

# 8

*Summary and discussion*



I have described the first part of a longitudinal study on cognition, brain structure, and hormonal levels during adolescence. Data were collected in nine-year-old twins and their nine-to-fourteen year old siblings who are registered with the Netherlands Twin Register (NTR). This thesis focuses on cognition and its relation to brain structure. This last chapter first summarizes the results from the previous chapters and then discusses these with reference to other publications that resulted from this study.

## **Chapter 2: Endophenotypes for intelligence in children.**

In adults, a small set of endophenotypes for intelligence is already available. In children, however, much less is known about the suitability of these cognitive measures as endophenotypes for intelligence. Chapter 2 identified promising endophenotypes for intelligence in children and adolescents for future genetic studies in cognitive development. Based on the available set of endophenotypes for intelligence in adults, cognitive tasks were chosen covering the domains of working memory, processing speed, and selective attention. This set of tasks was assessed in a test-retest design and their correlation with intelligence was examined in children and in adolescents. The test battery included the  $n$ -back task, Eriksen flanker task, and the  $\pi$ -inspection time task.

All test-retest correlations in children exceeded .60, except for accuracy and stimulus congruency effects of the flanker task. For the adolescents the same holds true, with an exception of the 2-back ( $r = .16$ ) and the  $\pi$ -inspection task ( $r = .58$ ). In both children and adolescents  $n$ -back performance was significantly related to IQ. Better performance on the  $n$ -back task was related to higher IQ-scores. Reaction time on the congruent and incongruent trials of the flanker was significantly related to IQ in children only; the longer the reaction time, the lower the IQ. Incongruency effects on reaction time, accuracy on the congruent and incongruent trials, as well as incongruency effects on accuracy were not related to IQ in children or in adolescents. Inspection time was related to IQ in children, the shorter the inspection time the higher the IQ, but was not significantly related to IQ in adolescents.

Working memory capacity seems a good endophenotype for intelligence in children and adolescents: it can be reliably assessed using the  $n$ -back and it correlates with intelligence. Processing speed is not an optimal endophenotype for intelligence in children and adolescents. Once corrected for working memory, it contributes only a very small part

to the variance of intelligence. Selective attention, at least when measured as the flanker incongruency effect on reaction time and accuracy, is not a suitable endophenotype for either age group.

**Table 8.1.** *Heritability of cognitive measures*

Measure	<i>heritability</i>
IQ (Raven) <sup>a</sup>	.67
IQ (WISC-III) <sup>a</sup>	.75
Reading ability (OMRT) <sup>a</sup>	.83
Verbal IQ (WISC-III) <sup>b</sup>	.81
Verbal comprehension (WISC-III) <sup>a</sup>	.79
Perceptual organization (WISC-III) <sup>a</sup>	.56
Processing speed (WISC-III) <sup>a</sup>	.58
Verbal learning (AVLT) <sup>b</sup> :	.46
Learning speed <sup>c</sup>	.43
Forgetting speed <sup>c</sup>	.20*
Letter Fluency (COWA) <sup>b</sup>	.40
Category Fluency (COWA) <sup>b</sup>	.29
Verbal STM (DSF) <sup>a</sup>	.47
Visuospatial STM (Corsi) <sup>a</sup>	.47
Verbal WM (DSB) <sup>a</sup>	.35
Visuospatial WM (2-back) <sup>a</sup>	.47

Note \*heritability in twins only, for siblings .30; <sup>a</sup>based on data-analysis in this thesis; <sup>b</sup>Hoekstra et al., in revision); <sup>c</sup>Van Soelen et al. (in revision)

### Chapter 3: Genetic architecture of memory

Chapters 3 and 4 examined the heritability of various cognitive measures, including working memory which had proven in chapter 2 to be a reliable endophenotype in children and adolescents. Table 8.1 offers a summary of the heritabilities that were observed for these measures, as well as for psychometric IQ based on the analyses described in this

thesis and as published by others from the same study (Hoekstra, Bartels, Van Leeuwen, & Boomsma, submitted; Van Soelen et al., in revision). Heritability estimates ranged from .20 to .83, with the highest estimates seen for IQ, either total or verbal IQ, and for reading ability.

