The aim of this thesis was to explore how genetic and environmental influences affect brain maturation and cognition around puberty in an epidemiological sample of children from the general population in the Netherlands. For this purpose, a large cohort of children was studied within a three year interval. The sample was recruited from the Netherlands Twin Register (NTR) and consisted of 112 families at baseline, including 9-year-old twins and an older sibling. There were 89 families (80%) who returned for the follow-up assessment. Data on cognitive abilities were collected with psychometric IQ tests and a comprehensive neuropsychological testing protocol. Brain anatomy was acquired by 1.5T magnetic resonance imaging (MRI).

9.1 Summary

The studies described in this thesis all include an epidemiological sample of children, aimed to obtain a population based sample from across the Netherlands (see **Chapter 2**). This thesis includes studies of genetic and environmental influences covering a broad range of aspects of structural brain maturation and cognition. See for an overview of the main findings Table 9.1. The aim of these studies was to gain insight into how events around birth can have an effect on brain development and cognition in later life, to describe the extent to which genetic factors influence individual differences in brain development and cognition and to study the relation between brain structure and cognition at ages 9 and 12 years. Its strength includes the large group of twins followed longitudinally with narrow age range at both assessments. This longitudinal, genetically informative design allows modeling of genetic influences across development. The key questions that were addressed are whether the same genes act across ages 9 and 12 years, or whether there are age-specific genetic factors that are expressed at one age but not at another, to what extent genetic and environmental influences act on structural brain changes between 9 and 12 years of age, and to what extent genetic and non-genetic influences on cognition and brain structure overlap. In this last chapter the main results of the study are summarized and their implications for further research are discussed.

Effects of premature birth

The aim of **chapter 3** was to assess the effects of gestational age (i.e. pregnancy duration) and birth weight on brain volumes and cognition at a later age. Nine-year-old twins (N = 192 twins) were included in this study with a gestational age between 32 and 40 weeks and within the normal range of birth weight, from 1525 to 3820 g. The main findings of this study were that shorter pregnancy duration was associated with a smaller cerebellar volume at the age of 9 years, when correcting for birth weight, gender, and age at scanning. A lower birth weight was also associated with lower intelligence quotient (IQ) at age 9, but this effect disappeared when intracranial volume differences were taken into account. This study, in a population-based sample of children, contributes to the understanding that long-term effects of preterm birth are not limited to the group of very preterm infants or infants born with very low birth weight.

Heritability of cognition

Chapter 4 and **chapter 5** focus on the influence of genetic factors on cognition throughout childhood and adolescence. In **chapter 4**, the genetic background of verbal learning, was studied in detail. The Dutch version of the Auditory Verbal Learning Test (AVLT) was used to assess individual

differences in dynamic measures of verbal learning ability in children. In this study 9-year old twins (N=112 twin pairs) and an older sibling between 10 and 14 years old (N = 99 individuals) were included. A list of 15 unrelated, concrete nouns was presented to the children by a neutral computerized voice over 5 identical trials. The children had to recall as many words as possible directly after each trial. Non-linear curves were then fitted for each child individually, resulting in two parameters; Learning Speed (LS), representing the proportion of verbal material not yet recalled in a previous trial that is recalled in a following trial; and Forgetting Speed (FS), representing the proportion of material that was successfully remembered previously, and that can no longer be recalled in a following trial. The main finding was that children improved with age in the capacity to add more new words to their phonological loop (reflected by an increase in LS). Differences in verbal learning abilities were moderately heritable in the 9-year olds (LS 43%; FS 20%), and in the 10-14 year olds (LS 43%; FS 30%).

For general cognitive abilities, as assessed by the Wechsler Intelligence Scale for Children (WISC), the stability is high: the longitudinal correlations between full scale intelligence scores (FSIQ), verbal (VIQ) and performance (non-verbal; PIQ) intelligence scores were .72, .72, and .56 between childhood (age 9-11 years), and early adolescence (age 12-14 years). In **chapter 5**, these longitudinal IQ data were analyzed in the twins and their siblings to answer the question to what extent heritability differed for FSIQ, VIQ, and PIQ between the two age groups. The main results were that there was an increase in heritability of all intelligence scales during the transition from childhood to early adolescence. Heritability of FSIQ increased from 34% in childhood to 65% in early adolescence. Common environmental influences on the other hand, decreased with age for FSIQ, namely from 43% in childhood down to 18% in early adolescence. For VIQ a similar pattern of genetic and environmental influences was observed. Heritability increased from 37% in childhood up to 51% in adolescence, while the contribution of common environmental factors decreased from 42% down to 26%. For PIQ, common environment influences did not reach significance for PIQ in both age groups. Heritability was 64% in childhood and 72% in early adolescence. Next, the causes of stability were explored. The stability of FSIQ and VIQ across time was explained by genetic and to a smaller extent by common environmental influences, while stability of PIQ was completely explained by genetic influences. The results of this chapter confirm the robust findings of increased heritability of general cognitive abilities during the transition from childhood to adolescence, and the differences found between verbal and performance IQ suggest that these findings verbal and nonverbal domains have different developmental trajectories.

