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## **Rhythms of resilience: individual differences in genetic and environmental effects on brain development**

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### **Citation**

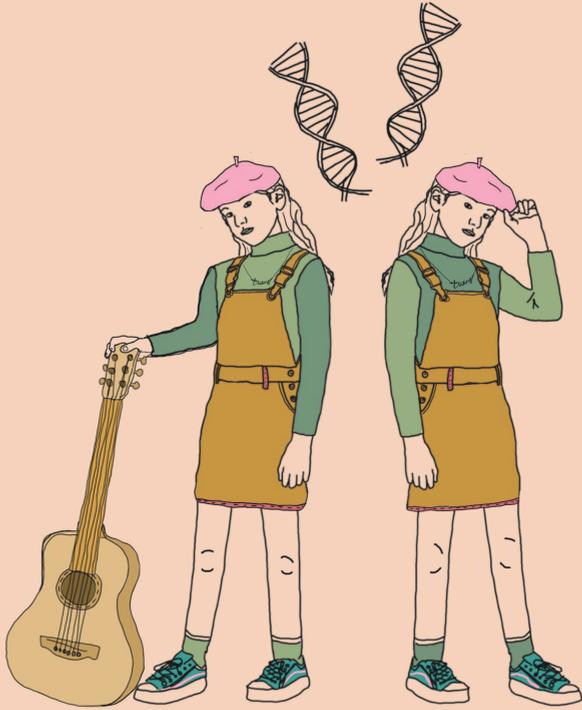
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# CHAPTER 1

General Introduction

Consider two teenagers participating in a music band. One of them may possess a strong sense of timing allowing one to keep a steady beat and easily synchronize with music, while the other might excel in improvisation and composing music. Or consider that adolescents may differ in social skills that can be evident during interpersonal interactions, such that some adolescents exhibit higher levels of empathy enabling them to possibly form close bonds more easily (Eisenberg et al., 2015) while others may struggle with understanding and acting upon the feelings of others. Moreover, young people may also differ in how they perceive and define themselves, with some believing strong in their abilities leading to a positive self-concept, whereas others question their capabilities possibly leading to a self-doubting or negative self-concept.

These examples show how individual differences contribute to the diversity of talent, cognitive strategies, social skills, and self-evaluations during human development. One important underlying mechanism influencing these differences in abilities and behaviors between individuals may be the variation in brain structure, -function, and -development (Becht et al., 2021; Bos et al., 2018; Kanai & Rees, 2011; Mills et al., 2014; Shaw et al., 2010; Sowell et al., 2004; van der Crujisen et al., 2023; van der Meulen et al., 2023). However, it is not well understood *what* specific factors and *how* these factors drive variations in brain trajectories from childhood to adolescence. The present thesis examines individual differences in genetic and environmental effects on structural and functional brain development in 7-14-year-old twins by aiming to answer the following overarching questions: To what extent are variances in structure, function, and development of brain regions influenced by genetic and environmental contributions? And how do enriched and/or deprived environments (e.g., musical skills and practice, the experience of the COVID-19 pandemic) contribute to individual differences in structural brain development from middle childhood to adolescence?

In this thesis, I will focus on a developmental period of rapid neural and behavioral changes; the transition from middle childhood to early adolescence. This developmental period spans approximately from ages 7 to 14 and is an important developmental period marked by increased physical, cognitive, social, and emotional growth (Choudhury et al., 2006; Crone & Dahl, 2012; Crone & Fuligni, 2020; Del Giudice et al., 2009; Glowiak & Mayfield, 2016; Goodway et al., 2019; Steinberg, 2005). Physically, the development of fine motor skills (Goodway et al., 2019) enables teenagers to better participate in, for instance, musical activities (Drewing et al., 2006). During this time, children experience rapid advancements

in cognitive abilities, such as problem-solving skills, social inhibition, and language development (Crone & Steinbeis, 2017; Dobbelaar et al., 2023; Feinstein & Bynner, 2004; Glowiak & Mayfield, 2016; Huizinga et al., 2006; Menyuk et al., 2005). Socially, they form lasting peer relationships and learn interpersonal skills (e.g., empathy) as their social worlds expand (Crone & Dahl, 2012; Crone & Fuligni, 2020; Del Giudice et al., 2009; van der Meulen et al., 2023).

It is also a time where a shift in cognition and social behavior takes place, that affect their concept of self. Ongoing development of their self-concept from early childhood to adulthood is formed by advancing cognitive abilities (e.g., perspective taking) and socialization experiences that influence self-evaluations in academic skills and social relationships (Harter, 2012; Marsh & Ayotte, 2003; Muris et al., 2003; Rochat & Striano, 2002). To this end, this developmental phase of middle childhood/emerging adolescence serves as a bridge between early childhood and adolescence/adulthood, shaping the developmental trajectory that is suggested to influence the child's future development and well-being (Bracken, 2009; Feinstein & Bynner, 2004; Rubin et al., 2008). Therefore, it is important to better understand the changes in brain development and environmental experiences that underlie and/or explain why some children thrive while others experience more difficulties during their development.

