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

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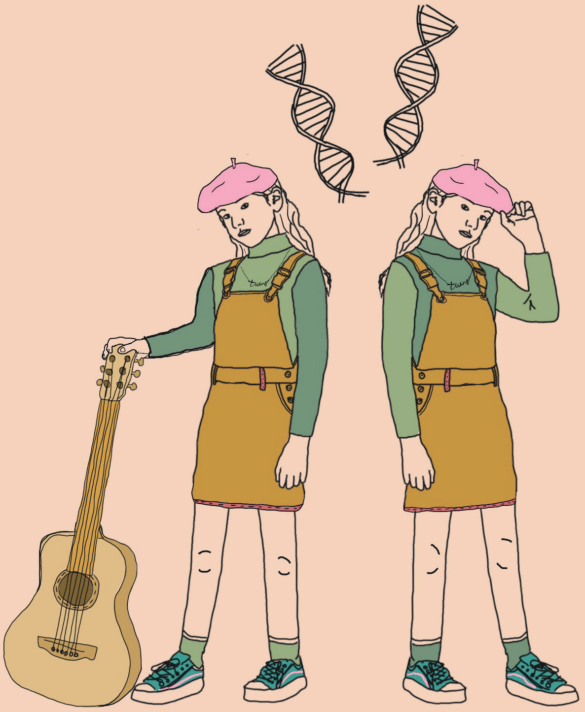

CHAPTER 6

General Discussion

SUMMARY

The developmental period spanning middle childhood to early adolescence represents an important time window characterized by changes in physical, cognitive, social, and emotional domains (Choudhury et al., 2006; Crone & Dahl, 2012; Crone & Fuligni, 2020; Del Giudice et al., 2009; Glowiak & Mayfield, 2016; Goodway et al., 2019; Steinberg, 2005). During this developmental period, no two individuals follow identical developmental pathways. An important factor contributing to individual differences in ability and behavior may stem from variations 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 Cruijsen et al., 2023; van der Meulen et al., 2023). While it is apparent that the brain undergoes rapid growth and organization across various global MRI dimensions (Aubert-Broche et al., 2013; Bethlehem et al., 2022; Gilmore et al., 2018; Mills et al., 2016; Tamnes et al., 2017; Wierenga et al., 2014; 2014), the goal of this thesis was to gain a deeper understanding of *what* specific factors and *how* these factors contribute to variations in brain trajectories from childhood to adolescence. In this chapter, I summarize the findings of the studies that are part of this thesis below, followed by a general discussion, methodological considerations, and potential directions for future research.

Genetic and environmental effects on brain structure and development

Differences in brain structure and development may result from a complex interplay of genetic, environmental, and experiential factors. To explore their relative contributions, longitudinal twin designs offer a promising approach for studying the impact of genetics and environment on structural brain development. This thesis included data from the longitudinal Leiden Consortium on Individual Development (L-CID) study in which monozygotic and dizygotic twins were tested yearly from childhood (7-8 years) to early adolescence (11-13 years) with bi-annual MRI assessments. **Chapter 2** of this thesis investigated genetic and environmental effects on various dimensions of brain structure in middle childhood (i.e., intercept) and development (i.e., slope) from middle childhood to early adolescence, using twin modeling. In this study, I explored sensorimotor, social, and affective brain regions that are known for their protracted development

(Mills et al., 2014; Sanders et al., 2022; Tamnes et al., 2017), considering regional-, dimensional-, within-subject, and between-subject-dependencies. The brain regions of interest included the somatosensory cortex, DLPFC, premotor cortex, cerebellum (i.e., sensorimotor network), mPFC, TPJ, STS, precuneus (i.e., social network), amygdala, hippocampus, and nucleus accumbens (i.e., affective network). I explored two measures of structural brain development: surface area and cortical thickness, as both have previously been related to individual differences (Foulkes & Blakemore, 2018).

The results highlight a few key aspects. First, a combination of both genetic and environmental contributions explained variances in brain structure and longitudinal brain changes. More specifically, in middle childhood, brain structural measures showed largely genetic contributions (ranging from 18-59%) with additional location-specific contributions of shared environment in the somatosensory cortex, primary motor cortex, DLPFC, TPJ, STS, precuneus, hippocampus, amygdala, and nucleus accumbens (ranging from 5-30%). For longitudinal structural brain changes, genetic factors primarily accounted for the variances (ranging from 1-29%). Additional location-specific shared environmental factors influenced developmental changes in the somatosensory cortex, DLPFC, cerebellum, TPJ, STS, and hippocampus. Second, this study allowed us to answer a longstanding question of whether the surface area or cortical thickness of brain structures and development was more sensitive to environmental influences (Foulkes & Blakemore, 2018). I observed that surface area at the start of the study was more influenced by genetic predictors compared to cortical thickness. Conversely, longitudinal changes in surface area were slightly more influenced by shared environmental factors than cortical thickness. Therefore, it is important to study and compare cortical thickness and surface area as complementary measures of brain development.