Heritability of structural brain changes

In **chapter 6** and **chapter 7**, genetic influences on structural brain changes were explored. In **chapter 6,** the extent to which genes influence volumetric brain measures at age 9 (N = 190 twins) and 12 (N = 125 twins), and volumetric changes between age 9 and 12 was investigated. An additional question was whether brain volume changes might reflect the strong increase in height that occurs in children at the beginning of puberty, or whether different processes, controlled by other genes are involved. The main findings were that at age 9 and 12, height and brain volumes were highly heritable. Heritability estimates at age 9 and 12 were high for height (93% / 93%), total brain (93% / 96%), total cerebral (93% / 96%), total cerebellar (95% / 95%), cerebral gray matter (88% / 92%), cerebral white matter (88% / 88%), and cerebellar gray matter (93% / 80%) volume. Heritability of lateral ventricle volume was (80% / 75%), and reached (61% / 59%) for third ventricle volume. Somewhat lower heritability estimations were observed for the cerebellar white matter volume (64 % / 49 %). For all brain volumes high genetic correlations over time were observed, indicating that individual variation in these brain volumes at the ages of 9 and 12 years were completely explained by the same genetic factors.

Between the age of 9 and 12, there were volumetric brain changes. Total brain volume increased on average with 14.6 ml, which is an increase of 1.1% change from baseline. The most pronounced volumetric change was observed for the cerebellum (increase of 4.2%). Cerebral gray matter volume was the only volumetric measure that showed a decrease in volume between 9 and 12 years of age (decrease of 1.6%). Individual differences in volumetric brain changes were partly under genetic control (change in cerebral volume was 20% heritable and in cerebellar volume 45%). The association between changes in cerebellar and cerebral volumes (r_p = 0.49) was driven by shared genetic influences and, to a smaller extent, by shared unique environmental influences. Thirdly, the change in height was highly heritable (73%), but was influenced by other genetic factors than the genetic factors implicated in changes in cerebral volume. What little was shared between height and cerebellar growth (r_p = 0.24), could be attributed partly to shared genetic influences (r_g = 0.48). We can conclude that we find developmental brain changes in this three year interval, as reported earlier over larger age spans in children and adolescents (Giedd et al., 1999), and that these changes are heritable. Furthermore, these changes in cerebral volume are not shared with the increase seen in height, while the change in cerebellar volume is partly (genetically) correlated with changes in height.

Overall, cerebral gray matter volume decreased during the three years period that the sample was followed. Locally this decrease in gray matter volume was associated with cortical thinning during adolescence. **Chapter 7** describes to what extent genetic influences affect the individual differences in cortical thickness changes across time or across regions. In the same twin sample as described in **chapter 6**, the thickness of the cortex was computed across the cerebrum at age 9 and at age 12. The main findings were that at age 9, several areas of the cortex showed significant heritability estimates ranging up to 78% in the left and up to 73% in the right hemisphere. Areas that showed significant contributions of genetic influences at age 9 were located bilaterally in frontal, midsagittal frontal, temporal and inferior parietal areas, inferior and medial insula, cingulate, the anterior paracentral lobule, lingual gyrus, precuneus, cuneus, calcarine sulcus, lateral occipital areas, and left parahippocampal gyrus. At age 12, heritability estimates were up to 88% and 91% in left and right hemispheres, respectively. Significant heritability estimates were located bilaterally in the precuneus, left inferior, and midsagittal superior frontal areas, left anterior paracentral lobule, left inferior temporal, and left lateral occipital gyri. It the right hemisphere, significant heritability estimates were found in the superior frontal, inferior parietal, inferior temporal, and cuneus.

Considerable thinning of the cortex was observed within the three year interval, most pronounced in the frontal pole and orbitofrontal, sensory-motor and visual cortices. This process was heritable (locally up to 79%), and the degree of genetic influence differs for the various areas of the brain. The same genetic factor operates in language areas (e.g., left inferior frontal (superior of) Broca's and left parietal (superior of) Wernicke's area). In these areas amplification of the same genetic factors across ages 9 and 12 was observed. Between these two regions, the genetic factors acting on cortical thinning were completely overlapping. This factor was independent from the genetic factor influencing left anterior paracentral (sensory motor) cortical thinning. Cortical thinning in the left and right frontal poles is driven by two genetic factors: one factor of decreasing influence over time, and another independent genetic factor at age 12 in left and right frontal poles. Thus, developmental thinning of the cerebral cortex in children and adolescents (Gogtay et al., 2004) is heritable in children between ages 9 and 12. Different genetic factors are responsible for variation in cortical thickness at ages 9 and 12, with independent genetic factors acting on cortical thickness across time and between various brain areas.

