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## Genetic Influences on Brain Developmental Trajectories on Neuroimaging Studies: From Infancy to Young Adulthood

Vanessa Douet, Linda Chang, Christine Cloak, and Thomas Ernst

Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii, 96813, USA

### Abstract

Human brain development has been studied intensively with neuroimaging. However, little is known about how genes influence developmental brain trajectories, even though a significant number of genes (about 10,000, or approximately one-third) in the human genome are expressed primarily in the brain and during brain development. Interestingly, in addition to showing differential expression among tissues, many genes are differentially expressed across the ages (e.g., antagonistic pleiotropy). Age-specific gene expression plays an important role in several critical events in brain development, including neuronal cell migration, synaptogenesis and neurotransmitter receptor specificity, as well as in aging and neurodegenerative disorders (e.g., Alzheimer disease or amyotrophic lateral sclerosis). In addition, the majority of psychiatric and mental disorders are polygenic, and many have onsets during childhood and adolescence. In this review, we summarize the major findings from neuroimaging studies that link genetics with brain development, from infancy to young adulthood. Specifically, we focus on the heritability of brain structures across the ages, age-related genetic influences on brain development and sex-specific developmental trajectories.

### Keywords

Brain development; Neuroimaging; Genetic; Heritability; Sexual dimorphism

## INTRODUCTION

Human brain development involves a cascade of processes that starts two weeks post conception, when the first cell differentiates. These processes interact with each other and have different dynamics and termination times: some are completed at birth, whereas others continue to develop throughout the lifespan (Figure 1). By 3–4 weeks of gestation, the neural tube is formed, which then differentiates into the full nervous system between 4 to 12 weeks. Cells proliferate and give rise to neurons. From 12 to 20 weeks, these neurons migrate along the radial cells to their final destination and form the cortex (Rakic 1990).

Between 24 weeks into gestation to 4 weeks after birth, the first apoptosis occurs, reducing

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Corresponding author: Vanessa Douet, Department of Medicine, John A. Burns School of Medicine, The Queen's Medical Center, 1356 Lusitana Street, UH Tower, room 716, Honolulu, HI 96813, douet@hawaii.edu, Phone: +1 808 586 7468, Fax: +1 808 545 8970.

### CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

the number of neurons by half. Concurrently, myelination begins at 29 weeks of gestation in the brain stem and develops primarily from inferior to superior and from posterior to anterior directions (Volpe, 2000; Huppi et al, 2001). By early childhood, most of the axons are myelinated, although myelination continues through adolescence and across the second and third decades of life (Yakovlev 1967; Benes et al. 1994; Blakemore 2012; Lebel et al. 2012). Synaptic proliferation and organization starts at about 20 weeks of gestation, and synapses continue to proliferate from birth to 2 years after birth (Huttenlocher 1979; Huttenlocher and de Courten 1987). However, a regional reorganization occurs most predominantly during childhood and adolescence (Blakemore 2012).

Overall, the brain grows rapidly during fetal life through childhood, and matures more slowly during adolescence and young adulthood until its development plateaus and/or follows a declining trajectory with aging. After birth, brain development primarily depends on individual experiences (“self-organization”) (Lewis 2005), along with many other variables (Andersen 2003). However, of the whole human genome, 10,000 genes (approximately one-third) are only expressed during brain development (Johnson et al. 2009; Zhang et al. 2011). Change in gene expression is fastest in human brain tissue during fetal development, slows through childhood and adolescence, stabilizes through adulthood, then speeds up again after age 50, with distinct redirection of expression changes prior to birth and in early adulthood (Colantuoni et al. 2011). Genes with high expression during fetal development have the greatest decreased expression in the aging cortex, whereas genes with low expression during fetal development show increased expression in aging and neurodegeneration (Colantuoni et al. 2011). Recently, an increasing number of studies have attempted to examine the complex interactions between genes, environment and the developing brain. The cumulative data clearly indicates that brain development is under tight genetic control across the lifespan.

Recent studies using brain imaging techniques confirmed that the brain develops throughout childhood and young adulthood, and that the various brain structures follow different trajectories of development and maturation (Gogtay et al. 2004; Westlye et al. 2010; Lebel et al. 2012). Since genes influence developmental trajectories, neuroimaging provides a powerful, non-invasive tool to investigate the phenotypic variations during brain development in relation to genetic differences and age or sex-specific gene-expression.

### Techniques commonly used to study brain development

While electroencephalography (EEG) was mainly used to study babies and young children, magnetic resonance imaging (MRI) and functional MRI (fMRI) are widely used for brain research because of its high resolution, multiple advances in image analyses, and the large range of image contrasts that they provide. Structural MRI provides information on brain morphometry, such as cortical thickness or area, and cortical and subcortical volumes. Using specific stimulation paradigms, functional MRI (fMRI) can yield information on functional networks dedicated to a particular task and their connectivity. Similarly, resting-fMRI (rs-fMRI) or task-free fMRI can provide an estimate for the functional connectivity in the brain at rest (without an activation paradigm). These task-free brain activities appear to reflect coordinated and intrinsic spontaneous fluctuations in brain activity at baseline (Gusnard and

Raichle 2001). Rs-fMRI provides insight into the unprompted activity that is naturally produced within the brain, which subsequently promotes communication across regions.

White matter (WM) constitutes various networks across brain regions and is important for efficiency and integration of information between cortical regions. WM integrity can be assessed using diffusion tensor imaging (DTI), which provides fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) or axial diffusivity (AD) in specific regions of interest (ROIs) or the whole brain.

Neurochemicals that are present in large millimolar quantities can be assessed using proton magnetic resonance spectroscopy ( $^1\text{H}$ -MRS), which is a non-invasive MR technique that can measure levels of N-Acetyl Aspartate (NAA, neuronal marker), total Creatine (tCr, metabolic marker), total Choline (tCho, cell-membrane marker), and Myo-inositol (mI, glial marker). However, quantitative MRS has lower spatial resolution and requires advanced sequences and post-processing compared to structural MRI, making it less commonly used in the clinical setting. However, MRS can provide insights into the chemistry underlying structural changes, and chemical alterations commonly precede structural abnormalities during disease progression.

Neuroimaging techniques have yielded valuable data on trajectories of the developing brain and made it possible to evaluate the role of environment and genetics in normal brain development.

### Studies on genetic influences on brain development

In this review, we will focus on genetic influence on “normal” or typical brain development from neonates to young adulthood, and will summarize current results conducted in pediatric populations linking brain imaging to genetics. We will concentrate specifically on age-by-gene or gene-by-heritability interactions, since age-related changes in heritability may be linked to the timing of gene expression. Knowledge of when a given brain structure is particularly sensitive to genetic or environmental influences during development may also have important educational and therapeutic implications.