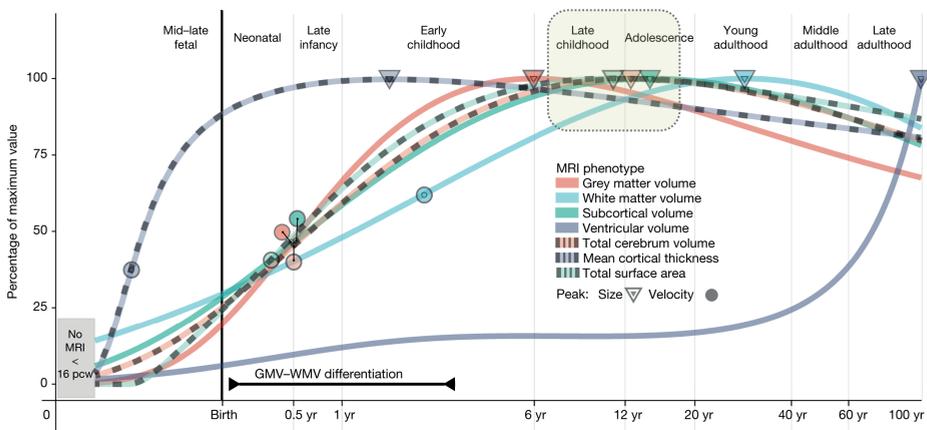
## **Brain development**

Historically, animal and human post-mortem research contributed to the broader understanding of brain function and structure. Animal models enabled exploration of causal links between neural processes and behavior (Delgado, 1976) while post-mortem studies offered a direct examination of human brain tissue (e.g., insights into anatomy, cellular construction, and molecular characteristics) as well as pathological changes related to neurological disorders (Birkmayer & Riederer, 1975). However, these approaches lacked the capability to non-invasively study the living human brain.

From the 1990s, Magnetic Resonance Imaging (MRI) technology made significant progression in our knowledge on the structure of the living human brain, leading to more precise medical diagnoses and innovative neuroscientific knowledge (Giedd et al., 1996, 1999, 2015; Pfefferbaum et al., 1994). Also, functional MRI (fMRI) emerged as a tool for mapping brain activity by measuring increases in blood flow and this pioneering advancement allowed neuroscientists to investigate the neural

correlates of behavioral functions directly. The use of MRI technology enabled researchers to better understand the complex and dynamic processes of cortical and subcortical brain development that occurs throughout an individual's life, from the early stages of fetal development into adolescence and even adulthood.

From conception to the first 4-5 years of life, the brain's cortex undergoes rapid growth and organization (Giedd et al., 1999; Gilmore et al., 2018; Tamnes et al., 2017) that is characterized by processes such as neurogenesis (i.e., the forming of neurons), neuronal migration (i.e., migration of newly generated neurons to their accurate position in cerebral cortices) and the formation of synaptic connections (e.g., synapses) and white-matter tracts (e.g., connecting cortical regions for information transmission) (Eriksson et al., 1998; Giedd et al., 1999; Sidman & Rakic, 1973). As individuals become teenagers, the brain experiences grey matter decreases which is suggested to be the result of an increase in specialization of the adolescent brain (Casey et al., 2005; Gogtay et al., 2004) through processes of synaptic pruning (i.e., elimination of weaker synapses by neuronal regulation), myelination (i.e., improving conduction by the formation of myelin sheath around nerve), and the refinement of neural circuits and networks (Natu et al., 2019; Stiles & Jernigan, 2010). Figure 1 shows a graphical summary of typical developmental trajectories for distinct brain measures captured with MRI.



**Figure 1.** Visualization of typical brain developmental trajectories for various global MRI dimensions including developmental milestones plotted against log-scaled age (N=101.457; 115 days post-conception – 100 years old), adapted from Bethlehem et al (2022). The green transparent box shows the developmental period that is addressed in the present thesis. Triangles represent peak volume whereas circles represent peak growth rates for each dimension. GMV = total cortical grey matter volume; WMV - total cortical white matter volume.

## **Morphological dimensions of the cortex: Cortical thickness and surface area**

The cerebral cortex can be conceptualized as a folded sheet situated on the pial surface. Two dimensions that can be derived from the cortex are surface area and thickness. Here, cortical volume is defined as the product of cortical thickness and surface area. The cellular construction of the cortex postulates that cortical volume combines characteristics that are unique to surface area or thickness. Such that prior work already showed that neurons in the cerebral cortex are organized in columns that run vertically to the surface of the brain (Mountcastle, 1997). The number of cells and columns are reflected in the size of cortical thickness and surface area respectively (Panizzon, Fennema-Notestine, Eyer, Jernigan, Prom-Wormley, Neale, Jacobson, Lyons, Grant, Franz, et al., 2009; Rakic, 1988). The development of surface area and cortical thickness are possibly driven by different cellular mechanisms. It has been demonstrated that distinct genetic factors influence cortical thickness and surface area (Panizzon, Fennema-Notestine, Eyer, Jernigan, Prom-Wormley, Neale, Jacobson, Lyons, Grant, Franz, et al., 2009) and that developmental trajectories differ by cortical dimension (Wierenga et al., 2014).

