The interrelation of maternal and paternal hostility with both child and parent brain morphology in the association with child aggressive behavior. A population-based neuroimaging study

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ABSTRACT

Background: Parental hostility is associated with differential aspect of child and family functioning including high levels of parental conflict, depression, and parental-child relationship quality. In children, parental hostility can lead to prolonged disruption in emotional security and heightened levels of aggression. However, little is known whether parental hostility is associated with long-term disruption on parents and child brain using magnetic resonance imaging (MRI).

Objectives: We aimed to investigate the degree to which associations of prenatal and childhood parental hostility would be associated with differences in maternal, paternal and child brain structure if analyzed together, i.e. as triads.

Methods: This population-based cohort study was embedded in Generation R, a multiethnic population-based cohort from fetal life onward. Mother- and father-rated hostility was repeatedly measured by the Brief Symptom Inventory. High-resolution structural neuroimaging data of children aged 10 years, and the parental brain (mothers M_{age} = 41.6, and fathers M_{age} = 43.6), were collected with a single 3-T magnetic resonance imaging system. Child aggressive behavior were assessed with the Child Behavior Checklist.

Results: Prenatal maternal-reported hostility but not mid- or late childhood was associated with smaller total white matter, gray matter, and hippocampal volumes in adolescents. Our findings highlight the role of each parent's ability to transpire hostile behaviors to his or her partner and the child. The contribution of prenatal parental hostility to child aggressive behavior was partially mediated by both hippocampal volumes of children and, importantly, also of mothers.

Conclusion: This population-based neuroimaging study suggests that parental hostility from pregnancy onward is associated not only with differences in the behavior of other family members but also their brain morphology.

INTRODUCTION

Parental hostility is defined as an overt behavior and communication between parents and children characterized by arguing, angry comments, contempt, yelling, swearing, name-calling and or physical aggression.[1,2] Hostile behavior of a parent is associated with different aspects of child and family functioning including high levels of parental conflict, depression, and parental-child relationship quality. In children, parental hostility can lead to prolonged disruption in emotional security and heightened levels of aggression.[3,4] which in turn increases the risk for a wide variety of other negative mental health outcomes.[5,6] Children exposed to family hostility appear to live in a state of chronic psychological stress[7] and recent evidence suggests that this may be associated with disruption in brain development.[8] Although the interest on the effects of parental hostility and child adjustment dates back to early 20th century, the parent and child brain affected by early-life events is a recent area of inquiry. Brain imaging studies can deepen our understanding of the neurobiological underpinnings of parent-child functioning.

Reviews of the literature within the framework of 'risky' family environments have shown that aggression, conflict, and disengagement in the family, parent-child, or interparental context are risk factors for the persistence of negative mental health outcomes.[9,10] Parental hostility often co-occurs in the parents.[4] This can be due to socio-economic and other demographic factors, assortative mating, and one parent's hostility may induce the other parent's hostility. Research suggests that what transpires in one family subsystem, e.g. hostility among parents, is related to what transpires in other subsystems, e.g. mother-child or father-child, and can negatively child development, either directly or indirectly.[11] A large body of evidence shows that family relationships function as unitary systems and are built on the ongoing transactions between family members.[12,13] Childhood behavioral problems, and in particular aggression, are often the result of interparental conflict and interrelated parental psychopathology.[14] When one parent is hostile, the child is at risk developmentally; when both parents are hostile, the risk increases further.[15] Although mothers and fathers have different kinds of relationships with children that evoke different behaviors,[16] one parent's hostility is thus likely to affect all members of the family and relationships within family.

Functional imaging studies suggest that stress and psychopathology in mothers after the birth of a child correlate with pronounced long-term changes in the mother's brain.[17,18] Differences are most marked in the limbic and frontotemporal brain structures implicated in maternal motivation and behaviors. The amygdala and the hippocampus are two major components of the limbic system implicated in learning, memory, and emotion.[19] A recent study that assessed brain-to-brain synchrony between mothers and their children at age 3-4 and its association with stress suggests that higher parenting stress experienced

by mothers associated with reduced brain-to-brain synchrony.[20] Finally, research is beginning to address the effects of parenthood on the father's brain suggesting different and similar responses as found in mothers.[21] In 'risky families', parents and children often experience some form of psychopathology, and parents as well as children are likely to exhibit similar or different neuroendocrine, immunological, and cardiovascular correlates of persistent stress.[22] Thus, the environmental and biological changes that occur in pregnancy and early childhood may potentially be accompanied by maternal, paternal and offspring brain differences in specific brain areas such as limbic and frontotemporal brain regions.[17] While suggestive, previous brain imaging studies, however, did not examine these pathways of family psychopathology and disruption jointly in parents and children.

No study to date addressed the key question of whether parental hostility is associated with long-term disruption on parents and child brain using magnetic resonance imaging (MRI).

In the present study, we aimed to investigate the degree to which associations of prenatal and childhood parental hostility would be associated with differences in maternal, paternal and child brain structure if analyzed together, i.e. as triads. In addition, we investigated whether the associations between parental hostility and child brain morphology differed between mothers and fathers. We examined both global brain outcome measures including total gray and cerebral white matter volumes, and hippocampal and amygdala volumes. The current study had three main aims. First, we aimed to examine the associations of parental hostility measured repeatedly over time with child brain development. Second, we aimed to examine whether each parent's hostility would be associated with differences in parental brain structure outcomes (within-parent analyses), and whether these associations would be associated with his or her partner's brain characteristics (across parent analyses). Our third aim was to investigate to what extent the persistent association of prenatal parental hostility with preadolescent aggressive behavior is mediated by subcortical brain volumes of mothers, fathers, or children.

Methods

Participants

Data were collected in the Generation R Study, a multi-ethnic population-based cohort from fetal life onwards. The Generation R Study has been described in detail previously.[23] Briefly, all pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate. Neuroimaging data were obtained for 3,937 children from the late-childhood (M_{age} = 10 years) assessment wave from 2012 till 2015.[24] We excluded 657 children with poor imaging data (n = 638) quality or incidental findings (n = 19).[25] Between 2017

and 2019, neuroimaging data for parents were obtained as part of the Generation R Parent Scan Study. T_1-weighted data were available for 958 parents (630 mothers, 328 fathers/partners). We excluded 30 parents because of insufficient quality of the scans. Of the remaining 605 mothers and 323 fathers, those with no data on parental hostility or missing partner imaging (409 mothers and 127 fathers) were excluded. That is, all individuals were nested within families. For the current study, families were included if mother, father and their child had neuroimaging data in a triadic family. The final sample consisted of 196 mother-father-child triads (Supplementary Figure 1).

The study was conducted in accordance with the guidelines as set by the World Medical Association Declaration of Helsinki. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam (registration number MEC 02.1015). Written informed consent was obtained from all adult participants and from both the parents of minors.