To summarize the studies in **chapter 6** and **7,** it is evident that the brain undergoes dramatic structural brain changes, now shown for the first time in a specific small time window at the

onset of puberty. Overall, brain volumes increased, and only cerebral gray matter volume decreased (**chapter 6**). The gray matter volume decrease was accompanied by thinning of the cerebral cortex, which differed in magnitude across different regions of the cerebrum (**chapter 7**). The areas that contained the most pronounced thinning were in the regions of the frontal pole and orbito-frontal, sensory-motor and visual cortices, and partly overlapped with previous findings of a time-region specific pattern of cortical maturation (Gogtay et al., 2004; Sowell et al., 2002). We found that changes in brain volumes and local cortical thickness are under genetic control.

Association between brain structure and cognition

In **chapter 8**, cortical thickness was computed for 78 regions of interest (ROIs) for all 9 and 12 year old twins with available MRI data (total N = 315 twins; as described previously in **chapter 6** and **7**). Full scale, verbal and nonverbal IQ (previously described in **chapter 5**) were correlated with cortical thickness (ROIs) at both ages. At age 9 the correlation between cortical thickness and IQ was small and not significant. At age 12, an association emerged between IQ and cortical thickness, revealing that a thinner cortex was correlated with a higher IQ. Phenotypic correlations reached up to -0.32. The observed correlation between IQ and cortical thickness, was mainly driven by verbal IQ and particularly so in the left frontal cortex (correlations of -0.21 up to -0.29). The associations between (verbal) IQ and cortical thickness were largely explained by shared genetic factors between IQ and cortical thickness.

Cortical thickness and gray matter volume were (genetically) unrelated at age 9 ($r_p = 0.09$) and only moderately correlated at age 12 ($r_p = 0.24$; $r_g = 0.34$). Total cortical surface area was relatively highly correlated with cortical gray matter volume at age 9 ($r_p = 0.72$; $r_g = 0.79$; $r_e = 0.36$) and at age 12 ($r_p = 0.69$; $r_g = 0.74$). Intelligence was positively correlated with cortical gray matter volume at age 9 ($r_p = 0.38$; $r_g = 0.52$) and at age 12 ($r_p = 0.22$; $r_g = 0.38$). Also cortical surface area was positively correlated with intelligence at age 9 ($r_p = 0.29$; $r_g = 0.34$) and at age 12 ($r_p = 0.32$; $r_g = 0.38$). Thus, both cortical gray matter volume and surface area were positively correlated with level of intelligence, while cortical thickness displayed a negative correlation. From this chapter it can be concluded that brain areas contributing to verbal intellectual performance are specializing with the onset of puberty under the influences of overlapping genes between verbal IQ and cortical thickness.

9.2 General discussion

Children undergo considerable changes in brain structure and function during the transition from childhood into adolescence. To get a better understanding of why individual differences in healthy brain development arise, using twin studies it is possible to explore to what extent genetic and environmental factors explain individual differences in brain development and cognition. This thesis has brought together a series of studies trying to get a more comprehensive view on the normative brain development by looking at the effects of birth parameters on later brain volumes and cognition at a later age, and genetic and environmental influences on different aspects of brain structure and cognition around puberty. How these results should be viewed in the light of current knowledge on healthy development, and developmental models of psychopathology and what their possible implications for further developmental studies are, will be discussed in the last part of this thesis.

Healthy and disrupted brain development

Very preterm birth has profound effects on brain development in infants (see for review, Hart et al., 2008; Weindling, 2010), but also in adolescence (Skranes et al., 2005; Allin et al., 2001; Parker et al., 2008). The cerebellum is under rapid development in the last trimester of the pregnancy (Limperopoulos et al., 2005), and therefore the development of this structure in postnatal life might be particularly vulnerable to preterm birth (**chapter 3**). Interestingly, the association between gestational age and cerebellar volume was absent at the age of 12 years. The relatively large increase in cerebellar volume observed between age 9 and 12 (**chapter 6**) is consistent with previous findings that the cerebellum is maturing at a later age than the cerebrum (Tiemeier et al., 2010). It can also be speculated that in this sample, the relatively large increase in cerebellar volume is partly compensating the effects of preterm birth that were found at age 9.

Since the majority of psychiatric disorders emerge during adolescence (Shaw et al., 2010; Gogtay et al., 2002), understanding the relative influences of genetic and environmental effects on brain development during this crucial period may elucidate biological processes underlying these illnesses. Why an individual develops a psychiatric disorder or not is most likely a result of interacting mechanisms of genetic predisposition and environmental factors that a person can encounter in early or later in life. The neurodevelopmental model for schizophrenia assumes that brain development is disturbed at a critical moment, which will lead to a predisposition, or a vulnerable state of the brain, already in an early stage in life (Weinberger, et al., 1987; Murray & Lewis, 1987). When first episodes of psychosis become apparent in late adolescence or early adulthood, this can be a result of compensatory systems no longer being sufficient to handle underlying disrupted processes (Thompson and Levitt, 2010). In combination with the extensive brain changes during puberty it might be that the brain is more sensitive or vulnerable to environmental factors, that could determine whether or not a person will develop schizophrenia (e.g., Insel, 2010). However, full siblings of childhood-onset schizophrenia (COS) patients exhibited gray matter deficits at a young age, but did not eventually progress into the gray matter deficits that were observed in their affected siblings in adolescence (Gogtay et al., 2007). In fact, at the age of 18-20 years, gray matter deficits found in COS patients, were no longer present in full siblings who ultimately remained healthy (Gogtay et al., 2007). The authors state that the exact causal mechanisms remain unknown (Gogtay and Thompson, 2010), but it seems that although these subjects have a (genetic) predisposition, they also have some protection for the actual development of the psychiatric diagnosis. This further highlights the complex interplay between genetic and environmental influences and development.

