., 2005).

Evidence for environmental influences comes from twin studies, which sometimes find a significant influence of the environment that is shared between twins (Olson, Keenan, Byrne, & Samuelsson, 2014; Taylor, Roehrig, Hensler, Connor, & Schatschneider, 2010). This could be due to environmental transmission from parent to child, or due to other, indirect, effects having to do with sharing a household. Several studies indicate which shared household factors correlate with reading ability. Aspects identified thus far include the number of books in a household, how much parents read, and socio-economic status (Evans, Kelley, Sikora, & Treiman, 2010; Leseman & de Jong, 1998; Manolitsis, Georgiou, & Parrila, 2011). However, correlates that are observed in the home environment do not necessarily represent an environmental cause, since such factors may be influenced by the genotype of the parents who provide the home environment (Kendler & Baker, 2007). As parents both transmit their genes and provide the child with the home environment, this may induce a gene-environment correlation, that is, the home environment that the child experiences is related to his or her genotype. If a parental characteristic (e.g., reading ability) still influences an offspring's characteristic after controlling for common genes that influence both generations, then this influence acts through the environment, referred to as cultural transmission.

Thus far, only a few studies explored the association between children's and parents' reading ability. A Dutch and a Finnish familial risk study showed a moderate correlation between parents' and children's reading fluency (Torppa, Eklund, van Bergen, & Lyytinen, 2011; van Bergen, de Jong, Plakas, Maassen, & van der Leij, 2012). A recent Dutch family study (based on an unselected sample) reported a parent-offspring correlation for reading fluency of 0.35 (van Bergen, Bishop, van Zuijlen, & de Jong, 2015). Two English studies tried to disentangle genetic and environmental influences within the family. A study that included parent and (adoptive) child data (Kirkpatrick, Legrand, Iacono, & McGue, 2011) provides a genetically sensitive design. The study employed a broad construct of literacy (Wide Range Achievement Test), but did not explicitly test the nature of familial transmission. However, the pattern of correlations did not point to cultural transmission. Another adoption study (Wadsworth, Corley, Hewitt, Plomin, & Defries, 2002) showed that reading accuracy of parents and their biological offspring correlated around 0.2, whereas the association among parents and adopted children was absent. As adoptive children can only resemble parents because of cultural transmission, this study suggests that cultural transmission of reading ability is lacking.

We aim to further investigate this possibility in an extended twin design, that combines the strength of the classical twin study with the option to study cultural transmission, when twins and their parents have been phenotyped on the same measures. In our study, we used a fluency task in a different orthography, thereby extending empirical research on genetic and cultural transmission of reading in a different culture.

Returning to van Bergen et al., (2015) and Wadsworth et al., (2002), they report spouse correlations of 0.16 and 0.26 respectively, indicating non-random, or assortative, mating. We are unaware of other studies reporting assortative mating for reading ability, but its presence is important for several reasons: it may bias heritability estimates downwards if not taken into account in a classical twin design (i.e., data from mono- and dizygotic twins), while simultaneously suggesting a larger influence of shared environment (Cavalli-Sforza & Bodmer, 1971; Eaves, Fulker, & Heath, 1989). Assortative mating may also signify that offspring of dyslexic parents are particularly vulnerable, as they may inherit genetic and environmental risk factors from both parents.

Here, we aimed to explore the association between parents' and offspring's reading skills further: in a sample of Dutch twins, their siblings and their parents, we estimated resemblance of family members on a commonly used word-reading task. We test if offspring resemble their parents, if there is assortative mating between parents, if there is resemblance among offspring and if this resemblance is larger for monozygotic twin pairs than for dizygotic pairs and non-twin siblings. This is the first general-population study that explores the family resemblance of reading ability in a genetically-sensitive design.

Methods

Participants

Participants were recruited from the Netherlands Twin Register (NTR, Boomsma et al., 2006; van Beijsterveldt et al., 2013; Willemsen et al., 2013). Reading scores were collected in two samples. The first sample, which we will refer to as the twin-sibling sample ($n = 310$ NTR participants), consists of twin pairs with their older sibling from a longitudinal study on the development of brain and cognition (BrainScale, van Soelen et al., 2012a). Measurements took place around the twins' 9th, 12th and 17th birthday. If available, reading data of the first measurement were used ($n = 294$), otherwise from the third measurement ($n = 16$). This sample consisted of 47 monozygotic (22 male, 25 female) and 70 dizygotic twin pairs (21 male, 21 female, 18 opposite sex). Data for 41 brothers and 53 sisters aged between 9 and 21 years ($M = 12.62$, $SD = 2.61$) were simultaneously collected.