As shown in Figure 1, cortical thickness development follows a global pattern of an early increase during infancy followed by a subsequent decrease from 2 to 5 years of age that continues into adolescence and early adulthood (Aubert-Broche et al., 2013; Bethlehem et al., 2022; Giedd et al., 1999; Mills et al., 2016; Tamnes et al., 2017). In contrast, cortical volume and surface area development both follow a global curvilinear trajectory including an early increase that continues into late childhood and a subsequent gradual decrease into adulthood (Wierenga et al., 2014). Greatest increases of surface area occurs first in the sensory areas, and latest in association areas (Brown & Jernigan, 2012; Schnack et al., 2015). These findings indicate that there are regional differences in cortical thickness and surface area developmental trajectories and timing. Although possibly different underlying (biological) mechanisms (e.g., genetic and environmental effects) are involved in the development of these cortical dimensions, most studies have predominantly focused on isolated features of brain regions such as cortical volume (i.e., product of both) or cortical thickness. To fully understand the effects of genetic and environmental factors it is important to study and compare both surface area and thickness, as they are related but complementary measures. This is important for

the examination of brain-behavior or brain-environmental associations as one morphological dimension may show to be related while the other is not.

Cognitive, social, and behavioral changes between childhood and adolescence are accompanied by substantial developmental changes in brain structure (Blakemore, 2008; Gilmore et al., 2018; Mills et al., 2014, 2016; Tamnes et al., 2017; Wierenga et al., 2014; 2014). This indicates that individual differences in brain development may be a potential underlying factor influencing behavioral changes. Indeed, prior work already showed that the developmental rates of cortical thickness development are associated with cognitive performance, such as IQ (Sowell et al., 2004), and psychopathology (Bos et al., 2018; Muetzel et al., 2018; Whittle et al., 2020). Furthermore, these structural brain changes that take place during the teenage years insinuate possibly enhanced susceptibility to environmental factors (Blakemore & Mills, 2014; Crone et al., 2020). This proposition is accompanied by prior work showing that children and adolescents from families in low socio-economic status (SES) environments (Khundrakpam et al., 2019; Parker et al., 2017; Piccolo et al., 2016) and those who go through changes in social contexts such as friendship quality (Becht et al., 2021) were associated with accelerated brain development.

Very few studies have directly investigated surface area with behavioral or environmental changes. For example, one study demonstrated that influences of parental occupation were associated with cortical thickness and surface area in different regions in children and adolescents. Specifically, low parental occupation was associated with decreased surface area of the orbitofrontal cortex, and with decreased cortical thickness of the inferior and superior parietal cortex. Furthermore, children who grew up in families with lower parental occupation and who showed decreased cortical thickness but not surface area, exhibited lower self-esteem (Khundrakpam et al., 2020). In this case, the brain can be seen as a resilience factor, as children in high SES environments may encounter protective elements, such as increased cortical thickness, mitigating the effects of lower self-esteem. Additionally, in clinical populations (e.g., depression) it has been shown that thickness and surface area display different alterations compared to control groups (Schmaal, 2019). These findings stress the need for further exploration of genetic and environmental effects on distinct features of structural brain development that ultimately may have different impacts on cognitive, social, and behavioral changes.

Taken together, investigating brain-behavior associations between childhood and adolescence and the genetic and environmental contributions on these measures may reveal unique neural markers for cognitive, social, and behavioral development, based on indices including cortical thickness and surface area. Furthermore, it can inform us what the individual differences in brain development mean, such as whether *attenuated* or *accelerated* brain trajectories are beneficial for behavioral outcomes or not. Before I address this question, I will first describe the three networks in the brain that are associated with motor, social, and affective functions.

## **Brain networks supporting motor, social, and affective functioning**

The brain is an interconnected organ and functionally relies on neural networks (Park & Friston, 2013). These networks are composed of groups of brain regions that interact to perform specific functions, ranging from basic sensory processing to higher-order cognitive tasks. The identification of *functions* of brain regions can provide a foundation for investigating the underlying *structure* supporting these functions. Some important higher-order networks that show protracted structural growth continuing into adolescence and adulthood, suggestive of prolonged sensitivity for environmental effects (Tooley et al., 2021), are the sensorimotor, social, and affective networks (Mills et al., 2014; Sanders et al., 2022; Tamnes et al., 2017). Hence, examining the degree of genetic and environmental contributions and evaluating the distinct influences of environmental factors will indeed yield insights into the sensitivity of environmental effects on these specific brain networks. As such, previous functional neuroimaging studies, discussed below, have shown with increased activation patterns which brain regions were related to the behaviors of interest. Figure 2 shows a visualization of the brain regions that are part of the sensorimotor, social, and affective network. As a subsequent step, it is key to identify which *structural* features of these brain regions are associated with behavioral outcomes or environmental experiences.