Parental hostility

Parental hostility was assessed with the Brief Symptom Inventory (BSI). Mothers and fathers reported their hostile symptoms at 20 weeks pregnancy and again when their child was 3 and 10 years old. The BSI is widely used instrument to measure self-reported psychological symptoms in samples of psychiatric patients and community non-patients.[24] We used the hostility subscale of the BSI, a validated self-report questionnaire answered on a five-point scale, ranging from 0 = 'not at all' to 4 = 'extremely'.[26,27] This instrument encompasses symptom dimensions covering clinically relevant psychiatric and psychosomatic symptoms.[26] The hostility subscale consists of 5 items: "easily becoming bored or feeling irritable", "uncontrollable bursts of anger", "an urge to hit, injure or cause pain to others", "an urge to damage or break things", and "often getting involved in arguments". High validity and reliability were reported for the Dutch translation.[28] In the current study, internal consistencies (Cronbach's alpha) for parental hostility ranged from 0.60 to 0.71.

Child aggressive behavior

The Child Behavior Checklist for older children (CBCL/6-18)[29,30] was used to obtain standardized parent report s of children's problem behaviors. The CBCL/6-18 contains 118 problems items. Each item is scored on a three-point rating scale *0 = 'not true', 1 = 'somewhat or sometimes true', and 2 = 'very true or often true'*, based on the preceding two months. We used the continuous Aggressive Problems score at age 10 as outcome measure, which comprised items such as: "My child gets in many fights", and "My child destroys others' things". This scale consists of 19 items scored on a three-point Likert scale, in our sample (α = .85). Good reliability and validity have been reported for the CBCL/6-18.[29] The scales were generalizable across 23 societies, including the Netherlands.[31]

Image Acquisition

Neuroimaging data were acquired with a 3 Tesla GE Discovery MR750w MRI System (General Electric, Milwaukee, WI, USA) and an 8-channel receive-only head coil.[24] T_1-weighted images were acquired in the children with a coronal inversion recovery fast spoiled gradient recalled sequence (T_R = 8.77 ms, T_E=3.4 ms, T_I = 600 ms, flip angle = 10°, field of view = 220 mm × 220 mm, acquisition matrix = 220 × 220, slice thickness = 1 mm, number of slices = 230). The parental images were collected with a similar sequence but with an axial orientation.[32]

Morphological Image Processing

The T_1-weighted images were processed through the FreeSurfer analysis suite, version 6.0. The details of the processing steps for the child data have been described elsewhere[33], and the parental images were processed with the exact same protocol. Briefly, nonbrain tissue was removed, voxel intensities were normalized for B1 inhomogeneity, whole-brain tissue segmentation was performed, and a surface-based model of the cortex was reconstructed. Global metrics of volume were extracted (e.g., total brain volume and subcortical volume), and a number of cortical and subcortical structures (amygdala, hippocampus, etc.) were automatically labeled. All measures were averaged across the left and right hemispheres. Surface reconstructions were visually inspected for accuracy and data not suitable for statistical analysis were excluded.[33] We also used a metric of image quality which automatically characterizes the amount of motion/artifact based on signal intensities outside of the brain.[34]

Covariates

Child and parental age at MRI (based on date of birth) and sex were obtained from birth records. Maternal and paternal age were assessed at intake. Parental ethnicity was categorized into three groups: Dutch, other Western, and non-Western national origin.[35] Parental education was classified in three levels: 'low' (maximum of three years general secondary school); 'medium' (>3 years general secondary school; intermediate vocational training); and 'high' (bachelor's degree or higher academic education). Information about smoking during pregnancy (three categories: no smoking; smoked until pregnancy recognized; and continued smoking), alcohol intake during pregnancy (four categories: no alcohol consumption; alcohol consumption until pregnancy recognized; continued occasionally (<1 glass/week); and continued frequently (>=1 glass/week)) was assessed prenatally using self-report questionnaires.

Statistical Analysis

To study the associations of parental hostility and structural brain morphology of both parent and children, we have primarily created a data file in which mother, father, and child were treated as a family unit.[36] That means, we focused on the triads of mother,

father, and child. Analyses defined the parental hostility measures paired with each other as independent variables and maternal, paternal, and children brain measures (including total white matter, gray matter, hippocampus or amygdala volumes) as the dependent variables (i.e., all individuals were nested within families).

In a first step, however, we examined in separate linear regressions the associations of maternal and paternal reported hostility during pregnancy and ages 6 and 10 with parents and child brain measures to examine period-specific exposure associations. In all models, we adjusted for age of the parents at baseline, but performed no additional adjustment for parental age at MRI scan as the results remained essentially unchanged.

We then used structural equation models (SEM) path analysis to test whether maternal and paternal hostility from pregnancy onward is associated with maternal, paternal, and child brain morphology. The general strategy in specifying path models with triadic data is that each parent's hostility score used as predictor variable for her or his own outcomes, her or his partner's outcomes, as well as child outcomes, i.e., brain structures. We correlated all variables across triad members, and correlations across parents (i.e., maternal and paternal hostility) were added to the model (Supplementary Table 5). Maternal, paternal, and child brain outcomes were not nested within one family score. As such, we examined the extent to which one parent hostility is associated independently of the other parent's and child brain morphology.

The parameter estimates were used to create a variance-covariance matrix among the observed variables. The fit of the model was tested by comparing this variance-covariance matrix with a chi-square test based on parent's hostility and parent and child brain discrepancies. We performed all models adjusting for the confounders described above and intracranial volume.

Finally, we examined whether brain morphology of mothers, fathers, or children mediated the association between prenatal maternal- and paternal-reported hostility and preadolescent aggressive behavior at age 10 years. No association were found between parental hostility and child amygdala volumes. Based on the results, we only examined mediation for the hippocampus, a subcortical brain measure in the relation between parental hostility and preadolescent aggressive behavior related. The mediation analysis framework provides estimates of the natural direct effect, the natural indirect effect, and the total effect.[37] All models were adjusted for baseline confounders and child aggressive behavior when the child was 1.5 years old to help rule out a reverse association.[38] A latent construct based on maternal and paternal hostility reported by mothers and fathers was used in relation with child hippocampal volume and aggressive behavior (Methods in the Supplement).

False Discovery Rate (FDR) was applied to adjust for multiple comparisons.[39] We adjusted for multiple hypothesis testing of 3 outcomes such as maternal, paternal, and child brain structures (total white matter, gray matter, hippocampus or amygdala volumes), and the 3 relevant exposure periods (prenatal mid- and late childhood) in the multiple testing correction (9 comparisons). The unstandardized β coefficients (B) and 95% confidence intervals (CIs) were calculated. All analyses were performed using SAS 9.4 software.

Results

The descriptive sample characteristics regarding triadic parental socio-economic factors, child and parental age at the MRI are described in Table 1. The mean age of the children at scanning was 10.1 years (standard deviation (SD) = 0.6). Half (49.1%) of the children were boys. In total, 28.1% of mothers and 24.9% of fathers had a non-Western national origin. The mean age of the mothers at scanning was 41.6 years (SD = 23.5); fathers were 43.6 years (SD = 17.9).

Table 1. Child and parents' sociodemographic characteristics (N = 196 triads).