The second sample is a parent-offspring sample, consisting of 894 NTR participants from a population-based study on cognition and psychophysiology (Swagerman et al., 2015a). For this study, we included 436 twins (34 male and 72 female MZ twin pairs, 19 male and 40 female DZ twin pairs, and 50 opposite sex pairs), 33 brothers (mean age 35.91, $SD = 16.10$), 38 sisters (mean age 35.67, $SD = 18.79$), 125 fathers (mean age 63.95, $SD = 10.20$), and 158 mothers (mean age 61.34, $SD = 10.83$).

In total, data were available for 1100 participants from 431 families, of which 386 had at least two family members. On average, the mean age of this sample was 34.40 ($SD = 22.92$). These participants are representative of the general population: on average, adults had engaged in 14 years of education (range 6-20 years).

Materials

Reading test

Participants were given a list of Dutch words and were asked to correctly read out loud as many words as possible within one minute. Each participant was assessed on one of two highly similar tests, which we will refer to as one-minute-test 1 (OMT1) and one-minute-test 2 (OMT2).

OMT1. The OMT1 consists of 120 multisyllabic words, increasing in difficulty from two to four syllables (list 3C, Verhoeven, 1995). The manual reports a reliability of 0.86-0.92 in 9- to 12-year-olds (Moelands, Kamphuis, & Verhoeven, 2008).

OMT2. The OMT2 consists of 116 words of increasing difficulty (list B of Brus & Voeten, 1999). The first 10 words are monosyllabic. Thereafter they increase from two to four syllables. The reliability is 0.76-0.96 in 9- to 13-year-olds (van den Bos, Lutje Spelberg, Scheepstra, & de Vries, 1994).

The OMT1 was used on the first measurement of the twin-sibling sample (209 twins and 85 siblings), and the OMT2 was used on the third measurement of the twin-sibling sample and in the parent-offspring sample (443 twins, 80 siblings, all fathers and mothers). Both OMT1 and OMT2 were assessed in an independent sample of 122 9-year olds (end Grade 3; unpublished data of Peter F. de Jong). In this sample the tasks correlated 0.90. This correlation falls in the range of test reliabilities and corroborates that the OMT1 and OMT2 measure the same construct.

Procedure

Participants were first approached by mail, followed by a telephone call asking about willingness to cooperate and possible exclusion criteria.

Data collection in the twin-sibling sample took place in the University Medical Center Utrecht and Vrije Universiteit (VU) Amsterdam, and participants in the parent-offspring sample could choose if they preferred a home assessment or a lab assessment (at the VU or the Amsterdam Medical Center). Prior to starting the test protocol, procedures were explained to the participants, who signed informed consents. For children up to 16 years parents had to give consent as well. Procedures for both studies were approved by the Medical Ethics Review Committee of the Vrije Universiteit Medical Center Amsterdam and the Central Committee on Research Involving Human Subjects.

Statistical analyses

As an indicator of sample representativeness, we compared raw reading scores of 9-year olds ($n = 210$) to available national norms. For adults no norm scores are available. Raw test scores showed a good approximation to a normal distribution with a tail towards the lower scores, with 50% of the participants scoring between 90 and 120. Approximately 10% of all participants was able to read all the words of the list within a minute, but since they often made 1 or 2 mistakes, 5% of the participants had a final score of 116 words within a minute. First, using SPSS (IBM Corp., 2011), test scores were corrected for linear and quadratic effects of age in participants under age 18 (Figure 1), because reading ability increases throughout the first years of education. The standardized residuals (z-scores) were saved for further analyses. Test scores of participants over age 18 were standardized to z-scores without correcting for age. Figure 1 illustrates how the age correction and standardization of scores results in a mean score around 0 across samples, tests, and age.

Figure 1. Scatterplot of raw (panel A) and standardized (panel B) reading scores against age. Panel A shows the linear relationship in the OMT1 where reading score increases with age (including 95% confidence interval).

