Cognitive performance across the lifespan and domains

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Chapter 1

General introduction

Cognitive functioning refers to a person's ability to process thoughts and use existing knowledge to generate new knowledge. It encompasses the set of all mental abilities and conscious and unconscious processes related to for example attention, memory and working memory, judgment and evaluation, reasoning and "computation", problem solving and decision making, speech and comprehension of language. In most healthy individuals the brain is capable of learning new knowledge in each of these areas. This capacity is most notable in infanthood and early childhood, the periods of time when most humans are best able to absorb and use new information. Children learn new words, concepts, and ways to express themselves on a weekly or even daily basis. The capacity to learn slows down as the individual ages, but overall cognitive function should not diminish on a large scale in healthy adult individuals. In later adulthood, however, effects of cognitive aging will increasingly come in play, although not equally strong in all domains. Functioning in some cognitive domains decreases predictably, such as speed of information processing and working memory, whereas functioning in other domains can be maintained or even improved with aging, such as vocabulary, knowledge and wisdom (deeper understanding to apply knowledge, Blazer, Yaffe, & Liverman, 2015).

Cognitive functioning is associated with multiple components of mental health and well-being: cognitive dysfunctions (in attention, working memory, executive functioning and memory) are often part of psychiatric disorders (e.g., schizophrenia and depression), or a key component in developmental disorders like dyslexia (reading problems), dyscalculia (arithmetic problems), attention deficit hyperactivity disorder (ADHD) or autism (characterized by social and communication problems, and repetitive and inflexible behaviors). Optimal development and maintenance of cognitive abilities is therefore of great importance to all members of the population: not only to excel in academics or work, but also to reduce problems in everyday life. In older adults, staying sharp of mind and retaining a good memory is a major concern as they impact on the ability to carry out daily activities and retaining autonomy and quality of life (Blazer et al., 2015). Cognitive aging presents an important societal challenge as our current society is faced with increasing numbers of elderly people, with an expected increase in the percentage of people of over 65 years in Europe from 14% in 2010 to 25% in 2050 (World Health Organization, 2015).

Within psychology, the concept of cognitive functioning is closely related to abstract concepts such as mind and intelligence, and global indices of cognitive functioning are often indexed by general intelligence ('IQ') or educational achievement. However, many more separate cognitive functions, like attention, working memory, reasoning or emotion processing, can be assessed separately by a variety of neurocognitive tests. Whether operationalized as intelligence or as the performance on neurocognitive tests of more specific cognitive skills, large individual differences are found across the entire life span. In view of the importance of cognitive functioning for mental health and well-being in everyday life, understanding the determinants and modifiers of these differences remains a major research mission.

Causes of individual differences

Multiple factors cause differences between individuals in their level of cognitive functioning. Two of these, age and sex, are fixed effects that cannot be changed by any intervention. They should always be taken into account in the analysis of individual differences as they can exert substantial effects. This is most evident for age. During childhood and adolescence many cognitive functions are still developing, whereas cognitive performance gradually declines during older age (Salthouse, 2009).

Sex differences for some cognitive functions are apparent already during childhood (Gur et al., 2012) and further increase during adolescence. Sex differences may be related to the fact that males and females differ in hormone levels as well as brain structure, but sociocultural factors have also been suggested to play an important role (Halpern, Benbow, Geary, Hyde, & Gernsbacher, 2007). The most commonly suggested sex differences are a female advantage for verbal skills and a male advantage for spatial skills. However, sex differences may not be limited to these domains but also be present in, for example, memory functioning (Andreano & Cahill, 2009). Men and women appear to differ in their sensitivity to effects of cognitive aging, with cognition in women relatively more spared (Maylor et al., 2007). This sex by age interaction is complicated by detrimental effects of menopause. However, overall, meta-analyses suggest that for the majority of traits sex differences are small or trivial (Hyde, 2014).

Even when accounting for age and sex by stratification or covariate analysis, vast individual differences in cognitive abilities remain and these differences are seen across the large arsenal of neurocognitive tests available. Performance on these neurocognitive tests relies on the activation of specific brain areas and networks, and this activation also differs among people. Functional magnetic resonance imaging (fMRI) studies have shown that intelligence is associated with neural activation patterns and brain connectivity (Bassett et al., 2009; Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012; Koenis et al., 2015; Langer et al., 2012; Park & Friston, 2013; Ramsden et al., 2011). Further, more efficient brain networks are associated with higher intelligence scores (Schmithorst & Holland, 2007; Song et al., 2008; van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009).

Neurobiological markers are not only associated with cognitive functioning, but with other components of mental health as well, as abnormal structure and function have been shown for the majority of psychiatric disorders (Etkin, Gyurak, & O'Hara, 2013).

