

# General discussion



## GENERAL DISCUSSION

The development of the child is neither a function of the child alone nor of experience alone, but a product of the combination of an individual and his or her experience. Epidemiology has the potential to identify the risk factors that can affect child development. It is particularly effective if conducted using longitudinal designs in child and general psychiatry as well as in other fields.<sup>1</sup> The current thesis addresses the complexity of child development by investigating how family disruption occurring prenatally and early childhood explain child neurodevelopment and well-being. Most importantly, findings presented in this thesis reflect the availability of large data sets for analyses and the ability to examine change over time. In this final chapter, I will interpret the overall findings presented in this thesis in light of the larger body of published literature, address methodological considerations, and outline the clinical and public health implications, as well as provide directions for future research.

### Family adversities and neurobehavioral development

Over the past decades, a vast body of evidence has accumulated that family environmental risk factors impact child developing psychopathology. There are multiple explanations for how exposure to family adversities, during pregnancy or early life, has an impact on the risk of developmental delays and mental health. Perhaps the most compelling example of family risk factors for childhood psychopathology comes from the now classic examples of Rutter and coworkers in 1977.<sup>2,3</sup> These studies in British children revealed several factors within the family environment that are associated with childhood disturbances including marital conflict, low social class, and maternal psychopathology. More recently, studies suggest that the impact of family adversities on child neurodevelopment begins in the womb.<sup>4</sup> However, changes that have their origin in the womb do not mean that they cannot be altered again later. Thus, environmental influences that affect the brain and behavior of the offspring begin prenatally and continue through adolescence and early adulthood. For example, we showed evidence that exposure to poor family functioning or conflict influence child development differently than parental separation does. Moreover, we demonstrated that such disruption extends over time rather than occurring at one time point. In the following paragraphs, I will discuss the evidence for the association between prenatal and early environmental factors and child behavioral outcomes, with a special focus on neurodevelopmental outcomes, and evidence that some component of these associations is due to specific mediators.

### Types of adversities and offspring behavioral development

It is now widely recognized that children exposed to poor family functioning or conflict, poor parenting practices, and separation during childhood are at risk for a variety of behavioral, cognitive, and psychological consequences. Traditional understanding of

child behavioral development has focused on the influences of family functioning and separation without disentangling the differential effects of these specific exposures.<sup>5</sup> More recently, the characterization of adverse exposures has provided evidence supporting the critical role that family environmental factors have in modifying developmental processes. As we present in chapter 2, children exposed to family disruption (including family conflict and separation) witness a breaking expectable environment. We present data showing that such exposures, if occurring during a critical period of development such as pregnancy or early childhood, have detrimental effects. These early family disruptions are likely to be long lasting risk factors for poor child behavioral outcomes. However, it is not difficult to think of possible ‘common’ causes of parental conflict or poor parenting and their consequences for children.<sup>6</sup> The key issue is thus whether or to what extent child problems can be attributed to parental separation. For this reason, we modelled the complex mediation and interaction between family conflict and separation on child problems to best identify interventions that will improve child outcomes. Specifically, we test pathways through which parental conflict might influence child problems and whether these pathways are primarily a function of parental separation or reflect an interaction of family conflict and separation. It gives insight into the role of different pathways of parental conflict and separation.

We showed that at low levels of conflict not all children are affected by parental separation and those that are can be affected in different ways.<sup>7</sup> The applied method to simultaneously examine the mediation and additive interaction illustrated that there was no evidence of a pure indirect effect of parental separation on child problem behavior. The direction of this effect did, however, suggest that parental separation might have some protective effect on child problems behavior in those children who were exposed to low levels of parental conflict. Examining possible beneficial effects merits further investigation. The interpretation of these findings must account for the influence of potential confounding by baseline family environmental factors. This includes exposure to unfavorable socio-demographic factors, prenatal smoking and alcohol consumption, and parental psychopathology. However, after adjusting for potential confounding influences we still found an additional direct effect of prenatal and childhood family disruption on child emotional and behavioral problems. In addition, we showed in a sensitivity analysis that it is unlikely that unmeasured confounding would have changed the conclusions.