	Mother	Father
Age, M (SD)	31.1 (4.7)	33.5 (5.3)
Ethnicity		
Dutch, (%)	62.6	69.3
Other Western, (%)	9.3	5.8
Non Western, (%)	28.1	24.9
Education level		
High, (%)	42.9	50.7
Middle, (%)	45.9	41.0
Low, (%)	11.2	8.3
Alcohol use during pregnancy		
No consumption during pregnancy, (%)	37.4	
Until pregnancy recognized, (%)	13.8	
Continued occasionally, (%)	38.4	
Continued frequently, (%)	10.4	
Smoking during pregnancy		
No smoking during pregnancy, (%)	79.8	
Until pregnancy recognized, (%)	12.5	
Continued during pregnancy, (%)	7.6	
Parents' age at the MRI scan, years, M (SD)	41.6 (23.5)	43.6 (17.9)
Child sex, (% boy)	49.1	
Child age at the MRI scan, years, M (SD)	10.1 (0.6)	

Note: Numbers denotes children included in one or more analyses. Values are frequencies for categorical and means and standard deviations (M ±SD) for continuous measures.

Parental hostility with parent and child brain morphology

The associations of the child's exposure to parental hostility with brain morphology are shown in Supplementary Table 1 and 2. Prenatal maternal but not paternal hostility was associated with differences in child white matter, gray matter, as well as hippocampus volumes. In contrast, in mid- or late-childhood parental hostility scores was not related to any brain measure in fully adjusted models. Mothers and fathers with higher levels of hostility during offspring pregnancy or early childhood had smaller white matter, gray matter, amygdala and hippocampal volumes (Supplementary Table 3 and 4).

Parental hostility and child brain morphology

In the triadic model, the association of maternal and paternal hostility from pregnancy onward were examined in relation to children's brain structures. We observed that prenatal maternal but not paternal hostility was associated with differences in child cortical white matter volumes (B = -0.05; 95% CI, -0.07, -0.03) and gray matter volumes (B = -0.06; 95% CI, -0.08, -0.03) (Figure 1 and 2), as well as with smaller child hippocampal volumes after adjusting for intracranial volume (B = -0.03; 95% CI, -0.05, -0.02), (Figure 3). These associations survived multiple testing correction. In contrast, no associations were observed for mid- and late childhood mother hostility or any father hostility measure with the child's cortical white matter, gray matter, or hippocampal volumes. Adjusting for baseline confounders and parental smoking and alcohol consumption did not meaningfully change this association. No associations were observed between prenatal and early childhood parental hostility and child amygdala volume (Figure 4).

Parental hostility and parents brain morphology

Next, we found that maternal and paternal hostility measured during pregnancy and earlier child's life were associated with smaller white matter, gray matter, amygdala and hippocampal volumes of that parent (i.e., within-parent analyses). Moreover, both maternal and paternal hostility scores were associated with their partner's smaller white matter and gray matter volumes brain morphology 10 years later (across parent analysis) (Figure 1 and 2). However, no associations were observed between parental hostility with hippocampal and amygdala volumes of the partner (i.e., across parents)(Figure 3 and 4). That is, maternal and paternal hostility score were related to their own subcortical brain measures, but not partner's subcortical brain outcomes.

Taken together, these results indicate that the observed associations of maternal and paternal hostility co-occur and were related to individual differences of parent and child brain outcomes in the triadic model.

The associations between parental hostility and white matter microstructure for parents and children (N = 196 triads).

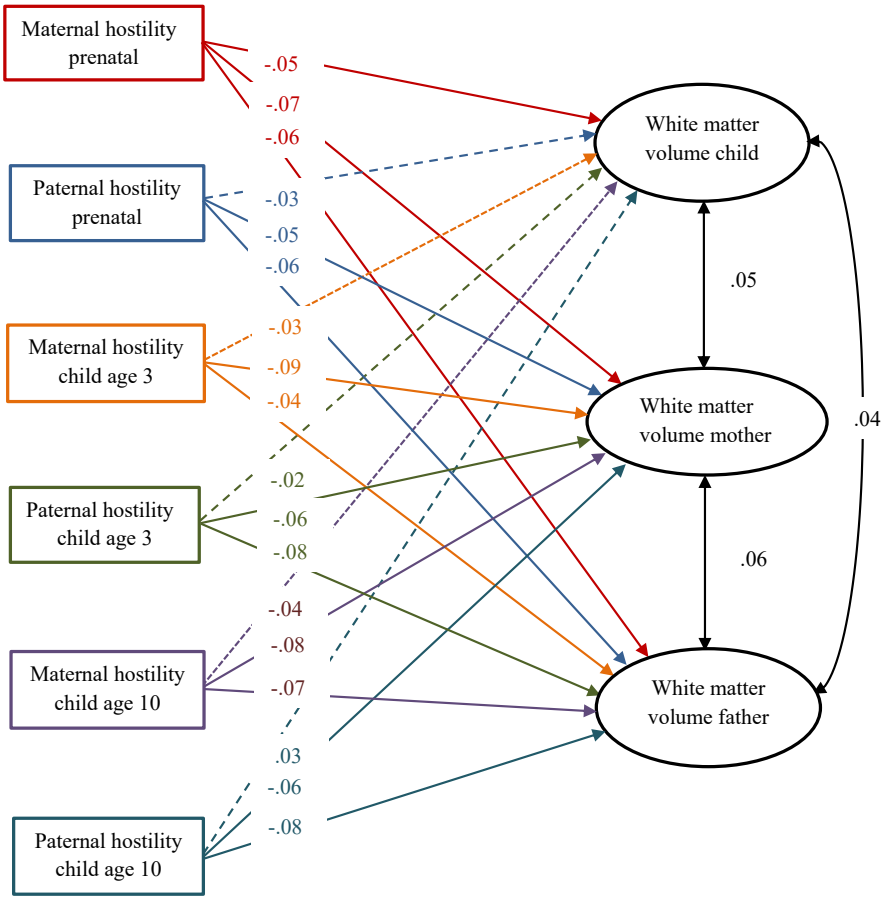


Figure 1. Structural equation modeling of parental hostility and cortical white matter volumes of parents and children. Numeric values are unstandardized path regression coefficients. Models are adjusted for child age at brain MRI scan, child sex, age, ethnicity and education, smoking and alcohol consumption reported by mother and father. The dotted line represents the non-significant associations. (RMSEA=0.01; CFI=0.97; TLI=0.90). Mother father-child triadic data (n = 196). Associations survived the false discovery rate correction for multiple testing. Number of tests = 3 outcomes and the 3 relevant exposure periods (prenatal, mid- and late childhood). Critical value for FDR = 0.05.

Mediation analysis

Lastly, we investigated the potential mediating role of hippocampal volumes of the mothers, fathers, and their children each separately in the association between prenatal parental hostility and child aggressive behavior at age 10. As Figure 5 illustrates, hippocampal volumes of the mother, but not the father, partially mediated the association of prenatal parental hostility (latent construct) and preadolescent aggressive behavior (B = 0.01; 6.25% of the total effect; 95% CI, 0.01, 0.03). In addition, we found evidence that smaller hippocampal volumes of the child also partly account of the observed pre-

The associations between parental hostility and cortical gray matter microstructure for parents and children (N = 196 triads).