Currently, many studies focus on trajectories of abnormal brain development, in addition to structural alterations at a specific time point (Giedd et al., 2015; Gu et al., 2015; Rapoport & Gogtay, 2008). This stresses the importance of healthy brain structure and function for normal cognitive and mental functioning. The brain is still under intense development in children and adolescents. Of special relevance is an understanding of brain development during adolescence, as the brain undergoes extensive reorganization both structurally and functionally during this period of life, when there is significant cognitive, emotional and social development but also the highest incidence of onset of psychiatric disorders (Lenroot & Giedd, 2006; Paus, Keshavan, & Giedd, 2008). Knowing which factors influence variation in brain structure and function throughout the lifespan provides insight into the pathways guiding normal and abnormal brain development, and ultimately into mechanisms underlying neuropsychiatric disorders.

Genes and environment as causes of individual differences

The etiology of variation in cognitive and neurobiological functioning is for a significant part explained by genetic differences between individuals. Studies of general intelligence (IQ), brain volume and brain function indicate that these traits are under relatively strong genetic influence, although the size of heritability estimates (the proportion of total trait variance explained by genetic factors) may depend on age. In this sense, age not only influences the level of cognitive function of an individual, but also modifies the importance of genetic factors.

The heritability of IQ is well established and increases from childhood to adulthood (Haworth et al., 2010), but the heritability of specific cognitive skills is less clear, partly because fewer studies have focused on the assessment of specific skills, and partly because a broader range of instruments has been used across studies. For brain volumes and brain function, a similar situation exists. The heritability of global brain volumes (e.g., total brain, total grey matter and total white matter volume) is high (Peper, Brouwer, Boomsma, Kahn, & Hulshoff Pol, 2007; Thompson et al., 2001) and well established, whereas fewer studies have focused on more specific indices of brain structure and function (Blokland, de Zubicaray, McMahon, & Wright, 2012). For brain function, as assessed by fMRI or ERP studies in twins and families, heritability tends to be somewhat lower (Jansen, Mous, White, Posthuma, & Polderman, 2015).

Interestingly, several studies have shown that the association between intelligence and brain structure and function is, at least to a large extent, due to shared genetic factors (Brouwer et al., 2014; Koenis et al., 2015; Posthuma et al., 2002).

In genetic epidemiological studies, that make use of the classical twin design, the environmental factors are operationalized as latent factors in e.g., a structural equation model and there is no need for their measurement. The term environmental factors in such models contains all influences on a trait that are modifiable. In this thesis, these factors are labelled under 'environment' at least to the extent that these factors are not themselves caused by genetic factors (Vinkhuyzen, van der Sluis, de Geus, Boomsma, & Posthuma, 2010). When considering cognitive performance, two concrete examples of modifiable environmental influences may be lifestyle factors and current physical health. Modifiable lifestyle factors that are of specific interest include diet and lack of exercise, and physical health includes risk factors for cardiovascular disease, of which chronic hypertension has long been postulated to influence cognitive and brain functioning. For example, people lead increasingly sedentary lifestyles as there is less physical exertion necessary for means of transportation, during day jobs and leisure time activities. It has been suggested that increasing physical activity levels might prevent dementia, and help maintain good brain function in the elderly (Hooghiemstra et al., 2012). In addition, the prevalence of hypertension is increasing, in part because of the increased prevalence of obesity, whereas successful antihypertensive treatment is available. If cognitive functioning is affected by blood pressure, a clear opportunity would present itself. However, the currently hypothesized relationships between exercise and cognitive function and between blood pressure and cognitive function are not supported by uniform and abundant empirical data (Novak & Hajjar, 2010; Singh, Uijtdewilligen, Twisk, van Mechelen, & Chinapaw, 2012).

Measurement of individual differences in cognitive functioning

Individual differences in specific cognitive functions have thus far been studied less frequently and less comprehensively than studies of general intelligence. Different aspects of cognitive performance tend to be positively correlated, but such correlations are not very high. Therefore, measurement of cognitive functions would ideally be performed using instruments that assess the entire cognitive spectrum and distinguish effects of accuracy and speed.

The Brain and Behavior Laboratory of the University of Pennsylvania has developed a test battery that aims to provide exactly this opportunity. For the past few decades, they have been developing and optimizing the web-based Computerized Neurocognitive Battery (CNB), that enables a fast and easy, but yet comprehensive and reliable assessment of the entire range of cognitive functions (Gur et al., 2010). First, the test battery is computerized and web-based, which has several advantages. Test scores will be less influenced by effects due to the researcher collecting the test data, as test instructions are highly standardized and test scores are not sensitive to errors in scoring and calculating. Secondly, there is less of a paper trail compared to traditional pen and paper tests, which is in particular an advantage for studies involving large numbers of participants. Further, the easy and quick assessment creates possibilities for including large numbers of participants in a study.

This makes the CNB a suitable instrument for all studies requiring large sample sizes, for example genome wide association studies. Importantly, test scores on the computerized version compare well to traditional test instruments measuring the same cognitive constructs, and tests have shown to be sensitive to cognitive dysfunctions seen in for example schizophrenia (Gur et al., 2001a; 2001b). In addition, whereas traditional test scores are often based on accuracy, and sometimes use a time limit or response time as the outcome variable, all tests of the CNB (with exception of the motor test) provide an accuracy score and median response time (of all correct responses). Finally, tests were designed to activate specific brain areas: these neuroscience-based tests thus reflect distinct mental processes.