It is important to realise that cross-sectional studies, where group level differences are explored (e.g. between different age groups, or comparing pediatric with adult samples), are not informative regarding the developmental trajectory of the individual brains (Karmiloff-Smith, 2010). Because of this, longitudinal studies are of great importance. Using a developmental approach, i.e. mapping cortical gray matter changes in normal development can create opportunities for modelling disrupted trajectories in psychopathology (Gogtay and Thompson, 2010). Gray matter development in childhood ADHD seems to be associated with cortical developmental curves that show similar typical characteristics as healthy trajectories, but seems to be shifted along the age axis, resulting in a delayed cortical maturation (Shaw et al., 2007a). In COS, developmental trajectories seem to be characterized by differences in the velocity of developmental changes, i.e. the basic shape of neurodevelopmental curves remains intact, but with disrupted tempo (Arango et al., 2008; Thompson et al., 2001).

How should we map the developing brain?

When exploring brain development, there are different methods to map structural brain changes. In this thesis the main focus was on brain volumes and the thickness of the cortex. Although it seems logical that the product of cortical thickness and cortical surface areas gives the resulting cortical gray matter volume, this does not automatically imply that cortical thickness and volumetric measures of gray matter tap into the same underlying construct. Indeed, as reported in this thesis cortical gray matter volume was uncorrelated with the thickness of the cortex at age 9, and only to a small extent correlated with each other at age 12 (**chapter 8**). Cortical gray matter volume was strongly correlated with cortical surface (Schnack, et al, *in preparation*; **chapter 8**). These finding are in line with previous studies in adult samples, where cortical surface was uncorrelated with cortical thickness (Panizzon et al., 2009). Another study that replicated this finding included volume measures as well, confirming that cortical surface is indeed more related to cortical volume than to cortical thickness (Winkler et al., 2010). The surface area is also dependent on factors that reflect the shape of the cortex, e.g. cortical folding or the amount of gyrification. Previous studies reported that surface area is increasing in childhood (Sowell et al., 2002), and also changes in gyrification during adolescence are observed (White et al., 2010). In addition, the finding that IQ is correlated negatively with cortical thickness at age 12, while a positive correlation exist between IQ and gray matter volume at the same age (**chapter 8**), creates room to discuss how these measures of structure are capturing different concepts of the developing cerebral cortex.

Imaging techniques like magnetic resonance imaging are limited in exploring the actual changes at neuronal and cellular levels (e.g., dendrites, spines, synapse connections). The cortex is shaped by neurons that are parallel aligned in different lamina (cortical layers), and the composition of these layers differs across the cortex. The underlying biological mechanisms that cause changes in the cortex like increasing surface or thinning of the cortex remains under debate (e.g., decrease of gray matter or increase of myelination). The same accounts for the developmental changes of cortical folding or gyrification during adolescence (White et al., 2010). This illustrates the importance of combining different morphological measures to get a more comprehensive view on individual differences in structural brain development. Maybe a specific measure of brain structure characterizes a disorder, which would not be detected using other measures. For instance, in a study of aging, differences in structural changes in the medial temporal lobe were explored between healthy aging and Alzheimer patients. Decreased volumes and surface area were observed in both groups, but in de Alzheimer patients, stronger thinning of the cortex was also observed (Dickerson et al., 2009). In adults with autism, age was found to be associated with a thicker cortex, but not with greater surface area (Raznahan et al., 2010).

Development in cognitive function

The period of childhood to adolescence is characterized by cognitive maturation (Casey et al., 2005b;Keating, 2004;Steinberg, 2005). Children improve considerably in specific cognitive functions, such as information processing (Demetriou et al., 2002), working memory (Gathercole et al., 2004), and verbal learning (van den Burg and Kingma, 1999). In **chapter 4**, the older participants (siblings of 9-year olds twins) had higher LS scores, meaning that they had a steeper learning curve, reaching a higher number of new words that they could remember in a fewer numbers of trials. There were no other specific cognitive tasks included in this thesis exploring increased performance within different cognitive domains, possibly in combination with structure brain measures (e.g., short term and long term memory, working memory, verbal fluency, and more). It was clear that all subjects increased their performance with age on the cognitive tasks included in the neuropsychological testing protocol, as reported in **chapter 2** (Table 2.3).