Chapter 3 examined the heritability of verbal and visuospatial working memory (WM) and short-term memory (STM) in a developmental study on the genetic and environmental relationship between these four measures. Although a wealth of studies on individual differences has focussed on the relation between STM and WM in adults (e.g. Conway, Cowan, Bunting, Theriault, & Minkoff, 2002; Kane et al., 2004) as well as children (e.g. Alloway, Gathercole, & Pickering, 2006; Bayliss, Jarrold, Baddeley, & Gunn, 2005; Kail & Hall, 2001), the extent to which verbal and visuospatial WM and STM tests measure the same or multiple constructs is still unclear. Likewise the relationship between WM and STM across development is not known. These questions were addressed studying the current cohort and a cohort of 186 families of young adult twins and siblings. Verbal and visuospatial WM and STM were measured using the Corsi block tapping task (Corsi, 1974), *n*-back task (Gevins & Cutillo, 1993), and the digit span forward and backwards task (Wechsler, 1997; Wechsler et al., 2002).

In the young adult cohort the relationship between the four measures was best captured by a model consisting of two correlated factors for verbal and visuospatial memory explaining all genetic variance, one common environmental factor for the visuospatial memory tasks, and one specific environmental factor for each variable. In the child cohort most of the phenotypic correlations were explained by a genetic factor for verbal and a genetic factor for visuospatial memory. However, the results in the children also indicated significant differences in the genetic structure of cognition in children as opposed to young adults: STM and WM in children were also influenced by specific genetic factors. Thus, from a genetic viewpoint one could say that WM and STM are part of the same system, and verbal and visuospatial information are processed using two partly overlapping memory pathways. Second, during the course of development the specific genetic factors, which create differences between the four abilities, disappear. This suggests that with aging these cognitive abilities start to become part of two genetic systems, one for verbal memory and one for visuospatial memory.

#### **Chapter 4: Genetic architecture of reading ability**

Chapter 4 investigated the genetic relationship between reading ability, intelligence and verbal and visuospatial WM and STM. The study used WISC IQ, performance on the One Minute Reading Test (OMRT; Cito, 1995) as a measure of reading ability, and measures of verbal and visuospatial WM and STM.

The relationship between reading ability and IQ has been well established in non-affected and in groups affected with reading disability (Tiu, Jr., Thompson, & Lewis, 2003). The association between reading disability and memory is still subject of debate (Cohen-Mimran & Sapir, 2007; Gathercole, Alloway, Willis, & Adams, 2006; Kercher & Sandoval, 1991; Swanson & Jerman, 2007) and literature on the genetic relationship between memory and reading abilities is scarce. Resolving the etiology of the relationship between IQ, memory and reading abilities, may give information whether impairments in memory and IQ in children with reading disability is a sign of the severity of the reading disability or a symptom of reading disability per se (Bishop, 2006).

The phenotypic correlations between reading ability and the other measures ranged between .24 and .44. The phenotypic correlations between IQ, WM, STM and reading ability were completely explained by common sets of genes. The model which explained these phenotypic correlations best consisted of: a common genetic factor for all variables; a common genetic factor for visuospatial STM and verbal and visuospatial WM; a common genetic factor for verbal memory and reading ability; a specific genetic factor for visuospatial WM; and a specific genetic factor for reading ability. Forty-seven percent of variation in additive genetic variance in reading ability was specific for reading ability.

#### **Chapter 5: Intelligence**

In Chapter 5 the presence of assortative mating (non-random mating), Gene-Environment (GE) interaction (people with a certain genotype are more vulnerable to a certain environment) and the heritability of intelligence in childhood was assessed using a twin family design with twins, their siblings and parents. With this design, cultural and genetic transmission can be studied while taking into account spousal resemblance. Two competing hypotheses about the causes of assortative mating in intelligence were evaluated: social homogamy (spouses meet each other within an environment which is correlated with intelligence) and phenotypic assortment (spouses choose each other based on intelligence or

a trait related to it), and their implications for the heritability estimate of intelligence. Intelligence was assessed using the Raven's Progressive Matrices (Raven, Raven, & Court, 1998; Raven, 1960) in both the parental and the offspring generation. IQ scores were estimated based on a Rasch model (Rasch, 1966).