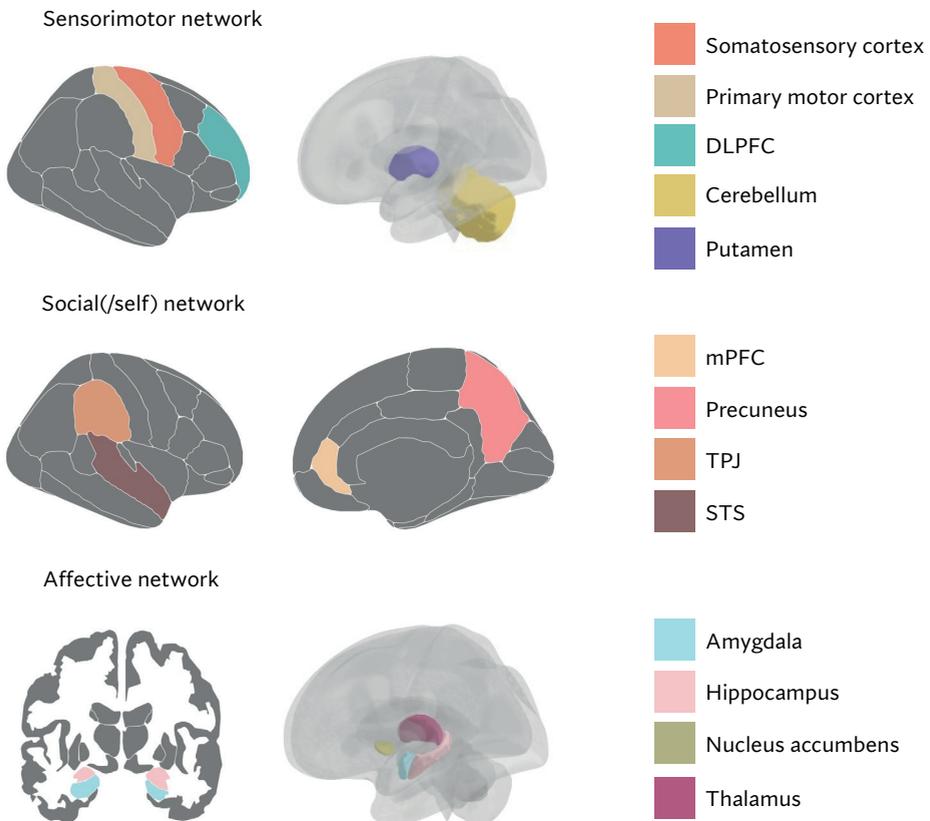
In the investigation to motor functioning, research have shown that the sensorimotor system is involved in the support of complex cognitive and sensorimotor skill learning (Altenmüller & Furuya, 2016; Crone, 2009; Drewing et al., 2006; Germine et al., 2011; Lakhani et al., 2016; Luna et al., 2015; Taubert et al., 2011). This network

contains several key regions, including the primary motor cortex, premotor cortex, somatosensory cortex (or known as supplementary cortex), dorsolateral prefrontal cortex (DLPFC), cerebellum, and putamen (situated in the basal ganglia). These regions are important for controlling and executing voluntary movements (primary motor cortex; Sanes & Donoghue, 2000), planning and organizing movements and actions (premotor cortex; Haines, 2012), receiving sensory input and controlling of movements (somatosensory cortex; Raju & Tadi, 2020), refinement and coordination of movements (cerebellum; Miall & Jenkinson, 2005), selection of action (DLPFC; Hasan et al., 2013), and motor control and fine-tuning of motor skills (putamen; Vicente et al., 2012). Taking together, these sensorimotor regions work together to facilitate the integration of sensory information and motor commands, which may ultimately contribute to a wide range of motor skills.

The social network is shown to be involved in the support of social cognition and interpersonal skills (Blakemore, 2008; van der Meulen et al., 2023). The social brain includes the medial prefrontal cortex (mPFC), temporoparietal junction (TPJ), superior temporal sulcus (STS), and the precuneus. These regions are involved in socio-cognitive processes, defined as the ability to understand the perspective of someone else (Blakemore, 2008; van der Meulen et al., 2023). More specifically, the mPFC is crucial in the understanding of mental states to oneself and others (Frith & Frith, 2003;2007; Van Overwalle & Baetens, 2009). The TPJ is suggested to be involved in perspective taking which is important for emphatic understanding (Will et al., 2015), while the STS is involved in the perception and processing of more general social cues such as the interpretation of facial expressions (Frith & Frith, 2003;2007; Van Overwalle & Baetens, 2009). The precuneus is thought to be included in social decision-making, such as retrieval of social information (Pfeifer et al., 2007) and emphatic responding (Masten et al., 2011). To this end, the interconnected social brain regions can possibly contribute to the complexities of social interactions, such as recognizing emotions, understanding social cues, and forming and maintaining social relationships.

The affective brain network, also part of the limbic system, is thought to be involved in emotion, motivation, learning, and memory (Rolls, 2019). Several key brain regions including the amygdala, hippocampus, thalamus, and ventral striatum (e.g., nucleus accumbens) are part of this network. Prior work showed that the amygdala plays a role in the processing of emotions, and in particular stress responses (Rolls, 2014). Also, it is thought to be involved in the consolidation of

emotional memory (McGaugh, 2004). The hippocampus is essential in the formation of memories, specifically those related to stress experiences (Riedel & Micheau, 2001). The thalamus is a hub station that integrates sensory perception with cognition such as emotional responses, important for sensory processing, motor control, and regulation of consciousness (Wolff et al., 2021). And finally, the nucleus accumbens, which is part of the ventral striatum, is seen as a key component in the reward system (Delgado, 2007) and suggested to have a function in positive social experiences (Harbaugh et al., 2007). The affective network interacts with other brain regions (e.g., cingulate cortex) to possibly support the modulation of social and emotional responses and to contribute to cognitive processes (Rolls, 2019).