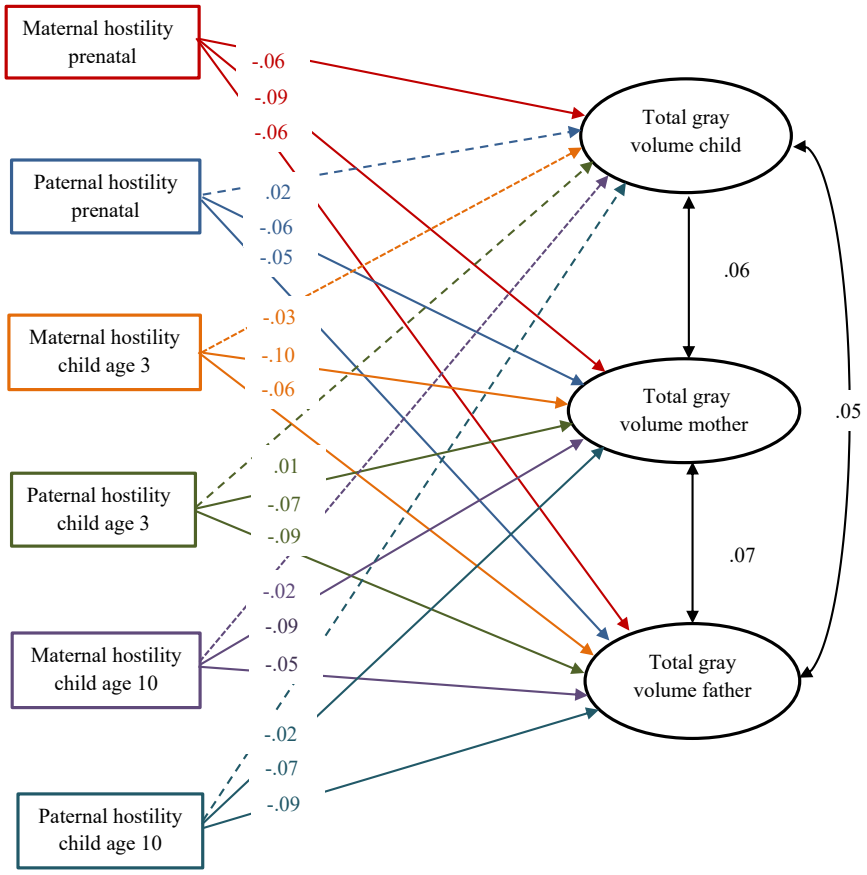


Figure 2. Structural equation modeling of parental hostility and cortical gray matter volumes of parents and children. Numeric values are unstandardized path regression coefficients. Models are adjusted for child age at brain MRI scan, child sex, age, ethnicity, education, smoking and alcohol consumption reported by mother and father. The dotted line represents the non-significant associations. (RMSEA=0.01; CFI=0.94; TLI=0.90). Mother father-child triadic data (n = 196). Associations survived the false discovery rate correction for multiple testing. Number of tests = 3 outcomes and the 3 relevant exposure periods (prenatal, mid- and late childhood). Critical value for FDR = 0.05.

adolescent problem behavior during late childhood (B = 0.02; 10% of the total effect; 95% CI, 0.01, 0.05). Additional adjustment for pre-existing child aggressive behavior at 1.5 years, resulted in no meaningful change in mediation results, suggesting that the behavioral changes did not precede the observed brain differences in the child.

The associations between parental hostility and hippocampus volume for parents and children (N = 196 triads).

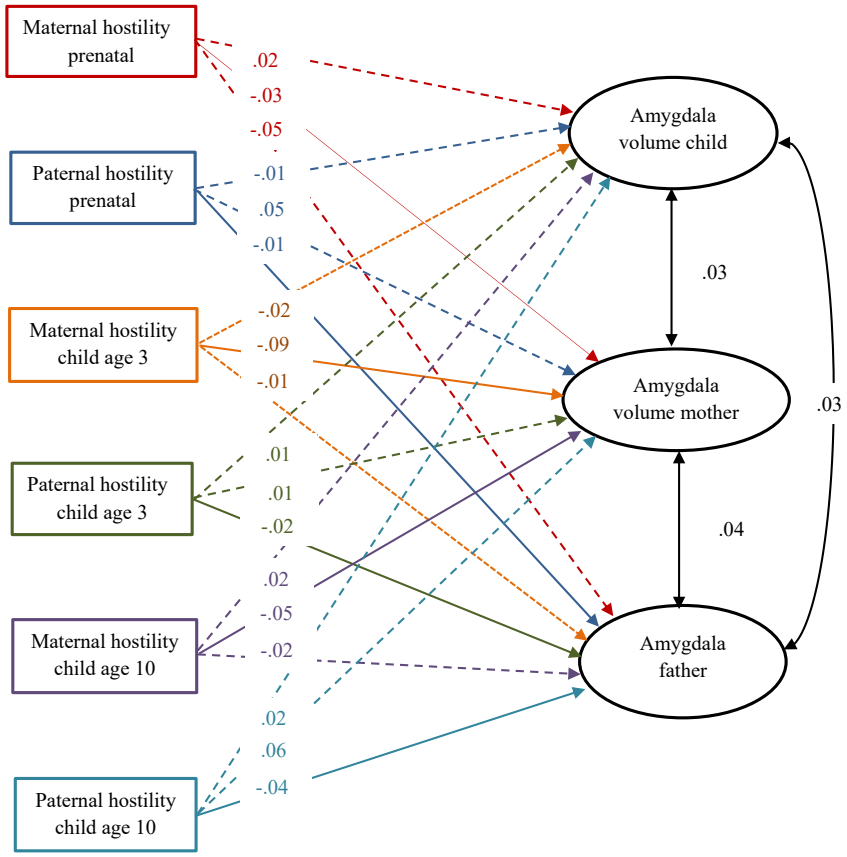


Figure 3. Structural equation modeling of parental hostility and hippocampus volumes of parents and children. Numeric values are unstandardized path regression coefficients. Models are adjusted for child age at brain MRI scan, child sex, total ICV, age, ethnicity, education, smoking and alcohol consumption reported by mother and father. The dotted line represents the non-significant associations. (RMSEA=0.01; CFI=0.95; TLI=0.90). Mother, father, and child triadic data (n = 196). Associations survived the false discovery rate correction for multiple testing. Number of tests = 3 outcomes and the 3 relevant exposure periods (prenatal, mid- and late childhood). Critical value for FDR = 0.05.

DISCUSSION

This population-based neuroimaging study suggests that parental hostility from pregnancy onward is associated not only with differences in the behavior of other family members but also their brain morphology. We highlight four main findings. First, we observed smaller total white matter, gray matter, and hippocampal volumes in children exposed to maternal hostility occurring during pregnancy. Second, our findings highlight the role of each parent's ability to transpire hostile behaviors to his or her partner and the child. Third, our results suggest that within parents, parental hostility

The associations between parental hostility and amygdala volumes for parents and children (N = 196 triads).