Next, we studied the impact of family factors on cognitive development. Children exposed to poor pre- and postnatal family functioning or separation are at risk for cognitive delays, which is a likely contributor of lower school achievement. Until now, accumulating evidence has demonstrated that family disruption may influence child school achievement,<sup>8,9</sup> but none had determined whether family disruption from pregnancy

onward is associated with later offspring school achievement. Attention problems in children are also a known contributor of low school attainment exposed to early family disruption. We aimed to unravel the association of parental education, parenting practices and offspring school achievement. Not surprisingly, in chapter 2.3 we first observed that higher parental education is associated with good parenting practices, which in turn are associated with higher school achievement. Jointly, the findings described in chapter 2.2 and 2.3 support a significant role of family disruption in child school achievement, whether characterized by poor family functioning, poor parenting practices, or parental separation.

Children influence their environment and environments influence children, it is thus clear that a bidirectional model must be employed in particular in the interrelation between parental and child psychopathology. In chapter 3, we used measures of maternal and paternal psychopathology as well as with maternal and paternal ratings of child problem behavior to examine whether within-rater and across bidirectional associations of parent and offspring psychopathology can be consistently detected. Within-rater associations assess the change of symptoms over time, across-rater associations compare symptoms between individuals. Firstly, we found no difference between mothers and fathers in any of the observed associations between parent and child. Secondly and importantly, child psychopathology was hardly associated with parental psychopathology later in time. We found no evidence for cross-rater child-to-parent associations. This suggests that the within-rater child-to-parent associations, which we did find, reflected shared method variance. This describes the phenomenon that using the same rater for a subjective exposure and outcome might have inflated the observed associations. Thus, it is very likely that parent's reports on their child's problems could be biased by their own cognition, or by poor understanding of the questions, or by their temperament or how they tend to answer questions on emotions.

To further highlight the processes between experience and development, we carried out an autoregressive cross-lagged model. With this approach we disentangled the contribution of within- between-person variation in bidirectional associations of environmental exposures to offspring psychopathology. The two levels of this analysis (within- and between-individual associations) clearly carry different substantive interpretations.<sup>10,11</sup> For example, within individual variability (intra-individual change) refers to the underlying question of how the child psychopathology changes or remains stable based on only their individual level of exposure. While the between individual observation refers to, on population mean level, children who are exposed to parental psychopathology tend to show more psychopathology symptoms than children who are exposed to a lower level of parental psychopathology. Nevertheless, the between-person observation (inter-individual differences) reflects the aggregate  $n$  within-individual observations in

which exposure to higher levels of parental psychopathology led to higher levels of child psychopathology. We observed that within-person levels of psychopathology explained substantial variance of child psychopathology, and vice versa.

From a social information perspective, a child is an individual in the context of social exchanges that unfold over time, rather than, say, a system of temporally ordered-person distributions in which children's rank orders shift conditionally over time (i.e., between-person associations).<sup>11</sup>

Next, we turned to loneliness as a risk factor for long-term mental health. Studies showed that loneliness is associated with generalized anxiety disorder, major depression, and dementia among adults.<sup>12</sup> Available evidence is mostly based on studies within one developmental period, studies of long-term effects across developmental periods are scarce. Thus, the impact of childhood loneliness has not been studied in light of possible persistent effects in mental health outcomes. The results we describe in chapter 4 are the first longitudinal evidence of the association between childhood loneliness and adult psychiatric disorders. Using data from a population-based cohort with up to 25 years follow-up and data collection using multiple informants, we were able to extend previous findings across developmental periods. Our results indicate that loneliness experienced in childhood had particularly robust associations with adult self-reported anxiety and depression outcomes. Notably, adjustment for childhood adversities did not meaningfully change the observed associations. Such findings suggest that, long-term effects of loneliness across significant developmental transitions contribute to the occurrence of adulthood psychiatric disorders.