Genetic influences on brain development and cognition

Genetic influences that act on developmental changes between age 9 and 12 are of major significance. In **chapter 4**, the genetic contribution on parameters that described the learning curve of performance on a verbal learning task in childhood was reported. Cognitive abilities can be an indicator of psychiatric disorders later in life (Woodberry et al., 2008; Reichenberg et al., 2010; van Oel et al., 2002). More specifically, memory impairments are one of the most commonly found cognitive deficits in patients with schizophrenia (Toulopoulou et al., 2003). A recent study including a large sample of adult patients with schizophrenia showed that they performed worse on several aspects of the Rey's auditory verbal learning task compared to healthy age and IQ matched controls (Badcock et al., 2011). Also in healthy relatives of patients with schizophrenia, decreased memory functioning has been reported, confirming the association between genetic influences on memory functioning and the genetic susceptibility to schizophrenia (see for review, Reichenberg and Harvey, 2007). Genetic overlap was indeed found on verbal learning performance and schizophrenia liability (Owens et al., 2011; Toulopoulou et al., 2010). However, heritability on a specific trait or psychiatric disease is no guarantee for success in genome wide association studies (Manolio et al., 2009; van Haren et al., 2008). If dynamic measures of verbal memory (**chapter 4**) could act as an intermediate phenotype for schizophrenia should be further explored in future research (Gur et al., 2007; de Geus et al., 2001).

General cognitive ability is stable across life, and the increase in genetic influences with increasing age, together with decreasing common environmental influences, is a common finding (Deary et al., 2009; Davis et al., 2009; Haworth et al., 2010). Longitudinal twin studies have generally found that variation in IQ is explained by the same genetic factors at different ages and in in this thesis, an increase in heritability across the different IQ scales was also reported (Davis et al., 2008; Bartels et al., 2002; Davis et al., 2009; Lyons et al., 2009; Boomsma and van Baal, 1998). The increase in heritability of intelligence may be the result of several processes. Genetic amplification has been suggested as the most likely explanation (DeFries et al., 1987), and this is what was observed in **chapter 5**. As children grow older they are more likely to select or even create their own environment, driven by their genetic disposition, resulting in an increased expression of their genetic potential (Plomin et al., 1977) and this explanation is compatible with the amplification hypothesis. Simultaneously, common environmental influences that are present in childhood diminish with increasing age. The increase of genetic and decrease of common environmental influences on IQ could be a result of children becoming more independent of their familial environmental and parental influences (Scarr and Mccartney, 1983). The increase of genetic and decrease of common environmental influences on IQ was mainly driven by the verbal counterpart of intelligence, and not by nonverbal abilities (**chapter 5**), in line with previous findings in an independent Dutch sample (Hoekstra et al., 2007). An interpretation of common environmental influences acting on verbal IQ in childhood and early adolescence can be for instance socioeconomic status (SES). SES is a measure of one's overall status and position in society, and has effects on cognition, academic, achievement and mental health (see for review, Hackman et al., 2010), and is assumed to be similar for family members. A family's SES has been increasingly recognized as an important influence on the development of children (Hackman and Farah, 2009). More specifically, SES has been implicated in explaining individual differences in vocabulary, phonological awareness and processing, and syntax in children (Whitehurt, 1997), which is under strong developmental changes up to puberty (Sakai, 2005).

Previous studies have indicated that the genetic influences acting on brain morphology overlap with genetic influences on intelligence in adults (Posthuma et al., 2000; Hulshoff Pol et al., 2006), and in childhood and adolescence (van Leeuwen et al., 2009; Betjemann et al., 2010; Wallace et al.,

2010). The correlation between cortical thickness and IQ at age 12 (see **chapter 8**), was largely explained by shared genes between IQ and cortical thickness. The emergence of the relation between cortical thickness and intelligence, and more specifically with verbal intelligence at age 12 coincides with a changing etiology of full scale and verbal intelligence: around the start of puberty, genetic influences on full scale and verbal intelligence increase, while the environment becomes less important (Hoekstra et al., 2007; **chapter 5**).

Other studies have reported high heritabilities for aspects of brain anatomy, assessed by different imaging techniques in children and adults. Different brain volumes and the microstructural properties of white matter are heritable (Peper et al., 2007; Brouwer et al., 2010; Peper et al., 2009; Wallace et al., 2006; Baare et al., 2001). Heritability for local cortical thickness throughout the cortex was previously reported in children (Yoon et al., 2010; Lenroot et al., 2009), adults (Brans et al., 2010), and for a region of interest approach in middle-aged men (Kremen et al., 2010; Panizzon et al., 2009). This thesis now described for the first time that genes affect individual differences in brain changes at onset of puberty.

