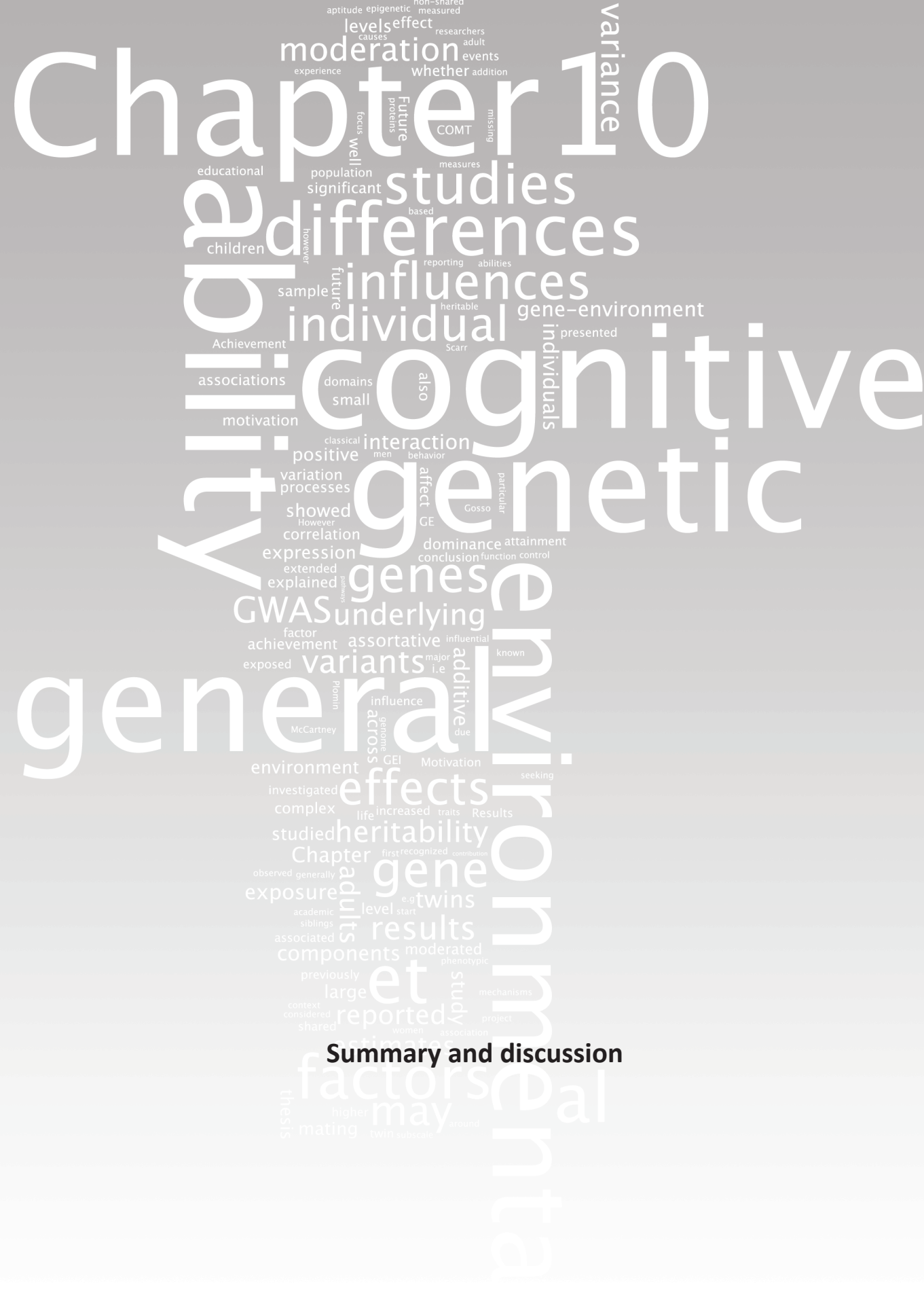
Chapter 10
Summary and discussion

SUMMARY AND DISCUSSION

At the start of this project, it was well recognized that individual differences in general cognitive ability are to a large extent due to differences at a genetic level (Bouchard, Jr. & McGue, 1981; Plomin, 1999), with increasing heritability estimates from childhood to adulthood (Haworth et al., 2009). These estimates were, however, based on classical twin studies in which the possible interplay between genes and environment, and processes such as assortative mating and cultural transmission, were not always considered. In this PhD-project, I aimed to elucidate causes of individual differences in general cognitive ability in adults beyond the regular sources of additive genetic effects, shared environmental effects, and non-shared environmental effects. I investigated four potential mechanisms that might have an effect on heritability estimates of general cognitive ability, namely gene-environment correlation ($r_{(GE)}$), gene-environment interaction (GEI), assortative mating, and cultural transmission. To this end, I collected measures of general cognitive ability as well as measures of putative environmental factors important for general cognitive ability in a large sample of twins and their extended family members (N=1419). The sample included adult twins and their siblings, the spouses of the twins and siblings, and either the parents or the adult children of the twins and siblings. In addition, in an independent sample of adolescent twins, we investigated whether the variance decomposition differed for aptitude (domain-specific skills within the normal ability range) and talent (domain-specific skills of exceptional quality) across different domains of intellectual, creative and sports abilities.

In Chapter 3 of this thesis, we showed that when relatives of twins are included and more sources of variation can be estimated, individual differences in general cognitive ability in adults are not only due to additive genetic and non-shared environmental effects, but also to genetic dominance and genetic variation caused by positive assortative mating. Although considerable spousal correlations have been reported previously for general cognitive ability (Reynolds et al., 2000; Mascie-Taylor, 1989; Jencks et al., 1972; Loehlin, 1978), we were the first to model their effect on the variance decomposition of general cognitive ability within an adult extended twin family design. The results are a valuable addition to previous theoretical studies (Jinks & Fulker, 1970; Fulker, 1982) in which researchers hypothesized that the presence of positive assortative mating may lead to increased genetic resemblance between dizygotic twins, and, if assortative mating is not considered, to increased estimates of shared environmental factors. Our results, however, showed that in adults, classical twin studies generally underestimated influences of genetic dominance, rather than overestimated shared environmental influences.