Musical ability as a model for environmental enrichment: Sensorimotor synchronization

Given the observed environmental contributions on brain development in Chapter 2, the next goal was to examine what environmental factors, and if also how an enriched environmental factor influenced brain developmental trajectories in a region-of-interest study (**Chapter 3**). Cognitive enrichment is defined as

the opportunity to gain additional experiences in one specific field, in this case motoric training that can aid the development of music abilities. I did so by first investigating whether brain developmental trajectories of sensorimotor and affective regions (longitudinal; aged 7-14) predicted sensorimotor synchronization performance (cross-sectional; aged 11-14), which can be seen as a key element in musical ability (Bailey & Penhune, 2010; Hannon et al., 2018; Karpati et al., 2016; Repp, 2006). Moreover, sensorimotor synchronization performance showed to be related to musical experience as tapping performance was superior in musicians, who had formal musical training, compared to non-musicians (Karpati et al., 2016). Subsequently, I tested to what extent the association between brain development and sensorimotor synchronization performance was driven by genetic and/or environmental contributions using bivariate genetic modeling, specifically to find out whether genetic and/or environmental influences impact changes in both brain and behavioral measures. Of note, the L-CID design involves a typical sample of non-musicians with variation in experiences. To assess sensorimotor synchronization performance, a stability finger-tapping task was incorporated using an anti-phase metronome and an in-phase music-cued condition. This study resulted in several important findings at both behavioral and neural levels.

Behaviorally, results indicated that condition difficulty was successfully manipulated. Children showed better sensorimotor synchronization performance in anti-phase metronome and simple music-cued conditions compared to the complex music-cued task conditions. Furthermore, music practice on an instrument was related to better tapping stability within all task conditions, suggesting that sensorimotor synchronization performance can be seen as an important indicator of musical ability. We accounted for parental education (PE) as a control variable in our analyses, as socioeconomic status (SES) can influence musical education (Ballantine et al., 2021; Feldman & Matjasko, 2007; Klinedinst, 1991). Indeed, higher sensorimotor synchronization performance was observed in the high PE group in comparison with the middle PE group. Children in the high PE group also had more musical practice, possibly indicating greater parental resources for formal musical training compared to the middle PE group.

On a neural level, results indicated that 6 out of 15 sensorimotor and affective brain regions of interest were associated with sensorimotor synchronization performance. Out of the 6 brain-behavior associations, 4 regions showed that *attenuated* brain development was related to high sensorimotor

synchronization performance. More specifically, the majority of the brain regions (i.e., inferior frontal gyrus including pars orbitalis and pars triangularis, cerebellum, amygdala) showed that attenuated brain development was associated with high sensorimotor synchronization performance. Note that two regions (i.e., fusiform gyrus, postcentral/somatosensory gyrus) demonstrated accelerated brain development as a predictor of high sensorimotor synchronization performance. The brain-behavior effects were mostly observed in measures of cortical thickness and sensorimotor synchronization performance in complex musical task conditions. Furthermore, bivariate genetic modeling showed the observed brain-behavior associations were at least partly driven by shared (ranging from 1%-13%) and unique environmental factors/measurement error (ranging from 81%-91%), and to genetic factors (ranging from 7%-19%). Possibly, musical practice impacted changes in both sensorimotor synchronization performance as well as brain development, which was most evident in the complex music-cued task condition. Moreover, although PE was positively associated with sensorimotor synchronization performance in the complex music-cued task condition on a behavioral level, PE did not explain the brain-behavior associations. Taken together, this study provides evidence that an enriched environment for music experience and practice is related to attenuated patterns of brain development.