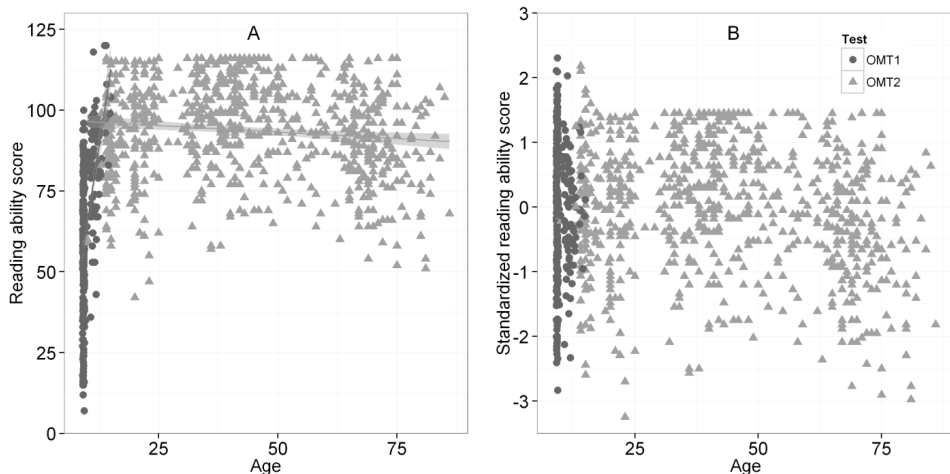
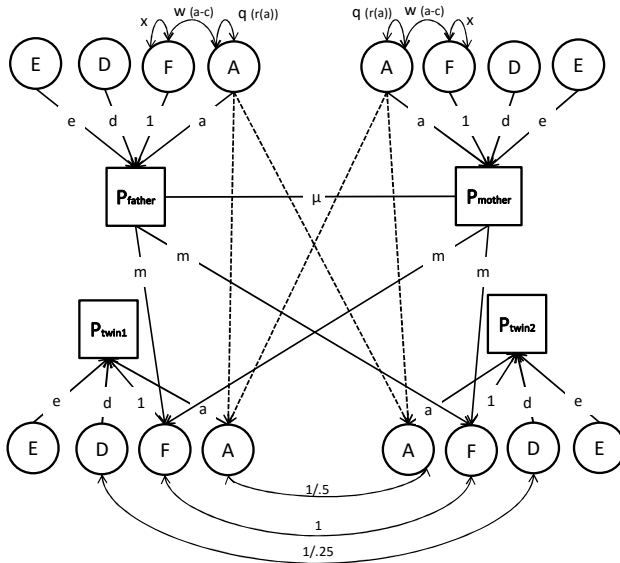


Figure 2. Path diagram of the extended twin family design.

P = phenotypic variance of father, mother or twin (siblings are not represented in this figure). A = additive genetic effects, E = unique environment including measurement error, D = non-additive genetic effects, F = family environment, μ = assortative mating co-path, m = cultural transmission, q = additive genetic covariance, x = family environment covariance, w = covariance between A and F (variances of other latent factors are 1). The dotted line is fixed to 0.5.

All standardized scores were analyzed using structural equation modeling in OpenMx (Boker et al., 2011). Figure 2 represents a path diagram of the extended twin family design (ETFD, Heath, Kendler, Eaves, & Markell, 1985; Keller et al., 2009). In the ETFD, the covariance structure between family members can be used to estimate the relative contribution of additive genetic (A), non-additive genetic (or dominant, D), family environment (F, passed on via cultural transmission from parents to offspring), sibling environment (S, shared by twins and siblings only) and unique environmental factors including measurement error (E).

Including data of parents reduces parameter bias if there is assortative mating present because assortative mating induces correlated genetic effects between parents and offspring which inflate correlations amongst offspring (Eaves et al., 1989; Fulker, 1982; Heath et al., 1985). Furthermore, data of siblings has been shown to increase statistical power to detect non-additive genetic influence (Posthuma & Boomsma, 2000). Parents transmit half of their segregating genes to offspring (dotted line in Figure 2 between A parent and A twin).

Monozygotic twins (MZ) share (nearly) 100% of their genetic material, whereas dizygotic twins (DZ) and non-twin siblings share on average 50% of the additive and 25% of the dominant genetic variance. This is represented as correlations of 1.0 between MZ twins and 0.5 (A) and 0.25 (D) between DZ twins and siblings. The family environment (F) correlates 1.0 between twins / siblings. However, a model estimating A, E, D, F and S simultaneously is not identified: therefore either D, F or S should be fixed to 0. The ETFD provides the possibility to model assortative mating between spouses (μ in Figure 2), which, if present, would result in an increased resemblance between all twins and siblings. Lastly, cultural transmission is indicated in Figure 2 by path *m*.