In Chapter 4, we studied the extent to which specific, measured environmental factors, which have been hypothesized to contribute to individual differences in cognitive abilities, are under genetic control themselves. Results clearly revealed that individual differences in four environmental domains (i.e., *Childhood Environment*, *Social Environment and Behavior*, *Leisure Time Activities*, and *Influential Life Events*) reflected individual differences at a genetic level. Overall, the mean broad sense heritability of these environmental factors calculated across all domains was 49%, implying that factors we tend to call 'environmental' are generally also under genetic control, rendering the terms $r_{(GE)}$ and GEI not fully unambiguous. The significant heritability of various aspects of the

environment as reported in this thesis, nicely adds to discussions on whether and how people shape their own environment (Scarr & McCartney, 1983; Plomin et al., 1985; Plomin & Daniels, 1987). Scarr and McCartney (1983) proposed a developmental theory in which genetic differences were suggested to affect phenotypic differences via passive, active, and evocative gene-environment correlation. By showing that environmental factors putatively related to cognitive functioning and general cognitive ability are not randomly distributed across the population but reflect individual differences at a genetic level, our results stress the role of genetic factors in determining exposure to environmental factors as was suggested by Scarr and McCartney (1983).

Prior to Chapter 6, in which we studied moderation effects of achievement motivation on the variance components underlying general cognitive ability, we studied the factor structure of the Dutch Achievement Motivation Test (DAMT), and the presence of sex-related bias in Chapter 5. Two main underlying factors in the DAMT were distinguished: General Achievement Motivation (with subscales Dedication and Persistence) and Academic Achievement Motivation (with subscales Pressure, Accomplishment, Work Approach, Future Orientation, and Competition). Sex differences were reported for the Dedication subscale, with women reporting higher levels of dedication to their academic work than men, and for the Future Orientation subscale, with women reporting lower levels of future orientation than men. Sex differences were marginally significant for the Competition subscale, with women reporting to be less actuated by competitive motives than men. Furthermore, sex bias was observed for five of the twenty-eight achievement motivation items. These biased items were subsequently eliminated from the analyses in Chapter 6.

In Chapter 6, we studied whether academic achievement motivation and general cognitive ability moderated genetic and environmental variance components underlying educational attainment. Educational attainment was selected as a dependent variable because it is often considered to be influenced by both academic achievement motivation and general cognitive ability, and not the other way around. Results demonstrated that environmental variance components of educational attainment were moderated by general cognitive ability (shared environmental influences were slightly increased in individuals with either low or high levels of cognitive ability) and academic achievement motivation (non-shared environmental influences were considerably increased in individuals with higher levels of achievement motivation). Moderation of genetic variance components was not significant.