**Figure 2.** Visualization of brain regions that are part of the sensorimotor, social(/self), and affective networks showing protracted growth into adolescence and adulthood; DLPFC = dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; TPJ = temporoparietal junction; STS = superior temporal sulcus.

However, pronounced differences in rate and timing of brain structures and development are observed *within* and *between* individuals (Gogtay et al., 2004; Mills et al., 2021; Wierenga et al., 2014). An example of a study assessing *within* individual variation in the prefrontal cortex, known for its high cognitive function such as decision-making and impulse control (Miller & Cohen, 2001), concludes that the PFC continues to develop into adolescence. In contrast, the somatosensory and visual cortex, both critical for vision and sensation, mature earlier (Gogtay et al., 2004; Shaw et al., 2008; Sowell et al., 2004). In addition, subcortical brain development follows a more variable pattern of volumetric change than cortical development. A substantial diversity in the developmental trajectories was observed between various subcortical regions, with inverted U-shaped developmental patterns for the hippocampus, thalamus, amygdala, pallidum, and cerebellum, while linear decreases were found in the putamen, caudate, and nucleus accumbens (Wierenga et al., 2014). It is suggested that these regional differences are partly influenced by puberty development (Goddings et al., 2014; Wierenga et al., 2018).

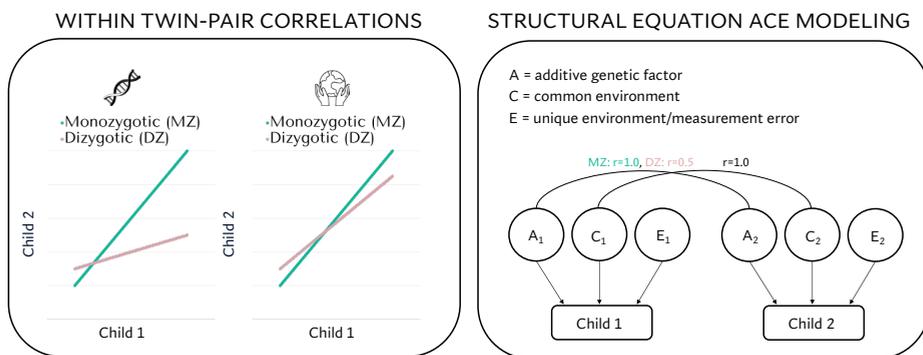
As for differences *between* individuals, prior work described large variances in terms of intercept (overall level, e.g., cortical thickness) and slope (developmental trajectory). Such that individual differences in intercept were explicitly observed in cortical brain regions, whereas individual differences in both intercept and slope were primarily observed in subcortical brain areas (Foulkes & Blakemore, 2018). Still, little is known about how these individual differences originate and whether they are accompanied by changing cognitive and social abilities. Variability in brain structure and development may arise from an interplay of genetic, environmental, and experiential factors. To address this question, longitudinal twin designs provide a promising direction to study genetic and environmental effects on brain development and longitudinal measures are needed to enable the examination of growth trajectories in brain structures within the same individuals, rather than relying on comparisons between different age groups. Therefore, in this thesis I first investigate the genetic and environmental effects on brain structure (i.e., intercept), function, and development (i.e., slope) from middle childhood to early adolescence using longitudinal twin modeling in **Chapters 2 and 5**.

## Twin modeling

One way to test individual differences in structural and functional brain development is by assessing heritability estimates. Applying this method on a developmental sample may also shed light on sensitive periods for environmental influences (Blakemore & Mills, 2014; Crone et al., 2020). For example, an underlying factor of why one individual is more talented in musical activities than the other is perhaps through genetic predisposition of specific brain regions (Seither-Preisler et al., 2014). Additionally, environmental factors (e.g., musical practice) can also affect brain regions that may lead to improvement in musical skills (Habibi et al., 2018). Previous studies indicate a predominant influence of genetics on brain structure (Jansen et al., 2015; Peper et al., 2007; Teeuw et al., 2019). Limited longitudinal studies exist on the heritable contribution to brain developmental patterns. There has been work showing heritability rates in cortical thickness development in children (Brouwer et al., 2017; Teeuw et al., 2019; van Soelen, Brouwer, van Baal, et al., 2012) and environmental effects on subcortical volume development (Brouwer et al., 2017; Swagerman et al., 2014). However, a comprehensive comparison of the relative contributions of genetic and environmental factors to developmental changes in various dimensions of brain structure and regions within one longitudinal study are rare, especially during the developmental phase between childhood and early adolescence. Twin designs are needed to examine whether variances in brain structure, -function, and -developmental trajectories can best be explained by genetic and/or environmental factors. Here, genetic factors can consist of one or more genes, while environment includes shared (e.g., home environment) and unique environment/measurement error (e.g., individual experience/noise in data) (McLoughlin et al., 2007).