Concerning the heritability on global volumetric changes; genetic factors acting on volumes at age 9 were completely overlapping with the genetic factors acting on volumetric changes between 9 and 12 years of age (**chapter 6**). In adults, there was evidence for distinct genetic factors acting on brain volumes and for genetic factors acting on volumetric changes (Brans, 2009). For local cortical thickness there were regions where increased or decreased influence of the same genetic factors acting at age 9 and 12 were observed (**chapter 7**). In addition, regions were identified with independent genetic factors at age 9 and 12, possibly reflecting specific genetic influences emerging for developmental processes in the cortex at the onset of puberty. This was partly similar to findings in adults, where local cortical thickness and the change in cortical thickness with increasing age was explored, and where also different genetic factors acted on change and on cortical thickness itself (Brans et al., 2010). These regions did not overlap between adults and children however.

Thus, when genetic influences on global volumes are explored, amplification (also observed for IQ) of the same genetic factor across time is observed, while for local thickness of the cortex other genetic mechanisms are observed over time. These differences between adults and children emphasize further that brain changes in adolescence have different underlying mechanisms or are for a different purpose, (i.e., maturation of the brain), than brain changes observed in adulthood.

In a large cross-sectional pediatric study with a wide age range of 5 up 19 years of age, Schmitt et al., reported that regions that were functionally or anatomically connected with each other were more likely to be under control of the same genetic factors (Schmitt et al., 2008). Results from this thesis now showed that this phenomenon might also hold for genes acting on the amount of thinning of the cortex (**chapter 7**).

Underlying genetic mechanisms and candidate genes

Searching for the actual genes that are involved in healthy brain development can help us to understand the genetic basis of disorders that are characterized by disrupted brain development or impaired cognitive functioning. For instance, many of the risk alleles that are associated with schizophrenia have been found to be involved in developmental processes (Walsh et al., 2008; Nakata et al., 2009; Colantuoni et al., 2008). There are many underlying biological processes that affect a phenotype such as brain structure or the complex trait of intelligence, which in turn involves probably a large set of genes, although each single gene might only represent a small proportion of the complete variance of a phenotype.

We measured changing genetic influences on cortical brain development between 9 and 12 years of age. It is likely that more age-specific genetic factors come into play at specific points in the maturation process when children go through later stages of puberty. The search for genes associated with the developing brain becomes more challenging when considering that genes can change their expression patterns across time, which is likely to be linked to specific developmental stages or brain regions. Different forms of gene and environment correlations or the presence of gene by environment interactions can arise or change throughout life, especially in the life period of entering adolescence.

Gene-environment correlation occurs when genetic factors influence the person's exposure to the environment. Gene by environment interaction is about the genetic sensitivity or susceptibility to specific environments. At this moment, gene-environment interaction is getting more attention in different fields on research and different psychiatric disorders (e.g., Thapar et al., 2007; Hodgins-Davis and Townsend, 2009; Plomp et al., 2009). It is important to be aware of the consequences of correlation or interaction when they are not explicitly modelled (e.g., Purcell, 2002). When genetic variance is correlated with common environment, this will result in increased common environmental variance (i.e., passive; heritage of genes by parents and the home environment), or when the correlation is linked to unique environmental factors this can result in increased unique environment (i.e., evocative; based on genotype, individuals can attract specific environment to themselves, or active; individuals seek or create their own environment based on their genetic preposition). When gene-by-environment interaction is present it will increase the unique environmental variance if the interaction is with unique environment, if the interaction is with common environment, then the variance of the interaction term is included with the genetic variance. Genetic and environment correlation has been hypothesized previously in the case for IQ when children grow up. Changes in expression patterns of genes or the interaction with environmental factors can be one explanation for the changes in heritability, amplification of genetic variance (observed on measures of IQ, brain volumes and cortical thickness changes), or the independent genetic factors observed for local cortical thickness.

Finding the actual genes that are associated with developmental brain changes and / or are linked with cognitive functions is not straightforward. In the last few years, genome-wide-association studies were the dominating approach to find specific genes for wide variety of traits. For psychiatric disorders some findings have started to emerge (e.g., for schizophrenia and bipolar disorder). However, the number of individuals included in consortium based meta-analyses of cognition, psychological or psychiatric phenotypes does not yet approach the numbers that have been analyzed in genome-wide-association studies of e.g. height (Allen et al., 2010), BMI (Speliotes et al., 2010), blood lipids (Teslovich et al., 2010), and other metabolic traits for example (e.g., Manolio et al., 2009).