In Chapters 7 and 8, we studied whether variance components underlying general cognitive ability were moderated by exposure to influential life events and experience seeking behavior, respectively. Results demonstrated that both genetic and environmental variance components were moderated by exposure to several influential life events (i.e., Retirement, Being fired, Unemployment, Severe offence, Breaking up with friends/relatives, Trouble with friend/relatives, Birth of a child, Death of friends/relatives, and Moving house) and by experience seeking behavior.

The results presented in Chapters 6, 7 and 8 led us to conclude that the relative contribution of genetic and environmental factors to individual differences in general cognitive ability and educational attainment in adults, is not stable across the entire population, but varies as a function of exposure to environmental conditions

and personality factors. These results corroborate to earlier studies that investigated moderation effects on the variance components of general cognitive ability. Moderation effects on genetic influences have been reported in studies in children (e.g., moderation of parental educational level and social economic status; Rowe et al., 1999; Turkheimer et al., 2003; Harden et al., 2007), but had not been replicated in studies based on adults (Kremen et al., 2005; van der Sluis et al., 2008b). We were the first to show significant moderation on genetic influences underlying general cognitive ability in adults.

In Chapter 9, we studied causes of individual differences in aptitude and talent across different domains of intellectual, creative, and sports abilities in a sample of adolescent twins. Results showed that genetic influences explained the major part of the substantial familial clustering in the aptitude measures, heritability estimates ranged from 32% to 71%. Heritability estimates for talents were higher and ranged between 50% and 92%.

All in all, these results imply that the well known large influence of additive genetic effects on individual differences in general cognitive ability in adults partly reflects more complex processes such as gene-environment correlation ($r_{(GE)}$), gene-environment interaction (GEI), genetic dominance, and positive phenotypic assortment.

IMPLICATIONS OF THE RESULTS OF THIS STUDY

This PhD project started in 2006, some years after the completion of the human genome project which greatly facilitated gene finding studies (Collins et al., 2003). In 2006, researchers had investigated a number of genetic variants associated with individual differences in general cognitive ability. The few variants that were putatively associated with general cognitive ability, together explained a very small proportion of the variance (i.e., < 2%). In addition, the majority of those genetic variants had not been replicated, with the exception of the apolopoprotein E (*APOE*) gene (Small et al., 2004), the catechol-O-methyltransferase (*COMT*) gene (Savitz et al., 2006), the cholinergic muscarinic receptor 2 (*CHRM2*) gene (Comings et al., 2003; Gosso et al., 2006b), and the *SNAP25* gene (Gosso et al., 2006a; Gosso et al., 2008). (For an overview, see Posthuma et al., 2009; Deary et al., 2010).

Major advances in genotyping technology led to the start of the so-called 'GWAS' era in 2006/2007. GWAS refers to genome wide association studies, in which hundreds of thousands of genetic variants are genotyped across the entire human genome in thousands of individuals. Together this multitude of genetic variants captures between 60-80% of all genomic variation. At the start of the GWAS era scientists anticipated major results in gene finding studies for highly heritable traits, including general cognitive ability. Four years and ~900 GWAS studies later, the general conclusion of GWAS is that with the exception of some major genes for nearly Mendelian disorders, most GWAS studies detected very few genetic variants and most of these variants explain only a very small proportion of the variance in complex traits (Hardy & Singleton, 2009). This observation has become known as the case of the missing heritability (Maher, 2008). Missing heritability is as true for general cognitive ability as it is for most other heritable, complex traits. Hitherto, no large scale GWAS for general cognitive ability has been conducted. Recently, Ruano et al. (2010) showed in a relatively small GWAS sample of 627 individuals that there were no genome-

wide significant genetic variants associated with general cognitive ability. However, when these researchers looked at the joint effect of multiple genes that were grouped according to cellular function (functional gene group analysis) they were able to demonstrate that the group of genes that code for G proteins (synaptic heterotrimeric guanine nucleotide binding proteins) explained 3.3% of the observed variation in general cognitive ability. Although this effect is larger than any previously reported effect of a single gene on general cognitive ability, 3.3% is still small compared to heritability estimates based on classical twin studies for general cognitive ability around 40% in children and around 80% in adults. The 'missing heritability' thus remains a challenging problem.