Experiencing the COVID-19 pandemic as a model of environmental deprivation

The understanding of whether insights gathered from deprived environments on brain development complement findings associated with enriched environments on brain development remains unclear. Therefore, in this thesis, I additionally investigated the effects of a deprived environmental factor (i.e., experiencing the COVID-19 pandemic) on brain development in early adolescents. The COVID-19 pandemic, initiated in 2020, provided a large global environmental intervention that impacted behavior and resulted in social consequences, such as social distancing, post-infection isolation, limited interactions with friends, and multiple school closures (Andrews et al., 2020; Orben et al., 2020). In particular, teenagers suffered from the behavioral interventions related to the pandemic, as they experienced more negative feelings and lower mental well-being in comparison with older age groups (Carstensen et al., 2020; Green et al., 2021).

I examined using a longitudinal study the impact of experiencing the pandemic on brain development, specifically focusing on regions previously implicated in social cognition (Blakemore, 2008; Mills et al., 2014) and stress (Kim et al., 2015; Tottenham & Sheridan, 2010; Woon & Hedges, 2008). Hence, the present region-of-interest study (**Chapter 4**) examined in teenagers (aged 9-13) *whether* and *how* COVID-19-related behavioral interventions affected their brain development in regions correlated with social (i.e., mPFC, TPJ) and stress (i.e., hippocampus, amygdala) processes. I did so by comparing two age-matched groups, one was tested before (n=114) and the other during (*peri*-pandemic; n=204) pandemic. In addition, I explored whether the duration of the pandemic was associated with resiliency or accumulating effects of brain development.

The findings revealed accelerated development in mPFC thickness and hippocampus volume among teenagers in the *peri*-pandemic group (i.e., participants who experienced the pandemic) compared to the *before*-pandemic group. Additionally, TPJ thickness and surface area growth showed immediate effects of the pandemic, returning to a typical developmental trajectory when the pandemic lasted longer. No pandemic group effects were observed for the stress-related amygdala. Taken together, these findings show that deprived and stressful experiences can have an effect on brain development, but we also observed evidence for potentially subsequent resilience to negative effects.

The nature of the self in middle childhood

Whereas the first three chapters examined structural development and explanations for individual differences, in the final empirical chapter I examined brain-behavior effects more directly using functional MRI (fMRI). Although MRI and fMRI have different strengths, such that MRI is important for detailed structural information and fMRI for capturing functional dynamics in the brain, they can be used together to gain a more comprehensive understanding of the brain's structure and direct neural processes underlying behavior. Moreover, exploring genetic and environmental effects on brain function can also shed light on individual differences observed in specific cognitive abilities and behavior. I focused specifically on cognitive function that is expected to be highly sensitive to individual differences and social experiences, that is, the appraisal of self. The ability to describe oneself in multiple domains improves considerably during middle childhood through increased

social comparisons (Harter, 2012), which introduces the possibility for enhanced environmental contribution on brain and behavior. Therefore, **Chapter 5** dived into investigating how domain-specific (i.e., social, academic) self-concept is related to neural correlates in relatively young twins (aged 7-9), and to what extent neural and behavioral correlates of self-concept are driven by genetic and/or environmental factors. Results revealed two key elements.

First, neural evidence of activation patterns in the cortical midline structures and prefrontal cortex (PFC) regions in children aligned with previous studies conducted in adolescents (van der Cruijsen et al., 2018) and adults (Denny et al., 2012; Moran et al., 2006; Murray et al., 2012; Northoff et al., 2006). More specifically, results indicated greater activation in the mPFC during self-related evaluations compared to control trials. This effect was more prominent for social self-evaluations than academic self-evaluations, while stronger activation in the DLPFC was observed for academic compared to social self-evaluations. These findings indicate early development of brain regions underlying distinct domains of self-concept that are already active in middle childhood. An interpretation of this might be that a well-balanced self-concept can have a positive influence on the child's social functioning which can potentially serve as an important factor for protection and adjustment against problem behavior (Ybrandt, 2008).

Second, results underscored the domain-specific impacts of genetic and environmental factors on the observed behavior and neural correlates of self-concept in middle childhood. Notably, stronger environmental influences were observed in the social domain compared to the academic domain, whereas stronger genetic effects were observed in the academic compared to the social domain. More specifically, considering the distinct genetic and environmental influences on academic and social self-evaluations observed at a behavioral level, I examined the possibility of identifying similar domain-specific effects in neural activity. Indeed, two neural findings validated the domain-specific heritability effects for self-evaluations versus control trials and negative versus positive self-evaluations. Variation in mPFC and right anterior PFC activity related to *academic traits* was partially explained by *genetic* factors, while mPFC and right anterior PFC activity linked to *social* traits were influenced by *shared environmental* factors. Taken together, in this last empirical chapter I confirmed that genetic and environmental influences are important for developing a coherent sense of self, with a stronger effect of environmental factors on social self-development.