We fitted a model with A, E, F and D parameters, including cultural transmission to be able to test our primary hypothesis regarding cultural versus genetic transmission. Given that the DZ twin correlations are less than half the MZ correlation and the correlation between parents and offspring is low, dominance genetic effects (D) were modeled instead of shared sibling environment ($S = 0$). Since there may be sex differences in reading ability (Rutter et al., 2004), sex was included as a covariate. Parameter estimation was by raw-data maximum likelihood as implemented in OpenMx. The fit of nested submodels was compared by likelihood-ratio tests, based on the difference in minus twice the log likelihood (-2LL) between two models. The difference has a chi-square (χ^2) distribution with the degrees of freedom (df) equaling the difference in df between the two models. If constraining parameters in a nested model did not result in a significantly worse fit ($\alpha = 0.05$) this more parsimonious model was deemed the best fitting model. In submodels, the different means for family members, the significance of the covariate sex, and the significance of assortative mating and cultural transmission were tested by setting this parameter to 0.

Results

The average score of 9-year olds on the OMT1 was 56.95 ($SD = 19.57$), which falls within the 40-60th percentile of the national norm scores (Jongen & Krom, 2010). On the OMT2 the average score for participants of 18 years and older was 94.42 ($SD = 14.67$). For participants under 18, there was a significant effect of age ($\beta = 3.1$, $p < 0.001$) and age squared ($\beta = -2.5$, $p < 0.001$). There was no significant effect of sex on the mean ($\beta = 0.12$, $\Delta\chi^2(1) = 1.75$, $p = 0.19$). The MZ twin correlation was 0.62 (confidence interval (CI): 0.51-0.73) whereas the dizygotic correlation and twin-sibling correlation was 0.26 (CI: 0.17-0.32). The MZ correlation thus was larger than twice the DZ or sibling correlation. The parent-offspring correlation was 0.18 (CI: 0.03-0.31) and there was a spouse correlation of 0.38 (CI: 0.22-0.53).

Such a pattern of correlation among family members is consistent with a model that attributes resemblance to additive genetic factors, these are the factors that contribute to resemblance among all biological relatives, and to non-additive genetic factors. Non-additive genetic factors, or genetic dominance, contributes to resemblance among siblings, but not to the resemblance of parents and offspring (Falconer & Mackay, 1996). Maximum likelihood estimates for the additive genetic factors were 28% (CI: 0-43%) and for dominant genetic factors 36% (CI: 18-65%), resulting in a broad-sense heritability estimate of 64%. The remainder of the variance is attributed to unique environmental factors and measurement error (35%, CI: 29-44%). The path loading of the co-path between spouses (μ in Figure 2) was 0.38, indicating significant assortative mating: dropping this parameter from the model resulted in a significantly worse fit ($\Delta\chi^2(1) = 13.61, p < 0.001$). Dominance could not be omitted from the model without a significant change of fit ($\Delta\chi^2(1) = 19.4, p < 0.001$). There was no evidence for cultural transmission ($m = 0.006, \Delta\chi^2(1) = 2.9, p = 0.09$). Therefore the ADE model without cultural transmission was deemed the best fitting model.

Discussion

In this study we aimed to test if the family resemblance which has been reported for reading ability and disability is caused by genetic or cultural transmission. To our knowledge, we were the first to explore this using a sample including twins, their parents and siblings. Secondly, we aimed to test if assortative mating is present. We found that individual differences in reading ability were mainly caused by genetic factors, both additive and non-additive. Environmental factors that are shared between parents and children did not contribute to familial resemblance and no evidence was found for cultural transmission from parents to their offspring. In the remainder we will start with limitations, followed by discussion of modelling findings and their scientific and clinical implications.

This study has some limitations. First of all, although the sample size is considerable (> 1000 individuals), on the family level this study is smaller. Therefore we may be under powered to detect small effects. Secondly, the assumption of the ETFD is that etiological sources of variance are the same for parents and their offspring. That is, that the same genes play an equally large role for all family members, even if they belong to different generations. However, this is not necessarily the case: the influence of genetic factors may increase with age, as is shown for psychometric IQ (Haworth et al., 2010). In our sample, the twin group includes children, adolescents as well as adults and elderly (20% is over 40 years of age).