A twin design allows for comparison between monozygotic (MZ) twins, who share 100% of their genes, and dizygotic (DZ) twins, who share approximately 50% of their genes. Note that it is assumed that MZ and DZ twin-pairs are raised in the same family and share a similar home environment. Also, it is assumed that twin-pairs are of the same sex. Herewith, a within twin-pair correlation that is significantly higher in MZ than DZ twins, signifies genetic contribution. Furthermore, twin pair-correlations that are both high in MZ and DZ twins indicate contribution of shared environment. Whenever MZ and DZ within twin-pair correlations are not significant, unique environment/measurement

error possibly drive variances in brain structure and development. As a next step, structural equation “ACE” modeling, based on twin similarities and dissimilarities, can be used to obtain the relative contributions of additive genetic (A), common environmental (C), and unique non-shared environmental/measurement error (E) factors (Neale et al., 2016). As MZ twins share 100% of their genes and DZ twins 50% of their genes, the correlations within a twin-pair between A is set to  $r=1.0$  for MZ twins and  $r=0.5$  for DZ twins. Also, as MZ and DZ twins both share the same environment at home, the correlation of C is set to  $r=1.0$ , whereas E is freely estimated. See Figure 3 for a schematic overview of the steps that are taken in twin modeling.



**Figure 3.** Schematic visualization of twin modeling steps. Higher within twin-pair correlation in monozygotic (MZ) twins than dizygotic (DZ) twins are an indication of genetic influences. High within twin-pair correlations in both MZ and DZ twins indicate shared environmental influences. Structural equation ACE modeling provides the relative contributions of heritability estimates by testing the variance that is explained by additive genetic factors (A), common (shared) environment (C), and unique environment/measurement error (E).

## Individual differences in brain development: Attenuated or accelerated?

After I address the question which brain regions are sensitive to genetic and environmental factors in their developmental time course using twin modeling, the next question I address is *which* environmental experiences have *what* effect on the brain. In the investigation to individual differences in longitudinal brain changes, accelerated and attenuated brain development may represent two distinct trajectories. Here, *accelerated* brain development refers to a pattern

where brain regions progress more rapidly than typical developmental norms, while *attenuated* brain development signifies deceleration or delay in typical developmental trajectories. These processes can be interpreted as early maturation in terms of accelerated brain patterns and late (or delayed) maturation in terms of attenuated brain patterns and are thought to be influenced by enriched and deprived environments (Tooley et al., 2021).

Cognitive enrichment is defined as the exposure to a multifaceted environment with a diversity in experiences which may include a range of educational materials. Conversely, the lack of cognitive enrichment is regarded as deprivation (McLaughlin et al., 2014; Sheridan & McLaughlin, 2014). A multidimensional construct that often has been used to measure deprivation in developmental research is socio-economic status (SES). This measure typically includes economic or educational markers on household (e.g., parental income) or neighborhood (e.g., poverty). As such, children and adolescents growing up in families with lower SES have been related to greater chronic stress (Baum et al., 1999) and other conceptions of severe stress (Belsky, 2019; Callaghan & Tottenham, 2016b, 2016a; Sheridan et al., 2012). Several additional studies on infants, children, and adolescents have observed that lower SES was associated with accelerated brain development (Jha et al., 2019; Khundrakpam et al., 2019; Parker et al., 2017; Piccolo et al., 2016; see review of Tooley et al., 2021).

Herewith, certain models propose that the lack of cognitive enrichment in specific domains can lead to *accelerated* synaptic pruning in brain regions associated with the processing of higher-order and complex cognitive and social stimuli. On the other hand, the counterargument posits that certain enriched cognitive inputs could *delay* synaptic pruning in relevant brain regions, suggestive of prolonged maturational processes (Tooley et al., 2021). In line with these proposed models, prior work showed that children raised in higher SES settings tend to encounter more complex and cognitively stimulating environments (Bradley et al., 2001). Adding to this, another study showed that cognitive stimulation, a factor associated with improved cognition in children (Sheridan et al., 2017), played a mediating role in the relationship between SES and increased cortical thickness in prefrontal brain regions (Rosen et al., 2018). This underscores the potential role of the effects of high SES or other enriched environments on structural brain development between childhood and adolescence. Therefore, further investigation is needed to examine how enriched

and deprived environments impact brain development and whether accelerated or attenuated growth is advantageous for developmental outcomes.