Some genetic variants have been associated with disorders where cognitive functioning is in some way affected (Flint, 1999; Deary et al., 2009). For most imaging genetics studies that are now reported a candidate gene approach is used, instead of a whole genome search, although first attempts to conquer the statistical challenges by collaboration between different imaging laboratories are on the way (Thompson and Martin; Shen et al., 2010; Stein et al., 2010). A candidate gene that is of interest for the developing brain is for example the Brain-Derived Neurotrophic Factor (BDNF; Cohen-Cory et al., 2010)). This gene is highly expressed in the cerebral cortex, and has an important role during brain development and in synaptic plasticity (Cohen-Cory et al., 2010), and has been associated with prefrontal cortex and hippocampal volume in healthy individuals (Pezawas et al., 2004). The expression pattern of BDNF is peaking around adolescence, was found to be unique for different anatomical regions, and coincides with maturational timing of different anatomical regions of the cortex (Webster et al., 2002; Webster et al., 2006; Wong et al., 2009). BDNF has also

been linked to cognitive abilities, but these studies are mainly conducted in elderly samples (e.g., Miyajima et al., 2008). Changes in expression levels in the prefrontal cortex were also found for dopamine receptors (DAR1), $GABA_A$ receptor alpha-subunits, and Apolopoprotein-D (Duncan et al., 2010; Kim et al., 2009; Weickert et al., 2007). Another example is the Met/Met variant of catechol-O-methyltransferase (COMT) that was previously associated with a thicker cortex in adolescents (Shaw et al., 2009) and adults (Cerasa et al., 2010), and also with a higher cognitive functioning (e.g., Savitz et al., 2006). Furthermore, the Epsilon 4 allele of the Apolipoprotein gene (APOE), which is commonly known to be associated with Alzheimer disease, was not only associated with gray and white matter reduction in elderly, but also with an altered brain developmental trajectory in children, as well as the resting brain activity in young adulthood (Shaw et al., 2007b).

These are only a few examples of candidate gene studies, and how their results should be viewed in combination with environmental factors is unclear. The search for the actual genes that are involved in developmental changes of the anatomy and function of the brain is challenging (Casey et al., 2010). Trying to find the link between specific genes and brain structure and brain function (and eventually behaviour) remains difficult considering the fact that they are end products of the combination of genotype, environment, and development. Genetic effects are not static throughout life, or between individuals, but emerge from dynamic processes like changing environmental during different developmental periods (see for more discussion; Casey et al., 2010).

9.3 Future directions

Each new step forward in research will automatically raise new questions as well. Next to biological changes during adolescence, emotional and motivational changes occur, which in turn could influence behavioral tendencies (Forbes and Dahl, 2010). Therefore, the possible role of environment (i.e., SES; Hackman and Farah, 2009;Hackman et al., 2010), or the hormonal status of the periods in adolescence development should be taken into consideration (Blakemore et al., 2010; Peper et al., 2011).

Considering phenotypes to map brain development it is important to realize that brain measures may capture different aspects of the brain, and that there are distinct genetic factors acting on these measures. Although measures like cortical volume, surface area, cortical thickness, sulcal depth, measures of cortical folding or gyrification are of course to some level associated with each other, they can capture more specific components of (cortical) development. This is not only important for the comparison between different groups of subjects, but also from a genetic perspective. Most of these measures have a genetic component (Kochunov et al., 2010; Rogers et al., 2010; Rogers et al., 2007), and therefore these measures could serve as an intermediate phenotype to facilitate the search for genetic factors or the actual genetic variants linked with healthy neurodevelopment or with psychopathologies. Furthermore, using or combining these measures holds promise for developmental studies (White et al., 2010), or for psychiatric disorders (White et al., 2003; Palaniyappan et al., 2011). Looking at individual differences in developmental brain changes is distinct from exploring individual differences at brain structures at a given age. As a result, this also has consequences for imaging studies exploring heritability of searching the genetic variants that could explain individual differences in developmental trajectories throughout puberty.

This thesis focuses on structural brain changes and cognition, and is one of the first to explore how changes in brain anatomy are linked to cognitive functions from a genetic perspective at two specific ages. A more integrative approach of structural and functional imaging will become more important in the future. Several studies have tried to link specific cognitive domains to brain regions

Table 9.1 Main findings of the studies described in this thesis.

Chapter	Aim	Main findings
3	To asses the effects of GA and BW on brain volumes and IQ in a population-based sample of children at the age of 9 (N=192 twins).	1) Shorter GA was associated with a relatively smaller CB volume at age 9. 2) Lower BW was associated with lower IQ scores at age 9.
4	Exploring the heritability of individual differences in dynamic measures of verbal learning ability in 9-year-old twins (N=112 pairs) and their older siblings (N=99)	1) Individual differences in verbal learning abilities were moderately heritable. The heritability of LS was 43% for both twins and siblings. Heritability for FS was 20% in 9-years-old twins and 30% in the older siblings.
5	To what extent contribute genetic and/or environmental factors to IQ scores at two age groups (9-11 years & 12-14 years) and on the stability of IQ scores across time.	1) Heritability increased for all IQ scales; FSIQ from 34% to 65%; VIQ from 37% to 51%; PIQ from 64% to 72%. Influences of C decreased over time; FSIQ from 43% to 18%; VIQ from 42% to 26%; PIQ, C was not significant. 2) Stability of FSIQ (r_p=.72) and VIQ (r_p=.72) was explained by influences of A and C. Stability of PIQ (r_p=.56) was completely explained by influences of A.
6	To explore to what extent brain volumes at age 9 (N=190) and 12 (N=125) are heritable, and whether volumetric brain changes are heritable. Furthermore, it was explored whether they are related to genetic factors influences the amount of overall increase in height.	1) Height and brain volumes were highly heritable at ages 9 / 12; height (93% / 93%); TB (93% / 96%); BB (93% / 96%); CB (95% / 95%); BB GM (88% / 92%); BB WM (88% / 88%); CB GM (93% / 80%); CB WM (64 % / 49 %); lateral ventricle (80% / 75%); third ventricle (61% / 59%). For all brain volumes high r_g over time were observed (>0.89). 2) All brain volumes increased, only BB GM volume decreased (-1.6%). Change in volume was heritable for TB (19%), BB (20%) en CB (45%). Change in BB volume was associated with change in CB (r_p =.49; r_g =.88; r_e =.34). 3) Change in height was heritable (73%) and partly correlated with changes in CB (r_p =.24; r_g =.48), but not BB.