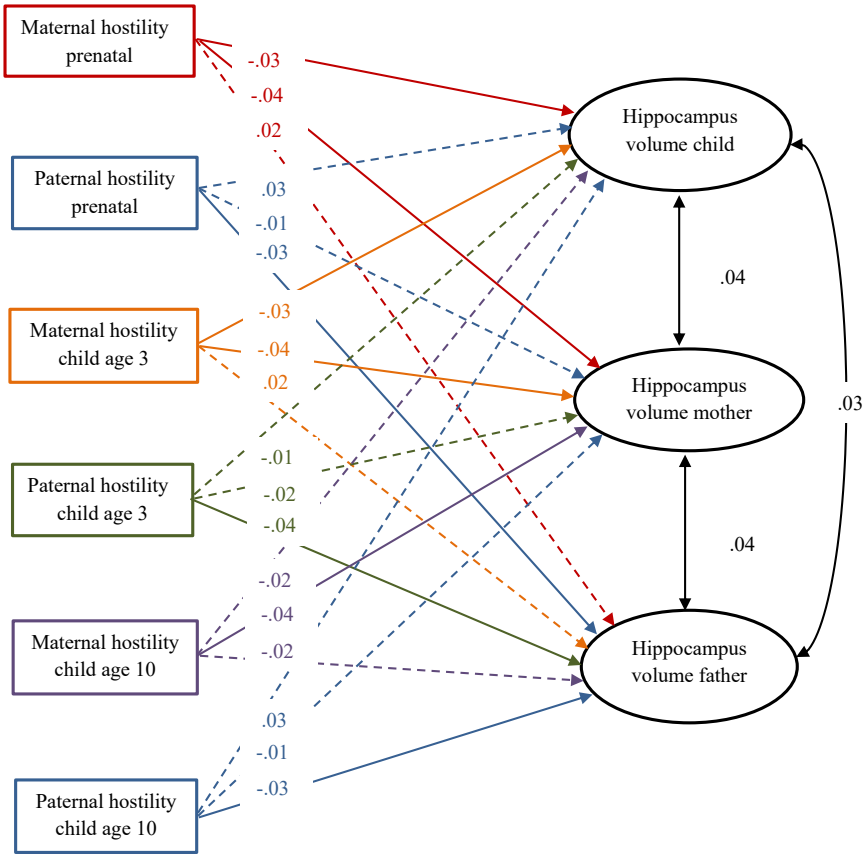
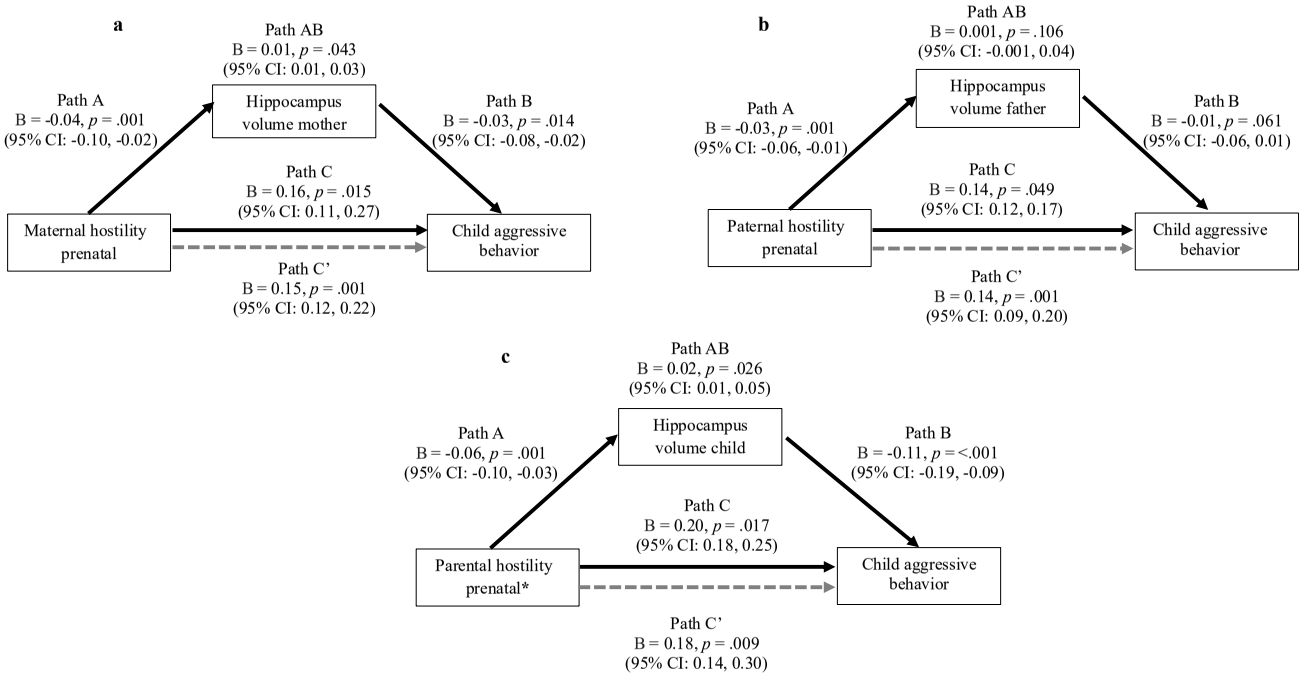


Figure 4. Structural equation modeling of parental hostility and amygdala volumes of parents and children. Numeric values are unstandardized path regression coefficients. Models are adjusted for child age at brain MRI scan, child sex, total ICV, age, ethnicity, education, smoking and alcohol consumption reported by mother and father. The dotted line represents the non-significant associations. (RMSEA=0.01; CFI=0.92; TLI=0.90). Mother father-child triadic data (n = 196). Associations survived the false discovery rate correction for multiple testing. Number of tests = 3 outcomes and the 3 relevant exposure periods (prenatal, mid- and late childhood). Critical value for FDR = 0.05.

is associated with differences in parental total white matter, gray matter, hippocampus, and amygdala volumes. Moreover, parental hostility is associated with differences in parental total white matter and gray matter volumes across parents. Last, we showed that prenatal parental hostility to child aggressive behavior was partially mediated by both hippocampal volumes of children and, importantly, also of mothers. These associations remained after adjusting for baseline family factors and multiple testing. Overall, the findings elucidate how hostility of a parent negatively relates to different family subsystems.

Figure 5. Hippocampal volumes of parents and children as mediator of the association between prenatal parental hostility and child aggressive behavior.