GENERAL DISCUSSION

Taken together, the studies described in the present thesis revealed two important main outcomes. First, by providing a comprehensive comparison of genetic and environmental factors on various dimensions of brain structure and function, and developmental changes, I observed subtle and anatomically distinct patterns of genetic and environmental influences across the brain. However, it is important to avoid overgeneralization and to acknowledge the complex interplay of genetic and environmental influences on the brain. Second, by introducing the effects of environmental enrichment and deprivation on brain development, I gathered knowledge on how individual differences in developmental trajectories were distinctively associated with these environmental factors. These outcomes emphasize the important phase of opportunity and resilience in brain development, between middle childhood and early adolescence.

Patterns of genetic and environmental effects on brain structure and function

That the structural brain in childhood was largely driven by genetic factors (**Chapter 2**) is in line with prior work investigating heritability on brain structure in children (Lenroot et al., 2009; Panizzon, Fennema-Notestine, Eyler, Jernigan, Prom-Wormley, Neale, Jacobson, Lyons, Grant, & Franz, 2009; Peper et al., 2009; Schmitt et al., 2007; Strike et al., 2019; van Soelen, Brouwer, Peper, et al., 2012; Yoon et al., 2010, 2011) (see also reviews of Jansen et al., 2015; Peper et al., 2007). Furthermore, in the investigation of genetic and environmental influences on development of brain structure, previous studies already revealed that a large part of variations in developmental trajectories are explained by genetics (Brouwer et al., 2017; Swagerman et al., 2014; Teeuw et al., 2019; van Soelen, Brouwer, van Baal, et al., 2012). Possibly, a genetic blueprint provides the foundational framework for the structural organization of the brain (Fox et al., 2010). This framework might serve as the basis for receiving, interpreting, and acting on the surrounding environment (Hammock & Levitt, 2006) from which a more defined structure will emerge. Refinement of brain structure involving cognitive, emotional, social, and physical behavior is thought to be driven by both genetic and environmental factors and experiences (Fox et al., 2010; Lindenberger & Lövdén, 2019).

Indeed, the findings of **Chapter 2** highlight the additional shared and unique

environmental/measurement error contributions that explained variations in brain structure in middle childhood and development between middle childhood and early adolescence of multiple brain regions involved in the sensorimotor, social, and affective networks. These environmental contributions to brain structure and development were region specific. In particular, these location-specific environmental contributions on developmental changes may suggest distinct sensitive windows of various regions across the brain. Sensitive windows reflect developmental phases during which individuals are more susceptible to environmental influences in comparison to periods preceding or following this window (Gabard-Durnam & McLaughlin, 2020). I address the possibilities of distinct sensitive windows below in more detail specified per brain network (sensorimotor, social, and affective).

Environmental effects were most pronounced on the somatosensory and primary motor cortex within the sensorimotor network, indicating a potentially sensitive period for brain plasticity around age 7 that is possibly influenced by activities such as sports (Gerver & De Bruin, 2003) or practicing a demanding musical instrument (Penhune, 2021). Additionally, the cerebellum exhibited the most significant environmental effects on developmental trajectories, implying heightened susceptibility to environmental alterations *after* middle childhood, possibly contributing to the refinement of movements (Mottolese et al., 2013). In the social network, environmental effects influenced the brain structure and development most in the TPJ and STS and the structure of precuneus to a smaller extent. These regions are involved in social cognition, perspective-taking, and social decision-making respectively (Blakemore, 2008) and are thought to depend on social experiences in childhood and adolescence (Crone & Dahl, 2012; Crone & Fuligni, 2020). The absence of environmental contribution to the mPFC can be attributed to age-dependent plasticity, indicating greater susceptibility to environmental effects on the mPFC after middle childhood. This aligns with previous research demonstrating the relation between mPFC and changes in friendship at age 14 (Becht et al., 2021). In the affective network, the most pronounced environmental effects were observed on the structure and development of the highly plastic hippocampus (Hanson et al., 2015; Kim & Diamond, 2002). The structure of the nucleus accumbens and amygdala showed some influence from environmental factors, but this effect was not observed in longitudinal changes. This may suggest that these regions may be more sensitive to environmental input before and during middle childhood than after.