7	To explore genetic influences on CT at age 9 (N=190) and 12 (N=125), and on the change in CT between ages 9 and 12. Furthermore, it was studied whether there are stable or age specific genetic factors acting on CT between the ages 9 and 12.	1) 2) 3)	CT was heritable at age 9 (mean CT=65%; local max. up to 78%), and at age 12 (mean CT=82%; local max. up to 91%) Considerable thinning of the cerebral cortex was found between ages 9 and 12 (0.05 mm on average). This process was heritable (up to 79%), and the degree of genetic influence differs for the various areas of the brain. Different genetic factors are responsible for variation in cortical thickness at ages 9 and 12, with independent genetic factors acting on cortical thickness across time and between various brain areas.
8	The association between brain structure and IQ was explored at two ages; childhood (age 9) and early adolescence (age 12). It was studied to what extent these associations are caused by shared genetic factors acting on both CT and IQ scores.	1) 2) 3)	At age 9, CT was not correlated with IQ scores, but at age 12 higher IQ scores were associated with a thinner cortex (r_p = -,32). This effect was mainly driven by verbal IQ (mainly in left frontal cortex). The correlations between IQ and CT were driven by shared genetic factors.

A = Additive genetic influences; BB = Cerebrum; BW = Birth Weight; C = shared environmental influences; CB = Cerebellum; CT = Cortical Thickness; GA = Gestational Age; FS = Forgetting Speed; GM = Gray Matter; IQ = Intelligence quotient; LS = Learning Speed; r_e / r_p / r_g = unique environmental / genetic / and phenotypic correlations; TB = Total Brain; WM = White Matter

or trying to locate IQ in the brain, but this is a challenging job (see for review, Cabeza and Nyberg, 2000; Deary et al., 2010). A more likely explanation is that not the anatomy or activation of a brain region is of importance, but that it is shaped by the activation within networks, involving multiple, interconnected regions (van den Heuvel and Hulshoff Pol, 2010). Cognitive maturation during adolescence is therefore not a direct reflection of brain regions that mature at different ages, but more of the development of networks obtaining more efficient strategies to perform a task (e.g., Casey et al., 2005a; Durston et al., 2006). Genetic influences on brain activation in neural networks supporting digit working memory tasks were found in an adult sample (Koten et al., 2009).

Many studies nowadays also explore the connectivity of the brain at rest, i.e. not performing a task during brain scanning (van den Heuvel et al., 2009; van den Heuvel and Hulshoff Pol, 2010). Genetic influences have been found for brain connectivity (Smit et al., 2008), activation of the default network (Glahn et al., 2010), and the cost-efficiency of functional network in adults (Fornito et al., 2011). A rapidly increasing number of studies now illustrate that indeed the development of the brain is not only reflected by structural changes, but is also associated with changes in connectivity between brain regions. Overall, long-range connections increase with age and short-range connections decrease with age. This indicates that the organizational characteristics of the brain network seem to differentiate from more local to a more distributed organization with increasing age (Fair et al., 2009; Supekar et al., 2009; Supekar et al., 2010; Dosenbach et al., 2010; Power et al., 2010).

9.4 Concluding remarks

This thesis aimed to gain insight how events around birth can have an effect on brain development and cognition in later life, to describe the extent to which genetic factors influence individual differences in brain development and cognition and to study the relation between brain structure and cognition at ages 9 and 12 years. In addition to studies exploring static brain structure and function during puberty, the dynamics of the adolescents brain will also become increasingly important in future research (Shaw et al., 2010; Karmiloff-Smith, 2010; Insel, 2010). To what extent genetics can explain individual differences in these developmental trajectories will become very important for the understanding of healthy but also disrupted brain development. Therefore, it is of great importance to embrace longitudinal projects, and continue ongoing projects. At this moment the children in the twin sample included in this thesis will return for a third follow-up. This will open up new opportunities for non-linear modelling of brain changes and cognitive functioning, and for exploring the link with functional MRI. Also the effects of more complex mechanisms of genes and environment are an important issue in future research. This will provide leads into fully understanding how individual differences in brain development occur to help every child to achieve it's best possible developmental trajectory.

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