## **Musical ability as a model for environmental enrichment: Sensorimotor synchronization**

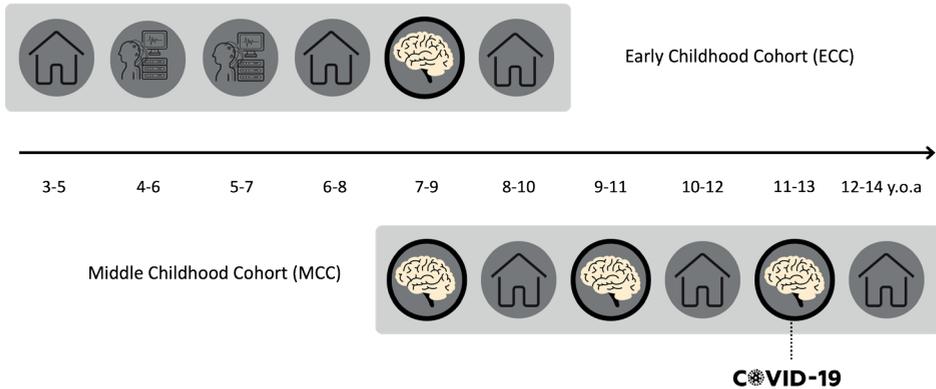
While the impact of experience on brain development has predominantly been explored within the framework of deprived environmental conditions, such as the influence of SES (see review of Tooley et al., 2021), there is a limited understanding of how enriched environments may shape developmental trajectories in the brain. Additionally, it remains unclear whether the insights assembled from enriched environments complement or diverge from the findings related to deprived environments. Musical ability can be seen as an enriched environmental factor for brain development due to the cognitive and neurobiological engagement it demands. Such that playing an instrument can foster sensorimotor coordination (Molinari et al., 2007), learning and performing music can improve attention and executive functioning (Rodríguez-Gomez & Talero-Gutiérrez, 2022), musical group performances can contribute to enhance social interactions (Feldman et al., 2011; Trehub, 2003), and playing or listening to music has been shown to have stress-reducing (Linnemann et al., 2016) and emotion regulatory-improving effects (Blasco-Magraner et al., 2021). Also, distinct neural systems are involved including regions that have been related to auditory, motor, somatosensory, executive, and affective functioning (Altenmüller & Furuya, 2016; Gaser & Schlaug, 2003; Groussard et al., 2010; Habibi et al., 2018; Jäncke, 2009; Koelsch, 2014; Li et al., 2014; Peretz & Zatorre, 2005; Zatorre et al., 2007; Zendel et al., 2013).

Sensorimotor synchronization (SMS) tasks are often used to measure musical ability because they provide a method to assess an individual's ability to coordinate motor actions with auditory stimuli (see reviews of Repp, 2005; Repp & Su, 2013), which is a key aspect of musical performance (Karpati et al., 2016). In these tasks, individuals synchronize their movements, such as tapping to a given external rhythm. The goal is to achieve precise timing and coordination between the sensory input and motor output. In this thesis, I examined the association between individual differences in structural brain development and sensorimotor synchronization in **Chapter 3**.

## The Leiden Consortium on Individual Development twin study

The detailed studies in the present thesis utilized data from the Leiden Consortium on Individual Development (L-CID), which is a cohort-sequential longitudinal twin study (Crone et al., 2020; Euser et al., 2016). The L-CID study covers two cohorts: an early childhood cohort (ECC; N=476 including 238 twin pairs), monitored from ages 3 to 9, and a middle childhood cohort (MCC; N=512 including 256 twin pairs), monitored from ages 7 to 13. Both cohorts underwent six consecutive years of observation, alternating between annual home visits and laboratory sessions involving EEG/MRI assessments. Notably, the ECC and MCC cohorts overlapped in age at two specific points: the concluding two time points of the ECC and the initial two time points of the MCC. See Figure 4 for a visualization of the L-CID design. The unique design of the L-CID study enabled the exploration of why some children thrive and others experience more difficulties during development based on differential neural and behavioral measures, twin effects, and environmental factors. Most studies in the present thesis (chapters 2, 3, and 4) are based on data from the MCC and one study included fMRI data of the ECC (chapter 5).

During the acquisition of data for MRI time point 3, also referred to as “wave 5” (see Figure 4 lower half), the Netherlands underwent a lockdown in response to the COVID-19 pandemic, which commenced on March 16th (2020). This lockdown led to the nationwide closure of all schools. The data collection for MRI time point 3 restarted on July 25<sup>th</sup> (2020) and finished on April 28<sup>th</sup> (2021). The disruptive influence of the COVID-19 pandemic presented an opportunity to compare behavioral and brain developmental changes between participants in the *pre*-pandemic and *peri*-pandemic groups, further allowing an exploration of the effects associated with the duration of the pandemic. In this thesis, I examined the association between individual differences in structural brain development and experiencing COVID-19 pandemic (i.e., deprived environment), in **Chapter 4**.



**Figure 4.** Display of the L-CID twin study design. The L-CID study includes an early childhood cohort (ECC; ages 3-10) and a middle childhood cohort (MCC; ages 7-14). Black rounds indicate the waves of data that are utilized in the present thesis.

## Self-concept fMRI paradigm

So far, I mainly discussed research on structural brain development. Interestingly, fMRI studies in adolescents and adults demonstrated that self-processing activation is mainly observed in the cortical midline structures. These structures include the essential role of the mPFC, which is also important in previously described social processes, the medial parietal cortex, and the anterior and posterior cingulate cortices (ACC/PCC) (Denny et al., 2012; Lieberman et al., 2019; Northoff et al., 2006; Pfeifer et al., 2007).