### **Types of adversities and offspring neurodevelopment**

In the last years, epidemiological studies advanced the idea that early family disruptions compromise neural and psychological outcomes. Recent work in neuroscience has begun to shed light on how family disruption that occurs during a critical period of brain development, accounts for altered developmental outcomes. Such an impact of family environment on child neurodevelopment begins in the womb, can alter the development of the fetus, with a long lasting effect on the child.<sup>4</sup> Our findings from chapter 5 suggest that prenatal maternal-reported poor family functioning is associated with smaller hippocampal and occipital lobe volumes in preadolescents. Importantly, upon analyzing combined maternal and paternal functioning, we observed similar results; however, maternal-reported poor family functioning largely drove the associations. It is known that the intrauterine environment significantly influences growth and development via dysregulation of the hypothalamic pituitary-adrenal axis,<sup>13,14</sup> but it may also affect brain development through inflammatory responses and changes in the balance of the autonomic nervous system.<sup>15</sup> Specifically, no such association was found for poor

family functioning reported later in childhood, i.e., at ages 6 and 10. Thus, the timing of exposure is important in considering the effects of family disruption on brain development, which brings us to the role of sensitive or critical periods.

If physiological changes occur in the womb, this does not imply that they cannot be altered again later. For example, some of the neurodevelopmental effects of prenatal stress exposures or raised in the utero cortisol can be buffered by poor parenting between parent and the child postnatally.<sup>16</sup> Notably, the results we describe in chapter 5 provide evidence that the association of maternal-reported poor family functioning during pregnancy with preadolescent problem behavior was partially mediated by hippocampal volumes. Thus, some of the brain changes that are observed in response to poor prenatal family functioning, may cause changes in problem behavior later in life.

In a further study of family disruption, we investigated the associations of family functioning from pregnancy onward and global white matter microstructure. Our findings suggest that higher levels of prenatal family functioning were associated with greater white matter microstructure in preadolescent children (chapter 5.1). A growing number of studies have indicated that both negative and positive experiences occurring prenatally, and in childhood alter white matter structural development.<sup>17,18</sup> For example, maternal prenatal anxiety is associated with less white matter microstructure. In contrast, we did not find evidence suggesting an association between mid-childhood family functioning and white matter microstructure. The reported results demonstrate that the fetal and infant brain may be vulnerable to poor family functioning, such as conflict.

When a family member is assessed this measurement will reflect not only the respondent's mind set but also reflect the influence of other family members, the respondent's relationship to the other family members, and the whole family.<sup>19</sup> Thus, by using triadic data analysis (mother-father-child) in chapter 6, we elucidate what is occurring in families. For instance, we found that the interrelations between parental hostility (dyad mother-father) within family contribute to the triadic mother-father-child brain function. This method assumes that dyad members are distinguishable, which enabled us to test whether there are empirically meaningful differences between the member of the family. Our findings suggest that maternal and paternal hostility is associated with smaller parental brain structures as well as with smaller preadolescent brain development. By conducting mediation analyses, we found that parent and child brain morphology contributed to child aggressive behavior in children exposed to parental hostility. Specifically, smaller maternal and child hippocampal volumes, but not paternal, contribute to more aggressive behavior in preadolescents exposed to prenatal parental hostility. This implies, that parental hostility is accompanied by structural differences in maternal and

paternal brain structures as well as with differences in preadolescent brain development, which in turn increases preadolescent aggressive behavior.

### Methodological considerations

*Although we all have a strong desire for straightforward explanations of life, development is complicated and models for explaining it need to be complicated enough to usefully inform our understanding.*

*Arnold Sameroff, 1975*

### Stability and change

An important question which continually confronts the researcher in the study of child development is how to best characterize the nature of developmental change. Simply put, we can ask whether development is best characterized by stability (e.g., does a child behavior or a trait, such as externalizing problems, remain stable in its expression over time?) or change (e.g., could an individual's degree of externalizing problems fluctuate across the life span?). An important aspect of the debate on stability versus change has to do with the degree to which early experiences play a formative role in later development. A series of studies investigating the effects of early experience in children's social, physical, and cognitive development was conducted by the British psychiatrist Michael Rutter. Rutter and his colleagues were able to investigate whether the degree of children's recovery from these early experiences was affected by how long they had been institutionalized in Romanian orphanages.<sup>20</sup>

To answer the questions mentioned above, we have traced an epidemiologic sample of children and their parents across childhood by using repeated assessments of the exposure and the outcome. Thinking of stability as consistency and instability as a change, the most important study design characteristics that we applied in this thesis are to develop well-defined research questions, to combine different analytical methods, and to aim to diminish of bias. Methodology for how studies of children exposed to family disruption across time could test the potential for change in behavior is described in each chapter of this thesis.

