Cognitive performance across the lifespan and domains

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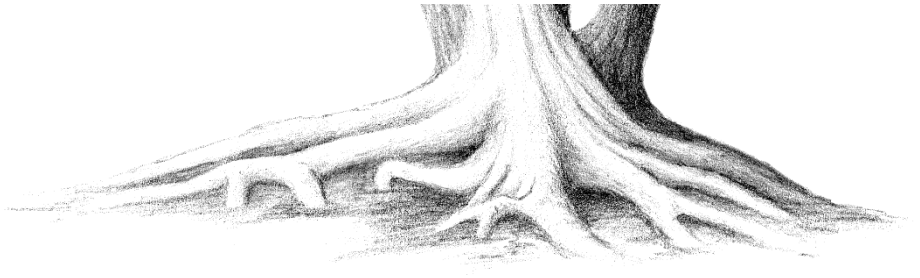
Chapter 9

Summary and general discussion



The present thesis examined the influence of genetic and environmental factors on the individual differences in a broad spectrum of cognitive functions, and in subcortical brain volumes. Two modifiable factors that have been hypothesized to influence cognitive functions, i.e. exercise behavior and blood pressure, were studied in detail, while simultaneously recognizing the influence of age and sex on these factors and the outcome traits.

To assess cognitive functions in a large sample with a large variation in age, we translated and validated the well-known Computerized Neurocognitive Battery (CNB). This battery was originally developed by The Brain and Behavior Laboratory of the University of Pennsylvania, with as the main purpose to provide an efficient method to assess performance in a range of cognitive domains that are linked to specific brain systems. This battery has been applied in genetic and treatment studies in English speaking settings. With the Dutch adaptation of the CNB, data were collected in participants registered with the Netherlands Twin Register (see **Chapter 2 and 3**) ranging in age between 10 and 86 years, including a large group of young twins and their siblings who take part in the longitudinal BrainScale project (van Soelen et al., 2012a).

In this last chapter I give a concise summary of the main results, followed by a discussion that integrates these findings and presents their implications for further research.

Summary

Reading

Perhaps the most crucial skill in the early development of cognitive skills is the ability to read fluently and with comprehension. **Chapter 4** focused on reading ability, and the causes of family resemblance in this trait and related disorders, like dyslexia. To explore whether family resemblance is because of transmission of genes from parents to child, or because of shared environmental factors like the household, reading data of twins, their parents and their siblings were analyzed. A model with phenotype information from parents and their twin offspring enables estimation of parameters representing the genetic transmission from parent to child, as well as cultural transmission (that is, transmission through pathways that are not genetically mediated). Individual differences in reading ability were mainly caused by genetic factors, both additive and non-additive (also known as dominant genetic factors), resulting in a broad-sense heritability of 64%. Environmental factors that are shared between parents and children did not contribute to familial resemblance: no evidence was found for cultural transmission from parents to their offspring. In addition, from the parent data, it was clear that there was significant assortative

mating for reading ability, as there was a spouse correlation of 0.38. This study confirms the widely accepted phenomenon that reading (dis)ability tends to "run in families", but is one of the first to study the nature of the transmission from parents to children. The results of this chapter show that this resemblance is due to the transmission of genes, and that there is no additional contribution from the home-literacy environment parents create.

Computerized Neurocognitive Battery

The Computerized Neurocognitive Battery (CNB) was developed by the Brain and Behavior Laboratory of the University of Pennsylvania, and was translated into Dutch by the Department of Biological Psychology, Vrije Universiteit Amsterdam in close collaboration with drs Ruben and Raquel Gur. Chapters 5, 6 and 7 are based on cognitive data collected using the CNB.

First, in **Chapter 5**, reliability and validity of the Dutch translation of the CNB were established, by comparing several outcome measures to those obtained in the U.S. (Gur et al., 2010). Mean accuracy scores on the tests obtained in the Dutch sample were comparable to the U.S. sample, as were intercorrelations between test scores. Further, high Cronbach's alpha's were reported across tests. The (small) deviations in mean scores and intercorrelations from measures in the U.S. sample were most likely due to the use of shortened tests in the Dutch sample, as well as the wider age range including more elderly participants. Validity was confirmed by similar effects of sex and age in the Dutch and US samples. I further explored these age effects by also including non-linear effects of age into a regression model. Linear and non-linear age effects showed a decline in the performance across tests that accelerated around age 50, though in varying degrees. The decline and its acceleration at higher ages were most notable for speed outcomes. Further, cognitive decline as a result of linear age effects was strong for accuracy on e.g., abstraction and mental flexibility, nonverbal reasoning and emotion identification. Non-linear age effects were strong, besides for speed, for accuracy in attention and working memory. Other domains, like verbal reasoning, also showed strong non-linear effects with a late peak around 40-50 years with relative sparing afterwards.