Although there was no shared environmental contribution to the structural properties of the mPFC (a crucial region for social and self-processing), I did observe shared environmental input on the activity of the mPFC during social self-evaluations (aged 7-9) using fMRI in **Chapter 5.** This study investigated genetic and environmental effects on neural and behavioral correlates of self-concept. By specifying self-concept in two domains (i.e., academic, social), I was able to demonstrate domain-specific heritability effects on both a behavioral and neural level, resulting in heightened environmental contribution on social self-concept whereas genetic contribution on academic self-concept. As such, mPFC (and right anterior PFC) activity was driven by environmental contribution for social self-evaluations and by genetic factors for academic self-evaluations. A possible explanation for the domain-specific heritability findings might be that cognitive ability plays a more significant role in evaluating one's academic self (Bong & Skaalvik, 2003), while the social environment (e.g., peers, parents) is more influential in evaluating one's social self. Adding to this, previous research has indicated that cognitive abilities are largely driven by a genetic contribution (Haworth et al., 2010), whereas environmental factors primarily influence social behavior (van der Meulen et al., 2018).

Taken together, through the examination of both structural and functional brain measures and by demonstrating diverse findings contributing to variations in brain structure and function, this thesis underscores the need for cautious consideration of overgeneralization in heritability estimates. It emphasizes the complex interplay of genetic and environmental influences on the brain. Therefore, to enhance the understanding of individual differences in genetic and environmental effects on brain development, a comprehensive insight is required using an incorporation of a combination of brain measures including structure (i.e., cortical thickness and surface area), function, development, and genetic and environmental influences. Furthermore, applying genetic modeling on a developmental sample showed that the developmental phase between middle childhood and early adolescence is sensitive to environmental influences. Hence, in the second part of the general discussion, I will address the influence of specific environmental factors on brain trajectories during this developmental period and draw implications from the findings.

Individual differences in brain development: Attenuated or accelerated?

By studying the effects of enriched and deprived environments on brain development, I showed that an enriched environment (e.g., musical ability and training) is associated with predominantly *attenuated* brain development while a deprived environment (e.g., experiencing the COVID-19 pandemic) with *accelerated* brain development. **Chapter 3** aligns with the idea that an enriched environment may impact brain development in an attenuative matter, reflecting possibly processes related to plasticity, and perhaps even to meta-plasticity (see review of Tooley et al., 2021). The possibility of this reflection can be supported by the finding that the association between sensorimotor synchronization performance and brain development was partly influenced by environmental factors (e.g., musical practice) and not solely by genetics. While attenuative brain development may not be a direct indication of brain plasticity or meta-plasticity, it can be viewed as a potential outcome of the brain's adaptive capabilities in response to environmental enrichment. Adding to this, attenuated growth associated with enriched environments, such as musical ability, may indicate a delay of maturational processes, which can lead to a prolonged and enhanced window of plasticity.

This suggestion can be made based on prior animal work (e.g., mice, rats, rodents) that investigated the causal impact of cognitive enrichment on brain development. Environmental enrichment in young and adult animals has been demonstrated to increase cortical thickness, involving enhanced dendritic volume (i.e., extensions of neurons that stimulate communication between neurons), branching (i.e., neuronal process that enhances circuit complexity), synaptogenesis (i.e., forming of synapses between neurons), and glial cell multiplication (i.e., cells that require physical and chemical support to neurons) (see review of Markham & Greenough (2004)). Increased synaptogenesis, dendritic plasticity, and glial cell multiplications may suggestively indicate a prolonged window of maturation that results in the development of enhanced complex brain circuitry (Tooley et al., 2021). Gaining insights into how experiences in childhood impact the rate of brain maturation holds implications for brain plasticity and meta-plasticity on a cellular level. That is, juvenile enrichment reduced perineuronal nets (i.e., synaptic stabilization), boosted synaptic plasticity (i.e., long-term potentiation/depression), and impacted parvalbumin-positive neuron expression (i.e., GABA interneuron; providing feedback and -forward

synaptic inhibition) based on animal studies (Baroncelli et al., 2010; Carstens et al., 2016; Duffy et al., 2001; Favuzzi et al., 2017; O'Connor et al., 2019; Pekarek et al., 2020). Inhibition levels following the impact of parvalbumin-positive neuron expression in the juvenile period, that is crucial for regulating plasticity (Rupert & Shea, 2022), were maintained in adulthood. That these inhibition levels maintained during both periods may indicate an extension of early plasticity periods (Brainard & Knudsen, 1998; Greifzu et al., 2014, 2016). The impact of cognitive enrichment on neural plasticity in humans at a cellular level is not yet fully understood. It requires further exploration to fully capture the cognitive, social, and emotional aspects associated with being raised in a cognitively enriched environment. However, the observed attenuated growth in relation to a cognitive enrichment in **Chapter 3** may reflect similar underlying cellular processes as described in the prior animal studies.