Mediation analysis of hippocampal volumes of parents and children in association with maternal and paternal hostility during pregnancy with preadolescent aggressive behavior at age 10. Model is adjusted for child age at brain MRI scan, child sex, total ICV, maternal age, race/ethnicity, education, smoking and alcohol consumption, and prior child aggressive behavior when child was aged 1.5 years.

a Path A is the association of prenatal maternal- or paternal-reported hostility with maternal or paternal hippocampal volumes, and path B is for the association of maternal or paternal or child hippocampal volumes with preadolescent aggressive behavior. Path C (in black) is the total association between prenatal maternal or paternal hostility and preadolescent aggressive behavior with hippocampal volumes not in the model. Path C′ (in gray) is the direct association between prenatal maternal-reported poor family functioning and preadolescent problem behavior factor with hippocampal volume in the model.

* The latent construct of maternal- and paternal-reported hostility. Parental hostility factor captures covariation across raters, or the extent to which a given dimension is reflected across parents (i.e., a between-rater dimension factor).

Parental to child associations

Previous studies indicate that the development of brain structures and function is shaped by a complex interaction between pre- and postnatal environmental factors continuously affecting the neural architecture throughout lifetime.[40,41] Brain development might be vulnerable and these environmental factors thus particularly significant early in life.[38] Our findings provide evidence that prenatal maternal but not paternal hostility was associated with smaller white matter, gray matter and hippocampal volumes of the child. Thus, it is likely that hostility is associated with the intrauterine environment, which in turn impairs child development.[42-44] Several mechanisms could explain this association. First, mothers with high levels of intrusive behavior during interactions with partners likely experience stress, which in turn dysregulates the hypothalamic-pituitary-adrenal axis and in turn affects child development, but it may also affect brain development through inflammatory responses and changes in the balance of the autonomic nervous system.[45] Another potential mechanism is an unhealthy maternal diet during pregnancy by which a variation in maternal nutrition (either a surplus or paucity of maternal nutrition) is significantly related to child's future neurodevelopment.[46]

Maternal hostility and differences in maternal brain

There is some evidence that maternal depression and anxiety during pregnancy and early childhood are related to structural changes in the maternal brain.[17] Similarly, our findings underscores that differences maternal hostile behavior were associated with maternal brain morphology. In a previous study, positive experiences during early postpartum period co-occurred with structural changes in mothers' brain regions susceptive to stress exposure including, gray matter volumes and prefrontal cortex in a study of 19 women.[47] Several mechanisms could explain the observed associations between parental hostility of both parent and child brain morphology. Pre-existing familial vulnerability factors such as parental psychopathology might be one mechanism that explaining the association with parental brain differences, which in turn increase child's aggressive behavior. Importantly, such associations could also be explained by genetic influences. Genetic predisposition could underlie difference in parent and child brain morphology. Recently, a genome-wide association meta-analysis identified a few genetic loci associated with hippocampal volume,[48] which could be (indirectly) associated with parental psychopathology. The co-occurrence in parents could possibly reflect assortative mating, while the association with the child could signal direct genetic or indirect transmission, the latter being dynastic effects.

Paternal hostility and differences in paternal brain

The present study extends the available neuroimaging data on parents and underscores the multiple pathways by which not only maternal but also paternal hostile behaviors during prenatal and earlier child's life may impact family life. We found fathers who

were more hostility during pre- and postnatal period had lower total white matter, gray matter and hippocampal volumes. Indeed, the accumulating evidence suggests that fathers' psychopathology poses many challenges to men's lives and mental health.[49] The timing of paternal psychopathology before and after child's birth is just recently being studied and placed into a biological framework that could involve brain morphology.[21] Researchers have consistently reported that adults with psychopathology have smaller hippocampus and amygdala volumes, two major components of the limbic system implicated in learning, memory, and emotion.[50] For example, smaller amygdala and hippocampus have been shown in mothers with postpartum depression, trauma, or substance use.[51-53] The present findings indicate that in addition to pre-existing familial factors and genetic predisposition, different influences of environment such as learning through observation, parenting practices and emotional climate in the family (triadic model) can affect both parents and children psychopathology.[54,55]

Within and between parents findings

Our findings show that one parent's hostility occur together with his or her partner's hostility, which has important implication for family health and well-being. A potential mechanism for the correlation of hostile behaviors between parents is assortative mating,[56] which suggests that mothers' and fathers' psychopathology may be similar before engaging in a relation.[57] That is, both partners may, for example, share common environments affecting the main trait with genetic and phenotypic resemblance. As such, partner resemblance arises because 'like mates with like' rather than 'mates become alike'. Such parental concordance for hostility is known to be related to more child aggressive behavior in children.[58] Poverty is another factor that could be associated not only to parents mental health but also to their functioning and brain characteristics. The stress experienced by maternal low socio-economic status may result in brain changes, and in turn increase risk for parental psychopathology.[59] However, in our study this remains speculative as a clear temporal direction was lacking; parents were imaged only once.

Mediation findings

The association between prenatal parental hostility and child aggressive behavior was partially mediated by the child's hippocampal volumes. Although the common variance is shared across mother and father-reported hostility, the association with prenatal exposure suggests that direct maternal physiological influences may underlie the findings. This is consistent with prior research in the present cohort showing that smaller offspring hippocampal volumes partially mediate the association between prenatal family disruption and child adjustment problems.[60] However, maternal, but not paternal hippocampal volumes partially also mediated the associations of prenatal parental hostility with child aggressive behavior. This could be explained in part due to the specific role of the mother

in the postnatal period which together with the intrauterine period is considered a critical period for optimal child development.[61] As infants are highly dependent, this critical period of nurturance and care requires a tremendous maternal investment. Whether this reflects that pregnancy has a long-lasting impact on maternal brain or background risk factors is unclear. However, the maternal hippocampal volume is related both to maternal hostility and may underlie the child problems. We cannot conclude which of these mechanisms contributed most to these associations, but our findings help guide a more comprehensive understanding of interrelated familial mechanisms.

There are several limitations of this study. First, as with all observational studies, the relative homogeneity of the population limits its generalizability. Second, given the lack of the repeated measures of both parents and child brain morphology, we cannot assess the directionality of the associations between parental hostility and the brain characteristics of the parents. Third, parental genetic variation could possibly predispose parents to higher levels of hostility while also affecting their child's brain structure. The strengths of the study lie in its large population-based sample and the SEM approach in the unique triadic data to testing the associations of prospectively measured exposure data with two parents' and child brain outcomes measured at 10 years of age. Furthermore, we included both maternal and paternal reports hostility and therefore could examine how one parent's hostility affects all members of the family. The methodology used in this study enabled us to separate associations of mother-related risk of hostility from those of father-related risk of hostility and assess their differential associations on the parent-child and family associations.

In conclusion, our findings suggest that prenatal parental hostility is associated with smaller volumes of total gray matter, white matter, and the hippocampus in children, suggesting that parental psychopathology may have long-lasting neurodevelopmental correlates in children. Moreover, maternal and paternal hostility were each associated with differences in his or her own brain morphology as well as his or her partner's total white and gray matter volumes. Our findings suggest that parental hostility has the potential to compromise child neurodevelopment and well-being long-term. The association of parental hostility during pregnancy and child aggressive behavior was partially mediated by the child's as well as maternal hippocampal volumes. Further research with repeated neuroimaging is required to identify distinctive changes in both parent and child brain structures among 'at-risk' parents and their children, in order to test the directionality and to direct specific and early interventions appropriately.