*Models of developmental changes in childhood* – After I identified the behavioral consequences of family disruption, I will discuss how this behavior changes and whether any change is stable. In addition to representing conceptually different temporal patterns of stability and change, we have employed multivariable linear regression with generalized estimating equations (GEE)<sup>21,22</sup> approach to simultaneously examine repeated measures of family disruption in relation to neurobehavioral outcomes (i.e., whether family functioning measured during different time points was associated in the same manner to child neurobehavioral outcomes). To explore the possibility of unique periods of



susceptibility, we tested the interaction with the child's age in the associations between family disruption and neurobehavioral outcomes (e.g., poor family functioning x exposure period interaction  $p$ -value = .001). Although this approach retains the interpretation of a set of separate multiple regressions (by providing a single estimate of effect for exposure at each time point), it takes the variance between family disruption over time into account, while assessing the differences in associations between poor family disruption and child neurobehavioral outcomes.

*Between-individual variation of change* - In spite of the results described in this thesis indicating relatively high stability coefficients over time, all types of behavioral and family adversities yielded variance in change of child development over time. Thus, the specific exposure adversities are associated with a change in symptoms from pregnancy onward. In addition to the fact that we were measuring exposures in a period of life that give rise to rapid changes in child neurodevelopment, changes in symptoms of all adversities were also detected. For instance, in chapter 5 we found that poor family functioning from pregnancy onward was associated with child neurodevelopment and well-being.

*Sensitive periods under developmental change* - The notion of a sensitive period implies that a certain experience at a certain time during development may give rise to a change in the future developmental outcome. Research shows, however, that events subsequent to the sensitive period may also modify or undo earlier effects constituting a further change at later point in development.<sup>23</sup> Thus, another strength of this method is to the ability to detect developmental windows, which underlie critical and sensitive period phenomena, and must be differentiated from the effect of change of exposure over time. As illustrated in Chapter 2 and 5, we identified particularly important windows of time when environmental exposures such as poor prenatal family functioning impact child neurodevelopment.<sup>24</sup> That is, a sensitive period describes the effects an experience has on the development during narrow windows of time.<sup>23</sup> In contrast, critical periods result after sensitive period ends but negative experiences may continue to affect child brain function. For example, we found that postnatal family disruption such as harsh parenting might affect brain development in childhood. Thus, sensitive and critical period models rely on experience that facilitate biological encoding of expectable environment during developmental windows; these models have distinct implications for our understanding of the impact of adversity.<sup>25,26</sup> We can hypothesize that family disruption during sensitive and critical periods of development is more likely to have persistent effects on neural and behavioral function later in time.

Indeed, even within a domain of sensory development or psychopathology such as anxiety and depression there will be different sensitive and critical periods.<sup>27</sup> For example, there are multiple critical and sensitive periods for different forms of psychopathology.

However, few studies have shown interest in identifying whether family risk factors at any time point or during sensitive period are associated with child neurobehavioral development. Finally, given the complexity of the different types of adversity in child development, further research may want to consider the use of mixture models for combinations of adverse experiences to identify how different types of adversity interact and lead to effects of child neurodevelopment.

*Bi-directionality and developmental change over time* - We have repeatedly emphasized the importance of studying bidirectional associations in the transactions between parents and children. We have highlighted this as important for identifying developmental change and stability, but the contribution of within- between-person variation in bidirectional associations of environmental exposures to offspring psychopathology is relatively understudied. In other words, how a person varies from his or her own baseline level (in our study the baseline was psychopathology during pregnancy). The two levels of analysis - within and between individual variation - clearly carry different substantive interpretations.<sup>10,11</sup> Our logic to analyzing between-person and within-person effects is to estimate how much of its variation is due to each source. We found evidence for between person-person variation (person-to-person differences in mean psychopathology levels) as well as within-person variation (i.e., variation around a person's level with more or less psychopathology at a given time) in bidirectional associations of parent and offspring psychopathology. That is, even though psychopathology levels vary across time, to the extent that some individuals report more psychopathology at a certain time point, psychopathology will also vary across people and these latter variations may explain association ascribed to the first.