Middle childhood is described as a transitional phase in cognitive and social behavior (Del Giudice et al., 2009), also with regards to self-concept. Specifically, in early childhood, children primarily engage in temporal comparisons by evaluating themselves in relation to their past selves. However, in middle childhood, a notable shift occurs as children begin to actively partake in social comparisons (Harter, 2012). This shift introduces the potential for heightened social environmental influences shaping their self-concept. In these studies, typically an individual can describe oneself in different aspects such as in the social or academic domain. Prior work in adolescents and adults showed that the processing of these domains was accompanied by differential neural activation, such that social self-evaluations elicited more mPFC activation while academic self-evaluations more lateral prefrontal (PFC) activation (Jankowski et al., 2014; van der Crujisen et al., 2017, 2018). Yet, there is little understanding on whether children elicit similar neural activation as adolescents and adults and remained to be investigated.

Therefore, the examination of genetic and environmental influences on neural and behavioral correlates of self-concept can shed new light on the effects of genetics and the environment on shaping self-concept. In this thesis, I will study the role of heritable and social environment factors on self-concept development at a functional level in **Chapters 5**.

## Outline thesis

The main aim of the present thesis is to examine individual differences in genetic and environmental effects on structural and functional brain development in the period spanning middle childhood and early adolescence. One section of the thesis is focused on the extent to which genetic and environmental contributions influence variances in structure, function, and developmental trajectories of brain regions (**Chapter 2** and **5**). The other section of the thesis (**Chapter 3** and **4**) explores how enriched and deprived environments contribute to individual differences in structural brain development.

In **Chapter 2**, I first examined whether there are variations in genetic and environmental contributions on differential brain features (i.e., cortical thickness, surface area, and subcortical volume) in middle childhood (at age 7) between brain regions within the sensorimotor, social, and affective networks. Subsequently, I evaluated the degree to which genetic factors, shared environment, and unique environment/measurement error contribute to individual differences in the developmental trajectories (ages 7-14) of differential brain features of brain regions within the sensorimotor, social, and affective networks. Addressing these aims provided insights into the heritability estimates of protracted developmental brain structures, considering regional-, dimensional-, within-subject-, and between-subject-dependencies. For this project, up to three MRI assessments of the middle childhood cohort were included.

In **Chapter 3**, I first explored *how* developmental trajectories of sensorimotor and affective brain regions are associated with sensorimotor synchronization (SMS) performance. In the present thesis, the TeensyTap framework was employed for recording SMS performance. This digital communication tool incorporates a graphical user interface, facilitating the simultaneous presentation of an auditory pacing signal (metronome), the measurement of motor action timing, and the generation of auditory feedback (Schultz & van Vugt, 2016; van Vugt, 2020). Early adolescents were instructed to synchronize their finger taps

with the regular beats of the metronome or music songs, aiming to maintain a stable and accurate tempo. Performance on SMS task is considered a proxy for musical skills (Bailey & Penhune, 2010; Hannon et al., 2018; Repp, 2006) and is notably heightened in musicians compared to non-musicians (Karpati et al., 2016).

Subsequently, I tested whether the relation between brain development and SMS performance is driven by genetic and/or environmental contribution, using bivariate genetic modeling. To do so, the longitudinal framework including up to three waves of MRI data and performance on a SMS task at the final wave as outcome variable (cross-sectional) was used. Addressing these aims offered insights into how an enriched environment can influence individual variations in structural brain development. Additionally, the results revealed insights into what extent brain and behavior are influenced by shared genetic and/or environmental factors, impacting changes in both measures.

In **Chapter 4**, I investigated the impact of experiencing COVID-19 pandemic on brain developmental trajectories of social and affective (stress) brain regions in 9-13-year-olds. These regions are thought to be affected based on the serious social and stress consequences during the pandemic. To do so, I examined longitudinal structural alterations in brain regions associated with social processing, including the medial prefrontal cortex (mPFC) and temporoparietal junction (TPJ), alongside stress-related areas like the hippocampus and amygdala, utilizing two waves of MRI data of the middle childhood cohort. We were able to test this aim by selecting two age-matched subgroups, approximately one half was tested before (N = 114) and the other half during (N = 204) the COVID-19 pandemic. I additionally tested whether pandemic length was associated with accumulating or resilience effects of brain development. Exploring the impact of this deprived environmental condition, the COVID-19 pandemic, yielded insights into whether the conclusions drawn from enriched environments (**Chapter 3**) align with or deviate from the findings related to deprived environments (**Chapter 4**).

In **Chapter 5**, I studied how domain-specific (e.g., social, academic) self-concept is related to neural correlates in young twins (ages 7-9), and to what extent neural and behavioral correlates of self-concept are influenced by genetic and/or environmental factors. Both academic and social self-concepts were assessed since middle childhood is an important time window for taking on new social roles in academic and social contexts (Harter, 2012). For this project, fMRI data of wave 5 in the early childhood cohort was included. The present thesis incorporated a

self-concept fMRI paradigm, based on the study of van der Crujisen et al (2018). In the MRI scanner, participants responded to brief statements about academic and social self-traits, such as “I am kind” or “I am unintelligent,” by selecting “Yes” or “No”. Each domain (academic and social self-traits) included positively valenced and negatively valenced self-evaluations. Together, these results show at a functional brain level whether separable aspects of self-concept are differentially sensitive to heritable and environmental experiences.