The research in this thesis describes the validation of the Dutch CNB and the analysis of data collected with the CNB in a large Dutch sample, which includes a subgroup of children who are part of BrainScale (van Soelen et al., 2012a): a longitudinal project that follows twin pairs and their siblings from age 9 into adolescence and assesses brain structure, hormone levels and cognition. In this thesis, I seek answers to questions such as: are individual differences in cognitive function and brain development mainly due to genetic factors, and how do effects of genes and environment differ for different cognitive functions? And to what extent do lifestyle and health related factors such as exercise and blood pressure influence cognitive performance?

To address such questions, studies should be carried out in samples that are representative of the general population. Twins are born in every country worldwide, and in many countries, including the Netherlands, and their numbers are increasing (Glasner, van Beijsterveld, Willemsen, & Boomsma, 2013). In the Netherlands, the majority of all twins are dizygotic, meaning that they originate from two individually fertilized egg cells. This makes them genetically as similar as other brothers and sisters: they share on average 50% of their segregating genes. Other twins are monozygotic, originating from a single fertilized egg cell that, for unknown reasons, splits within the first days after gestation. This results in two individuals who are genetically identical; they share the same DNA sequence. As far as we know, differences at the sequence level are very rare in identical twin pairs (van Dongen, Slagboom, Draisma, Martin, & Boomsma, 2012). Both monozygotic and dizygotic twins share a part of their environment, including prenatal effects, and grow up in the same household and neighborhood, and possibly attend the same school. Of course, both are also exposed to environmental factors that are unique to the individual (for example friends or activities they don't share with their co-twin) and a large proportion of twins will attend separate schools.

The classical twin design uses the difference in genetic similarity between mono- and dizygotic (MZ and DZ) twins to estimate the proportion of total variance in a trait that can be attributed to genetic factors, to shared environmental factors, and to unique environmental factors (Plomin, Defries, Knopik, & Neiderhiser, 2013). In this thesis, some chapters will be based on data from MZ and DZ twins, other chapters include additional family members of twins that took part in the data collection. These additional family members allow for extra hypotheses to be tested, most importantly the hypothesis that cultural transmission may play a role in explaining resemblances of family members.

Outline of this thesis

This thesis addresses neurocognitive test performance across the entire spectrum, across sex and across all ages, and explores how individual differences can be explained by genetic and environmental factors, lifestyle factors in particular.

First, in **chapters 2 and 3** an overview of the main research projects that form the basis of this thesis are described, with respect to the sample of participants and the data collection.

Chapter 4 turns to reading, an important developmental ability that often shows familial risk, where parents with dyslexia have a high change of offspring with reading problems. This chapter explores whether family resemblance for reading (dis)ability might be due to transmission of a genetic liability or due to family environment, including cultural transmission from parents to offspring. In this study, the participants consist of parents and their offspring (twins and siblings).

This design makes it is possible to study cultural transmission from parents to offspring, that is, factors not included in genetic transmission. Further, this design enables a correction of heritability estimates for assortative mating, the phenomenon where partners resemble each other on a given trait. As a result of (strong) assortative mating, siblings (and DZ twins) will be more than 50% genetically alike, which will influence the estimates of the variance components for a trait: estimates of the shared environment will be overestimated and heritability will be underestimated.

The Dutch translation of the CNB first required careful validation, which will be presented in **chapter 5**. In this chapter, I report on reliability indices and effects of age, sex and education on test performance of the CNB. In addition, the possibility of using the CNB as a proxy for traditional intelligence batteries is explored. Next, linear and non-linear effects of aging are presented, and finally heritability of all tests is presented based on analyses in twins, as well as the entire pedigree.

In the next part of the thesis the CNB is used to explore the importance of regular exercise behavior and high blood pressure for individual differences in cognitive functioning across the 17 different domains of the CNB. In **chapter 6** the effect of voluntary exercise behavior on cognitive performance is assessed, while controlling for potential important confounders (sex and age). In **chapter 7** the association between blood pressure and cognitive performance is assessed, again controlling for sex and age.

Neurocognitive testing involved a large sample of children whose brain development had been followed from age 9 onwards. **Chapter 8** examines the heritability and development of subcortical brain volumes during childhood. In a longitudinal twin study, the extent to which subcortical brain volumes are influenced by genetic factors at ages 9 and 12 is explored. This design enables the possibility to test whether new genes are expressed at age 12 and whether there is evidence for genotype by sex interaction. The results are discussed in the broader context of other studies (mainly in adults) on heritability of subcortical structures.

The thesis concludes with a summary and discussion and includes a series of Appendices that detail the data collection and the procedures used to approach and recruit the twin families in these projects, whom I very much want to thank and acknowledge. Without their participation this project would not have been possible.