We performed a search in PubMed®, limited to “human subjects” and combinations of the following keywords: brain morphometry, DTI, MR Spectroscopy, fMRI, heritability, genetic, children, adolescents, brain development, age, age-related, and sexual dimorphism. The studies queried were included in the review if they were published in English in a peer-reviewed journal and involved the investigation of genetic factors. Conference abstracts, case studies or qualitative studies were excluded. If available, information on the number of subjects, average age and age range of the sample, type of analysis, and heritability estimates with their 95% confidence intervals were extracted from the papers.

## HERITABILITY IN BRAIN DEVELOPMENT: FAMILY AND TWIN STUDIES

Heritability is the proportion of the observed variation in a particular trait that can be attributed to inherited genetic factors. It is measured by estimating the relative contributions of genetic and non-genetic factors to the total variation of that trait in a population. Although

heritability estimates are difficult to compare across studies, for a given trait, heritability ( $h^2$ ) of less than 0.30 can be considered low, between 0.30 and 0.60 is moderate and above 0.60 is high. Family- and twin-based studies allow the evaluation of separate and combined effects of genetic and environmental contributions on any trait. Monozygotic (MZ) and dizygotic (DZ) twins share the same or very similar family environments if the twins are raised together. MZ twins are almost genetically identical while DZ twins share only half their genes, like non-twin siblings. Univariate studies evaluate differential correlations of a particular phenotype in MZ and DZ twins to estimate the heritability of a trait (Plomin et al. 1994), whereas multivariate studies can analyze the links between genetic and environmental effects on specific regions of interest in the brain. Contributions of additive genetic (A), common or shared environmental (C), and unique environmental (E) effects on variations of a phenotype can be modeled using structural equation modeling (SEM). SEM allows for parameter estimations, while the Falconer method uses correlation analysis to test whether genetic or environmental factors contribute significantly to individual differences (parameter calculation). SEM can also be used to determine whether the traits defined by neuroimaging are heritable, and how heritability can explain brain development.

### Brain morphometry studies on heritability

Brain morphometry, especially cortical volume and thickness, has been the most studied MR-based phenotype for heritability (Table 1). Structural MRI provides images of the brain that can be processed to produce quantitative measures of brain size (volume or thickness) and shape (including surface area). Because MRI does not involve ionizing radiation, it is ideally suited for repeated measurements during development to chart brain growth trajectories. Two major longitudinal studies evaluated heritability of brain morphometric measures over time. The first study is the Brain SCALE study (Brain Structure and Cognition: an Adolescent Longitudinal Twin Study into the Genetic Etiology of Individual Difference, Netherlands); it evaluated pre-adolescents at 9 and 12 years of age with psychometric, neuropsychological, and neuroimaging measures (van Soelen et al. 2012a; van Soelen et al. 2012b). The second study, conducted by investigators from the Child Psychiatry Branch of the National Institute of Mental Health (USA), followed children and adolescents from 5 to 18 years of age (Wallace et al. 2006; Lenroot et al. 2009; Ordaz et al. 2010). In these youth, heritability of global brain and intracranial volumes were similar to those reported in adults. Heritability of total gray matter was lower in neonates (56%) compared to 5–18 year old children (~77–85%) (Wallace et al. 2006; Giedd et al. 2007; Peper et al. 2008) and adults (82%) (Baare et al. 2001). Heritability of total white matter volume in neonates (85%) was similar to that in 5–18 year old children (85%) (Peper et al. 2008; Wallace et al. 2006) and in adults (87%) (Baare et al. 2001). However, within the age range from 5 to 18 years, heritability of total gray matter decreased with age, while that of total white matter increased with age (Wallace et al. 2006; Giedd et al. 2007). Cerebellar volumes showed increasing heritability with age, from low (17%) in neonates to moderate (49%) in children (Wallace et al. 2006) and high (>60%) in adults (Wright et al. 2002). In contrast, lateral ventricle volumes showed a higher heritability (71%) in neonates (Gilmore et al. 2010) than in children (~30–35%) (Wallace et al. 2006; Schmitt et al. 2007; Peper et al. 2009) and in adults (<10%) (Chou et al. 2009).

Heritability of the total cortical thickness was less in 6 and 8 years old children (65–71%) (Yoon et al. 2010; van Soelen et al. 2012b; van Soelen et al. 2013) than that in 12 and 14 years old adolescents (80–81%) (van Soelen et al. 2012b; Yang et al. 2012; van Soelen et al. 2013) or in mid-aged adults (81%) (Panizzon et al. 2009). In 8 year old children, overall cortical thickness in the frontal, temporal, parietal and occipital lobes exhibited moderate to high heritability (53–72%), whereas regional thickness of the lobules in the inferior and superior parietal and inferior temporal cortices showed low heritability (<30%) (Yoon et al. 2010). In adolescents, the thickness of the prefrontal cortex, including bilateral dorsolateral and superior frontal regions, and the middle temporal and supramarginal cortices, had heritability greater than 75% (Schmitt et al. 2009; Lenroot et al. 2009; Yang et al. 2012). As in adults (Tramo et al. 1998; Joshi et al. 2011), differences in heritability were observed between hemispheres in adolescents in multiple frontal regions (Schmitt et al., 2009; Yang et al. 2012). In 9 and 12 years old children, heritability of cortical thinning was predominantly found in superior and middle frontal regions, superior temporal cortices, cingulate, sensorimotor cortices, and primary visual and lateral occipital cortices (van Soelen et al. 2012b). Inferior regions of the primary motor and sensory cortex in the frontal and postgyral cortices that are associated with facial recognition functions showed a higher heritability in early development compared to other brain regions, and an increasing heritability with age (Lenroot et al. 2009; van Soelen et al. 2013). From later childhood through adolescence, heritability increased most markedly in dorsolateral prefrontal, superior parietal and temporal cortices, and in language-related regions in the left hemisphere including Broca and Wernicke's areas (Lenroot et al. 2009; van Soelen et al. 2013).

Overall, primary sensory regions that mature first had higher heritability than later maturing brain regions, such as the frontal cortex (van Soelen et al. 2013). However, late maturing regions showed an increase in heritability with age until 18 years and stabilize thereafter, whereas the heritability of primary sensory regions was stable across the age range of 21–27 and 51–59 years (Rimol et al. 2010; Joshi et al. 2011).

### **White Matter Integrity-Studies for heritability**

In the last two decades, neuroimaging studies revealed the importance of WM in several psychiatric and neurodegenerative disorders. Although genetics may play a role in WM integrity during brain development, heritability in WM integrity has not yet been examined extensively across the lifespan. Most studies to date involved adults since the peak maturation of the WM occurs at the age range of 25–40 years. However, three longitudinal twin studies examined the heritability of WM integrity with age in infants (Y. Chen et al. 2009) and adolescents (Chiang et al. 2011; Brouwer et al. 2012), while two other studies evaluated heritability cross-sectionally in neonates at 40 days post birth (Geng et al. 2012) and at 9 years of age (Brouwer et al. 2010).