The spousal correlation was .33, monozygotic (MZ) correlation was .63, and dizygotic (DZ) correlations, twin-sibling correlations and parent offspring correlations varied between .25 and .38. A simple model with only additive genetic effects and non-shared environmental effects explained the correlations between family members best. Comparing the phenotypic assortment model and the social homogamy model, the model assuming phenotypic assortment appeared superior. Thus spouses choose each other based on intelligence or on a related trait.

There was no significant contribution of cultural transmission and therefore no passive Genotype-Environment (GE) correlation. The study design of Chapter 5 was not suited to uncover GE correlations other than one resulting from simultaneous genetic and cultural transmission (i.e. reactive or active GE correlation). However, if there is GE correlation, it is more likely that either reactive or active GE correlation are of importance and that the role of parents is limited to responding to the needs and interests as indicated by the child. Such correlations, which are "part of the genotype of the child" are embedded in the heritability estimates in the current study.

To detect and estimate GE interaction the association between MZ intrapair sum and difference scores was examined (Jinks & Fulker, 1970). The estimate for the correlation between intelligence sum and difference between MZ twins was -.30. When there is a negative correlation between intrapair sum and absolute differences, less intelligent individuals are less similar than more intelligent individuals (Finkel & Pedersen, 2001). This suggests that the environment is relatively more important in explaining individual differences for low IQ groups than for high IQ groups.

### **Chapter 6: Intelligence and brain volumes**

Chapter 6 employed a multivariate twin design to investigate the association between total brain volume, gray matter and white matter volume and intelligence as assessed by the Raven IQ test and verbal comprehension, perceptual organization and processing speed as assessed by the WISC-III. Phenotypic correlations between the brain volumes and

intelligence traits ranged between .20 and .33. Processing speed and brain volume did not correlate. The relation between brain volume and intelligence was entirely explained by a set of genes influencing both intelligence and brain volume.

The phenotypic correlations between WMV and GMV and the intelligence measures corrected for TBV indicated that intelligence was not related to proportion WMV/GMV. The association between intelligence and WMV and GMV disappeared once corrected for TBV. Nevertheless from the partial correlation analyses it can not be concluded that intelligence is only influenced by TBV and that WMV and GMV by themselves do not influence intelligence.

Genetic and environmental correlations gave an indication for the direction of causation for the association between intelligence and brain volume. The heritability estimates for the brain volumes are around 90%. In contrast, variability in intelligence is for about 60% caused by differences in genotypes. If intelligence causally influences brain volumes, this would be reflected in genetic as well as environmental correlations: all genetic and environmental factors that influence intelligence would, through the causal chain, influence brain volume (De Moor, Boomsma, Stubbe, Willemsen, & De Geus, in press). However, Chapter 6 showed that only the genetic correlations are significant. In fact 85% to 100% of the covariation between brain volume and intelligence are caused by shared genetic factors.

### **Chapter 7: Twin separation in primary school**

At present there is hardly any research comparing the adjustment of twin pairs who are separated versus those kept together at school. Therefore, in Chapter 7 the short- and long-term effects of classroom separation in twins on behavior problems and academic performance were studied in twin pairs selected from the NTR. Short-term effects were studied at age 7 in twins separated at age 5 and long-term effects at age 12 in twins who had been separated or together most of the time at school. Behavior problems were rated by mothers (Child Behavior Checklist at ages 3, 7 and 12; Achenbach & Dumenci, 2001) and teachers (Teacher Report Form at ages 7 and 12; Achenbach, 1991). Academic achievement was measured at age 12 using a national academic achievement test (CITO; Bartels, Rietveld, Van Baal, & Boomsma, 2002a).

At age 7, twins from separated pairs had more internalizing and externalizing problems than non-separated twins, as rated by both mothers and teachers. However, only



for the maternal ratings of internalizing problems these effects could be attributed to the separation itself and not to pre-existing problems (at age 3) between separated and non-separated twins. Long-term effects of separation were significant for maternal and teacher ratings of internalizing and externalizing problems, but these effects could be explained by pre-existing differences between separated and non-separated groups. Thus, for behavioral problems at the age of 7 years, it may matter whether twins are separated or not. The separation of twins at school leads to internalizing problem behavior. However, all findings represent small effect sizes. Furthermore, at age of 12, this effect has disappeared. There were no differences in academic achievement between the separated and non-separated group.