Further validity was shown by the positive associations between cognitive accuracy and speed with educational attainment, both of participants themselves and of their parents. As a last part of the validation procedure, a latent factor model showed that the variance across accuracy measures of the CNB tests was identical to the variance among traditional general intelligence scales. The correlation of 0.82 between the CNB factor scores and Total IQ indicated that performance on the CNB can be used to obtain an approximation

of general intelligence. This suggests that the CNB has purposes beyond research, and may be meaningful in the clinical neuropsychological setting as well.

The heritability of the CNB's cognitive test performance was estimated for all tests. In the first set of analyses data of mono- and dizygotic twin pairs were analyzed, who are of the same age by definition, and it was estimated to what extent their resemblance was due to shared genes, or to common environmental influences shared by offspring growing up in the same family. The other part of the sample with CNB data consisted of family members of twins: parents, siblings, and children of twins and siblings. Therefore, in the second set of analyses data of all family members were analyzed, where cross-generation resemblance was analyzed simultaneously with the resemblance in twin pairs. Overall, estimates based on twin data closely resembled those that were estimated from family data, demonstrating that, where twins form a perfectly controlled design because of equal environmental factors like age and prenatal environment, heritability estimates from multi-generation data do not differ from those based on twin data. This indicates that it is likely that the same genes for cognition are expressed across the lifespan. Family resemblance was to the largest part due to shared genetic factors, and less so due to shared environmental factors, with moderate estimates with wide ranges for both accuracy (1-52%) and speed (14-50%). The latent intelligence factor extracted from the CNB tests was 70% heritable.

After establishing the influence of genetic factors on the cognitive domains of the CNB, the next two chapters focused on the influence of exercise and blood pressure. Unlike sex and age, these factors can to some extent be modified. If clear relationships exist between these two examples of modifiable influences and cognitive functioning, these would present suitable targets for prevention and intervention of cognitive decline or deterioration.

Chapter 6 focused on a generally accepted phenomenon of beneficial effects of regular exercise on cognitive function. Several sources of heterogeneity were addressed in this chapter, including the definition of the phenotype. This chapter made use of a well-defined and reliable measure of voluntary regular leisure time exercise behavior, so the effect of chronic exercise, as opposed to a single bout, was studied. That is, for each participant the average energy expenditure per week (weekly METhours) was calculated, based on the type of exercise and frequency and duration derived from interview data. In addition, effects were studied across cognitive domains to be able to detect whether certain domains were more sensitive to effects of regular exercise than others. Finally, after initially applying univariate regression models between weekly METhours and

cognitive accuracy and speed, these analyses were repeated while correcting for the significant effects of sex, age, and age^2 that were detected in Chapter 5. The univariate models suggested mainly positive associations between weekly METhours and cognitive functions, but after correction for sex and age these associations were small to absent. Even though the relationship may seem intuitive, and is generally accepted by lay people and professionals alike, results of this chapter suggest that in the existing literature, effects of age, sex and exercise on cognitive performance may be confounded.

The associations between cognitive functions and blood pressure (BP) are suspected to be complex, since harmful effects of both high and low BP have been reported, and high BP may be beneficial in specific clinical (e.g., elderly) samples. Therefore, in **Chapter 7** linear and nonlinear effects of diastolic and systolic BP across cognitive domains were studied. In these analyses, cognitive function and BP were corrected for effects of age (linear and quadratic) and sex. Secondly, the possibility that any association between BP and cognition is not necessarily causal was tested. This was done through analyzing data of the monozygotic twins, comparing cognitive test scores of the twins with the higher BP to the co-twins with the lower BP. As monozygotic twins are of the same age and sex, and can be assumed genetically identical, any difference in their cognitive scores must be due to the difference in BP. Causality would be indicated when the MZ twin with the higher blood pressure than the co-twin showed reduced cognitive functioning. Both types of analyses in this chapter failed to provide evidence for a causal effect of blood pressure on cognitive functioning.