Heritability of FA and RD in the whole WM was higher in neonates (FA=60% and RD=53%) (Y. Chen et al. 2009; Geng et al. 2012) compared to children (for FA~ 54%) (Brouwer et al. 2010; Brouwer et al. 2012; Chiang et al. 2011) and adults (FA=52% and RD=37%) (Kochunov et al. 2010). Likewise, AD heritability was moderate (57%) in

neonates (Geng et al. 2012), but lower (33–46%) in children (Brouwer et al. 2010; Brouwer et al. 2012) and not significant in adults (Kochunov et al. 2010). AD reflects the axonal organization and is often used to assess for possible injury to fiber bundles (Budde et al. 2007), and therefore may provide a sensitive measure of environmental influences in the brain during development.

Regional heritability (FA and AD) varied with maturation status. Heritability was typically high in WM structures that mature earlier (Lee et al. 2009; Kochunov et al. 2010; Geng et al. 2012). However, at any age, heritability of FA in the corpus callosum was higher in the genu, which develops later than the splenium, but FA heritability for both genu and splenium decreased at the same rate over time (Brouwer et al. 2010; Kochunov et al. 2010; Brouwer et al. 2012).

During maturation, changes in RD may reflect axonal myelin synthesis and proliferation of glial cells, while changes in FA may reflect fiber organization, but is also influenced by changes in RD (Partridge et al. 2004). Therefore, more than one diffusion measure is required to fully characterize the maturation process (Table 2).

### Functional Brain Networks-Studies of heritability

Functional MRI (fMRI) and electroencephalography (EEG) allow the measurement of brain function and activity. To our knowledge, only one study examined heritability of the functional brain networks using fMRI in the younger population (van den Heuvel et al. 2013). Connectivity density is defined as the total number of brain connections, and cortical network efficiency is assessed by the temporal dependency of neuronal activation patterns of anatomically separated brain regions. Independent of the connectivity density, heritability of the global cortical network efficiency was moderate (42%) at 12 years of age (van den Heuvel et al. 2013), and higher (60%) in adults (Fornito et al. 2011).

EEG showed low heritability (11–27%) of frontal asymmetry in 9 to 10-year old children (Gao et al. 2009), similar to that in adults (Coan and Allen 2003; Anokhin et al. 2006; Smit et al. 2008). In contrast, EEG alpha power was highly heritable (70–85%) in children (Gao et al. 2009; van Baal et al. 2001), and in older adolescents and adults (van Baal et al. 1996). EEG alpha power scores increased from 9 to 10 years of age (Gao et al. 2009) and from 15 to 17 years of age (McGuire KA 1998), despite these narrow age ranges. Although these studies involved small sample sizes, the findings suggest that heritability of global functional brain connectivity increases during brain development, while heritability of the architecture and maturation in the frontal cortex is relatively stable across the age range.

### Magnetic resonance spectroscopy (MRS) studies of heritability

Brain metabolite concentrations measured by <sup>1</sup>H-MRS change throughout the lifespan, with the greatest changes occurring early (Kreis et al. 1993; Pouwels et al. 1999) and late in life (Chang et al. 1996). Only one study examined the heritability of brain metabolites and how they change with age (Batouli et al. 2012). In elderly twins (65–88 years), only NAA levels showed a high heritability (72%) in the posterior cingulate cortex (Batouli et al. 2012); sex appeared to have no significant effects on heritability. More studies on the heritability of these brain metabolites throughout the life span should be performed.



## EPIGENETICS IN BRAIN DEVELOPMENT

Epigenetics is the study of gene expression that has been modified by various factors, such as DNA methylation, histone modifications, microRNAs, and long noncoding RNAs, typically in response to environmental exposures. Modified gene expression may last across the lifespan or even become heritable (Weaver et al. 2004). Histone and DNA methylation are epigenetic phenomena that change in the human brain from childhood to adulthood, suggesting that the epigenetic pattern may modify brain development. However, only one study examined the global cytosine methylation of DNA with age in humans (Siegmund et al. 2007). From 17 weeks of gestation to 104 years of age, DNA methylation levels increased in genes that show decreased mRNA expression. Emerging data from studies on gene-by-environment-by-age interactions of DNA methylation show that epigenetic effects may influence processes such as fetal programming, in which events that occurred during gestation may last across the lifespan. Stable and long-lasting epigenetic alterations in the brain also has been suggested to cause some psychiatric disorders (Feinberg et al., 2007; Gardner et al. 2007; Simmons 2009), leading to the hypothesis that many adult diseases with epigenetic underpinnings have fetal origins (Bezek et al. 2008; Doherty et al. 2009). In this way, epigenetics may shape human behaviors, and environmental events may have heritable impact on the genes.

An ongoing twin study aims to unravel influences in epigenetic mechanisms throughout the lifespan (Tan et al. 2013). This study should improve our understanding of age-by-gene and age-by-epigenetic interactions, and how molecular pathways are modified during brain development.

## GENE SPECIFIC EXPRESSION IN BRAIN DEVELOPMENT

Brain development depends on finely controlled expression of genes. Developmental changes in gene expression are well established in animal models, but data are rare in humans and even rarer in the pediatric population. Genome-wide association studies (GWAS) use a non-hypothesis-driven approach to interrogate genetic variants across the whole genome. To our knowledge, only one study to date used this approach in a healthy pediatric population and showed that the genotype for DOK5, encoding for a protein mediating neurite outgrowth and activation of the MAP kinase pathway, modifies the activation of the amygdala during face processing in children (9–18 years, (Liu et al. 2010)). Other studies examined candidate genes based on prior evidence and biological plausibility. Most of these studies showed genetic influences on brain morphometry and brain connectivity (i.e. fMRI after a specific task), while only three studies reported on the relationship between genetic variants and DTI measures (Pacheco et al. 2009; Thomason et al. 2010; Sundram et al. 2010).