Therefore, should it be the case that heritability increases with age, our estimate would represent an average over the lifespan and will therefore be somewhat higher than if it were based on younger twins alone. In addition, we found a somewhat larger component of E on reading ability compared to other genetic studies which found estimates around 10% (Harlaar, Spinath, Dale, & Plomin, 2005; Samuelsson et al., 2007). This may reflect larger measurement error, or reflect genuine environmental influences that are not shared among family members. Adding a second measure of reading ability and working with a common-factor score may have reduced measurement error and allowed for the possibility to distinguish between these alternatives.

Notwithstanding these limitations, this is the first study to analyze data on reading ability with parents and their twin-offspring. This design is better suited to provide a comprehensive understanding of why family members resemble each other. From the model-fitting analysis it can be concluded that familial resemblance is caused by genetic factors: the broad sense heritability (variance due to additive + non-additive genetic factors) is 64%. We do not know of other studies that have found evidence for non-additive (or dominant) genetic influence on reading (dis)ability (e.g., Kirkpatrick et al., 2011).

Reading ability of spouses appeared to be correlated (assortative mating, 0.38), which is in line with findings from Wadsworth et al., (2002: 0.26) and other studies of traits that correlate with reading, like intelligence (Vinkhuyzen, van der Sluis, Maes, & Posthuma, 2012: 0.37), but lower than found by van Bergen et al., (2015: 0.16). As noted in the introduction, assortative mating may render children of a parent with dyslexia extra vulnerable, as their other parent may also exhibit below-average reading skills. Indeed, children of a dyslexic parent who go on to develop dyslexia themselves are more likely to have a second parent with reading difficulties (Gilger, Hanebuth, Smith, & Pennington, 1996; van Bergen, de Jong, Maassen, & van der Leij, 2014). Another implication of the finding of assortative mating is that future studies should take this into account, as it may bias the heritability estimates. Some twin studies report evidence for shared-environmental influences (reading disability e.g., Friend, Defries, & Olson, 2008; Harlaar et al., 2005; reading ability e.g., Petrill et al., 2007; Taylor & Schatschneider, 2010). However, these influences may have been overestimated in the presence of assortative mating. Regarding parent-offspring resemblance, the estimate of the parent-offspring correlation (0.18) is of similar magnitude to correlations with biological children reported by Wadsworth et al., (2002: 0.16-0.26) but lower than reported on another Dutch sample (van Bergen et al., 2015, 0.32-0.38). One consequence of genetic non-additivity (genetic dominance) is that parent-offspring resemblance is lower than sib-sib

resemblance. Whereas siblings share part (25%) of the variance due to genetic dominance, parents and offspring do not (Falconer & Mackay, 1996).

In conclusion, after taking into account the genetic liability that is passed on from parent to child and assortative mating, there is no additional effect of parental reading ability to offspring reading ability. This absence of cultural transmission is in line with the findings from Wadsworth et al., (2002), despite differences in reading measure, language, culture, and study design. For psychopathology in contrast, cultural transmission has sometimes been demonstrated (Maes, Silberg, Neale, & Eaves, 2007; McAdams et al., 2014). Therefore, for psychopathology, intervention aimed at the parents would also benefit mental health of their children. In the case of children with reading disability, we would advise that interventions should focus on the child's, and not the parents' reading skills. However, this does not mean that parental characteristics other than reading ability are not passed on through cultural transmission. An example of this might be the school parents choose for their child: school choice may not be related to parents' reading ability (but e.g., based on religious affiliation), but school choice may impact on children's reading ability (Taylor et al., 2010). School choice would then be an environmental influence which is passed on from parent to child.

As mentioned in the introduction, familial risk studies seek neurobehavioral precursors of dyslexia. The current study speaks to whether familial risk is in fact genetic or environmental in nature. The types of analyses that were employed in this paper depend on population-based data and would not be possible in dyslexic families: there would be a restriction of range within parental reading scores (i.e., they all score in the lower tail of the distribution) and without substantial variance, computing covariance would be futile. Our results suggest that the precursors for reading disability observed in familial risk studies are caused by genetic, not environmental, liability from parents. That is, having family risk does not reflect experiencing a less favorable literacy environment, but receiving less favorable genetic variants.