## **Discussion**

Early adolescence (the gradual transition between childhood and adulthood) is the focus of this thesis since this is a critical period in cognitive and brain development with important changes in brain structure and cognitive abilities (e.g. Durston et al., 2001; Spear, 2000). Both these developmental changes may be essential for optimal adult functioning. Diseases that affect the integrity of the brain at a young age, such as schizophrenia are likely to display their first symptoms during this period (Van Oel, Sitskoorn, Cremer, & Kahn, 2002). To get a better understanding of the development of these diseases, it is important to learn more about the genetic and environmental processes underlying the transition from childhood into adulthood in healthy children (Luna & Sweeney, 2001).

Studies generated from the first wave of data collection in this longitudinal twin study investigated the relationship among cognitive measures, brain volumes and intelligence, and hormonal levels and brain structure (this thesis; Hoekstra, Bartels, Van Leeuwen, & Boomsma, in revision; Peper et al., 2008; Peper et al., in press). These studies showed that in preadolescence the relationship among these measures are mainly caused by overlapping sets of genes, rather than by environment. This finding regularly returns in the literature on individual differences: genetic influences tie together diverse measures of cognitive functioning, whereas environmental effects drive wedges between different dimensions of cognitive processing (Luo, Petrill, & Thompson, 1994; Pedersen, Plomin, & McClearn, 1994). This applies also to the relation between brain structure and cognition, as shown in adults by e.g. Posthuma et al. (2002, 2003) and Hulshoff Pol et al. (2006). This

thesis shows that in children genes also are the binding factor for the coherence between various cognitive traits and between cognition and brain structure.

Further, the developmental studies (this thesis; Hoekstra, et al., in revision) on cognitive measures showed that during the course of development genetic correlations between these measures increase. However, this conclusion was based on cross-sectional studies. By following this sample longitudinally, it can be confirmed whether this truly is the case. At this moment the first follow-up measurement is taking place, now that the twins are almost twelve years old.

The relationship between intelligence and brain volumes might be caused by overlapping sets of genes, as suggested by the results in Chapter 6. However, nested on the genetic pleiotropic model, are several phenotypic causation models which might also explain the association between intelligence and brain volume. Recent evidence showed that for specific traits, like juggling or knowing your way around London as a taxi driver, a causal relation from training to increased local gray matter volume can be inferred (Draganski et al., 2004; Maguire, Woollett, & Spiers, 2006). For the relation between intelligence and brain volume in children a direction-of-causation model seems less likely. Environmental stimulation to increase intelligence does not influence total brain volumes. As put forward by De Moor et al. (2008) such a model requires that all genetic and environmental factors that influence intelligence would, through the causal chain, also influence brain volume.

This thesis did not find evidence of influence of shared environment on any of the cognitive measures that were included in the protocol. This is in contrast with previous findings in children which reported a contribution of shared environmental influences on aspects of intelligence (Bartels, Rietveld, Van Baal, & Boomsma, 2002b; Rietveld, Dolan, Van Baal, & Boomsma, 2003; Scarr & Weinberg, 1983). In adults, shared environment does not contribute to the variability in cognition (Bouchard, Jr., Lykken, McGue, Segal, & Tellegen, 1990; Posthuma, 2002). There may be several reasons why we did not observe any influence of C. First, it should be recognized that with 112 families, the statistical power to detect shared environmental is not large (Martin & Eaves, 1977; Purcell, Cherny, & Sham, 2003; Visscher, Gordon, & Neale, 2008). However, for most cognitive measures twin correlations did not suggest an influence of shared environment. The influence of shared environment in childhood may be confined to traits like vocabulary and general knowledge and may be so small that we did not detect it. A second

hypothesis is suggested by Guiso, Monte, Sapienza, and Zingales (2008) who observed that girls close the gender gap (differences between girls' and boys' scores on math and reading) by becoming better in both math and reading in countries where women are equal in economic and political opportunities, education, and well-being. This may also suggest that when the opportunities provided by society are adequate, genotypes can come fully to expression. Thus, maybe in recent years, environment in the Netherlands has changed in a way, e.g. equal educational opportunities for all children, which made it possible for children to reach the cognitive level in accordance with their genotype at an earlier age than before.