The most studied genes in pediatric populations are those encoding the dopamine inactivator catechol-O-methyl transferase (COMT), neurotrophin, brain derived neurotrophic factor (BDNF, (Casey et al. 2009; Knickmeyer et al. 2013; Mueller et al. 2013)), the schizophrenia candidate gene neuregulin (NRG1, (Knickmeyer et al. 2013)), and the serotonin transporter (5-HTT, (Pacheco et al. 2009; Lau et al. 2009; Wiggins et al. 2012)). Amongst these, the

COMT genotype was the only one found to influence brain morphometry (Raznahan et al. 2011; Knickmeyer et al. 2013), white matter integrity (Thomason et al. 2010; Sundram et al. 2010) and brain connectivity (Mechelli et al. 2009). A longitudinal study in healthy children additionally demonstrated that a greater COMT Val158Met Val allele dose is associated with a decrease in the cortical thickness loss in the prefrontal cortex from 9 to 22 years of age (Raznahan et al. 2011). Genetic variants in the following genes *APOE*, *DISC1*, *GAD1*, *GPCD1*, *ESR1*, *DYX1C1*, *DCD2*, *KIAA0319*, *HOXA1*, *DTNBP1*, *OXTR*, *MAOA*, *IL-6*, *MET* and *PER2*, have been associated with neuroimaging phenotypes, raising the possibility that they may be involved in brain development (Shaw et al. 2007; Reiman et al. 2009; Furman et al. 2011; Tognin et al. 2011; Darki et al. 2012; Hedrick et al. 2012; Raznahan et al. 2012; Forbes et al. 2012; Ziermans et al. 2012; Knickmeyer et al. 2013). However, these studies need replication in independent cohorts, in part to evaluate for possible racial and ethnic differences, since the study populations were primarily Caucasian. Moreover, potential interactions between genetic variants, sex, and age need to be investigated further.

## SEXUAL DIMORPHISM IN BRAIN DEVELOPMENT

Evidence from historic post-mortem studies to recent meta-analyses indicate that the brain is structurally, metabolically, and functionally sexually dimorphic (Sacher et al. 2013). In adults, men have larger brains and volumes of gray and white matter than women (Peters 1991; Passe et al. 1997; Good et al. 2001; Luders et al. 2005), while women have greater gray matter-to-white matter ratios than men (R. C. Gur et al. 1991; Nopoulos et al. 2000; J. M. Goldstein et al. 2001; Allen et al. 2003; Luders et al. 2005; X. Chen et al. 2007). The size of white matter structures, such as the corpus callosum, differs by gender although controversies existed since the first description (Oppenheim et al. 1987; Holloway et al. 1993; Bishop and Wahlsten 1997; Dorion et al. 2001). Brain activation patterns show gender differences during a variety of cognitive tasks (R. E. Gur and Gur 1990; R. C. Gur et al. 1995; R. C. Gur et al. 2000; Speck et al. 2000; Weiss et al. 2003; Bell et al. 2006). However, sexual dimorphism of brain measurements in adults can be biased by multiple factors, such as environment and most obviously height differences (Dekaban 1978; Fausto-Sterling and Balaban 1993). Cumulative mean height within the first 15 years of life varies by only 1% between boys and girls, and girls are taller from 10 to 13.5 years old (Kuczmarski et al. 2002). Therefore, studying sexual dimorphism on brain measures across the age span from birth to young adulthood has the advantage of identifying factors that could influence gender-specific differences, and when (e.g., perinatal, childhood, adolescence) and why (e.g., gene specific, hormonal, environmental) these differences arise. This section provides a comprehensive review on how structural and functional neuroimaging deciphers genetic-by-gender-by-age interactions on the developing brain.

### Sexual dimorphism in brain morphometry

The earliest sexual dimorphism observed in life is that of head circumference, which was assessed by prenatal ultrasound as early as the second trimester of pregnancy (Joffe et al. 2005). Although it is the least heritable, the cerebellum is the most sexually dimorphic brain structure. Boys have larger total cerebellar volume than girls and the magnitude of sex-differences varies significantly with age: 10% at 8 years and 13% at 20 years of age



(Tiemeier et al. 2010). Likewise, the volumes of cortical gray and white matter are generally larger in boys than in girls (Figure 2A). Cortical gray matter volumes increase somewhat more rapidly with age in boys than in girls: 6–7.5% differences were observed in neonates and children, and ~10% differences during adolescence (Reiss et al. 1996; Caviness et al. 1996; Giedd et al. 1996; Giedd et al. 1999; Lenroot et al. 2007; Gilmore et al. 2007). Gender-specific differences in cortical white matter volume are greater in adults than in children and adolescents: 15–17% differences were observed from childhood to young adolescents (De Bellis et al. 2001; Perrin et al. 2008; Perrin et al. 2009). Boys have greater rates of age-dependent increase in total white matter volume than girls (De Bellis et al. 2001; Lenroot et al. 2007). Regionally, sexual dimorphism of developmental trajectories is observed more for the frontal and occipital lobes (gray and white matter), whereas no sex-differences in developmental trajectories were found for the temporal and parietal lobes (Giedd et al. 1996; Giedd et al. 1997; Lenroot et al. 2007; Sowell et al. 2007). Between the ages of 4 to 18 years, age-dependent increases in the amygdala, caudate and putamen volumes were observed only in boys (e.g., amygdala in boys increases by 53%) while an age-dependent increase of the hippocampal volume was found only in girls (Filipek et al. 1994; Giedd et al. 1996; Giedd et al. 1997; Sowell et al. 2002; Lenroot et al. 2007; Neufang et al. 2009).

Sexual dimorphism for cerebral asymmetry is already present at birth as a result of genetic programming, but the pattern of cerebral asymmetry changes after birth, suggesting that asymmetry may depend on shared environment as well as genetic factors. In neonates, cerebral asymmetry was more pronounced in girls than in boys in the prefrontal and occipital regions (Gilmore et al. 2007; Tanaka et al. 2012), while little consistency exists in sex-related and hemispheric differences in regional cortical volumes (Good et al. 2001; Raz et al. 2004). However, the left-greater than-right asymmetry in fetuses and neonates (Hering-Hanit et al. 2001; Gilmore et al. 2007; Ratnarajah et al. 2013) is opposite to that observed in older children (Caviness et al. 1996; Giedd et al. 1996; Reiss et al. 1996; Matsuzawa et al. 2001) and in adults (Nopoulos et al. 2000; Toga and Thompson 2003; Raz et al. 2004).

In contrast, intracranial volume is consistently larger in boys than in girls, starting with neonates (+2–9%) (Gilmore et al. 2007; Qiu et al. 2013) and continue to persist in adolescents and in adults (+11.9 to 14.6%) (Blatter et al. 1995; R. C. Gur et al. 1999; Raz et al. 2004). Neither the volumes of lateral ventricle or corpus callosum show a gender-by-age interaction during the development, with boys having larger ventricle volumes but girls showing larger corpus callosum relative to the total brain volume across the age span (Giedd et al. 1996; Lenroot et al. 2007).

One of the most striking findings of these pediatric studies is that most adult patterns of sexual dimorphism are already present at birth and are therefore primarily under genetic control (inherited). In contrast, gender-specific changes in brain structures that develop after birth typically occur at puberty, suggesting that the neuroanatomical development in certain brain regions are mediated by physiological processes associated with puberty (e.g. hormonal changes). However, no direct measures of puberty were evaluated in the majority of these studies.