Subcortical brain volume

Heritable individual differences in cognitive functioning have been linked to differences in total brain volumes and to measures in cortical structure (Brouwer et al., 2014; Jung & Haier, 2007; Posthuma et al., 2002). Recently, in a large imaging-genetics study genes for subcortical structures have been identified (Hibar et al., 2015), clearly adding to the validity of heritability estimates of subcortical structures in adults (e.g., den Braber et al., 2013a) and in children (e.g., Yoon et al., 2011). However, studies in children are scarce. **Chapter 8** is based on data from a longitudinal study in which magnetic resonance imaging (MRI) scans of the brain were made in addition to cognitive testing. Brain volume data of seven subcortical brain volumes (thalamus, hippocampus, amygdala, putamen, caudate, pallidum and nucleus accumbens) of twins at age 9 and 12 of age were analyzed. First, changes in volume between ages were investigated. Increases in volume were seen for left and right hemisphere volumes of the thalamus, pallidum, hippocampus and amygdala, while volumes of the caudate, nucleus accumbens, and putamen (bilaterally in boys; right-sided only in girls)

decreased. In a bivariate genetic model, effects of genes and environment were estimated at both ages, showing that heritability of all volumes is high from childhood onwards with no evidence for new genetic effects at age 12. Even though the brains of boys and girls show slightly different volumes and develop in a different pattern, genetic effects were similar for boys and girls.

Discussion

This thesis combines cross-sectional and longitudinal data to explore to what extent genetic and environmental factors explain individual differences in cognitive functions throughout life. To do so, multiple indicators of functioning across a wide selection of cognitive domains were obtained in a large twin-family based sample. This effort does not stand alone, as previous twin studies have addressed the genetic architecture of cognition (Polderman et al., 2015). A relatively large amount of these twin studies on cognition are based on measures of general intelligence, as assessed by psychometric IQ tests. These studies have consistently found that heritability of intelligence increases from childhood into adulthood, up till about 80% (Haworth et al., 2010), consistent with findings from several longitudinal studies in Dutch children, which reported increasing heritability of intelligence from (young) childhood into adolescence of about 30 to 60% (Bartels, Rietveld, van Baal, & Boomsma, 2002; van Soelen et al., 2011). Similar increases are seen for verbal and performance IQ (Hoekstra, Bartels, & Boomsma, 2007).

As has become apparent in this thesis, however, different cognitive functions show different sensitivity to sources of genetic and environmental variance. Moreover, the genetic variance is much smaller than that of summary measures like IQ. We found hardly any influence of genetic factors on abstraction and mental flexibility, and most other cognitive functions tested by the CNB showed only small to moderate heritability. These results are congruent with those of a number of previous twin studies addressing the heritability of cognitive test performance on reaction time tasks, working memory tasks, memory tests, attention tests, and WAIS-intelligence subscales and -tests (Kan et al., 2013; Kremen et al., 2011; Kremen, Eisen, Tsuang, & Lyons, 2007; Polderman et al., 2009). The overarching conclusion is that tests of separate cognitive functions are less heritable than more general measures of intelligence. There are two major reasons for this finding that are not mutually exclusive. First, following the logic of 'generalist genes' (Plomin & Kovas, 2005), there may exist a number of genetic variants that have a small but directionally consistent effect on multiple basic cognitive functions. As IQ scores reflect the synergy of all these functions, i.e. the sum of their main effects and any possible interaction terms, the relatively small genetic contribution to each basic cognitive function adds up

to a larger genetic contribution to the so-called 'g-factor'. Likewise, assuming that the measurement errors of each of the tests of basic cognitive functions are uncorrelated, any summary measure of the joint performance on all tests (like IQ) may have a reduced measurement error compared to individual tests. This would lead to higher heritability estimates for IQ as measurement error is part of E.

Our findings showed that research on general cognitive ability can be served by a detailed neurocognitive battery as the latent factor derived from the subtests gives the same answers as using full scale IQ. However, the main aim for developing such batteries has of course not been to replace IQ tests. The raison d'être for these tests is their clinical use in the neuropsychological setting. Many more traditional tests of cognitive functioning are developed to be sensitive, and most ideally specific, to dysfunction that is part of a certain disorder or disease. They were therefore most often not developed to be sensitive to individual differences in cognitive performance. The Computerized Neurocognitive Battery (CNB) was shown in Chapter 5 to be able to validly measure individual differences in a multitude of cognitive domains.