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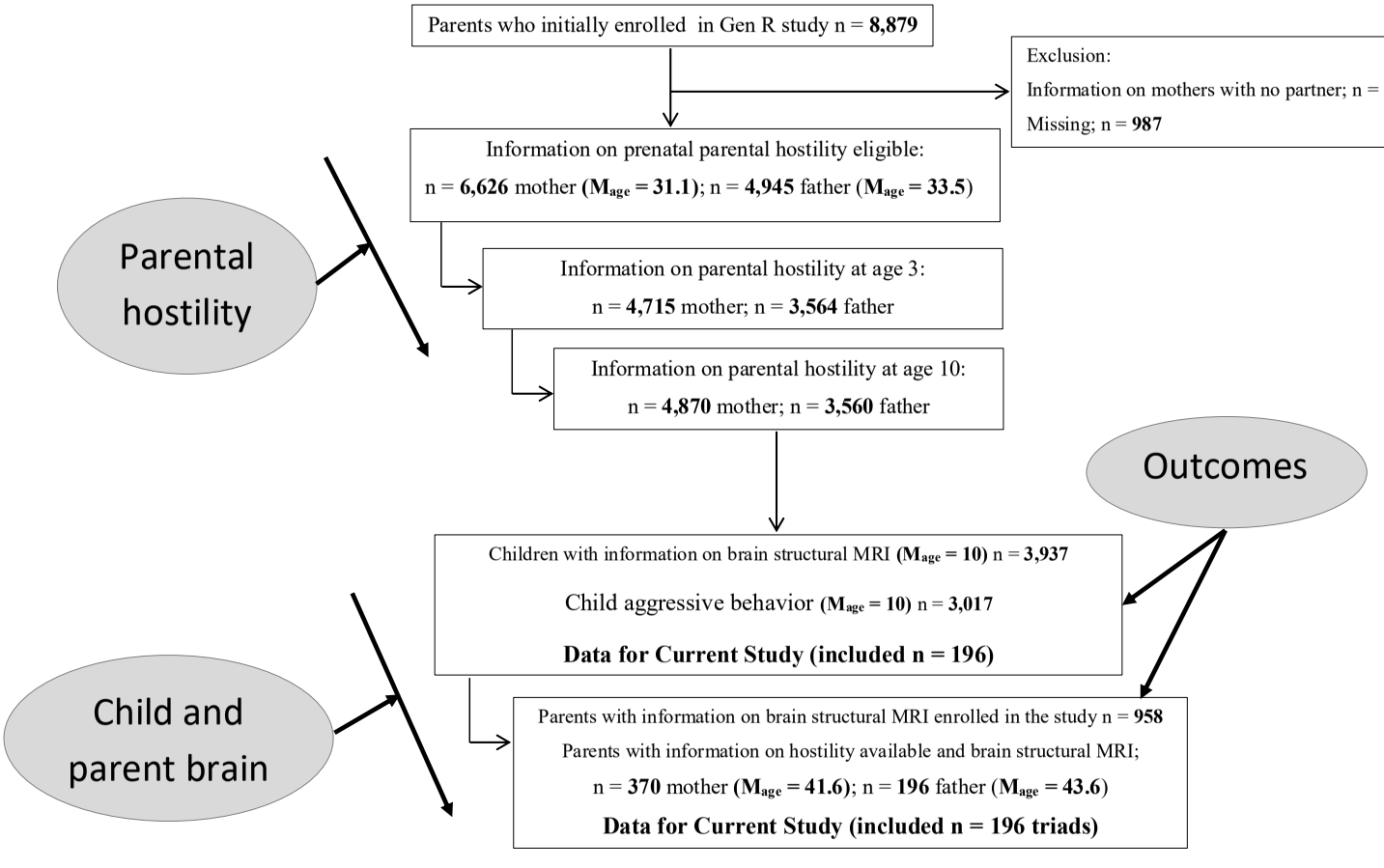
SUPPLEMENTARY METHOD.

Latent factor analysis

Latent factors analysis maternal- and paternal-reported parental hostility were modeled as latent variable via common confirmatory factor analytic (CFA) methods. The models were allowed to correlate, and were estimated with the robust maximum likelihood estimator using standardized latent variables. The latent parental hostility factor was used in mediation model to test whether the associations between prenatal parental hostility factor and child aggressive behavior was mediated by hippocampal volumes (Figure 5). The association between the latent construct of parental hostility with child hippocampal volumes and aggressive behavior captures covariation across raters, or the extent to which a given dimension is reflected both across parents (i.e., a "between-rater" dimension factor). The latent constructs showed good model fit as judged with the comparative fit index (CFI, acceptable fit ≥ .90).[1] The goodness of fit of these models was compared with the Bayesian information criterion (BIC) and Akaike's information criterion (AIC). A lower value for AIC and BIC indicates a better fit.[2]

Supplementart Figure 1. Inclusion of the Study Sample



Supplementary Table 1. The associations between maternal-reported hostility and child brain morphology (N = 196 triads).

	Child brain morphology (N = 196)							
	Global brain measures				***Specific brain volumetric measures***			
***Mother-reported* hostility**	**Cerebral white matter, (cm^3)**		**Total gray volume, (cm^3)**		**Amygdala volume, (cm^3)**		**Hippocampus volume, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Hostility, prenatal								
Model 1	-0.23 (-1.81 to -0.12)	.001	-0.38 (-1.44 to -0.15)	.001	0.07 (-0.09 to 0.02)	.362	-0.12 (-0.24 to -0.04)	.001
Model 2	-0.10 (-1.17 to -0.04)	.016	-0.13 (-1.12 to -0.02)	.009	0.03 (-0.13 to 0.09)	.537	-0.07 (-0.21 to -0.02)	.001
Hostility, child age 3								
Model 1	-0.11 (-1.12 to 0.07)	.312	-0.14 (-1.01 to 0.09)	.122	-0.06 (-0.05 to 0.04)	.331	-0.11 (-0.31 to -0.01)	.026
Model 2	-0.03 (-1.28 to 0.03)	.723	-0.03 (-1.13 to 0.07)	.443	-0.03 (-0.06 to 0.04)	.504	-0.04 (-0.30 to -0.01)	.035
Hostility, child age 10								
Model 1	-0.07 (-0.85 to 0.02)	.159	-0.08 (-0.93 to 0.02)	.067	0.05 (-0.02 to 0.03)	.938	0.05 (-0.02 to 0.11)	.165
Model 2	-0.05 (-0.74 to 0.06)	.663	-0.02 (-0.69 to 0.07)	.299	0.02 (-0.04 to 0.04)	.811	0.03 (-0.07 to 0.05)	.644

Linear regression analysis of maternal-reported hostility and child brain morphology outcome. B statistics are averaged from 10 imputed data sets. Model 1 is adjusted for child age at brain MRI scan, child sex, and total ICV. Model 2 is additionally adjusted for maternal age, race/ethnicity, education, and smoking and alcohol consumption. Global brain measures are not adjusted for total ICV.