These different levels of inference also carry different strength and weaknesses. For instance, when bidirectional associations are fixed within individuals, each child serves as his or her own control group. That means we estimated the effect based only on within child variation (e.g., the child compared to him/herself). In contrast, between child estimates carry the advantage of accounting for aspects that differ systematically between children, such as temporally stable aspects of child psychopathology. However, in analyses of between-person associations, biases due to unobserved confounding cannot be ruled out. Moreover, it is difficult to refer a developmental theory underlying the between-person associations between parent and offspring psychopathology. Rather, developmental theory is largely a within-individual endeavor.

### **Mediation and interaction models**

The methodology for examining mediation analysis has expanded dramatically over the past 10 years. It is common for the effect of one exposure on an outcome to operate in some way through the presence or absence of another exposure (a potential mediator).

One issue that has seen increasing interest is the interaction between two environmental exposures, but interaction that occurs between genetic and environmental exposures has received particular interest. Interaction between two (causally) related exposures is one manifestation of this complexity and thus traditional methods of mediation were extended to allow for exposure-mediator interaction or nonlinearities.<sup>28,29</sup>

For these reasons, we have used an approach that more fully encompasses mediation and interaction simultaneously. In Chapter 2 we show that the overall effect of prenatal parental conflict on child problem behavior, in the presence of parental separation as a mediator with which family conflict may interact, can be decomposed into four components: (i) how much of an effect is mediated, (ii) how much is due to interaction, (iii) how much is due to both mediation and interaction together, and (iv) how much is due to the direct effect of exposure.<sup>30</sup> The intuition behind this decomposition is that if the parental conflict affects child maladjustment, then at least one of these four conditions must be met. This four-way decomposition method showed that prenatal family conflict to some extent affects child problem behavior through the pathway of parental separation. Finally, and perhaps most importantly, parental separation was not associated with child problem behavior in absence of family conflict. That is, we did not find a risk increasing effect of separation on child emotional and behavioral problems; the association was tentative at best, given the lack of statistical significance and broad CIs. Furthermore, because no post-separation conflict data were obtained in our sample, we cannot establish the effect of parental post-separation conflict on children's adjustment to separation.

The similar findings between traditional mediation and four-way method highlight the fact that controlled direct effects are of interest in policy evaluation because they consider what the effect of the exposure would remain if we were to intervene on the mediator across the population.<sup>29,31,32</sup> In our case the controlled direct effect represents the impact of parental conflict on child behavior problems if we were to successfully intervene and reduce the prevalence of parental separation.

### **Modeling the difference between and within (over time) individuals**

As discussed in the section above on stability and change, the idea of dynamic, bi-directional association processes between experience and development is core of most developmental models. Developmental continuity and change of most complex traits are assumed to be driven by self-organizing transactions between individual and context over time.<sup>33</sup>

One of the most well-known and often used models to test bi-directionality is structural equation modeling (SEM). We saw an example of this in Chapter 3. We studied bi-

directionality in the association between parent and child psychiatric symptoms with separate measures of maternal and paternal psychopathology as well as separate ratings of child internalizing and externalizing problems by both mothers and fathers. We were able to show that only within-rater (i.e., both the rating on parental psychopathology and child outcomes were obtained from the same parent) bidirectional associations of parent and offspring psychopathology could be consistently detected. Structural equation models are often criticized for not adequately addressing issues of confounding,<sup>28</sup> and yield estimates that are difficult to interpret meaningfully. Moreover, the parameters are typically interpreted as between-person effect.<sup>34,35</sup> However, if issues of confounding are adequately addressed by including all relevant confounders, then the SEM approach can be a useful tool for an estimated population average mean.