The results from **Chapter 4** postulate that experiencing behavioral interventions during the COVID-19 pandemic, such as possibly stressful and socially isolating changes, had accelerating effects on the hippocampus and mPFC development of 9-13-year-olds. This result aligns with prior work showing that children growing up in environmental deprivation, such as low SES backgrounds, also showed 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).

There are a few explanations for why deprived environments can lead to accelerated brain development. Environmental deprivation is often associated with multiple forms of (chronic) stress and can ultimately influence the pace of brain development (Belsky, 2019; Callaghan & Tottenham, 2016b; Sheridan & McLaughlin, 2014). First, based on the 'developmental support hypothesis' (Snell-Rood & Snell-Rood, 2020), children can interpret stressors or threats as an indicator of insufficient support and protection by perceiving signals that their environment demands maturity. This can subsequently initiate adaptive top-down processes that possibly result in accelerated brain development since parental investment was associated with slower maturation in previous studies (Snell-Rood et al., 2011; Snell-Rood & Snell-Rood, 2020). Second, deprived environmental experiences such as repeated stress (McEwen, 1998) or lower sleep quality (Mezick et al., 2008) can result in faster cellular aging of the body. Specifically, methylation, which causes alterations in epigenetic processes, have been detected in children from lower SES backgrounds (Austin et al., 2018; Miller et al., 2011; C. Mitchell et al., 2014). In line with this cellular aging interpretation,

children who experience deprivation and threat can enter puberty earlier (Colich et al., 2020; Sun et al., 2017). Conversely, early puberty may perhaps also induce faster brain organization and development (Goddings et al., 2014; Wierenga et al., 2018). A final explanation might be that repeated detection of stressors in the brain circuitry of stress regulation, such as the mPFC and amygdala regions, can also result in accelerated brain connectivity and maturation between these regions (Herringa et al., 2016; Thijssen et al., 2020).

Although these are all plausible explanations for how accelerated brain development can follow the experience of deprivation, it is important to better understand which of these mechanisms impacted brain acceleration after experiencing COVID-19 pandemic measures. Currently, there is still limited understanding of the specific social and stress experiences during the pandemic and their impact on early adolescents' daily lives. Some children mentioned more tension and negative feelings and others described more engagement in positive media experiences and online social interactions (de Leeuw et al., 2022; Masten & Motti-Stefanidi, 2020). The next step, therefore, would be to find out what specific factors during the pandemic are leading to acceleration and recovery of brain effects (such as for the TPJ) over a more extended period during and after the pandemic. This should be assessed in follow-up MRI assessments within L-CID in combination with detailed behavioral experiences. Identifying the factors contributing to accelerated development enables future studies to construct more effective intervention strategies.

METHODOLOGICAL CONSIDERATIONS

The studies in this thesis included distinct and novel methodologies, such as growth-, genetic, and linear mixed modeling, to enrich the literature addressing individual variations in brain development from childhood to early adolescence. While the outcomes show important implications for the developmental neuroscientific field, two methodological considerations are mentioned for future perspectives below.

Genetic modeling

Chapters 2 and 5 in the present thesis report genetic and environmental effects on brain structure, function, and development using a novel structural equation ACE modeling approach. This approach allows researchers to differentiate genetic factors

from environmental influences. However, some methodological limitations should be considered in the interpretations of these findings. First, the studies mainly interpreted additive genetic (A) and common shared environmental (C) factors because unique environment (E) also involves measurement error that cannot be disentangled using the L-CID design. Future designs should incorporate information on additional family members in combination with classical twin data to be able to interpret both non-additive genes (D) and unique environment (E) (Keller et al., 2009). Furthermore, **Chapters 2 and 5** revealed a combination of genetic and environmental influences on brain structure, function, and development at a group level that indirectly may indicate interactions between genes and environment. Future research should identify which individual neurobiological mechanisms can explain increased environmental susceptibility to be able to measure direct gene by environment interactions. Gene-by-environment interaction characterizes varying responses to environmental exposures based on genotype. Failure to include gene-by-environment interaction in the model may lead to increased estimates of unique environmental variance when it is present (van Soelen, Brouwer, van Baal, et al., 2012).