Supplementary Table 2. The associations between paternal-reported hostility and child brain morphology (N = 196 triads).

	Child brain morphology (N = 196)							
	Global brain measures				*Specific brain volumetric measures*			
***Father-reported* hostility**	**Cerebral white matter, (cm^3)**		**Total gray volume, (cm^3)**		**Amygdala volume, (cm^3)**		**Hippocampus volume, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Hostility, prenatal								
Model 1	-0.08 (-0.35 to -0.05)	.019	-0.03 (-0.34 to 0.01)	.046	-0.01 (-0.05 to 0.03)	.774	-0.03 (-0.11 to 0.06)	.507
Model 2	-0.05 (-0.21 to 0.17)	.385	0.04 (-0.25 to 0.01)	.179	-0.01 (-0.05 to 0.04)	.843	0.01 (-0.10 to 0.07)	.787
Hostility, child age 3								
Model 1	-0.04 (-0.19 to 0.07)	.403	-0.03 (-0.33 to 0.08)	.343	0.02 (-0.03 to 0.03)	.371	0.03 (-0.07 to 0.01)	.601
Model 2	-0.02 (-0.15 to 0.06)	.591	0.02 (-0.27 to 0.01)	.199	0.01 (-0.05 to 0.07)	.741	-0.01 (-0.13 to 0.02)	.305
Hostility, child age 10								
Model 1	0.05 (-0.17 to 0.02)	.217	-0.05 (-0.41 to 0.03)	.177	0.05 (-0.03 to 0.01)	.540	0.05 (-0.09 to 0.03)	.079
Model 2	0.04 (-0.16 to 0.03)	.432	-0.04 (-0.34 to 0.02)	.307	0.03 (-0.04 to 0.01)	.459	0.03 (-0.08 to 0.03)	.095

Linear regression analysis of paternal hostility and child brain morphology outcome. B statistics are averaged from 10 imputed data sets. Model 1 is adjusted for child age at brain MRI scan, child sex, and total ICV. Model 2 is additionally adjusted for paternal age, race/ethnicity, education, and smoking and alcohol consumption. Global brain measures are not adjusted for total ICV.

Supplementary Table 3. The associations between maternal-reported hostility and maternal brain morphology (N = 196 triads).

	Maternal brain morphology (N = 196)							
	Global brain measures				*Specific brain volumetric measures*			
Parental hostility, mother rating	**Cerebral white matter, (cm^3)**		**Total gray volume, (cm^3)**		**Amygdala volume, (cm^3)**		**Hippocampus volume, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Hostility, prenatal								
Model 1	-0.11 (-0.39 to -0.02)	.001	-0.15 (-0.47 to -0.06)	.001	-0.04 (-0.12 to -0.01)	.009	-0.07 (-0.12 to -0.04)	.001
Model 2	-0.10 (-0.36 to -0.04)	.014	-0.13 (-0.41 to -0.05)	.003	-0.04 (-0.13 to -0.01)	.010	-0.06 (-0.10 to -0.02)	.001
Hostility, child age 3								
Model 1	-0.12 (-0.27 to -0.03)	.001	-0.16 (-0.38 to -0.04)	.001	-0.08 (-0.14 to -0.03)	.010	-0.06 (-0.12 to -0.02)	.004
Model 2	-0.12 (-0.34 to -0.03)	.003	-0.15 (-0.32 to -0.05)	.001	-0.07 (-0.13 to -0.02)	.017	-0.06 (-0.15 to -0.02)	.016
Hostility, child age 10								
Model 1	-0.09 (-0.47 to -0.03)	.001	-0.12 (-0.29 to -0.04)	.001	-0.07 (-0.15 to -0.02)	.004	-0.05 (-0.09 to -0.02)	.001
Model 2	-0.09 (-0.49 to -0.02)	.002	-0.12 (-0.33 to -0.03)	.001	-0.06 (-0.16 to -0.03)	.003	-0.05 (-0.10 to -0.02)	.003

Linear regression analysis of maternal-reported hostility and maternal brain morphology outcome. B statistics are averaged from 10 imputed data sets. Model 1 is adjusted for maternal age at intake, race/ethnicity, education, and total ICV. Model 2 is additionally adjusted for maternal smoking and alcohol consumption. Global brain measures are not adjusted for total ICV.

Supplementary Table 4. The associations between paternal-reported hostility and paternal brain morphology (N = 196 triads).

	Paternal brain morphology (N = 196)							
	Global brain measures				*Specific brain volumetric measures*			
***Father-reported* hostility**	**Cerebral white matter, (cm^3)**		**Total gray volume, (cm^3)**		**Amygdala volume, (cm^3)**		**Hippocampus volume, (cm^3)**	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
Hostility, prenatal								
Model 1	-0.08 (-0.46 to -0.01)	.001	-0.09 (-0.43 to -0.02)	.001	-0.03 (-0.15 to -0.01)	.026	-0.05 (-0.09 to -0.01)	.009
Model 2	-0.07 (-0.41 to -0.02)	.002	-0.08 (-0.39 to -0.02)	.001	-0.03 (-0.12 to -0.01)	.040	-0.04 (-0.10 to -0.01)	.002
Hostility, child age 3								
Model 1	-0.09 (-0.37 to -0.05)	.001	-0.12 (-0.52 to -0.04)	.001	-0.04 (-0.09 to -0.01)	.024	-0.06 (-0.11 to -0.02)	.001
Model 2	-0.09 (-0.38 to -0.04)	.001	-0.11 (-0.47 to -0.04)	.002	-0.04 (-0.08 to -0.01)	.038	-0.05 (-0.13 to -0.03)	.014
Hostility, child age 10								
Model 1	-0.10 (-0.27 to -0.04)	.001	-0.13 (-0.39 to -0.03)	.001	-0.05 (-0.16 to -0.02)	.001	-0.05 (-0.11 to -0.05)	.010
Model 2	-0.09 (-0.17 to -0.04)	.001	-0.13 (-0.34 to -0.05)	.002	-0.04 (-0.13 to -0.03)	.001	-0.05 (-0.13 to -0.04)	.019

Linear regression analysis of paternal-reported hostility and paternal brain morphology outcome. B statistics are averaged from 10 imputed data sets. Model 1 is adjusted for paternal age at intake, race/ethnicity, education, and total ICV. Model 2 is additionally adjusted for paternal smoking and alcohol consumption. Global brain measures are not adjusted for total ICV.

Supplementary Table 5. Correlation coefficients between maternal and paternal report of hostility.

	1	2	3	4	5	6
Parental hostility						
1 Prenatal, mother report	-					
2 Prenatal, father report	.27**	-				
3 Age 3, mother report	.32**	.13**	-			
4 Age 3, father report	.14**	.34**	.25**	-		
5 Age 10, mother report	.31**	.09**	.39**	.12**	-	
6 Age 10, father report	.11**	.29**	.14**	.37**	.18**	-

**Correlation is significant at the 0.01 level (2-tailed).