### Sexual dimorphism in white matter integrity

Findings on sexual dimorphism for DTI metrics are controversial and inconsistent. Two studies examined gender differences in FA, RD and AD across the lifespan (Westlye et al. 2010; Lebel et al. 2012), two found no gender differences in DTI parameters in young children; (Gilmore et al., 2007; Geng et al., 2012), and others reported mixed results based on narrow age ranges of the subject populations (Abe et al. 2002; Ota et al. 2006; Schneiderman et al. 2007; Hsu et al. 2008; Schmithorst et al. 2008; Bava et al. 2011; Chiang et al. 2011). Only one study examined age-related differences in sexual dimorphism of the WM integrity during childhood and adolescence (Schmithorst et al. 2008). In neonates, sexual dimorphism was not observed for any of the DTI (FA/RD/AD) parameters in the basal ganglia and thalamus (Qiu et al. 2013). In children and adolescents, higher FA values in the caudate and thalamus were found in boys than in girls (Menzler et al. 2011; Pal et al. 2011), suggesting that sexual dimorphism of anisotropy in the deep GM structures arises after birth. Girls from 5–18 years old displayed a trend toward increased FA with age only in the right hemisphere (arcuate fasciculus, frontal lobe and occipito-temporo-parietal white matter) while boys displayed this trend only in the left hemisphere frontal lobe (Schmithorst et al. 2008). Girls also showed a greater MD increase with age compared with boys in associative regions (Schmithorst et al. 2008). In young adults, men have higher FA than women in the genu and the splenium of the corpus callosum (Westerhausen et al. 2004; Chiang et al. 2011), while women have higher FA in the middle and superior occipital gyri (Chiang et al. 2011). In the genu and splenium of the corpus callosum, the external and internal capsules and the superior fronto-occipital fasciculus, genetic influences account for approximately 80% of the variation in FA in men (Figure 2B) (Chiang et al. 2011). No gender differences in brain structures were found for RD (Perrin et al. 2009; Bava et al. 2011) across childhood and adolescence, suggesting that myelination is not sufficient to characterize white matter disparities.

Sexual dimorphism during brain development was also found using magnetization transfer imaging (MTI), which provides estimates of the macromolecular content (e.g. myelin content) in white matter tissue. Age-dependent decreases in MT were found across adolescence in boys only (Perrin et al. 2008; Perrin et al. 2009).

Overall, findings from these DTI and MTI studies suggest that sexual dimorphism for WM is in part under genetic control, but may also be influenced by microenvironmental factors (e.g. hormones) that ultimately change the brain structures.

### Sexual dimorphism in functional brain networks

Sexual dimorphism on functional MRI was reported in only three studies of healthy children and adolescents (Zuo et al. 2010; Wu et al. 2013; Ratnarajah et al. 2013). However, multiple fMRI studies in adults found evidence for sexual dimorphism in emotional perception and memory, fear conditioning and visuospatial abilities (Sacher et al. 2013). While no age-by-gender interactions in global network parameters were found, girls and boys have different developmental patterns of the functional brain networks associated with visuospatial function (left cuneus and left superior parietal gyrus) and emotion processing (left rectus gyrus). Boys showed an age-related increase, while girls showed age-related decrease, in the

regional nodal properties in the left superior parietal gyrus (Wu et al. 2013). No gender differences in structural connectivity asymmetry was found in neonates (Ratnarajah et al. 2013) despite the rapid synaptic proliferation in neonates (Gilmore et al. 2007; Qiu et al. 2013).

Across the age span of 7 to 85 years, resting state functional connectivity (rsFC) increased with age in boys but decreased with age in girls in the dorsolateral prefrontal cortex (DLPFC) (Figure 2C) (Zuo et al. 2010). However, in the amygdala, an opposite pattern was observed with an age-related decrease of rsFC in boys and an age-related increase of rsFC in girls (Zuo et al. 2010). These findings demonstrate gender differences in the developmental trajectory of functional homotopy (i.e. the high degree of synchrony in spontaneous activity between geometrically corresponding interhemispheric regions) in the amygdala and within the DLPFC (Zuo et al. 2010).

Sexual dimorphism in the developmental trajectories of functional connectivity may underlie sex differences in the functional maturation of these specific networks, and ultimately the sex-related cognitive differences in children and adolescents.

### **Sexual dimorphism on magnetic resonance spectroscopy**

Few MRS studies evaluated brain development in relation to genetic factors. Multiple studies showed that brain metabolites change rapidly early in life and then more subtly and linearly after puberty (Kreis et al. 1993; Pouwels et al. 1999; Kadota et al. 2001; G. Goldstein et al. 2009). To date, only one MRS study evaluated sexual dimorphism across the lifespan (4–88 years), using the NAA/Cho ratio in the centrum semiovale (Kadota et al., 2001). Boys exhibited a steeper age-related increase in NAA/Cho in the white matter than girls, and the age-dependent trajectory of the NAA/Cho peaked 1 to 3 years earlier in boys than in girls (Kadota et al. 2001). Cerebral laterality in WM NAA/Cho ratios also differed by sex: greater NAA/Cho ratios were found in the right compared to the left WM in boys, but not in girls. In adults, age-related changes in brain metabolites were reported but considerable heterogeneity of metabolite concentrations across studies were found (Kadota et al. 2001; Baker et al. 2008; Maudsley et al. 2009; Chang et al. 1996). Note also that metabolite ratios are difficult to interpret since it is unclear what proportion of the age-dependent increase in NAA/Cho reflects age-dependent increase in NAA, because Cho concentration also increases with age during adolescence (Cloak et al. 2011). Therefore, future MRS studies investigating metabolite changes related to age and sex, or the additional influence of genetic factors, should measure metabolite concentrations rather than ratios.

### **Dosage of genes on the X-chromosome**

A different approach to studying sex-specific genetic influences on brain development is to evaluate individuals with sex-chromosomal abnormalities, such as boys with XXY (e.g. Klinefelter syndrome) or 49, XXXXY syndrome, or girls with the commonly studied Turner syndrome (X-monosomy). Individuals with Klinefelter syndrome have reduced gray matter in the insula, temporal gyrus, amygdala, cingulate and hippocampus (Giedd et al. 1996; Patwardhan et al. 2002), while 49, XXXXY boys have smaller total brain size and abnormal development of the white matter with a thinner corpus callosum and multifocal WM lesions

(Blumenthal et al. 2013). Brain morphometry studies show that girls with Turner syndrome (TS) have larger volumes of the amygdala and orbitofrontal cortex (Good et al. 2003), as well as larger superior temporal gyrus (Kesler et al. 2003). They also have smaller volumes in parieto-occipital regions and parietal lobes (Murphy et al. 1993; Reiss et al. 1995; Brown et al. 2002; Brown et al. 2004), and reduced FA in parieto-occipital regions along the superior longitudinal fasciculus (Holzapfel et al. 2006). TS girls also have abnormal patterns of brain activation in frontal and parietal cortices and subcortical regions, such as the caudate during visuospatial tasks (Kesler et al. 2004), executive function (Haberecht et al. 2001; Hart et al. 2006) and arithmetic tasks (Kesler et al. 2006).