The results presented in this thesis may, however, provide important clues for the case of the missing heritability. First, the well recognized large contribution of additive genetic factors (~80%) to individual differences in general cognitive ability seems overrated. Using an extended twin-family design, estimates of additive genetic effects were adjusted downwards when positive assortative mating was taken into account. Additive genetic factors explained no more that 47% of the individual differences in general cognitive ability, while genetic dominance, that was previously assumed to be absent, explained at least 27%. GWAS studies generally assume an additive model as inclusion of non-additive effects in GWAS increases the multiple testing problem and thereby decreases the statistical power to detect association effects. However, if non-additive genetic influences are known to be of importance, such genetic influences should be taken into account in GWAS studies for general cognitive ability.

Second, the estimates of genetic and environmental influences vary as a function of exposure to environmental factors. When this is observed, genes determine an individual's vulnerability to environmental influences which in turn affect general cognitive ability, or vice versa, environmental influences may affect the regulation of gene expression. Statistical associations between genetic variants and general cognitive ability are then diluted. To this end, future research should not merely focus on associations between genetic variants and levels of general cognitive ability, but also on the influence of environmental factors on these gene-trait associations. Alternatively, when particular environmental factors, such as influential life events, control the expression of particular genes, some genes have large effects on individuals exposed to an environmental factor while the same genes may have small or no effects in individuals that are not exposed to this environmental factor. Consequently, associations between these genes and general cognitive ability in the total population may be very low, while associations are expected to be higher in a subpopulation that is exposed to the environmental factor. In this situation, researchers might consider stratifying their study population for GWAS analyses according to the participants' exposure to particular environmental factors (such as life events or experience seeking behavior).

FUTURE PERSPECTIVES

The results presented in this thesis provide recommendations for future study designs (as discussed above), but may also guide future projects that take these results one step further. For example, we showed moderation of genetic effects for cognitive ability genetic correlations between *'environmental'* factors and general cognitive ability. However, we did

not investigate the exact mechanism underlying the moderation and correlation. Questions such as why and on which level moderation occurs (e.g., genes, proteins, neurons), and what kind of biological processes are involved, remain as yet unanswered. A first step to elucidate these processes would be to study moderation effects of reported environmental moderators on influences of a priori selected genes (i.e., candidate genes). Thus far, 'measured gene - measured environment' interaction with respect to general cognitive ability has been reported in one study in children (Caspi et al., 2007). In this study, which is still awaiting replication, the positive association between breastfeeding and general cognitive ability was moderated by a variant in the *FADS2* gene, which is involved in the genetic control of fatty acid pathways. In the context of attention in children, interaction has been reported between the catechol-O-methyltransferase (*COMT*) gene and parenting (Voelker et al., 2009), whereas in the context of adolescents' reading comprehension, interaction has been reported between the *COMT* gene and maternal rejection (Grigorenko et al., 2007). Future moderation studies may focus on genes that previously have been associated with general cognitive ability, such as the *FADS2, COMT, APOE, CHRM2*, *SNAP25* and G-protein genes, and include some of the environmental moderators identified in this thesis. Furthermore, technological progress in microarray technology allows us to identify genes whose expression has changed in response to exposure to environmental influences by comparing gene expression in exposed and non-exposed individuals. Studying genetic variants and gene expression in the context of environmental moderation may clarify underlying mechanisms of interaction and as such increase our understanding of the relation between genes, environment and general cognitive ability.

Alternatively, heritable differences may not only be due to structural differences in the DNA, but also to epigenetic effects (Johnston & Edwards, 2002; Fraga et al., 2005). Recent findings from epigenetic studies may help us to understand the underlying mechanisms of moderation. Epigenetic differences may reveal how environmental influences can affect genetic influences on general cognitive ability (e.g., gene expression or gene methylation levels may be altered by environmental influences). Future studies may focus on whether environmental factors cause epigenetic changes, and how these changes affect individual differences underlying general cognitive ability.

GENERAL CONCLUSION

Based on an extended twin-family study, we showed that the well recognized high influence of additive genetic factors on individual differences in general cognitive ability in adults partly reflects more complex processes such as genetic dominance, positive phenotypic assortment, gene-environment correlation ($r_{(GE)}$) and gene-environment interaction (GEI). The outcomes of the studies presented in this thesis increase our understanding of causes of individual differences in general cognitive ability. Considering the complex interplay between genes and environment in future studies may help us to reveal neurobiological pathways underlying variation in general cognitive ability and understand why people differ in general cognitive ability.