There was no evidence for cultural transmission or shared environmental influence on general IQ. This does not imply that environment does not influence cognition. It merely means that environmental variation, which is shared between siblings and influences these siblings in the same way, does not play a role in variability in cognition. Shared environment is not the same as for instance parental style or stimulation. Parents do not treat all their offspring exactly in the same way independent of the phenotype (or genotype) of their children. Chapter 5 even shows that depending on the genotype of the child the environment plays a more or less important role. This study showed that in children with a genetic predisposition to be less intelligent, environmental stimulation is more influential. Moreover, Chapter 5 shows that genetic studies on intelligence should take GE interaction into account, because else heritability estimates will be inflated.

Combining the results of Chapter 3 and 4 gives some insight what kind of processes are captured by the two common genetic factors involved in the relation between verbal and visuospatial WM and STM. In Chapter 4 three factors were involved in the relation among the memory measures: 1) a genetic factor common to the memory measures and intelligence and reading ability; 2) a genetic factor common to visuospatial STM and verbal and visuospatial WM; 3) a genetic factor common to verbal memory and reading ability. The first factor seems to involve general intelligence, the second factor probably involves an ability which is essential for complex memory, and the third factor seems to embody the ability to code information phonemically or verbally. Therefore, the overlap between the two memory factors which were derived from the genetic analysis of WM and STM seem to represent general intelligence and processing of complex memory tasks. The specific genetic factor involved in verbal memory most likely represents verbal coding.

Chapter 7 showed that putting twin pairs in separate classes does not lead to extra environmental variation between separated and non-separated twin pairs in variability in intelligence (at least at age twelve). This has important consequences for twins and their parents. Schools in the Netherlands often have a policy of separating twins. Our study shows, that if anything, this policy is harmful because it leads to an increase in internalizing problems. The effects of separation into different classrooms did not show up for educational attainment. This implies that for cognitive traits, data from twins can be generalized to the non-twin population.

Several traits studied in this thesis seem suitable endophenotypes for intelligence: all traits are reasonably reliable, heritable, genetically associated with intelligence, and these genetic associations seem theoretically meaningful (De Geus & Boomsma, 2001). For the relationship between brain volumes and intelligence, the theoretical meaningfulness of this relation is obvious, but also memory measures are theoretically meaningful endophenotypes. Memory performance has been included in theories of intelligence since the beginning of the development of psychometric IQ (Ackerman, Beier, & Boyle, 2005). The greater an individual's STM capacity and therefore its WM capacity, the more information the individual has simultaneously available for use in solving problems (Fry & Hale, 2000; Just & Carpenter, 1992). The question is however, whether these traits are not too complex by themselves. One of the complications with identifying genes affecting complex traits is that they are influenced by many genes, and therefore each gene is likely to have a relatively small effect (Plomin, DeFries, McClearn, & McGuffin, 2001) and therefore difficult to identify. Further research, like genome wide association studies (Kruglyak, 2008), should point out if these traits indeed can aid the search for genes involved in intelligence.

Several relationships among brain structure, cognition and hormonal levels remain to be elucidated. Chapter 6 showed that intelligence is related to brain volume; however this thesis did not look in to the relationship between specific brain regions and intelligence. Are the same brain regions implicated in the relationship between intelligence and brain structure in children as in adults?

Peper et al. (in press) showed that children, who are more advanced in puberty stage, are also more advanced in brain development. Decreases were found in frontal and parietal gray matter density, areas involved in higher level cognition. It is unclear which

implications these decreases in gray matter have for cognition and cognitive development. Shaw et al. (2006) showed that it is rather the trajectory of change in the thickness of the cerebral cortex, rather than cortical thickness itself, which is most closely related to level of intelligence. Extremely intelligent children seemed to be delayed in brain development compared to average and high intelligent children. Is the trajectory of change in thickness of the cortex related to physical maturation? Or are the specific brain regions which development is related to puberty different from the specific brain regions implicated in intelligence? Further longitudinal research in this sample should point this out.

Another area, which remained unstudied, is the relation between brain structure and other domains of cognition besides intelligence. For instance the study on brain volumes and intelligence did not reveal a relationship between processing speed and brain volumes. A possible explanation for this finding is that processing speed as measured by the WISC is confounded with motor speed. Another possibility is that processing speed is only related to specific white matter areas. Using inspection time as measure of processing speed and VBM should point out whether processing speed indeed is related to increased speed of cortico-cortical connections by means of increased myelination (Miller, 1994).

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