Longitudinal models in developmental neuroscience

In the era of increasing longitudinal studies in Developmental Neuroscience, the expansion of statistical models to choose from poses a significant challenge in deciding upon the most suitable option (McCormick, 2021; McCormick et al., 2023). This challenge of model options also applies to the L-CID study that involving complex (non-)linear longitudinal brain changes (i.e., 2-year interval of 3 timepoints with some individuals overlapping in age), potential influences of sex and/or pubertal effects, the presence of multicollinearity within twin-pairs, and demands novel statistical models to assess which important predictors contribute to individual differences in brain development. Currently, using models from the Research Methods and Statistics discipline based on simulated data provides a valuable starting point, such as latent (class) growth, latent change, and random intercept cross-lagged models.

Yet, pervasive issues encountered while using L-CID data in innovative developmental models including complexity of the data (i.e., within-twin dependency, developmental age effects, longitudinal within-person dependency) and its variability in addition with missing values, that is inherent to real-world

information. These challenges persisted and led to, for instance, nonconvergence problems at times. Moreover, there were several other challenges that we had to deal with. First, we had to deal with possible developmental age effects within the 2-year interval of MRI assessments and that some individuals overlapped in age between assessments. Addressing these challenges can be approached by utilizing TSCORES in Mplus, as demonstrated in one of the studies, to account for age effects rather than time point effects. Second, another complication arises from potential multicollinearity effects involving changes in age and puberty, along with brain and behavioral development. A solution might involve running the model both with and without age (Vijayakumar et al., 2018), however, the primary focus of the studies in this thesis was on age effects. And finally, addressing sex effects posed a challenge, primarily due to variations in total brain volume. We either ran separate models for males and females (resulting in reduced statistical power) or attempted to control for sex in models (encountering nonconvergence issues); nevertheless, both approaches presented difficulties. Therefore, collaborations between researchers in Developmental Neuroscience and Research Methods and Statistics would be advantageous in addressing these challenges together.

FUTURE DIRECTIONS

Based on the findings and implications discussed in the present thesis, I underscore two essential directions for future research that would capture a more comprehensive insight into individual differences and milestones in brain development between middle childhood and early adolescence.

Links between environment, brain development, and mental health outcomes

First, this thesis can be used as building block for further investigations testing the relations between environmental influences, structural brain development, and developmental outcomes such as mental health and well-being. Hence, an ecological neuroscientific approach is needed to better understand the onset and maintenance of mental health (problems) among adolescents (Hyde et al., 2020). Linking the influence of environmental factors on brain development and exploring how this relation ultimately contributes to mental health may provide insights into the balance between mental *well*-being and *ill*-being (see review of Ferschmann

et al., 2022). Prior longitudinal work demonstrated that brain development was associated with depression, externalizing behavior, or psychotic outcomes (Bos et al., 2018; Mancini et al., 2020; Whittle et al., 2014). As such, the pace of brain maturation (e.g., accelerated, attenuated) is assumed to be a (risk) factor for mental health (Paus et al., 2008), although the direction of the developmental effects varied between the studies. Therefore, we still cannot conclude whether accelerated or attenuated is advantageous for developmental outcomes or not. One promising way to unravel whether individuals show atypicality is by incorporating statistical normative modeling, allowing for the observation whether an individual deviates from the norm by comparing their characteristics to the entire spectrum of variability within a typically developing population (Marquand et al., 2019).

Impact of (pre)pubertal hormones on brain development

This thesis showed that a combination of genetic and environmental contribution drives variances in brain developmental trajectories (**Chapter 2**). While the studies described in the present thesis focused on what environmental factors impacted brain development (**Chapter 3 and 4),** a second future direction should be on what genetic factors influence differences in brain changes. More specifically, it is important to consider that variations in brain development may be sensitive to two specific genetic factors: puberty and sex. In **Figure 1,** I show a schematic visualization of several factors possibly contributing to individual differences in brain structure and function. Several studies showed associations between brain development and pubertal characteristics (Bramen et al., 2011; Goddings et al., 2014; Herting et al., 2015). Specifically, it was suggested that males and females show differences in brain developmental patterns (Bramen et al., 2011), partly driven by pubertal development (Lenroot et al., 2007). However, this suggestion is primarily based on cross-sectional studies (see review of Herting & Sowell, 2017), which have fallen short in capturing individual variations in pubertal and brain maturation. This is important because facets of pubertal maturation differ not only between males and females but also among individuals of the same sex.