Importantly, building on the recent discussions on disaggregating the within- and between-person associations we have employed, in the same chapter, autoregressive latent trajectory with structured residuals (ALT-SR)<sup>10</sup> to better understand developmental processes. Interestingly, the ALT-SR suggested that bidirectional associations were actually explained by both the within- and between-individuals of parents and child psychopathology. Thus, from a substantive view, the bidirectional associations were evident at the level of analysis that is arguably the most relevant to developmental theory, i.e., the within-person level. From a methodological view, this means that bidirectional associations remained after accounting for many potential confounders (certainly those that do not vary with time). However, parent and offspring psychopathology were consistently associated within-raters but not across-raters. A methodological strength of within subject analyses is ‘fixing’ of associations to reflect only within-child variation. This provides evidence that there is a causal relation between parents and offspring psychopathology captured by the within- and between-individual component of the model. However, we did not examine bidirectional associations between the within-person interactions with time or bidirectional interactions between within- and between-individual parent and offspring psychopathology, and that the bidirectional estimates do not vary randomly across children.<sup>36,37</sup> In terms of multiple levels of inference, such as within- and between-individual variances, each association requires sufficient statistical power. Specifically, statistical power can also be affected by the number, timing, the reliability of variables and their distributions, model size, missing data, and so forth.<sup>38,39</sup> Given this complexity, it is important that the Generation R Study has a robust sample size and a relatively high number of longitudinal behavioral observations.

### Multi-informant approach

The question is, does the average self and other agreement in child or parent psychiatric symptom rating account for a psychometric challenge? Yes, indeed! The estimates that are averages between two judges found in both child and adult literature lead to a

psychometric challenge with a clear prescription: Use more judges.<sup>40</sup> As we indicated in all chapters of this thesis, when assessing data from multiple informants such as child and parents it is now commonly accepted that each informant provide potentially valuable data.<sup>41</sup> However, inconsistencies often arise among multiple informants referred to as ‘informant discrepancies’,<sup>42</sup> even when informants complete parallel or identical measures.<sup>43</sup>

Two methods, both implemented in this thesis, lead our discussion about principles underlying the use of multiple informants’ reports. First, the use of a single informant’s report involves testing whether each informant observes child behavior in a particular context. However, a frequently encountered problem in the study of child psychopathology is that shared-rater variance might inflate the associations when they are measured by the informants on the same survey. Thus, when the same reporter provides ratings on the predictor and the outcome, part of the explained variance may be due to the informant who is reporting rather than to the constructs the measures are assumed to represent. As described in Chapter 3, the fact that associations of parent to offspring psychopathology were largely observed only within and not cross-rater, could in principle reflect three factors, namely cross-rater disagreement,<sup>42,44</sup> information bias, and importantly, shared-rater variance, which is a particular form of information bias.<sup>45-47</sup> There are three factors/mechanisms that may lead to informant discrepancies and possible attribution bias: including informant attributions (different perceived causes of the problem behavior), informant perspectives (does the problem behavior warrant treatment), and goal of assessment process (differences in the perceived outcomes of the assessment).<sup>44</sup> Moreover, to minimize shared-rater variance, information on predictor and outcome variables must be obtained from multiple sources or informants. For example, it would be advantageous if other informant ratings on problem behaviour were obtained, such as father ratings on maternal psychopathology, mother ratings on paternal psychopathology, clinician’s ratings on parental psychopathology and teacher-, clinician- or (if the child were old enough) self-reports on child problem behaviour.

Second, we used a statistical method to investigate, in combination, multiple measures of a single assessment to create a ‘latent’ variable representation of that assessment. This method focuses on the variance shared among multiple informants (e.g., maternal and paternal reports) of the same assessment and time point. By using combinational algorithms, structural equation models (e.g., Chapter 5 and 6), latent factor reflects the common variance across mother and father-reported family disruption. As a result, only a small percentage of variance was explained within these models, suggesting it would be helpful to consider additional variables to account for variance in various common and informant perspective factors. However, in their study examining how repeated measurements of self-, parent and teacher-reported problems in adolescence relate to

internalizing and externalizing DSM disorders in adulthood, Van der Ende et al., (2020) showed that the added value of an additional informant may not add much to a carefully selected informant beyond the precision of the estimate.<sup>48</sup>

### **Implications and future perspectives**

From this thesis several lessons can be learned. First, the potential for prevention and treatment of family dissolution in light of persistent effects in mental health outcomes in childhood, deserves advocacy to both clinical settings and in public health. Preventive interventions with small effects at the individual level, and relatively minor decrease in family disruption could have a major impact on the burden of functioning at the population level.