Altogether, these results suggest that the dosage of genes on the X chromosome plays an important role in determining the development of brain structures (gray and white matter) and brain function.

### Sex steroid receptors and hormone levels

Gender differences are also observable at the molecular level, although there is a scarcity of human studies (Lenroot et al. 2007; Schmithorst and Holland 2007). Adolescent brain development is mediated by both sex steroids: androgens (MacLusky et al. 2006) and estrogens (Galea et al. 2006). Sex steroid hormones are involved in brain “organization” that first establish sexual dimorphism of brain morphology leading to sexual behavior and physiology in adulthood, and in brain “activation” to further maintain gender-specific behaviors in adulthood (Cooke et al. 1998). However, the role of sex steroids and hormones on brain development was investigated only by a few neuroimaging studies.

In girls, estradiol levels were negatively associated with global gray matter volumes and regionally with the inferior frontal gyrus (Peper et al. 2009). In contrast, testosterone levels correlated positively with gray matter volumes in boys (Peper et al. 2009). Testosterone levels also correlated with white matter volumes depending on the androgen receptor (AR) genotype: boys with the more “efficient” (short) AR gene had greater WM volume than those with the less “efficient” (long) AR gene (Figure 2D) (Perrin et al. 2008). Similarly, boys with the more “efficient” AR gene had a less-steep age-related loss in cortical thickness at the inferior parietal lobule. However, girls with the more “efficient” short AR gene had more rapid thinning of the left inferior frontal gyrus (Raznahan et al. 2010; Raznahan et al. 2010). Since the left inferior frontal gyrus is involved in language and impulse-control domains, the more rapid thinning of this brain region suggests earlier maturation in the girls. This longitudinal study of changes cortical thickness in adolescents showed that the AR gene contributes to sexual dimorphism during brain development. Additionally, manipulation of androgens early in life may have functional consequences on cortical function. For example, object discrimination, a task associated with the prefrontal cortex, is performed better in normal adolescent males and androgen-exposed females relative to unexposed normal females (Clark and Goldman-Rakic 1989). In contrast, pubertal increases in sex hormone levels attenuated pre-pulse inhibition (Morris et al. 2010).

To our knowledge, only one study investigated the role of non-steroid hormones on brain development and its role on sexual dimorphism (Peper et al. 2008). Luteinizing hormone (LH) is one of the first endocrine markers of puberty, and was positively associated with

larger white matter volume in the left cingulum, middle temporal gyrus (left and right) and splenium of the corpus callosum, as well as with higher WM density in the left anterior cingulum (Peper et al. 2008). Interestingly, moderate to high heritability in relation to LH levels were found in the splenium of the corpus callosum (39%) and the left cingulum (43–65%) (Peper et al., 2008). However, since LH stimulates the Leydig cells to produce testosterone, these associations may in part be due to the effects of testosterone on brain development and on heritability.

Taken together, both non-steroid and steroid sex hormones may play important roles in sexual dimorphism of brain morphometry. Changes or abnormalities in the levels of these hormones may therefore contribute to the susceptibility of neuropsychiatric disorders that are known to emerge at puberty and to have gender-specific prevalence rates.

## CONCLUSION AND FUTURE STUDIES

This review highlights the important contributions of neuroimaging in understanding the role of genetics on brain development, and how genetics influences brain developmental trajectories. Future studies can be augmented by linking genetics and neuroimaging with biomarkers and cognitive neuroscience, in order to define more reliable endophenotypes. The emergence of multiple datasets also highlights several methodological issues that lead to difficulties in interpreting or comparing findings across studies. Some of these methodological issues include the selection of diverse human subject populations, the various neuroimaging acquisition parameters, differences in behavioral assessments, and the complex statistical comparisons. Resolving these issues and sharing of protocols across studies might lead to shared data resources that ultimately could provide a better understanding of normal brain development. Having a normative neuroscience database across the ages would provide a critically important foundation for elucidating how genes might influence brain disorders across the lifespan.

Finally, genetic effects are not static but may change with age and modified by environment. However, most human studies were conducted cross-sectionally, and the few longitudinal studies across wider age ranges are limited by relatively small sample sizes. Overall, studies on age-related genetic influences on brain development are lacking and needed to improve our understanding of the developing brain. Knowledge derived from genetic influences on brain development and aging may lead to new strategies for more personalized therapeutic interventions, especially for the neuropsychiatric disorders that emerge at puberty and for many neurodegenerative disorders that occur with aging.