Originally, the CNB cognitive domains were selected because they correspond to specific brain systems. This link between cognitive function and brain system would provide clinical utility since it provides endophenotypes, or biomarkers, of psychopathology. This has been validated in two ways. First, Roalf et al. (2014) confirmed the association of the CNB domains to different brain systems. Although execution of the tests in the five neurobehavioral functions showed some overlap in activated brain areas, there was also test-specific activation of brain systems consistent with other neuroimaging studies. The test of mental flexibility and abstraction activated mainly frontal areas, the attention test activated the frontal-parietal network, the episodic memory tests activated frontal and temporal regions, and the emotion test activated temporo-limbic regions.

The robustness of the structure of the cognitive domains of the CNB is further attested by using different ways of analyzing the performance data. All chapters in this thesis report on analyses that are performed separately for speed and accuracy, but it is also possible to analyze efficiency scores, which are calculated as follows: accuracy / log(speed). Efficiency scores may be most directly comparable to traditional cognitive tests, where speed and accuracy scores are often confounded. However, analyzing them separately would be preferable, as the relation between accuracy and speed may differ per test: they may interact and show a trade-off where a better accuracy score requires longer deliberation before responding. Efficiency scores of tests belonging to the same

cognitive domain showed factor loadings that aggregated within their domains, varying between .45 and .79 (Moore, Reise, Gur, Hakonarson, & Gur, 2015). However, there was a high correlation between the Complex cognition factor and the Executive control factor (.94), suggesting that they are basically the same construct. This was replicated when accuracy scores were analyzed. However, speed scores provided two factors, one for tests that require deliberation, and one for tests that require fast responses and vigilance (attention, working memory, and motor test). Interestingly, correlations between factors were quite high (between .64 and .78), suggesting the presence of an underlying factor that influences all tests. This corresponds to the common factor that was found in Chapter 5.

Sex differences and cognitive functioning across the age range

Sex differences are present across cognitive domains, but they are often of small magnitude, as is clear from the data reported in Chapter 5. While sex differences in certain domains are present in childhood already (Gur et al., 2012) it is unlikely that large and global sex differences exist in cognitive functioning. Prudence dictates that sex is treated as a covariate in cognition research, but generally results will not be strongly affected if one fails to do so. This contrasts sharply with the differences in cognitive functioning found across the life span. This thesis clearly shows that age is a factor that strongly determines cognitive test performance. Moreover, as was shown in Chapter 5, the age effect has significant linear as well as non-linear components for most cognitive domains.

A first source of the deviation from a linear age effect is seen in the period from childhood to adolescence. Accuracy in these domains shows a clear increase in children age 8 to young adults age 21 (Gur et al., 2012). Improvement of cognitive function was most pronounced for executive functions (attention specifically) and motor speed. However, memory was quite good at young ages already and showed relatively minor improvements after age 8. Cognitive development in puberty and adolescence is accompanied by changes in the brain. Specific brain structures develop at a different speed (Gogtay et al., 2004; Lebel & Beaulieu, 2009) and it is possible that the differences between domains of cognitive development are related to differences in timing of local brain development. The developmental patterns of cortical thickness (Brouwer et al., 2014; Burgaleta, Johnson, Waber, Colom, & Karama, 2014; Schnack et al., 2015; Shaw et al., 2006), gray matter density of the cortex (Ramsden et al., 2011) and the white matter network (Koenis et al., 2015) are associated with the level of intelligence, and depend on the brain region. These developmental patterns could be crucial for healthy development, as deviations from this pattern have

been associated with psychiatric disorders (Giedd et al., 2015; Greenstein et al., 2006; Paus et al., 2008; Rapoport & Gogtay, 2008).

There may be valuable information in the individual differences in this maturation process. This was illustrated by Erus et al. (2014) who derived a brain development index in participants up to age 22. This index can identify subjects with brain maturation delay or those who are ahead of their chronological age. Interestingly, subjects with a brain development index that is higher than their age showed better cognitive processing speed on CNB tests, rather than better accuracy.