Herein, an important direction is to understand the influence of specific hormones on brain changes. Most of the prior work included gonadarche hormones (e.g., testosterone), while animal studies demonstrated that adrenarche hormones (e.g., prepubertal DHEA-S) can promote synaptogenesis for social learning, stimulate

neurite growth and neurogenesis, adjust neural activity, and have neuroprotective effects (see review of Byrne et al., 2017). In addition, the timing of the onset of adrenarche may correlate with brain developmental trajectories, indicating a potential brain organizational function (Byrne et al., 2017). Hence, a better understanding into the role of both gonadarche and adrenarche in pubertal brain developmental processes could help better understand individual differences in brain development. A better understanding would ultimately allow for a better insight into sex and gender effects in neuroscience of mental health outcomes (Wierenga et al., 2023), see **Figure 1**.

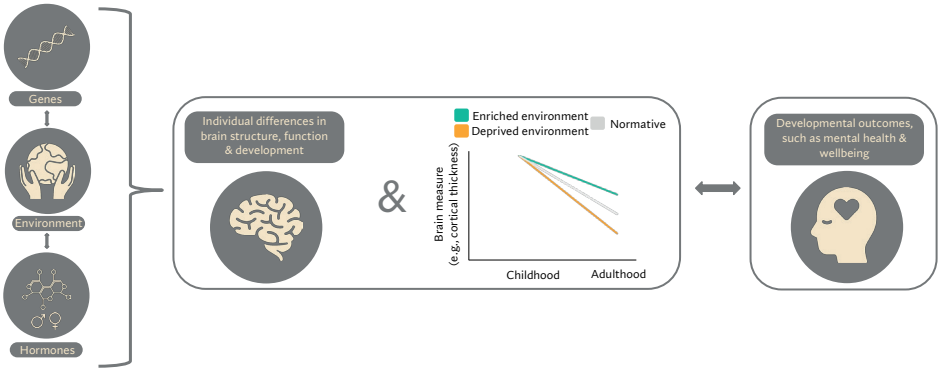

Figure 1. To fully capture individual differences in brain structure, function, and development between childhood and adolescence, it is key to consider the underlying mechanisms of genetic (e.g., Brain-Derived Neurotrophic Factor in the cerebral cortex and dopamine receptors in the prefrontal cortex), environmental (e.g., enriched, deprived), and (pre)pubertal hormonal (e.g., testosterone, DHEA-S) influences. Note that these contributors interact and that relations can be bi-directional with brain development. Subsequently, specific environmental factors may lead to accelerated or delayed brain development (e.g., accelerated/attenuated decrease of cortical thickness). Ultimately, a combination of all these factors may account for later developmental outcomes, such as mental health and well-being.

CONCLUSION

The focus of the present thesis was two-fold. First, I identified underlying mechanisms contributing to individual differences in brain structure, developmental changes, and function. Second, I explored the effects of an enriched and deprived environment on the direction of brain developmental trajectories from middle childhood to early adolescence (aged 7-14). I observed subtle and distinct patterns of genetic and environmental effects on the developing brain during middle childhood and early puberty. The results confirmed that a large part of variances in brain structure and developmental changes are driven by genetic contribution, including additional location-specific environmental influences. Even though combining studies that investigated genetic and environmental influences on activation and structural properties of brain regions revealed overlapping and distinct outcomes, it is essential to also recognize the complex interplay of genetic and environmental influences on the brain. Together, the combination of MRI and fMRI methodologies revealed a comprehensive insight into how individual differences can arise.

This thesis further revealed distinct effects of specific environmental influences on the pace of brain development. That is, an enriched cognitive environment, as indicated by musical ability, was predominantly associated with attenuated development, while a deprived cognitive environment, marked by exposure to COVID-19 pandemic measures, had an accelerated impact on development. Finally, the results of this thesis suggest that the brain also shows resilience to adverse effects, specifically in TPJ growth during the continuation of the pandemic. Possibly, these findings postulate specific adaptive brain processes to environmental effects that are pronounced in the developmental phase between childhood and early adolescence. Future studies can build on these findings by examining whether the relation between environmental effects and pace of brain maturation is linked to advantageous mental health outcomes. Ultimately, an important next step is to identify behavioral or contextual interventions that can help ensure all children thrive throughout their development.