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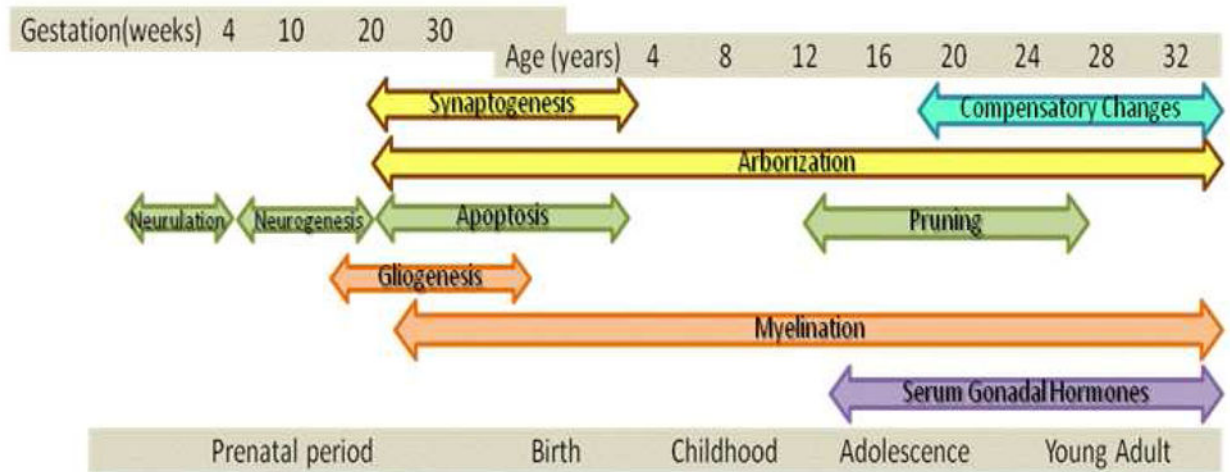
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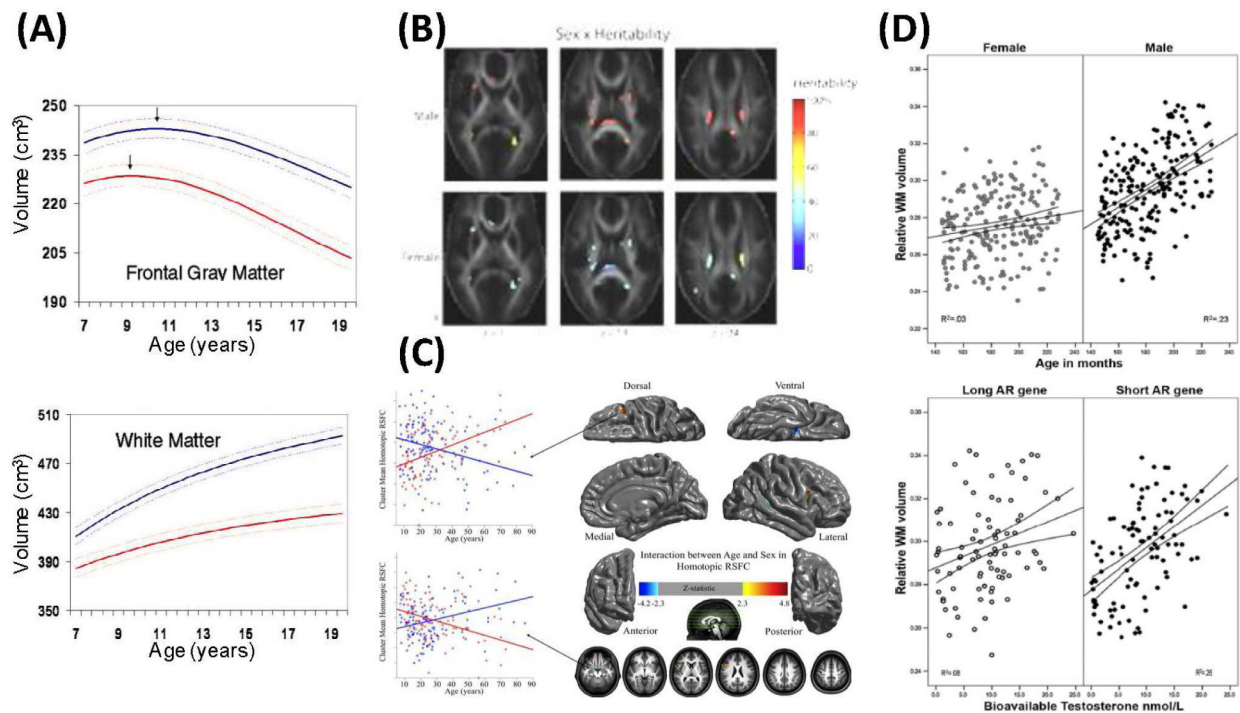
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**Figure 1. Key events of the human brain development**

Human brain development can be schematized into present different periods.



**Figure 2. Multiple imaging modalities illustrating sexual dimorphism in the brain across the lifespan**

**(A)** Across the ages 7–20 years, girls (red) have smaller volumes of white and frontal gray matter than boys (blue). Compared to girls, boys showed a greater age-related increase of white matter volume, and a steeper age-related decline in the frontal gray matter (adapted from Lenroot et al. 2007).

**(B)** Heritability accounts for about 80% of the variation in fractional anisotropy in adult males (top row, red color voxels). (Adapted from Chiang et al. 2011).

**(C)** Age-by-sex interaction on homotopic resting state functional connectivity (rsFC). Statistical maps are visualized as six hemispheric surfaces (showing cortical regions) and six axial slices (showing subcortical regions). The top scatter plot show opposite brain activation patterns in males (red) and females (blue) that are different in the dorsolateral prefrontal cortex (top scatter plot) compared to the amygdala (bottom scatter plot) (Adapted from Zuo et al. 2010)

**(D)** Interactions between age and sex, or genetic influence on testosterone levels, on relative white matter (WM) volume. Top panels: Between the ages of 11–20 years, boys show steeper age-dependent increase in relative WM volume (corrected total brain volume) compared to girls. Bottom panels: Boys with the more efficient short AR gene and higher plasma levels of bioavailable testosterone had larger relative WM volumes. (Adapted from Perrin et al. 2008).

Table 1

**Heritability values for macrostructural brain traits**

Percentage of heritability for each brain morphometry traits is summarized. P-values, age ranges and population characteristics are reported for each pediatric study.

	Authors	Subjects Age Range	Population	Brain Regions	Heritability (%)	p-values
Thickness	Schmitt et al. NeuroImage. 2009	214 MZ, 94 DZ, 284 singletons 5.4–18.7 yrs	Caucasian (>85%)	Total Cortical Thickness	60	<0.05
				Frontal Lobe, Middle Temporal Lobe, Supramarginal Gyrus	>75	<0.05
	Lenroot et al. Hum Brain Mapp. 2009	214 MZ, 94 DZ, 284 singletons 5.4–18.7 yrs	Caucasian (>85%)	Left Angular Gyrus	51	
				Superior Frontal Gyrus (R/L)	45–51	<0.005
				Middle Frontal Gyrus	43–38	<0.03
				Inferior Frontal Gyrus	52–44	<0.008
				Precentral Gyrus	43–52	<0.005
				Lateral Orbitofrontal Gyrus	38–34	<0.05
				Cingulate	36–40	<0.004
				Medial Frontal Gyrus	38–50	<0.02
				Superior Parietal Gyrus	44–30	<0.05
				Supramarginal Gyrus-left	Ø-30	0.003
				Postcentral Gyrus	57–48	<0.002
				Superior Temporal Gyrus	41–40	<0.01
				Middle Temporal Gyrus	33–39	<0.05
				Inferior Temporal Gyrus	38–47	<0.005
				Occipital Ole	Ø-41	0.018
				Superior Occipital Gyrus	Ø-37	0.045
				Middle Occipital Gyrus	Ø-33	0.032
	Yoon et al. NeuroImage. 2010	57 MZ, 35 DZ 8.24–8.7 yrs	Quebec	Total Left	71	<0.05
				Frontal Left	72	<0.05
				Parietal Left	59	<0.05
	Yang et al. NeuroReport. 2012	27 DZ, 27 MZ, 108 singletons 14 yrs	Usa	Occipital Left	67	<0.01
				Prefrontal Cortex (Superior Frontal Gyrus)	>80	<0.05