Whereas cognitive function shows increasingly better performance during the childhood and adolescent years, performance levels peak relatively early in adulthood followed by a decrease towards older ages. This decrease is a second source of the non-linear age effect as it shows acceleration for some but not all of the cognitive functions. Accelerated loss is most apparent for accuracy on the executive function domains, whereas verbal reasoning shows less decrease into old age, probably caused by an increasing number of words existing in the lexicon. It is tempting to explain the non-linear effect of age in the elderly population as a superposition of normal 'linear' cognitive aging and pathological aging in a subset of the elderly, the size of which grows with increasing age. Naturally occurring brain atrophy is suggested to start in early adulthood, and is reflected in altered function, structure and perfusion of the brain (Tarumi & Zhang, 2015). This pathological aging can be related to the various forms of dementia that take an increasing toll on Western societies with a vast burden to these individuals, their families and society. Even before the onset of dementia, declines in memory cause many elderly significant stress and worry. Different types of dementia's are sometimes directly related to neurological abnormalities, like neurofibrillary tangles in Alzheimer, or to vascular damage in frontotemporal dementia. Where loss of neurons is a part of Alzheimer pathology, this does not occur in normal aging. Human and animal studies suggest that normal aging co-occurs with variations in synaptic integrity and plasticity, possibly in networks that are involved in memory and executive functions. Understanding cognitive aging is complicated for several reasons: even at older age the plasticity of neurons enables learning of new or improved skills; general decline may become (temporarily) interrupted by for example stress or medication; or because certain people may more easily find compensatory strategies for their problems (Blazer et al., 2015). This may explain the relatively recent interest in mild cognitive impairment (MCI), an interim clinical diagnostic phase sometimes preceding onset of dementia, but not necessarily so. Because of the impact of even mild cognitive problems on every-day life and wellbeing, biomarkers are required that will predict which persons

will continue to develop severe cognitive problems. Thus far, sensitive biomarkers that can reliably diagnose and predict deviations from normality have been difficult to find.

A thorough understanding of normal cognitive and brain development throughout life will have great clinical utility, as it may provide "growth charts" that may form an instrument to detect deviations or delays from normality. Such understanding may prove crucial for optimizing detection of, and intervention on, impaired cognitive functioning. It is therefore important to know which factors contribute to stability of these traits, and which factors may provide opportunities for change. The present thesis is based on data of both a longitudinal and a cross-sectional study. Ideally, these two types of studies should be combined more often. The strength of the BrainScale study is that it includes a sample of twins that are nearly of the same age, thus minimizing effects of age. Longitudinal designs track individual change and stability over time, and are therefore optimally suited to study cognitive and brain development. However, longitudinal testing of cognitive performance might lead to decreased reliability because of possible test-retest effects. This would mean that the fact that one has previous experience with test administration will influence their scores on a consecutive occasion (Salthouse, 2009). On the other hand, cross-sectional studies cannot control for cohort effects like the Flynn effect (Hofer & Sliwinski, 2001). The Flynn effect is the phenomenon where intelligence in the population increases with time. Both designs have their merits and their disadvantages, and by combining them, a more comprehensive understanding of sources that cause both inter-individual and intra-individual differences will be obtained. An attractive alternative is the parent-offspring design, which can be seen as a 'short-cut' to longitudinal studies and which is well suited, as I showed for reading, for traits that are heritable.

Genetics of brain structure

It is now well known that heritability of global measures of brain (e.g., total brain volume) and cognition (e.g., intelligence) is high. In this thesis I show that measures of subcortical brain structures are highly heritable too and that this is already true in childhood (Chapter 8). This is just a beginning. The field of behavior genetics has in the past decades developed tools to move beyond the first crucial step of estimating the contribution of genetic factors to a variety of traits (Polderman et al., 2015). It is now feasible to study interactions of the genome with sex, age and environmental exposures (GxE interaction). These studies address the difficult questions of genotype-environment covariance, as arising for example from cultural inheritance, decomposing the covariance or comorbidity among traits and studying the longitudinal stability and change in

phenotypes as a function of genes and environment and their interplay (de Kort et al., 2014).

To this new twin methodology the genomic era has added many tools that allow us to go beyond sheer biometric modeling of (latent) genetic effects. Genetic (or genome-wide) association (GWA) studies measure associations of phenotypes with genetic markers covering the entire genome with the aim of identifying the actual causal variants. Because these tests involve large amounts of markers, GWA studies depend on large sample sizes to overcome the large burden of multiple tests. Until recently, performing GWAS on MRI data was difficult because this expensive way of data collection results in relatively small sample sizes. For this reason, the Enigma consortium was established, providing protocols for centers around the world to be able to perform a GWAS on their data (Thompson et al., 2014). After this, results are pooled, resulting in sample sizes large enough to obtain reliable results. One of the efforts undertaken within the ENIGMA consortium was a GWAS on the subcortical brain structures, obtaining several genetic variants related to volume of the hippocampus and putamen (Hibar et al., 2015; Stein et al., 2012).