The large number of adverse consequences associated with behavioral outcomes during childhood support the notion that this is a large public health concern, both for individuals and society. In order to prevent child maladjustment, it is important to identify family risk factors and indicators. As for interventions, we believe that there is enough evidence to pursue poor family functioning as a risk factor for child maladjustment. Continuous monitoring of child maladjustment occurrence is crucial to detecting changes relevant to the individual and to public health. At the same time, practitioners should be aware that if poor family functioning, parenting practices, and separation occurs in early childhood, some proactive intervention may be needed to help the children adjust and prevent low school achievement. Hence, school-based or health-care-based screening for maladjustment problems and low school achievement in children experiencing family disruption would be helpful as a prevention measure.<sup>49</sup> Post-separation conflict and children's overall adjustment is a theme that merits further research. Clinicians know through their own experience that many children of parental separation do well. Well-designed longitudinal studies are needed to examine possible beneficial effects of parental separation. The last factor to consider is the number of disruptions the children will experience. This factor has not been directly studied by researchers because repeated disruptions are hard to specify and quantify.

We described in this thesis that children are neither condemned nor protected by their own characteristics or by their characteristics of parents alone. The complexity of parental psychopathology opens up the possibility for many paths of intervention to facilitate the development of children and their families. Thus, the psychopathology of parents is a crucial target of prevention and intervention efforts for children with developmental problems. Where relationships are problematic, intervention should be directed at one or more these three parts (e.g., mother, father, child). However, whether interventions for children with psychopathology should largely focus on parents with psychiatric problems, only on children, or on both depends on the child's age, the developmental

status, and cognitive capacities. Moreover, any intervention to interrupt the negative transactional processes between parental and offspring psychopathology would need to be aware of other social influence and complexities determining when and in whom to intervene. Although we can learn from observational studies of the development of different groups of children or parents, we can never fully test causal hypotheses for most groups of interest because we cannot randomly assign infants to different emotional and behavioral problems or parents to competence or incompetence. However, the converging evidence for the existence of bidirectional associations between parents and children provides a strong basis for intervening more effectively to improve the lives of families facing challenges from either child or parent.

Finally, subcortical brain changes found after more than 10 years of follow-up suggests that the fetal and infant brain may be vulnerable to family disruption, such as poor functioning and parental hostility. This serves as a powerful reminder that clinicians need to address family factors and, where necessary, intervene or refer to specialists. Parallel research on parents and children interventions could help identify at-risk individuals for more efficient allocation interventions to optimize maternal-paternal-child neurodevelopment. Moreover, multiple repeated measures of imaging data starting early in childhood would be necessary to test the directionality between behavior and brain development. Research on the parental brain, particularly studies testing brain response to parent-child interactions, can uncover how the brain reacts to social stimuli. Assessing such patterns in relation to the child's long-term development can offer new insights into the origins of psychopathology. Another unresolved issue in population neuroscience is the need to shift research from the functioning of a single brain to the coordination of several brains, to understand how brain-to-brain synchrony enables formation of social bonds and collaboration among families and groups.

### **Concluding remarks**

Findings of this thesis illustrated how prenatal and childhood family disruption result in neurodevelopmental vulnerability to develop emotional, behavioral, and cognitive problems. Bidirectional associations between parental psychology and child externalizing and internalizing problems were consistently associated only within-raters but not across-raters. Thus, these observations are likely to reflect shared-rater variance. At the level of the brain, poor family functioning was associated with changes in brain development that in turn contributed to preadolescent problem behaviors. Finally, we found that the dyadic mother-father characterized by hostility is associated with the mother and father structural brain differences as well as with children's brain development. Differences in brain structures of parents and children underlie the associations between parental hostility and preadolescent aggressive behavior.



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