	Authors	Subjects Age Range	Population	Brain Regions	Heritability (%)	p-values
				Right Frontal Pole, Inferior Frontal Gyrus, Posterior Supramarginal Gyrus And Fusiform Gyrus	>80	<0.05
Volumes	Baaré et al. Cerebral Cortex. 2001	54 MZ, 58 DZ, 34 singletons 17.9–45.8 yrs	Netherlands	Intracranial Volume	88	<0.001
				Total Brain	90	<0.001
				Gray Matter	82	<0.001
				White Matter	87	<0.001
				Total Cerebral	89	<0.0001
	Wallace et al. J Child Psychol Psychiatry. 2006	90 MZ, 37 DZ, 158 singletons 5–19 yrs	Caucasian (>85%)	Total White Matter	85	<0.0001
				Total Gray Matter	82	<0.0001
				Frontal, Temporal And Parietal Lobes	77–88	<0.0001
				Cerebellum	49	0.01
				Caudate	80	<0.0001
				Corpus Callosum	85	<0.0001
				Lateral Ventricles	31	0.09
				Cerebrum	88(68)	<0.01
				Lateral Ventricles	32(17)	<0.01
				Corpus Callosum	75(65)	<0.01
				Thalamus	72(42)	<0.01
				Basal Ganglia	81(64)	<0.01
				Cerebellum	55(24)	<0.01
				Intracranial Volume	91	<0.001
	Peper et al. Hum Brain Mapp. 2009	45 MZ, 62 DZ 9–9.66 yrs	Dutch	Total Brain	94	<0.001
				Gray Matter	77	<0.001
				White Matter	84	<0.001
				Lateral Ventricles	35	0.08
				Cerebellum	88	<0.001
	Chou et al. Neuroimage. 2009	76 MZ, 56 DZ 20–27 yrs	Australia	Lateral Ventricles	7.3	0.001
	Gilmore et al. Hum Brain Mapp. 2010	41 MZ, 50 DZ, 35 singletons neonates: about 40 weeks	Caucasian (>70%)	Intracranial Volume	73	<0.0001
				Total Gray Matter	56	0.0017

	Authors	Subjects Age Range	Population	Brain Regions	Heritability (%)	p-values
	Yoon et al. NeuroImage. 2010	57 MZ, 35 DZ 8.24–8.7 yrs	Quebec	Total White Matter	85	<0.0001
				Lateral Ventricles	71	0.0045
				Cortical Gray Matter	58	0.0017
				Cortical White Matter	85	<0.0001
				Subcortical Gray Matter	62	0.0191
				Parietal Gray Matter	65	0.0089
				Occipital Gray Matter	57	0.0179
				Prefrontal White Matter	53	0.0117
				Frontal White Matter	84	<0.0001
				Parietal White Matter	72	0.0033
				Occipital White Matter	86	0.0001
				Total Brain	71	<0.05
				Total White Matter	80	<0.05
				Corpus Callosum	51	<0.05

MZ: Monozygotic, DZ: Dizygotic.

Table 2

Heritability values for microstructural brain traits

Percentage of heritability for each DTI traits is summarized. P-values, age ranges and population characteristics are reported for each pediatric study.

Authors	Subjects Age Range	Population	DTI/MTR values	Brain Regions	Heritability (%)	p-values
Kochunov et al. NeuroImage. 2010	467 subjects 19–85 yrs	USA	FA	Genu Of Corpus Callosum	66	10 <sup>−9</sup>
				Corpus Callosum	57	
				Corona Radiata	56	
				Splenium Of Corpus Callosum	47	<0.001
Brouwer et al. NeuroImage. 2010	39 MZ, 43 DZ, 21 singletons 9.0–9.6 yrs	Netherlands	MTR	Genu Of Corpus Callosum	31	n.s.
				Superior Longitudinal Fasciculus	61–50	<0.001
			RD	Genu Of Corpus Callosum	32	<0.001
				Splenium Of Corpus Callosum	33	<0.001
				Left Uncinate Fasciculus	29	<0.001
				Superior Longitudinal Fasciculus	64–27	<0.001
				Genu Of Corpus Callosum	33	<0.001
				Splenium Of Corpus Callosum	46	<0.001
			AD	Right Superior Longitudinal Fasciculus	35	<0.001
				Superior Longitudinal Fasciculus	35	<0.001
			Chiang et al. NeuroImage. 2011	26 MZ, 60 DZ, 12 yrs 26 MZ, 62 DZ, 16 yrs	Australia	FA
Genu Of Corpus Callosum	32	n.s.				
FA	Splenium Of Corpus Callosum (Left) Right Inferior Longitudinal Fasciculus Inferior Fronto-occipital Fasciculus	70–80				
	Total Brain WM	60.95				0.0021
Geng et al. Twin Res Hum Genet. 2012	31 MZ, 32 DZ, 47 singletons 269.2–308.8 days (gestational age)	USA, Caucasian (>68%)	RD	Total Brain White Matter	57.95	0.0021
				Superior Frontal Gyrus	62–52	<0.0017
				Inferior Occipital Gyrus	84–Ø	0.0001
				Middle Occipital Gyrus	86–54	0.0002
				Superior Corona Radiata	63–62	<0.00001
				Posterior Corona Radiata	80–77	<0.00001

Authors	Subjects Age Range	Population	DTI/MTR values	Brain Regions	Heritability (%)	p-values
Brouwer et al. PlosOne 2012	57 MZ, 64 DZ 8.89–12.25 yrs	Netherlands	AD	Superior Longitudinal Fasciculus	51–53	0.0002
				Total Brain White Matter	53.95	0.0039
				Superior Frontal Gyrus	58–50	0.005
				Superior Corona Radiata	63–71	0.0004
				Posterior Corona Radiata	70–92	0.0001
				Total White Matter	24–33	<0.05
			FA	Arcuate Left	54–42	<0.05
				Arcuate Right	34–31	<0.05
				Cingulum Left	51–36	<0.05
				Cingulum Right	54–35	<0.05
				Fornix Left	18–29	<0.05
				Fornix Right	21–39	<0.05
				Genu Of Corpus Callosum	28–38	<0.05
				inferior longitudinal fasciculus Left	28–21	<0.05
				inferior longitudinal fasciculus Right	37–49	<0.05
				Inferior Fronto-occipital Fasciculus Left	7–15	<0.05
				Inferior Fronto-occipital Fasciculus Right	22–35	<0.05
				Splenium	42–42	<0.05
				Uncinate Left	22–44	<0.05
				Uncinate Right	27–37	<0.05

FA: Fractional Anisotropy; RD: Radial Diffusivity; AD: Axial Diffusivity; MTR: Magnetization Transfer Ratio; MZ: Monozygotic, DZ: Dizygotic.