Genetics of cognitive performance

Specific cognitive functions do not show heritability estimates similar to intelligence or academic achievement. Heritability estimates of cognitive domains are mostly low to moderate (Chapter 5), where reading ability was relatively high (Chapter 4). Heritability of reading and the cognitive domains of the CNB were obtained from samples with a wide age range, and include family pedigrees. These types of analyses thus assume that sources of variance are of equal magnitude for all members in a family, regardless of age. In Chapter 5 heritability was estimated in a twin group as well, in which similar estimates were obtained. This confirms that estimates of genetic and environmental factors are not biased due to this assumption. This provides further opportunities, as this shows that heritability analyses do not necessarily have to include twins, but can be based on nuclear families in a reliable way as well.

For intelligence, a greater number of GWA studies have been performed (e.g. Benyamin et al., 2014; Davies et al., 2011). Several genetic variants were replicated across studies (often expressed in the brain) and across related phenotypes, like educational achievement and school performance (Rietveld et al., 2013; Ward et al., 2014). These genome-wide association studies offer great possibilities to understand the biological pathways to behavior and disorders, even though most behavioral phenotypes are most likely affected by a great number of genes, all with small effect sizes, and related to environmental factors (Davies et al., 2011).

Modifiable effects on cognitive performance

The relatively moderate heritability estimates of performance on tests in the five neurobehavioral functions of the CNB make clear that a moderate to large part of the variance in these functions is caused by environmental factors, leaving room for intervention on the part of the environmental factors that can be modified by behavioral or pharmacological approaches. In Chapter 6 and 7 two such variables were investigated: exercise behavior and blood pressure, both of which are viable targets for intervention. To explore the possibility of beneficial effects of exercise and low blood pressure on cognition, a multitude of cross-sectional studies has tested the association between these variables. This has led to conflicting results. After addressing major sources of heterogeneity in the findings, this thesis found no evidence that regular voluntary exercise in leisure time or low blood pressure are associated with benefits for cognitive performance across the five cognitive domains tested.

It is important to note here that these null-findings do not preclude possible beneficial effects in specific samples. Chapter 6 replicated previous findings: that individuals with attention deficit hyperactivity disorder may benefit from regular exercise as performance on the attention test was positively associated even after taking age and sex into account. In addition, in the elder part of the population, the subset of individuals with beginning pathology, which was very small in our sample, may still prove responsive to physical activity intervention. Several studies have shown that regular and aerobic exercise attenuate the decline in cognitive performance, linked to a protective effect on brain structure and function (Colcombe & Kramer, 2003; Erickson et al., 2011; Steves, Mehta, Jackson, & Spector, 2015). Tarumi and Zhang (2015) further describe how aerobic exercise benefits brain functions, through improvements in arterial pressure regulation (less risk of stiffening of the aorta, atherosclerosis and high blood pressure), blood flow homeostasis (better perfusion of the brain) and metabolic waste clearance (preserving blood supply). Finally, the cognitive effort that is part of exercise activities may itself also account for cognitive improvements (van der Niet et al., 2015). An added complexity is that little is known about the optimal dose of exercise to protect cognition. While it is likely that exercise should be of moderate to vigorous intensity in order to cause substantial benefits, too strenuous or insufficient recovery time may have adverse effects, causing atrophy and lesions in brain matter (Tarumi & Zhang, 2015).

Concluding remarks

This thesis has addressed influences of age, sex, education, heritability and environmental factors across a range of cognitive domains. Potential

determinants of cognitive performance that could be modifiable, exercise behavior and blood pressure, did not show effects on cognition in this general population sample. Clearly, not every person may benefit equally to the same type of intervention. Genetics may offer suggestions for interventions, by suggesting which pathways are involved when networks of genes are found in GWA studies. To create optimized, and maybe even personalized, prevention and intervention options for the young and old, genetically sensitive studies should ideally be combined with longitudinal studies. These are optimally suited to understand the factors that cause individual differences in trajectories of development and aging.

While the majority of cognitive and neurobiological studies is aimed at understanding abnormal development and behavior, disease and disorders, studies in healthy population samples are equally important. This thesis has provided substantial first input for a normative database on cognitive functioning across the lifespan, which will hopefully will be extended by future endeavors using the CNB. This database will help us address a number of pressing questions on the complex effects of genetic and modifiable factors on cognitive functioning, and the intermediate role of brain structure and function.